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Neurophysiology and Recovery in Neurological Disorders: Mechanisms, Neuroplasticity, and Therapeutic Horizons

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Abstract

This thesis details a series of experimental studies and theoretical reviews I conducted during my PhD, aimed at improving our understanding of recovery mechanisms in various neurological disorders, especially stroke, and exploring innovative neurophysiological and neuromodulatory tools to enhance functional recovery outcomes. Rooted in the fundamental belief that brain functions arise from the coordinated activity of distributed and dynamic networks, this work focuses on developing and validating biomarkers and interventions targeting these networks to guide and enhance functional recovery strategies.

First, the thesis begins with a general introductory chapter (Chapter 1) on stroke that emphasizes neurorehabilitation needs, especially motor skills, and highlights the importance of identifying reliable biomarkers for objectively characterizing deficits and predicting recovery trajectories, as well as tools to enhance functional recovery in patients. The next part focuses on early predictors of motor recovery after stroke. Specifically, two studies—one multimodal (Chapter 2) and one electroencephalography (EEG)-based (Chapter 3)—examine, respectively, the integration of kinematic and EEG data at four weeks post-stroke and the role of event-related desynchronization during action observation (i.e., a biomarker of mirror neuron system [MNS] function) to characterize and predict functional recovery in stroke patients. These chapters collectively support the use of non-invasive, real-world applicable tools to assess individual trajectories and tailor rehabilitation strategies from the early subacute stroke phase.

The second section emphasizes the cerebellum, a critical structure frequently neglected in clinical practice yet fundamental to numerous brain functions, especially pertinent in patient populations. Indeed, despite its importance, it remains poorly understood, especially in stroke patients, for functions essential to their recovery, including sensorimotor integration, temporal processing, and motor learning. Therefore, after a thorough review of cerebellar functions relevant to this context (Chapter 4), the thesis explores cerebellar roles in post-stroke adaptation through experimental studies, highlighting functions such as practice-dependent motor learning (Chapter 5) and temporal information processing (Chapter 6), which are not yet fully understood in stroke populations. Importantly, this evidence indicates that these functions can be measured and characterized using brief, ecologically valid tasks, opening new avenues for bedside assessments.

In the latter part of this thesis, I examine the emerging potential of non-invasive brain stimulation (NIBS) techniques to both investigate and therapeutically target cerebellar function. Although traditionally underrepresented in neuromodulatory research, the cerebellum has recently gained recognition as a crucial structure not only for sensorimotor integration but also for higher-order cognitive and social functions. Therefore, Chapter 7 describes NIBS as a valuable tool for investigating neurophysiological mechanisms and supporting functional recovery, with a special focus on cerebellar applications. Building on this framework, Chapter 8 examines the relationship between the cerebellum and the MNS, providing a new perspective that emphasizes the cerebellum's role in shaping cortical brain functions through

targeted modulation of inhibitory interneurons. This conceptual bridge enables experimental methods that can selectively influence cerebello-cortical circuits involved in motor and social-cognitive functions. Chapter 9 constitutes a fundamental element of this research, introducing an innovative neuromodulation protocol based on the resonance principle. Specifically, this protocol combines cerebellar transcranial alternating current stimulation at theta frequency (θtACS) with intermittent theta-burst stimulation (iTBS). The combined stimulation method promotes the entrainment of endogenous cerebellar rhythms and significantly enhances iTBS-induced synaptic plasticity. Through five experiments involving both healthy subjects and chronic stroke patients, we observed consistent, frequency- and site-specific improvements in both cortical excitability and fine motor control, with effects persisting for up to 30 minutes. These findings establish a resonance-based mechanism for circuit-specific engagement, positioning cerebellar θtACS-iTBS as a scalable, mechanistically grounded therapeutic strategy. Therefore, cerebellar neuromodulation may serve as a crucial tool for promoting functional recovery in neurorehabilitation treatments.

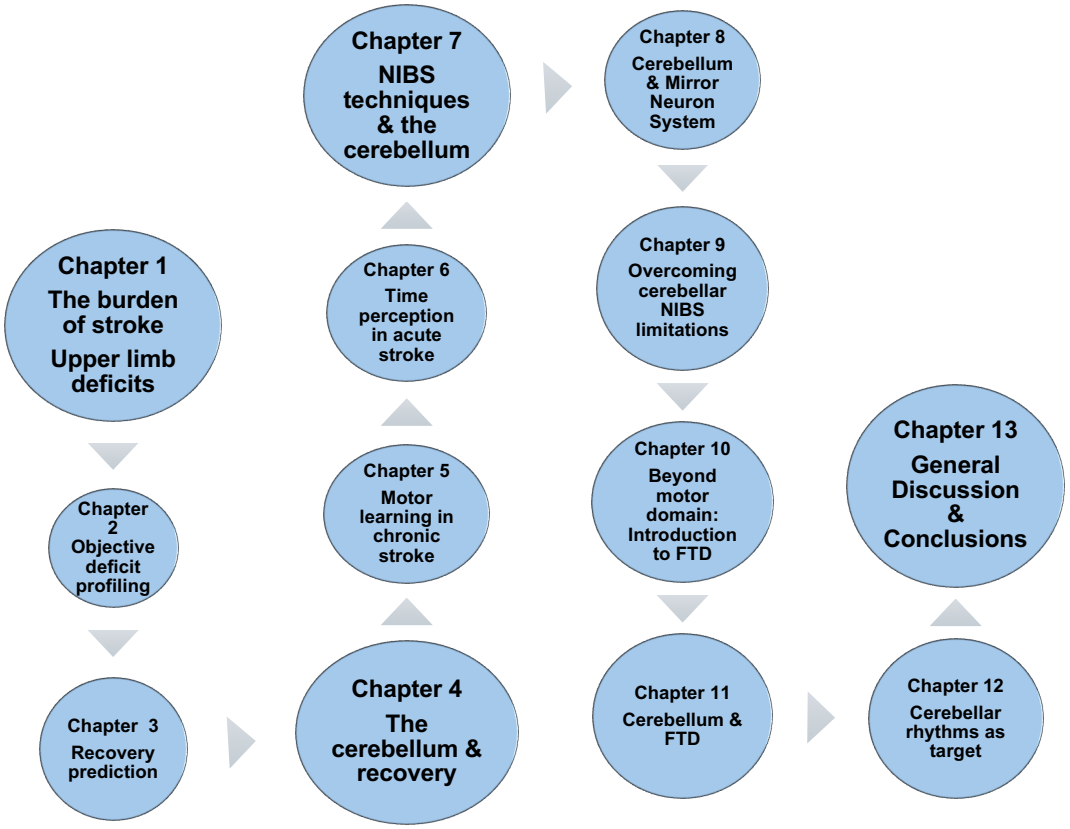
Building on this, Chapters 10 and 11 examine the translational potential of cerebellar NIBS beyond the motor domain. Specifically, Chapter 10 offers a comprehensive overview of frontotemporal dementia (FTD), emphasizing its diagnostic challenges and underscoring the need for new, physiology-based approaches. Moreover, Chapter 11 expands on this idea by suggesting the cerebellum as an often overlooked yet promising neuromodulatory target in FTD, especially considering its role in cognitive functions and behavior regulation—areas heavily impacted by the disorder.

Subsequently, Chapter 12 reviews current evidence on cerebellar oscillations and neuromodulation, offering a conceptual and methodological framework for future research. This comprehensive overview suggests that cerebellar rhythms could act as gateways to influence a broad spectrum of brain functions in motor, cognitive, and affective areas.

Finally, Chapter 13 offers a comprehensive discussion of the themes discussed in the previous chapters, synthesizing their importance within an integrated framework. This section not only highlights the broader implications of the findings but also outlines potential directions for future research, serving as a conceptual bridge between current knowledge and emerging avenues of investigation.

Together, these chapters focus on a compelling idea: developing scalable tools for clinical practice that facilitate the characterization and prediction of functional recovery, as well as enhance understanding of cerebellar functions—particularly in pathological cases—represents a primary focus of contemporary research. Consistently, cerebellar-targeted NIBS, particularly when guided by intrinsic rhythmicity and network-specific principles, holds transformative potential—not only for motor recovery after stroke, but also for addressing dysfunctions in neurodegenerative and neuropsychiatric conditions. Therefore, a more comprehensive understanding of the cerebellum, its functions, and how these change in pathological contexts will facilitate the further optimization of these promising strategies. I hope that this thesis may offer an integrated perspective on how these findings could influence the development of the next generation of personalized, mechanism-based neurorehabilitation and neuromodulation protocols.

CONCEPTUAL ROAD-MAP



Chapter 1. Stroke

1.1 An Introduction to Stroke

Brain stroke continues to be a leading cause of death and long-term disability worldwide, placing a heavy burden on healthcare systems and society, along with substantial economic, health, psychological, and social impacts (Feigin et al., 2017). Traditionally, stroke has been defined as a “clinical syndrome consisting of rapidly developing signs of focal or global disturbance of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” (Sacco et al., 2013). However, this definition, primarily based on temporal criteria, has gradually evolved due to significant advances in neuroimaging. Indeed, historically, the clinical detection of stroke has relied mainly on brain computed tomography (CT), which, although widely available, often does not have enough resolution to spot early or small ischemic lesions, especially in hard-to-reach areas such as the brainstem, posterior fossa, or deep brain structures like the basal ganglia (Liu et al., 2025). This technological limitation caused frequent misclassification of minor ischemic strokes as transient ischemic attacks (TIAs), especially in cases with subtle clinical signs and negative CT results (Sadighi et al., 2019). Importantly, the advent and growing accessibility of magnetic resonance imaging (MRI), especially diffusion-weighted imaging (DWI), have significantly improved diagnostic accuracy (Li et al., 2023). Indeed, it has become evident that many cases previously identified as TIAs show radiological signs of acute infarction (Easton et al., 2009). This shift from a time-based to a tissue-based definition has important clinical implications, as misclassification could delay proper secondary prevention and rehabilitation, resulting in worse long-term outcomes (Degan et al., 2017). This technological advancement indicates that many patients could benefit from interventions aimed at preventing long-term impairments, even if those impairments are subtle and clinically inconspicuous. Therefore, finding effective strategies for this purpose is a key focus of current research.

From a pathophysiological perspective, stroke can be broadly divided into ischemic (around 85% of cases) and hemorrhagic subtypes, each with different mechanisms and treatment strategies. Ischemic stroke typically results from thromboembolic occlusion of cerebral vessels, whereas hemorrhagic stroke involves vessel rupture and bleeding into the brain parenchyma or surrounding spaces (Amarenco et al., 2009). Over the past two decades, the acute management of ischemic stroke has undergone significant advancements due to the development of reperfusion therapies, including intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy (Bonaventura et al., 2016; Munich et al., 2019). Importantly, recent clinical trials and the implementation of advanced imaging software capable of quantifying the diffusion-perfusion mismatch have allowed for an extension of the therapeutic window well beyond the previously established time limits (Fainardi et al., 2023; Heiss and Zaro-Weber, 2019). These innovations have significantly improved the prognosis for many stroke patients, provided that appropriate infrastructure and timely intervention are available (Stemer and Lyden, 2010; Wechsler et al., 2023).

However, despite these advancements, the global burden of stroke remains alarmingly high, especially in low- and middle-income countries, where incidence rates and stroke-related complications continue to increase (Ezejimofor et al., 2016; Feigin et al., 2025). Contributing factors include limited access to acute care services, underdiagnosis of risk factors, and inadequate secondary prevention strategies (Mendis, 2010). Another critical consideration is the impact of population aging. As life expectancy rises worldwide, the occurrence of age-related diseases, including stroke, is expected to increase substantially (GBD 2019 Demographics

Collaborators, 2020; Yousufuddin and Young, 2019). Indeed, older adults are not only at greater risk of experiencing a stroke, partly because of the cumulative burden of comorbid conditions such as diabetes and cardiovascular diseases, but they are also more likely to face severe long-term consequences, including persistent disability, reduced independence, and a higher need for institutional care (Béjot et al., 2021; Howard et al., 2023; Long et al., 2016; Renedo et al., 2024; Satue et al., 2016). This highlights the urgent need for a two-part strategy: firstly, strengthening primary and secondary prevention efforts by improving risk factor management and health education; secondly, boosting post-stroke rehabilitation to maximize functional recovery. The main goal is not only to reduce mortality rates but also to improve quality of life and preserve independence for stroke survivors, especially among vulnerable and aging populations.

1.2 Risk Factors and Pathophysiology

The brain's blood supply is typically divided into 60% anterior and 40% posterior (ten Donkelaar et al., 2020). The anterior circulation, predominantly supplied by the internal carotid arteries, provides blood to the frontal, parietal, and lateral temporal lobes, as well as to the anterior region of the deep cerebral hemispheres. Conversely, the posterior circulation, supplied by the vertebral and basilar arteries, mainly supplies the brainstem, cerebellum, occipital lobes, and some deep brain areas, such as specific thalamic regions. As previously mentioned, the cause of stroke is multifactorial, with many modifiable and non-modifiable risk factors contributing to its onset (Boehme et al., 2017). Among the most significant modifiable risk factors are arterial hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, hyperhomocysteinemia, physical inactivity (or, more specifically, the absence of regular and appropriate exercise), atrial fibrillation, and, more generally, cardioembolic conditions (Di Legge et al., 2012). Conversely, non-modifiable factors include advanced age, male sex, and genetic predispositions that increase cerebrovascular risk, often indicated by a family history of stroke or other cerebrovascular disorders (Nindrea and Hasanuddin, 2023). A common characteristic of most risk factors is their ability to induce pathological changes in cerebral circulation, with specific mechanisms varying depending on the nature of the underlying risk. Notably, several of these factors contribute to the progressive development of atherosclerotic disease in the cerebral vasculature (Libby, 2021). Over time, this leads to atherosclerotic plaque buildup and gradual narrowing of the blood vessels, which can result in significant reductions in brain blood flow or complete blockages—mechanisms that cause atherothrombotic stroke (Asada et al., 2020). Typically, this process develops slowly, allowing collateral circulation—alternative blood vessel pathways, often originating from the opposite hemisphere—that can compensate for reduced blood flow (Leng and Leung, 2023). However, this reliance on collateral efficiency also makes deep brain structures, which are distant from these compensatory routes, especially vulnerable to ischemia (Maguida and Shuaib, 2023). The resulting damage often appears as chronic cerebrovascular injury, including silent microinfarcts or overt lacunar strokes—small, subcortical ischemic lesions commonly seen in areas such as the basal ganglia, thalamus, and internal capsule (Huang et al., 2024; Yaghi et al., 2021). Clinically, these stroke categories may be preceded by TIAs or present with a stepwise or fluctuating neurological deficit, indicating a gradual decline in perfusion reaching a critical threshold (Amin et al., 2023; Gutierrez et al., 2022; Lavallée et al., 2023). In certain situations, atherosclerotic plaques can become unstable, such as through ulceration or hemorrhage within the plaque, which can trigger the sudden formation of a blood clot and lead to rapid and severe vascular blockage (Chiorescu et al., 2022; Miceli et al., 2024). All identified risk factors

contribute to the high prevalence of atherothrombotic disease, especially among older adults, making this subtype a significant factor in the global stroke burden (Herrington et al., 2016; Spence et al., 2020).

By contrast, embolic strokes occur when an embolus suddenly blocks a cerebral vessel, that is, a blood clot or other material that travels from a distant source and becomes lodged in a smaller downstream artery (Kamel and Healey, 2017). Common sources of emboli include thrombi formed in the heart (especially in cases of atrial fibrillation), ulcerated plaques at high-turbulence arterial bifurcations, or paradoxical emboli traveling from the venous to arterial circulation through a patent foramen ovale or pulmonary arteriovenous malformation (Ferro, 2003; Holzer and Cua, 2016; Kent and Wang, 2025; Perera et al., 2016; Saric and Kronzon, 2012). The risk of these conditions increases with certain predisposing factors, such as genetic mutations affecting the coagulation cascade, tumors, or chronic inflammatory conditions, all of which can raise the likelihood of procoagulant states (Cate et al., 2017; Falanga et al., 2013; Petäjä, 2011). Embolic strokes typically occur suddenly and often affect cortical or distal arterial areas, leading to symptom patterns that differ from those seen in large-vessel occlusion (Chung, 2017; Markus, 2016). In some cases, no clear source can be identified despite thorough investigation; such cases are defined as cryptogenic strokes, often linked to (presumed) embolism sources that remain undetected through various tests (Diener et al., 2022; Hart et al., 2017).

Hemorrhagic stroke, on the other hand, occurs when a cerebral blood vessel ruptures, causing bleeding either into the brain tissue (intracerebral hemorrhage) or into the subarachnoid space (subarachnoid hemorrhage) (Shi, 2017). Intracerebral hemorrhages are frequently linked to chronic hypertension, which damages deep perforating arteries, resulting in what are known as "typical" hemorrhages in regions such as the thalamus, internal capsule, basal ganglia, and corona radiata (O'Carroll et al., 2021). Conversely, cerebral amyloid angiopathy—characterized by the deposition of amyloid in cortical vessel walls—is associated to "atypical" lobar hemorrhages, especially in the occipito-parietal brain regions, and can present with superficial siderosis or subdural hematomas (Koemans et al., 2023). It should be noted that, in addition to disrupting blood supply, the rupture of blood vessels can cause secondary complications such as compressive effects that may lead to herniation of brain structures (resulting in focal neurological deficit and decreased consciousness) and, due to specific mediators like endothelin, vasospasm of the surrounding cerebral vessels, which further decreases blood flow (Ciurea et al., 2013; Kalita et al., 2009).

However, regardless of the cause, stroke results in a sudden halt in brain blood flow, leading to neuronal hypoperfusion, mitochondrial energy failure, and—if not treated promptly—permanent cell damage or death (Tuo et al., 2022). This evolving cascade establishes a critical therapeutic window, during which acute interventions like intravenous thrombolysis or endovascular thrombectomy can restore perfusion and preserve neuronal tissue (Yang and Liu, 2021). Ultimately, the clinical presentation of stroke is heavily affected by its timing of onset, anatomical location, collateral circulation status, and the functional specialization of the affected brain regions (Maguida and Shuaib, 2023; Mangiardi et al., 2023; Murphy and Werring, 2023; Ryu et al., 2022).

1.3 A Brief Overview of Clinical Presentations

As previously discussed, the clinical presentation of stroke is closely linked to the specific site of damage within the central nervous system (CNS) and the organization of its neurovascular system architecture (Hu et al., 2017; Murphy and Werring, 2023). Importantly, the two main vascular systems that supply the brain—the anterior circulation (via the internal carotid arteries) and the posterior circulation (through the vertebral and

basilar arteries)—converge at the circle of Willis, a vital anastomotic structure located at the base of the brain (Patel et al., 2024). This arterial ring acts as a compensatory mechanism, maintaining redundancy and continuous blood flow to the brain in case of partial vascular blockage, providing some protection against ischemic events (Vrselja et al., 2014). Nevertheless, this protective effect is not always enough, especially in cases of systemic diseases, like arterial hypertension or atherosclerosis, that impair the body's ability to maintain proper cerebral blood flow (Denswil et al., 2016; Iadecola and Davisson, 2008). Furthermore, congenital anatomical variations in the configuration of the circle of Willis, which are common in a significant portion of the population, may reduce the effectiveness of collateral circulation and increase the risk of ischemia (Ayre et al., 2022). Consistently, recent studies have demonstrated that specific variants of the circle of Willis may predispose individuals to cerebrovascular pathologies, including cerebral aneurysms and ischemic stroke (Haghighimorad et al., 2022; Negatie et al., 2025).

Despite significant progress in neuroimaging technologies, stroke diagnosis still primarily relies on clinical assessment, especially for quickly identifying focal neurological deficits (Patil et al., 2022). Indeed, an accurate and timely neurological examination not only facilitates urgent inclusion in time-sensitive therapeutic pathways but also allows for an initial localization of the cerebral lesion (Murphy and Werring, 2023; Rennert et al., 2019; Sparaco et al., 2019). Indeed, this localization provides valuable insights into the probable cause of the stroke and helps tailor early treatment strategies, which can influence the patient’s prognosis and recovery path. This information is crucial for the immediate management of adjustable parameters, such as arterial pressure, blood glucose levels, and fluid-electrolyte balance, which can significantly impact clinical outcomes (Ellis and Resser, 2013; Gąsecki et al., 2020; Wang et al., 2023).

Importantly, although stroke symptoms encompass the full spectrum of neurological manifestations depending on the affected brain region, the involved vascular territory often aids in identifying characteristic clinical features and unique syndromes (Barbato et al., 2022). These syndromes, although sometimes approximate, offer useful frameworks for quick clinical reasoning and decision-making. Below are the primary stroke syndromes associated with occlusion of specific cerebral arteries:

- Anterior Cerebral Artery (ACA) Syndrome (Kumral et al., 2002): The ACA mainly supplies the medial and superior parts of the frontal and parietal lobes. Therefore, infarction in this area typically results in contralateral motor and sensory deficits, with greater involvement of the lower limb than the upper limb and face; transcortical motor aphasia (especially if the dominant hemisphere is affected); gait apraxia; and frontal lobe release signs such as the grasp reflex and paratonic rigidity. Because of the limited overlap with other vascular territories, ACA strokes generally cause more localized and specific syndromes (Kang and Kim, 2008).
- Middle Cerebral Artery (MCA) Syndrome (Asaithambi et al., 2014; Wong et al., 2002): The MCA is the primary artery of the anterior circulation and supplies about two-thirds of the lateral cerebral hemisphere, including the primary motor and somatosensory cortices (especially for the face and upper limb), Broca’s and Wernicke’s language areas in the dominant hemisphere, the insula, and neighboring frontal, parietal, and superior temporal cortices. A stroke within this area may cause contralateral hemiparesis and hemisensory loss, mainly affecting the face and arm; contralateral homonymous hemianopia; aphasia, which can be non-fluent, fluent, or global, especially when the dominant hemisphere is involved; hemispatial neglect; anosognosia; and visuospatial deficits when the nondominant hemisphere, usually the right, is affected. The MCA territory is the most frequently

affected area in ischemic stroke and often leads to severe neurological deficits when occlusion occurs proximally or extensively (Heiss, 2015; Huttner and Schwab, 2009).

- Posterior Cerebral Artery (PCA) Syndrome (Salerno et al., 2022; Schulz and Fischer, 2017): This vessel supplies blood to the occipital lobe, inferomedial parts of the temporal lobes, sections of the thalamus, the upper brainstem, and the posterior limb of the internal capsule. Infarctions in this area can produce a wide range of symptoms depending on the specific location of the blockage, including visual deficits such as homonymous hemianopia or cortical blindness (especially with bilateral involvement); thalamic syndromes like sensory loss, thalamic pain, or dysesthesia; consciousness impairments; cranial nerve palsies; and brainstem syndromes. Severe infarctions involving the basilar artery and its PCA branches can impact the brainstem, leading to outcomes from coma to death due to disruption of vital cardio-respiratory centers (Lieschke et al., 2025; Parvizi and Damasio, 2003).
- Lacunar Syndromes (Arboix and Martí-Vilalta, 2009; Jiang et al., 2021; Yaghi et al., 2021): As mentioned earlier, lacunar infarcts occur when small penetrating arteries that supply the deep parts of the brain, such as the basal ganglia, thalamus, internal capsule, corona radiata, and pons, become occluded. Although often small and initially clinically silent, these infarcts can cause classic clinical presentations, such as pure motor, pure sensory, sensorimotor, ataxic hemiparesis, and dysarthria–clumsy hand syndrome. Lacunar strokes are frequently associated with chronic hypertension and microangiopathy. Although their symptoms are typically less severe, they can accumulate and lead to vascular cognitive impairment or subcortical dementia in the long term (Kwan et al., 2021; Ohlmeier et al., 2023).

Therefore, the clinical signs of stroke significantly reflect the topographical and functional organization of cerebral blood flow territories damage. Although individual cases exhibit significant variability, owing to factors such as the timing of onset, quality of collateral circulation, comorbidities, and anatomical differences, identifying the involved vascular territories offers a crucial framework for diagnosis, prognosis, and early therapeutic decision-making (Chun et al., 2023; Meschia, 2002).

1.4 Consequences of Stroke

As previously outlined, stroke can cause an extremely wide range of neurological signs and symptoms, reflecting the heterogeneity of the affected brain structures and vascular territories. The clinical presentation is, therefore, highly variable and depends on multiple factors, including the location and extent of the lesion, the patient's genetic background, and premorbid health status (Murphy and Werring, 2023). However, among the most common impairments, several key domains can be identified:

- Motor dysfunctions often appear as paresis or plegia, presenting as a loss of voluntary movement control, especially for tasks that require fine motor skills like precise finger movements (Arene and Hidler, 2009; Raghavan, 2015). These deficits are often associated with abnormalities in muscle tone, typically characterized by a biphasic pattern: an initial flaccid hypotonia in the acute phase, followed by spastic hypertonia due to the loss of supraspinal inhibitory control over spinal reflex circuits (Kwakkel et al., 2003; Persson et al., 2020). It should be noted that long-term motor impairment is the most common outcome after a stroke, especially in the upper limb (Pollock et al., 2014).
- Sensory disturbances are also common and may include either complete loss (anesthesia) or partial or altered sensory perception (hypoesthesia, paresthesia, or dysesthesia), depending on the location

of the affected sensory pathways (Kessner et al., 2021; Sullivan and Hedman, 2008). Such deficits may impair tactile discrimination, proprioception, or more complex integrative sensory functions (Hoh and Semrau, 2025).

- Coordination and balance disorders are common in many post-stroke patients, with a significant risk of falls, especially among older adults (Campbell and Matthews, 2010; Pollock et al., 2011; Wade and Hewer, 1987). Ataxia, or the impaired ability to coordinate voluntary movements, may result from either cerebellar lesions or sensory deficits disrupting proprioceptive feedback loops (Marsden, 2018; Zhang et al., 2021). Clinically, this leads to an unsteady gait, dysmetria, and difficulty performing smooth and targeted motor sequences, which significantly affect the ability to carry out normal activities safely.
- Visual disturbances after a stroke can range from visual field deficits, such as homonymous hemianopia or quadrantanopia, to diplopia, especially when the cranial nerve nuclei responsible for eye movement are affected (Hanna et al., 2017; Sand et al., 2013). Amaurosis, or sudden loss of vision in one eye, can also happen, particularly during TIAs or retinal artery occlusion (Mbonde et al., 2022).
- Swallowing disorders are also common among many stroke patients. Specifically, dysphagia is frequent, especially during the acute phase of stroke, and it significantly increases the risk of aspiration pneumonia. (Dziewas et al., 2021). Although it frequently improves with time, early identification and management are vital to prevent complications (Arreola et al., 2019).
- Autonomic disturbances may include cardiovascular dysregulation, such as fluctuations in heart rate and blood pressure, sudomotor and vasomotor instability, and genitourinary issues like acute-phase incontinence (Armstrong et al., 2022; Lago et al., 2025). These impairments reflect the involvement of central autonomic regulatory networks, with important implications for managing acute patients and assessing short-term mortality risk (Damkjær et al., 2023; Jimenez-Ruiz et al., 2021).
- Pain is another major concern, especially in cases involving specific brain areas like the thalamus, which can lead to central post-stroke pain syndromes (Cheng et al., 2023; Harrison and Field, 2015). These issues stem not only from direct sensory pathway damage but also from complex interactions with spasticity, abnormal postures, and dysregulation of regional autonomic responses. Notably, shoulder pain is common and often linked to shoulder-hand syndrome, which can significantly hinder upper limb rehabilitation and lead to learned non-use (Dyer et al., 2020). Importantly, pain substantially impacts the patient's quality of life, mental health, and motivation for rehabilitation (Aprile et al., 2015; Khatooni et al., 2025).
- Cognitive impairments and symbolic deficits commonly occur in stroke survivors and are closely linked to the location of the lesion (Cramer et al., 2023; Rost et al., 2022). These may encompass:
    - Language disorders, including aphasia, differ from mere speech articulation dysfunctions (such as dysarthria, which is very common after a stroke) and involve impaired production and/or comprehension of spoken and/or written language (Alyahya et al., 2020; Mackenzie, 2011; Sheppard and Sebastian, 2021). Either fluent or non-fluent forms can be observed, depending on the cortical areas involved.
    - Executive dysfunction, including attention deficits, along with issues in planning, organizing, goal-directed behavior, and working memory (Sakai et al., 2024).
    - Memory and learning impairments hinder the ability to acquire and retain new information (Al-Qazzaz et al., 2014; O'Sullivan et al., 2023).

- Although often underrecognized, stroke significantly impairs the brain's ability to perceive, process, and use temporal information, such as estimating, producing, or interpreting durations and intervals (Coelho et al., 2022). This temporal processing dysfunction is crucial for effective neurorehabilitation treatments, as accurate timing is vital for coordinating actions, predicting changes, and interacting smoothly with the environment (Hass and Durstewitz, 2016; Hogendoorn, 2022). These changes may stem from damage to brain regions involved in temporal processing, including the basal ganglia, cerebellum, and prefrontal cortex, which support interval timing, estimation, and the integration of temporal cues into goal-directed behavior (Koch et al., 2009).

- In addition to neurological and cognitive effects, stroke survivors often face psychological and emotional challenges, which can include depression—a common and frequently underdiagnosed condition with a significant impact on functional recovery and participation in rehabilitation—as well as anxiety, often expressed through restlessness, fear of recurrence, or general worry (Medeiros et al., 2020; Wright et al., 2017). Moreover, stroke patients often experience reduced motivation, self-efficacy, and resilience, which further complicates the recovery process (Jones and Riazi, 2011; Korpershoek et al., 2011).

Taken together, these relevant and sometimes disabling deficits, ranging from sensory-motor to cognitive and psychological areas, have a significant functional impact on daily life after a stroke. Indeed, their combined effect often results in substantial limitations in daily functioning, including in Activities of Daily Living (ADL, such as dressing, feeding, and personal hygiene) and in Instrumental Activities of Daily Living (IADL, such as meal preparation, managing finances, and using transportation) (Brown et al., 2012; Galeoto et al., 2019; Hartman-Maeir et al., 2007). Furthermore, they frequently harm interpersonal and family relationships, leading to significant social and psychological effects on patients' well-being (McCarthy et al., 2020). Finally, they often hinder a return to work or independent mobility (Edwards et al., 2018; Wesselhoff et al., 2018). These consequences highlight the complex and multifaceted process of stroke recovery and underline the importance of personalized, multidisciplinary rehabilitation programs involving physicians, physical and occupational therapists, speech and language specialists, psychologists, and social workers (Langhorne et al., 2011; Li et al., 2024). The ultimate goal is to restore the highest achievable level of independence and quality of life by customizing therapeutic approaches to each patient's unique combination of deficits and personal resources. In this complex process, two elements are key in interacting with each other: spontaneous recovery and compensation.

1.5 Stroke Motor Recovery, Motor (Re)Learning, and the Role of Neurorehabilitation

Evidence indicates that motor recovery after stroke occurs in two main phases, known as the early and late recovery stages (Kwakkel et al., 2023). Although conceptually distinct, these phases operate together in a dynamic and complementary manner, collectively impacting functional outcomes. In the early phase, usually covering the initial weeks to a few months after a stroke, there is a temporary period of increased neuroplasticity (Dimyan and Cohen, 2011). This period aligns with natural biological recovery processes, driven by the nervous system's intrinsic neural repair and reorganization mechanisms. During this period, it consistently shows an increased ability to adapt both structurally and functionally in response to injury, possibly due to an environment that promotes plasticity (Aderinto et al., 2023; Joshua, 2022). In contrast, during the

later stages of stroke, beyond the initial 6-month period, functional improvements are thought to mainly rely on experience and practice, characterized by motor learning and skill reacquisition rather than spontaneous recovery (Gregor et al., 2021; Winterbottom and Nilsen, 2024). Consistently, functional gains during this stage are more closely associated with training, repetitive practice, and task-specific rehabilitation. Importantly, in this context, a key conceptual distinction is often made between "true recovery," which involves restoring motor functions using the same strategies and effectors as before the stroke, and "compensation," referring to performing motor tasks through alternative, often less efficient, movement patterns—such as reliance on the non-paretic limb or the adoption of maladaptive synergies (Levin et al., 2009). Consistently, compensatory strategies may enable task completion but are usually linked to lower movement quality and may involve the use of non-traditional effectors or suboptimal biomechanics. While these adaptations are crucial for achieving functional independence, their promotion must be carefully balanced to avoid maladaptive plasticity, such as learned non-use or inefficient movement patterns (Jones, 2017). Notably, spontaneous recovery is not limited to motor function in the upper and lower limbs, as it can also include sensory, language, and cognitive domains (Boccuni et al., 2018; Byblow et al., 2015; Lendrem and Lincoln, 1985; Veerbeek et al., 2018; Winters et al., 2017). This process is triggered by the ischemic cascade, which starts within minutes of stroke onset. Indeed, the cascade involves energy failure, mitochondrial dysfunction, and the death of both neuronal and glial cells (Andrabi et al., 2020; Xing et al., 2012). Notably, the biological response to these events also involves mechanisms that support recovery, such as dendritogenesis, axonal sprouting, unmasking of pre-existing latent synapses, and rewiring of neural networks (Rajan, 2025). These processes are driven by changes in the excitatory/inhibitory balance, local inflammation, and shifts in the neurochemical activity environment (Anrather and Iadecola, 2016; Han et al., 2023; Páscoa dos Santos and Verschure, 2022). Perilesional areas, in particular, may exhibit a heightened sensitivity to rehabilitative input during this phase, supporting activity-dependent reorganization through selective and competitive plasticity mechanisms (Joy and Carmichael, 2021). This is especially true within the first 8–10 weeks post-stroke, when the brain’s response to training is most robust (Zeiler and Krakauer, 2013).

Therefore, the interaction between spontaneous biological recovery and rehabilitation-induced motor learning forms the foundation for early, intensive neurorehabilitation (Maier et al., 2019). Crucially, motor neurorehabilitation aims not only to support biological recovery but also to optimize compensatory performance when restitution is not possible (Kwakkel et al., 2015). Therefore, effective interventions must be repetitive, goal-oriented, properly dosed, progressively challenging, and context-specific (Kwakkel et al., 2023). Robust evidence now supports the principle that early initiation of rehabilitation is essential for maximizing outcomes, as it leverages the transient neuroplastic state and helps prevent maladaptive behaviors such as learned non-use, learned bad-use, or motor forgetting (KRISHNAN, 2006; Maier et al., 2019; Molle Da Costa et al., 2019; Raghavan, 2015).

Importantly, despite advances in stroke treatment, a major limitation remains: the lack of reliable biomarkers able to accurately predict long-term functional recovery after a stroke (Boyd et al., 2017; Stinear, 2017). This presents a significant challenge in settings with limited resources, where it is crucial to identify patients most likely to benefit from targeted rehabilitation to inform clinical decisions and improve health system efficiency. Numerous candidate markers, including baseline clinical severity, integrity of the corticospinal tract, pre-stroke functional status, and various neurophysiological metrics, have shown promise (Gandolfi et al., 2017; Grefkes and Fink, 2020; Milani et al., 2022; Stinear, 2017). However, none have yet shown enough sensitivity or

specificity to accurately predict individual recovery paths. This reflects the highly complex, multifactorial, and nonlinear nature of post-stroke recovery, which likely involves variables that are still poorly understood or remain unmeasurable (Alawieh et al., 2018; Latifi and Carmichael, 2024; Mohan et al., 2021). Currently, rehabilitation pathways are mostly influenced by clinicians' subjective assessments and expectations, which can lead to variability and possible disparities in access to rehabilitative care services (Stinear et al., 2019). Moreover, notably, patients with moderate-to-severe deficits, who are likely to benefit the most from neurorehabilitation, are often those for whom prognosis is hardest to determine based on clinical judgment alone (Stinear, 2017).

A key aspect in this context is evaluating whether stroke survivors retain the ability for motor learning, which is the neurobiological foundation on which the success of rehabilitation ultimately depends (Krakauer, 2006). Motor learning is broadly defined as the capability to acquire new motor skills or enhance performance through practice, resulting in optimized outcomes (Spampinato and Celnik, 2021). It encompasses a wide range of functions, including skill acquisition, motor adaptation, and decision-making—that is, the ability to select the appropriate movement within the correct context (Krakauer, 2006). Indeed, importantly, preserved motor learning mechanisms enable patients to adaptively acquire or reacquire functional strategies, even in the absence of full restitution. Unfortunately, this awareness has only emerged relatively recently, whereas in the past, rehabilitation was mostly limited to passive mobilization of the affected body segments after a stroke and treatment of spastic hypertonia, which is now understood to be often unrelated to recovery trajectories (Ferrarello et al., 2015; Sommerfeld et al., 2004). Notably, extensive evidence shows—both in healthy individuals and in stroke patients—that motor learning is closely connected to forming and constantly updating internal models (as discussed in the chapter on the cerebellum in this thesis) (Kiper et al., 2016; Pierella et al., 2019). These internal models allow the CNS to adjust motor commands by predicting the expected sensory outcomes of an action, thereby improving the connection between the system's internal state and the external environment (Spampinato and Celnik, 2021). A key feature of these models is their potential for generalization: that is, once created, an internal model optimized for one type of movement can often be used for other motor tasks (Censor, 2013; Sarwary et al., 2015). This ability to generalize has essential implications for post-stroke recovery, where rehabilitation could benefit from transferring learning across various functional areas. Thus, a key goal of neurorehabilitation is to develop and strengthen internal models that can accurately translate environmental interactions into coordinated motor responses (Cano-de-la-Cuerda et al., 2015). Interestingly, multiple factors are known to affect the effectiveness of the internal model development. These include the amount and distribution of motor practice, the timing of rehabilitation initiation (with early intervention being markedly more effective than delayed onset), and the capacity of training protocols to unmask latent cortico-cortical connections (Biernaskie et al., 2004; Jacobs and Donoghue, 1991; Shea and Kohl, 1991). Early and intensive training, in particular, appears to capitalize on windows of increased neuroplasticity to promote more substantial reorganization within the motor networks (Aderinto et al., 2023; Gazerani, 2025). These insights into motor learning have directly informed the design of modern rehabilitation strategies grounded in neuroscientific evidence. Consistently, approaches such as impairment-oriented training, constraint-induced movement therapy, robot-assisted therapy, and virtual reality-based interventions all rely on principles of experience-dependent plasticity and motor re-education (Demers et al., 2021; Grosmaire et al., 2022; Krakauer, 2006; Kwakkel et al., 2015; Takeuchi and Izumi, 2013). Altogether, these findings underscore the importance of deepening motor learning mechanisms in the post-stroke brain. Enhancing our knowledge in

this area is pivotal to refining therapeutic strategies and optimizing functional recovery for this complex and heterogeneous patient population. Consistently, understanding individual profiles of motor learning could inform personalized rehabilitation strategies, as different learning mechanisms (e.g., error-based learning, reinforcement learning, use-dependent learning) may be differentially preserved or impaired depending on the type and extent of the stroke lesion (Abram et al., 2025; Branscheidt et al., 2025; Dahms et al., 2020; Spampinato and Celnik, 2021). Furthermore, the ability to assess motor learning capacity—especially in chronic stages where spontaneous recovery has plateaued—could be crucial for predicting treatment response and developing effective long-term rehabilitation strategies. However, current methods for evaluating motor learning potential are technically demanding, often requiring specialized instrumentation or protocols that are not feasible for routine clinical application. The development of scalable, accessible tools to evaluate this capacity continues to be a key priority for enhancing the accuracy and effectiveness of post-stroke rehabilitation.

Given the central role of internal model formation and updating in motor learning after stroke—and the cerebellum's well-established contribution to these processes—it is not surprising that an increasing amount of evidence highlights the cerebellum as a key structure in supporting motor recovery post-stroke (Delion et al., 2025; Kiper et al., 2016; Pierella et al., 2019; Spampinato and Celnik, 2021). Supporting this view, a longitudinal study of patients in the subacute phase of stroke recovery demonstrated that macrostructural neuroplasticity, especially within the cerebellum, likely reflecting the formation of new internal models, underpins relevant aspects of motor improvement (Hanakawa et al., 2023).

Moreover, recent findings in chronic stroke patients—i.e., individuals well beyond the window of heightened neuroplasticity traditionally associated with early recovery—have shown that structural remodeling not only persists years after the event, but that cerebellar-specific changes may keep contributing to functional recovery even at this late stage (Yoo et al., 2025). Further supporting this perspective, studies in the chronic phase have demonstrated that the persistence of structural crossed cerebellar diaschisis (characterized by reduced cerebellar activity due to disrupted input from damaged cerebral regions), as indexed by decreased volume in specific cerebellar lobules, correlates with the degree of residual clinical disability (Guder et al., 2023). Importantly, the same cerebellar regions affected by diaschisis consistently engage during motor learning tasks involving the upper limb, especially in motor sequence learning paradigms (Hardwick et al., 2013). This overlap indicates a direct connection between cerebellar plastic reserve, motor learning ability, and the degree of compensatory recovery after stroke.

Taken together, these findings underscore the importance of investigating cerebellar function in post-stroke recovery—encompassing both motor learning and wider cognitive and sensorimotor domains—as such understanding may be instrumental in enhancing rehabilitation strategies.

1.6 Outline of the Present Thesis

Based on these premises, the upcoming chapters will first explore strategies aimed at improving our ability to characterize and predict motor recovery in stroke patients using neurophysiological methods—specifically, electroencephalography and kinematic analysis. As previously discussed, such tools might be essential for personalizing treatment pathways and maximizing therapeutic efficiency. Next, the cerebellum will be explained in more detail, and two original studies will be shown. The first explores motor learning in chronic stroke patients using accessible, easy-to-implement tools—a topic still underexplored in the literature. On the other hand, the second examines the ability to process temporal information in the acute phase of cerebellar and basal ganglia stroke, another area of growing interest. Finally, the thesis will discuss non-invasive brain stimulation (NIBS) techniques, both as a way to investigate cerebellar neurophysiology and as a potential treatment to improve functional outcomes. Specifically, evidence will be presented on how the cerebellum interacts with the mirror neuron system, an area of growing interest due to its significant implications for neurorehabilitation, especially considering the emerging potential to non-invasively influence these systems' interactions. Following this, the thesis will present a study that explored an innovative, combined strategy to modulate cerebellar oscillatory activity to improve the long-term neuroplastic effects previously shown by specific NIBS protocols. This study provides both neurophysiological and behavioral evidence, moving from experiments on healthy individuals to applications in patients with chronic stroke, with crucial neurorehabilitation implications. While already demonstrating promise in post-stroke rehabilitation, cerebellar NIBS may also have translational value for other neurological disorders, such as frontotemporal dementia. This will be introduced as a complementary clinical model to further emphasize the cerebellum's broader role in neurorehabilitation and cognitive neuroscience. Subsequently, the thesis will review the oscillatory dynamics that characterize cerebellar circuitry, highlighting their potential as a tool to modulate the cerebellum's complex computational processes. This investigation is especially relevant given the insights from previous chapters. The main goal is to develop tools based on solid neurophysiological principles with strong potential to improve functional outcomes across various neurological conditions, as discussed in the final chapter.

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Chapter 2. A multimodal analysis to explore upper limb motor recovery at 4 weeks after stroke: insights from EEG and kinematics measures

In Chapter 2 of this thesis, I present a study that examined early motor recovery after stroke using a multimodal assessment that combines electroencephalography (EEG) and kinematic analysis. Building on the neurorehabilitation research priorities framework outlined in the previous chapter, this study aimed to investigate the neural and behavioral correlates of upper limb motor function four weeks post-stroke. The results revealed that both EEG and kinematic biomarkers captured meaningful data on post-stroke recovery, offering insight into early-stage motor reorganization. Crucially, combining electrophysiological and biomechanical data provided complementary insights, enabling a more comprehensive understanding of the mechanisms behind functional improvement. These findings underscore the potential of multimodal approaches to inform patient-specific neurorehabilitation strategies and highlight the utility of such tools in the early identification of individuals with favorable recovery trajectories. Therefore, this study supports one of the main goals of this thesis by emphasizing the clinical relevance of early neurophysiological assessment and advocating for the use of non-invasive techniques in developing precision rehabilitation protocols.

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2.1 Abstract

Stroke is a leading cause of death and disability worldwide, and there is a very brief window of increased synaptic plasticity, which is essential for motor recovery. Therefore, it is important to gather data to inform rehabilitation treatment. Promising results have been obtained from kinematic and neurophysiological data, but few studies currently combine these different modalities. We examined the relationships between standardized clinical scales, kinematic data, and electroencephalography (EEG) measures four weeks post-stroke. A total of 26 patients were included in the study. Of these, 20 also underwent EEG testing in addition to kinematic analysis at 4 weeks. Our findings indicated correlations between Fugl-Meyer Assessment-Upper Extremity scores, movement duration, smoothness measures, and velocity peaks. Furthermore, EEG data indicated that in patients with better clinical status, the healthy hemisphere tended to compensate for the affected one. These findings show the importance of kinematic measures, especially movement duration and smoothness, along with EEG biomarkers, in assessing post-stroke recovery. We highlight the relevance of combining clinical data with kinematic and EEG analyses early in stroke recovery to optimize rehabilitation strategies and take advantage of the brief window of heightened synaptic plasticity.

2.2 Introduction

Stroke is a major cause of death and disability worldwide (Muratova et al., 2020). Given the challenges in post-stroke rehabilitation, extensive research has been conducted to identify biomarkers that can predict motor recovery, often measured by standardized clinical scales (Gladstone et al., 2002; Stinear, 2017). Depending on the stroke site, various prognostic and therapeutic implications arise, leading to varied rehabilitation considerations (Kim and Caplan, 2016). Therefore, one of the primary goals is to identify personalized and customized biomarkers for post-stroke rehabilitation (Hatem et al., 2016). Moreover, considering that standardized measurement scales may not fully capture the complexity of individual conditions, it is important to supplement clinical assessments with additional sources of information. This helps improve patient characterization and supports more personalized approaches in neurorehabilitation.

Electroencephalography (EEG), especially quantitative EEG (qEEG), is a non-invasive, simple, repeatable, and inexpensive technique that offers valuable insights into cortical activity changes after a stroke. Typically, stroke patients display increased power in slow EEG rhythms, mainly in the theta and delta bands (Finnigan and van Putten, 2013). EEG recordings can be conducted either at rest (resting state) or during mental or motor tasks. In this study, we examined resting state recordings, focusing on the delta-alpha ratio (DAR) and the Brain Symmetry Index (BSI), both derived from EEG data. The DAR indicates the proportion between slow (lesional) and faster (physiological) rhythms. Research suggests that subacute stroke survivors tend to have higher DAR values compared to healthy controls, particularly in the early stages after stroke (Finnigan et al., 2016), driven by increased delta activity during the acute/subacute phase, which tends to normalize in the chronic phase (Saes et al., 2019). The delta+theta/alpha+beta ratio (DTABR) is related to DAR but also reacts to theta and beta activity, which can sometimes provide useful information (Finnigan et al., 2016). The BSI assesses the imbalance in spectral power between the two hemispheres (Agius Anastasi et al., 2017). It could be a valuable metric for evaluating how the cortex reorganizes following a stroke, particularly by analyzing the healthy hemisphere's role in compensating for the impaired functions of the damaged side (Milani et al., 2022). Directional BSI (dirBSI) offers insights into the asymmetry between spectral powers from the hemispheres and considers the direction of this asymmetry (Saes et al., 2019); dirBSI = 0 indicates perfect symmetry, while

positive values (0-1) show greater power in the affected hemisphere, and negative values indicate the opposite. For stroke survivors, a positive value indicates greater power in the affected hemisphere than in the unaffected one. QEEG measures are especially valuable during stroke recovery, as patients experience structural and functional brain reorganization aimed at restoring impaired functions through changes in cortical-subcortical networks (Hara, 2015; Milani et al., 2022).

The window for neuroplasticity to assist recovery is very brief, so starting rehabilitation early after a stroke is essential (Hara, 2015). Recently, integrating clinical and neurophysiological data with kinematic analyses has gained significant support, providing valuable insights into movement characteristics. Kinematic parameters enable detailed analysis of movement quality, revealing the strategies and motor patterns employed. This helps differentiate proper motor recovery from compensatory movements, particularly when achieving true recovery is not possible (Villepinte et al., 2021). In this study, we investigate the possible relationship among clinical assessments, reaching task kinematic data, and qEEG measures to evaluate motor recovery four weeks post-stroke.

2.3 Methods

We detail a cross-sectional observational clinical study conducted from April 2019 to April 2021 (NCT04637984). Patients with a first-time stroke admitted to the Neuroscience and Rehabilitation Department at Ferrara University Hospital were enrolled. These patients underwent assessments and interviews to verify inclusion and exclusion criteria, were informed about the study procedures, and provided informed consent. The inclusion criteria included being aged 18 or older, experiencing a first-ever ischemic or hemorrhagic stroke confirmed by brain imaging, and being evaluated within 7 days of stroke using the PREP2 algorithm (Stinear et al., 2017) for upper limb motor deficit. Exclusion criteria included cerebellar stroke or bilateral cerebral stroke, any medical or neurological conditions that could hinder safe participation or understanding, severe cardiopulmonary, renal, or hepatic diseases, and pregnancy. All participants signed an informed consent.

2.4 Procedures

2.4.1 Clinical and instrumental evaluations

Data were gathered at 3-7 days (T0) and 4 weeks (T1) following the acute cerebrovascular event. As per the PREP2 algorithm (Stinear et al., 2017), the National Institutes of Health Stroke Scale (NIHSS), the SAFE Score, and Transcranial Magnetic Stimulation (TMS) were recorded at T0. Meanwhile, the Action Research Arm Test (ARAT), the Fugl-Meyer Assessment - Upper Extremity (FMA-UE), kinematic data, and resting state EEG were collected at T1.

NIHSS is an essential predictor of outcomes, consisting of a scale that effectively quantifies overall severity (Ortiz and L. Sacco, 2014). ARAT is an observational assessment employed to evaluate upper limb function. (McDonnell, 2008). FMA-UE is a commonly used scale in the rehabilitation field, widely recognized for its validity and reliability in assessing upper limb impairment, especially in quantifying the influence of pathological synergies on current motor activity (Fugl-Meyer et al., 1975; Gladstone et al., 2002). Single-pulse TMS was applied to the primary motor area (M1) to assess corticospinal tract excitability by recording Motor Evoked Potentials (MEPs) from the first dorsal interosseous muscle (FDI) of both hands at baseline, which served as a potential prognostic indicator. The resting motor threshold (RMT)—the lowest stimulation intensity needed

to evoke 5 out of 10 MEPs with a peak-to-peak amplitude of at least 50 μV—was measured for each hemisphere. Ten TMS pulses were administered using a figure-of-eight coil connected to a MagStim 200 monophasic stimulator at 120% RMT. The presence of MEPs serves as an early prognostic marker of functional recovery, reflecting the condition of the corticospinal tract (Escudero et al., 1998).
Finally, an EEG was recorded during the resting state, including 3 minutes with eyes open and 3 minutes with eyes closed. During the 'open eyes' phase, subjects were required to fixate on a white cross against a black background. Participants were instructed to remain seated and try not to move throughout the entire recording.

2.4.2 Kinematic Recording and Data Analysis

Subjects sat on a backless bench with hips and knees flexed at 90° to acquire kinematic data. They performed two movements: Reach Up and Reach Out (see Figure 1). During the Reach Out, participants had a table with a target-can (weighing about 300 grams) aligned with their midline at a distance equal to their upper limb length. Each movement, conducted with the impaired limb, was repeated five times; the three best performances were recorded. Participants were instructed to perform each movement at a self-selected speed. A 14-camera Vicon system tracked reflective markers on the upper body throughout the movements. Nexus 2.8.1 software analyzed the motion kinematics from these markers' position data. The start and end of each reaching movement were identified manually, using the marker at the index finger's metacarpophalangeal joint, and verified visually. Joint angles were estimated using Nexus software 2.8.1 with a standard biomechanical model (Cutti et al., 2005), which depicts the anatomical joints as universal joints. The data were imported into MATLAB (R2019a, The MathWorks Inc., Natick, MA, USA), where custom scripts computed a range of kinematic parameters. A marker on the index finger's metacarpophalangeal joint tracked movement duration (both total and relative to the first and second phases), maximum velocity, peak velocities for each phase, the number of peak velocities, and the logarithm of the a-dimensional jerk (Balasubramanian et al., 2015) as indicators of smoothness. Movement duration and smoothness indicated the precision and efficiency of the movement, while peak velocity reflected the movement planning. Additionally, a subset of markers on the UE and trunk was used to assess the shoulder and elbow range of motion. Compensatory movements were identified by measuring trunk displacement in both the transverse and sagittal planes.

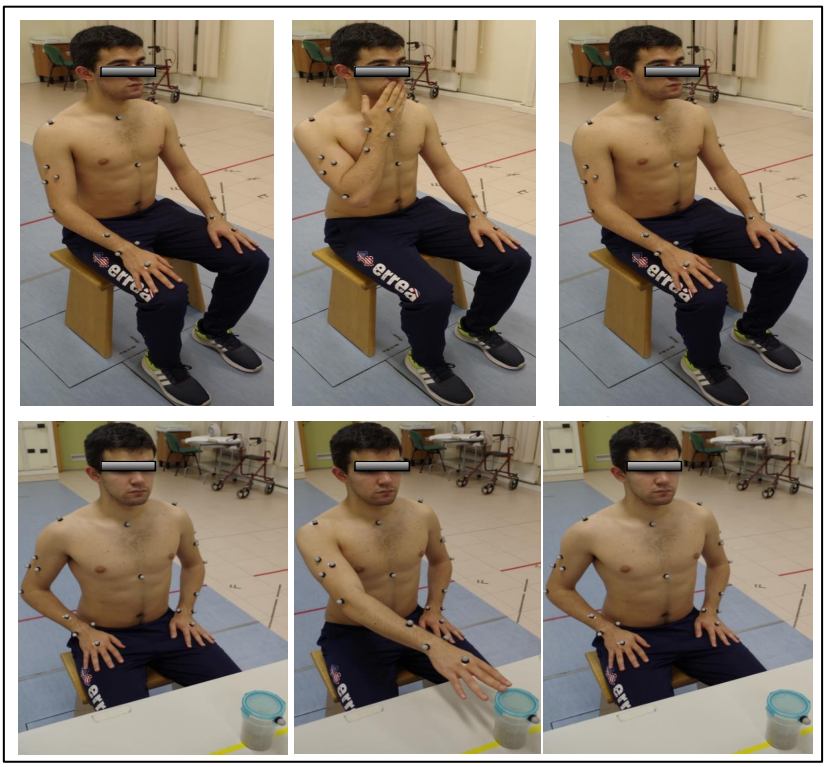


Figure 1. Movement performed with the impaired limb. Reach Up (above): Start with the hand resting on the distal third of the thigh. The subject is asked to bring the hand toward the mouth, touching the lips with the palm-up hand (Step 1), then return to the starting position (Step 2). Reach Out (below): Begin with the hand resting at the root of the thigh. A table with a jar is positioned in front of the subject. The subject should reach out and touch the jar lid (Step 1), then return to the initial position (Step 2).

2.4.3 EEG Recordings and Data Analysis

The EEG was recorded with the BrainAmp System (Brain Products, Munich, Germany) using a 32-channel headset with electrodes placed according to the International 10-20 System. The acquisition frequency was 1000 Hz, with the FCz electrode serving as the reference. Data were stored on a hard disk for subsequent analysis. An online 50-Hz notch filter was applied to reduce external noise (mains power frequency), and impedance was checked before each session; it was deemed acceptable if below 20 kΩ. The signal was recorded and monitored via a computerized system (Brain Vision Recorder, Brain Products, Munich, Germany). Vertical and horizontal electro-oculographic signals were recorded using electrodes placed above and below the eye on the same side as the paretic hemisoma, as well as at the bilateral external canthi. Analysis was performed in MATLAB using FieldTrip (Oostenveld et al., 2011). EEG data were filtered offline using a second-order Butterworth band-pass filter from 0.5 to 45 Hz. Channels lacking data or with poor quality were discarded, while brief artifacts in individual channels were interpolated based on neighboring electrodes and then re-referenced to the new average. Subsequently, ocular and muscular artifacts were manually eliminated through independent component analysis (ICA) (Makeig et al., 1995). Power spectral density (PSD) was calculated using a Fast Fourier Transform (FFT) for each channel with a Hanning window of 2 seconds, without zero padding or overlap. From the average power spectra, the PSD for the following frequency bands was determined: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta (13–35 Hz) (Finnigan et al., 2016). DAR and DTABR were calculated as the ratios of absolute power in each band relative to the bands of interest,

both as a total average and separately for the affected hemisphere (AH) and the unaffected hemisphere (UH). (Finnigan and van Putten, 2013). DirBSI was calculated as described by Saes and her team (Saes et al., 2019), covering the full range of 1-35 Hz and separately for delta, theta, alpha, and beta.

2.5 Statistical Analysis

Baseline (T0) characteristics were described using median and interquartile range, mean and standard deviation, or frequency and percentage. Statistical analysis was conducted with the free software Jamovi (Jamovi, 1.6). Our primary goal was to examine the relationships between the extracted kinematic features and clinical evaluation scores, as well as their associations with EEG parameters. Spearman's correlation coefficient was employed to detect significant trends, both across the entire group and within the subgroup with EEG and kinematic assessments. The threshold for statistical significance was set at $p < 0.05$. Additionally, a multiple regression analysis was performed to identify which parameters among those with significant correlations are the most influential in assessing post-stroke motor recovery.

2.6 Results

58 patients had been enrolled by November 2021, and 26 patients were included in this study. This group mostly comprised those who had completed the upper limb kinematic analysis protocol at 4 weeks and for whom the recorded tests could be reconstructed and analyzed without technical issues. Patients with more severe motor deficits were excluded because they were unable to complete the movements described above. Specifically, 32 patients were excluded: 29 because of severe motor deficits preventing completion of movement, and 3 due to technical problems hindering data reconstruction. Of the 26 considered patients, 20 also underwent an EEG at 4 weeks (11 men and 9 women, with an average age of about 65 years). In some cases (n=5), EEG assessment was not possible due to clinical instability or COVID-19 restrictions; others were excluded due to excessive EEG artifacts that compromised analysis (n=1).
The analysis was based on a sample of 26 subjects, whose characteristics are outlined in Table 1.

	Stroke patients (n = 26)
Age, years	66.5 (59.5 – 74.25)
Gender, no, male (%)	15 (57.7)
Time since stroke, days	9.5 (5-11)
Affected hemisphere, no. left (%)	13 (50)
MEPs, n(%)	7(26.9)*
Ischemic stroke (%)	20 (77)
NIHSS	7 (5-11.5)
ARAT 4th week	52 (44-56.5)
FMA-UE 4th week	52.16 (16.7)

Table 1. Participants' Characteristics at Baseline. Baseline characteristics were reported as mean and standard deviation, median and interquartile range, or frequency and percentage.

The sample included 15 men and 11 women, with an average age of about 67 years. Approximately 80% had an ischemic stroke, with the affected hemisphere being similar across cases. The mean NIHSS at admission was 8.25; at one month, the mean FMA-UE and ARAT scores were 52 and 44, respectively. Nine patients underwent TMS; eight showed MEPs, while one did not. The results are mainly illustrated in graphs, in which clinical assessment values (FMA-UE) were correlated with kinematic parameters (measured during Reach Up and Reach Out movements) and EEG measures collected at the specified time points. We selected key kinematic measures relevant for stroke patients: movement duration (total, and relative to the first and second phases); peak velocity; peak velocity of the first and second movement phases (see Figure 1); number of peak velocities (#PV); and logarithm of the dimensional jerk (Jerk), as indicators of smoothness; shoulder and elbow range of motion; and trunk displacement (flexion/extension).

In both Reach-up and Reach-out tasks, the initial movement phase was consistently shorter than the second phase. The overall movement duration—both total and within sub-phases—showed a strong correlation with FMA-UE scores: patients with lower FMA-UE values generally took longer to complete the movements. Conversely, maximum speed (PV) recorded during Reach Up and Reach Out had weak correlations with FMA-UE. The correlation was stronger for smoothness measures: for Reach Up and Reach Out, the R^2 values for the number of velocity peaks (#PV) were 0.5872 and 0.5084, respectively, while R^2 for the logarithm of the a-dimensional jerk (Jerk) were 0.5921 and 0.7159. A multiple regression analysis was performed to predict FMA-UE scores based on kinematic measures. The results were statistically significant: for Reach-up (R^2=0.80, $F(3, 21)$=28.87, $p<0.0001$); for Reach-out (R^2=0.75, $F(1, 23)$=70.35, $p<0.0001$). Specifically, the duration (β = -9.39, p=0.019), peak velocity (β=3.36, p=0.012), and smoothness (β=13.77, p=0.039) during Reach-out, along with the duration of Reach-up (β=-8.84, $p<0.0001$), significantly predicted FMA-UE scores. As expected, higher FMA-UE scores (indicating better motor recovery) were associated with shorter movement durations and greater smoothness. Regarding joint angles, measured as absolute ROM in the sagittal plane, no clear correlation with FMA-UE was observed. See Figure 2 and Figure 3, which display data for Reach Up and Reach Out movements. Unless otherwise noted, p-values are < 0.05.

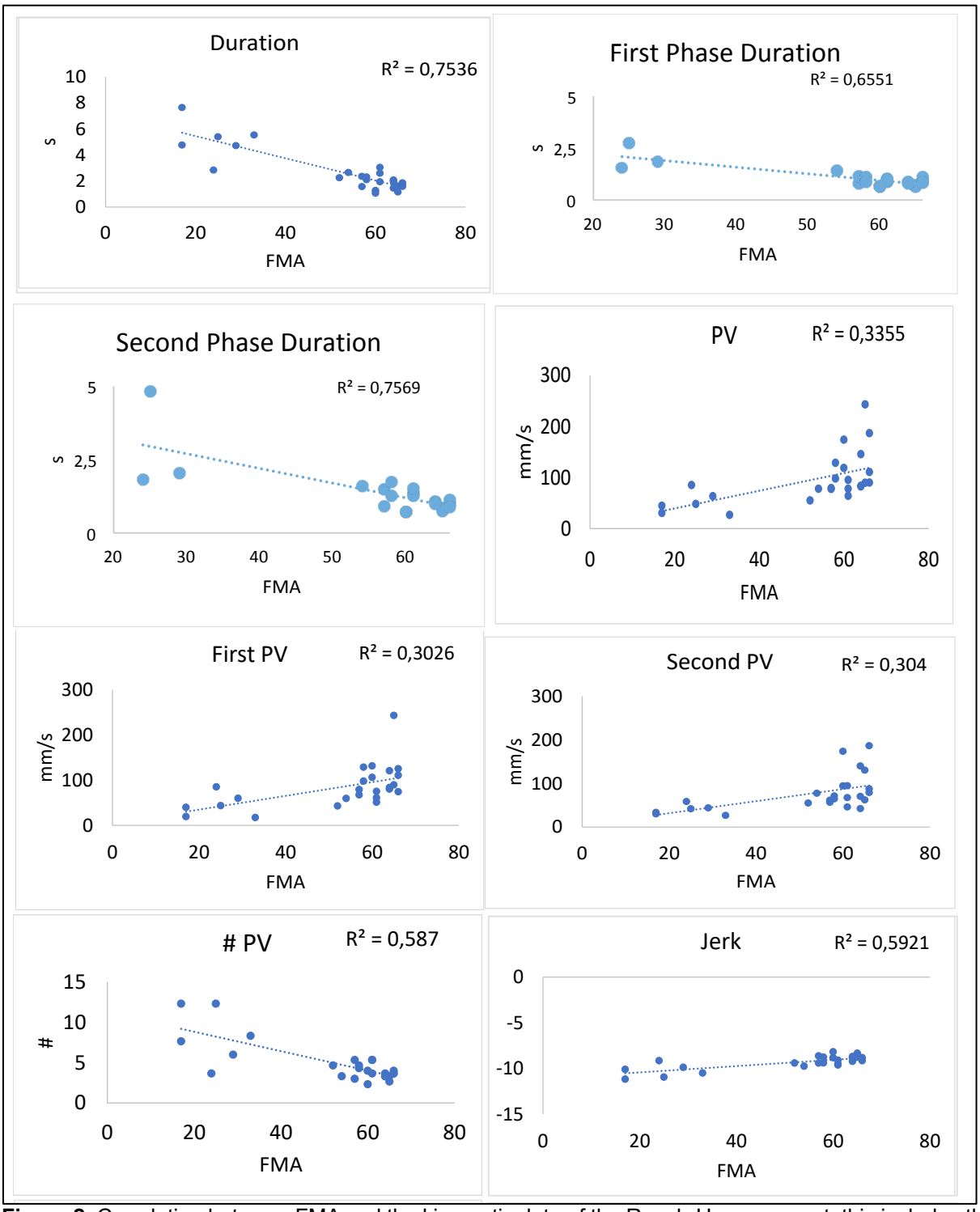


Figure 2. Correlation between FMA and the kinematic data of the Reach-Up movement: this includes the total movement duration, durations of the first and second movement phases, peak velocity (PV), PV during each phase, the number of peak velocities (# PV), and the log of adimensional jerk (Jerk). In the EEG subgroup, analysis of relative band power revealed a pronounced alpha-rhythm dominance in each patient's EEG.

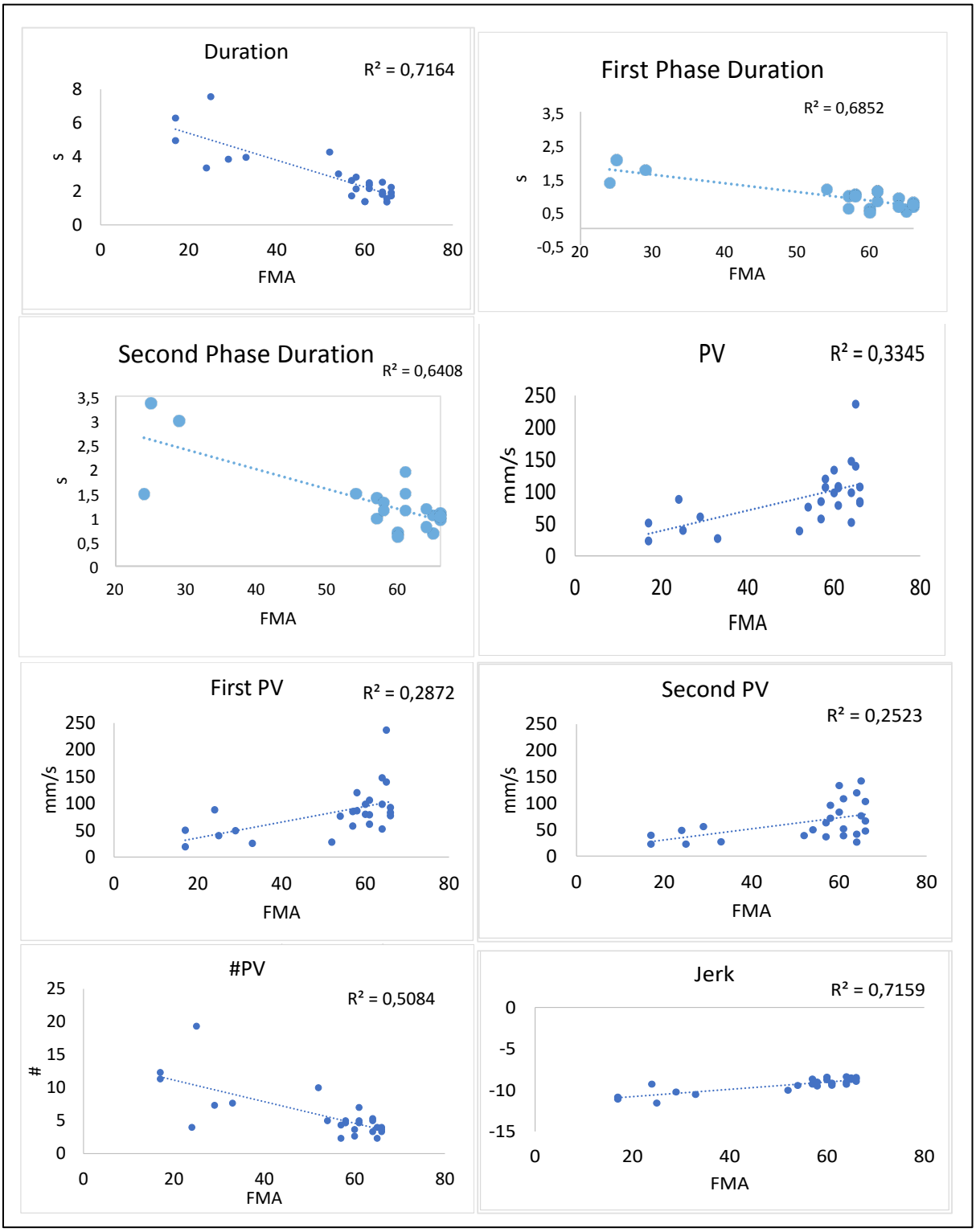


Figure 3. Correlation between FMA and kinematic data of Reach-Out movement. Reach Out: correlation between FMA and, in the following order: total movement duration, the duration of the first and second movement phases, peak velocity (PV), PV during the first and second phases, the number of peak velocities (# PV), and log adimensional jerk (Jerk).

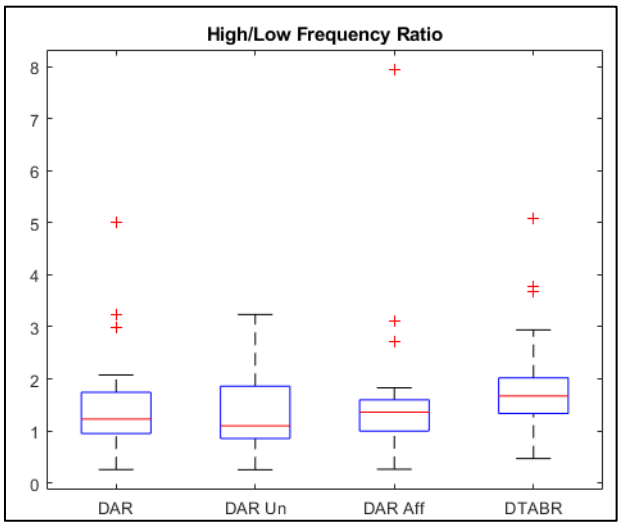


Figure 4. Boxplot displaying DAR and DTABR in EEG measures, showing the delta/alpha ratio (DAR) and delta+theta/alpha+beta ratio (DTABR) values.

Figure 4 illustrates the DAR and DTABR. The DAR exceeded 1 when considering the bihemispheric EEG recording, and was even higher when focusing solely on the affected hemisphere. The average DTABR overall fell between 1 and 2. According to Finnigan and colleagues, a typical or normal value for both DAR and DTABR is around 1 or less, while values exceeding 2 are considered abnormal (Finnigan and van Putten, 2013).

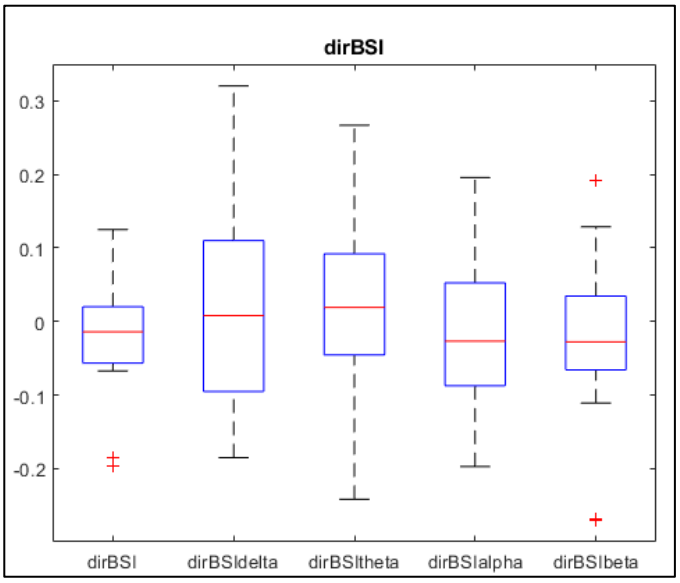


Figure 5. dirBSI in EEG measurements. Boxplot showing dirBSI values, calculated over the entire 1-35 Hz range and separately for delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz). DirBSI = 0 indicates perfect symmetry; positive values (0-1) reflect higher power in the affected hemisphere, while negative values indicate higher power in the healthy hemisphere.

In Figure 5, it is shown that dirBSI was positive for the delta and theta bands and negative for alpha and beta rhythms. Specifically, positive values in delta and theta bands suggest increased spectral power in the affected hemisphere, whereas negative values in alpha and beta bands indicate increased power in the healthy hemisphere. Notably, the dirBSI beta correlated negatively with the average PV during the Reach Out movement, where higher beta-band spectral power in the affected hemisphere was associated with lower

average maximum velocities ($p=0.008$, $R^2=0.33$). Data analysis for ARAT did not reveal any significant correlation.

2.7 Discussion

To our knowledge, only a few studies have explored post-stroke upper limb motor recovery by integrating multiple data sources. The correlations observed between standardized clinical measures, kinematic data, and qEEG biomarkers provided varied insights into motor recovery. These data are crucial not only for personalizing patient care but also for enhancing our understanding of recovery dynamics. Our kinematic analysis revealed a strong correlation between FMA-UE scores and both smoothness measures and movement duration for Reach-up and Reach-out, which were also key predictors in our multiple regression model. In the EEG subgroup, the dirBSI beta showed a negative correlation with the mean maximum velocity during Reach Out, indicating that higher beta-band spectral power in the affected hemisphere was associated with lower maximum velocities.

Despite many advancements in diagnosis, early intervention, and outcome prediction, stroke remains the primary cause of long-term disability (Guzik and Bushnell, 2017). Cortical plasticity and functional reorganization play vital roles in post-stroke motor recovery. It is essential to differentiate between mechanisms that support true restitution and those that lead to compensation. Since neural repair primarily occurs within the first five weeks after a stroke, this period is considered a critical window for rehabilitation (Cortes et al., 2017; Raghavan, 2015). Clinical and instrumental data each offer unique and complementary insights for accurate patient assessment. Specifically, qEEG analysis provides neurophysiological metrics related to the functional state of the cerebral cortex and motor system, whereas kinematic analysis delivers objective data on movement quality and its evolution over time (Carozzo et al., 2020; Tscherpel et al., 2020). While clinical data are often insufficient to predict recovery, combining multiple measures and integrating these methods can assist in planning the patient's personalized rehabilitation (Pierella et al., 2020).

This study emphasizes some interesting aspects regarding both kinematic and qEEG measures. In recent decades, interest in kinematics data within post-stroke recovery has grown substantially, though a standardized methodology still remains absent, as shown by numerous recent literature reviews and roundtables (Adans-Dester et al., 2020; de los Reyes-Guzmán et al., 2014; Kwakkel et al., 2019; Mohamed Refai et al., 2021; Schwarz et al., 2019). Some studies have demonstrated a strong correlation between kinematic parameters and motor outcome assessment scales (van Dokkum et al., 2014). Our work also examined the same relationship. In our dataset, movement duration—both total and relative to each sub-phase—showed a strong correlation with upper limb motor impairment (FMA-UE) during reaching tasks. Patients with lower FMA-UE scores tended to take longer to complete movements. Additionally, we observed a significant correlation between FMA-UE and smoothness indicators, such as the number of velocity peaks and the logarithm of a-dimensional jerk. Moreover, the overall movement duration was positively associated with smoothness measures. These parameters are crucial for post-stroke motor recovery and are frequently used to evaluate the quality of movement of the affected upper limb during reaching tasks (Balasubramanian et al., 2015; Mohamed Refai et al., 2021). Indeed, smooth movements are typical of healthy, well-trained motor behavior (Sejnowski, 1998), and movement fluidity improves with neurodevelopment (Berthier and Keen, 2006), motor learning (Balasubramanian et al., 2012), and motor recovery following stroke (Krebs et al., 1998).

Peak velocity positively correlates with upper limb motor impairment and movement duration. This finding aligns with previous research, emphasizing that movement duration is closely linked to peak velocity, while the timing of reaching peak velocity (time to peak velocity) offers insight into movement construction (van Dokkum et al., 2014). In healthy individuals, peak velocity occurs during the last moments of the first half of the reaching phase, reflecting efficient movement with minimal corrections during deceleration towards the target. In contrast, stroke patients typically exhibit longer movement durations, with a smaller peak velocity occurring before the halfway point, followed by an extended deceleration phase (Langhorne et al., 2009; van Dokkum et al., 2014). Therefore, we can hypothesize that speed profiles indicate the effectiveness of motor control and serve as an index of movement strategy. Notably, the association between these measures and FMA was verified using a multiple regression model, which identified the total duration of movements and smoothness (especially during Reach Out) as the most significant factors influencing post-stroke motor recovery.

Analyses of joint angles showed weak correlations with FMA-UE, as expected: even healthy individuals, despite following similar movement paths, display variability in the motor strategies they use for certain functional movements at the individual level — especially in shoulder intra-extrarotation, abduction-adduction, elbow flexion-extension, and prone-supination (Krüger et al., 2011). Therefore, in stroke patients, greater joint angle variability complicates comparative analyses (Kempski et al., 2018). However, what is more clinically relevant is the intra-subject monitoring of changes in these kinematic parameters over time, which is why our study focused on these measures.

About the qEEG biomarkers, we observed that the alpha rhythm was predominant, aligning with existing literature (Halgren et al., 2019). Alpha activity that remains unaltered has been linked to healthy brain function (Bazanova, 2012), while hemispheric strokes are linked to increased oscillations in the delta and theta bands (Andraus and Alves-Leon, 2011; Britton et al., 2016; Finnigan and van Putten, 2013). The DAR was higher than 1 based on bihemispheric EEG recordings, and even higher when considering only the affected hemisphere. This finding aligns with current evidence showing that subacute stroke survivors have increased DAR values compared to healthy individuals (Finnigan et al., 2016; Sheorajpanday et al., 2009). Indeed, at least during the early post-stroke phase, delta activity is elevated. It tends to decrease and approach normal levels in the chronic phase. Consistently, DAR in chronic stroke patients is not significantly different from that in healthy individuals (Saes et al., 2019). Therefore, differences in DAR might result from variations in stroke timeframe evaluation.

The overall mean DTABR value fell between 1 and 2. Finnigan et al. noted that an overall DAR or DTABR of about one or less is considered normal, whereas values above 2 are indicative of pathology (Finnigan and van Putten, 2013). As most of the patients included showed a mild level of impairment, this result aligns with the previous interpretation.

Agius Anastasi and colleagues investigated the role of BSI in poststroke patients and demonstrated correlations between this EEG measure and various functional scales (Agius Anastasi et al., 2017). Our study did not find results supporting this interpretation. However, Saes et al. reported significant negative correlations between BSI and FMA-UE, but only in patients with greater asymmetry differences in the delta and theta bands—specifically, those with poorer outcomes—who were underrepresented in our sample (Saes et al., 2019). Regarding the direction of interhemispheric asymmetries, positive dirBSI values in the delta and theta bands indicate greater spectral power in the affected hemisphere at these frequencies, whereas negative values in the alpha and beta bands suggest higher spectral power in the contralateral hemisphere (Saes et

al., 2019). Few studies analyze the changes in this EEG measure during post-stroke recovery, making it difficult to compare different research. However, Saes et al. demonstrated that in the most severely affected stroke survivors, the affected hemisphere produced more power than the opposite hemisphere, particularly in the delta and theta frequency ranges (Saes et al., 2019). Numerous studies have demonstrated that the beta rhythm is most closely associated with motor activity (Rabiller et al., 2015). In this study, dirBSI beta negatively correlated with the average maximum velocity during reaching tasks. This indicates that increased spectral power in the beta-band of the affected hemisphere (dirBSI beta > 0) is associated with lower mean maximum velocities, while higher spectral power in the contralateral hemisphere (dirBSI beta < 0) is linked to higher velocities. Thibaut et al. found that motor function positively correlates with beta rhythm in the central regions of the unaffected hemisphere but negatively correlates in the affected one. Additionally, lower FMA-UE scores are observed when beta activity is higher in the affected hemisphere compared to the healthy one (Thibaut et al., 2017). Thibaut et al. used the beta ratio (the ratio of beta values between the two hemispheres), while we analyzed the dirBSI beta (the ratio of the difference between the two beta values in both hemispheres to the total). Despite differences in the parameters studied (beta ratio vs. dirBSI beta) and in the study populations (chronic vs. subacute), the findings appear consistent. Therefore, given that maximal speed is an indicator of motor control that positively correlates with FMA-UE, we suggest a tendency towards "lateralization," with higher beta-band spectral power in the unaffected hemisphere, suggesting that these patients may compensate for the affected hemisphere with the healthy one.

This study has several limitations: a small sample size; clinical, EEG, and kinematic data recorded only 4 weeks after stroke, which prevents tracking changes over time; the absence of a control group; most patients have mild hemiparesis, allowing for kinematic analysis of functional movements. However, this excludes severe patients, which reduces heterogeneity and limits insights, especially from the EEG perspective.

2.8 Conclusions

Identifying biomarkers—whether kinematic or neurophysiological—of early motor recovery is essential for selecting the most effective rehabilitation strategies. Future research should aim to differentiate these biomarkers from compensation indicators to develop appropriate assessment scales (Cortes et al., 2017). Furthermore, future research is necessary to better understand the potential relationships between kinematic parameters and EEG data, possibly tracking their development throughout the stroke recovery process, thereby enhancing understanding of post-stroke motor recovery patterns. Notably, our study indicates that among all kinematic and EEG parameters that can be assessed early after stroke, total movement duration, smoothness, and dirBSI (particularly in the beta band) are the most indicative of motor recovery. In summary, this study highlights the importance of combining information from multiple sources for accurate clinical evaluation of stroke patients and, consequently, selecting the most appropriate rehabilitation approach.

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Chapter 3. Event-related Desynchronization during Action Observation is an early predictor of recovery in subcortical stroke: An EEG Study

In this chapter, I present a study that further examines the neurophysiological correlates of motor recovery in the early post-stroke phase, focusing on the role of action observation and its cortical signature, specifically event-related desynchronization (ERD), as a predictive marker of upper limb outcomes. As part of the broader research on early indicators of functional recovery in stroke patients using non-invasive neurophysiological tools, this study complements the findings from the previous chapter by focusing on action observation, a process closely linked to the mirror neuron system (MNS) (see Chapter 9 of this Thesis). The results showed that the degree of ERD over specific brain areas during action observation significantly predicted motor improvement at follow-up in patients with subcortical lesions. These findings indicate that the residual integrity and initial response of cortical motor networks, especially those associated with MNS function, even when activated indirectly through passive observation, may imply a preserved capacity for neuroplastic reorganization. Importantly, this study highlights the importance of action observation paradigms in the clinical setting, not only as a therapeutic approach but also as a tool to assess recovery potential in the subacute stroke timeframe. By emphasizing an easily accessible electroencephalography (EEG)-based marker of motor recovery, this work advances the goal of finding scalable and time-efficient assessment methods to help create personalized rehabilitation plans. It also strengthens the relevance of integrating neurophysiological and behavioral data as a foundation for precision neurorehabilitation. Together with the findings from kinematic-EEG integration presented in the previous Chapter, this study underscores the crucial role of motor system probes in capturing recovery-relevant brain dynamics after stroke.

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Cerebral stroke is the second leading cause of death and long-term disability worldwide (Saini et al., 2021). After a stroke, the central nervous system generally tries to restore impaired functions by reorganizing cortical networks in both the damaged and the healthy hemispheres, to recover and vicariate the activities originally performed by the lesioned areas (Milani et al., 2022). This process is favoured by increased cortical plasticity following a stroke, which occurs during a narrow time interval (Zeiler and Krakauer, 2013). In this critical timeframe, biomarkers that can predict prognosis and assist in the choice of rehabilitation treatments are crucial (Connell et al., 2018). Considering the complexity of the reorganization of motor networks after a stroke, it is important to integrate clinical information with other data to determine the prognosis and treatment options (Milani et al., 2022). Electroencephalography (EEG) is a non-invasive, low-cost, and reliable tool that provides useful information to guide rehabilitation (Milani et al., 2022; Sutcliffe et al., 2022). Much attention is currently focused on event-related potentials (ERP), i.e., the time-locked electrophysiological response related to an internal or external event. An ERP can be linked to a change in the EEG (not time-locked) that shows increased or reduced coordination of activity, labelled event-related desynchronization (ERD) or synchronization (ERS), respectively (Tangwiriyasakul et al., 2014). Notably, research on the mirror neuron system (MNS) has shown that the neurons that are activated during voluntary movements are also recruited during the observation of the same motor acts, with important neurophysiological and rehabilitation implications (Garrison et al., 2010). Specifically, so-called action-observation therapy leverages the MNS to promote motor recovery in people who are unable to perform movements adequately (Zhang et al., 2018). However, although the role of cortical areas in the MNS has been well characterised, the function of subcortical regions is less well understood, especially in the context of stroke (Bonini, 2017; Garrison et al., 2010). Therefore, it seems very useful to evaluate the characteristics of these neurophysiological biomarkers during action observation (AO) in people with subcortical stroke. Here, we studied electrophysiological activity recorded in the motor area during AO 4 weeks after stroke as a predictor of arm recovery at 12 weeks.

This is a longitudinal observational clinical study conducted at Ferrara University Hospital (Italy). Procedures conformed to the Declaration of Helsinki and were approved by the local Ethics Review Committee: the Area Vasta Emilia-Centro Ethics Committee (NCT04637984). Inclusion criteria: right-handedness, age ≥ 18 years; diagnosis of first cerebral stroke (ischemic or haemorrhagic) in a subcortical site verified by brain imaging with onset within 4 weeks; and motor deficit of the upper limb. Exclusion criteria: cerebellar or bilateral cerebral stroke; a medical or neurological condition interfering with the safe completion of the protocol or with the ability to give informed consent; severe medical conditions; upper limb somato-sensory disorders; spatial neglect; and pregnancy. The 20-minute AO session, conducted 4 weeks after stroke (T1), included observing a transitive gesture on video (a hand – contralateral to the affected hemisphere – shown reaching for and grasping a can) with simultaneous EEG recording, while seated in a dimly lit room at 90 cm distance from a 20" cathode-ray tube monitor. Videos were presented 20 times, interspersed with a fixation interval. EEGs were acquired with the BrainAmp System (Brain Vision Recorder and Brain Products, Munich, Germany), with 32-channels, sampled at 1000 Hz, referenced at electrode FCz, with a 50-Hz notch filter, and impedances <20 KΩ. Stimulus and EEGs were synchronized via E-Prime 2.0. Clinical evaluations at 12 weeks (T2) after stroke included the Fugl-Meyer Motor Assessment Scale Upper Extremity FMA (FMA-UE). We labelled participants with FMA-UE ≤ 25 points as having severe impairment and those with FMA-UE > 25 points as having moderate impairment (Woytowicz et al., 2017). Offline EEG analysis was conducted using MATLAB (R2019a, The Mathworks) with FieldTrip. Data were segmented into 20 epochs, each 4s long, including 1s before and 3s

after stimulus onset. Trials with motion-driven artefacts or amplitude >100 μV were excluded; only participants with at least 80% clean trials were included. Independent component analysis further removed components, endowing artefacts. Time-frequency analysis of each epoch was performed with Morlet wavelets (5; 32 Hz). ERS/D was computed as *100·(E-R)/R*, with *E* the power in the 0 to 2.5s time after video onset, and *R* the power in the -0.5 to -0.1s range before onset (baseline). ERS/D in the alpha band (8 to 13 Hz) were computed at electrodes (F3, F4) for premotor areas, (C3, C4) for primary motor cortex, and (P3, P4) for sensorimotor integration. We used Jamovi to compare alpha ERD/S between the severe and moderate groups. Within-group and between-group differences were tested using paired and unpaired t-tests, respectively, and Spearman's correlation was used to identify any significant correlations. Statistical significance was set at p<0.05.

We screened and enrolled 16 people. Participant characteristics at baseline are reported in Table 1 for the whole sample and for the group with severe motor impairment (FMA-UE ≤25), and the group with mild/moderate motor impairment (FMA-UE >25).

	Severe (n=6)	Mild/Moderate (n=10)	Total (n = 16)
Age, years (median, IQR)	62 (49; 78)	63.5 (57.75; 74)	63.5 (56.25; 74)
Sex, n, male (%)	3 (50)	4 (40)	7 (44)
Time since stroke, days (median, IQR)	6.5 (3; 12.75)	7 (3.75; 10)	5 (4; 10)
Affected hemisphere, n, left (%)	1 (17)	5 (50)	6 (37)
MEPs, n (%)	3 (50)*	2 (20)*	5 (31)*
Ischemic stroke, n (%)	4 (67)	8 (80)	12 (75)
NIHSS (median, IQR)	12.5 (6.25; 17.75)	7 (5.75; 12)	8.5 (6; 12.5)
FMA-UE 4th week (mean, ± SD)	10.2 ± 4.5	61.6 ± 3.8	42.3 ± 26.01
ARAT 4th week (median, IQR)	1.5 (0; 4)	54.5 (51.75; 57)	51.5 (3.25; 55)
Arterial hypertension, n (%)	3 (50)	9 (90)	12 (75)
Smoking, n (%)	1 (17)	2 (20)	3 (19)
Diabetes mellitus type II, n (%)	1 (17)	3 (30)	4 (25)
Dyslipidaemia, n (%)	3 (50)	3 (30)	6 (37)
Hyperhomocysteinemia, n (%)	1 (17)	1 (10)	2 (12)
Previous myocardial infarction /heart failure, n (%)	1 (17)	1 (10)	2 (12)
Previous oncological history, n (%)	1 (17)	2 (20)	3 (19)
Autoimmune disorders, n (%)	0	4 (40)	4 (25)
Mild-moderate renal failure, n (%)	0	2 (20)	2 (12)
Intravenous thrombolytic treatment, n (% among ischemic strokes)	0	2 (25)	2 (17)

Table 1. Baseline characteristics according to the degree of severity of arm paresis, as assessed by the FMA-UE. Data are median and interquartile range (IQR), mean and standard deviation (SD), or frequency and percentage. *indicates some missing data.

Furthermore, common risk factors for stroke (e.g., hypertension, dyslipidaemia, smoking) are reported, as well as the number of participants with ischaemic stroke who underwent intravenous thrombolytic treatment. We compared EEG data recorded at T1 with the scores of clinical scales collected at T2, in particular the ERD and FMA-UE. Alpha desynchronization in the affected parietal (R^2=0.47; P=0.03) and central electrodes (R^2=0.53; p=0.017) at 4 weeks correlated negatively with FMA-UE at 12 weeks in the moderate group. This implies that

the greater the desynchronization at 4 weeks, the more marked the motor recovery was at 12 weeks. In contrast, there was a positive correlation between alpha desynchronization in the unaffected frontal electrodes and FMA-UE score in individuals with severe arm paresis (R^2=0.93; p=0.03), indicating that greater alpha desynchronization was a predictor of poorer motor outcome at 12 weeks. The ERD/ERS expressed as a percentage is shown in Figure 1 for each group (mild-moderate vs severe). All participants with a left lesion were mirrored by "shifting" the lesion to construct a meaningful representation. Hence, although the images show lesions on the right side, they are illustrative of the entire sample. Alpha ERD/ERS was calculated for both moderate and severe groups, and negative values (range 0; 30%) show desynchronization, whereas positive values (range 0; 10%) indicate synchronization (Figure 1).

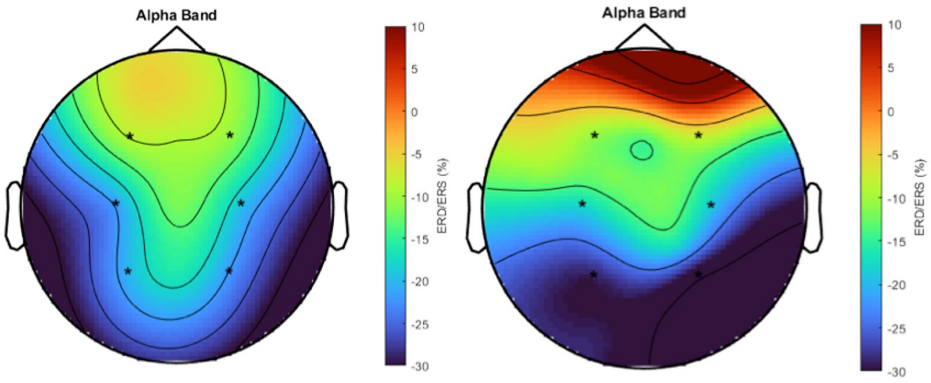


Figure 1. Topoplot of event-related desynchronization (ERD) in alpha dynamics for participants with mild-moderate impairment (on the left) and severe impairment (on the right). Right side = affected hemisphere.

Power spectrograms during AO showed significant alpha desynchronization in the affected central electrodes in the moderate group, which started approximately 0.3 seconds after the onset of the AO and lasted for the entire time window (Figure 2, left). A similar pattern was found in the affected parietal electrodes but with less power (Figure 2, right). In the severe group, we found a focal frontal desynchronization in the unaffected hemisphere in the time range between +1 and +1.5s, which started in the theta band, peaked in the alpha band (skimming the low beta band), and then decreased until +2 seconds from the AO onset (Figure 2, bottom).

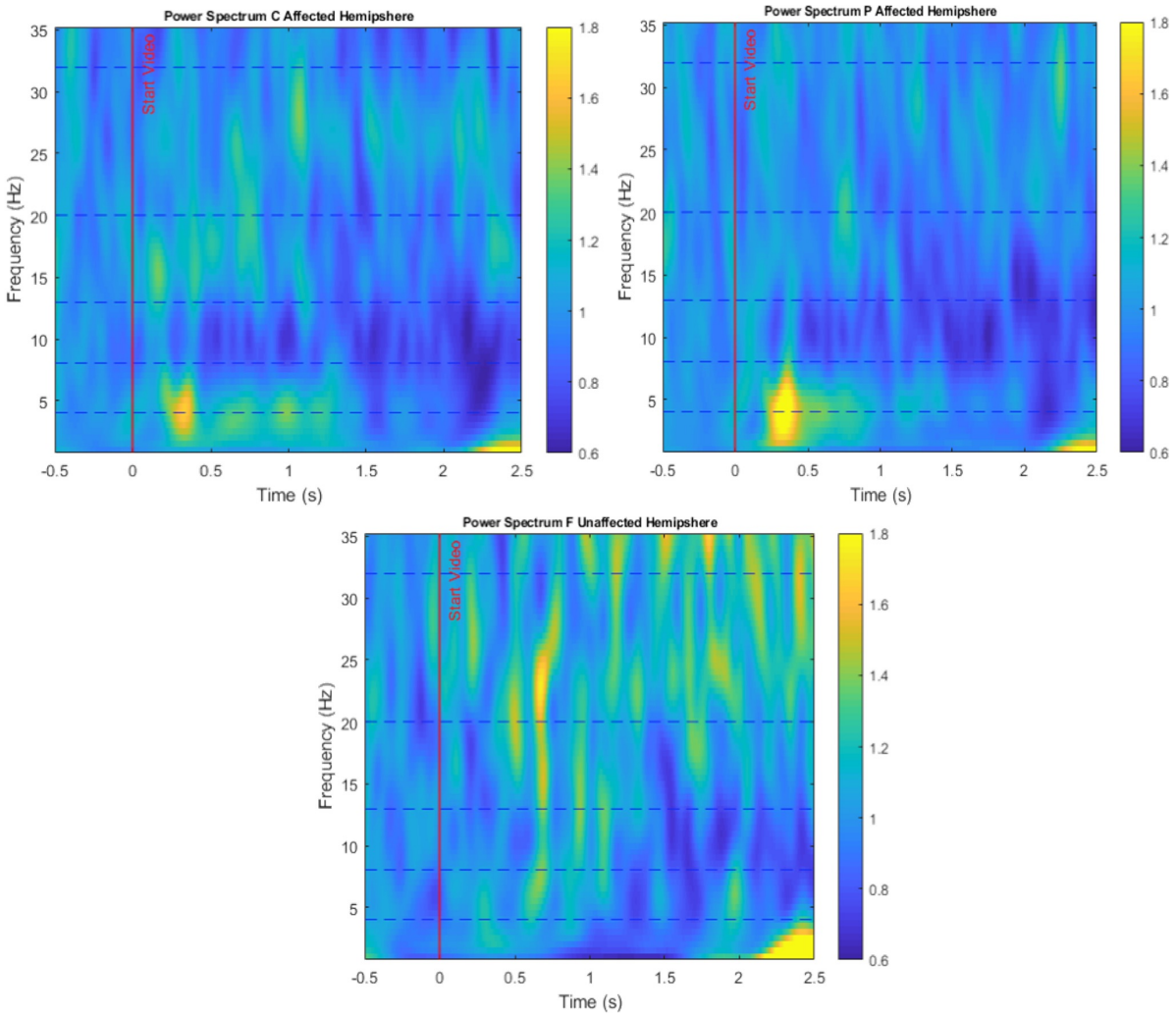


Figure 2. Power spectrogram recorded during action observation (AO) in the electrodes positioned over the affected central (top left) and parietal (top right) areas in the group with mild/moderate impairment and the electrodes over the unaffected frontal areas in the group with severe impairment (bottom).

As recently highlighted, EEG can provide information on cortical reorganization processes related to post-stroke plasticity that can guide clinicians in choosing the best rehabilitation strategies (Cassidy et al., 2022). Using a method similar to that described here, a recent study found that AO has greater effects than simple motor imagery after stroke. Indeed, AO increased ERD power twice as much as motor imagery (Tani et al., 2018). Our results confirm those of Tani's group, showing that ERD is particularly informative, even in individuals with severe deficits. Interestingly, a recent study showed that AO involves the efferent motor system even when the hand used to respond is unable to perform the observed action due to a cortical lesion, further supporting the use of AO in stroke motor rehabilitation (Craighero et al., 2023). The stroke lesion site can also influence motor recovery by different mechanisms (Lopez-Larraz et al., 2017). Indeed, cortical stroke can directly damage the neurons responsible for EEG signals, whereas a subcortical lesion alters the cortical-subcortical loops, with an expected different effect on neurophysiological measures (Attal et al., 2012). Notably, as assessed by the FMA-UE, the prognosis was poor when the unaffected hemisphere had to vicariate the functions of the affected hemisphere early after the stroke, especially in the frontal area. In contrast, the prognosis was better when the affected hemisphere could reorganize its activities from the acute stages. These

results are consistent with those of other studies, highlighting that the lateralization of activity towards the affected hemisphere and the decrease in activity in the unaffected hemisphere are associated with good functional recovery (Feydy et al., 2002). Indeed, activation of the hemisphere ipsilateral to the movement could indicate the need for more neural resources to perform the action, similarly to activation requirements during more complex movements in healthy individuals (Seidler et al., 2004). Of all the lobes, the frontal lobe has the greatest involvement in tasks requiring high attentional load and cognitive resources (Chayer and Freedman, 2001); this could be consistent with its involvement in individuals with more severe stroke. Studies conducted over extended periods have consistently shown that as the effort required to perform paretic hand movements decreases, unaffected hemisphere activity decreases (Tangwiriyasakul et al., 2014). In agreement with our results, Boni et al. found an absence of activation of the central affected hemisphere electrodes in participants with more pronounced motor deficits, suggesting a more significant impairment of the MNS in individuals with severe impairment and, consequently, a lower ability to recruit cortical resources related to a specific action during AO, with important therapeutic implications (Boni et al., 2023). Finally, our interpretation is coherent with the model investigated in the seminal study by Di Pino et al., in which it is hypothesized, owing to the asymmetry of function between the hemispheres after stroke, that the unaffected hemisphere exerts an inhibitory effect on the affected hemisphere, thus hindering the recovery of impaired function (Di Pino et al., 2014). Our data could therefore facilitate the development of rehabilitation protocols, including non-invasive brain stimulation techniques, that consider this hemispheric asymmetry and its functional implications.

This study has some limitations: the topoplots, which are very intuitive graphical representations of desynchronization on a scalp model using a colour scale, were probably partially affected by the activation of cortical areas linked to vision, which possibly underlies the significant activation observed in the occipital-parietal areas. Furthermore, a t-test comparison of the mean and ERD peak graphs by individual recording electrodes led to statistical significance only for specific electrodes and in certain frequency bands. In addition, the sample size was small, which makes it difficult to generalise the results. Finally, it would also have been interesting to investigate a more extended time interval after stroke to assess the change over time of EEG measurements and the correlation with clinical data.

We confirm the role of ERD during AO as an early predictor of motor recovery after stroke. The potential role of EEG for assessing changes in the motor network after stroke, even in individuals who cannot perform movements through the activation of the MNS during both execution and observation of actions, is very promising in the rehabilitation field. By integrating these neurophysiological measures with clinical data and those provided by other sources (e.g., kinematics), it will be possible to characterize the individual at an early stage. This approach provides important prognostic information that can be used to optimise treatment choices.

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Chapter 4. The cerebellum

4.1 A historical background

The cerebellum—literally "little brain" from Latin—is a central nervous system (CNS) structure located in the posterior cranial fossa. Traditionally regarded as a region primarily dedicated to motor functions, recent scientific advancements over the past few decades have substantially modified this perspective (D'Angelo, 2018). Notably, the cerebellum is one of the few examples in neuroscience where a detailed understanding of fine neuroanatomical organization has been successfully linked to complex neurophysiological mechanisms. Pioneering neuroanatomists such as Santiago Ramón y Cajal, Camillo Golgi, and Jan Evangelista Purkinje laid the foundation for our understanding of cerebellar circuitry (D'Angelo et al., 2011). For instance, the Purkinje cells—named after the latter—remain unique within the CNS due to their elaborate dendritic trees and computational capacity (Cerminara et al., 2015). These early discoveries uncovered a paradox: although the microstructure appears stereotyped across different cerebellar regions, the underlying circuitry is surprisingly complex, raising important questions about its larger functional role (D'Angelo, 2018). Cerebellar neurophysiology started to be studied through pioneering electrophysiological research in the 19th century (D'Angelo, 2018; Flourens, 1842).

Though our understanding has greatly improved since then, there is still much that remains unclear. For a long time, the cerebellum was viewed as solely responsible for motor coordination. Clinical evidence from individuals with cerebellar damage—including soldiers with traumatic injuries and patients with congenital malformations—highlighted a distinct set of signs: ataxia (a loss of coordination), muscle tone abnormalities, gait and balance disturbances, intention tremor, dysarthria, and oculomotor issues (Bodranghien et al., 2016; Lanska, 2009). These observations corroborated the preliminary assumption that the cerebellum's principal function is to refine sequences of motor actions, operating in conjunction with cortical motor and sensory networks to facilitate smooth and precise execution. This motor-centric perspective was further supported by the observation that, even in cases of cerebellar lesions, basic motor execution and sensory perception remained intact, although their quality was impaired.

However, more recent experimental and clinical data have convincingly demonstrated that the cerebellum's predictive and coordinating capacity extends beyond the motor domain. Indeed, damage to cerebellar regions, particularly those densely interconnected with associative cortical networks, may result in the so-called "dysmetria of thought"—a term referring to the Cognitive-Affective Cerebellar Syndrome (Argyropoulos et al., 2020; Schmahmann, 2019). This concept has been introduced to differentiate non-motor cerebellar impairments from their traditional motor manifestations. Consequently, the cerebellum is now widely seen as a forward controller: a structure that can predict a system's internal state using contextual information and past experiences (Welniarz et al., 2021). It updates the internal models that control interactions with the external environment, adjusting them when there are mismatches between expected and actual outcomes (Streng et al., 2022). Importantly, this predictive function does not require executing movements; it can also operate through internal simulation and mental rehearsal, a capability likely supported by cerebellar-hippocampal connectivity (Rondi-Reig et al., 2022). Such mechanisms facilitate anticipatory behavioral adjustments, critical for navigating and adapting to an ever-changing environment. Notably, this framework aligns with the cerebellum's uniform microcircuit architecture: a "generalized cerebellar algorithm" that performs nearly identical computational operations across its regions (D'Angelo, 2018). What gives specificity to the cerebellar

contribution across motor, sensory, cognitive, and emotional domains is not the internal circuitry itself, but rather the unique input-output connectivity of each subregion.
In the following sections, the cerebellum's macroscopic and microscopic anatomy, along with its afferent and efferent connections, will be discussed. These foundational concepts are essential for understanding the various and integrated roles played by the cerebellum in both health and disease.

4.2 Macroscopic anatomy of the cerebellum

As previously mentioned, the cerebellum is located in the posterior cranial fossa and, from an embryological perspective, originates from the brainstem, to which it remains firmly connected via three pairs of cerebellar peduncles: inferior, middle, and superior (Amore et al., 2021). These peduncles serve as essential pathways, transmitting all incoming and outgoing signals between the cerebellum and the rest of the CNS. From a macroscopic perspective, the cerebellum is divided into two primary regions: the cerebellar cortex, which forms the outermost layers, and the deep cerebellar nuclei (DCNs), located within the cerebellar white matter (Lara-Aparicio et al., 2022). The DCNs act as the main output stations of the cerebellum, receiving processed information from the cortex and relaying it to various targets within the brainstem and cerebral cortex (Kebschull et al., 2024). This anatomical division is also visible to the naked eye in a midsagittal or coronal section, where the cerebellar white matter, branching through the grey cortex, forms the distinctive tree-like structure known as the "arbor vitae" (Maryenko and Stepanenko, 2024). Importantly, the cerebellum works as an integrated unit with the inferior olivary (IO) nucleus, forming what is often called the olivo-cerebellar system. This connection is essential for regulating motor learning and timing through complex feedback loops (Lang et al., 2017). Anatomically, the cerebellum consists of two hemispheres and is generally divided into three main regions (Amore et al., 2021):

- The flocculonodular lobe, located in the anteroinferior portion;
- The vermis, a midline structure extending along the rostro-caudal axis,
- The hemispheres, which occupy the more lateral and evolutionarily recent parts.

From a phylogenetic perspective, the expansion of the cerebellar hemispheres has paralleled that of the cerebral cortex, especially in great apes and, most notably, in humans (Balsters et al., 2010). Indeed, while the flocculonodular and vermal regions are consistently well developed across most vertebrate species, the hemispheres exhibit a dramatic enlargement in humans, reflecting their integrative role within the complex cortico-cerebellar loops involved in higher-order processing (Magielse et al., 2023). Furthermore, a distinctive macroscopic feature of the cerebellum is the presence of folia, which are transversely oriented, tightly packed folds of the cerebellar cortex. These laminar folds increase the cortical surface area within the constraints of the rigid skull, maximizing the density of cerebellar neurons, especially Purkinje cells and granule cells (Zheng et al., 2024).
Furthermore, the cerebellum is divided into lobules, which are traditionally marked with Roman numerals I through X. Some of these extend into the cerebellar hemispheres, such as Crus I and II of lobules VIIA and VIIB, which are particularly important for non-motor processing (Guell and Schmahmann, 2020; Lara-Aparicio et al., 2022). Interestingly, to a considerable extent, the outlined anatomical partitioning aligns with functional specialization (Roostaei et al., 2014). The flocculonodular lobe is primarily connected to vestibular-ocular integration, playing a crucial role in regulating oculomotion and maintaining postural balance. Conversely, the

vermis and the adjacent paravermal regions participate in integrating motor and multisensory signals that are critical for axial and proximal motor control. Finally, the cerebellar hemispheres, on the other hand, are involved in higher cognitive functions, such as executive function and sensorimotor integration, which are necessary for complex, goal-directed behaviors.

These distinctions lay the foundation for a refined understanding of how different cerebellar subregions contribute to the regulation of motor, cognitive, and emotional functions.

4.3 Cerebellar connections and functional organization

The cerebellum receives input from nearly every major structure of the CNS, positioning it as a central hub for integrating sensorimotor, cognitive, and contextual information. Among its most prominent sources of afferent input are the cerebral cortical areas, particularly those in the frontal, parietal, and temporal lobes (Prati et al., 2024). These cortical projections are relayed to the cerebellum via the middle cerebellar peduncle, following synaptic transmission through the pontine nuclei, specifically, the anterior pontine nuclei. As previously mentioned, these cortico-ponto-cerebellar pathways carry rich contextual information. One notable example is the efference copy (or corollary discharge)—an internal duplicate of the motor commands sent from the cerebral cortex to peripheral effectors. This internal feedback allows the cerebellum to predict and compare planned actions with actual outcomes (Welniarz et al., 2021). Additional inputs include real-time somatosensory information and experience-based expectations stored in memory, both of which are essential for predictive coding and adaptive control (Caligiore et al., 2017; Pezzulo et al., 2015; Rondi-Reig et al., 2014). Beyond cortical input, the cerebellum also receives afferent signals from various brainstem nuclei. These include the IO, the reticular formation, the superior and inferior colliculi, and the vestibular nuclei, as well as from the spinal cord via the dorsal and ventral spinocerebellar tracts (Amore et al., 2021; Prati et al., 2024). These fibers mainly enter the cerebellum through the inferior cerebellar peduncles and provide vital information about posture, proprioception, and eye position. Once this diverse input is integrated and processed by the cerebellar cortex, the only output from the cerebellum is generated by the DCNs, each of which is functionally connected to specific cerebellar regions:

- The fastigial nucleus, linked to the vestibulocerebellum (primarily the flocculonodular lobe), projects to the vestibular nuclei and selected areas of the reticular formation. These connections are crucial for gaze stabilization and balance control, particularly through the regulation of ocular movements and axial musculature (Kheradmand and Zee, 2011; Morton and Bastian, 2004).
- The interposed nucleus, which includes the globose and emboliform nuclei, is connected to the spinocerebellar system. It transmits processed information to the red nucleus and the ventrolateral thalamic nucleus, which then project to the motor cortex and spinal cord. These pathways regulate activity in flexor and extensor muscles, which are crucial for maintaining posture and enabling coordinated movement during gait (Glickstein et al., 2011).
- The dentate nucleus, the largest and most lateral of the DCNs, is functionally linked to the lateral cerebellar hemispheres. It primarily sends projections to the thalamic nuclei, and to a lesser extent, to specific areas of the red nucleus. These thalamic relay stations subsequently interact with a broad network of frontal, parietal, and other associative cortical areas that are engaged in high-level cognitive functions, such as working memory and sensorimotor integration (Guell et al., 2020; Salmi et al., 2010).

Figure 1 illustrates the functional organization of the cerebellum.

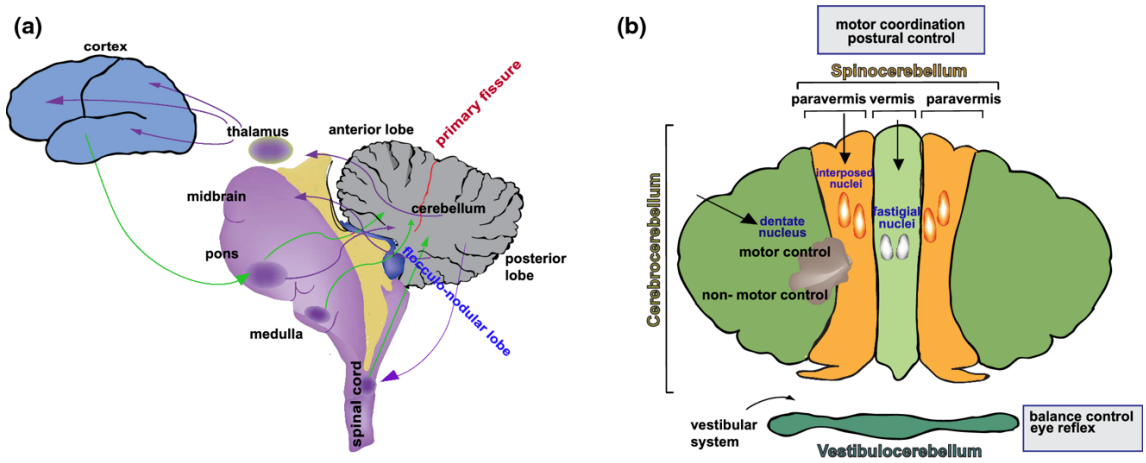


Figure 1. Schematic representation of the functional anatomy of the cerebellum, from (Farini et al., 2021).

This anatomical and functional organization forms multiple closed-loop circuits in which the cerebellum not only receives information from specific CNS regions but also sends processed signals back to them (Houck and Person, 2014). Such bidirectional communication facilitates ongoing monitoring, prediction, and—when needed—adjustment of activity in the sending regions, thus supporting dynamic fine-tuning of behavior and cognition (Caligiore et al., 2017). Among the most well-characterized circuits are the cerebro-cerebellar loop, mediated by the pontine nuclei and thalamus, which connects the cerebellum to regions of the cerebral cortex, and the spino-cerebellar loop, involving brainstem nuclei and the spinal cord, both of which are essential for sensorimotor coordination and postural control (Belkhiria et al., 2017; Houck and Person, 2014; Middleton and Strick, 2000). Importantly, the precise location of these incoming and outgoing connections also explains the wide range of symptoms that can occur after a cerebellar injury, despite the uniformity of its microcircuitry (as will be described in later sections) (Bodranghien et al., 2016). For example, oculomotor and balance disorders can be expected if the lesion affects the vestibulocerebellum (or its specific connections), whereas a "drunken" gait would be anticipated if the lesion were located in the spinocerebellar system.

It is also important to note that, because of its crossed connections, each cerebellar hemisphere mainly interacts with the contralateral cerebral cortex while controlling the ipsilateral hemibody (D'Angelo, 2018). This configuration explains why cerebellar lesions typically lead to motor deficits on the same side of the body as the lesion. Finally, it is important to consider that not only the brain but also the cerebellum displays a somatotopic organization, i.e., an ordered spatial arrangement of sensory and motor representations (See et al., 2021). Specifically, the cerebellum exhibits a highly intricate and somewhat unconventional somatotopic organization (Boillat et al., 2020). Sensory afferents from modalities such as vision and hearing are primarily localized in the vermis and the flocculonodular lobe, while somatic sensory signals form three overlapping homunculi: representations of the head and trunk are mainly found in the vermis. At the same time, regions for the distal limbs are mapped within the intermediate zones (D'Angelo, 2018). Unlike the orderly somatotopic maps observed in the neocortex, cerebellar representations are less strictly organized, often displaying redundancy, regional overlap, and multiple mappings of the same body parts across different cerebellar areas. This phenomenon has been described as a "fractured somatotopy", reflecting the cerebellum's modular and distributed processing strategy (Grodd et al., 2001).

4.4 Microscopic anatomy and modules of the cerebellum

As outlined in the preceding sections, the cerebellum's intricate microcircuitry is remarkably consistent throughout its entirety, with only a few regional exceptions (Carey, 2024; D'Angelo, 2018; Miall, 2022). Structurally, the cerebellar cortex is traditionally organized into three distinct layers, each characterized by its unique cellular composition. Figure 2 provides a schematic overview of the cellular organization of the cerebellum.

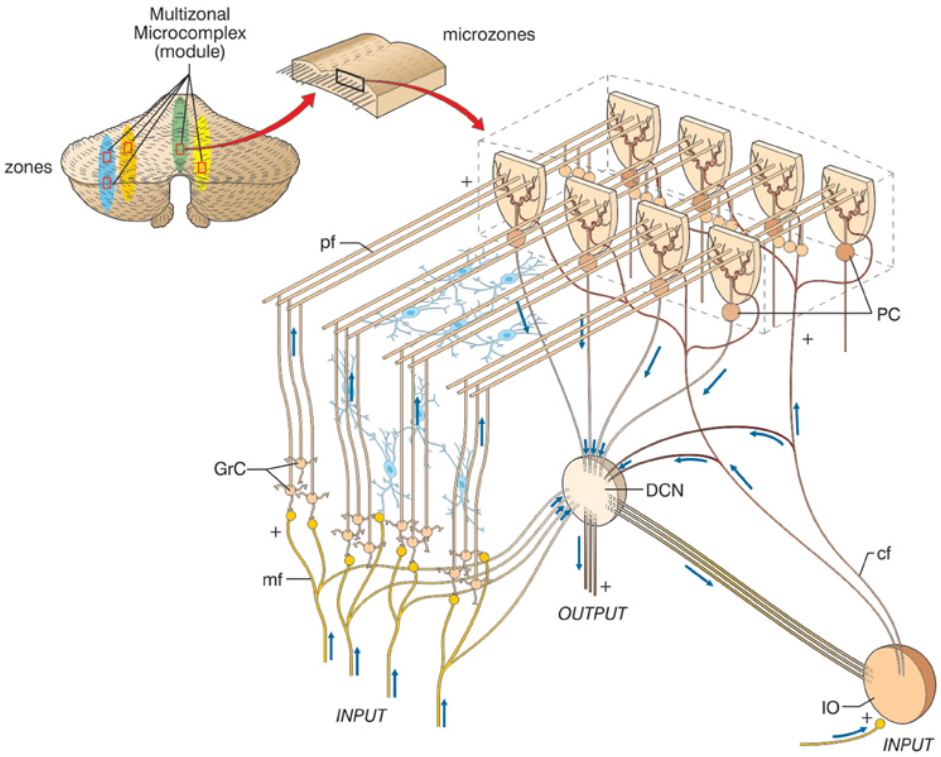


Figure 2. A schematic overview of the multi-level organization of the cerebellum, from (D'Angelo and Casali, 2012).

The deepest layer is the granule cell layer, which is made up of the most numerous and smallest neurons in the CNS. In fact, the cerebellum alone contains more than half of all neurons in the human brain, with granule cells comprising the majority (Carey, 2024). Uniquely among cerebellar neurons—excluding the unipolar brush cells (UBCs), which are exclusively located in the vestibulocerebellum—granule cells remain electrically inactive at rest unless stimulated (Arenz et al., 2008; D'Angelo, 2022; Mugnaini et al., 2011). They receive excitatory input from mossy fibers, which transmit contextual information from interconnected brain regions, including copies of motor commands (efference copies or corollary discharges), current sensory states, and memory-based expectations. The structural-functional unit known as the cerebellar glomerulus consists of a mossy fiber terminal, the dendrites of four or five granule cells, and the axon terminals of Golgi cells, which are inhibitory interneurons (Hull and Regehr, 2022). Once activated, granule cells extend a single axon that ascends through the Purkinje layer to the molecular layer, where it bifurcates into parallel fibers. These fibers travel transversely across the molecular layer, sometimes over long distances, allowing for integration across multiple cerebellar microzones. Parallel fibers provide excitatory input to nearly all other cerebellar neuron types, most of which demonstrate intrinsic rhythmic activity, modulated rather than triggered by external stimuli

(D'Angelo, 2018). A major target of the parallel fibers is the dendritic arborization of Purkinje cells, whose cell bodies are located in the intermediate layer named after them. Purkinje cells are the largest and most morphologically complex inhibitory neurons in the CNS, acting as the only output of the cerebellar cortex and sending inhibitory signals to the DCNs (Bower, 2015). Interestingly, recent evidence suggests that Purkinje cell axons may also collaterally inhibit neighboring Purkinje or granule cells (Guo et al., 2016; Witter et al., 2016). Purkinje cells show two different firing patterns: simple spikes, produced by parallel fiber input, and complex spikes, triggered by climbing fibers originating from the IO (Brown et al., 2024; Muller et al., 2023). Each climbing fiber forms hundreds of synaptic contacts as it ascends the Purkinje dendritic tree, producing a high-fidelity complex spike characterized by spikelets and a prolonged calcium influx, which serves as a powerful teaching signal for synaptic plasticity (Carey, 2024). Parallel fibers also synapse onto inhibitory stellate and basket cells in the molecular layer, inhibiting Purkinje cells at the dendritic and somatic/axon initial segment levels, respectively. This feedforward inhibition sharpens the output of Purkinje cells, thereby constraining the spatial spread of parallel fiber signals and preserving functional specificity (Prestori et al., 2019). Additionally, parallel fibers stimulate Golgi cells, which are located in the granule layer but extend dendrites into the molecular layer. Activated by both mossy and parallel fibers, Golgi cells provide both feedforward and feedback inhibition to granule cells, finely regulating afferent transmission both vertically (toward the cortex) and laterally (across glomerular clusters) (D'Angelo et al., 2013). Other inhibitory interneurons in the granule layer include Lugaro cells, which modulate the activity of Golgi cells via neuromodulators, and UBCs, which are exclusive to the flocculonodular lobe and amplify mossy fiber input, likely crucial for the rapid integration required for oculomotor control and vestibulo-ocular reflexes (Prestori et al., 2019). This exquisitely organized architecture forms the basis of the cerebellum's impressive computational capacity, which, although built on a relatively uniform microcircuit, gains functional diversity from the topographic specificity of its afferent and efferent connections (Stoodley and Schmahmann, 2018).

It is also essential to emphasize that the cerebellar cortex consists of many zones, each of which can be further divided into hundreds—if not thousands—of microzones, which serve as the true functional units of this structure (Voogd, 2011). In addition to these, multizonal microcomplexes have been identified (Apps and Garwicz, 2005; D'Angelo et al., 2016a). These arise from convergent connections involving the same group of DCNs and IO neurons, suggesting a highly conserved topographical organization that extends from large-scale loops down to the microscopic level. Indeed, the topography of cerebello-cortical circuits is mirrored at the microcircuit level. Specifically, mossy fibers not only project to specific regions of the cerebellar cortex, targeting granule cells whose parallel fibers activate distinct Purkinje cell populations, but also send collateral branches that directly contact the same DCN neurons influenced by the Purkinje cells they indirectly excite (Voogd, 2012). A similar dual-targeting pattern is observed for climbing fibers, which originate from the IO: a single climbing fiber can branch and innervate up to ten non-adjacent Purkinje cells, while also projecting to the associated DCN neurons (Cerminara and Apps, 2011).

This complex anatomical and functional organization underpins the formation of cerebellar modules—longitudinally oriented parasagittal bands of Purkinje cells that receive selective input from climbing fibers and/or mossy fibers (via granule cells) and converge onto specific subregions of the DCN (D'Angelo, 2018). Although most synaptic interactions within the cerebellum occur intramodularly, intermodular communication is possible, primarily through the broad transverse extension of parallel fibers. Recently, additional pathways for intermodular integration have been identified, including parasagittal connections mediated by collateral

branches of Purkinje cell axons and outputs from the DCNs (Gao et al., 2016; Witter et al., 2016). While cerebellar modules are essentially homogeneous in their basic architecture, functional specializations have been documented. Notably, certain sagittally oriented stripes revealed by immunohistochemical markers like zebrin exhibit distinct molecular signatures (De Zeeuw and Ten Brinke, 2015; Lin et al., 2020). Although their precise functional roles remain to be fully elucidated, these stripes are hypothesized to regulate neuronal firing rates and contribute to the intrinsic oscillatory dynamics of the cerebellum, which are fundamental for modulating temporal patterns across various sensorimotor and cognitive functions (as will be explored in the following sections) (Cerminara et al., 2015; De Zeeuw and Ten Brinke, 2015).

4.5 Functions of the cerebellum

As outlined in the previous sections, the cerebellum is connected both topographically and functionally to nearly all other regions of the CNS, while its internal architecture remains remarkably uniform across its various territories (see Figure 3 for a schematic overview of the widespread connectivity between the cerebellum and the brain patterns).

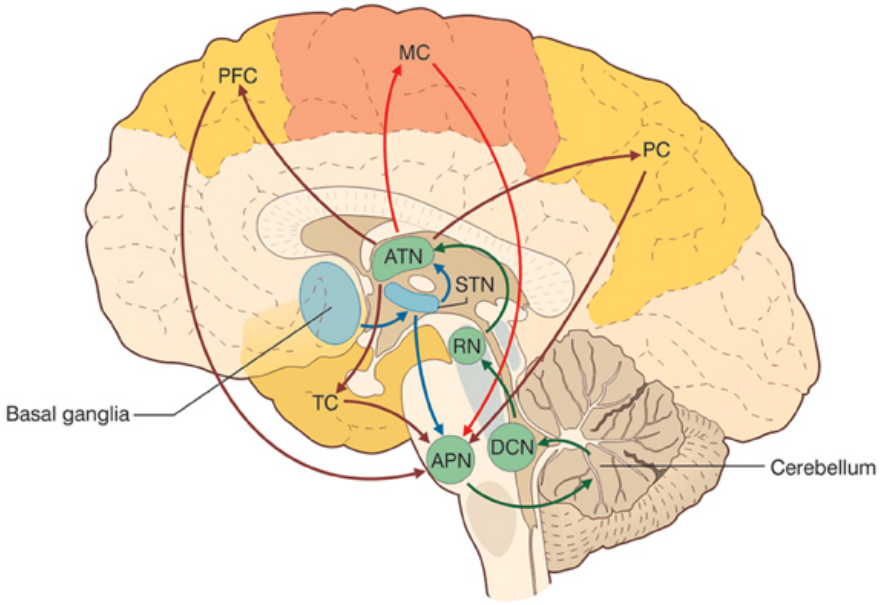


Figure 3. Schematic representation of the main cerebellar-thalamus-brain circuits, from (D'Angelo and Casali, 2012).

This structural consistency suggests that the cerebellum may perform similar computational operations across various domains, including sensorimotor control, cognitive processing, and emotional regulation, although the evidence remains inconclusive in this regard (Diedrichsen et al., 2019; Schmahmann et al., 2019). This hypothesis aligns with a well-established perspective in neuroscience: the CNS continuously generates internal representations of the body's interaction with the environment, not only to guide real-time responses but also, critically, to predict the most likely sensory consequences of future actions (Petzschner et al., 2021). This predictive capability is central to motor planning, which, by definition, entails anticipating a desired sensory outcome (Rao, 2024). Such predictive encoding is the hallmark of a "forward controller", i.e., a system that combines contextual inputs and prior experiences to generate internal models of current states and forecast the sensory effects of motor commands (Miall and Wolpert, 1996). Notably, there is strong evidence supporting

the cerebellum's role as a forward controller (Ebner and Pasalar, 2008). This role allows the cerebellum to not only anticipate sensory outcomes (thus avoiding dependence on delayed feedback) but also to generate error signals when there is a discrepancy between predicted and actual outcomes—signals that drive corrections in future behavior. If the mismatch persists despite ongoing corrections, the cerebellum updates its internal models to better reflect the current sensorimotor contingencies (Ito, 2005).

This function has been extensively studied in the context of motor control and motor learning. As previously discussed, the motor areas of the cerebral cortex send a copy of their outgoing motor commands (known as "efference copy" or "corollary discharge") to the cerebellum via the cortico-ponto-cerebellar tract. The cerebellum integrates this information with contextual inputs to predict the sensory consequences of the action, refining the motor output accordingly (Xiao et al., 2023). Neurophysiological investigations into this process, often referred to as procedural learning, have revealed two distinct stages. Initially, rapid yet transient changes occur within the cerebellar cortex. These changes are then transferred to the DCNs, where they are consolidated into longer-lasting memory traces, which are subsequently moved to relevant interconnected brain regions for long-term storage (Kim et al., 2025; Shutoh et al., 2006; Tzvi et al., 2020).

Therefore, under physiological conditions, the cerebellum operates silently and efficiently, orchestrating motor behavior with seamless efficiency. Its contribution to smooth, coordinated movement is so automatic that we are rarely aware of it (Carey, 2024). Indeed, in healthy individuals, the cerebellum integrates visual and proprioceptive inputs to guide upper limb movements accurately toward their intended targets (D'Angelo, 2018). However, after cerebellar damage, especially in its anterior regions, which are more closely linked to sensorimotor networks, this smoothness is disrupted. The result is ataxia: movements become erratic, delayed, and defined by wide oscillations. A notable feature of this dysfunction is the inability to coordinate agonist and antagonist muscles, leading to irregular changes in velocity and trajectory that cause the limb to undershoot or overshoot the target—a phenomenon collectively known as dysmetria (Grimaldi, 2022). At the core of this deficit is the loss of the cerebellum's anticipatory control over both the timing and strength of muscle contractions (Tanaka et al., 2021). This impairs the ability to generate appropriately sequenced and scaled motor commands, disrupting the execution of even the simplest movements. Notably, the cerebellum influences both alpha motor neurons (via projections to the vestibular nuclei) and gamma motor neurons (through connections with the reticular formation), thereby modulating not only muscle contraction but also muscle tone and stretch reflex sensitivity (D'Angelo, 2018). Besides these peripheral motor functions, the cerebellum is essential for motor planning and programming through its links with premotor and prefrontal cortical areas (Picazio et al., 2016). Therefore, cerebellar dysfunction can have significant consequences for the execution of daily motor patterns that depend on precision, coordination, and adaptability.

While most of this knowledge has historically been derived from motor paradigms, the cerebellum's extensive connectivity with associative neocortical areas suggests that similar feedforward computations also occur in cognitive and emotional domains (Tanaka et al., 2020). Indeed, through its well-defined cerebro-cerebellar loops, the cerebellum interfaces not only with frontal-parietal-temporal cortical areas (e.g., prefrontal, sensorimotor, and parietal loops) but also with basal ganglia, limbic structures, and the hippocampus (Bostan and Strick, 2018; Habas, 2023; Rondi-Reig et al., 2022; Salmi et al., 2010).

Consistently, despite being thought initially to contribute mainly to motor adaptation—a form of implicit learning in response to sensorimotor perturbations—the cerebellum is now recognized for supporting a wider range of motor learning processes (Spampinato and Celnik, 2021; Taylor and Ivry, 2014). Recent studies highlighted

the mono- and disynaptic connections between the cerebellum and the basal ganglia, a subcortical network that is central to reinforcement learning (Bar-Gad et al., 2003; Bostan and Strick, 2018; Spampinato and Celnik, 2021). These connections suggest that the cerebellum may also play a role in simulating and reinforcing internal models related to maximizing dopaminergic release, thereby optimizing behaviors that are likely to be rewarded (Todorov et al., 2019; Yoshida et al., 2025). Likewise, cerebellar-hippocampal pathways may aid in encoding contextual information crucial for refining internal models, while interactions with the limbic system might prioritize emotionally significant patterns, especially those linked to autonomic and behavioral responses triggered by affective states (Rondi-Reig et al., 2014; Schmahmann et al., 2022; Yu and Krook-Magnuson, 2015). Furthermore, the established role of the cerebellum in temporal perception and integration, likely in collaboration with the extensive network of regions with which it is interconnected, underscores its broader and translational significance in overall CNS functioning (Spencer and Ivry, 2022). Indeed, precise timing is crucial for almost every part of daily life—from coordinating movements to predicting sensory events—and damage that interferes with processing temporal information can profoundly impact the activities carried out by different brain networks and, in turn, affect patients' autonomy and quality of life (Hove and Keller, 2015). Importantly, as already mentioned, the influence of the cerebellum extends beyond the motor domain. Just as lesions in the anterior cerebellum lead to impaired motor coordination, damage to posterior cerebellar regions—or their connections with frontal-parietal-temporal cortical networks—can result in cognitive dysmetria: the disrupted coordination of thought processes (Argyropoulos et al., 2020; Schmahmann, 2023, 2019). Consistently, patients with cerebellar damage may experience deficits in executive functions, language, motivation, and goal-directed behavior, reflecting a failure to integrate and sequence higher-order cognitive operations. These impairments, once overlooked, are now recognized as critical components of cerebellar pathology, highlighting the broader significance of cerebellar integrity for both movement and cognition.

Together, these findings emphasize that the cerebellum is not only a key regulator of motor control but also a powerful, domain-general optimizer of brain function. This role is crucial under physiological conditions and may also be essential in pathological contexts. Indeed, in cases of CNS injury or disease, the cerebellum's ability to refine and adapt residual neural resources may play a crucial role in enabling compensation, functional reorganization, and recovery (Arleo et al., 2024; Celnik, 2017; Zhang et al., 2019). Its ability to refine response patterns—motor and otherwise—positions it as a promising target for therapeutic strategies aimed at restoring function across a wide range of neurological disorders.

4.6 The neurobiological basis of cerebellar computations

As discussed in the preceding sections, the cerebellum plays a crucial role in supporting a wide array of functions with remarkable efficiency. However, understanding the neurobiological foundations that enable these operations has required extensive research and remains, in many ways, an ongoing effort. Current evidence indicates that the cerebellum's core computational functions, particularly those involving information integration, timing, and the coordination of inputs and outputs, fundamentally depend on mechanisms of synaptic plasticity occurring throughout its microcircuitry (Cheron et al., 2016).

Among all regions of the CNS, the cerebellum exhibits particularly pronounced plastic synaptic properties, demonstrating the capability to strengthen or weaken synapses over time based on experience and activity. These dynamic changes are now deemed essential for the cerebellum's function in adaptive computations (Mitoma et al., 2021). Almost all cerebellar neurons consistently exhibit short-term plasticity mechanisms that

are especially important for modulating signal transmission during bursts of activity (D'Angelo, 2014; Mapelli et al., 2014; Wilms and Häusser, 2015). These changes can be facilitatory, such as those between granule cells and inhibitory interneurons, or inhibitory, as seen with climbing fiber inputs to Purkinje cells. However, long-term synaptic plasticity is thought to be most critical for cerebellar function (Gao et al., 2012). These mechanisms are typically calcium-dependent and influence the expression of genes encoding proteins that either strengthen (long-term potentiation, LTP) or weaken (long-term depression, LTD) synaptic connections (Mateos-Aparicio and Rodríguez-Moreno, 2020). LTP is typically linked to high-frequency stimulation and involves an increase in presynaptic neurotransmitter release and/or enhanced expression of postsynaptic receptors. In contrast, LTD generally follows low-frequency stimulation and modest postsynaptic depolarization, which results in a decrease in synaptic efficacy (Bliss and Cooke, 2011). Since the initial discovery of LTD at parallel fiber–Purkinje cell synapses, over 15 distinct forms of long-term synaptic plasticity have been recognized within the cerebellar circuitry (D'Angelo et al., 2016b; Ito et al., 2014). These forms differ in their induction mechanisms, molecular pathways, and functional roles. Importantly, these phenomena have been demonstrated not only in isolated cellular preparations but also in vivo, indicating that cerebellar computations are consistently influenced by real-time synaptic adjustments (D'Angelo, 2018; Johansson et al., 2014; Ramakrishnan et al., 2016). These findings have not only enhanced our understanding of cerebellar neurobiology but have also connected physiological mechanisms with behavioral functions. Notably, early theoretical models by Marr and Albus proposed that the cerebellum is the site of motor skill learning, facilitated by LTD between parallel fibers and Purkinje cells, coinciding with instructive climbing fiber signals (Albus, 1971; Marr, 1969). Indeed, as already mentioned, these climbing fibers trigger complex spikes and a massive calcium influx in Purkinje cells, effectively marking sensorimotor prediction errors. By selectively weakening synaptic connections that encode inaccurate associations, the cerebellum can refine motor output and enhance precision (Ito, 2013; Ito and Kano, 1982). This theoretical framework is supported by seminal work from Ito, who demonstrated the role of these plastic mechanisms in vestibulo-ocular reflex adaptation, serving as an example of how climbing fibers act as "teaching signals" (Ito, 1998). Similar principles have been extended to describe behavioral conditioning paradigms, such as eyeblink conditioning, as well as more complex tasks (Bracha, 2004; Tzvi et al., 2022). Figure 4 presents a schematic representation of several primary synaptic plasticity mechanisms in the cerebellar circuitry.

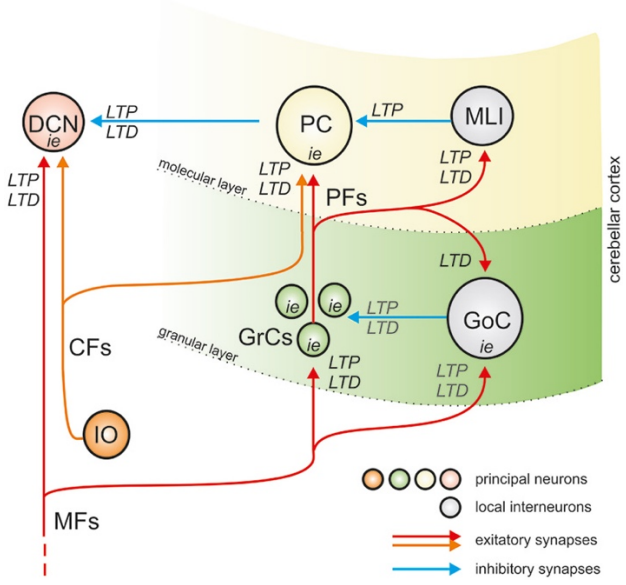


Figure 4. Schematic overview of the organization of plasticity mechanisms in the cerebellar circuitry, from (Mapelli et al., 2015).

Besides these established mechanisms, different evidence indicates that other, less explored factors influence cerebellar plasticity. These include synaptic spillover within cerebellar glomeruli and the molecular layer, as well as modulation by various neuromodulators (D'Angelo, 2018; Mitchell and Silver, 2003; Szapiro and Barbour, 2007). Consistently, brainstem nuclei send cholinergic, serotonergic, and noradrenergic projections to the cerebellum, which interact with a wide range of neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), and glycine, as well as purines (Hirano et al., 2023; Oostland and van Hooft, 2016; Turner et al., 2011). These neuromodulatory systems probably alter the overall dynamics of cerebellar networks and affect both short-term and long-term plasticity (Marder and Thirumalai, 2002; Prestori et al., 2013; Rousseau et al., 2012). Intriguingly, this complex crosstalk between the cerebellum and brainstem neuromodulatory centers may also underlie the cerebellum's emerging role in sleep regulation (Canto et al., 2017). For instance, its influence on thalamic activity and the generation of sleep spindles highlights yet another aspect of cerebellar involvement in overall brain function (Habas et al., 2019; Xu et al., 2021).

In addition to modulating the strength of synaptic responses to external stimuli, the mechanisms discussed above may also play a pivotal role in refining the spatiotemporal configuration of cerebellar neural activity patterns in response to incoming signals. Specifically, when granule cells receive activation from mossy fiber inputs—an effect further influenced by inhibitory Golgi cell activity—they tend to fire in center-surround clusters (Diwakar et al., 2011; Mapelli and D'Angelo, 2007). This spatial organization facilitates efficient encoding of both gain and phase of afferent signals. It seems reasonable that this spatiotemporal organization is critically shaped by plasticity mechanisms that influence the excitability of cellular elements, making them more or less responsive to input (D'Angelo, 2008; D'Angelo et al., 2016b; Marek et al., 2018). For instance, plasticity could limit lateral spread, that is, the number of Purkinje cells and associated cerebellar modules recruited by a given stimulus, or it could regulate the number of activated cerebellar glomeruli, thereby modulating both the identity and dynamics of inhibitory feedforward and feedback mechanisms involved. Furthermore, this becomes particularly important given the fine-grained topography of synaptic connectivity. Consistently, the functional effect of a single input pathway can vary based on which microcircuit elements are involved. For example, molecular layer inhibitory interneurons exert a differential influence depending on whether Purkinje cell excitation comes from ascending axons or parallel fibers (Mapelli et al., 2010). Thus, cerebellar modulation is highly sensitive to a wide range of spatiotemporal parameters.

What emerges is a complex computational landscape where synaptic plasticity dynamically shapes the spatial and temporal integration of granule layer inputs, the nonlinear response properties of Purkinje cell dendritic trees, and the filtering behavior of local interneuron networks (Jörntell et al., 2010; Masoli et al., 2017, 2015; Valera et al., 2016). Collectively, these interactions determine how the cerebellum decodes incoming information and selects appropriate output responses. At the heart of this process lies the IO, whose electrical coupling via gap junctions and inhibitory modulation from DCNs orchestrates rhythmic internal activity patterns. These patterns, conveyed by climbing fibers, selectively influence groups of Purkinje cells by highlighting relevant mossy fiber input configurations (D'Angelo, 2014; Han et al., 2020; Libster et al., 2010; Welsh and Turecek, 2017). As noted previously, this precise timing modulation is crucial for inducing various forms of synaptic plasticity, which ultimately support observable behavioral outcomes, including learning and adaptation

(Cheron et al., 2016). A key aspect of this functional refinement involves spike-timing-dependent plasticity (STDP), a type of synaptic modification where the direction and magnitude of plasticity depend on the relative timing of pre- and postsynaptic action potentials (Caporale and Dan, 2008). Specifically, when a presynaptic spike occurs before a postsynaptic one within a critical time window, the synapse is strengthened (i.e., LTP). Conversely, if the order is reversed, the synapse is weakened (i.e., LTD). These dynamics reflect Hebbian principles of plasticity and now have clear neurophysiological grounding within cerebellar circuits (Luque et al., 2016; Sgritta et al., 2017). Crucially, STDP provides a conceptual and mechanistic link between synaptic plasticity and the intrinsic rhythmicity of the cerebellum, as well as its oscillatory dynamics, which will be discussed in detail in the next section.

4.7 The intrinsic oscillations and rhythms of the cerebellum

Brain rhythms, or neural oscillations, refer to rhythmic patterns of activity across neuronal populations and have been consistently studied using neurophysiological techniques, particularly electroencephalography (EEG) (Herrmann et al., 2016). These oscillations allow groups of neurons to synchronize their activity, even without direct anatomical connections or when situated in distant brain regions. Their emergence arises from a delicate balance between excitatory and inhibitory synapses and the interaction between the cortex and the thalamus, which serves as the primary relay station for signals that must access the cortex and functions as an adaptive filter with a crucial modulatory role (Deco et al., 2014; Shine et al., 2023). Substantial evidence has shown that this synchrony is essential for supporting computational processes in the CNS, primarily by regulating the timing and integration of information flows (Buzsáki et al., 2013). Consistently, oscillatory activity serves as a temporal scaffold, creating windows during which sensory inputs are filtered, prioritized, and processed based on their timing. Each region of the brain exhibits intrinsic resonant frequencies, which are characteristic rhythms associated with the baseline activity of that area and at which they respond most strongly to input signals or their role in specific functions (Klimesch, 2018). For example, the primary motor cortex (M1) typically resonates in the beta band (12–30 Hz), while the primary visual cortex oscillates in the alpha range (8–12 Hz) (Guerra et al., 2020; Pant et al., 2023). Importantly, when involved in specific tasks, brain regions tend to shift their intrinsic oscillatory patterns to facilitate functional communication across networks. A well-studied example is the cross-frequency coupling (CFC) between theta (4–8 Hz) and gamma (30–80 Hz) rhythms (Canolty and Knight, 2010; Lisman and Jensen, 2013). Here, the slower theta rhythm structures temporal windows for receiving input, while the faster gamma rhythm transmits information packets in synchrony with the most receptive phases of the theta cycle. These windows correspond to dynamic changes in neuronal excitability, optimizing the effectiveness of interregional communication. Notably, this coordination extends beyond simple frequency coupling. Indeed, phase and amplitude modulation (i.e., phase-amplitude coupling) of EEG signals across regions also shapes the efficiency of neuronal interactions, potentially altering the number and identity of neurons recruited in each process (Munia and Aviyente, 2019). Such dynamics underscore the central role of brain rhythms in virtually all CNS operations. Indeed, distinct oscillatory patterns have been demonstrated to support a wide range of functions, from basic sensory perception and sensorimotor integration to higher-order cognitive processes, including attention, memory, and language processing (Buzsáki and and Watson, 2012; Kopell et al., 2010).

Many neurological disorders are consistently linked to specific disruptions in oscillatory activity, sometimes even occurring before the onset of clinical symptoms (Alvi et al., 2022; Chetty et al., 2024). For example,

following a brain stroke, i.e., ischemic or hemorrhagic damage to the CNS, lesioned brain areas frequently exhibit delta-band activity (1–4 Hz) (Finnigan et al., 2016). While historically regarded as a passive marker of damage, this slow-wave activity is now believed to reflect an active attempt by the injured brain to re-engage in network communication and re-establish functional connectivity (Assenza and Di Lazzaro, 2015). Some researchers have drawn parallels between this delta activity and slow-wave sleep, which plays a crucial role in homeostatic regulation, synaptic plasticity, and memory consolidation (Cirelli and Tononi, 2022; Massimini et al., 2024; Sarasso et al., 2025). Together, these insights highlight the vital role of brain rhythms in not only understanding the physiological function of the CNS but also in interpreting how damage affects these dynamics.

While the role of cortical brain rhythms has been extensively studied—although still not fully understood—the oscillatory activity of the cerebellum remains relatively underexplored, especially in humans. This knowledge gap primarily arises from the technical challenges associated with non-invasively recording cerebellar oscillations using techniques such as EEG. Several factors contribute to these challenges, including the deep anatomical location of the cerebellum, which diminishes signal transmission; frequent contamination from muscle artifacts, often indistinguishable from rapid cerebellar activity; and, most notably, the intricate folding of the cerebellar cortex. This complex architecture, featuring densely packed folia arranged in various directions, disrupts the summation of electrical fields and complicates source localization (Andersen et al., 2020). Although recent technological advancements, such as magnetoencephalography (MEG) and advanced EEG source reconstruction algorithms, are beginning to address these challenges, the functional significance of cerebellar oscillations remains only partially understood (Andersen et al., 2020; Kumar et al., 2025). This is particularly concerning considering that the cerebellum is one of the few CNS structures capable of expressing a wide range of neural rhythms, from very slow to extremely fast frequencies (De Zeeuw et al., 2008).

For instance, delta-theta oscillations in the cerebellum are thought to arise from the rhythmic coupling of neurons within the IO, mediated by gap junctions (Leznik and Llinás, 2005; Matsumoto-Makidono et al., 2016). These low-frequency oscillations are associated with the generation of complex spikes in Purkinje cells and are believed to play a crucial role in timing-dependent learning, particularly in the context of unexpected events (Lang et al., 2006; Van Der Giessen et al., 2008). Therefore, theta-band activity originating from the IO has been proposed as a principal coordinating signal for cerebellar cortical activity, supporting both sensorimotor and cognitive processing (D'Angelo, 2018; Llinás, 2014). Moreover, theta rhythms are intrinsic to granule cells, where they support sensory-motor processing, including intermittent motor control and state estimation, also influenced by the shaping provided by Golgi and Lugaro cells (Courtemanche et al., 2009; D'Angelo et al., 2001; D'Angelo and De Zeeuw, 2009; Dieudonné and Dumoulin, 2000; Hartmann and Bower, 1998; Lainé and Axelrad, 2002). In contrast, Purkinje and Golgi cells display preferences for beta-band activity, which is crucial for brain-cerebellar interactions during both active and passive movement, and for synchronizing the cerebellum with M1 and somatosensory cortex during sensorimotor integration (Courtemanche and Lamarre, 2005; Soteropoulos and Baker, 2006). While these lower-frequency oscillations have been associated with relatively well-defined functions—primarily due to the cerebellum's effect on the vestibular nuclei and the thalamus, a central modulator of cortical rhythms—far less is known about the functional implications of higher-frequency cerebellar oscillations (De Zeeuw et al., 2008).

Specifically, gamma-band activity in Purkinje cells and inhibitory interneurons, as well as even faster oscillations such as very fast oscillations (VFO, 80–160 Hz) and very high-frequency oscillations (VHFO, 160–

260 Hz), remain poorly understood (de Solages et al., 2008; De Zeeuw et al., 2008; Whittington et al., 2011). VFOs are believed to arise from gap-junction-mediated coupling in the cerebellar cortex, while VHFOs may reflect recurrent collateral activity. It has been hypothesized, in line with cortical models, that a CFC may occur between slower rhythms (e.g., from IO neurons) and faster ones (e.g., Purkinje cells), enhancing information integration and coordination (Lang et al., 2006; Wise et al., 2010). However, it is also plausible that high-frequency rhythms, such as those associated with activities carried out by cerebellar inhibitory interneurons, independently support essential computational functions, including information encoding, transmission, and retrieval, without the need for cross-frequency modulation (Jörntell et al., 2010; Sejnowski and Paulsen, 2006). Importantly, it is now well-established that the activity of the primary targets of the DCNs, namely, the IO (forming a short feedback loop), the thalamus (which relays signals to the cortex), and the mesodiencephalic junction (MDJ, a target of collaterals from corticopontine fibers and, in turn, involved in inhibiting the IO), is critically shaped by the synchrony of Purkinje cell firing (De Zeeuw et al., 2008; Gauck and Jaeger, 2000; Habas et al., 2019; Wang et al., 2022).

Therefore, although Purkinje cells are the only output neurons of the cerebellar cortex, the precise regulation of oscillatory dynamics across cerebellar microcircuits can substantially alter the temporal structure and firing patterns transmitted to these downstream targets. For instance, cerebellar modulation has been shown to enhance gamma-band oscillations in thalamocortical neurons, highlighting the cerebellum's crucial role in shaping thalamic activity and, consequently, the function of widespread cortical networks (Habas et al., 2019; Heck et al., 2023; Timofeev and Steriade, 1997). This regulatory capacity is further supported by the observation that the intrinsic oscillatory characteristics of the IO and thalamus are strikingly similar (Huguenard and McCormick, 2007; Llinás, 2009). Together with the presence of reciprocal cerebellar loops connecting these regions, this indicates a shared operational mechanism between the cerebellum and cerebrum cortex. Overall, these findings show that the functional impact of cerebellar cortical output is influenced by its oscillatory dynamics. Thus, understanding these rhythms is crucial for deciphering the complex interactions of cerebellar microcircuitry within a broader neurophysiological context. Furthermore, this expanding knowledge provides the foundation for innovative neuromodulatory and therapeutic strategies, such as non-invasive brain stimulation (NIBS) techniques, designed to restore or enhance functional communication in both physiologically and pathologically disrupted neural systems.

4.8 References

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Chapter 5. Characterizing practice-dependent motor learning after a stroke

In Chapter 5 of this thesis, I present an experimental study aimed at characterizing the mechanisms underlying practice-dependent motor learning in individuals with chronic stroke. Building on the neurophysiological framework established in the previous Chapters on stroke deficits and the cerebellum, which is critically involved in motor learning, this study was designed to explore performance during the chronic stroke timeframe.

The results show that, even during the chronic phase of stroke, motor learning mechanisms remain intact and are affected by individual-specific factors. Furthermore, these findings provide valuable insights not only into the potential for patients—well beyond the period of heightened neuroplasticity typical of the early post-acute phase—to enhance their motor performance, which has significant implications for neurorehabilitation strategies, but also into the practicality of using a simple, time-efficient computerized tool to assess individual motor learning profiles. This task, which can be performed at the bedside in just a few minutes, offers a practical and scalable way to evaluate motor learning potential in clinical settings, aiding more personalized rehabilitation planning.

This study enhances the Thesis by analyzing post-stroke motor learning mechanisms and highlighting the need for personalized rehabilitation strategies. It also aligns with the overarching goal of this research project. Considering the well-established role of the cerebellum in error-based motor adaptation and internal model updating, these findings further confirm the cerebellum's essential role in motor rehabilitation and assist in identifying clinical tools to evaluate the potential for improvement in stroke patients.

The study was published in Neurological Sciences as:

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5.1 Abstract

After a stroke, patients must learn to use their residual motor function correctly. Consistently, motor learning is crucial in stroke motor recovery. We assessed motor performance, practice-dependent on-line motor learning, and factors potentially affecting them in stroke patients. This is a cross-sectional observational study. Twenty-six patients with first brain stroke leading to upper limb motor deficit in the subacute or chronic timeframe were enrolled. They performed a Finger Tapping Task (FTT) with both the affected and unaffected limbs. We assessed how patients learn to perform motor tasks despite the motor deficit and the differences in performance between the unaffected and affected limbs. Furthermore, by randomizing the order, we evaluated the possible inter-limb transfer of motor learning (i.e., transfer of a motor skill learned in one limb to the opposite one). Moreover, sleep, attention, anxiety, and depression were assessed through specific tests and questionnaires. Improved FTT accuracy and completed sequences for the affected limb were observed, even if lower than for the unaffected one. Furthermore, when patients initially performed the FTT with the unaffected limb, they showed higher accuracy in subsequent task completion with the affected limb than subjects who started with the affected limb. Only anxiety and attentional abilities showed significant correlations with motor performance. This work provides relevant insights into motor learning in stroke. Practice-dependent on-line motor learning is preserved in stroke survivors, and an inter-limb transfer effect can be observed. Attentional abilities and anxiety can affect learning after a stroke, even if the effect of other factors cannot be excluded.

5.2 Introduction

Cerebral stroke is a leading cause of death and long-term disability worldwide (Saini et al., 2021). Despite recent advances in its management, stroke patients with long-term outcomes are still very common (Singh et al., 2018). Thus, identifying effective strategies to ensure complete functional recovery is crucial. Upper limb motor deficits are critical because of their impact on activities of daily living (ADL) and the resulting loss of independence. Indeed, restoring post-stroke upper limb motor patterns is challenging due to the complexity of motor behaviours (Raffin and Hummel, 2018). Importantly, after stroke, the central nervous system (CNS) undergoes increased neuroplasticity aimed at promoting the neural reorganisation that accounts for spontaneous recovery (i.e., the return to the premorbid motor level). However, it manifests within a restricted time interval and, often, does not lead to full restoration of impaired function (Joy and Carmichael, 2021). Indeed, stroke patients in the chronic phase are often characterized by persistent and even severe outcomes (Mooney et al., 2020). Since several weeks after stroke the neurobiological mechanisms associated with true recovery are over, it is fundamental to properly use residual effectors to accomplish tasks (i.e., compensation) (Levin et al., 2009). Notably, recent advances in motor learning, i.e., processes aimed at learning and refining new skills through practice, could play a fundamental role in stroke rehabilitation (Maier et al., 2019). Consistently, several studies proved that chronic stroke patients not only retain the ability to learn motor skills, e.g. a motor sequence with the affected arm, but also that this is crucial for maintaining their ADLs (Fleming et al., 2018; Kantak et al., 2018). Such simple tasks allow not only to assess stroke patients' motor abilities, but also to study their improvement during the task itself (i.e., on-line learning), which is a form of practice-dependent learning relevant from a neurorehabilitation perspective (Wang et al., 2020). Indeed, motor learning encompasses separate phases: acquisition, marked by performance enhancements during practice (on-line changes), and retention, evident in performance after a break (off-line changes) (Spampinato and Celnik,

2021). Recent studies confirmed that chronic stroke patients exhibit both acquisition and retention of motor skills. However, the results are often heterogeneous, reasonably due to a complex interplay between numerous factors (Fleming et al., 2018; Kantak et al., 2018). Consistently, although the neurophysiological mechanisms are partially unknown, numerous reports suggest a role of multiple factors on motor skills acquisition, e.g., psycho-emotional conditions (e.g., anxiety and depression, attentional skills) (Song, 2019; Subramanian et al., 2015), sleep (Gudberg and Johansen-Berg, 2015), and smoking (Campos et al., 2016). Importantly, stroke patients are often characterized by post-stroke depression, sleep disturbances, and cognitive impairment, which adversely affect their motor performance (Al-Dughmi et al., 2017; Baylan et al., 2020; Rost et al., 2022; Subramanian et al., 2015). Thus, collecting data on motor learning strategies after stroke, both in the subacute and in the chronic phase, and on factors that may influence these mechanisms is a fundamental goal of modern neurorehabilitation (Mooney et al., 2020). Indeed, considering their clinical stability, these stroke timeframes are the most suitable for assessing the characteristics of motor learning and the role of factors that could affect it.

Here, we evaluated motor performance and practice-dependent on-line motor learning in stroke patients with an upper limb motor deficit in a subacute and chronic timeframe. These periods are critical for optimizing compensation strategies, as post-stroke neuroplasticity, which facilitates true recovery, is markedly reduced. Participants performed a simple motor task using unaffected and affected limbs. We assessed how patients learn to perform motor tasks despite the motor deficit and the differences in performance between the unaffected and affected limbs. Furthermore, by randomizing the order, we evaluated the possible inter-limb transfer of motor learning (i.e., transfer of a motor skill learnt in one limb to the opposite one), and investigated its characteristics between the two limbs (Ehrensberger et al., 2016). We collected data on factors reasonably influencing motor learning, e.g., mood, attention, and sleep. The aim was to assess the characteristics of this complex neurophysiological mechanism after stroke and the influence of potentially modifiable factors.

5.3 Materials and Methods

5.3.1 Study design

We performed a cross-sectional observational clinical study at the Ferrara University Hospital between December 2022 and April 2023. All the procedures were conducted according to the Declaration of Helsinki and approved by the Area Vasta Emilia-Centro Ethics Committee (Protocol ID 641/2018/Sper/AOUFe) (General Assembly of the World Medical Association, 2014). This study is reported according to the STROBE guidelines.

5.3.2 Subjects recruitment

Subjects admitted to the Ferrara University Hospital were recruited. Subjects' eligibility was assessed based on inclusion and exclusion criteria. Subjects were interviewed and informed about the study's objectives and procedures, and informed consent was obtained. Inclusion criteria were: males and females aged≥18 years; diagnosis of first cerebral stroke verified by neuroimaging in the subacute (between one and six months from the onset) or chronic period (after at least six months from the onset); upper limb motor deficit, but not preventing the execution of computer tasks, as assessed by a score>39 on the Action Research Arm test scale (Chen et al., 2012); at least five years of education. Exclusion criteria were: cerebellar or bilateral cerebral stroke; any medical or neurological conditions, other than stroke, that could prevent the safe completion of the

study protocol or receipt of informed consent (including aphasia and apraxia); visual or auditory disturbances that could hinder the task performance; diagnosis or previous history of substance abuse, traumatic brain injury, neurosurgical interventions, severe psychopathology, cognitive decline or dementia (as assessed by a Mini Mental State Examination score<24) (Bour et al., 2010); pregnancy.

5.4 Procedure

5.4.1 Motor task

Motor learning was assessed through a Finger Tapping Task (FTT) (Cellini, 2017). Specifically, FTT is a motor sequence learning task in which subjects are asked to tap with their hand a 5-digit sequence quickly and precisely by using the numerical keys on a computer keyboard. FTT reflects the acquisition of sequential movements progressively structured into a precise and well-articulated behaviour, including a learning and a testing phase. In order to minimize the demand on working memory, the numeric sequence to replicate and five empty circles remain visible at the center of the screen during the entire task. This method offers several advantages: firstly, it standardizes the experimental session by ensuring uniform conditions for all participants (Guérin et al., 2021; Nettersheim et al., 2015); secondly, it provides immediate visual feedback on task progression (Nettersheim et al., 2015); and lastly, the view of the sequence on the screen enhances participants' ability to memorize it (Guérin et al., 2021). During the task, every time the participant presses a key, one of the circles turns into a red dot regardless of the correctness of the response (i.e., marking only the task progression), to focus on practice-dependent learning and to avoid potential confounders related to different types of motor learning (e.g., reinforcement, error-based) (Nettersheim et al., 2015; Spampinato and Celnik, 2021). Figure 1 shows the experimental set-up.

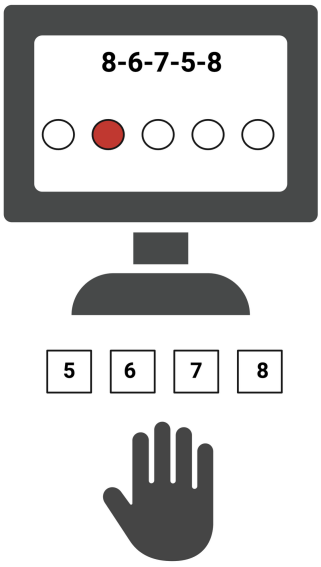


Figure 1. Graphical representation of the Finger Tapping Task. Created with BioRender.com

Subjects were seated in a comfortably lit room at a distance of 90 cm from a 20” computer monitor. All participants confirmed they could see both the screen content and the keys to be pressed without difficulty under the proposed lighting conditions. A stimulus presentation was performed by Pyschopy2 (Peirce et al., 2019), and the experimenter monitored the participants' behaviour throughout the tests. For all subjects, the task was performed with both the affected and unaffected limbs in a different order according to randomization

criteria. During the learning phase, participants were required, by explicit request, to memorize a sequence consisting of five numbers (86758). This phase was structured in 6 blocks of 90 seconds, divided between a resting part, in which a fixation cross simply appeared (30 seconds), and the motor execution phase, during which the subject was required to perform the sequence (60 seconds). The learning phase was preceded by a practice phase, in which the participant was asked to complete a test sequence (56785) to clarify how the actual task would be carried out. The participant was asked to be as accurate and fast as possible since measures of accuracy and the number of completed sequences were used to quantify learning performance. Specifically, three parameters of motor performance were derived:

- ACC (accuracy): it expresses the number of sequences correctly completed.
- Seq (sequences): it corresponds to the number of completed five-number sequences, regardless of their correctness.
- ACC/Seq (accuracy/sequences): it combines the two previous parameters and is the percentage ratio between the number of accurate sequences and the number of sequences typed (formula=ACC/Seq*100).

The on-line motor learning ability of the affected and unaffected limb was also investigated for the three variables ACC, Seq, and ACC/Seq by calculating the percentage variation between the average scores of the 5th and 6th block and the 1st block divided by 1st block score. Specifically:

- ACC_on-line= [(ACC V block + ACC VI block)/2 - ACC I block] / ACC I block*100
- Seq_on-line= [(Seq V block + Seq VI block)/2 - Seq I block] / Seq I block*100
- ACC/Seq_on-line= [(ACC/Seq V block + ACC/Seq VI block)/2 - ACC/Seq I block] / ACC/Seq I block*100

While ACC, Seq, and ACC/Seq provided a snapshot of the participant's performance at specific points in time, the on-line parameters focused on dynamic changes in performance, showing improvement during the task. The on-line learning parameters provide insights of how practice influences motor learning, whereas ACC, Seq, and ACC/Seq provide just a measure of performance at given points.

5.4.2 Neuropsychological evaluation, questionnaires, and clinical assessment scales

Before the motor task, the patients underwent the following neuropsychological evaluation and questionnaires:

- Stroop Color Word Test (Stroop) - Short Version: it is a simple and quick instrument to assess selective attention, cognitive flexibility, and sensitivity to interference. The Stroop effect is evaluated by calculating a time interference effect and an error interference effect (Scarpina and Tagini, 2017);
- Karolinska sleepiness scale (KSS): it assesses the subject's level of sleepiness during the previous 10 minutes (in this case, while performing motor tasks). It is based on nine levels, ranging from one, reflecting maximum alertness, and nine, highlighting maximum sleepiness. A score of 7 is considered pathological sleepiness (Miley et al., 2016);
- Epworth Sleepiness Scale (ESS) is a self-administered questionnaire for assessing the average subjective propensity to sleep during real-life situations. It is considered an indicator of daytime sleepiness (Walker et al., 2020);
- Pittsburgh Sleep Quality Index (PSQI): the 19 items are grouped into seven composite items that represent the components of the questionnaire, i.e., subjective sleep quality, sleep latency, sleep

duration, habitual sleep efficiency, sleep disturbances, use of hypnotic medication, and disturbances during the day. The overall score ranges from 0 to 21, with higher scores indicating more significant sleep quality impairment. The cut-off of sleep disturbance and excessive daytime sleepiness is 5 (Buysse et al., 1989).

- Zung's Anxiety and Zung's Depression Self-Assessment Scale: they are aimed at describing the mood during the last week (Dunstan et al., 2017). About anxiety, a total score from 0 to 20 indicates that the level of anxiety could be very low, 21 to 40 low, 41 to 60 moderate, and 61 to 80 high. The Zung's Anxiety Self-Assessment Scale primarily assesses anxiety state, which refers to how a person feels at a specific moment and can fluctuate in response to various contextual factors. In contrast, anxiety trait represents a more stable aspect of personality and describes a persistent tendency to experience anxiety (Endler and Kocovski, 2001). Therefore, while anxiety trait reflects a general disposition and has a lesser impact on immediate performance, anxiety state might significantly affect both motor performance and motor learning. Conversely, about depression, scores from 20 to 31 indicate that the level of depression could be very low, 32 to 43 low, 44 to 55 moderate, 56 to 67 high, 68 to 80 very high (Dunstan et al., 2017).
- National Institute of Health Stroke Scale (NIHSS): it measures the severity of neurological deficits, with a direct proportionality between score and clinical severity. It analyses level of consciousness, gaze, visual field, facial weakness, limbs motor function, limb ataxia, sensory, aphasia, dysarthria, and extinction (Kwah and Diong, 2014).

5.5 Statistical analysis

Demographic and psychological characteristics were reported as mean (or frequency) and standard deviation. The variation in the three learning variables across the six performance blocks was analyzed through RM-ANOVA tests with Tukey's post-hoc correction. Moreover, the interaction of the side (affected or unaffected) and randomization order (unaffected-affected) on ACC, Seq, ACC/Seq, and their online version was revealed with two-way ANOVA tests. Finally, an ANOVA test was performed to assess the possible influence on on-line learning of concordance (i.e., whether the affected upper limb was the dominant one or not), randomization order and interaction between them. The influence of demographic and clinical factors in the learning variables was tested with the Kruskal–Wallis test for categorical variables (gender, lesion type, lesion site, stroke phase) and by correlation tests (Spearman's rho) for continuous variables. Analyses were conducted with STATA 13, and significance was set at $p<.05$.

5.6 Results

5.6.1 Sample description

5.6.1.1 Demographic and clinical variables

Twenty-six patients were enrolled and evaluated. Table 1 summarises the enrolled patients' baseline characteristics. Based on previous studies that specifically investigated motor learning in stroke patients, we deemed that this sample size would be adequate to address our research aim (Al-Dughmi et al., 2017; Dirnberger et al., 2013; Fleming et al., 2018; Rösser et al., 2008).

	Mean/frequency
Age, years (± SD)	60.15 (10.8)
Gender, no, (male %)	12 (46)
Time since stroke, months (± SD)	39.34 (55.84)
Hemiparesis side (right, no, %; left, no, %)	10 (38.5); 16 (61.5)
Stroke timeframe (subacute, no, %; chronic, no, %)	6 (23.1); 20 (76.9)
Ischemic stroke (%)	23 (88.5)
NIHSS* (± SD)	8.36 (3.53)
Hand dominance (right, no, %; left, no, %)(Oldfield, 1971)	22 (84.6); 4 (15.4)
Stroke site (cortical, no, %; subcortical, no, %; cortical-subcortical, no, %)	3 (11.6); 12 (46.1); 11 (42.3)
Concordance§ (%)	10 (38.5)
Smoking, no (%)	13 (50)
Vascular atheromasia, no (%)	6 (23.1)
Dyslipidaemia, no (%)	9 (34.6)
Hyperhomocysteinemia, no (%)	8 (30.8)
Hypertensive cardiopathy, no (%)	4 (15.4)
Arterial hypertension, no (%)	16 (61.5)

Table 1. Baseline characteristics of enrolled patients. *at the time of admission to the Neurology Unit; §evaluates the correspondence between the manual dominance and the affected limb. *Abbreviations:* NIHSS = National Institute of Health Stroke Scale, SD = standard deviation.

5.6.1.2 Neuropsychological variables (sleep, anxiety, depression, attention)

The mean error and the mean time on the Stroop test were 0.85 (1.22) and 46.47 s (17.39) respectively. The mean score on the KSS was 1.96 (1.11), while on the ESS was 4.30 (2.11). The PSQI score was 11.34 (6.92), indicating a general poor sleep quality and sleep disturbances in this sample(Buysse et al., 1989). The mean score on the Zung's Anxiety and Depression Self-Assessment test was 36.92 (7.95) and 38.92 (7.04) respectively, indicative of a low level of anxiety and depressive symptoms(Dunstan et al., 2017).

5.6.2 Motor task

The FTT was performed with both the affected and unaffected limb: Figure 2 and Table 2 summarise their performance for the ACC, Seq, and ACC/Seq variables. About ACC, a significant block effect ($p<0.001$, $F_{5,250}=16.88$, $\eta^2=.252$) was shown, whereas no effect was found due to the side ($p=0.23$, $F_{1,250}=1.47$, $\eta^2=.00$) or the side/block interaction ($p=0.33$, $F_{5,250}=1.15$, $\eta^2=.022$). There was no difference between the two sides in terms of accuracy. Similarly, about Seq, there was only a significant block effect ($p<0.001$, $F_{5,250}=15.72$, $\eta^2=.239$). In contrast, the side effect ($p=0.23$, $F_{1,250}=1.43$, $\eta^2=.00$) and the side and block interaction ($p=0.28$, $F_{1,250}=1.25$, $\eta^2=.024$) were not significant. Finally, only a significant block effect ($p=0.02$, $F_{5,249} = 2.70$, η^2 .051) was evident for the ACC/Seq, in contrast to the side effect ($p=0.89$, $F_{1,249} = 0.02$, η^2 .00) and the side and block interaction ($p=0.33$, $F_{5,249}=1.14$, $\eta^2=.02$). Specifically, about the unaffected limb**,** there was a progressive and significant increase in accurate sequences ($p<0.001$), completed sequences ($p<0.001$), and in their ratio

(p=0.01) (see Tab. 2, Unaffected limb section, and Fig. 2). On the other hand, the affected limb showed a slight increase in accuracy (p<0.001) and in the number of completed sequences (p<0.001), while the ratio ACC/Seq had a reasonably stable trend, except for a peak increase at the fourth block, without significant change (p=0.37) (see Table 2 and Figure 2). Overall, the mean change in accuracy during testing (Acc_on-line) of the affected limb was 41.16% (61.84%) while, for the unaffected one, it was 81.15% (98.11%). About the variation in the number of completed sequences (Seq_on-line), the average was 35.8% (50.55%) in the affected limb, while for the unaffected one, it was 47.28% (44.47%). The final parameter (ACC/Seq_on-line) had a mean change of 1.32% (18.46%) in the affected limb, while for the unaffected one, it had a mean change of 16.54% (35.49%).

Limb	**Measure**	**Block 1**	**Block 2**	**Block 3**	**Block 4**	**Block 5**	**Block 6**	**P value**
Unaffected limb	**ACC**	9.23 (6.73)	12.26 (6.92)*	12.07 (7.54)*	12.8 (7.77)*	13 (7.82)*	14.03 (8.11)*	< 0.001
	Seq	10.19 (6.54)	12.92 (7.32)*	12.53 (7.54)*	13.42 (7.73)*	13.53 (7.75)*	14.30 (7.97)*	< 0.001
	ACC/Seq	82.59 (24.74)	94.58 (8.4) *	91.35 (20.94)	92.41 (15.18)	93.93 (15.93)	97.01 (8.25)*	0.01
Affected limb	**ACC**	7.96 (5.21)	9.34 (5.85)	10.19 (6.74)*	10.84 (5.79)*	11.03 (6.96)*	10.84 (6.67)*	< 0.001
	Seq	8.88 (4.73)	9.88 (5.92)	10.84 (6.51)*	11.23 (6.12)*	11.65 (6.78)*	11.42 (6.41)*	< 0.001
	ACC/Seq	88.56 (21.99)	92.1 (24.18)	87.98 (18.35)	97.52 (10.86)	91.34 (12.03)	92.22 (17.29)	0.37

Table 2. FTT results reported by the unaffected (first section) and by the affected limb (second section). *p<0.05 Tukey's post-hoc test compared with the first block. *Abbreviations:* ACC = accuracy, ACC/Seq = accuracy/sequences, FTT = Finger tapping task, Seq = sequences.

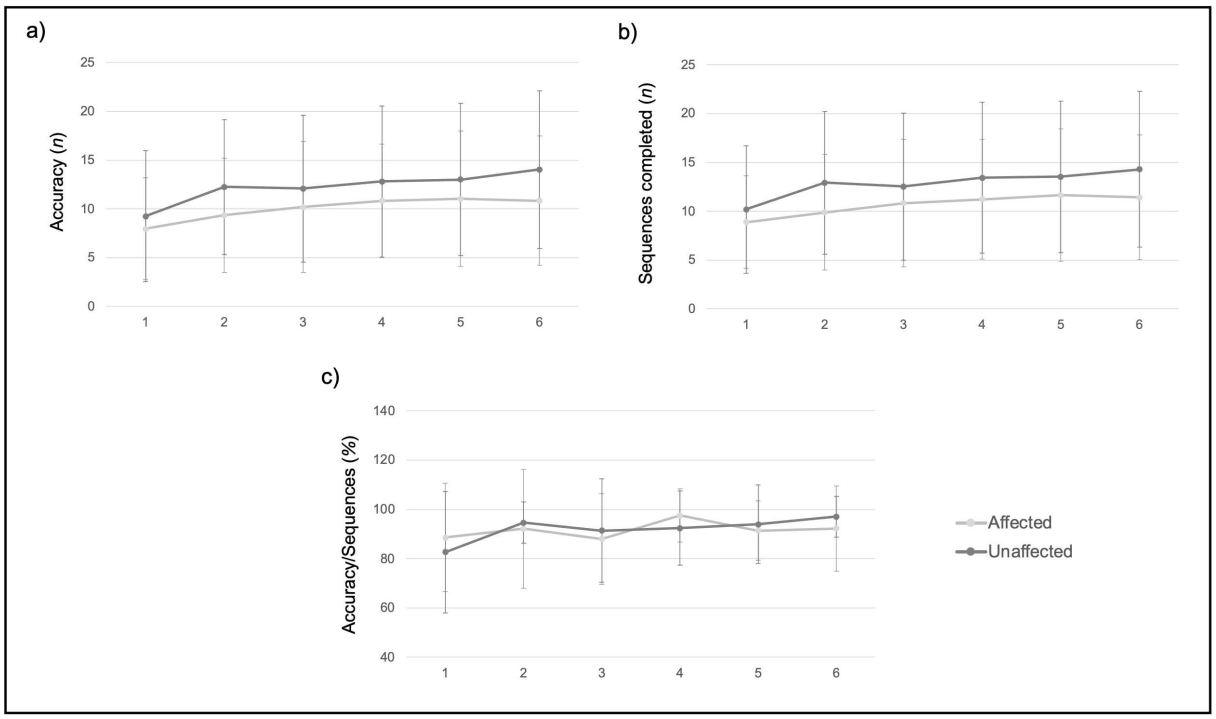


Figure 2. Graphical representation of the average trend of the parameters ACC (a), Seq (b), and ACC/Seq (c) at the FTT of the unaffected (dark grey) and affected limb (light grey) in the 6 trials performed. Error bars represents the standard deviation. *Abbreviations:* ACC = accuracy, ACC/Seq = accuracy/sequences, FTT = finger tapping task, Seq = sequences.

5.6.3 Inter-Limb Transfer

A trend toward an inter-limb transfer was shown only for the affected side with an interaction of randomization and block (p=0.06, $F_{5,120}$=2.20, η^2=.08). The analyses showed that patients who started the test with the unaffected limb had a higher accuracy at the first block with the affected one, in particular, 10.53 (5.51) vs. 5.38 (3.42) (p=0.01), as shown in Figure 3. Finally, the ANOVA showed that concordance didn't affect the on-line learning (i.e. ACC_on-line) (p=0.217, $F_{1,22}$=1.62, η^2=.047), whereas randomization (p=0.035, $F_{1,22}$=5.06, η^2=.147) and its interaction with the concordance (p=0.026, $F_{1,22}$=5.67, η^2=.165) displayed statistically significant effects.

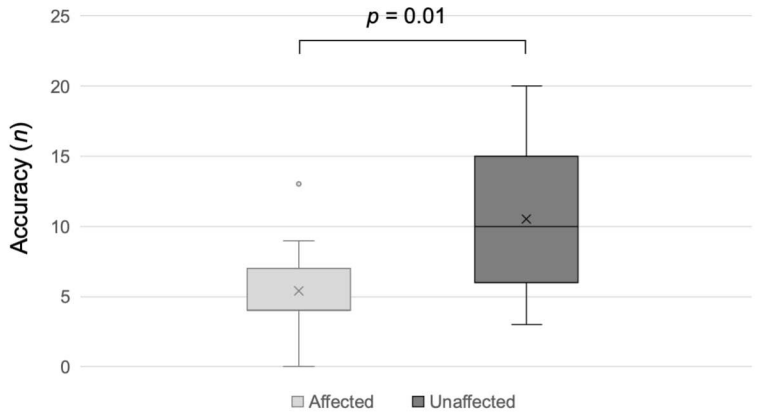


Figure 3. Boxplots of the difference in accuracy at the first block of the FTT between the patients who started the test with the affected (light grey) and unaffected limb (dark grey). Whiskers represent the minimum and maximum values of the sample. The x represents the mean. *Abbreviations:* FTT = Finger tapping task

5.6.4 Clinical and demographic factors affecting on-line learning

The influence of demographic factors (gender, stroke timeframe, type of stroke, and stroke site) on on-line learning was analyzed. There were no differences between the two sides in the accuracy of the FTT according to gender, stroke timeframe (i.e., subacute or chronic), type of stroke (i.e., ischemic or haemorrhagic), nor according to the stroke site, i.e., cortical, subcortical, or cortico-subcortical. Specifically, none of these factors influenced the performance of the FTT. Similarly, the obtained results showed no correlation between the accuracy in performing the FTT and parameters such as age at the time of the stroke onset, the time elapsed between the event and the assessment, and the NIHSS value calculated at the time of admission for both the affected and unaffected limb. Finally, subjects who made fewer errors on the Stroop test had similar accuracy between the unaffected and affected limbs. In comparison, those who made more errors had higher accuracy in the unaffected limb than in the affected one (rho=0.35, p=0.09). No difference between the affected and unaffected limb in improving accuracy (ACC_on-line) was recorded in patients who completed the Stroop test without errors. Furthermore, no significant associations were observed between the FTT parameters and ESS, KSS, PSQI, and Zung's Depression Self-Assessment Scale. A negative correlation was found between the ACC/Seq of the affected side and the score on the Zung's anxiety Self-Assessment Test (rho=-0.39, p=0.05), showing that subjects with a lower level of anxiety achieved a better trade-off between the accuracy on motor task execution and the number of completed sequences.

5.7 Discussion

One of the most debilitating consequences of stroke is upper limb motor impairment, highlighting the importance of understanding how the CNS learns basic motor strategies post-stroke to optimize rehabilitation strategies. Motor learning is an extremely important field of study in this context, as it makes it possible to characterize how motor performance is acquired and perfected, which is particularly important following stroke (Raffin and Hummel, 2018). Our results on subacute and chronic stroke patients showed a slight but stable increase in the accuracy and number of completed sequences in an FTT performed with the affected limb. As expected, both the unaffected and affected limbs improved in these parameters, confirming that the performance enhancement depends on the amount of practice (Krakauer, 2006). Our results are particularly relevant, suggesting that learning sequence-specific motor skills might be an important stimulus to remedy maladaptive patterns of brain activity after stroke (Boyd et al., 2010). Moreover, our results highlight the potential for motor recovery even in stroke patients in the chronic phase. Previous studies in chronic stroke patients showed that Constraint-Induced Movement Therapy improves motor performance through exercises that offer a proportionally increasing 'challenge' to the paretic limb movement (Taub et al., 1993). Our data emphasize the ability of stroke patients to retain motor skills even long after the acute event; furthermore, a simple tool as the FTT seems able to improve motor learning through repetition of sequences, without any additional challenges. Indeed, although various tasks are currently available for assessing motor learning abilities in stroke patients, the FTT offers several advantages. It is easy to understand and execute, without requiring high cognitive load (Cellini, 2017). Additionally, it allows the assessment of fine motor control and

finger movements, frequently impaired in stroke patients (Arunachalam et al., 2005; Xu et al., 2015). FTT provides a standardized non-operator dependent evaluation easily implementable in clinical practice. Indeed, it only requires a computer support and a user-friendly software for the collection of relevant measurements, representing a promising tool for the assessment of motor learning in the neurorehabilitation field.

Improvements in motor performance are reasonably due to use-dependent learning. This simple, goal-independent process forms motor memories to make movements more similar to the previous one (Spampinato and Celnik, 2021). Our results show that this type of motor learning is also maintained in stroke patients, even with a simple task and a small number of repetitions. Considering that on-line practice-dependent learning represents a prerequisite for the subsequent retention and transfer phases, our study confirms that even patients far from the true recovery phase (i.e., the acute timeframe characterized by augmented neuroplasticity) can improve their motor skills, enhancing their daily performance (Spampinato and Celnik, 2021).

With our study, we highlighted an interesting difference between the affected and the unaffected limb in the ratio accuracy/completed sequences. Specifically, the affected limb didn't increase in accuracy respect to the number of completed sequences; conversely, the unaffected limb increased its accuracy more markedly than the relatively less pronounced increase in the number of completed sequences. We can hypothesize that this result reflects a resource allocation strategy. Specifically, the affected limb, with lower maximum resource compared to the unaffected one, has to compromise between the accuracy and the number of completed sequences; instead, the unaffected one, which can complete a fair number of sequences, can invest more in accuracy. Finally, we can assume a crucial role of attention in this process. The subjects who completed the Stroop test with few errors showed similar accuracy between the two limbs; those who made more errors showed higher accuracy of the unaffected limb than the affected one. Given the pivotal role of attention in motor performance, it's unsurprising that deficits in attention have a more pronounced impact on the affected limb's performance compared to the unaffected one. The latter typically maintains accuracy owing to the preservation of motor patterns, requiring less cognitive load from the patient (Lewthwaite and Wulf, 2017; Song, 2019). Furthermore, when subjects started the FTT with their unaffected limb, they showed higher accuracy in the subsequent task performed with the affected limb compared to subjects who started with the affected one, reaching values near statistical significance ($p=0.06$). This finding shows that, when the motor task is initially performed by the unaffected limb, it better fixes the model to be learned and transferred to the affected one, resulting in higher accuracy compared to when the affected limb performs the task first. The inter-limb transfer is a phenomenon in which a training effect is transferred from a trained limb to an untrained one (Calvert and Carson, 2022) but its rehabilitative implications have only been partially explored. Indeed, few studies have investigated the effect of inter-limb transfer to improve dexterity performance of the paretic upper limb in post-stroke patients (Ausenda and Carnovali, 2011; Ehrensberger et al., 2016). In the clinical setting, training of the impaired limb has been considered an essential component of rehabilitation, based on evidence supporting the importance of use-dependent and repetitive training effects (Corbetta et al., 2015; French et al., 2016). However, the inter-limb effect could represent an excellent therapeutic strategy in patients with severe limb paralysis, making the interest in its application recently growing (Smyth et al., 2023). Notably, we also highlighted that, while hand concordance (whether the affected hand matches the dominant one) doesn't affect on-line performance (i.e., ACC_online), it significantly interacts with randomization order. This suggests that the motor pattern is most effectively executed (and consequently best transferred to the contralateral side)

when initially performed with the unaffected dominant hand. These data support the usefulness of this rehabilitation strategy after the acute stroke timeframe, with interesting consequences from a functional point of view. For example, when a stroke affects the right brain hemisphere in a patient with right-hand dominance (i.e., the most common in the general population), this model suggests that starting the rehabilitation treatment with the dominant (i.e., unaffected) limb in this situation will yield the maximum clinical benefit for the subsequent performance of the affected limb. Figure 4 summarises the hypothesized model of inter-limb transfer based on our results.

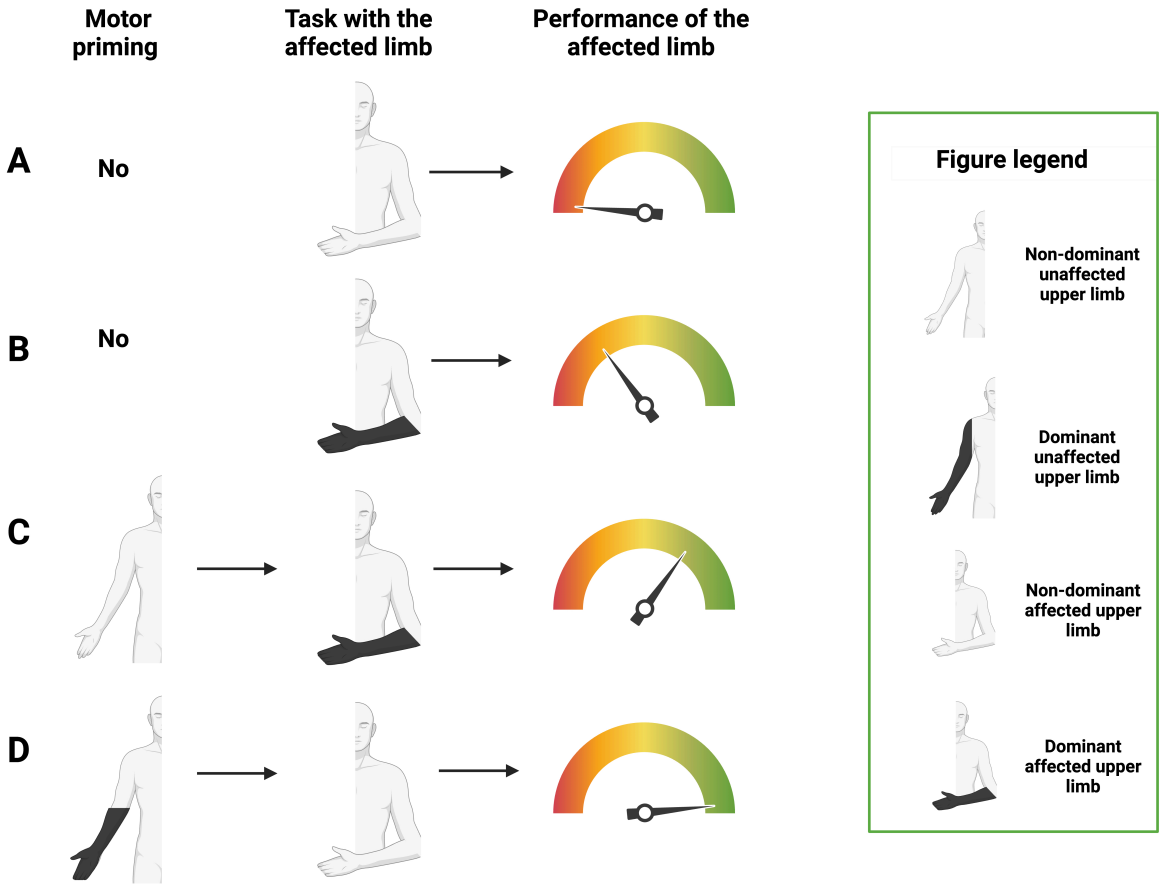


Figure 4. Graphical representation of the hypothesised model of inter-limb transfer in stroke patients. The first column depicts the effect of randomization (i.e., performing the task first with the affected or unaffected limb) and concordance (i.e., whether the dominant hand matches the paretic one) on the performance of the affected upper limb (second column displaying ACC_online). A and B show conditions where the task is performed first with the affected upper limb, resulting in low or moderately low performance depending on whether the paretic hand does not match (A) or matches (B) the dominant one, respectively. Conversely, C and D show conditions where the task is performed first with the unaffected limb, assessing the effects of this motor priming on subsequent performance of the affected limb. Considering the hypothesized inter-limb transfer of learning, the performance of the affected upper limb is moderately high if the unaffected limb does not match the dominant one (C) and high if it matches the dominant one (D). C and D suggest that better performance with the first limb (the unaffected and dominant limb) corresponds to greater motor pattern consolidation and performance of the affected limb. Created with BioRender.com.

About sleep, anxiety, and depression, no relevant correlations were found with the FTT performance, probably due to the complexity and multifactorial nature of these aspects, only partially investigated by questionnaires (Einola and Alvesson, 2021). Additionally, the patients recruited exhibited satisfactory sleep quality and mild levels of depression based on questionnaire scores. Only for the affected limb, we highlighted a correlation between ACC/Seq and anxiety, particularly subjects with a lower level of anxiety, who achieved a better compromise between the accuracy of motor task execution and the number of completed sequences. While both anxiety state and trait might be relevant in this context, the first seems to be more appropriate for understanding its impact on motor learning performance in stroke patients. In fact, a recent study proved that stroke patients with high level of anxiety state were more adversely affected by challenging dual-task conditions (Hejazi-Shirmard et al., 2020). This focus allows for more targeted and effective intervention strategies during rehabilitation and aligns with existing literature suggesting that tasks demanding rapid performance can elevate anxiety levels in subjects, potentially resulting in performance decline (Calvo et al., 1990). Individuals experiencing high levels of anxiety are unable to offset the cognitive deficit induced by their concern, resulting in diminished benefits from practice and reduced learning outcomes. Furthermore, there might exist a bidirectional causality between anxiety and performance, as worries could stem from perceived inadequate performance, subsequently impacting performance further by disrupting attentional focus (Eysenck et al., 1987). Finally, it is conceivable that, among high-anxiety individuals, some exhibit sufficient competencies but show poor performance due to anxiety, while others may exhibit poor, ineffective practice strategies, contributing to their learning or performance deficits and generating anxiety (Naveh-Benjamin et al., 1987).

The present study has some limitations that may affect the interpretation of our results. Firstly, we recorded data from a small sample not homogeneous for several aspects (time since stroke and performance level). However, we merged findings from both stroke patients groups (i.e. subacute and chronic) since evidence suggest that neuroplasticity is most pronounced in the acute and early subacute stroke phases, whereas our subacute patients were primarily between two and three months post-stroke, nearing the conclusion of this interval (Kwakkel et al., 2023) Consistently, subgroup analysis comparing subacute and chronic patients did not reveal statistically significant differences, reinforcing this choice. Secondly, we recruited only subjects with mild to moderate hemiparesis due to motor competencies required for the execution of the FTT, excluding a broad spectrum of stroke survivors with poor motor skills. Thirdly, we performed a single assessment, whereas motor learning paradigms commonly encompass three discrete phases: an acquisition session involving motor skill practice, a maintenance session evaluating skill performance following rest intervals, and a transfer test to assess skill generalization to similar or varied tasks (Maier et al., 2019). However, literature supports our choice of a single assessment as adequate for characterizing motor learning in stroke patients (Fleming et al., 2018). Furthermore, as our study only assessed motor performance and the potential for improvement through practice-dependent learning in the context of a specific task (i.e., the FTT), it cannot provide data on the generalizability of these improvements to other tasks (e.g., the ability to increase autonomy in ADLs). However, it seems reasonable to hypothesize that these patients could leverage these abilities to enhance their performance in various daily activities in which manual dexterity is often crucial (Levin and Demers, 2021). Further studies are needed to evaluate the correlation between improvements in FTT performance and autonomy in daily life. In addition, motor learning is an extremely complex phenomenon affected by numerous factors and variables, which are challenging to control entirely in the clinical setting (Truong et al., 2022). It is also important to note that the discussed inter-limb transfer effect did not reach statistical significance, although

the observed trend approached it closely. Likely, the aforementioned limitations prevented us from achieving significance. Therefore, these implications should be interpreted with caution, and further research will be required to confirm these findings and develop robust models of their clinical practice applications. Finally, a significant number of the recruited patients were inexperienced with computer use, increasing the complexity of the evaluation and exacerbating difficulties and anxiety, with potential negative impact on performance (Hertzum and Hornbæk, 2010).

5.8 Conclusions

Our findings highlighted that, in stroke patients, motor learning of the upper limb is maintained even in the subacute and chronic phases, but is reduced in the affected one. Notably, the preservation of the on-line practice-dependent learning suggests that even patients far from the true recovery phase can acquire effective compensation strategies to improve their motor performance. Among the factors potentially affecting motor learning, only attention and anxiety were confirmed as influencing learning, probably due to their complex and multifactorial nature difficult to capture entirely with simple questionnaires. The inter-limb transfer phenomenon could be a useful strategy for the rehabilitation of stroke patients, even in the chronic timeframe. Considering future applications, it would be interesting to carry out an analysis of neural correlates of FTT in order to observe the brain circuits involved in its modifications during learning. Finally, it might be useful to validate this motor task as an outcome measure in stroke patients, both in research and clinical settings.

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Chapter 6. Time perception in cerebellar and basal ganglia stroke patients

In this chapter, I present a key study from my doctoral research that conceptually expands on the cerebellum's broader role in sensorimotor integration and its interaction with cortical networks. Specifically, this study investigates the cerebellum's role in a key cognitive area: time perception. Temporal processing is essential not only for motor coordination but also for social interaction, predictive coding, and learning. Notably, the scientific literature highlights the key role of the cerebellum and basal ganglia in processing temporal information, likely in a way that depends on the specific time interval and involves critical interactions with important cortical areas, based on the task. However, evidence is still inconclusive in this regard, especially because most findings stem from neurodegenerative conditions, which are characterized by widespread and late progressive damage. Therefore, examining how cerebellar and basal ganglia circuits contribute to time estimation after a stroke could be a useful tool to address these limitations, and also represents a logical extension of the framework presented earlier.

Consistently, this cross-sectional study aimed to characterize the impact of focal lesions in the cerebellum and basal ganglia on the ability to process temporal intervals. We recruited patients with well-defined stroke lesions in these structures and assessed their performance on multiple timing tasks. These findings provide consistent evidence that different subcortical structures each have distinct roles in critical aspects of timing mechanisms, thereby reinforcing the concept of a distributed network responsible for temporal processing. Furthermore, these findings support the idea that the cerebellum not only aids with basic sensorimotor timing but also impacts more complex temporal predictions essential for adaptive behavior.

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6.1 Abstract

The neural mechanisms underlying time perception remain elusive. Although the cerebellum (CE) and basal ganglia (BG) are considered fundamental, evidence primarily stems from studies on neurodegenerative diseases, where progressive and widespread damage complicates linking deficits to specific brain structures. In contrast, brain stroke affects focal areas suddenly, allowing for the assessment of immediate functional consequences. Here, we compared patients with acute stroke in the CE and BG to age-matched healthy controls (HC) on both explicit (time bisection, free and 1-second finger tapping) and implicit (rhythmic, temporal orienting) timing tasks. Concerning explicit timing, both CE and BG patients were faster than HC in their free finger tapping, while BG lesions showed greater variability than HC in the 1-second tapping. Similarly, performance on the bisection task suggested deficits more related to cognitive complaints in stroke than specific temporal dysfunction. In implicit timing tasks, BG patients, like HC, effectively used information provided by the rhythm and the temporal orienting cues to anticipate the target onset, whereas CE patients failed and showed longer reaction times. Therefore, before compensatory mechanisms can take effect, acute CE damage might hinder implicit timing, whereas BG lesions could disrupt explicit temporal representation when processed alongside other cognitive functions.

6.2 Introduction

Time perception is a crucial skill in everyday life and is even more relevant in activities that require fine motor planning and coordination, such as art and agonistic sports (Tanaka et al., 2024). Based on extensive behavioural research, current evidence suggests that time intervals between seconds and minutes are essential in decision-making, while milliseconds are crucial for speech, motor control, and art (Buhusi and Meck, 2005). Reasonably, the temporal processing of intervals longer than approximately one second requires cognitive involvement, whereas shorter intervals are highly perceptual, fast, parallel, and not accessible to cognitive control (Lewis and Miall, 2003; Mioni et al., 2014). In order to better understand the mechanisms by which the brain represents the passage of time, an important distinction between explicit and implicit timing tasks has been identified (Coull and Nobre, 2008). The former refers to tasks in which the participant must explicitly provide an evaluation of temporal duration, e.g. by judging whether one stimulus is longer or shorter than another (“perceptual timing”) or by producing motor acts that have a duration, latency, or periodicity corresponding to those of a given time interval (“motor timing”). Implicit timing tasks, on the other hand, have non-temporal task goals but still require adherence to a precise temporal framework both in terms of inputs (i.e. temporal predictability of the next stimulus) and motor outputs (as a by-product of motor control dynamics) in an unintentional (“exogenous”) or deliberate (“endogenous”) way (Herbst et al., 2022).

However, the neurobiological mechanisms and neurophysiological underpinnings of time perception remain unclear (Koch et al., 2009; Tanaka et al., 2024). Numerous theories and computational models have been formulated to identify the mechanisms accounting for the passage of time in the central nervous system (CNS), with some proposing time as an emergent property linked to the shared operational computations of all neuronal circuits (Hass and Durstewitz, 2014). However, these models often do not consider the possibility of combining temporal perceptions mediated by different sensory modalities (Buonomano and Karmarkar, 2002). Indeed, many studies highlighted that, although many different areas of the CNS are activated during temporal tasks (depending on, for example, the type of stimulus, cognitive load, and time interval), it is very unlikely that

there is absolute decentralization and that each modality-specific circuit contains independent time measurements (Mioni et al., 2020).

Therefore, currently, the prevailing models are population ones, wherein time perception arises as an outcome of the collective activity of extensive populations of dynamically interacting neurons (Zhou and Buonomano, 2022), and several possible frameworks for the mechanism of temporal perception have been hypothesised: the specialised timing model, according to which particular brain regions show the unique ability to represent specific features of temporal data, and the distributed network timing model, which predicts an interaction between vast networks of neuronal groups to mediate temporal perception (Ivry and Spencer, 2004). Although it is difficult to isolate the contribution of individual structures, considering the extensive connections between brain regions and the involvement of cortical areas in some temporal tasks - especially with a higher cognitive load (Koch et al., 2009; Merchant et al., 2013) – a great deal of evidence identifies the basal ganglia and the cerebellum as fundamental regions in time perception (Breska and Ivry, 2016; Spencer and Ivry, 2022; Tanaka et al., 2024).

Specifically, the basal ganglia seem to be involved in time intervals spanning both milliseconds and seconds range, and the dopaminergic circuit, encompassing the substantia nigra pars compacta, striatum, and frontal regions, might be an ideal candidate to perform this activity (Koch et al., 2009; Tanaka et al., 2024). Indeed, the basal ganglia are involved in most explicit timing tasks, both perceptual (Livesey et al., 2007; Pouthas et al., 2005) and motor (Bengtsson et al., 2004; Jantzen et al., 2007) ones, as long as they last at least a few hundred milliseconds (Coull and Nobre, 2008). However, it is worth noting that alternative interpretations suggest an important role even in time intervals greater than one second, particularly when time is processed consciously, highlighting that their functional specialization remains largely unknown, at least in the context of temporal information processing (Koch et al., 2009). Importantly, the administration of dopaminergic drugs or lesions affecting this network can significantly alter time perception (Matell and Meck, 2004). Moreover, Parkinson's disease (PD) patients, characterised by diminished dopamine levels resulting from substantia nigra degeneration, provide a direct means to assess the effects of this alteration and the differences observed following dopaminergic drug administration from a temporal perspective (Magalhães et al., 2018; Miyawaki, 2022). Importantly, PD patients show particularly marked alterations in explicit timing tasks in comparison to implicit timing ones, supporting the involvement of basal ganglia in this specific set of tasks (Mioni et al., 2018). However, the evidence is still often conflicting, reasonably due to different PD phenotypes (e.g. drug therapy, disease stage) (Greenland et al., 2019) and the potential impact of the dopaminergic system on other neural systems beyond the basal ganglia, which could affect performance in specific temporal perception tasks (Mitchell et al., 2018; Speranza et al., 2021). Therefore, it is possible that the widespread dopamine deficit that characterises PD is not ideal for assessing the implications on temporal perception.

Conversely, the cerebellum plays a key role especially when participants have to quickly estimate the passage of short time intervals and when time is processed in relation to specific salient events (Bareš et al., 2019; Ohmae et al., 2017). Indeed, it is fundamental in movement coordination, which implies a substantial temporal component, and its alterations can lead to a loss of temporal organisation of motor sequences (Antonioni et al., 2024). Importantly, patients affected by cerebellar lesions perform continuous movements smoothly, whereas movements requiring precise timing of particular salient events (such as rhythmically tapping fingers) are impaired (Ivry et al., 2002; Spencer et al., 2003). Moreover, cerebellar damage results in increased variability, particularly evident in tasks involving temporal production and the execution of precisely timed

isolated movements (Spencer et al., 2003), along with compromised ability in discriminating durations (Ivry et al., 2002; Nichelli et al., 1996). Thus, it is hypothesised that the cerebellum explicitly encodes the timing of discrete successive events, especially in the millisecond range (Koch et al., 2009), and it is particularly active in the explicit timing of motor, rather than perceptual, tasks (Jahanshahi et al., 2006). Interestingly, however, the cerebellum seems also involved in implicit timing, both in exogenous (Pollok et al., 2008) and endogenous (Sakai et al., 2002) temporal expectations.

Crucially, a recent study on patients affected by PD or cerebellar degeneration demonstrated a double dissociation in temporal tasks, showing that basal ganglia and cerebellum contribute to functionally distinct mechanisms of rhythm- and interval-based temporal prediction for attentional orienting, respectively (Breska and Ivry, 2018). Furthermore, another work by the same group showed that cerebellar degeneration leads to deficits in temporal interval tasks but not in rhythmic ones, emphasising that the functional specificity of the cerebellum for interval-based tasks involves several domains (including the attentional one), especially in the sub-second range (Breska and Ivry, 2021).

However, study models using slow-evolving pathologies (such as PD or cerebellar neurodegeneration) often do not allow changes related to the dysfunction of a system to be assessed on its own, as chronic progression enables the CNS to recruit other regions to mediate the impaired functions, making it difficult to discriminate the roles played by the different involved areas (Draganova et al., 2021; Navntoft and Dreyer, 2016; Sun et al., 2023). Moreover, neurodegenerative diseases, although mainly affecting certain systems, often also damage other CNS districts directly or indirectly, making the interpretation of results much more complex (Barone, 2010; Selvadurai et al., 2018).

Conversely, stroke is characterised by the sudden onset of an often focal neurological deficit that may affect specific brain areas depending on the vascular territory affected by the ischaemic or haemorrhagic damage (Saini et al., 2021). Therefore, excluding cases with massive extensions, it allows the functional consequences of focal damage to be investigated, and it has been used as a study model in numerous conditions (Idesis et al., 2022; Karnath et al., 2018). Indeed, since brain reorganisation processes that restore impaired functions and/or replace them using other areas take several weeks to complete, it is possible to assess the immediate functional consequences of an injury in a specific brain area (Vaidya et al., 2019). Moreover, brain stroke is the second most common cause of death and long-term disability worldwide (Saini et al., 2021) and, among the common deficits that follow cerebrovascular damage, altered time perception is often described (Coelho et al., 2022; Harrington et al., 2004; Mole et al., 2018).

These considerations are particularly relevant given that some studies examined patients with focal lesions in the basal ganglia and cerebellum, providing more precise insights into the roles of these structures in timing tasks. For instance, cerebellar lesions disrupt the precise timing of discrete movements but have less impact on continuous motor tasks, highlighting the cerebellum's critical role in discrete interval-based timing (Spencer et al., 2003). Notably, a functional specialization within the cerebellum itself has been suggested, with lateral regions playing a key role in the precise timing of discrete movements, while medial areas are more involved in the execution of coordinated movement sequences (Ivry et al., 1988). Conversely, patients with unilateral striatal lesions exhibit only minor impairments in force control and, compared to controls, no significant temporal performance alterations, even when using the hand contralateral to the brain damage (Aparicio et al., 2005). This is crucial, as suggested by the authors, in underscoring the need for caution when relying on neurodegenerative disease models to understand the functioning of neural networks. However, it is important

to note that such studies remain scarce in the literature, typically feature small sample sizes, frequently mix different pathological conditions (e.g., tumors, stroke, atrophy), and, most importantly, primarily focus on the chronic phase of the disease. By this stage, network reorganization may have already occurred, making it considerably more challenging to draw definitive conclusions.

Taken together, these findings suggest that stroke, especially in the early stages, represents a valuable model for assessing the functional consequences of damage to crucial areas in the physiological perception of time, i.e., the cerebellum and basal ganglia, and to shed light on the still controversial aspects of time perception. Indeed, although each study model entails specific strengths and limitations, an acute and focal injury of regions most critically involved in the perception of time, without the confounding linked to the involvement of other areas (which occurs at a later time), should allow us to understand the role physiologically played in this context by the cerebellum and basal ganglia and to assess their different contribution in the various temporal tasks (i.e. implicit vs. explicit, sub-second vs. supra-second).

Here, we investigated differences in time perception between acute phase stroke patients with basal ganglia (BG) or cerebellar (CE) lesions and healthy controls (HC), using four well-established paradigms in the framework of time perception research: a time bisection task and a finger tapping task, in order to evaluate the explicit timing; and, a rhythmic task and a temporal orienting task, in order to assess the implicit time processing. This allowed us not only to assess the differences between healthy individuals and acute stroke patients but also to evaluate the functional implications of basal ganglia and cerebellum lesions on different aspects of temporal perception.

6.3 Results

6.3.1 Neuropsychological Assessment

Separate one-way ANOVAs were conducted on performances at neuropsychological tasks in HC, CE, and BG participants. A significant difference was observed in the Rey Auditory Verbal Learning Test (RAVLT; delayed condition) between HC and CE (p = 0.020), indicating that HC were more accurate than CE; moreover, a significant difference was observed in the Rey-Osterrieth complex figure (ROCF; delayed condition) between BG and CE (p = 0.028) indicating that BG were more accurate than CE (Table 1).

Table 1. Descriptive measure of participants included in the study.

	Healthy older adults n=39	**Cerebellar patients** n=12	**Basal ganglia patients** n=18		
	M (SD)	M (SD)	M (SD)	*F*	*p*
Age (years)	64.46 (10.02)	67.67 (16.27)	62.33 (8.26)	0.69	0.512
Level of education (years)	12.33 (3.87)	12.25 (4.24)	11.33 (4.32)	0.35	0.707
Gender (M)	19	8	7		
MMSE	29.04 (0.89)	28.57 (1.51)	29.10 (0.99)	0.33	0.726
FAB	17.13 (1.24)	16.14 (1.77)	17.20 (1.13)	1.01	0.393
Token test	34.67 (1.52)	33.93 (1.17)	33.80 (2.15)	1.47	0.264
RAVLT (immediate)	44.82 (9.45)	37.00 (12.48)	41.22 (9.19)	1.52	0.259
RAVLT (delayed)	**9.36 (3.26)**	**5.71 (2.50)**	**8.67 (3.35)**	**5.44**	**0.019**
BSRT (immediate)	6.25 (1.51)	7.29 (1.81)	5.40 81.92)	1.93	0.190
BSRT (delayed)	6.14 (1.67)	5.77 (1.31)	4.38 (1.80)	3.38	0.077
TMT-a	62.00 (24.50)	69.86 (39.73)	67.00 (24.38)	0.24	0.791
TMT-b	126.20 (43.70)	111.80 (62.33)	149.75 (53.30)	0.80	0.483
Phonemic Verbal Fluency Test	37.49 (12.71)	30.86 (7.92)	37.40 (6.95)	1.86	0.186
ROCF (immediate)	33.13 (3.84)	29.96 (5.96)	34.22 (1.64)	1.95	0.186
ROCF (delayed)	**13.41 (5.79)**	**8.70 (6.73)**	**16.89 (3.04)**	**4.95**	**0.033**

Note: MMSE=Mini Mental State Examination; FAB=Frontal Assessment Battery; RAVLT= Rey Auditory Verbal Learning Test; BSRT= Babcock Story Recall Test; TMT=trial making test; ROCF= Rey-Osterrieth complex figure.

6.3.2 Explicit timing

6.3.2.1 Finger Tapping Task

Free finger tapping: As shown in Table 2 and Figure 1, the results indicated a main effect of Group when data were analysed in terms of mean Inter Tapping Interval (ITI) [$F(2, 39.4) = 7.79$, $p = 0.001$], highlighting that older adults were slower than CE ($p = 0.036$) and BG patients ($p = 0.012$). Moreover, main effect of Group was observed on Coefficient of Variability (CV) [$F(2, 23.4) = 3.61$, $p = 0.043$], however we found no significant differences at post-hoc comparisons.

1-sec finger tapping: The results presented in Table 2 and Figure 1, indicated no effect of Group on ITI ($p = 0.210$). Main effect of Group was observed on Coefficient of Variability (CV) [$F(2, 19.4) = 3.58$, $p = 0.047$]; post-hoc analyses indicated that BG patients were more variable than healthy older adults ($p = 0.001$); we found no significant differences between healthy older adults and CE patients ($p = 0.659$), nor between CE and BG patients ($p = 0.112$) (Table 2).

Table 2. Mean and standard deviation for the finger tapping task as a function of Group.

	Healthy older adults n=39	**Cerebellar patients** n=12	**Basal ganglia patients** n=18		
	M (SD)	M (SD)	M (SD)	*F*	*p*
Free finger tapping (ITI) ms	1197 (1245)	386 (164)	382 (407)	**7.79**	**0.001**
Free finger tapping (CV)	.26 (.28)	.49 (.32)	.51 (.59)	**3.61**	**0.043**
1-sec finger tapping (ITI) ms	1080 (470)	1827 (1616)	977 (358)	1.67	0.210
1-sec finger tapping (CV)	.14 (.04)	.17 (.10)	.25 (.19)	**3.58**	**0.047**

Note: ITI = Inter Tapping Interval; CV = Coefficient of Variability.

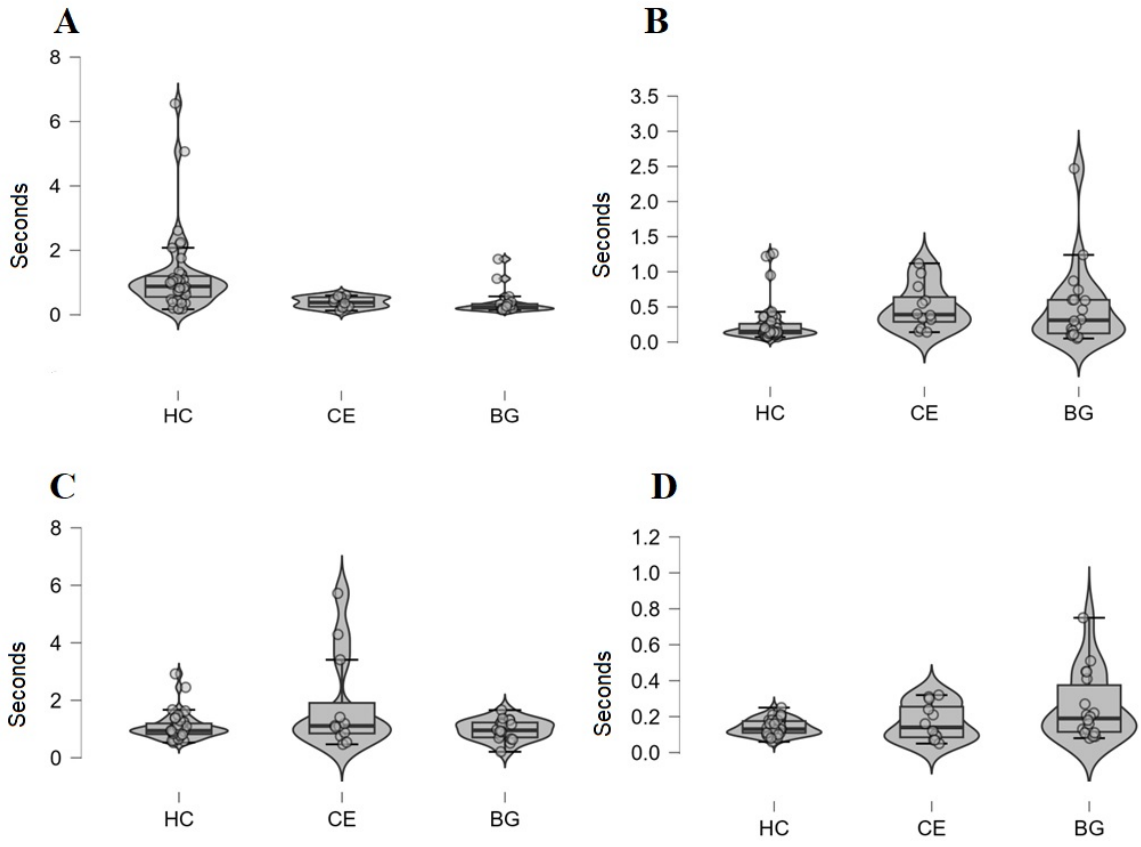


Figure 1. Free finger tapping task: (A) Mean Inter Tapping Interval (ITI) and (B) Coefficient of Variability as a function of Group. 1-sec finger tapping task: (A) Mean Inter Tapping Interval (ITI) and (B) Coefficient of Variability as a function of Group. Each dot represents a participant.

6.3.2.2 Time Bisection Task

Compared to HC, we found no significant differences in terms of accuracy for both the BG (risk ratio = 1.14, p = 0.445) and CE (risk ratio = 0.89, p = 0.513) groups. However, they significantly differed in terms of precision (BG: risk ratio = 0.67, p = 0.016; CE: risk ratio = 0.60, p =0 .005). As shown in Figure 2, both the BG and CE groups exhibited flatter psychometric curves compared to the HC group. To assess differences between BG and CE, we refitted the probit regression with BG as the reference level for the Group factor. Based on these results, we found no significant differences between the two groups in terms of accuracy (risk ratio = 0.78, p = 0.244) or precision (risk ratio = 0.90, p = 0.599).

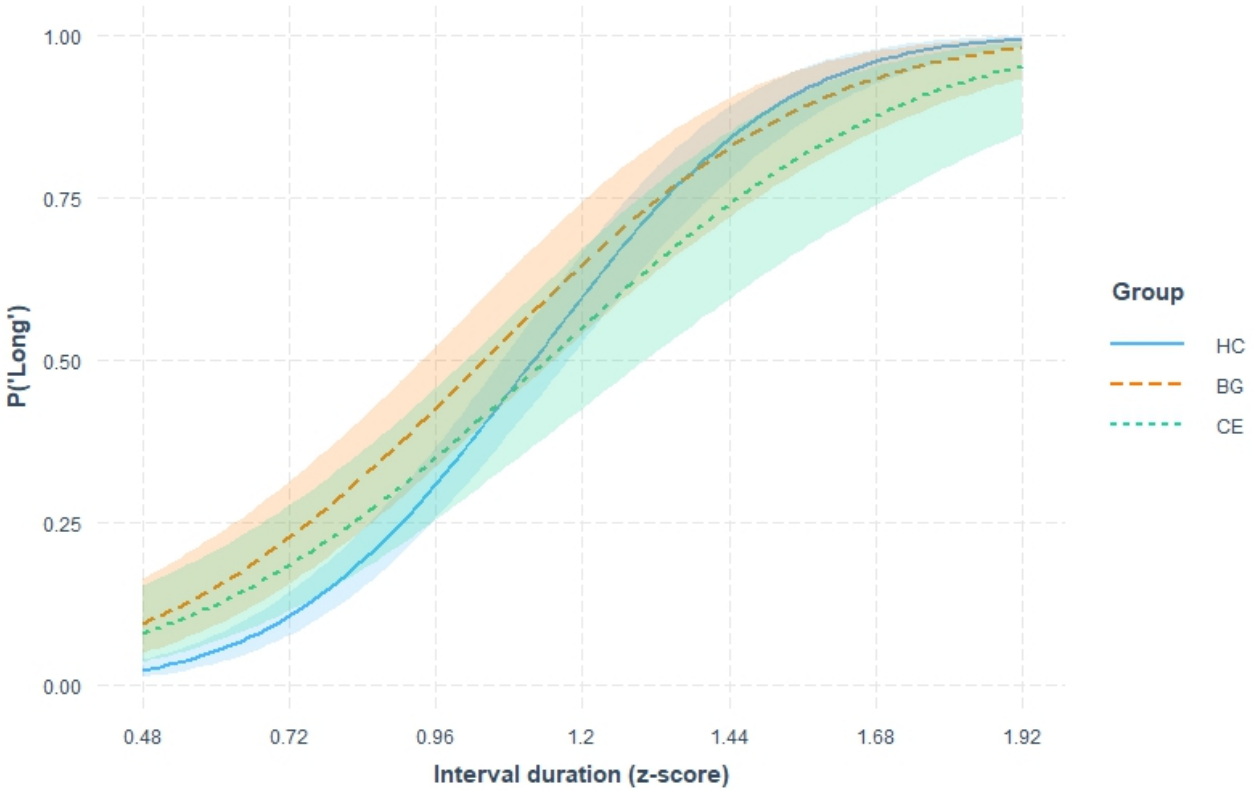


Figure 2. Psychometric curves for time bisection tasks. The figure shows the psychometric curves for the healthy control (HC; blue line), basal ganglia (BG; orange dashed line) and cerebellar (CE; green dotted line) groups. Flatter curves in basal ganglia (BG) and cerebellar (CE) groups indicate reduced precision compared to healthy controls (HC). For illustrative purposes, temporal intervals are reported on x-axes. Shaded error bars indicate 95% confidence intervals.

The probit mixed-effects regression offers information about the intercepts and slopes of psychometric curves. Past studies often focused on two key measures: the bisection point (BP) and just noticeable difference (JND), which reflect temporal discrimination accuracy and precision, respectively. To facilitate comparisons with earlier studies, as in Visalli and colleagues (2024) (Visalli et al., 2024), we fitted a probit mixed-effects regression without Group as a predictor and used the participants' random intercepts and slopes from the model to calculate BPs and JNDs. Table 3 presents the means and standard deviations of BPs and JNDs for each group, and Figure 3 provides a graphical representation of participants' performance. Oneway ANOVA was

conducted on BP and JND. No significant differences were found on BP between groups [$F(2, 64) = 0.25$; $p = 0.443$]; whereas significant differences were found on JND between groups [$F(2, 64) = 0.25$; $p = 0.443$] (BG vs. HC $p = 0.221$; CE vs HC $p = 0.053$; BG vs CE $p = 0.753$).

Table 3. Bisection Points (BPs) and Just Noticeable Differences (JNDs) by Group for the Time bisection task.

	BP		**JND**	
Group	**Mean**	**SD**	**Mean**	**SD**
HC	-0.09	0.39	0.73	0.32
BG	-0.23	0.43	0.91	0.38
CE	-0.07	0.40	1.01	0.46

Notes. HC: Healthy control; BG: basal ganglia; CE: cerebellar; CI: SD: standard deviation.

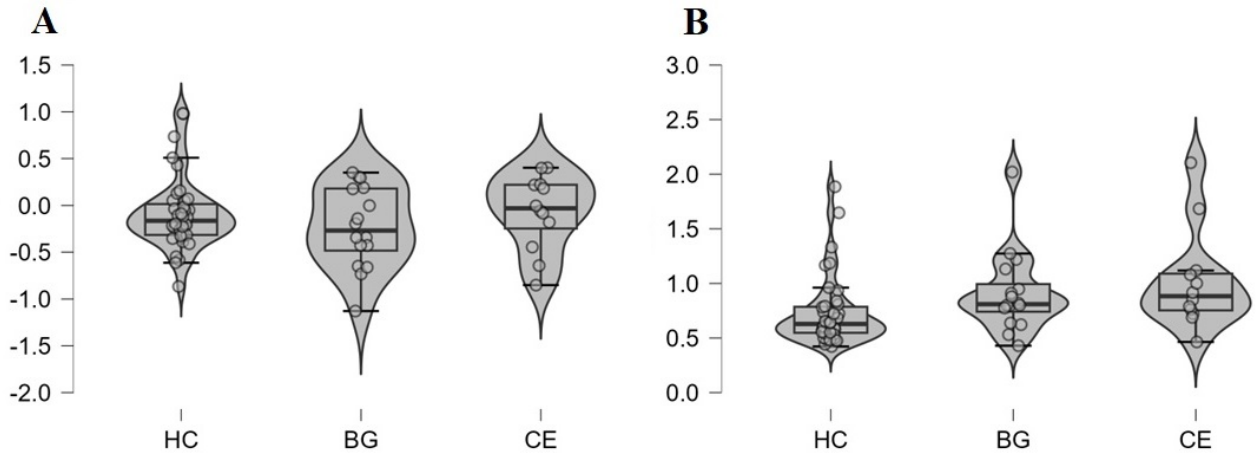


Figure 3. (A) Bisection Point (BP) and (B) Just Noticeable Differences (JNDs) by Group for the Time bisection task. Each dot represents a participant.

6.3.3 Implicit timing

6.3.3.1 Rhythm task

Concerning our effects of interest, we did not find any simple effect for BG (risk ratio = 0.07; $p = 0.671$) and CE (risk ratio = 0.11; $p = 0.564$). Moreover, we found a significant Rhythm effect, indicating an advantage in regular compared to irregular rhythmic sequences for the HC. Finally, concerning the interactions between Group and Rhythm, it was not significant for BG (risk ratio = 0.01; $p = 0.775$), but it was significant for the CE group (risk ratio = 0.14; $p = 0.008$). As shown in Figure 4, while both the HC and BG groups showed shorter

inverse-transformed Reaction Times (iRTs) after regular compared to irregular sequences, differences between regular and irregular sequences were negligible in the CE group.

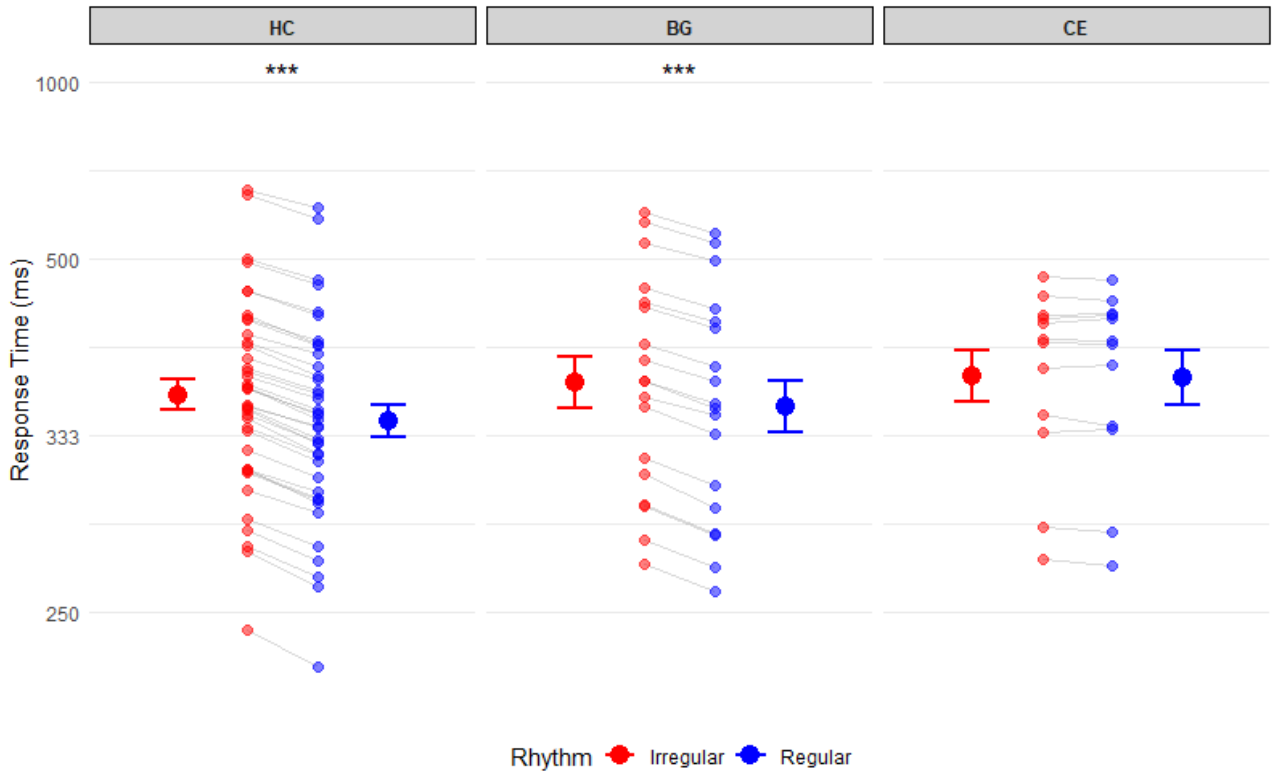


Figure 4. Interaction plot of the effects of Rhythm and Group in the rhythm task. The figure shows the estimated marginal means for the healthy control (HC; left), basal ganglia (BG; middle), and cerebellar (CE; right) groups in irregular (blue) and regular (orange) rhythm conditions. Error bars indicate 95% confidence intervals. The asterisks indicate significant differences between Irregular and Regular rhythms within each group, as determined by pairwise comparisons using estimated marginal means with $p < 0.001$. For illustrative purposes, inverse-transformed reaction times have been rescaled to show response times in milliseconds on the y-axis.

6.3.3.2 Temporal orienting task

The results of the linear mixed-effects regression are presented in Table 4. Concerning our effects of interest, we found a significant interaction between Cue and Stimulus Onset Asynchrony (SOA), indicating the presence of a temporal orienting effect in the HC group. When examining between-group differences, we found no simple or interaction effects for BG (all $p > 0.406$). However, for the CE group, we observed a significant three-way interaction ($p < 0.001$). As shown in Figure 5, while both the HC and BG groups exhibited shorter iRTs for validly-cued short SOAs compared to invalid ones, the CE group displayed longer iRTs for short SOAs, regardless of the cue.

Table 4. Temporal orienting task results (linear mixed-effects regression)

Predictors	**Estimates**	**CI(95%)**	***p***	***Standardized β***
Intercept	-2.00	-2.12 – -1.88	<0.001	-0.10
Trial order	0.00	-0.01 – 0.01	0.707	0.00
Block order	-0.01	-0.02 – -0.00	**0.005**	-0.03
Group (BG)	0.03	-0.19 – 0.25	0.780	0.06
Group (CE)	0.19	-0.07 – 0.45	0.152	0.38
Cue (late)	0.09	0.05 – 0.14	**<0.001**	0.19
SOA (1350 ms)	0.08	0.04 – 0.13	**<0.001**	0.17
Trial × Block	0.00	-0.01 – 0.01	0.450	0.01
Group (BG) × Cue (late)	0.03	-0.06 – 0.12	0.495	0.06
Group (CE) × Cue (late)	-0.07	-0.18 – 0.03	0.180	-0.15
Group (BG) × SOA (1350 ms)	-0.03	-0.11 – 0.04	0.406	-0.06
Group (CE) × SOA (1350 ms)	-0.25	-0.34 – -0.16	**<0.001**	-0.52
Cue (late) × SOA (1350 ms)	-0.14	-0.20 – -0.08	**<0.001**	-0.29
Group (BG) × Cue (late) × SOA (1350 ms)	-0.03	-0.14 – 0.08	0.563	-0.07
Group (CE) × Cue (late) × SOA (1350 ms)	0.25	0.11 – 0.38	**<0.001**	0.50

Notes. BG: basal ganglia; CE: cerebellar; CI: confidence interval; SOA: Stimulus Onset Asynchrony.

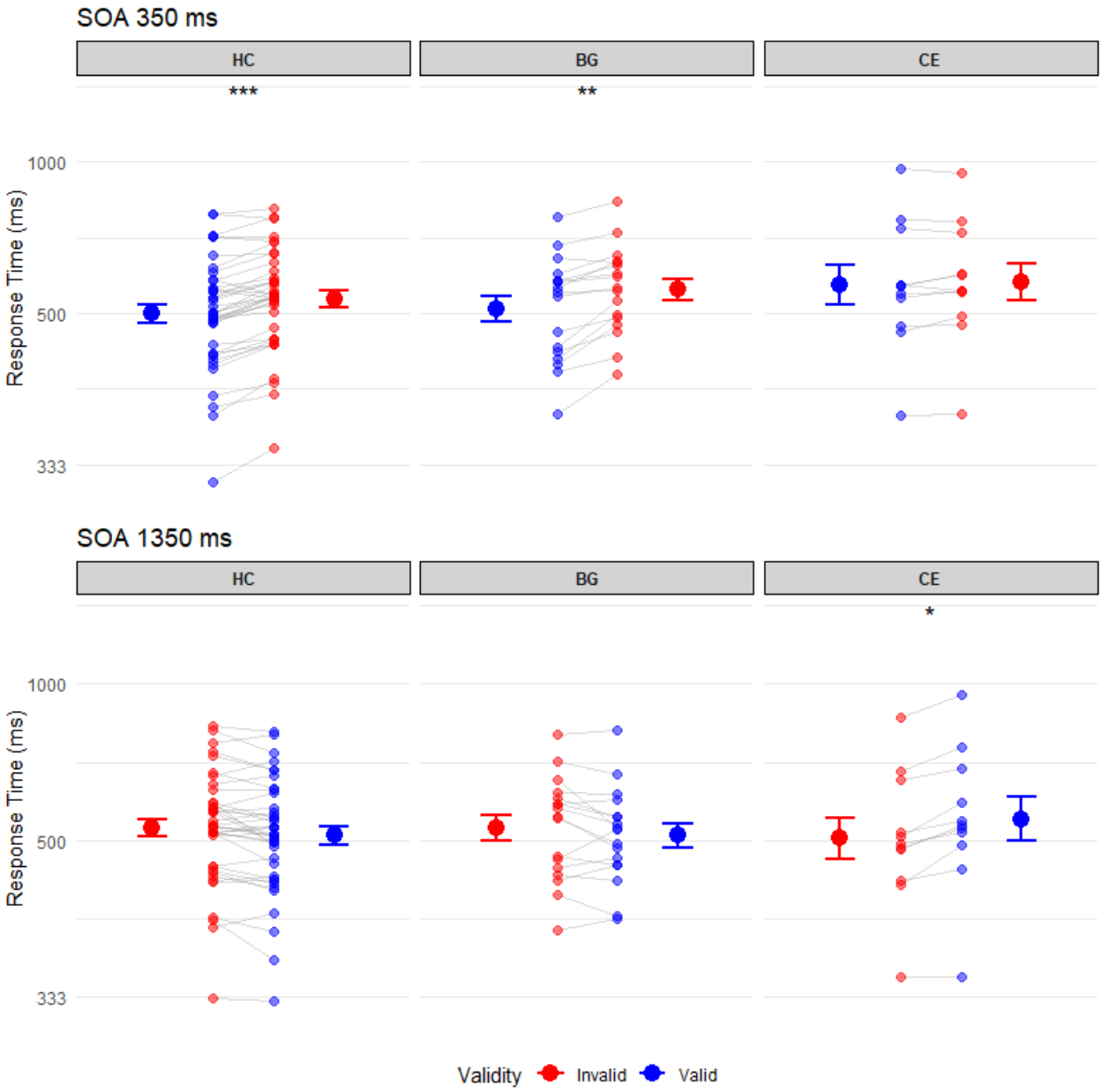


Figure 5. Interaction plot of the effects of Cue, SOA and Group in the temporal orienting task. The figure shows the estimated marginal means for the healthy control (HC; left panel), basal ganglia (BG; middle panel), and cerebellar (CE; right panel) groups in early and late cue conditions for 350 ms (top row) and 1350 ms (bottom row) SOAs. Blue points and lines represent valid trials, while red points and lines represent invalid trials. Large points and error bars indicate group means and 95% confidence intervals, respectively. Small points connected by grey lines represent individual estimates. For illustrative purposes, inverse-transformed reaction times have been rescaled to show response times in milliseconds on the y-axis. The asterisks above panels indicate the significance level of the difference between valid and invalid trials for each group and SOA condition (*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001), based on pairwise comparisons with Tukey's correction for multiple comparisons.

6.4 Discussion and conclusions

Time perception is a fundamental skill in everyday life, but its neurophysiological underpinnings are still largely unknown. Most studies have focused on disorders with widespread, slowly progressing alterations, which allow unaffected regions to compensate for the affected ones (Draganova et al., 2021; Navntoft and Dreyer, 2016; Sun et al., 2023). Consequently, while previous research identified the typical alterations in temporal task performance in pathological contexts such as PD or cerebellar degeneration, it might not be optimal to unambiguously attribute deficits to lesions affecting particular brain areas. Thus, here, we enrolled patients affected by early-stage cerebellar or basal ganglia stroke to assess the immediate consequences on temporal functions. Thereby, we aimed to evaluate their role in timing function and detail their specific contributions to this complex activity.

Importantly, stroke patients performed similarly to HC in neuropsychological evaluations. This allowed us to rule out the possibility that the differences in temporal task performance arose from age-related factors or baseline cognitive conditions. Exceptions were observed in the RAVLT and ROCF (both in the delayed phase) for CE patients, where HC performed better. However, memory performance alterations are a common finding after stroke irrespective of the damaged area, especially in episodic memory, and are at least partly due to the stress and significant emotional impact related to the clinical condition (Al-Qazzaz et al., 2014; Tang et al., 2020). Furthermore, the cerebellum's role in different cognitive functions, especially in complex tasks, even considering its significant connections with the frontal-parietal cortical network, which is pivotal in these activities, might provide a further explanation for these differences (Antonioni et al., 2024). Therefore, to minimise potential confounding factors, only patients able to fully understand and attentively participate were included, with ample practice opportunities and breaks provided as needed.

About the finger tapping task, which assesses the participant's ability to produce motor responses at an arbitrarily chosen or fixed rhythm of 1 second, significant differences were observed in both cases. Specifically, in the free finger tapping, HC tapped significantly slower than stroke patients, while we found no significant differences between CE and BG groups. Importantly, this suggests that the stroke itself, rather than the specific lesion site, leads to the choice of an arbitrarily faster rhythm compared to the preferred one of healthy age-matched participants. This finding may suggest a link between the emotional state of patients and the speed of the internal clock, possibly mediated by the cortical insular region and influenced by anxiety and concern about one's health condition (Craig, 2009). Such a link, consistent with known paradigms of sensorimotor integration, may have accelerated the patients' internal clock, resulting in a preference for a faster motor pattern, although further research is needed to confirm this hypothesis (Schwartze et al., 2011). However, stroke may also lead to a less efficient representation and functioning of internal models linking motor actions to sensory consequences, depending on the specific lesion site. Indeed, both cerebellar and basal ganglia lesions, key regions for generating and optimizing sensorimotor models, may result in a less effective representation of the sensorimotor relationship (Antonioni et al., 2024). This inefficiency could lead to a faster rhythm to increase the granularity of afferent information and provide more frequent updates to the internal models. This is particularly relevant considering recent evidence suggesting that both monosynaptic and disynaptic connections between the cerebellum and basal ganglia may be crucial for internal model updating (Antonioni et al., 2024; Bostan and Strick, 2018). Thus, damage in either structure could correlate with alterations in these functions.

While in the free finger tapping task, each participant chose the rhythm freely, in the 1-sec finger tapping, it was imposed by the experimental conditions. This method ensures greater consistency in the results, as participants were explicitly instructed about the specific rhythm to adopt. In other words, each participant was asked to identify the duration that ideally corresponded to one second and reproduce it during the task. Thus, participants likely held the absolute interval matching the required duration in their working memory (Dutke, 2005). Although none of the participants reported difficulties in performing the tapping itself, while we found no significant differences for CE patients compared to healthy controls, BG patients exhibited greater variability than controls. As mentioned above, although the existing literature is highly heterogeneous, these findings appear consistent with those reported in PD patients, who experience difficulty in rhythm extraction and comparing rhythmic sequences (Grahn and Brett, 2009). Furthermore, our results align with those previously reported by Schwartze et al., demonstrating that patients with focal lesions in the basal ganglia exhibit more heterogeneous individual rhythms and more significant tapping variability, even when synchronizing to an external rhythm rather than generating one internally (Schwartze et al., 2011). These findings support the role of the basal ganglia, as part of the cortico-striato-thalamo-cortical circuit, in temporal processing dependent on attention and interval-based timing (Buhusi and Meck, 2005). Although this function is typically supported by an extensive cortico-subcortical network, the lack of differences between patients and controls in neuropsychological tests assessing executive functions suggests that the alterations observed are primarily attributable to the basal ganglia rather than attentional or working memory differences associated with cortical areas, especially the prefrontal regions (Funahashi and Andreau, 2013). While previous studies have shown that cerebellar lesions can be associated with increased variability in rhythmic pattern execution, depending on the lesion’s location and extent, the stabilizing influence of task repetition may have reduced variability measures, as demonstrated by our results and suggested by other authors (Ivry et al., 2002; Schwartze et al., 2016, 2011).

Regarding the second explicit timing task, namely the time bisection task, our results highlight that patients perform worse than HC without specific differences related to the brain lesion site. In particular, the demonstration of a flattened psychometric curve in both patient groups suggests that this outcome may depend more on purely cognitive aspects rather than alterations of the internal clock functioning. Indeed, if the latter were true, one would expect differences between the two patient groups due to the functional specialization in temporal information processing of these brain regions, namely the cerebellum and basal ganglia (Tanaka et al., 2024). Conversely, the first hypothesis, consistent with our results, seems attributable to a 'noisier' memory representation of the standard interval durations. Indeed, as previously pointed out, patients differed from HC only in memory performance, as is often the case after a stroke (Al-Qazzaz et al., 2014). This is particularly true for CE patients, but even those with BG lesions reported lower scores than HC, although not significantly, on the RAVLT, which critically depends on the integrity of memory functions (Bowler, 2021). Importantly, various pieces of evidence correlated memory abilities with temporal bisection tasks (Capizzi et al., 2022; Kopec and Brody, 2010). Coherently, not only do these functions share anatomical underpinnings, but pacemaker-based models of time perception assign a crucial role to memory in temporal bisection performance (Lustig et al., 2005; Matthews and Meck, 2016; Üstün et al., 2017). This could explain the flattened curve resulting from a poor representation of the duration 'anchors' in memory. Notably, these findings are supported by a recent study demonstrating that explicit timing tasks, such as duration discrimination, are critically dependent on broader cognitive resources across the adult lifespan (Visalli et al., 2024). Indeed, the authors showed that

declines or reduced cognitive efficiency can lead to increased variability in explicit timing tasks, even in the absence of fundamental deficits in time processing. Consistently, the flattened psychometric curve observed in our patient groups could be interpreted as a consequence of such general cognitive challenges rather than a specific impairment in temporal information processing. Importantly, while these factors significantly affect explicit timing tasks, implicit ones appear to be less affected by such impairments (Visalli et al., 2024). This distinction highlights the role of cognitive load in explicit timing, particularly in conditions where neurological dysfunction may exacerbate cognitive inefficiency. Taken together, the results from the explicit timing tasks suggest an apparently limited (or at least not as dominant as expected) role for the basal ganglia, restricted to certain cognitively demanding tasks, and, especially, the cerebellum in this context, although some of the differences discussed earlier suggest that additional factors warrant further investigation. In contrast, the role of these subcortical regions - and the cerebellum in particular - was much more consistent in implicit timing tasks.

Specifically, in the rhythmic task, healthy controls, as expected, effectively used the information provided by the rhythm to prepare the subsequent motor response (Sanabria et al., 2011). However, notably, while BG patients exhibited a faster motor response when the target was preceded by a regular rhythm compared to an irregular one (i.e., they were able to use the preparatory effect provided by the rhythm), CE patients were unable to use this information to prepare the motor response. This finding is, in some respects, unexpected, as previous studies have shown a double dissociation in temporal tasks, specifically showing that basal ganglia regulate the mechanisms of rhythm-based temporal prediction, while the cerebellum those of interval-based prediction (Breska and Ivry, 2018). However, it is important to note that their sample consisted of patients affected by neurodegenerative diseases, leading to the already discussed limitations, i.e., slow progression and widespread damage. Additionally, they employed a different paradigm to assess the performance of the patients in the rhythmic timing. Specifically, while their timing target was entirely predictable - given that they selected intervals between all stimuli identical to the target interval in each trial, ensuring it occurred on-beat within the induced rhythm - our experiment was designed to evaluate both the presentation of a regular and an irregular rhythm within the same session, to assess performance differences based on the type of rhythmic information. Furthermore, notably, this paradigm allowed us to assess participants using a truly exogenous rhythmic task, whereas other approaches might also introduce an endogenous component due to the instructions provided to participants or the way rhythmic information was manipulated (Triviño et al., 2011). These methodological aspects might explain the differences from previous evidence, given that the study populations and task stimuli were different. Moreover, a recent study demonstrated that, even in the domain of speech, patients with cerebellar degeneration were largely insensitive to the speaker's rate and rhythm, whereas those with PD showed a stronger propensity to adapt than the controls (Späth et al., 2022). Consistently, our data suggest that the cerebellum may be critical in regulating the rhythmic aspect of motor behavior when it is based on repeated temporally salient events, which allow for the updating of the sensorimotor representation through each repetition (Del Olmo et al., 2007; Ivry et al., 2002). In contrast, the basal ganglia might be fundamental in shaping the most efficient motor pattern for performing the task through fine regulation of the effectors to be used (via the direct pathway) and inhibition of antagonistic or non-useful ones (via the indirect pathway) (Song et al., 2023). Accordingly, these complementary roles may explain the observed deficits. Indeed, in the case of cerebellar lesions, the inability to process rhythmic information prevents these patients from benefiting from the regular rhythm to facilitate the subsequent motor response.

Conversely, in basal ganglia lesions, the rhythm is still processed at the cerebellar level and provides preparation for the subsequent motor act, though likely with reduced efficiency due to impaired motor pattern optimization (Dhawale et al., 2021). However, as intriguingly suggested, the cerebellum could be dynamically involved in both types of predictions, one based on rhythmic information and the other on remembered temporal associations, depending on the time interval between the events (Terranova et al., 2023).

Finally, the temporal orientation task also revealed a prominent role for the cerebellum in temporal information processing. Indeed, not only HC but also BG patients were able to use the combination of cue and time interval to prepare their motor responses, highlighting that both these groups exhibited a temporal orienting effect. In contrast, CE patients showed longer reaction times, in particular for shorter intervals, regardless of cue validity. Thus, they demonstrated difficulty managing temporal information, especially at shorter durations. These results are consistent with recent findings showing preservation of facilitation of motor responses by temporal orienting in the context of basal ganglia lesions, such as in striatal damage or PD patients (Breska and Ivry, 2018; Mioni et al., 2018; Triviño et al., 2010; Zokaei et al., 2021). In addition, previous research highlighted that deficits in temporal orienting are critically associated with frontal lesions, particularly in the prefrontal areas (Triviño et al., 2011, 2010). These data suggest that the basal ganglia may not play a predominant role in temporal orienting effects, as observed in our study, while the cerebellum might be more relevant in this context. Indeed, given its fundamental connections with frontal cortical networks, the cerebellum might be involved in these activities and support the processing of such information within interconnected brain areas (Antonioni et al., 2024). Furthermore, it is noteworthy that these findings are consistent with recent evidence demonstrating the engagement of the cerebellum in perceptual processing based on temporal expectations (Breska and Ivry, 2021). This might explain the dissociation between CE and BG patients observed in our study as far as the time orientation effect is concerned.

Our study has several limitations. Firstly, the sample size is rather small, imposing caution when generalizing the results. Indeed, including patients in the acute stroke timeframe is complex due to several factors, primarily the clinical management in this serious stage of the disease. Additionally, the presence of symptoms that could potentially affect the correct execution of tasks (e.g., nausea, vomiting, oculomotion disturbances), as well as anxiety and concern for one's health, could limit the willingness to participate in clinical studies. Therefore, considering these relevant issues, although limited, our sample describes the immediate functional consequences of damage in these brain regions from a timing function perspective and, to our knowledge, few studies in the literature have explored these aspects within this study model. Moreover, it is important to note that, at present, the limited sample size precludes the possibility of investigating potential functional contributions specific to each hemisphere. For instance, future studies might explore a potential distinct computational allocation between explicit and implicit timing tasks, as suggested by some evidence in the literature (Coull and Nobre, 2008; Wiener et al., 2010). Another significant limitation is that not all patients underwent high-resolution neuroimaging (i.e., brain magnetic resonance imaging, MRI), with some only receiving a Computerised Tomography (CT) scan, which has lower resolution and consequently less precision in locating the damage. However, in these latter cases, patients generally underwent more than one CT scan, allowing for accurate lesion site identification and the exclusion of potential confounding factors related to artifacts. Another aspect to mention is that, unfortunately, due to the aforementioned neuroimaging limitations and the fact that stroke, although focal, rarely respects precise anatomical boundaries, we treated the cerebellum and basal ganglia as unified structures without considering the functional specialization of

individual regions within them (e.g., caudate, putamen, cerebellar lobules). However, the consistency of observed alterations within groups allows us to suggest that, while further studies are needed to delve into the specific functional contributions of each region, the overall role played by these subcortical structures appears well-defined and characterized. Another aspect we can only hypothesize is that BG patients, while able to benefit from the regular rhythm to prepare the motor response, may not choose the optimal effector pattern due to damage in the structures that maximize the efficiency of motor output. However, the lack of kinematic analysis prevents a definitive interpretation of their motor pattern efficiency, highlighting the need for further studies. Finally, despite the practice phase and the possibility for breaks and clarifications, many of the included patients, especially older ones, were unfamiliar with using computers, which could have heightened their anxiety and affected their performance. However, the presence of this limitation in both the HC and patient groups, along with the simplicity of the tasks, allows us to consider the potential impact of these difficulties as negligible.

Taken together, our findings in early stroke patients suggest that the cerebellum plays a crucial role in implicit timing, while the basal ganglia appear more relevant in processing explicit temporal information, particularly when time is processed alongside other cognitive functions. These results support previous interpretations in the literature, which propose that the cerebellum is primarily involved in processing temporally salient events, whereas the basal ganglia contribute when time is consciously processed in conjunction with other cognitive functions (Grondin, 2019; Koch et al., 2009). This distinction is critical, as it not only confirms prior research highlighting the involvement of these brain regions in temporal tasks but also demonstrates their functional specialization depending on the nature of the task and the associated cognitive demands. By assessing the immediate consequences of damage to these areas, our study demonstrated that the observed deficits were due to the lesions in these regions, excluding the potential compensatory mechanisms that may develop over longer periods. Consistently, prior research on patients with chronic unilateral striatal lesions failed to identify significant deficits in temporal information processing compared to HC, although such studies were often limited by small sample sizes (Aparicio et al., 2005). It is reasonable that, months after the stroke, the basal ganglia in the unaffected hemisphere compensate for the deficit, masking any alterations caused by damage to specific regions. In contrast, our study model—focused on the early phase before compensatory mechanisms can intervene—significantly reduces this possibility. Indeed, we observed differences compared to HC both in explicit (BG patients) and implicit timing tasks (CE patients). Future longitudinal studies in stroke patients will be fundamental to further explore the distinct contributions of the cerebellum and basal ganglia based on the timing of the injury, a critical factor for a deeper understanding of their complex roles in temporal processing. Based on these findings, our data align with the current literature and confirm that both the cerebellum and basal ganglia are critically involved in processing temporal information.

6.5 Materials and methods

6.5.1 Participants

Stroke patients, with brain damages to cerebellum or basal ganglia, were recruited and tested at the Ferrara University Hospital, Ferrara (Italy). Sixteen CE patients (mean level of education = 11.53 years; SD = 4.32; mean age = 65.94 years; SD = 17.32) and twenty BG patients (mean level of education = 11.00 years; SD =

4.58; mean age = 64.17 years; SD = 9.73) were selected. After inspection of MRI and CT scans 4 CE and 2 BG patients were excluded due to the impossibility of reconstructing clear lesion mapping.

The final clinical sample included 12 CE patients (Figure 6A) and 18 BG patients (Figure 6B) were included in the study (Table 1). CE patients were tested 7.33 (SD = 3.98) days (range 2-15 days) after stroke, and BG patients were tested 6.22 (SD = 8.49) days (range 2-36) after stroke. Within the CE group 8 had ischemic stroke and 4 hemorrhagic; while within the BG group 10 had ischemic stroke, 5 hemorrhagic and 3 not specified. Individual brain lesions were manually reconstructed from the patients' brain MRI Fluid Attenuated Inversion Recovery (FLAIR) images (N=6) or CT scans (N=24) using ITK-snap software(Yushkevich et al., 2019). A manual segmentation of each brain slice was performed by the authors (ZR, AA, and EMR). All images were reoriented and then normalized into MNI152 space using RegLSM software, running on Matlab (Biesbroek et al., 2019). Lesion overlays are depicted in Figures 6 A and B.

For BG patients, the maximal overlap (7 patients) occurred in the Putamen (MNI coordinates: X= 27, Y= -9, Z= 8). For the CE group, the maximal overlap (5 patients) occurred in Cerebellum 9 (MNI coordinates: X= -15, Y= -48, Z= -43). Brain regions labelling was based on the Automated Anatomical Labeling (AAL) atlas, present in MRIcron application. AAL template indicates the brain area corresponding to specific MNI coordinates.

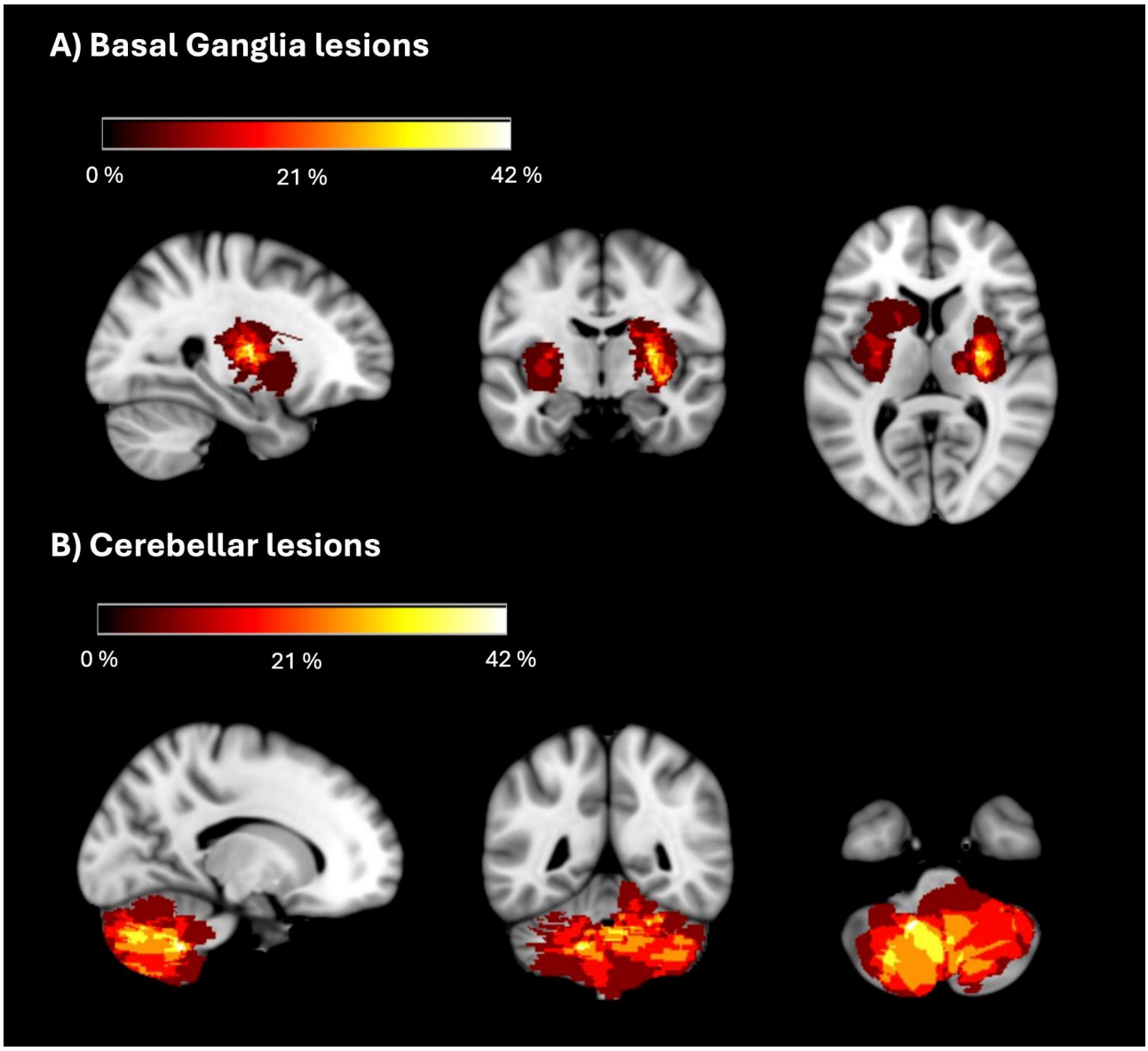


Figure 6. Manual lesion reconstructions of patients with BG (A) and CE (B) lesions. Different color codes indicate the amount of overlapping lesions, from dark red (no overlap/minimal overlap) to white (maximum overlap). Colors represent the percentage of patients with a lesion at a specific voxel.

For all participants, exclusion criteria included: previous hospitalisations for cerebrovascular events, dementia or severe cognitive impairment evaluated with the *Mini-Mental State Examination* (MMSE) (Magni et al., 1996), medications known to interfere with cognitive functioning, psychiatric disorders, upper limbs sensory-motor deficits that could affect the proper execution of tasks, or any condition (e.g., drowsiness, aphasia, apraxia) that would interfere with testing. Participants obtained at least a score equal to or greater than 26/30 at the MMSE (Magni et al., 1996). All participants performed an extensive neuropsychological evaluation to investigate their cognitive abilities (Table 1).

All stroke patients included in the study were right-handed (Oldfield, 1971) and were instructed to perform tasks not requiring the use of both hands (see subsequent sections) with their dominant one. The hand used for task completion was unaffected in 58% of patients in the CE group (including two patients with vermian

lesions, which are distant from areas involved in distal motor control) and in 61% of those in the BG group. Healthy older adults were volunteers from the local community of Padova (Italy).

6.5.2 Methods

6.5.2.1 Explicit timing

Finger tapping tasks

Participants were required to tap the spacebar as regularly as possible at the pace they preferred (spontaneous tempo) or at a 1-sec pace (1-sec tempo) (Perbal et al., 2003). Both conditions consisted of two experimental blocks separated by a voluntary pause period. The beginning of each block was marked by a white cross on a black background presented at the center of the computer screen. The participants began to tap when they first saw the cross, and they continued until it disappeared, which was after 45 inter-tap intervals in each block for a total of 90 trials in each finger tapping task.

Time Bisection Task

The experimental session started with the learning phase in which each participant memorised two standard durations: 480 ms (short standard) and 1920 ms (long standard) (Capizzi et al., 2022). The stimulus used was a dark grey circle on a white background. Both standard durations were presented 10 times in a fixed presentation order. After the learning phase, participants were required to judge the duration of new intervals and determine if they appeared more similar in duration to the short standard or long standard. Participants used their right and left index fingers to respond, and response keys were marked on the keyboard (S = Short and L = Long) after each response, there was a 1000-ms inter-trial interval. Seven comparison durations were used: 480, 720, 960, 1200, 1440, 1680, and 1920 ms. Participants performed two blocks, each duration was presented 6 times in a random order within each block (total of 84 trials). A practice phase was included to familiarise with the task.

6.5.2.2 Implicit timing

Rhythm task

The rhythm task was a visual adaptation of the auditory rhythm task developed by Cutanda et al. (2015) (Cutanda et al., 2015). In this version, participants responded to a green target circle (displayed for 100 ms), which was preceded by a sequence of six red circles (each displayed for 100 ms) presented in either regular (fixed inter-stimulus interval (ISI): 550 ms) or irregular rhythms (random ISIs: 150, 350, 550, 750, and 950 ms). In both conditions, the ISI between the final circle in the sequence and the target was 1100 ms (i.e., twice the ISI used in the regular sequence) (de la Rosa et al., 2012; Lange, 2010). Participants were instructed to press the spacebar upon target onset within a maximum response window of 1100 ms. The experiment included 72 randomized trials (regular and irregular), preceded by two practice trials, one for each condition.

Temporal orienting task

We used a shortened version of the go/no-go temporal orienting task as in Correa et al. (2010) (Correa et al., 2010). Participants were instructed to press the "B" key in response to go targets (the letters "O" or "X", displayed for 100 ms) and to withhold responses for no-go targets (the digit "8"). The onset of the targets was predicted by two temporal cues: either a short red bar (indicating a short foreperiod of 350 ms - early target onset) or a long red bar (indicating a long foreperiod of 1350 ms - late target onset), both displayed for 50 ms.

Participants were explicitly encouraged to use these cues to anticipate the target onset. A maximum of 2000 ms was given to respond.

The experiment began with a practice block of 16 trials (8 “early” trials with short-bar cues followed by 8 “late” trials with long-bar cues), with 100% cue validity (Capizzi et al., 2013). The experimental phase comprised two “early” blocks and two “late” blocks, with 75% cue validity. These blocks were presented alternately and counterbalanced across participants. Each experimental block consisted of 32 trials, 25% of which were no-go trials. Therefore, the composition of the trials within each block was as follows: 18 valid go trials (9 for each foreperiod), 6 valid no-go trials (3 for each foreperiod), 6 invalid go trials (3 for each foreperiod), and 2 invalid no-go trials (1 for each foreperiod).

6.5.3 Neuropsychological Assessment

General cognitive abilities

The MMSE (Italian adaptation (Magni et al., 1996; Measso et al., 1993) for stroke patients, depending on the age of the patients) is commonly used to evaluate the global cognitive functioning of elderly participants. The items are designed to assess orientation in time and space, attention, calculation, memory, language, and constructional apraxia. The maximum score is 30.

The *Frontal Assessment Battery* (FAB, Italian adaptation (Appollonio et al., 2005; Dubois et al., 2000) for stroke patients) is a short cognitive and behavioural six-subtest battery for the bedside screening of global executive dysfunction. It explores specific cognitive or behavioural domains such as conceptualisation, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. FAB's total score ranges from 0 to 18.

Verbal Comprehension

The *Token test* was included to examine auditory comprehension (Spinnler and Tognoni, 1987). The Token test contains 20 plastic token stimuli of two sizes (large and small), two shapes (square/rectangular and round), and five colors. The test has a variable number of sections that increase in sentence length and linguistic complexity (e.g., from “Point to a square” to “Put the small red square on the large blue circle”). Token test total score ranges from 0 to 36.

Memory abilities

The *Rey Auditory Verbal Learning Test* (RAVLT) consists of five consecutive immediate free-recall trials of 15 words pronounced by the examiner (immediate recall condition) and a recall trial after an interference period of 15 minutes (delayed recall condition) (Carlesimo et al., 1996; Rey, 1941). Performance is evaluated in terms of accuracy. Specifically, the number of words correctly recalled is calculated. The maximum score for the immediate part is 75 and for the delayed 15.

The *Babcock Story Recall Test* (BSRT) is a verbal memory measure in which participants are asked to provide immediate and delayed (after 20 minutes) recall of a brief story read by the examiner (Spinnler and Tognoni, 1987). Performance is evaluated in terms of quantity and accuracy of the reported information. Maximum total score is 16 (8 at the immediate + 8 at the delayed part).

Attention

The *Trail-Making Test* (TMT, Italian normative data in (Giovagnoli et al., 1996)) consists of two parts (TMT-A and TMT-B). In Part A, participants are asked to connect 25 numbers in numerical order, whereas in Part B they have to connect 25 encircled numbers and letters in numerical and alphabetical order, alternating between

numbers and letters. Part A is generally intended to test visual search and motor speed skills, whereas Part B is supposed to involve higher-level cognitive skills as well, such as mental flexibility. Performance is evaluated in terms of time (seconds) to complete the test accurately. In the present study, we considered the time to complete Part A and Part B.

Executive functions

Phonemic Verbal Fluency Test: The FAS Test (Italian normative data in (Carlesimo et al., 1996)) measures phonemic verbal fluency. Participants are asked to orally produce as many words as possible that begin with a given alphabetic letter (letters “F”, “A” and “S”) within a prescribed time interval (60 seconds per letter), excluding proper names, numbers and words that begin with the same suffix. This task requires executive control over cognitive processes such as selective attention, mental set shifting, internal response generation, and self-monitoring. The performance score is the total number (sum of the words starting with all the requested letters) of correct words pronounced, repetitions excluded.

Visuo-constructional ability and visual memory

The ROCF was included to evaluate visuospatial constructional ability and visual memory (Caffarra et al., 2002). It consists of two test conditions: Immediate Recall and Delayed Recall. In the first step, subjects are asked to draw the same figure. Subsequently, they are instructed to draw what they remembered.

6.5.4 Procedure

Psychopy (Peirce et al., 2019) and E-prime software (Taylor and Marsh, 2017) were used to program and run the experiments for both the controls and the stroke patients; we used the paper-pen version of the neuropsychological tests for all participants. During the experimental session, controls were seated at a distance of approximately 60 cm in front of a 15-inch PC monitor screen.

Stroke patients were tested during two experimental sessions that lasted approximately 60 minutes. We decided to test patients in two separate sessions, one dedicated to computerised timing tasks and one dedicated to neuropsychological evaluation. The patients performed the computer tests in their hospital rooms, appropriately positioned at the bedside with laptop support or at the table (depending on the clinical condition) so that they could perform the tasks comfortably. The assessments were carried out at times that did not interfere with clinical activities to not compromise the performance of the tasks. They were seated at a distance of approximately 60 cm in front of a 15.6-inch PC monitor screen (HP 255 G9 Laptop). The neuropsychological assessments were carried out in rooms on the in-patient ward or in the neuropsychology section to ensure that the patient was alone with the examiner (i.e. experienced neuropsychologists), comfortably seated with a dedicated bed support or at the table in appropriate conditions for the tests to be carried out correctly and without possible sources of disturbances. Healthy older adults were individually tested in person in their own homes in a quiet and normally illuminated room, and all of them received the same instructions. They were seated approximately 60 cm from the computer screen. Healthy participants were tested in one experimental session, timing tasks were performed first, followed by the neuropsychological evaluation. Participants took breaks if necessary. All participants in both the HC and stroke groups underwent computer testing in the same order, specifically free and 1-second finger tapping task, time bisection, rhythmic task, and temporal orienting. Written informed consent was collected from all participants and the study was conducted in accordance with the Helsinki Declaration (General Assembly of the World Medical Association, 2014). The study was approved

by the ethics committee of the Department of General Psychology (n° 4258) and by the Area Vasta Emilia-Romagna Centro Ethics Committee (AVEC, protocol number CEAVEC 1020/2020/Oss/AOUFe).

6.5.5 Statistical analyses

Finger tapping task

Trials with missing or anticipated responses (RT ≤ 100 ms) were excluded from analyses (mean percentage of excluded trials). Trials excluded: Free finger tapping = 2.69% and 1-sec finger tapping = 0.72% of the total number of trials (6210 trials). Post-hoc analyses were performed with a Tukey correction.

For the finger tapping tasks, the mean inter-response interval (IRI) and the coefficient of variation (CV=SD/mean) were calculated for the free and 1-sec finger tapping tasks. The CV was chosen as a measure of variability. One-way ANOVAs were carried out on each task to examine the differences in mean IRI and CV between patients and controls.

Time Bisection Task

Data from practice trials and trials without a response were rejected from the analysis. The mean percentage of excluded trials was as follows: HC = 4.2% (SD = 5.3%), BG = 4.8% (SD = 4.3), CE = 7.3% (SD = 9.1). Response data were analysed by means of mixed-effects probit regression(Capizzi et al., 2022) using the lme4 R library (Bates et al., 2015). Specifically, the probability of “long” responses was modelled as a function of interval duration (centered and scaled to improve their interpretation and the fit of the model), Group (three-level factor with HC as reference level), and their interaction. The model also included by-participant correlated random intercepts and slopes for the duration. This model provides information about the between-group differences in the intercept and slope of the psychometric curves. In detail, the simple effects for the BG and CE groups indicate differences compared to the HC group in the probability of saying “Long” at the intermediate duration, which is an index of accuracy. Significant interactions between interval duration and each of the BG and CE groups indicate differences compared to the HC group in the shape (slope) of the psychometric curve, which is an index of precision.

Rhythm task

Data from practice trials, trials with premature responses (i.e., before target onset), and trials with anticipated responses (i.e., RT < 150 ms) were excluded from the analysis. The mean percentage of excluded trials was as follows: HC = 2.8% (SD = 4.1%), BG = 11.6% (SD = 13.5), CE = 14.9% (SD = 17.9). Analyses were performed using a mixed-effects linear regression(Bates et al., 2015) on the inverse-transformed RTs (iRT), computed as -1000/RT (Brysbaert and Stevens, 2018) to control for the impact of positive skewness in the distribution of RTs. The fixed-effects part of the model included the factors Group and Rhythm (irregular vs. regular), along with their interaction. Additionally, we included the centered and scaled trial number to account for potential time-on-task effects, such as learning/adaptation or fatigue (Baayen R.H. and Linke M., 2020). Unlike our usual analytical approach for the control of autocorrelation in RT (Capizzi et al., 2022; Visalli et al., 2023), we could not include the response time from the preceding trial due to the need to exclude trials with missing responses at the previous trial, resulting in some patients having less than 30% of analysable trials. The random part of the model also included by-participant correlated random intercepts and slopes for rhythm. Visual inspection of the model residuals was performed to assess normality. Following Baayen and Milin

(Baayen and Milin, 2010), trials with absolute standardized residuals higher than 2.5 SD were considered outliers and removed (2% of the trials). After the removal of outlier trials, the model was refitted achieving reasonable closeness to normality. For the model interpretation, the simple effects for BG and CE groups indicate differences compared to the HC group in iRTs in the irregular rhythm condition, which is taken as an index of general response speed. Significant interactions between rhythm and each of the BG and CE groups indicate differences compared to the HC group in the iRT difference between regular and irregular conditions, which is an index of advantage/cost for regular rhythms.

Temporal orienting task

For the temporal orienting task, the analysis focused only on data from go trials, given the limited number of no-go trials in the invalid condition. Data from practice trials, trials with premature responses (i.e., before target onset), trials with anticipated responses (i.e., RT below 150 ms), and trials without a response were rejected from the analysis. The mean percentage of excluded trials was as follows: HC = 4.2% (SD = 2.0%), BG = 8.8% (SD = 5.3%), CE = 15.2% (SD = 25.5%).

Analyses were performed using a mixed-effects linear regression on the iRT. As effects of interest, the fixed-effects part of the model included the factors Group, Cue (late vs. early), and SOA (350 and 1350 ms), along with their interactions. Since this task was divided into blocks, the centered and scaled trial number within a block, the centered and scaled block number, and their interaction were included to account for potential time-on-task effects. The random part of the model included by-participant correlated random intercepts and slopes for Cue, SOA, and their interaction. Since visual inspection of the model residuals showed that they were skewed, trials with absolute standardized residuals higher than 2.5 SD were considered outliers and removed (2% of the trials). After the removal of outlier trials, the model was refitted achieving reasonable closeness to normality. For the model interpretation, significant three-way interactions between Group, SOA, and Cue are an index of between-group differences in temporal orienting effects.

6.6 References

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Chapter 7. Non-invasive brain stimulation (NIBS)

7.1 A general overview of NIBS techniques

Non-invasive brain stimulation (NIBS) techniques are methods that allow modulation of neuronal populations in the central nervous system (CNS) without surgery or other invasive procedures, such as implants (Polanía et al., 2018). These techniques have experienced significant progress over recent decades and are now considered essential tools in both neuroscientific research and clinical practice (even if to a lesser extent) (Bhattacharya et al., 2022). Interest in their application has increased significantly after numerous findings suggest they can provide important neurophysiological insights with key functional and neurotechnological implications. Specifically, these techniques generally involve two main types of stimulation. Some NIBS protocols primarily use weak electrical currents, known as transcranial electrical stimulation (tES), while others utilize magnetic fields, called transcranial magnetic stimulation (TMS), applied through the scalp to target neural activity in specific brain regions (Antal et al., 2017; Rossi et al., 2022). Although the site of stimulation indicates the brain region directly targeted by the chosen NIBS protocols, it is important to recognize that the effects of these interventions are not confined to the area beneath the electrodes or coil. Indeed, a growing body of evidence has demonstrated that NIBS can modulate activity in distant, yet anatomically and functionally connected brain regions (Mencarelli et al., 2020). This network-based propagation of effects illustrates the integrated architecture of the CNS, where localized disturbances can cause widespread changes through transsynaptic and large-scale connectivity pathways (Breakspear and Stam, 2005). These insights highlight the importance of viewing the brain as a dynamic, distributed system when designing and interpreting neuromodulatory interventions. Furthermore, importantly, the safety profile of NIBS techniques, which are generally well-tolerated and have only minor, transient side effects, has greatly contributed to their increasing use in both research and clinical practice (Antal et al., 2017; Rossi et al., 2021).

Among the various tES methods, transcranial direct current stimulation (tDCS) is one of the most widely studied, also due to its relative ease of use. Consistently, it involves applying a low-intensity, steady current (usually 1–2 mA) through two electrodes: an anode (which generally increases excitability) and a cathode (which typically has an inhibitory effect), positioned according to the targeted stimulation area (Jamil and Nitsche, 2017). This current alters the resting membrane potential of neurons, thereby affecting their firing probability and potentially engaging long-term neuroplastic mechanisms, such as long-term potentiation (LTP) or depression (LTD) (Kronberg et al., 2017). The recognition that stimulation can induce measurable neurobiological modifications has facilitated its application in investigating how cellular and molecular adaptations influence behavior. Indeed, in healthy individuals, tDCS has been explored as a method to enhance motor learning and cognitive performance, with promising results (Buch et al., 2017). Importantly, in clinical settings, it sometimes helps reduce symptoms of various conditions such as depression, Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), and it is also employed to investigate how specific brain regions contribute to disease mechanisms (Bocci et al., 2020b; Hiew et al., 2022; Majdi et al., 2022; Oliveira et al., 2022; Palm et al., 2016). Moreover, due to its ease of use and favorable safety profile, tDCS is increasingly being used for remote or home-based treatments, often under caregiver supervision and remote clinical monitoring, with the goal of reducing healthcare costs and improving access (Antonioni et al., 2024).

Other forms of tES, such as transcranial alternating current stimulation (tACS), deliver sinusoidal currents at specific frequencies to selectively entrain neuronal populations at the stimulation site through a phenomenon known as frequency-dependent resonance or stochastic resonance (Antal and Paulus, 2013). Indeed, each brain region has characteristic intrinsic resonance frequencies that can serve as an important tool to regulate ongoing oscillatory activity states (Hutcheon et al., 2000). By matching the stimulation frequency with the natural oscillatory properties of a neuronal subtype, tACS can synchronize activity across large networks, thereby enhancing phase alignment and boosting collective neural activity (Huang et al., 2021; Riddle and Frohlich, 2021). This provides a potentially powerful tool for selectively targeting specific cell types and adjusting circuit-level computations in a frequency-specific and personalized way. Finally, transcranial random noise stimulation (tRNS), another form of tES, delivers current in a randomly fluctuating pattern and is less well understood, even though it can reasonably enhance neural activity by increasing (at least apparently) causal oscillations that are normally present as spontaneous brain activity (Moret et al., 2019). Notably, some evidence suggests treatment possibilities that are even better than those demonstrated by other forms of tES (Murphy et al., 2020). Further investigation is needed to clarify its mechanisms of action and to determine its therapeutic potential. Figure 1 provides an overview of the stimulation waveforms associated with the different tES protocols.

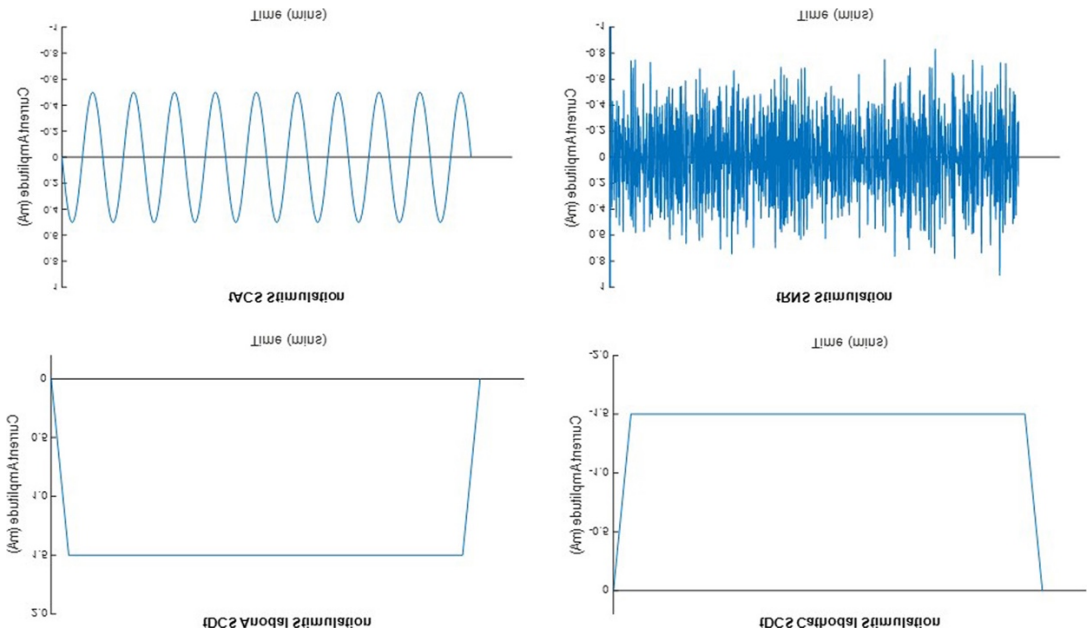


Figure 1. The different waveforms associated with tDCS (anodal and cathodal), tACS, and tRNS, which involve specific modulations of neuronal membrane excitability or neural population-level activity, from (Reed and Cohen Kadosh, 2018).

In addition to these electrical NIBS methods, magnetic-based stimulation has also achieved considerable progress. In its simplest form, TMS relies on Faraday's law of electromagnetic induction: a coil placed on the scalp sends a brief current that generates a perpendicular magnetic field, which passes through the skull and induces an electrical current in the underlying cortical tissue, leading to neuronal depolarization (Sack, 2006).

Single-pulse TMS has been widely used to study corticospinal excitability, especially in the primary motor cortex (M1). Indeed, when applied above the resting motor threshold (RMT), which is the minimum intensity needed to evoke a response with an amplitude of 50 microvolts or more in at least 5 out of 10 trials, it consistently activates pyramidal neurons (Borckardt et al., 2006). These neurons' signals travel through the corticospinal tract to spinal motor neurons, ultimately causing muscle contractions. These responses, recorded through electromyography (EMG), are called motor evoked potentials (MEPs) (Spampinato et al., 2023b). Notably, MEP amplitude and threshold measurements are essential for evaluating motor system function in both healthy people and patients with neurological disorders, offering valuable diagnostic and prognostic information (Karatzetzou et al., 2022; Simpson and Macdonell, 2015; Spampinato et al., 2023b).

Beyond single-pulse paradigms, which are crucial for assessing corticospinal excitability, paired-pulse TMS protocols enable a more detailed examination of excitatory and inhibitory intracortical circuitries. Indeed, short-interval and long-interval intracortical inhibition (SICI and LICI, respectively) assess gamma Aminobutyric acid (GABA)-A (ionophoric) and GABA-B (metabotropic) receptor-mediated pathways, respectively. In contrast, intracortical facilitation (ICF) relates to glutamatergic excitatory activity. These protocols provide fundamental neurophysiological biomarkers of cortical circuit dynamics (Chen, 2004). However, while these protocols usually do not cause long-lasting changes, repetitive TMS (rTMS) protocols aim to produce lasting plastic effects beyond the stimulation session (Jannati et al., 2023). Indeed, depending on the stimulation frequency, rTMS can produce either inhibitory effects (low-frequency stimulation, <1 Hz) or excitatory effects (high-frequency stimulation, >5 Hz), likely reflecting mechanisms similar to LTD and LTP (Sharbafshaaer et al., 2024). This frequency-dependent plasticity has established the basis for therapeutic uses, including in neuropsychiatric and neurodegenerative conditions. Moreover, recent advances have led to more time-efficient rTMS protocols, such as theta-burst stimulation (TBS), which delivers bursts of high-frequency stimuli (in the gamma range) repeated at theta intervals. Of note, intermittent TBS (iTBS) increases cortical excitability, while continuous TBS (cTBS) has an inhibitory effect (Wischnewski and Schutter, 2015). These protocols induce lasting neuroplastic changes and are increasingly utilized in research and clinical settings because of their brevity and effectiveness. Figure 2 shows different patterns of stimulation in various rTMS protocols.

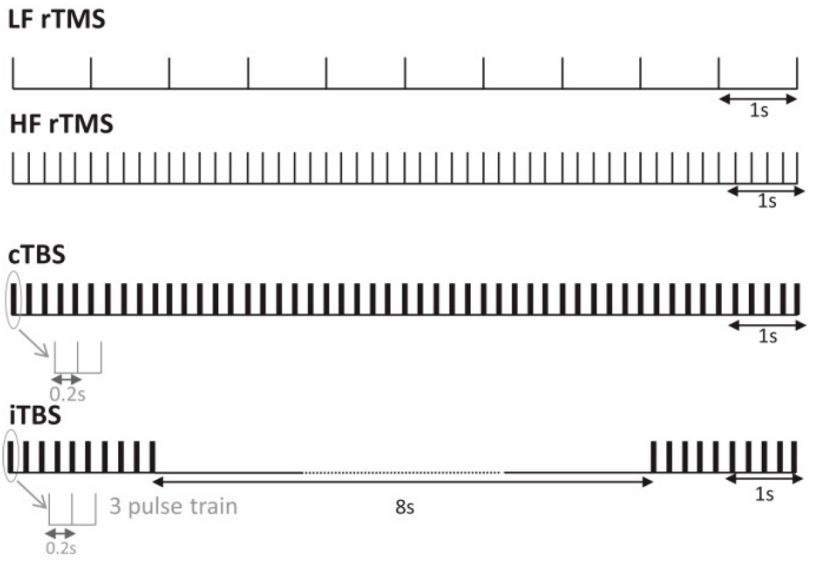


Figure 2. Overview of different rTMS protocols, including low-frequency rTMS (LF rTMS), high-frequency rTMS (HF rTMS), cTBS, and iTBS, adapted from (Tubbs and Vazquez, 2024).

However, it is also fundamental to acknowledge a key limitation of conventional NIBS techniques: their ability to directly affect only superficial cortical areas. Although remote modulation of connected regions via network dynamics is well-established, the ability to directly target and influence deep subcortical structures—such as parts of the basal ganglia or the brainstem—has traditionally been limited to invasive procedures like deep brain stimulation (DBS), which involves surgically implanting electrodes in subcortical regions (Kurz et al., 2019). Importantly, recent advances in non-invasive neuromodulation are starting to challenge this boundary. In particular, transcranial temporal interference stimulation (tTIS), which uses the interference of high-frequency electrical currents, has shown promising potential for reaching and modulating neuronal activity in deep brain structures (Esmaeilpour et al., 2021; Grossman et al., 2017; Violante et al., 2023). This breakthrough opens up promising new pathways for basic neuroscience—by enabling more precise studies of subcortical region functions—and for clinical practice, by offering innovative therapeutic options for disorders traditionally treated only with invasive methods. Therefore, taken together, NIBS techniques constitute a versatile and rapidly evolving toolkit for exploring and influencing the human brain function. Their flexibility, safety, and growing evidence base support their use in both research and clinical settings, from basic studies to practical medical applications.

However, despite these promising premises and the increasing evidence supporting the neurophysiological and functional effectiveness of NIBS techniques, several critical limitations have so far hindered their widespread use beyond the research setting. One of the main challenges is the absence of standardized stimulation protocols (Guerra et al., 2020a). Indeed, currently, methodological choices, including stimulation intensity, duration, number of sessions, and anatomical targets, vary substantially across laboratories. This variability complicates the comparison of results across studies, particularly since even slight changes in stimulation settings can lead to significantly different outcomes. An even greater challenge is the large variability in responses to NIBS protocols both within and between individuals (Guerra et al., 2020a; López-Alonso et al., 2014; Ziemann and Siebner, 2015). It has become clearer that various factors, including age, medications, lifestyle habits, sleep quality, alertness levels, hormonal status, and genetics, can significantly influence how an individual responds to stimulation. Importantly, these factors can affect outcomes not only across different people but also within the same person at different times. This variability makes predicting treatment success reliably difficult and may, at least in part, explain why the effects are often temporary (Goldsworthy et al., 2015). The situation becomes even more complex and unpredictable in pathological conditions, where structural and functional changes may disrupt the neurobiological mechanisms typically engaged by NIBS protocols. Such changes may also disrupt the functional connectivity of the stimulated networks, leading to diminished effects or, in some cases, responses opposite to expectations (Bange et al., 2025; Menardi et al., 2022). Among the most relevant factors thought to influence this variability is the spontaneous fluctuation of neuronal activity within the target areas (Bergmann, 2018). Consistently, brain regions show moment-to-moment fluctuations in their excitability, marked by different levels of depolarization or hyperpolarization (Hordacre et al., 2017). These fluctuations can significantly impact the response to stimulation, such as by saturating the depolarization potential and preventing LTP-like effects from occurring.

Therefore, there is an urgent need for tools that can modulate baseline neuronal activity in target regions to decrease variability and foster optimal network states conducive to the desired effects of stimulation (Guerra

et al., 2020b). In this context—and for reasons that will be discussed further in the upcoming sections of the Thesis—the cerebellum stands out as a particularly compelling and strategic target for neuromodulation.

7.2 Cerebellar non-invasive neuromodulation

7.2.1 Cerebellar neuromodulation in healthy populations

Due to its central role in a wide range of both motor and non-motor functions, the cerebellum is increasingly recognized as a crucial target for NIBS techniques, with growing evidence supporting its ability to modulate a broad range of brain activities (Manto et al., 2022). Indeed, as previously discussed, it maintains extensive reciprocal connections with various cortical networks, thereby supporting numerous sensorimotor and cognitive functions (Habas, 2023). Consistently, although its primary output is inhibitory, the cerebellar microcircuitry supports a much more complex computational architecture, and these dynamics provide the foundation for flexible information processing and adaptive modulation of cerebellar output (D'Angelo et al., 2025). Moreover, crucially, various forms of long-term plasticity, including LTP- and LTD-like effects, have been observed within the cerebellar cortex, driven by distinct molecular mechanisms and involving specific neuronal populations. Such plastic changes are widely regarded as the biological basis of learning-related behavioral adaptations and the neurobiological foundation of neuromodulatory effects associated with NIBS protocols, especially those with long-term outcomes (D'Angelo et al., 2016; Vallence and Ridding, 2014). Indeed, there is growing consensus that the neuromodulatory effects induced by NIBS are closely linked to mechanisms of synaptic plasticity. Importantly, NIBS protocols, by targeting different cellular components, can influence these molecular pathways, thereby shaping both physiological responses and behavioral outcomes. Figure 3 schematically illustrates the various possible long-term plasticity mechanisms that can be identified at the level of individual elements in the cerebellar circuitry with different types of NIBS protocols.

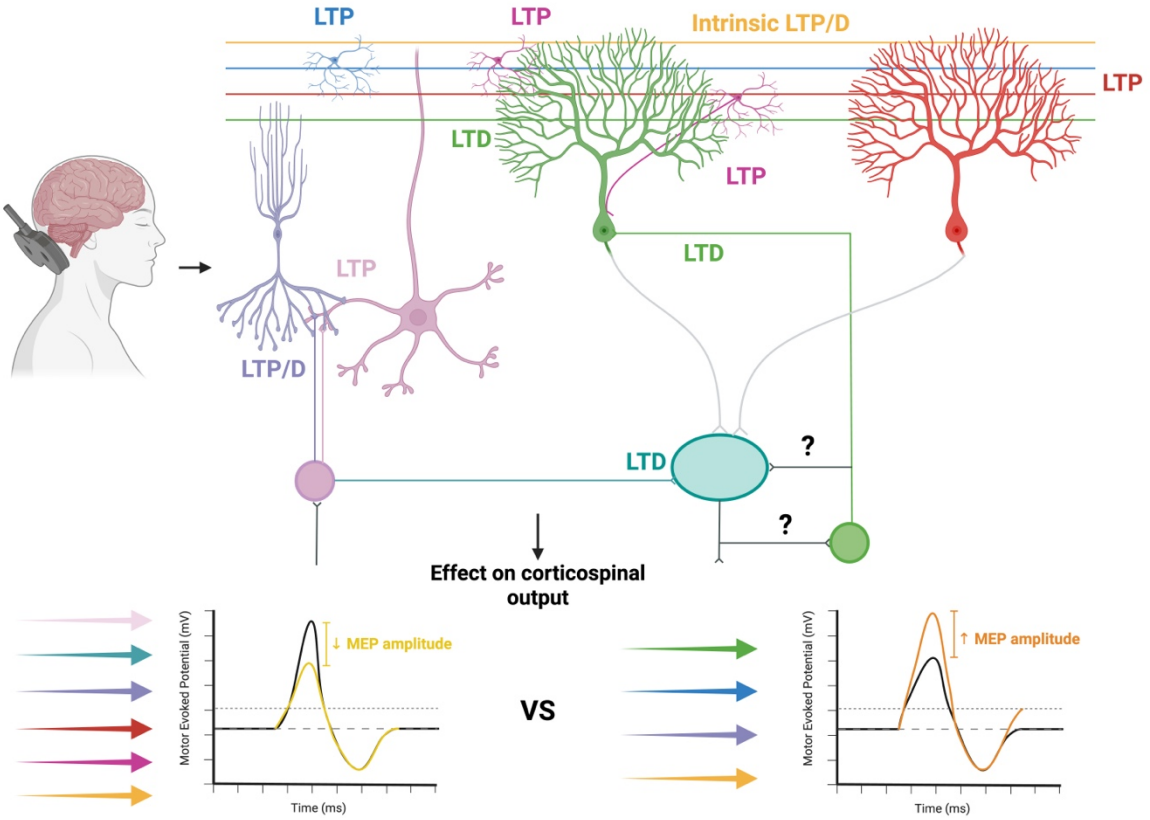


Figure 3. Different types of cerebellar LTP/D can be induced by modulating specific elements of the cerebellar circuitry using various NIBS protocols. Their network-level effects, assessed via MEPs recorded from the primary motor cortex, are illustrated using a color-coding scheme that links each circuit component and the direction of long-term plasticity with the corresponding changes in MEP amplitude. Based on (D'Angelo et al., 2016; Vallence and Ridding, 2014). Created with BioRender.com.

Some of the earliest evidence indicating the potential of using the cerebellum as a neuromodulatory target to affect interconnected brain regions arises from studies employing paired-pulse protocols. Indeed, paradigms involving a conditioning stimulus (CS) over the cerebellum, followed by a test stimulus (TS) to M1 after an inter-stimulus interval reflecting the conduction time between the two regions (i.e., 5–7 ms), typically result in suppressed MEP amplitudes, indicating reduced corticospinal excitability (Ugawa et al., 1997, 1994). These findings suggest a decrease in excitatory input across cortical layers, likely due to thalamic projections being modulated by cerebellar output. Consistently, this effect, now known as cerebellar-brain inhibition (CBI), is typically understood as increased activation of Purkinje cells in response to the CS, which then enhances their inhibitory effect on the deep cerebellar nuclei (DCNs) (Fernandez et al., 2018). This process, in turn, decreases the excitatory influence on the thalamus and subsequently on the motor cortex. In particular, thalamic projections to M1 influence both pyramidal output neurons in layer V and local inhibitory interneurons in layers II and III, potentially resulting in complex, multiscale modulations (Spampinato et al., 2023a). Although these early studies initially focused primarily on motor areas—largely due to the methodological constraints of the time, which often required the use of MEPs as indirect proxies to assess stimulation effects—it is now increasingly recognized that the cerebellum's functional reach extends far beyond the motor domain. Indeed, as previously noted, the cerebellum is anatomically and functionally connected in a topographically organized manner to a wide range of cortical and subcortical networks, including frontal, parietal, and temporal areas (notably the hippocampus), as well as subcortical structures such as the basal ganglia (D'Angelo, 2018; Habas, 2023; Rondi-Reig et al., 2022). This has paved the way for new applications of cerebellar stimulation, focusing on influencing cognitive, emotional, and associative functions beyond its traditional motor roles.

In this regard, tDCS has been widely applied over the cerebellum; however, the results have often been inconsistent in both neurophysiological responses and functional outcomes (Ferrucci et al., 2015; Grimaldi et al., 2016). These discrepancies are likely attributable, at least in part, to the substantial variability in stimulation protocols—including polarity (anodal vs. cathodal), intensity, and duration. Thus, while the overall body of evidence indicates that modulating the membrane excitability of cerebellar neurons can influence activity in connected brain regions, the notable variation in observed effects has prompted the search for more precise strategies. These efforts aim to achieve greater specificity in targeting neural circuits and, ideally, to enhance the stability and duration of stimulation-induced changes. This is of particular interest due to the cerebellum's remarkable cellular diversity and its broad oscillatory range, which extends from low-frequency delta rhythms (<4 Hz) to high-frequency gamma (30–80 Hz) and even ultra-high frequencies (De Zeeuw et al., 2008). Crucially, cerebellar tACS, although not directly inducing long-term synaptic modifications, can nonetheless entrain specific neuronal populations through frequency-dependent resonance effects, thereby enhancing the activities of these populations and, consequently, their effects in computational terms both locally and, notably, on interconnected networks (Ali et al., 2013). When applied to the cerebellum, for example, theta-tACS stimulation (~5 Hz) appears to primarily target granule cells, while gamma-band tACS preferentially influences

the activity of Purkinje cells (Miyaguchi et al., 2020, 2018; Spampinato et al., 2021). These effects range from modulating the corticospinal tract (as assessed with the CBI) to influencing behavioral performance in motor learning tasks, and they are sometimes shown to be phase-specific relative to the ongoing activity of the target neuron populations. This suggests that the overall effects of tACS are shaped by selective engagement of cell types according to their intrinsic frequency profiles, with relevant consequences also on connected brain regions.

While, as already mentioned, tACS does not appear to induce long-term changes but only online modulation of activity, other NIBS protocols that have demonstrated plasticity effects have been applied to the cerebellum with significant results (Hurtado-Puerto et al., 2020). Consistently, TBS, which alternates bursts of gamma-frequency pulses at theta intervals, provides an even more complex form of neuromodulation, possibly coordinating interactions among multiple cerebellar neuronal subtypes (Suppa et al., 2016). Hence, given the cerebellum's ability to oscillate across a wide frequency spectrum, TBS may serve as a powerful tool for precisely shaping cerebellar output over time. Consistently, a seminal study examined the effects of different TBS protocols applied over the lateral cerebellum on corticospinal excitability and intracortical inhibitory circuitry within M1 (Koch et al., 2008). Importantly, cerebellar cTBS reduced MEP amplitude and SICI while increasing LICI. Conversely, cerebellar iTBS raised corticospinal excitability and decreased LICI. These contrasting effects on corticospinal excitability and the specific modulation of intracortical GABAergic activity (both GABA-A and -B) suggest that, even if the cerebellar output is unique (i.e., Purkinje cells), the varied modulation of neuronal populations within the cerebellar circuitry and the induction of opposite neuroplasticity effects shape the cerebellum-thalamus-cortex communication pathway in a way that depends on the protocol used, opening important opportunities for protocol differentiation. To further analyze these effects not only in motor areas but also in connected parietal regions, recent studies have combined cerebellar TMS with EEG recordings to assess TMS-evoked potentials (TEPs), providing high-resolution temporal and spatial insights into cortical network responses (Casula et al., 2016). Focusing on the early components of the TEP, which reasonably reflect GABA-A (15–60 ms) and GABA-B (>100 ms) activity, findings confirmed that cerebellar iTBS decreases LICI and SICI, while cTBS produces the opposite pattern. Importantly, cortical oscillatory analyses also showed that cTBS reduces alpha activity in M1. At the same time, iTBS increases beta rhythms, indicating a different modulation of neural oscillations, which may be mediated by specific effects on inhibitory networks. Taken together, these findings highlight the cerebellum's crucial role in modulating corticospinal excitability, controlling inhibitory intracortical circuits, and regulating cortical brain oscillatory activity, while also demonstrating the far-reaching influence of cerebellar NIBS on distant yet interconnected cortical regions. Therefore, it is not surprising that various studies have aimed to deepen the behavioral correlates of these complex neurophysiological modulations associated with cerebellar NIBS.

Consistently, as previously discussed, the cerebellum holds a key position within the broader neural architecture involved in motor learning (De Zeeuw and Ten Brinke, 2015). Motor learning involves a complex set of neurophysiological processes that enable individuals to acquire new movement patterns or modify existing ones in response to environmental or bodily disturbances (Spampinato and Celnik, 2021). This ability is not only essential for skilled movement execution but also important for flexible adaptation to a constantly changing external environment and, in this regard, the cerebellum plays a vital role. Indeed, it specifically enhances internal models by encoding prediction errors, that is, the difference between the expected and actual sensory results of movement, which then guides corrective motor adjustments (Popa and Ebner, 2019).

This mechanism is essential for motor adaptation, where pre-existing motor commands are quickly recalibrated in response to perturbations like external force fields or visuomotor distortions (e.g., prism adaptation). Animal studies have identified cerebellar LTD at parallel fiber–Purkinje cell synapses as a cellular basis for adaptation, while human research has shown links between cerebellar excitability and adaptation performance (Schlerf et al., 2012; Zeeuw et al., 1998). Intriguingly, distinct nodes within the motor learning network appear to exhibit functional specificity. In visuomotor adaptation tasks, anodal tDCS applied over the cerebellum speeds up error reduction, while stimulation of M1 improves retention of the learned skills mapping (Galea et al., 2011). This indicates a division of work, with the cerebellum handling early error correction and cortical areas focusing on long-term learning (Krakauer and Shadmehr, 2006). Such interpretations are supported by similar findings in tasks involving gait adaptation, where cerebellar tDCS has also been shown to improve performance (Fernandez et al., 2017; Jayaram et al., 2012). Importantly, TBS protocols also show distinct effects: cerebellar iTBS tends to boost adaptation (Koch et al., 2020). At the same time, cTBS impairs it, probably because these protocols differently affect plasticity at the parallel fiber-Purkinje cell synapses or within the feedforward inhibition related to cortical inhibitory interneuron activity. Beyond adaptation, the cerebellum also plays a crucial role in motor skill learning—the gradual process of acquiring completely new movement sequences, which, through repetition, become more automatic, precise, and efficient (Spampinato and Celnik, 2021). Here as well, cerebellar anodal tDCS has been shown to improve performance, decrease error rates, and enhance learning outcomes (Cantarero et al., 2015; Wessel et al., 2016). Notably, many motor tasks involve cognitive processes such as attention, executive control, and strategic planning, which are increasingly recognized as functions critically modulated by the cerebellum (Schmahmann, 2019; Song, 2019). Consistently, numerous NIBS studies, especially those using rTMS and anodal tDCS, have demonstrated that cerebellar stimulation can influence both motor execution and the cognitive aspects involved in motor learning, with performance either improved or impaired depending on the stimulation settings (Ballard et al., 2019; Celnik, 2015; Manto et al., 2022).

These converging lines of evidence establish cerebellar neuromodulation as a promising tool for enhancing both motor and cognitive functions in healthy people. Its use spans various areas, from enhancing motor learning to investigating brain-behavior links, and lays a foundation for relevant clinical applications.

7.2.2 Cerebellar neuromodulation in pathological conditions

As previously discussed, stroke remains one of the leading causes of death and long-term disability worldwide, significantly affecting independence and quality of life (Feigin et al., 2017). Depending on the location and severity of the cerebrovascular lesion, stroke patients often need long-term care or institutionalization. Given this significant burden and the fact that current rehabilitation protocols are generally only partially effective, identifying new strategies to promote recovery and enhance impaired functions remains a primary goal of ongoing research. Importantly, in recent years, increasing evidence has identified the cerebellum as a key player in post-stroke recovery, due to its extensive and topographically organized connections with multiple cortico-subcortical networks, including those involved in motor, cognitive, and associative domains (Habas, 2023; Sadeghihassanabadi et al., 2022).

These extensive connections may be crucial in facilitating the reorganization of disrupted brain networks, especially through their impact on the thalamus, a central regulatory hub of cortical activity (Habas et al., 2019; Luft et al., 2008, p. 200; Rehme et al., 2012). Moreover, importantly, the thalamus not only acts as a relay

center but also plays a critical role in modulating the excitation-inhibition balance within the cerebral cortex, a dynamic that is often significantly disrupted after a cerebrovascular event (Cirillo et al., 2020; Ferguson and Gao, 2018; McCormick et al., 2015; Murphy and Corbett, 2009; Taub et al., 2013). By targeting cerebellar circuits, neuromodulation may help restore this balance and promote functional recovery by boosting the ability of thalamocortical loops to recalibrate and support adaptive plasticity in the post-stroke brain (Wessel and Hummel, 2018). Notably, this aligns with emerging evidence showing that macrostructural cerebellar neuroplasticity correlates with individual differences in motor recovery following stroke (Hanakawa et al., 2023). These findings indicate that the cerebellum plays a vital role not only in brain network compensatory reorganization but also in shaping the degree of functional recovery. In this context, non-invasive neuromodulation techniques that promote long-term plastic changes in cerebellar circuits could provide a promising therapeutic strategy, supporting adaptive reorganization of cortical networks and ultimately enhancing post-stroke rehabilitation outcomes.

Consistently, preclinical animal models have demonstrated that enhancing cerebellar-cortical communication following stroke can facilitate neuroplastic changes and functional improvements (Machado et al., 2013). These findings have been confirmed in human studies using functional neuroimaging, which have shown that greater activation of the contralesional cerebellum is associated with improved gait ability following a stroke (Luft et al., 2005). Crucially, in the first weeks after a stroke, the brain undergoes a period of increased neuroplasticity aimed at promoting structural and functional reorganization, which represents the neurobiological basis of the spontaneous recovery typically observed in the acute and early subacute phases (Kwakkel et al., 2023). Conversely, in patients with chronic stroke, where spontaneous enhanced neuroplastic mechanisms have typically plateaued, adjunctive cerebellar stimulation using tDCS or iTBS has led to significant improvements in balance, gait, and postural control when combined with standard rehabilitation (Hong-yu et al., 2023; Koch et al., 2019; Qurat-ul-ain et al., 2022). These improvements highlight the cerebellum's role in promoting brain network reorganization and motor adaptation by helping patients learn new, simple movement strategies that maximize the use of intact motor pathways. Moreover, importantly, these effects have also been documented in the acute and subacute phases of stroke, suggesting that cerebellar stimulation is not only safe shortly after the cerebrovascular event but also capable of enhancing early recovery mechanisms (Chen et al., 2021; Liao et al., 2021).

While motor impairments are the most common and often persistent effects of stroke, the condition can also lead to various other deficits. These include issues with higher cognitive functions, such as language, as well as attention problems, including hemispatial neglect. Importantly, beyond motor domains, cerebellar neuromodulation has been investigated for post-stroke cognitive and language impairments, such as aphasia, which significantly impact independence and social reintegration (DeMarco et al., 2021; Sebastian et al., 2017). Consistently, the cerebellum—especially the right hemisphere, through its crossed connections with the left cerebral hemisphere—has been linked to the language network, including speech planning, verbal fluency, and syntactic processing (Mariën and Borgatti, 2018). Early clinical studies have shown that cerebellar tDCS can enhance writing, speech production, and verbal fluency in patients with chronic post-stroke aphasia (Kim et al., 2024; Vila-Nova et al., 2019). This is particularly important because, in many stroke cases, cerebellar-cortical connections are at least partly preserved and continue to have extensive communication with motor and parietal regions (Casula et al., 2016; Koch et al., 2019). Therefore, the cerebellum becomes a vital

neuromodulatory target after a stroke, and developing strategies to enhance the effectiveness of these treatments is essential (Q. Liu et al., 2024).

Meanwhile, cerebellar neuromodulation is gaining traction in neuropsychiatric research, given the cerebellum's established role in emotional regulation, executive function, and cognitive flexibility, owing to its extensive connections to the frontal-parietal cortical networks (Schmahmann, 2023, 2019). Consistently, functional and structural imaging studies have implicated cerebellar dysfunction in the pathophysiology of bipolar disorder, major depressive disorder, anxiety disorders, and schizophrenia (Depping et al., 2018; Feng et al., 2022; Lee et al., 2021; Shinn et al., 2017). In line with these findings, combined stimulation protocols targeting the right cerebellum and the contralateral dorsolateral prefrontal cortex have demonstrated improvements in visuospatial memory and executive function in euthymic bipolar patients (Minichino et al., 2015). Similarly, in individuals with treatment-resistant obsessive-compulsive disorder, cerebellar tDCS paired with orbitofrontal stimulation yielded symptom relief when combined with standard pharmacotherapy (Bation et al., 2016). Furthermore, given the alterations in relevant brain networks in schizophrenia and the potential role of the cerebellum in modulating their activity to restore proper function, many NIBS studies have targeted the cerebellum to improve symptoms and quality of life, resulting in promising outcomes for this patient group as well (Hua et al., 2022). Therefore, although current evidence is still limited, these promising findings underscore the cerebellum’s broader role in psychiatric conditions and support the need for further trials.

Notably, cerebellar stimulation has been explored in other neurological diseases with encouraging, though preliminary, results. For instance, in Huntington’s disease, a progressive neurodegenerative disorder affecting the basal ganglia and leading to severe motor deficits, cognitive decline, and, ultimately, death, anodal cerebellar tDCS has been associated with modest motor improvements (Bocci et al., 2020a; Franklin et al., 2021). Similarly, in multiple sclerosis (MS)—a chronic autoimmune demyelinating disease of the CNS—iTBS applied over the cerebellum, when combined with vestibular rehabilitation, improved gait stability and balance control (Tramontano et al., 2020). These results are encouraging, particularly given the multifaceted, multisystem nature of MS, where standard rehabilitation typically yields limited results (Momsen et al., 2022).

Moreover, a particularly compelling application of cerebellar neuromodulation is in managing chronic pain, especially phantom limb pain (PLP). PLP occurs after limb amputation and is thought to result from maladaptive brain plasticity and sensorimotor mismatch (Wu et al., 2025). Several studies have demonstrated that the cerebellum plays a crucial role in pain perception and modulation, particularly by integrating sensory feedback and generating corrective motor responses (Li et al., 2024; Manda et al., 2025). Notably, this supports the hypothesis that PLP results from a mismatch between the predicted sensory outcome of a motor act and the actual sensory feedback, which is disrupted by the loss of the effector responsible for completing the sensorimotor process loop (Vittersø et al., 2022). Since the cerebellum is a crucial center for creating and constantly updating internal models that direct prediction and motor control, its role in the pathophysiology of PLP seems not only plausible but also likely essential (Li et al., 2024; Weiss et al., 2023). Modulating cerebellar activity could thus be a strategic way to recalibrate these predictive mechanisms, potentially reducing the maladaptive plasticity that causes PLP. Indeed, recent research shows that cerebellar NIBS can decrease pain intensity in PLP, likely by restoring cortical balance, updating internal body models, and reducing the discrepancy between predicted and actual sensorimotor functions feedback (Bocci et al., 2019).

Although the evidence supporting the effectiveness of cerebellar NIBS in these clinical contexts is still limited, it remains promising. However, in other pathological conditions, the involvement of the cerebellum is now well

established. In such cases, its role as a neuromodulatory target is not only more clearly defined but also offers significantly broader and more robust therapeutic potential. Specifically, neurodegenerative diseases include a diverse group of progressive disorders characterized by the accumulation of various misfolded proteins, leading to targeted and eventually widespread damage throughout the CNS (Sweeney et al., 2017). Because the cerebellum has extensive connections with many neocortical regions and plays a vital role in both motor and non-motor functions, it is increasingly regarded as an essential target for neuromodulation in these clinical contexts as well. Numerous studies consistently demonstrate that cerebellar stimulation can influence intracortical circuits, particularly in M1, and these physiological effects are often associated with significant clinical improvements. This is especially relevant for conditions like Parkinson's disease (PD), a synucleinopathy characterized by hallmark motor symptoms, including bradykinesia, resting tremor, rigidity, and postural instability (Bloem et al., 2021). In PD patients, CBI is often diminished or absent, regardless of the dopaminergic treatment status (Carrillo et al., 2013; Schirinzi et al., 2016). This suggests that, although PD is primarily recognized as a disorder of the basal ganglia circuit, the cerebellum may play a crucial role in its pathophysiology and is likely especially relevant to the onset and persistence of the tremor characteristic of this condition. Moreover, the specific CBI profile can aid in distinguishing PD from other movement disorders, such as dystonia, emphasizing its potential diagnostic value and supporting the idea that the cerebellum plays a significant role alongside basal ganglia dysfunction (Fernandez et al., 2018; Shirota et al., 2010). Though cerebellar involvement in PD is increasingly evident, its therapeutic potential remains underexplored. Importantly, studies have shown that rTMS targeting the cerebellum can modify M1 interneuronal activity, specifically reducing SICI while increasing LICI, and is associated with a decrease in levodopa-induced dyskinesia (Koch et al., 2009). This suggests that cerebellar neuromodulation may restore physiological inhibitory control in motor circuits and enhance motor regulation, even in advanced disease stages, thereby paving the way for relevant clinical applications. Together, these findings underscore the cerebellum's crucial role in the motor symptoms of neurodegenerative disorders and highlight the potential for targeted treatments. Notably, beyond motor domains, cerebellar NIBS has shown promise in Alzheimer's disease (AD), the leading cause of cognitive decline linked to primary neurodegeneration worldwide. In AD, where cholinergic deficits and impaired sensorimotor integration are key features, cerebellar rTMS has been linked to improvements in overall cognition and domain-specific skills, potentially by enhancing cerebello-cortical functional connectivity (Hampel et al., 2019; Nardone et al., 2008; Yao et al., 2022). Functional studies also demonstrate that cerebellar TBS can influence short-latency afferent inhibition (SAI)—a neurophysiological proxy for cholinergic circuitry activity—emphasizing its potential for mechanistic effects on neurotransmitter systems disrupted in AD (Di Lorenzo et al., 2013). Additionally, changes in SAI are linked to amyloid buildup and memory performance, highlighting its significance as both a biomarker and a therapeutic target (Bonnì et al., 2017; Martorana et al., 2012).

Recent research has also investigated the impact of cerebellar stimulation on specific higher-order functions. For instance, tDCS applied to the right posterolateral cerebellum has been shown to improve verbal fluency and semantic priming, while iTBS protocols have enhanced working memory and language processing in both healthy individuals and those with neurodegenerative diseases (Boehringer et al., 2013; D'Mello et al., 2017; Leggio et al., 2020; M. Liu et al., 2024; Rice et al., 2021). These findings are particularly relevant for cerebellar ataxias associated with dysarthria and deficits in speech motor planning (Schalling and Hartelius, 2013; Spencer and Slocomb, 2007). Consistently, cerebellar neuromodulation has demonstrated beneficial effects

in spinocerebellar ataxias, where motor and speech impairments are particularly pronounced. In these patients, cTBS targeting the right cerebellum improved audio-vocal integration (Lin et al., 2022). Moreover, it is worth noting that a patient with late-onset cerebellar atrophy and characteristic dysarthria showed improvement in both motor and speech performance following low-frequency rTMS over the right cerebellar hemisphere (Farzan et al., 2013). These results match findings in healthy individuals, suggesting that inhibitory cerebellar modulation may decrease maladaptive control or release hypoactive cortical regions from inhibition, depending on the baseline pathology. Meanwhile, studies on patients affected by progressive supranuclear palsy—a tauopathy marked by postural instability and speech issues—have demonstrated that cerebellar iTBS can reduce dysarthria with a selective modulation of CBI, indicating protocol-specific benefits even in tau-related syndromes as well (Armstrong, 2018; Brusa et al., 2014). It is important to note that both inhibitory and excitatory cerebellar stimulation protocols have shown improvements across various conditions, suggesting that disease-specific pathology and network involvement may influence the direction and extent of clinical effects response (Manto et al., 2022). Furthermore, recent hypotheses suggest that NIBS may provide additional benefits through anti-inflammatory effects and homeostatic modulation of thalamic-cortical pathways, thereby aiding a broader restoration of neural network dynamics (Ransohoff, 2016; Straudi et al., 2024; Taub et al., 2013). These complex mechanisms enhance the cerebellum's role as a key hub in coordinating sensorimotor, cognitive, and affective processes, making it a valuable target for intervention.

In conclusion, although more comprehensive clinical trials are necessary to verify efficacy and establish optimal protocols, current evidence indicates that cerebellar NIBS has significant therapeutic potential for various diseases. By modulating abnormal circuits and supporting neuroplastic rebalancing, cerebellar stimulation may offer new methods for improving motor control, cognition, language, and emotional regulation—even in disorders traditionally seen as beyond the reach of restorative treatments. Nevertheless, it is crucial to acknowledge that numerous functions of the cerebellum remain only partially understood, particularly its precise role in fundamental daily abilities such as motor learning and the processing of temporal information. This is particularly relevant in pathological conditions, where these functions are often impaired. Furthermore, a significant challenge is learning how to fully utilize the cerebellum's impressive computational and neuroplastic capabilities. Enhancing comprehension of effective engagement with cerebellar circuitry could potentially enhance neuromodulatory protocols, prolong their benefits, and ultimately promote their incorporation into standard clinical practice.

7.3 References

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Chapter 8. The cerebellum and the Mirror Neuron System: A matter of inhibition? From neurophysiological evidence to neuromodulatory implications

In this Chapter, I provide a thorough literature review of the interaction between the cerebellum and the Mirror Neuron System (MNS)—a topic that, despite its theoretical significance, has remained largely unexplored from an empirical and neurophysiological perspective for a long time. Indeed, while the MNS has been extensively studied for its brain cortical components and behavioral effects, the cerebellum has traditionally been overlooked in this context. However, emerging evidence suggests that the cerebellum may play an important role in controlling the inhibitory balance within MNS circuits, possibly influencing many functions connected to this large brain network. Accordingly, this chapter introduces an innovative framework that conceptualizes the cerebellum not merely as a passive observer but as an active modulator of cortical excitability and inter-regional communication, with particular emphasis on its influence on inhibitory circuits associated with the MNS. This conceptual model may serve as a neurophysiological foundation for a wide range of sensorimotor and cognitive functions, offering a unifying framework for the research questions discussed in the following chapters.

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8.1 Abstract

Mirror neurons show activity during both the execution (AE) and observation of actions (AO). The Mirror Neuron System (MNS) could be involved during motor imagery (MI) as well. Extensive research suggests that the cerebellum is interconnected with the MNS and may be critically involved in its activities. We gathered evidence on the cerebellum's role in MNS functions, both theoretically and experimentally. Evidence shows that the cerebellum plays a major role during AO and MI and that its lesions impair MNS functions likely because, by modulating the activity of cortical inhibitory interneurons with mirror properties, the cerebellum may contribute to visuomotor matching, which is fundamental for shaping mirror properties. Indeed, the cerebellum may strengthen sensory-motor patterns that minimise the discrepancy between predicted and actual outcome, both during AE and AO. Furthermore, through its connections with the hippocampus, the cerebellum might be involved in internal simulations of motor programs during MI. Finally, as cerebellar neuromodulation might improve its impact on MNS activity, we explored its potential neurophysiological and neurorehabilitation implications.

8.2 Introduction

8.2.1 A brief overview of the Mirror Neuron System

In 1992, a group of neuroscientists at the University of Parma identified a new class of visuomotor neurons in the monkey's ventral premotor cortex (specifically, area F5) that discharged both when the animal performed a goal-directed action (i.e. grasping pieces of food) and, of note, when the animal saw another individual performing the same action (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996). The same research group named this particular class of cells “mirror neurons” (MNs) to underscore the motor system's ability to "mirror" observed actions by engaging the same brain areas implicated in action planning and execution. Since this discovery, numerous studies in monkeys have identified neurons with mirror properties (as they “mirror” or reflect the action, i.e. represent both the execution and the observation of the action itself) in other brain areas, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), inferior parietal lobule (IPL) and primary motor area (M1) [for a review, see (Bonini et al., 2022)].

Importantly, the existence of neurons with mirror properties, within crucial nodes of the motor network, has led to speculations regarding their functional significance across the circuit responsible for action planning, programming, and execution, at various levels (Casile, 2013). In addition, three categories of MNs have been identified, namely: strictly congruent (discharging during both the observation and execution of the same action), broadly congruent (active during both the execution of one action and during the observation of another similar but not identical) and logically related (active during the execution and observation of different, but related, actions) (Gallese et al., 1996; Heyes and Catmur, 2022; Kilner and Lemon, 2013). The first two categories were those that mostly attracted research interest; however, the third category above all made it possible to hypothesise that MNs do not merely match observed and performed actions from a motor point of view (e.g. kinematic features) but, rather, that they also encode higher-order aspects of actions, in particular their purpose (Rizzolatti et al., 2014). Moreover, each area provides specific functional contributions. For example, while MNs in the ventral premotor cortex primarily encode the goal of the observed actions (even in cases of incomplete sensory information, as long as the available data are adequate to deduce the intention

behind the observed behaviour), those in the parietal cortex are more sensitive to sensory and kinaesthetic features (Carr et al., 2003; Miall, 2003; Umiltà et al., 2001).

Subsequently, the presence of MNs has also been demonstrated in other species, including birds, rodents, bats and, crucially, humans [see (Bonini et al., 2022)]. The first indirect evidence in humans emerged from a transcranial magnetic stimulation (TMS) study, which highlighted that the observation of actions (AO) increases the excitability of the motor system in an effector-specific fashion, showing a close alignment with the observed pattern (Fadiga et al., 1995). This allowed the authors to suggest the existence of a human system matching AO and execution, a seminal aspect to promote and inspire the extensive research efforts of recent decades in this field. In 2010, their presence was confirmed through a single-cell recording study, which documented neuronal activity during action execution and AO in the human medial frontal cortex and medial temporal cortex (Mukamel et al., 2010). Further research has shown that, in humans, in addition to the homologous areas in the monkey, mirror-like activities are also evident in the inferior frontal gyrus (IFG) and superior temporal sulcus (STS), which are involved in the regulation of language production and the integration of multi-modal information, respectively (Molenberghs et al., 2010). Moreover, a key role in action understanding has also been revealed for the ventral (mainly mediating distal motor actions, irrespective of intrinsic motor features and effectors) and dorsal premotor area, which, together with the superior parietal lobule, encode peripersonal space and guide reaching movements in this context (Cattaneo et al., 2010; Clavagnier et al., 2007). These areas have collectively been referred to as the Mirror Neuron System (MNS) or Action Observation Network (AON), i.e. a neural network that is activated both when individuals perform an action and when they observe someone else performing the same or similar action. It has been hypothesised that MNs are involved in a wide range of functions, including imitation and social learning, empathy and emotion recognition, communication, and theory of mind (i.e. the ability to attribute thoughts and intentions to others also to predict their behaviour) (Keysers and Fadiga, 2008; Rizzolatti, 2005).

Although different, their common aspects suggest that the MNS enables the subject to mentally simulate observed actions, find their correspondence (“direct resonance” or “direct matching”) in their own motor repertoire, and use this knowledge to infer the implications of the behaviour of others, also because of its wide connections with areas involved in planning, value attribution, and emotions (Du et al., 2020; Ferrari et al., 2017). Consistently, many studies suggests that the MNs matching mechanism maps the observed action onto the observer's own motor repertoire, leading to a direct comprehension of the action's goal (Errante and Fogassi, 2020). In other words, MNs process the observed actions by associating them with our representations and are consistently sensitive to the degree of correspondence between the observed action and the observer's motor skills (Fadiga et al., 1995; Gallese et al., 2004). Indeed, observing a movement performed by an artificial hand elicited notably less activity in the MNs compared to human hand movements and, similarly, biomechanically impossible actions do not activate these neurons (Perani et al., 2001; Stevens et al., 2000; Tai et al., 2004). These insights enabled significant improvements in robotics and its applications to neurorehabilitation, a promising and rapidly developing field (Maggio et al., 2021; Zahra et al., 2022). Moreover, the observation of complex movements (e.g. dancing) may recruit regions of the MNS to the extent that the observed action is represented in the subject's personal motor repertoire, i.e. to a greater extent in those who are experienced than those who are not. Specifically, the neural response to AO is shaped by both previous visual exposure and experiential motor engagement, meaning that AO entails matching the observed behaviour to one's motor repertoire beyond mere perceptual matching (Calvo-Merino et al., 2006). This also

suggests that the AON encodes particularly complex action patterns, not just simple component movements (Calvo-Merino et al., 2005). However, it has been suggested that observed actions are segmented into basic motor acts from one's motor repertoire, allowing for motor encoding and immediate forwarding to other structures within the MNS for replication (i.e. for the purpose of imitation, if needed) (Buccino et al., 2004). If, conversely, AO also requires the learning of a novel motor pattern, it entails the recombination of motor actions that have been previously "resonated" (Byrne, 2002; Rizzolatti and Craighero, 2004). Interestingly, neurons with mirror properties have also been shown in the hippocampal regions, and their functional significance is still only partly understood, although an involvement of AO in mnestic processes has been suggested (Calvo-Merino et al., 2005; Mukamel et al., 2010).

Importantly, MNS dysfunction has been highlighted in a number of neurological and psychiatric disorders, which have enabled the exploration of the functional significance of MNs and the evaluation of potential prognostic and therapeutic implications arising from their dysfunction (Farina et al., 2020; Hamilton, 2013; Mehta et al., 2014). Nevertheless, it is worth mentioning that even the most recent research tends to emphasize the role of neocortical regions, often overlooking the potential contribution of subcortical structures, like the cerebellum, to the MNS. Importantly, recent studies deepened cerebellar contribution in cortico-subcortical brain functions in physiology and pathology, such as in the context of motor control [see, for example, the review by (Caligiore et al., 2017b)]. However, the evidence on the influence of the cerebellum on brain areas with a specific focus on its role in the context of the MNS, as well as the neurophysiological and neurorehabilitative implications of cerebellar modulation on MNS activities, is still poorly explored. Therefore, in this review, we aimed to gather evidence, theoretically and experimentally, on the cerebellum's involvement in MNS functions and to discuss the hypothesis that cerebellar modulation on brain areas also depends on its influence on the MNs network. Given the fundamental role of MNs in many essential human activities, we hope to provide a comprehensive overview that enhances the understanding of the neurophysiological mechanisms linking the cerebellum to the MNS in both healthy and pathological contexts and to suggest potential neurorehabilitation and neuromodulation implications for aiding recovery in patients with various neurological conditions.

8.2.2 The human cerebellum: feed-forward internal models, predictive coding, and action selection

The cerebellum houses over half of the neurons of the central nervous system (CNS) (Roostaei et al., 2014). Although early evidence, primarily derived from observations of neurological patients with cerebellar damage, initially hinted at its role primarily in motor functions, particularly in coordinating and sequencing movements smoothly, recent research has unveiled its involvement in a broad spectrum of perceptual and cognitive processes (Manto and Mitoma, 2023). Indeed, anatomically, the cerebellum is segregated into two distinct regions: the anterior cerebellum, which interfaces with the sensory-motor regions of the cerebral cortex and primarily modulates motor functions, and the posterior cerebellum, which projects to an extensive network of frontal-parietal areas crucial for higher-level cognitive functions (Schmahmann, 2019). Moreover, there are two distinct body representations in the cerebellum, one located in the anterior lobe (lobules I-V) and the other in the inferior region of the posterior lobe (primarily lobules VIIb and VIII) (Grodd et al., 2001; Schlerf et al., 2010). Interestingly, the cerebellum shows a uniform modular organisation throughout its extension, characterised by a layer of granule cells, which receive input from both cortical areas (i.e. the mossy fibers) and the inferior olivary nucleus complex (i.e. the climbing fibers) and whose axons, i.e. the parallel fibers, synapse both with

Purkinje cells, which are the only output of the cerebellar cortex, and with inhibitory interneurons (i.e. the stellate and basket cells), which determine a feed-forward inhibition on Purkinje cells (D'Angelo, 2018). The latter are inhibitory cells and, when activated, they reduce the excitatory activity of the deep cerebellar nuclei (DCN), whose excitatory axons reach the other CNS stations. Specifically, the thalamus emerges as a significant target of DCNs (Habas et al., 2019). Furthermore, additional cell types such as Golgi, Lugaro, and unipolar brush cells finely modulate cerebellar activity, contributing to its remarkably refined computational potential (Schilling et al., 2008). Figure 1 schematises the complex circuitry of each cerebellar module, while Table 1 provides an overview of the functional roles of specific cerebellar regions.

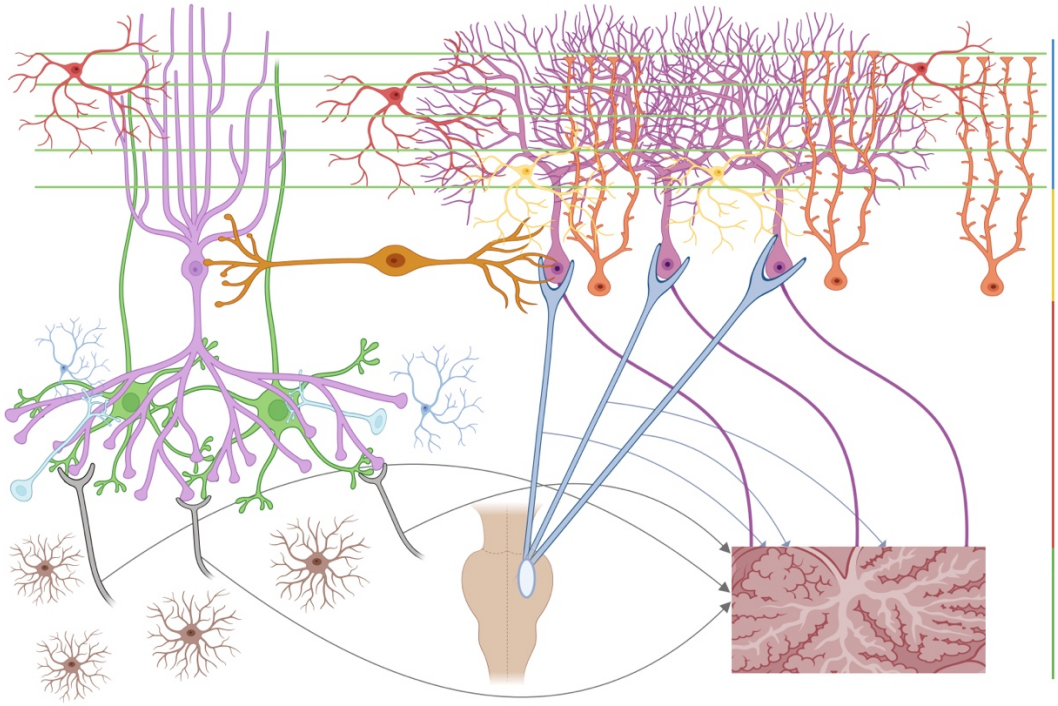


Figure 1. Schematic representation of the complex cerebellar circuitry and its main components. The vertical lines on the right show the subdivision into layers: the molecular layer (blue line), the Purkinje cell layer (yellow line), the granule cell layer (red line), and the layer of white matter fibers and the deep cerebellar nuclei (green line). On the left, examples of cerebellar glomeruli are shown, formed by the synapse between mossy fibers (in gray, originating from pontine nuclei that transmit information from cortical areas and also send a copy of this information to the deep cerebellar nuclei), the Golgi cell axon (violet cell), and the granule cell dendrites (green cell). In the same context, additional modulation is provided by the unipolar brush cells (light blue cells). The axons of the granule cells reach the molecular layer, where they give rise to parallel fibers, providing excitatory input not only to the extensive and branched dendritic arbors of the Purkinje cells (dark pink cells) but also to the inhibitory interneurons that feed-forward inhibit the Purkinje cells. Specifically, the stellate cells (red interneurons) mainly inhibit the apical portions of the Purkinje cell dendrites. In contrast, the basket cells (yellow interneurons) exert control primarily over the basal portion of the dendrites and the cell body of the Purkinje cells, which are located in the layer named after them, along with the soma of the Golgi cells and the Lugaro cells (dark orange cells). The climbing fibers, originating from the inferior olivary nucleus complex, also project 1:1 onto the soma of the Purkinje cells (similarly to the mossy fibers, they project a collateral branch to

the deep nuclei in a topographically specific way). The inhibitory axons of the Purkinje cells represent the only output from the cerebellar cortex and reach the deep cerebellar nuclei, which, in turn, project to numerous targets in the central nervous system mainly via the thalamus. Note that various types of astrocytes in the different layers provide trophic and metabolic support to the complex activities performed, such as brown, blue, and light orange cells. Based on (D'Angelo, 2018; Schmahmann, 2019). Figure created with BioRender.com.

Cerebellar area	Motor role	Cognitive role	Somaesthetic integration
Lobule I-II-III (B)	Verbal fluency	-Active maintenance -**Divided attention**	
Lobule IV	Motor planning (B)	-Interference resolution (L) -Divided attention (R)	**-Left hand presses (L)** **-Right hand presses (R)**
Lobule V	Motor planning (B)	-Interference resolution (L) -Divided attention (R)	**-Left hand presses (L)** **-Right hand presses (R)**
Lobule VI	**Saccades**	- Visual working memory - Visual letter recognition	
Lobule VIIb	Motor planning	-**Action observation** -Divided attention	
Lubule VIIIa	Motor planning	-**Action observation** -Divided attention	
Lobule VIIIb	Motor planning	-**Action observation** -Divided attention	
Lobule IX		-**Narrative (L)** -Language processing (B) -Emotion processing (L) -**Word comprehension (R)**	
Lobule X		-Visual working memory	
Crus I	Verbal fluency (R)	-Active maintenance (B) -**Divided attention (B)** -Mental arithmetic (B) -Visual letter recognition (R) -**Autobiographical recall (R)** -Interference resolution (R)	
Crus II	**Verbal fluency (R)**	-Emotion processing (L) -**Narrative (B)** -Language processing (B) -**Word comprehension (R)**	

Table 1. The functional roles of specific cerebellar regions. In bold the most representative functions. Abbreviations: B: bilaterally; L: left; R: right. Based on (King et al., 2019; Schmahmann, 2019)

Given this ubiquitous organisation across all its regions, it is hypothesised that the distinctive computational functions carried out by the cerebellum stem from its specific afferent and efferent connections. These connections facilitate bidirectional communication with neocortical areas, thereby modulating and facilitating

various brain processes (Argyropoulos et al., 2020; Habas, 2023). Each Purkinje cell receives information from all three medio-lateral zones via long parallel fibers. This input could integrate various sensory modalities, movement feedback, motor cortex commands, and plans from the PFC/premotor cortex, along with perceptual input from the parieto-occipital association cortex encompassing both intra-personal and extra-personal contexts (D'Angelo, 2018; Mugnaini, 1983). Nowadays, among its many functions, it is deemed pivotal in motor learning, specifically in error-based learning, allowing the subject to maintain its accuracy despite changes and perturbations in the environment and in the body itself (Spampinato and Celnik, 2021). Remarkably, the firing pattern of climbing fibers seems to be modulated by motor errors, leading to a selective weakening of synapses between parallel fibers and Purkinje cells engaged in erroneous performance, while reinforcing connections associated with correct executions (Zang and De Schutter, 2019). In particular, the cerebellum is thought to be pivotal in creating internal feed-forward models to minimise the difference between the predicted and the obtained sensory outcomes of a motor act based on the copy of the efference (i.e., the copy of the motor programme to be executed, which is sent to the cerebellum through the cortico-pontine fibres), the current sensory state of the system (based on vestibular and spinal cerebellar afferents), and the sensory feedback sent by the periphery upon movement completion (Ishikawa et al., 2016). It is worth highlighting that, while sensory feedback from the periphery reaches the cerebellum after the action, other inputs enable it to anticipate the likely sensory outcome and, in instances where there are disparities between expected and actual outcomes, the cerebellum implements corrective actions to minimize this difference (Tanaka et al., 2019). In this sense, the cerebellum is crucial in predicting the sensory consequences of motor acts and is critically involved in selecting the most appropriate actions to maintain coherence within the internal model of environmental interactions. More dated findings also attributed a pivotal function to the cerebellum in the inverse model, which, in contrast to the feed-forward model, computes the motor command to achieve the intended changes in the body's state, establishing the link between planned actions or goals and the motor instructions required to achieve them (Ito, 2013; Torricelli et al., 2023; Wolpert et al., 1998).

While the prevailing model of its operation is now considered the feed-forward one, it is evident that the cerebellum plays a crucial role in identifying the actions that align with the desired sensory outcome. Importantly, the MNS can also implement both hypothesised models of motor control. Specifically, the connections from STS to parietal cortex and, further, to MNs in the ventral premotor cortex could represent an inverse model, which converts the visual representation of observed actions into motor plans (Miall, 2003). Conversely, the reverse pathway from MNs in the ventral premotor cortex to parietal areas and, then, to STS could encode a forward model, leading to the conversion of the motor plans back into anticipated visual representations, which are compared with the actually observed visual images (Iacoboni et al., 2001). Thus, these dual streams potentially facilitate action imitation, since observed actions are initially transformed into potential motor commands by the inverse model, and the visual outcomes of these movements are then predicted by the forward model for comparison with reference visual images (Iacoboni et al., 1999). Given the cerebellum's extensive bidirectional connections with nearly all areas crucially implicated in both models, and its receipt of all requisite information to participate in both the inverse and feed-forward models, it seems reasonable that it could contribute to the function of the MNS in this regard (Caligiore et al., 2013; D'Angelo and Casali, 2012; Popa and Ebner, 2022). Indeed, as emphasised by Miall, research exclusively focusing on the involvement of neocortical areas in the MNS fails to acknowledge the significance of internal models produced by the cerebellum, which are arguably crucial in this context, and overlook its capacity to modulate

motor commands through its connections with premotor areas and its reception of sensory input from parieto-temporal regions (Dum and Strick, 2003; Kakei et al., 2019; Miall, 2003). Moreover, importantly, the cerebellum also shows numerous bilateral connections between neocortical areas with mirror properties, another aspect that could support its involvement in these tasks (Dum and Strick, 2003; Errante and Fogassi, 2020; Middleton and Strick, 1997).

Crucially, this cerebellar function has found considerable mathematical support in Active Inference Theory (AIT), which argues that the CNS operates in a Bayesian fashion by updating expectations about the sensory consequences of an action based on contextual information and a priori hypotheses, and adjusting internal models when inconsistencies arise (Pezzulo et al., 2015). Hence, the motor and sensory domains are intertwined, constituting a loop that enables continual refinement of interactions with the environment (Kim, 2021). According to this interpretation, the cerebellum is crucial in constantly updating the internal models and in assisting the selection of the most suitable actions to minimise the disparity between expected and achieved outcomes (Friston et al., 2016). Importantly, within this framework, the MNS might play a pivotal role in implementing Bayes-optimal perception of both self-generated and observed actions, representing the neuronal substrate that enables the simulation and understanding of actions executed by oneself or others (Friston et al., 2011).

Furthermore, it is noteworthy that the involvement of the MNS extends beyond motor functions, as multiple lines of evidence have revealed its participation in the somatosensory domain. Specifically, MNs exhibit activity during sensory perception and when observing another individual performing actions with similar sensory outcomes (Avenanti et al., 2007; Gazzola and Keysers, 2009). In this context, somatosensory areas could support the perception of others and, above all, of their actions, given their connectivity with key motor components of the MNS (Jacquet and Avenanti, 2015; Keysers et al., 2010). Specifically, while motor areas of the MNS may encode the motor features of observed actions, somatosensory areas might process the magnitude of perceived proprioceptive and tactile feedback (McGregor et al., 2016; Valchev et al., 2017). Indeed, arguably, the AON also entails simulations of the anticipated somatosensory outcomes during AO, integrating somatosensory and motor representations and supporting the current perspectives on the sensorimotor nature of the motor system (Gallivan and Culham, 2015; Valchev et al., 2016). Consistently, studies have highlighted that the somatosensory outcomes of AO impact activation within AON (Morrison et al., 2013). Thus, the MNS allows for the internal simulation of motor actions and the perceptual aspects of experiences. It could, therefore, represent the substrate for mental simulation and evaluation of implications in different components of the sensorimotor loop.

Since the MNS predicts the motor and sensory consequences of observed actions, it is reasonable to assume that the cerebellum collaborates closely with the cortical regions of the AON to achieve this purpose (Maranesi et al., 2014; Sokolov et al., 2017; Thach et al., 1992). Consistently, beyond its well-established role in the motor network, significant cerebellar activation on the sensory side has also been demonstrated, as it receives input from virtually all sensory systems, is activated by tactile stimulation without movement, and the dentate nucleus is closely related to sensory acquisition and discrimination tasks (Fox et al., 1985; Gao et al., 1996; Tanaka et al., 2021). Furthermore, the cerebellum is also critically involved in the so-called “principle of reafference”, which enables the subject to differentiate sensory consequences stemming from external events from those related to the subject's movements, likely due to the contribution of the efference copy (i.e. a strict

spatiotemporal contingency between the motor command and sensory outcome), which is crucial in the internal simulation processes of observed actions (Blakemore et al., 1999; Lindner et al., 2006).

To summarise, a cerebellar forward model could employ an efferent copy of motor commands from M1 and the premotor areas to facilitate somatosensory and/or visuomotor adjustments to the motor representation stored in the parietal areas (Allen et al., 2005; Picazio et al., 2016; Pisotta and Molinari, 2014; Welniarz et al., 2021). Thus, the cerebellum, together with the posterior parietal cortex, could be the crossroads between the motor and sensory systems, in order to process the implications of AO and support the AON in this complex process (Gazzola and Keysers, 2009). This interpretative model could elucidate the observation that AO does not invariably result in imitation, reasonably due to the involvement of a motor inhibitory mechanism where connections between the cerebellum and PFC might be pivotal, as demonstrated by imitative behaviours in patients with lesions affecting both these regions, as cerebellar lesions could manifest "frontal-like" symptoms (Botez-Marquard and Botez, 1993; Mandolesi et al., 2001; Picazio et al., 2020; Schmahmann, 2023). Importantly, the complex interplay among various regions of the AON may account for diverse levels of encoding of AO, ranging from fundamental representations to those invariants regarding trajectory and, ultimately, to those indifferent to the effector employed (Wolpert et al., 2003). Taken together, these findings imply that AO involves a complex interplay of factors, often recently identified, and further studies are needed to deepen their implications (Kemmerer, 2021). While basic action characteristics, such as kinematics, influence AO in a bottom-up manner, top-down factors like purpose and semantics, shaped by interactions between the cerebellum and neocortex, refine strategies aimed at ultimately imitating observed behaviours (De Marco et al., 2020; Errante and Fogassi, 2019; Li and Mrsic-Flogel, 2020; Xu et al., 2023). Indeed, learning by imitation is not a mere copying of AO, but rather a transformation into an action as similar as possible in terms of the goal and the motor strategies (Torriero et al., 2007). Consistently, the observer's motor system is not merely triggered by visual aspects of AO, but also aids in filling in gaps, providing an implicit understanding of others' actions. Therefore, essentially, the MNS may have the ability to anticipate action outcomes and select the best response to the observed behaviour (Caggiano et al., 2011; Craighero et al., 2008).

Here, evidence on cerebellar activity in the context of tasks involving the AON, i.e. AO and motor imagery (MI), will be analysed.

8.3 The cerebellum and AO in healthy subjects

AO is crucial in everyday life, as it not only allows one to perform numerous common actions but also to improve social interactions by interpreting other body signals to understand emotional states and intentions (Blake and Shiffrar, 2007; de Gelder, 2006). Moreover, observational learning significantly contributes to the acquisition of motor skills. Thus, a better understanding of the mechanisms underlying this complex phenomenon may improve the development of techniques to enhance the rehabilitation of motor skills after brain damage (Buccino, 2014; Garrison et al., 2013; Porro et al., 2007; Ramsey et al., 2021). Indeed, repeated AO has been shown to induce experience-dependent changes in the motor network, reflecting the acquisition of finely-tuned and effector-specific representations of movement based on the involvement of brain areas implicated in encoding observed actions (Celnik et al., 2006; Stefan et al., 2005; Valchev et al., 2015). Consistently, the visual perceptual system of vertebrates shows a selective preference and high efficiency for biological movements (i.e. motor patterns related to motion in living organisms) and, indeed, humans are able to recognize a conspecific movement in a series of point-lights attached to the limbs of an actor moving in a

way that simulates biological actions (e.g. running, dancing), but not under stationary conditions (Johansson, 1973; Vallortigara et al., 2005). This simple experimental paradigm allows the subject to discriminate the gender and identity of familiar individuals, walking direction, social dispositions, and complex actions (Cutting, 1978; Dittrich, 1993; Mather et al., 1992; McArthur and Baron, 1983). Importantly, recent evidence has confirmed the pivotal role of the MNS in performing these essential activities in everyday life (Troje and Chang, 2023; Ulloa and Pineda, 2007). Moreover, notably, recognising biological movements may serve as the foundation for imitation learning, where MNS is thought to play a crucial role (Huber et al., 2009; Iacoboni, 2009). Indeed, a study employing psychophysical and electromyographic assessments revealed enhanced learning of a new, complex motor skill when individuals observed another person learning the same task, compared to merely witnessing the task being performed or observing the learning of a different task (Mattar and Gribble, 2005).

Of note, it has been suggested that perception and recognition processes are based on the implicit understanding of motor rules, providing the basis for identifying biological movement and various evidence has pointed out that the cerebellum is an essential component of the neural circuitry involved in motion perception (Decety and Grèzes, 1999; Viviani and Stucchi, 1989). Indeed, the perception of a motor behaviour enacted by another individual likely triggers our prior knowledge about the action and its expected outcomes, effectively simulating its actual performance by engaging our action system through mental simulation, and the cerebellum is reasonably crucial in this regard (Savaki and Raos, 2019). Consistently, brain-cerebellar loops, employing the motor system as a forward model, could play a fundamental role in sensorimotor prediction and internal simulation of movement (Callan et al., 2013; Casiraghi et al., 2019). Unfortunately, functional magnetic resonance imaging (fMRI) investigations have yielded inconsistent findings regarding cerebellar activation during AO and, indeed, meta-analyses have shown highly varied outcomes, ranging from no (Caspers et al., 2010) or minimal (Molenberghs et al., 2012) to marked activity (Van Overwalle et al., 2014). However, an important study employing the 14C-deoxyglucose autoradiographic method in the rhesus monkey showed that the AO of a reaching and grasping movement correlates with selective activation of the lateral cerebellar lobules V/VI (Raos and Savaki, 2021; Stamos et al., 2010). Consistently, in humans (Grèzes et al., 2001; Grossman and Blake, 2001; Servos et al., 2002), some studies have confirmed significant activation, both in the anterior, near the midline, and in the lateral cerebellar regions during the perception of biological movements (Grossman et al., 2000; Vaina et al., 2001). Indeed, brain MRI and positron emission tomography (PET) studies have demonstrated significant cerebellar activation during the AO of human walking (Grossman et al., 2000; Ptito et al., 2003; Vaina et al., 2001). Moreover, Vaina et al. documented activation of the lateral cerebellum during the biological movement recognition task of walking (Vaina et al., 2001). Coherently, the cerebellum plays a key role in motor activities and is closely connected to the MNS areas, such as the STS. Thus, it is likely involved in mentally simulating observed actions, also in order to understand others' actions and intentions (Iacoboni and Dapretto, 2006; Puce et al., 1998; Rizzolatti and Fabbri-Destro, 2008). However, it is important to point out that the two cerebellar hemispheres have cross-connections with brain areas, and this could justify the functional specialisation of each hemisphere (Jansen et al., 2005; Wang et al., 2013).

Furthermore, it seems that AO, in addition to automatically triggering the motor resonance underlying action recognition, is also crucial for emotion recognition by similar mechanisms (Carr et al., 2003; Iacoboni, 2005). Interestingly, healthy subjects can easily infer emotions, desires, and intentions only through body motion dynamics. It is reasonable that the cerebellum, with its key role in the motor network and its connections to

limbic regions, is fundamental in this context (Chouchourelou et al., 2006; Heberlein et al., 2004; Jung et al., 2022). Similarly to the motor side, emotions are also characterised by an “unconscious drive” that prompts us to mimic the facial expressions of others instinctively, recognise the corresponding emotion and attribute it to the others (Dimberg et al., 2000; Leslie et al., 2004). This could represent the perceptual-motor resonance mechanism underlying the motor theory of empathy, in which the AON is crucial (Baird et al., 2011; Preston and de Waal, 2002; Rizzolatti and Craighero, 2005). Indeed, a specific cerebellar network activates during social mentalising (Van Overwalle et al., 2020, 2015a, 2015b). Notably, increased fMRI activation has been detected in the right STS, which shows a prominent role during visual processing of body motion, and the left lateral cerebellum (specifically crus I and lobule VIIB) (Sokolov et al., 2012), in particular when individuals detect false intentions during AO (Grèzes et al., 2004; Pavlova et al., 2007; Zacks et al., 2006). Coherently, a PET study has revealed an activation of the left lateral cerebellum, specifically during the identification of dynamic emotional facial expressions, as opposed to static ones, highlighting a cerebellar engagement in visual social cognition via body movement (Kilts et al., 2003). Similarly, as assessed through a fMRI evaluation, a left lateral cerebellar activation has been noted when perceiving dynamic emotional expressions of the entire body, in contrast to static ones (Grèzes et al., 2007). On the other hand, a PET evaluation has highlighted a right cerebellar activation during the observation of meaningless actions, perhaps because of its connections with the semantic areas of the left hemisphere to attempt to explain the observed behaviour (Grezes, 1998; Murdoch, 2010). Indeed, a PET study has shown that observation of meaningless actions is associated with activations in the right cerebellar hemisphere, while meaningful actions mainly activate the left cerebellar hemisphere (Decety et al., 1997). This emphasises that the AON is critically modulated by higher-order aspects of the AO, i.e. emotional aspects and meaning of actions, and that the cerebellum confirms functional lateralisation based on its connections with brain hemispheres (Bidet-Ildei et al., 2020; Cuijpers et al., 2006; Schmahmann, 2019). Interestingly, recent fMRI findings showed that cerebellar involvement in processing stimuli with an emotional valence spans beyond the visual domain and extends to the auditory side, as highlighted by studies on vocal emotion recognition (Adamaszek et al., 2017; Uono et al., 2017). Consistently, cerebellar regions such as the vermis, lobule VI, and crus I are connected to the dorsolateral PFC and auditory temporal regions, including the amygdala, which are crucial in the context of emotion recognition (Stoodley and Schmahmann, 2009). Given the complexity of these activities and the inter-subjective variability in assigning value to emotional stimuli, it is not surprising that literature findings are heterogeneous, with cerebellar activations ranging from unilateral (both in the right and in the left hemisphere) to bilateral (Alba-Ferrara et al., 2011; Kotz et al., 2013; Wildgruber et al., 2005). Reasonably, individual differences, experimental paradigms, and task complexity may partly explain different results. However, these findings support the cerebellum's involvement in recognizing the emotional valence of stimuli, regardless of their modality. This highlights its role not only in understanding others' behaviors, but also in predicting others' actions and updating internal response models coherently, probably also with the contribution of the basal ganglia, providing a cost-benefit assessment to modulate responses and avoid resource wastage (Adamaszek et al., 2019). Indeed, understanding a message's emotional content allows for verifying prior hypotheses about the nature of the interaction, updating internal models, and anticipating the consequences of potential discrepancies from expectations.

Notably, a recent work evaluated the specific localization of cerebellar regions engaged during AO of a grasping movement, highlighting an activation in cerebellar lobules VI, VIIb, and VIIIa and supporting its active

contribution in encoding the hand movements of others (Abdelgabar et al., 2019). This evidence aligns with other studies showing activation of these cerebellar regions, particularly during the performance of complex tasks, leading us to hypothesise that the involvement of motor control regions during AO suggests that cerebro-cerebellar circuits associated with precise hand movements might also play a role in analyzing subtle kinematic details during AO (Abdelgabar et al., 2019; Fuentes and Bastian, 2007; Schlerf et al., 2010). Indeed, a strong activation of lobules VI and VIIA is also noted during motor tasks, particularly when movements entail complex actions demanding higher levels of sensorimotor coordination beyond simple one-dimensional joint actions (Diedrichsen et al., 2005; Miles et al., 2006). Supporting this interpretation, Biagi et al. also demonstrated the activation of cerebellar areas during AO of varying difficulty, suggesting that it may support the computations of the parietal cortex particularly during the observation of complex actions, i.e. those in which feed-forward models are most involved (Biagi et al., 2010). These data are also in line with the findings of Schlerf et al., who pointed out that, while the anterior cerebellar regions are activated indifferently for both simple and complex tasks, the neocerebellum, on the other hand, shows greater activation as task complexity increases (Schlerf et al., 2010). Consistently, Errante & Fogassi highlighted that, both during AO and action execution, the activation patterns (as assessed by shared voxels in fMRI evaluation) are mainly bilateral in cerebellar lobules V, VI, crus I, VIIIa and VIIIb (Errante and Fogassi, 2020). Interestingly, this bilateral activation also seems to be modulated by the degree of task complexity, as more demanding tasks result in bilateral neocerebellar activation that may depend on a similar bilateral activation of connected brain regions, probably to coordinate multiple effectors during high-level motor planning (Hanakawa et al., 2005; Thach et al., 1992; Verstynen et al., 2005). Additionally, another recent study comparing AO and action execution by means of a grip task has demonstrated shared activation patterns in both the anterior and posterior cerebellar regions (Casiraghi et al., 2019). They align with a recent fMRI investigation within a neuropsychological test battery, revealing notable activation during AO in various cerebellar regions, notably the posterior hand motor area, and to a lesser extent, the anterior region linked to primary action execution (King et al., 2019). Notably, the activation pattern during complex movements supports the functional subdivision between anterior, linked to direct action execution, and posterior cerebellar regions, more involved in action planning and comprehension. Indeed, similarly, one study found that physical learning was most associated with activity in the left anterior/medial cerebellum, while observational learning led to an activation in the right posterior cerebellum (Cross et al., 2009). However, other evidence suggests that the left lateral cerebellum also participates in observational learning, probably depending on the type and complexity of the task and the subject's experience (Torriero et al., 2007). Furthermore, Calvo-Merino dissociated the motor aspects from the visual component of the AO, showing a greater activation in the MNS in subjects experienced in the observed complex action than in novices (Calvo-Merino et al., 2006). This correlation between cerebellar activity, the complexity of the observed task, and the subject's experience could be attributed to various non-mutually exclusive mechanisms. On one hand, it is plausible that complex actions require higher computational demands to process the action and predict its sensorimotor consequences. This task becomes increasingly demanding with the complexity of the movements (both executed and observed), and the cerebellum might be pivotal in this regard (Avanzino et al., 2015; Popa and Ebner, 2019). On the other hand, complex tasks activate a wide, sometimes even bilateral, range of cortical areas involved in sensorimotor integration and cognitive functions (such as attention and mental flexibility) (Gohil et al., 2015; Puglisi et al., 2018). Reasonably, the cerebellum actively supports these cortical areas by identifying the internal models that best match the observed action (Streng et al., 2022).

Furthermore, recent evidence suggests that the cerebellum is crucial in interpreting the so-called submovements, i.e. the elementary units composing seemingly fluid and continuous movements (Houk et al., 2007; Langlois et al., 2024). Indeed, although actions may appear similar in terms of movement and outcome, it has been shown that the combinations of submovements are numerous and depend on a complex interaction among various factors, including the subject's experience and ability to achieve optimal efficiency in effector combinations (Torricelli et al., 2023). Therefore, it is conceivable that, as a subject's experience in a particular context increases, the cerebellum can detect and compute differences in patterns of submovements compared to its own repertoire, evaluating finely the sensorimotor differences between various internal models (Habas et al., 2020; Langlois et al., 2024; Streng et al., 2022). Since movements may appear similar, the ability to perceive differences in submovement patterns is reasonably influenced by the subject's experience and, consequently, by the number of available internal models (Langlois et al., 2024). Therefore, a proportional cerebellar activation based on the subject's experience seems to be consistent with this interpretation. This is particularly relevant considering that submovements are now deemed fundamental in mediating interpersonal synchronization and coordination, essential for effective communication (Nazzaro et al., 2023; Tomassini et al., 2022). This evidence and the AON's crucial role in social interaction further support a connection between the cerebellum and the MNS, bolstered by these kinematic findings (Schmidt et al., 2021). Notably, the same correlation regarding cerebellar activation, task complexity, and subject experience is also observed in the context of MI, further supporting this perspective (see section 3). Moreover, consistently, cerebellar regions connected with the dorsal visual pathway could encode the kinematic features of observed actions. Together with the representation of the action goal, this process triggers an automatic motor resonance dependent also on the motor expertise of the observer (Calvo-Merino et al., 2006; Errante et al., 2023; Errante and Fogassi, 2020; Fukui and Inui, 2013). Similarly, instrumental and expressive contrasts have shown that, among the brain regions particularly associated with recognising gestures as opposed to simply observing them, the cerebellum demonstrates significant activation in the right cerebellar hemisphere, likely within the crus I or II regions (Gallagher and Frith, 2004). This confirms recent evidence suggesting a profound link between semantic comprehension and gesture recognition and highlights the cerebellum's involvement through its crossed connections between the right cerebellar regions and the language network, lateralized in the left hemisphere (Proverbio et al., 2015; Schmahmann, 2019).

Of note, shared activation during both AO and action execution is also detected in the dentate nucleus, which is the main output of the lateral cerebellum and is critically involved in the modulation of visuomotor tasks in a effector-specific way (Errante and Fogassi, 2020; Miall et al., 2001; Strick, 1985). Indeed, the cerebellar activity patterns are similar during both the observation and execution of hand, mouth, and foot actions, suggesting a segregation of activities in the MNS that also depends on the specific effector used (Errante et al., 2023; Gazzola and Keysers, 2009). Moreover, the ventral region of the dentate nucleus projects to the posterior parietal and the dorsal PFC which represent fundamental stations for cognitive functions (e.g. working memory) and for the “dorsal stream” of visual processing (Dum and Strick, 2003). This suggests the importance of this circuit in forming and detecting high-level goals and intentions (Caligiore et al., 2013). Additionally, a noteworthy observation is that a distinctive characteristic of the human MNS, compared to that of the monkey, is its ability to encode the temporal dynamics of observed actions. Given the cerebellum's significant involvement in temporal perception, it could potentially play a pivotal role in this aspect (Gangitano et al., 2001; Koch et al., 2009; Mioni et al., 2020). Indeed, cerebellar processing of temporal expectations utilises timing

cues to enhance motor or perceptual efficiency (Avanzino et al., 2015; Nobre et al., 2007). Taken together, these findings suggest that the motor system, especially during AO of complex behaviour, internally simulates the action also involving subcortical structures, as highlighted by the activation of the dentate nucleus and thalamus, which indicates a closed-loop simulation reasonably to achieve a prediction of sensory outcomes. Indeed, this cortico-cerebellar loop, akin to actual execution, updates cortical hand motor representations based on AO outcomes (Bijsterbosch et al., 2011; Errante and Fogassi, 2020).

However, it is interesting to note that areas active during both AO and execution of actions, including the cerebellum, display a significantly greater activity when the subject must later reproduce the observed action, perhaps because the modulation from higher brain regions influences pre-existing motor prototypes that represent individual actions or interactions between the subject and the environment (Frey and Gerry, 2006; Johnson-Frey et al., 2003). Specifically, Frey and Gerry showed a heightened bilateral cerebellar activation during passive AO. Crucially, this cerebellar activation is further increased by the subsequent intention to repeat and/or to learn the observed sequence of actions (Frey and Gerry, 2006; Grafton et al., 1998, 1996). This is particularly relevant as recent evidence has linked the cerebellum not only to motor learning processes but also to creativity, i.e. the ability to generate ideas fluidly and to devise alternative solutions (Adamaszek et al., 2022). Consistently, motor learning is not merely a motor repetition but often involves the integration of complex sequences and their adaptation in creative ways, suggesting a link between motor learning and creative thinking in which the cerebellum might be essential (Spampinato and Celnik, 2021; Sunavsky and Poppenk, 2020).

Notably, it has been recently suggested that the development of these cerebellar activities might have played a crucial role in driving technological advancement in humans, providing intriguing insights into the cerebellum's role from an evolutionary perspective (Vandervert et al., 2024).

Moreover, Decety highlighted that observing with the intention to recognise leads to an activation in structures involved in memory encoding, while observing with the intention to imitate is linked to activity in the dorsolateral PFC, the SMA, and the cerebellum (Decety, 1996). Importantly, a study has highlighted that bilateral cerebellar activation occurs specifically during AO intended for imitation, whereas mere observation without the subsequent intention to imitate is associated with significantly fewer activation patterns (Chaminade et al., 2002; Decety and Grèzes, 1999). Therefore, cerebellar activity, together with a broad network that also includes various cortical areas of the AON and subcortical regions such as the thalamus and basal ganglia, also seems relevant in the strategy used for imitation, reinforcing the postulated role in optimising the selection of actions to achieve the desired sensory outcome or, perhaps, in inhibiting the execution of the mentally simulated action until the proper moment to perform it (Grezes, 1998; Li and Mrsic-Flogel, 2020). While these hypotheses are not mutually exclusive, the latter possibility seems particularly coherent with the strong correlation between the cerebellum and the dorsolateral PFC. Indeed, the inhibitory role of the latter in motor control and its significance in planning and selecting optimal strategies is well-established (Habas, 2021; Oldrati et al., 2021). This suggests that the cerebellum strictly interacts with this neocortical area to select the optimal behavior for achieving goals in a context-specific manner (D'Mello et al., 2020). Finally, it is interesting to note that disinaptic pathways have been observed linking the cerebellum and the basal ganglia, suggesting a joint effort between the two subcortical regions to select the best action (the former) and reinforce it through the dopaminergic reward circuits (the latter) (Bostan et al., 2013, 2010; Hoshi et al., 2005; Manto et al., 2024). Table 2 (first section) summarises this evidence.

Evidence on the role of cerebellum in AO in animal models and healthy subjects			
Observed action	**Involved cerebellar areas**	**Method of assessment**	**Reference**
BM (monkeys observing human examiners)	Lobules IV–VI, crus II posterior, bilaterally	C-deoxyglucose autoradiographic method	Raos and Savaki, 2021
BM (video on a display; point-lights figures)	Anterior portion of the cerebellum	fMRI	Grossman et al., 2000
BM (video on a display, point-lights figures; face-gender discrimination)	Lateral cerebellum	fMRI	Vaina et al., 2001
BM (videos on a display; animals and dots)	Cerebellum (NS)	PET measuring cerebral blood flow	Ptito et al., 2003
BM (video on a display; human walking)	Crus I and lobule VIIB	fMRI and DCM	Sokolov et al., 2012
Dynamic facial expressions recognition	Cerebellum (NS)	PET measuring cerebral blood flow	Kilts et al., 2003
BM (human actions with the intent to imitate)	Left cerebellum	PET	Grèzes et al., 1998
BM (video on a display, in order to recognize or imitate actions)	Left cerebellum	PET	Decety et al., 1997
BM (video on a display, complex vs simple actions)	Cerebellum (NS)	fMRI	Biagi et al., 2010
BM (video on a display, object manipulation)	Lobules V, VI, crus I, VIIIa and VIIIb bilaterally	fMRI	Errante and Fogassi, 2020
BM (video on a display, object manipulation)	Lobule VI, crus I	fMRI	Casiraghi et al., 2019
BM (video on a display, observational learning)	Left lateral cerebellum	fMRI	Cross et al., 2009
BM (video on a display, emotional recognition)	Cerebellum (reasonably right crus I-II)	fMRI	Gallagher and Frith, 2004
BM (video on a display, passive vs observational learning)	Cerebellum (NS)	fMRI	Frey and Gerry, 2006
BM (video on a display)	Cerebellum (NS)	fMRI	Grèzes et al., 2004
BM (watching the examiner)	Right posterior cerebellum	PET	Grafton et al., 1996
Evidence on the role of cerebellum in MI in healthy subjects			
Action imagery	**Involved cerebellar areas**	**Method of assessment**	**Reference**
Right finger movement sequences	Right cerebellum (more active for complex movements)	$H_2{}^{15}O$ PET	Boecker et al., 2002
Simple and complex finger movements of the dominant and non-dominant hand	Right cerebellum (more active for complex movements)	fMRI	Kuhtz-Buschbeck et al., 2003
Silent recitation of the names of the months of the year (verbal MI)	Right cerebellum	fMRI	Ackermann et al., 1998
Finger tapping	Postero-lateral cerebellum	fMRI	Hanakawa et al., 2008
Tennis movements and silent counting	Cerebellum (NS)	SPECT	Decety et al., 1990
Finger opposition	Right postero-lateral cerebellum (imagining right hand)	fMRI	Luft et al., 1998

Tennis movements and silent counting	Infero-lateral cerebellum	SPECT	Ryding et al., 1993
Finger tapping	Postero-lateral cerebellum	fMRI	Hanakawa et al., 2003
Hand movements	Dorso-lateral cerebellum	fMRI	Lotze et al., 1999
Imagery of performing a displayed movement (MI+AO)	Cerebellar hemispheres bilaterally	fMRI	Nedelko et al., 2012
Gait imagery	Bilateral cerebellum	fMRI	Van der Meulen et al., 2014
Hand movement sequences	Right cerebellar lobule VI and VIII	fMRI	Krüger et al., 2020

Table 2. Summary of evidence on cerebellar involvement in AO (first section) and MI (second section) in animal models and healthy human subjects. Abbreviations: AO: action observation; BM: biological motion; DCM: dynamic causal modelling; fMRI: functional magnetic resonance imaging; MI: motor imagery; NS: not specified; PET: positron emission tomography; SPECT: Single Photon Emission Computed Tomography.

8.4 The cerebellum and MI in healthy subjects

MI, i.e., a dynamic phase in which the mental representation of a specific motor action is internally rehearsed without any observable motor output, represents a fundamental simulation mechanism when observing the actions of others (with the aim of imitating them or not) (Decety and Grèzes, 1999; Lotze and Halsband, 2006; Munzert et al., 2009). Indeed, similar to other types of memory, it is believed that individual motor acts are stored, modified, and recalled according to a precise hierarchical representation to compose specific sequences of actions (Sheahan et al., 2016; Stringer and Rolls, 2007). Importantly, however, MI entails a vivid mental simulation of movements and is associated with a kinesthetic sensation (Hurst and Boe, 2022; Jeannerod and Frak, 1999). Since all these processes require two phases, namely one of representing the body as a force-generator and a subsequent one of encoding the goal of the programmed action, the neural substrates largely overlap with those of motor planning and, therefore, with the AON (Grèzes and Decety, 2001; Kim et al., 2017; Stephan et al., 1995). Studies across psychology, electrophysiology, and neuroimaging suggest that performing a task and imagining it engage overlapping neural circuits both in the sensory (e.g. visual) and motor domains, leading to a subthreshold activation of descending motor pathways (Dijkstra et al., 2017; Pilgramm et al., 2016; Porro et al., 1996; Rizzolatti et al., 2002). Indeed, MI has been shown to activate a network of areas, including the SMA, premotor and parietal cortex, and the cerebellum (Jueptner et al., 1997; Parsons et al., 1995; Savaki and Raos, 2019). Consistently, a recent review has documented a specific cerebellar activation in the right lobule VI, which contains multiple body representations, during motor execution and, to a lesser extent, during MI (Buckner et al., 2011; Hardwick et al., 2018). It is possible that the cerebellum, together with other neocortical regions, analyses the efference copy from a motor and perceptual perspective to simulate the action and its most reasonably expected sensory consequences and, indeed, it appears that its activity during MI increases proportionally with the complexity of the task (importantly, as already discussed for AO) (Boecker et al., 2002; Cebolla et al., 2015; Grush, 2004; Kuhtz-Buschbeck et al., 2003; Yi et al., 2013). Indeed, MI of complex movement sequences leads to a significant cerebellar activation, as movement execution and AO do (Decety et al., 1990; Jokisch et al., 2005; Krüger et al., 2020; Luft et al., 1998; Ryding et al., 1993). Coherently, there is substantial evidence to show that the cerebellum is activated during sensory-motor imagery tasks, such as producing simple speech utterances, generating verbs to noun

stimuli or performing a finger tapping, highlighting a functional specialisation of the right cerebellar hemisphere for linguistic tasks and of the left cerebellar hemisphere for spatial tasks, reasonably due to the cross-connections with corresponding brain areas (Ackermann et al., 1998; Hanakawa et al., 2008; Petersen et al., 1989; Raichle et al., 1994; Stoodley, 2012).

Interestingly, the cerebellum shows extensive connections with the dorsolateral PFC, which is pivotal in working memory and could, indeed, play a role in the verbal rehearsal loop by comparing subvocal articulation with phonological representations through a MI speech mechanism, potentially correcting errors to maintain the integrity of rehearsed items (Deschamps et al., 2020; Desmond and Fiez, 1998; Fiez and Raichle, 1997). This seems similar to the proposed role of the cerebellum in episodic memory, wherein it could aid in self-initiated retrieval or the generation of 'candidate responses' during retrieval (Almeida et al., 2023; Bäckman et al., 1997; Cabeza et al., 1997). Consistently, subcortical structures, including the cerebellum, contribute to the spatiotemporal functions and programmes for self-generated movements (Deecke and Kornhuber, 1978; Kilteni and Ehrsson, 2020). Indeed, a simple imagination of a graphic movement (i.e. writing a number by simulating the action in the first person and 'feeling' the hand writing) leads to the activation of a network of areas that also includes the cerebellum, and the same occurs if one imagines a tennis practice (Decety et al., 1988; Decety and Ingvar, 1990). Importantly, a recent meta-analysis has confirmed the activation of several cerebellar regions during MI tasks (Hétu et al., 2013). Therefore, the cerebellum is involved not only during AO, but is also crucial when a subject makes use of one's internal (imagined) voice or sensation to represent, maintain, and process task-relevant information and conscious reflections, supporting its critical role in regulating internal models in order to achieve goals profitably and accurately (Ito, 2008; Strick et al., 2009).

Indeed, internal models can be conceptualised as forms of sensorimotor imagination that allow precise error detection based on the synchronous input from distinct representation maps (de Solages et al., 2008; Fuentes and Bastian, 2007; Gold and Ciorciari, 2021). Consistently, also in the context of MI, cerebellar activity is mainly located postero-laterally, supporting that this is not a simple motor act but rather a cognitive task that relies on interplay with other brain areas (Allen et al., 1997; Grami et al., 2022; Hanakawa et al., 2003). Some authors have suggested that, during MI, cerebellar activation indicates an inhibitory process that blocks efferent impulses, preventing their transmission to the medullary and muscle levels (Berthoz, 1996; Cengiz and Boran, 2016; Decety and Ingvar, 1990; Leonardo et al., 1995). Coherently, Sakai et al. reported a maximal activation of the lateral cerebellum (lobule VII) during non-go motor tasks, and it is reasonable that the same mechanism occurs during MI (Sakai et al., 1997). This aligns with evidence indicating that MI places greater demands on inhibitory mechanisms related to AO, attributed to the internally generated sensations of movement, and some authors interpret MI as involving conscious access to sensory-motor action contents, while the preparation of the movement remains subconscious until the action is initiated (Crammond, 1997; Lotze et al., 1999). Interestingly, cortical areas of the MNS are activated in a somatotopically specific fashion when a subject reads words related to the movement of particular body parts, and it appears that the cerebellum also intervenes in this internal simulation (Fuentes and Bastian, 2007; Hauk et al., 2004; Leslie et al., 2004). Furthermore, when examining studies regarding the MI of gait, seminal work has shown that it also critically involves the cerebellum, in particular the anterior lobe for the kinematic simulation of gait and lobules VI and VII (crus I and II) in relation to the vividness of MI and the complexity of the performed task (Cabaraux et al., 2023). Interestingly, increased bilateral activation of crus I and II distinguishes those with better MI of gait performance from poor “imagers” (van der Meulen et al., 2014).

Thus, mentally simulating motor behavior could activate the motor programme, by engaging various parts of the CNS that execute different aspects of the imagined action (Decety, 1996; Ladda et al., 2021). Supporting the interpretation that neural processes involved in executing specific motor tasks are also recruited when mentally simulating those movements, it has been shown that the time to act overlaps with that required for the MI of the same task (Decety et al., 1989; Decety and Michel, 1989). However, mentally simulating and physically executing simple actions, like grasping and picking up an object, activate cortical areas that exhibit only partial overlap (Decety et al., 1994; Grafton et al., 1996). Moreover, directly comparing mental rehearsal to physical performance has revealed partial involvement of distinct brain regions (Gerardin et al., 2000; Hanakawa et al., 2005, 2003). This suggests that, even if the same network is involved in action execution, AO and MI, the degree and specific locations of activation depend on the particular activity performed (Decety et al., 1997; Papitto et al., 2020; Van der Lubbe et al., 2021). Specifically, there may be a gradient of activation for areas within the AON, including the cerebellum, particularly its lateral-posterior areas, ranging from MI, to AO and, finally, to execution itself (Hardwick et al., 2018; Henschke and Pakan, 2023; Jeannerod, 2001; Lotze et al., 1999; Nedelko et al., 2012). According to some authors, given the relevant role of the cerebellum also in processing sensory input, it is possible that the lower activation during MI and AO compared to the execution itself also depends on the lack of sensory feedback (Baumann et al., 2015; Gao et al., 1996; Jueptner et al., 1997). However, interestingly, other authors have, instead, found a similar activation pattern between MI and execution in the cerebellum, probably justified by its involvement in motor planning (Kuhtz-Buschbeck et al., 2003), whereas yet other works have highlighted a higher cerebellar activation during MI than during execution, and have hypothesised that this may be due to the inhibitory mechanisms already examined, the computational load due to sustained motor representation or the retrieval of sensory impressions from memory, necessary to compute the feedforward model in the absence of external input (Annett, 1996; Berthoz, 1996; Cengiz and Boran, 2016; Jeannerod and Decety, 1995; Luft et al., 1998). This could also justify the possibility of using MI to perform perceptual tasks, e.g. a mental rotation task (Butson et al., 2014; Vingerhoets et al., 2002). A summary of these findings is provided in Table 2 (second section), while Figure 2 shows an overview of the brain-cerebellar loops active during the execution of movements, AO, and MI.

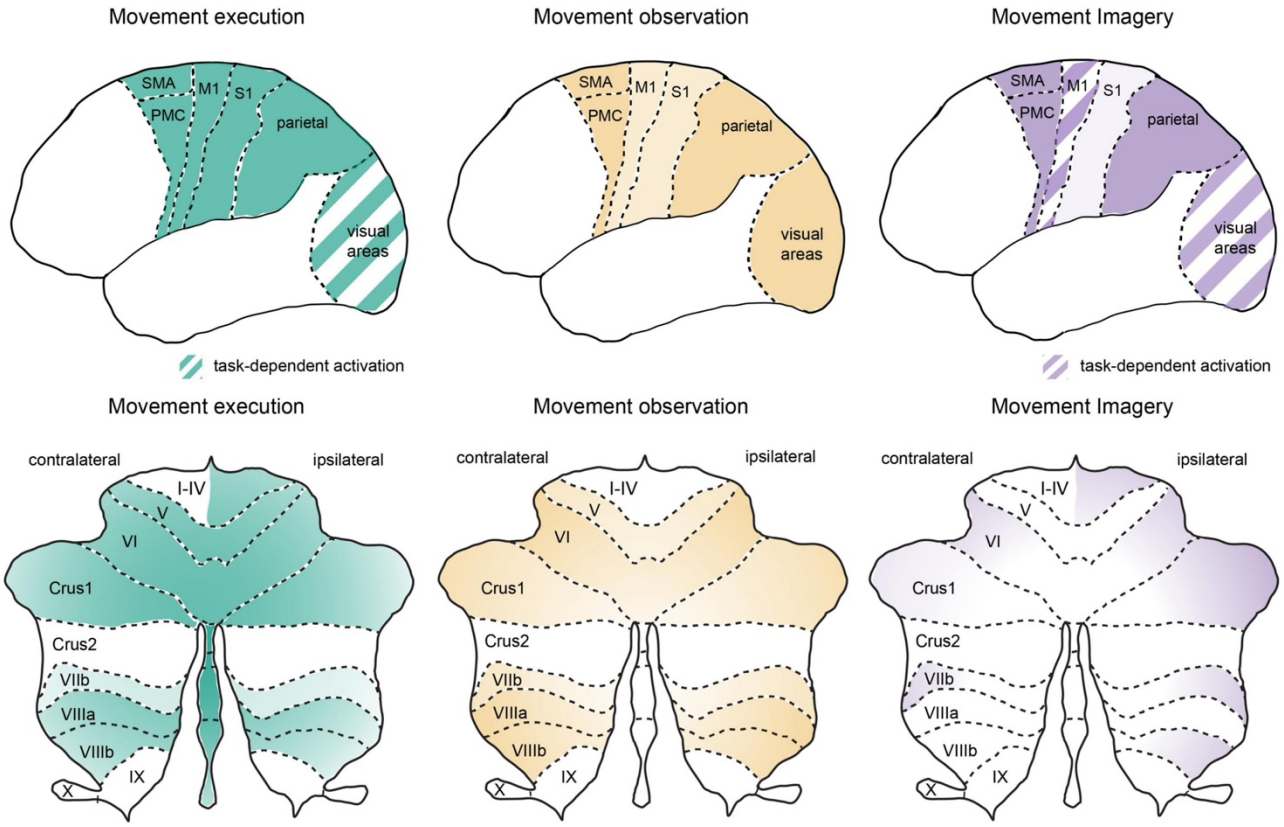


Figure 2. Activation patterns in cortical and cerebellar regions during movement execution, AO, and MI. The schematic representation displays cortical (upper panel) and cerebellar (lower panel) activation patterns during movement execution (left), AO (middle), and MI (right). Stronger relative activation is depicted by darker colors, while striped regions indicate areas with highly task-dependent activation patterns. Abbreviations: AO: action observation; MI: motor imagery; M1: primary motor cortex; PMC: premotor cortex; S1: primary somatosensory cortex; SMA: supplementary motor area. Reproduced in accordance with the copyright policy by Frontiers in Systems Neuroscience from (Henschke and Pakan, 2023), © 2023 Henschke and Pakan.

8.5 The cerebellum, AO, and MI in pathological conditions

A seminal demonstration of the importance of the cerebellum in the implicit learning by AO of a visuomotor sequence stems from animal model studies: it has been demonstrated that, when a rat sees another animal exploring a water maze, the observation has the same important enhancing effect in improving subsequent behaviour as the exploration performance itself (Petrosini et al., 2003). The cerebellum has been hypothesized to support the rehearsal of cortical action processes without overt movement (Leggio et al., 2000). However, crucially, if damage to the cerebellum is experimentally induced, the animal loses its ability to learn from observation while retaining access to declarative memory to improve performance (Graziano et al., 2002; Molinari et al., 1997; Petrosini et al., 2003). Of note, in this model, rats observed behaviours without an apparent goal, thus the cerebellum results fundamental in imitation learning by means of AO irrespective of their goal (which is probably more mediated by dopaminergic reward circuits) (Hart et al., 2024). Importantly, a human study that employed an inhibitory protocol of repetitive cerebellar TMS (rTMS) highlighted an inability to learn new visuomotor tasks through AO, without affecting established motor memories. This underscores its vital contribution to the initial stages of observational learning, specifically during the observation and

execution matching phase, and emphasises its role in combining sensory information (derived from environmental observation) and motor information (assessed by exploratory behaviour) during AO to generate internal models that underpin learning by imitation (Caligiore et al., 2013; Torriero et al., 2007; Wolpert et al., 1998). Furthermore, the specificity of the cerebellum during the acquisition phase is highlighted by its activity decline following prolonged practice, indicating optimized internal models and the resolution of discrepancies between predicted and actual outcomes (Penhune and Doyon, 2005). Reasonably, the cerebellum learns to associate specific contexts with consciously initiated movements leading, through repetition, to connections between contexts and movement patterns, enabling automatic action triggering when the context reappears (Kirsch and Cross, 2015; Thach, 1998). Theoretical models also support this evolution of brain activity, as the reduction in cerebellar function leads to so-called 'sensorimotor habits', i.e. the strengthening of the control process for actions that are habitually performed (Hua and Houk, 1997; Synofzik et al., 2008).

Further evidence is derived from diseases affecting human patients. Indeed, data from subjects affected by cerebellar lesions (e.g. atrophy, tumour, stroke, or an autoimmune injury) have shown an important role of the posterior cerebellar regions (particularly the vermis) in judging the speed of moving stimuli (Ivry and Diener, 1991). The authors also emphasised that this impairment is unlikely to depend primarily on disconnection from the cortical areas, not only because primates, which are characterised by a limited amount of connections from visual cortical areas to the cerebellum, show the same deficits in similar experimental contexts, but also because single-cell recordings in these regions demonstrate that cellular activity is best predicted by the speed of external stimuli (Glickstein et al., 1985; Suzuki and Keller, 1988). An important study by Christensen et al. examined this action-perception coupling in patients with chronic cerebellar lesions following tumour removal (Christensen et al., 2014). Interestingly, they demonstrated a dissociation between, on the one hand, the impairment of the sensory-motor representation following damage to the motor representation of the arm in the right anterior and posterior cerebellar cortex (lobules V, VI and VIII), especially in lobule VI, which is crucial for sensory encoding and for predicting and updating the sensory state (Miall et al., 2007; Schlerf et al., 2012); on the other hand, impairment of multisensory integration, depending mainly on lesions of lobule VII and the ventral portion of the dentate nucleus, which are involved in the cerebellar-parietal loop that is crucial for analysing information from different domains (Christensen et al., 2014; Greger et al., 2004; Strick et al., 2009). Consistently, Abdelgabar et al. compared the performance in recognising fine kinematic details of AO between healthy subjects and patients affected by spinocerebellar ataxia type 6 (SCA6, a neurodegenerative disorder that selectively affects cerebellar circuits), demonstrating that the latter show specific deficits in AO tasks (Abdelgabar et al., 2019). Indeed, SCA6 is characterised by a specific loss of Purkinje cells and a selective loss of grey matter in the lobule VI (Du et al., 2013; Rentiya et al., 2017). The authors provided further evidence supporting the notion that AO entails a cortical-cerebellar loop, converting sensory input into motor control strategies (inverse models) and anticipating sensory feedback from motor commands (forward models). Specifically, they attribute the observed deficits to damage of lobules VI and VIIb/VIIIa, aligning with the examined physiological models (see Section 2). Furthermore, Sokolov et al. emphasized the cerebellum's region-specific activity during AO, particularly in its lateral regions, as evidenced by the fact that tumours affecting the left lateral cerebellum significantly impair visual detection of human movement, whereas lesions in the medial regions have minimal impact on the perception of human locomotion (Sokolov et al., 2010). Of note, the cerebellar role in processing visual information, despite its relatively limited connections with the visual cortical areas, supports evidence pointing to its multiple sources of visual afferences. Specifically, some

visual information can rapidly access the cerebellum through a fast pathway originating from the superior colliculus in the midbrain, reaching the cerebellum (particularly the lobules VI and crus I and II) via pontine nuclei (Voogd et al., 2012). Additionally, several cortical areas (both strictly visual and, more prominently, associative in the temporo-parietal regions) provide the cerebellum with processed and integrated visual data through the pontine nuclei (Voogd et al., 2012). This dual source likely allows the cerebellum not only to obtain updated information on the sensory modality most relevant to humans but also to constantly compare bottom-up information from the superior colliculus (i.e. rapid and unprocessed, reflecting the current environmental condition and essential for faster actions such as adjusting eye movements for fast-tracking) with top-down data from cortical areas (i.e. reasonably integrating expectations based on priors and past experiences) (Krauzlis et al., 2013; Strick et al., 2009; Voogd et al., 2012).

It is also interesting to note that patients suffering from autism spectrum disorders (ASD), which are known to be characterised by reduced social skills, manifest not only peculiar alterations during AO and action imitation, suggesting a specific AON dysfunction, but also cerebellar abnormalities, both neuroanatomically and in terms of connectivity (e.g. a reduction in cerebellar white matter and changes in the function of Purkinje cells) (Allen, 2006; Catani et al., 2008; van der Heijden et al., 2021; Yang and Hofmann, 2016). Of note, neurocomputational models of ASD provided further support to the involvement of cerebellar abnormalities in the genesis of characteristic behavioral alterations (Trimarco et al., 2021). In addition, these patients also show alterations in the perception of biological movements (which correlate with alterations in the left superior cerebellar peduncle, closely connected with the right STS), as well as a hypersensitivity to sensory stimuli that may stem from difficulties in attenuating predicted stimuli due to alterations in spatio-temporal matching, a process which may be significantly influenced by cerebellar abnormalities, as previously discussed (Blake et al., 2003; Blakemore et al., 2006; Robertson and Baron-Cohen, 2017; Rogers et al., 2003). Importantly, a specific MNS dysfunction, underpinning a large amount of behavioural and motor alterations in ASD patients, has been suggested, as also demonstrated by fMRI studies showing reduced MNS activation during AO and imitation of facial expressions (Dapretto et al., 2006; Emanuele et al., 2021; Fishman et al., 2014; Williams et al., 2004).

Similarly, it is noteworthy that individuals with schizophrenia exhibit diminished attenuation of self-generated compared to external tactile stimulation, reflecting a re-afference impairment, which may stem from inadequate prediction of movement outcomes, a process in which the cerebellum plays a pivotal role (Shergill et al., 2005). These data are also supported by recent evidence demonstrating altered cerebellar-brain connectivity in schizophrenic patients that could account for their cognitive impairments (Cao et al., 2023; Cattarinussi et al., 2024; Kim et al., 2021; Saito et al., 2018). Importantly, epigenetic investigations have revealed an abnormal aging trajectory in the cerebellum of individuals with both ASD and schizophrenia. This finding may explain the shared anomalies among ASD and schizophrenia and their common alterations in social cognition, which could represent the neurophysiological underpinnings of their deficits in the perception of biological movements (Kim et al., 2005; Klin et al., 2009; Koldewyn et al., 2010; Liu et al., 2023). As suggested by Sokolov et al., these data are also supported by the altered functional connections between the right STS and the left cerebellar lobule Crus I, which are common to both pathologies (Kaiser et al., 2010; Sokolov et al., 2012). Consistently, schizophrenic patients show alterations in the emotion perception in dynamic facial expressions linked to the activity of the left cerebellar hemisphere (Kilts et al., 2003; Kohler et al., 2000).

Furthermore, interestingly, patients affected by neurodegenerative ataxia or generic cerebellar injury show a deficit in acquiring and automating the comprehension of social action sequences related to individuals' mental

states during AO, a finding that supports its critical role not only in sequence learning but also in social cognition (Leggio and Molinari, 2015; Van Overwalle et al., 2019, 2014; Vandervert et al., 2024). Nevertheless, most of the cases investigated so far concern chronic and multifaceted conditions that evolve over extended durations, thus allowing for the potential involvement of compensatory mechanisms. Consequently, attributing a definitive causal role to specific brain structures in the development of observed alterations becomes challenging (Draganova et al., 2021). In contrast, stroke is characterised by a sudden onset and, especially in some cases, selectively affects specific brain regions, making it possible to assess the functional consequences of an injury. Indeed, importantly, it has been shown that patients affected by median cerebellar lesions (in the vermis) show a deficit in motion direction perception not only in the acute phase but also in the chronic timeframe, without defective fixation and eye movements and despite the regression of other typical symptoms due to cerebellar lesions (Nawrot and Rizzo, 1998, 1995). On the other hand, Cattaneo et al. examined a group of chronic stroke cerebellar patients using a task in which they were asked to identify the intruder in a sequence of biological or inanimate actions, demonstrating marked impairment in both categories (Cattaneo et al., 2012). Of note, the task required them to mentally reconstitute the correct sequence, compare it with the options presented, and identify the inconsistent option. Hence, the authors proposed that the cerebellum, with its internal feed-forward models, plays a critical role in decomposing the sequence into basic motor acts, which are then arranged in a chronobiologically coherent way under normal conditions, whereas cerebellar damage prevented the patients from performing this task correctly (Cattaneo et al., 2012; Molinari et al., 2008). However, in another investigation involving post-acute cerebellar stroke patients, a selective deficit in the discrimination of movement direction but a sparing in the perception of biological movements have been observed, leading the authors to hypothesise that neocortical regions, such as the STS, might play an exclusive or compensatory role in this function, while the cerebellum might enhance efficiency but not necessarily be essential for performance (Bower, 1997; Jokisch et al., 2005). Indeed, some theories suggest that the cerebellum is useful but not indispensable for many brain activities. This notion finds support in the observation that its engagement increases proportionally with task complexity, particularly beneficial when cortical functions require additional support (Salmi et al., 2010; Xiang et al., 2003). However, it is possible that various factors, including the limited sample size, the precise lesion site, and the time from stroke onset (for the intervention of compensation mechanisms) may account for the observed differences. Furthermore, a specific deficit in the recognition and discrimination of cues from both facial and vocal expressions with basic emotional valence has been highlighted in a group of patients affected by cerebellar stroke, predominantly located in the dorsomedial parts of crus I and II (Adamaszek et al., 2019). Further studies have confirmed a selective impairment of vocal emotion recognition following stroke in lobules VIIb, VIII, and IX and in crus I and II, more frequently in the right cerebellar hemisphere (Thomasson et al., 2021, 2019). These findings support the cerebellum's role in recognizing emotional stimuli across various sensory domains, a crucial aspect of its contribution to the activities of the MNS and the regulation of social interactions.

Similar to AO, the lesion of cerebellar regions active during MI also impairs the performance and especially the learning of the same cognitive tasks (Fiez et al., 1992; Thach, 1998). Importantly, a study on patients affected by a unilateral cerebellar stroke showed that not only, as expected, the excitability of contralateral M1 was reduced (due to the well-known phenomenon of diaschisis), but also that motor facilitation during MI and the pre-movement facilitation were reduced, leading the authors to hypothesise a deficit due to the cerebellar lesion to prepare and imagine sequential movements (Battaglia et al., 2006). This result is also consistent with

another finding showing that unilateral cerebellar damage involving the dentate nucleus disrupts kinesthetic imagery of a complex motor task (González et al., 2005). Interestingly, another work compared healthy subjects with Parkinson's disease (PD) patients and highlighted that, while in the former MI led to a cerebellar activation regardless of the imagined hand, in the latter MI using the right ("akinetic") hand was characterised by a different motor network activity with a lack of cerebellar activation (Thobois et al., 2000). This evidence underscores that cerebellar lesions not only hamper execution but also affect AO and MI, reinforcing the notion that these activities rely on the MNS and that the cerebellum makes a crucial contribution to its functions. Table 3 summarises these data.

Evidence on the role of cerebellum in AO in pathological conditions				
Observed action	**Involved cerebellar areas**	**Method of assessment**	**Pathological condition**	**Reference**
Goal-directed hand actions	Lobules VI, VIIb and VIIIa	fMRI	SCA	Abdelgabar et al., 2019
Complex action performed by a human actor OR complex physical event occurring to an inanimate object	Cerebellum (different sites)	Behavioural outcome	Chronic isolated cerebellar ischemic lesion	Cattaneo et al., 2012
Moving objects (judging velocity)	Neocerebellum	Brain MRI; behavioural outcome	Crebellar atrophy, tumor, stroke, or autoimmune reaction	Ivry and Diener, 1991
Detection of masked BM and masked non-BM	Cerebellum (different sites)	Brain MRI; behavioural outcome	Ischemic cerebellar lesions	Jokisch et al., 2005
Random dot cinematograms	Cerebellum (midline regions)	Brain MRI; behavioural outcome	Acute midline cerebellar lesions	Nawrot and Rizzo, 1994
Random dot cinematograms	Cerebellum (midline regions)	Brain MRI; behavioural outcome	Chronic midline cerebellar lesions	Nawrot and Rizzo, 1998
Human walking (video on a display)	Left lateral cerebellum	Brain MRI; behavioural outcome	Tumors to the left cerebellum	Sokolov et al., 2010
Evidence on the role of cerebellum in MI in pathological conditions				
Action imagery	**Involved cerebellar areas**	**Method of assessment**	**Pathological condition**	**Reference**
Sequential opposition of the thumb	Cerebellum (hemispheric lesion)	TMS	Unilateral cerebellar stroke (PICA territory)	Battaglia et al., 2006
Piano movements	Cerebellum (different sites)	Behavioural outcome	Cerebellar stroke	Gonzàlez et al., 2005
Unimanual motor task	Cerebellum (NS)	$H_2{}^{15}O$ PET	PD	Thobois et al., 2000

Table 3. Summary of evidence on cerebellar involvement in AO (first section) and MI (second section) in pathological conditions. Abbreviations: AO: action observation; BM: biological motion; fMRI: functional magnetic resonance imaging; MI: motor imagery; MRI: magnetic resonance imaging; NS: not specified; PD: Parkinson's disease; PET: positron emission tomography; PICA: posterior-inferior cerebellar artery; SCA:

Spinocerebellar ataxia; SPECT: Single Photon Emission Computed Tomography; TMS: transcranial magnetic stimulation.

8.6 Neurophysiological and rehabilitation implications

Based on the findings above, the interest in AO and MI has increased in the last decades, both from a prognostic and, above all, therapeutic point of view (Antonioni et al., 2024a; Sun et al., 2016; Zhang et al., 2023). Indeed, reasonably, both MI, which promotes mental rehearsal, and AO, by activating representations within one's motor network corresponding to the observed behaviour, may elicit subthreshold activation of the motor system, thus enhancing performance through sensory-motor neuroplastic mechanisms, as evidenced by the heightened cortico-spinal excitability induced by both (Aoyama et al., 2020; Cochin et al., 1999; Mizuguchi and Kanosue, 2017; Romano-Smith et al., 2018; Tremblay et al., 2004). Consistently, both AO and MI facilitate subsequent motor performances, albeit to a different degree, as suggested by a study in which AO prevented the corticomotor depression induced by immobilization, but not MI (Bassolino et al., 2014; Chye et al., 2022; Gatti et al., 2013; Mulder, 2007). Specifically, multisensory AON enables individuals to (re)learn impaired motor functions by activating internal action-related models (Fadiga et al., 1995; Rizzolatti et al., 2009; Sale and Franceschini, 2012).

This evidence has sparked considerable interest in MI and Action Observation Treatment (AOT) from a neurorehabilitation perspective. These methods offer a non-invasive means to engage the MNS, even for patients unable to execute actions correctly, and by leveraging sensorimotor resonance mechanisms, they hold promise for enhancing performance. Indeed, their potential has been demonstrated across various pathological conditions, from stroke to PD (Binks et al., 2023; Caligiore et al., 2017a; Mao et al., 2020; Mulder, 2007; Small et al., 2012). Agosta et al. intriguingly implemented an AOT protocol in PD patients exhibiting freezing of gait, demonstrating its efficacy in enhancing motor performance and balance. Notably, only the experimental group (i.e. the AOT group) exhibited reduced activity in the cerebellar vermis and bilaterally in cerebellar lobule IV and V compared to the control group, underscoring its therapeutic significance (Agosta et al., 2017). Similarly, in stroke patients, the integration of MI with physiotherapy emerges as a viable and efficacious approach to enhance rehabilitation outcomes (Schuster et al., 2012). Significantly, recent research in severe stroke patients bolstered this crucial application in neurorehabilitation since AO has been shown to impact action prediction time, underlining the involvement of the MNS, even in cases where the affected hand is unable to perform the action (Craighero et al., 2023). Notably, another study on PD patients showed that AOT yields not only motor benefits but also cognitive ones, particularly on verbal and visuo-spatial memory and on attentional abilities (Caligiore et al., 2019). Moreover, these improvements were sustained even a month after the treatment, suggesting a long-term effect. This strengthens the idea that AOT acts influencing multiple cognitive-motor areas and the cerebellum, given its complex and relevant connections with various cortico-subcortical networks, could be pivotal in this context to explain the common positive effects across different domains.

Importantly, neurophysiological studies support the cerebellar role in neurorehabilitation, particularly concerning stroke patients. Indeed, a great deal of research underscores the significant role of the cerebellum in motor network reorganization during stroke recovery (Olafson et al., 2021). Furthermore, it is noteworthy that animal research has demonstrated that stimulating cerebellar-cortical networks can enhance functional recovery after stroke (Machado et al., 2013; Park et al., 2015). Additionally, fMRI studies in stroke patients

have revealed that heightened activity in the contralesional cerebellum correlates with improvements in gait ability (Luft et al., 2005). Stroke survivors frequently need to acquire novel motor strategies, and it stands to reason that the cerebellum plays a pivotal role in this regard (Dahms et al., 2020; Hermsdorf et al., 2020). Hence, given its critical involvement in motor and non-motor functions, the cerebellum is a key target for non-invasive brain stimulation (NIBS) techniques (Baroni et al., 2024). Consistently, research exploring the physiology of the cerebellar-thalamo-cortical pathway through TMS protocols indicates that stimulating the cerebellum activates Purkinje cells in the superior cerebellum. This activation leads to inhibition of the dentate nucleus, reducing its facilitatory drive on the contralateral motor cortex via the ventral lateral thalamus. Consequently, this process suppresses the contralateral motor area, known as cerebello-cerebral inhibition (CBI) (Fernandez et al., 2018; Manto et al., 2022; Ugawa et al., 1997, 1994). Indeed, paired-pulse NIBS protocol involving a TMS pulse applied over the cerebellum (conditioning stimulus, CS), followed by another to the M1 after 5-8 ms (test stimulus, TS), results in a decrease in the amplitude of motor evoked potentials (MEPs) compared to a single pulse applied to M1 with the same intensity (Fernandez et al., 2018). This suggests a decline in the excitability of motor regions, likely resulting from the suppression of excitatory signals originating from the ventrolateral thalamus to neurons located in cortical layers I, III, V, and VI (Daskalakis et al., 2004). Importantly, thalamic modulation through cerebellar stimulation does not only act on M1 directly but also indirectly through an action on the premotor cortex, which is, in turn, closely connected with M1 (Spampinato et al., 2023). Likewise, transcranial electrical stimulation (tES) targeting the cerebellum modulates connections between the dentate nucleus and motor areas. For instance, a recent investigation has demonstrated that a specific type of cerebellar tES, transcranial alternating current stimulation (tACS) at theta frequency (5 Hz), enhances CBI during the stimulation period. This effect is likely due to the theta rhythm aligning with the natural resonance frequency of granule cells, resulting in an "entrainment" phenomenon that enhances the modulation of the cerebello-cortical connection pathway (Spampinato et al., 2021).

Importantly, cerebellar stimulation allows the modulation of complex interneuronal circuits within cerebral cortex regions linked to the cerebellum through thalamic relay pathways. Indeed, paired-pulse protocols provide insights into neurophysiological measures reflecting the functional status of excitatory and inhibitory cortical circuits, typically assessed at M1 due to its accessibility and the availability of neurophysiological markers for use as outcome measures. For instance, short- and long-interval intracortical inhibition (SICI and LICI) describes the activity of ionophoric GABA-A and metabotropic GABA-B currents, respectively, reflecting the activity of cortical inhibitory interneurons. In contrast, intracortical facilitation (ICF) outlines glutamatergic excitatory activity (Ferreri et al., 2011). These metrics, assessed through the amplitude of MEPs at M1, offer insight into the modulation of cortical interneurons shaping motor responses (Klomjai et al., 2015). Significantly, a recent form of rTMS, known as theta-burst stimulation (TBS), utilises a high-frequency protocol able to induce long-lasting changes through neuroplastic mechanisms and shows shifts in cortical excitability across both motor and non-motor regions (Huang et al., 2005; Rocchi et al., 2016). Crucially, a seminal work applied TBS on the lateral cerebellum and highlighted, by means of a continuous TBS (cTBS), a reduction in SICI and an increase in LICI over M1. In contrast, an intermittent TBS (iTBS) led to a decrement in LICI (Koch et al., 2008). These changes have been ascribed to the ability of this cerebellar NIBS protocol to modulate intracortical GABAergic circuits and underscore the cerebellum's relevance in regulating the circuitry, especially inhibitory pathways, of interconnected brain areas (Koch et al., 2008). Additionally, a recent investigation paired cerebellar TMS stimulation with electroencephalography (EEG) recordings to evaluate TMS-evoked potentials

(TEPs), representing a gauge of overall cortical activation prompted by TMS across both M1 and parietal regions. This approach aimed to delve into the impact of cerebellar TBS on the contralateral hemisphere (Casula et al., 2016). Importantly, the focus was on the initial 200 ms components of TEPs, which rely on GABA-A activity within the first 15-60 ms post-TMS, while the subsequent phases are influenced by GABA-B modulation (Casula et al., 2014; Rogasch and Fitzgerald, 2013). By analysing TEPs, this study confirmed that cerebellar iTBS decreases LICI, whereas cTBS increases it, while cTBS also decreases SICI (Casula et al., 2016; Koch et al., 2008). Moreover, the authors also significantly underscored a TBS-induced modulation of M1 oscillatory activity. Specifically, they showed that cerebellar cTBS decreases TMS-evoked alpha (8-12 Hz) activity, while iTBS enhances the beta (13-20 Hz) activity (Casula et al., 2016). As posited by the authors, these changes in oscillatory patterns likely mirror the influence of this particular NIBS protocol on GABAergic interneurons, potentially at the thalamic or cortical levels or both. Therefore, it is reasonable to propose that an increase in GABA-mediated inhibition prompted by cTBS might have diminished the power of M1's intrinsic frequencies, whereas iTBS had the converse effect (Habas et al., 2019; McCormick et al., 2015). This emphasises not only the pivotal role of the cerebellum in modulating the activity of interconnected intra-cortical circuits, particularly inhibitory ones, but also its apparent involvement in regulating brain rhythms.

This holds particular significance as a specific EEG metric, namely the mu rhythm (8-13 Hz), was used to assess MNS activity from a neurophysiological standpoint. Indeed, the attenuation of the mu rhythm occurs both during AO and during action execution and is, indeed, regarded as a surrogate for MNS activation (Fox et al., 2016). Moreover, its suppression is most evident during the observation of a precision grip and when object interaction occurs, namely conditions characterised by a relevant and specific activation of the AON (Muthukumaraswamy and Johnson, 2004; Muthukumaraswamy et al., 2004). Of note, the mu rhythm is formed by the variable contribution of both alpha- and beta-band activity, and also the latter is suppressed by both action execution, MI and AO. Thus, both the alpha and the beta-band mu components appear to be modulated by MNS activity (Babiloni et al., 2002; Hobson and Bishop, 2016; Pozzo et al., 2017). Importantly, the two EEG frequency bands implicated in these processes align with those modulated by cerebellar NIBS (Casula et al., 2016). Moreover, crucially, a seminal study combined the spatial resolution of fMRI with the temporal precision of EEG, offering pivotal evidence that, during AO tasks, mu rhythm modulation correlated negatively with the blood oxygenation level-dependent (BOLD, reflective of neural activity) signal in the MNS areas, prominently involving the bilateral cerebellum (Braadbaart et al., 2013). Taken together, this evidence not only reinforces the cerebellar involvement in the MNS but, more importantly, suggests a potential role in modulating the cortical activity within this functional system.

Further support for this functional connection stems from neurophysiological investigations. Specifically, an analysis of various regions within the AON in a monkey study revealed insights into the temporal sequencing of motor events during AO. The discharge patterns of neurons with mirror properties, especially in the area F5 and, to a lesser extent, in the pre-supplementary area (F6), were found to align with profiles typically associated with inhibitory interneurons (Ferroni et al., 2021; Gold et al., 2006; González-Burgos et al., 2005). Importantly, also human studies have shown that AO influences the activity of the intra-cortical inhibitory circuitry of M1, notably by modulating SICI. Indeed, extensive research has demonstrated that AO can downregulate SICI in various contexts, including joint actions and during the observation of errors in others' actions. Thus, GABA activity serves as a marker for the inhibition necessary for rapid motor adaptation and the regulation of motor functions via both fast and slow modulatory signaling pathways, thereby amplifying the adaptability of motor

behaviours (Cardellicchio et al., 2020, 2018; Neubert et al., 2011; Patuzzo et al., 2003; Tritsch et al., 2016). Moreover, the so-called “beta-rebound” in EEG activity, occurring subsequent to both AO and execution, is consistently considered as reflecting an active inhibition of motor activity (Jurkiewicz et al., 2006; Koelewijn et al., 2008; Pfurtscheller et al., 2005). Notably, a recent study confirmed the modulation of SICI in the context of AO and demonstrated its potential utility in predicting AO-induced behavioural improvement (Nuara et al., 2023). Indeed, it is widely acknowledged that intracortical inhibitory circuits are crucial for achieving optimal movement speed and accuracy since they play a pivotal role in selecting precise neural representations required for executing the desired movements while preventing undesired motor outcomes (Beck and Hallett, 2011; Greenhouse, 2022). Hence, the balance between cortical excitation and inhibition is paramount for executing precise movements, particularly in visuomotor tasks where the cerebellum plays a pivotal role (Ebbesen and Brecht, 2017; Giboin et al., 2021; Spampinato and Celnik, 2021). Furthermore, the thalamus plays a critical role in shaping the excitatory and inhibitory activity of the cortex, with the cerebellum emerging as one of the main modulators of thalamic activity (Habas et al., 2019; Taub et al., 2013). Therefore, it is possible that, after an initial phase of increased corticospinal excitation produced by the AO due to the sensory-motor resonance mechanism already discussed, the subsequent modulation of inhibitory activity (as assessed by the modification of SICI) selects the most useful motor representations to shape a “meaningful behavioural outcomes” and, indeed, the greater the inhibitory modulation, the better the subsequent performance in the same observed behaviour (Byblow and Stinear, 2006; Giboin et al., 2021; Hannah and Aron, 2021; Naish et al., 2014; Nuara et al., 2023).

However, a role for GABA-B has also been highlighted in this context, evidenced by LICI reduction when the observed action does not correspond to the concurrent executed action (Cardellicchio et al., 2020). Of note, this evidence could also provide some insight into the origin of the MNs found in the AON. In fact, some authors claim that MNs acquire their ability to match observed actions through a typical process of sensorimotor learning since they initially act as simple motor neurons during action execution and, later, undergo associative learning through repeated experiences of observing and performing the same actions (Heyes and Catmur, 2022). Thus, reasonably, through this correlated experience, motor neurons establish robust connections with perceptual (e.g. visual) neurons specialised in similar actions. However, other researchers have recognised the importance of visuomotor learning in the context of MNS, but they have suggested a genetic predisposition for their formation or an innate nature that can be traced back to motor experiences from birth or even during gestation (Del Giudice et al., 2009; Gallese et al., 2011, 2009). Although a genetic predisposition for MNs, given their crucial role in many fundamental activities that characterise evolutionarily higher-order organisms, seems plausible, a great deal of evidence has not only shown that sensorimotor learning is crucial to achieve their formation, but has also revealed that 'counter-mirror' training can reverse the mirror response and that mirror and counter-mirror responses follow the same time course (Brunsdon et al., 2020; Catmur et al., 2011; Cavallo et al., 2014; Guidali et al., 2020; Zazio et al., 2019). Consistently, in 7-month-old infants, sensorimotor mu rhythm suppression was heightened when they had received more sensorimotor experience in previous training sessions, despite their inability to walk at that age (de Klerk et al., 2015). Similarly, children born with a severe bilateral cataract, surgically treated only after several years, show a lower propensity to imitate the observed behaviour, which supports the hypothesis that the sensorimotor matching is crucial in shaping and modulating MNS activities (McKyton et al., 2018).

Based on this evidence, although some motor neurons might have a predisposition to develop mirror properties, the sensory-motor matching provided by visual-perceptual learning could be crucial and, reasonably, the cerebellum is instrumental in sculpting these circuits. Indeed, in the early stages of motor learning, the cerebellum displays greater activity, likely driven by significant disparities between anticipated and actual outcomes, but also identifies, via its connections with neocortical regions implicated in motor planning and execution, the most effective patterns to minimize such discrepancies (Penhune and Doyon, 2005; Spampinato and Celnik, 2021). Given, as already discussed, the substantial activation observed in the cerebellum during AO, mirroring that observed during actual execution, it is highly plausible that a similar mechanism is at play in shaping observational learning. Indeed, evidence from animal models has shown that a cerebellar lesion prevents learning by observation but not the use of already established memories or the performance of exploratory motor behaviour (Graziano et al., 2002; Molinari et al., 1997; Petrosini et al., 2003). Of note, Koch et al. showed, using a cerebellar TBS protocol, that it can modulate the characteristics of learning in a visuomotor adaptation task. This modulation, dependent on whether it is facilitatory (iTBS) or inhibitory (cTBS), correlates with alterations in activity across interconnected sensorimotor regions, likely attributable to shifts in the excitation/inhibition balance (Koch et al., 2020). Furthermore, given the crucial modulation of GABA-A interneurons (measured via SICI) by AO, and the predictive nature of this modulation on subsequent performance during executed behaviour, alongside the demonstrated significant impact of cerebellar NIBS techniques on intra-cortical GABAergic circuits, it seems reasonable to hypothesise that the cerebellum modulates, throughout motor learning mechanisms, the activity of intra-cortical inhibitory interneurons, presumably the same ones influenced by AO and known to exhibit mirror properties (Cardellicchio et al., 2020; Casula et al., 2016; Ferroni et al., 2021; Koch et al., 2008; Nuara et al., 2023). This would also justify the different pattern of activity between the cerebellum, which is more active in the early phases of learning to sculpt the visuomotor association in the intra-cortical circuitry, and the neocortical areas, which are more active in the later phases, reasonably because the sensory-motor matching process has been optimised and the motor circuits are able to select the most suitable activity patterns without a cerebellar intervention (Spampinato and Celnik, 2021). Moreover, some evidence has suggested that anodal tDCS applied to the lateral cerebellum during the learning phase of a new temporal motor skill may also facilitate its retention due to a priming effect, likely by enhancing the consolidation of new information once training is completed (Wessel et al., 2016). This is particularly intriguing when considering that the cerebellum not only plays a role in motor learning associated with AO but also in learning that integrates auditory information to guide motor actions (i.e., audio-motor learning, such as in musical practice) (Kohler et al., 2023). These findings suggest the potential of cerebellar NIBS to improve motor learning in a cross-modal manner, potentially overcoming specific deficits in one sensory modality by leveraging others to achieve improvement, which is a relevant aspect for tailoring therapeutic interventions according to the peculiar impairments of each patient.

Thus, although predictive coding hypotheses suggest that the motor system computes the difference between expected and observed information, this evidence seems to indicate that, depending on the degree of correspondence between the predicted and the achieved outcome, the involvement of specific areas of the AON is different, and this also has implications from a clinical point of view (Kilner et al., 2007; Urgen and Miller, 2015). Of note, this interpretation aligns with findings observed post-stroke. Indeed, a randomised clinical trial conducted on stroke patients demonstrated that a combined intervention of cerebellar iTBS and physiotherapy resulted in greater improvements in balance and gait compared to sham-iTBS and

physiotherapy alone. This suggests that neuroplastic changes in the cerebellum may influence the functioning of the fronto-parietal network through modulation of intra-cortical GABAergic circuits via dentate-thalamus connections (Koch et al., 2019, 2008). Consistently, after stroke, patients often exhibit deficits linked to alterations in excitatory and inhibitory circuits within the motor network, which are crucial for motor control and the generation of voluntary movements (Hummel et al., 2009). Specifically, it is well-established that SICI decreases just prior to movement initiation, increases just before movement termination, and subsequently decreases again, returning to baseline levels (Zaaroor et al., 2003). Importantly, a number of studies has shown that, in the acute and subacute stroke timeframes, resting SICI is reduced in the damaged M1 (Bütefisch et al., 2008; Cicinelli et al., 2003; Liepert et al., 2000). Interestingly, one study documented that even LICI was abnormally reduced in the affected hemisphere in the acute phase and it was the only intra-cortical neurophysiological index correlating with functional status and predicting recovery at 3 months (Swayne et al., 2008). Furthermore, a study on chronic stroke patients (after 6 months from the event onset) showed not only a persistent reduction in resting SICI in those with a good recovery but also its abnormal persistence during paretic hand movement preparation (Hummel et al., 2009). Notably, this decline in the function of inhibitory intracortical circuits, coupled with typically normal intracortical facilitation (ICF), results in heightened excitability in M1, which is deemed a crucial mechanism for enhancing functional recovery, likely influenced by modulation from other areas within both the ipsilateral and contralateral motor networks (Bäumer et al., 2006; Cicinelli et al., 2003; Manganotti et al., 2002; Murase et al., 2004; Swayne et al., 2008; Talelli et al., 2006). Consistently, several studies revealed that a decreased inhibitory activity is crucial for creating a permissive environment for cortical reorganisation and the establishment of new cortical boundaries (Jacobs and Donoghue, 1991). Moreover, following a stroke, the observed disinhibition at rest in affected M1 might serve as a compensatory mechanism for the impaired ability to execute voluntary movements effectively. However, it could also impose constraints on the extent of pre-movement modulation in the affected hand (Hummel et al., 2009). Indeed, although the evidence is not always consistent, the most accredited models support this interpretation since numerous EEG studies have demonstrated that, when the injured hemisphere is able to reorganise its activity through diverse compensatory mechanisms, the prognosis tends to be more favorable. Conversely, if the healthy hemisphere needs to compensate, likely due to severe damage in the affected one, the recovery outcomes are markedly less satisfactory (Antonioni et al., 2023; Di Pino et al., 2014; Milani et al., 2022). These findings gain further support in a study revealing that intra-cortical inhibition undergoes an abnormal reduction in the acute stroke phase in both the injured and healthy hemispheres. Interestingly, one month post-stroke, restoration of intra-cortical inhibition occurs in the unaffected hemisphere among patients exhibiting good motor recovery whereas, in cases of poor recovery, this abnormality persists in the unaffected hemisphere even at this timeframe (Manganotti et al., 2002). Significantly, longitudinal tracking of the same cohort over several months revealed a consistent pattern (Manganotti et al., 2008). This supports the notion that hemispheric disinhibition mirrors its reorganisation and that the persistence of the involvement of the healthy hemisphere indicates a failure of recovery in the injured one, thereby suggesting a poorer prognosis. However, an alternative hypothesis posits that the reorganisation of the healthy hemisphere relies on neuroplastic mechanisms associated with heightened usage of the unaffected limb. Consequently, severe patients lacking functional capacity in the affected limb might exhibit a use-dependent modulation of the intra-cortical inhibitory circuits in the unaffected hemisphere (Liepert et al., 1998; Shimizu et al., 2002).

Furthermore, it is worth mentioning that alterations in SICI have been documented in many disorders (e.g. schizophrenia) characterised by altered MNS functioning, whereas LICI alterations have been reported in cerebellar degeneration, highlighting a correlation between the cerebellum, GABAergic intra-cortical circuits, and MNS even in pathological contexts (Chen, 2004; Wessel et al., 1996). However, crucially, these findings are supported by studies in stroke patients indicating that EEG desynchronisation during AO follows a similar pattern since it occurs in the affected hemisphere among individuals with milder impairments and in the unaffected one among those with more severe deficits. Additionally, it has been demonstrated that the outcome of AOT can be predicted by mu suppression, which serves as a measure of MNS integrity (Antonioni et al., 2024a; Boni et al., 2023). Hence, we suggest that cerebellar NIBS enhances outcomes in stroke patients by modulating MNS activity. Through the regulation of intra-cortical GABAergic circuits, it enables the adjustment of the excitation/inhibition balance, which is essential for effective motor function. This modulation likely targets inhibitory interneurons with mirror properties, facilitating the restoration of optimal perceptual-motor associations necessary for achieving intended outcomes (Caligiore et al., 2013; Ferroni et al., 2021; Koch et al., 2019, 2008). Indeed, it is likely that, when the lesioned hemisphere retains activity in its MNs, such as mu suppression during AO, it possesses sufficient elements with mirror properties. These elements could be subject to modulation by cerebellar influence, facilitating the recruitment of optimal representations to minimize discrepancies between predicted and realised outcomes. Consistently, cerebellar activity correlates with motor recovery post-stroke, underlining its significance in this context (Luft et al., 2005). Indeed, even if inhibitory cortical interneurons are fewer in number compared to excitatory neurons, their impact is disproportionately significant, likely owing to the strategic positioning of their synapses (Kätzel et al., 2011). In summary, we propose that cerebellar NIBS, by modulating the circuits of intra-cortical inhibitory interneurons with mirror properties, restores the correct MNS response observed during both AO and action execution, leading to better motor performance. Consequently, we speculate that cerebellar NIBS might enhance mu suppression during AO in stroke patients with diminished responses by shaping novel visuomotor associations crucial for neuronal activity within this network.

And what about the cerebellar contribution during MI? Research indicates that, similar to AO, MI elicits heightened corticospinal excitability and, importantly, diminishes SICI akin to the pattern observed during mild voluntary contraction. This implies that while both conditions similarly activate the motor programme, its peripheral execution is impeded during MI (Abbruzzese et al., 1999; Rossini et al., 1999). However, in this case, there are no external stimuli to activate the corresponding motor representations, and it is reasonable to assume that subjects use their own memories to activate the AON and mentally simulate the action. Consistently, we suggest that the fundamental component for MI involves neurons with mirror properties within the hippocampal circuitry - although, to the best of our knowledge, no single-cell recording studies are currently available to prove this correlation, thus this interpretation remains speculative as it is based on indirect evidence. Indeed, a seminal study performed extracellular recordings of individual neurons in frontal and temporal regions among patients with drug-resistant epilepsy and demonstrated the existence of MNs in areas including the hippocampus, parahippocampal gyrus, and entorhinal cortex. Importantly, these neurons exhibited responses to hand-grasping actions, facial emotional expressions, and associated acoustic signals (Mukamel et al., 2010). Of note, recent research has revealed the close interconnection between the cerebellum and the hippocampus, suggesting their pivotal role in spatial navigation, which was traditionally associated solely to the hippocampus (Lefort et al., 2015; Moser et al., 2017). For example, the dentate nucleus

is implicated in the acquisition phase of learning the Morris water maze task, particularly in mastering the navigation toward a hidden platform. However, its involvement does not extend to the retention of spatial memory (Locke et al., 2018). Similarly, a self-motion-based motor sequence is not correctly acquired following damage to the dentate nucleus (Gaytán-Tocavén and Olvera-Cortés, 2004). In particular, during a navigation task, activation has been observed in cerebellar crus I, along with the contralateral hippocampus and either the medial PFC or medial parietal cortex, underscoring its significance in the cognitive facets of spatial navigation (Rondi-Reig et al., 2022). Consistently, functional connectivity between the hippocampus and specific cerebellar regions, i.e. Crus I, lobules VI, IV/V, IX, and X, plays a crucial role in both sequence learning and execution (Babayan et al., 2017). This connectivity pattern, observed during sequence-based navigation, mirrors findings in early motor sequence learning and accurate prediction of finger movements (Doyon et al., 2003; Onuki et al., 2015). Additionally, interactions between the hippocampus and the cerebellum facilitate not only precise movement prediction but also the perception of visual-spatial changes (Hauser et al., 2019). Taken together, these findings suggest that the hippocampus and cerebellum cooperate in tasks requiring integration of spatial and temporal dimensions (Rondi-Reig et al., 2022; Yu and Krook-Magnuson, 2015).

Furthermore, crucially, compelling evidence suggests that the hippocampus assumes a pivotal role in navigation tasks by encoding relationships among diverse elements, regardless of their nature, e.g. spatial, sensory, or motor, a process akin to episodic memory (Eichenbaum and Cohen, 2014). Moreover, research indicates that the cerebellum contributes to integrating sensory inputs that impact the activity of hippocampal cells (Lefort et al., 2015; Rochefort et al., 2011). It is intriguing that communication between the cerebellum and hippocampal structures occurs within the theta rhythm (5-7 Hz), which aligns with the intrinsic resonance of cerebellar granule cells. Indeed, this rhythm also appears to significantly influence the connectivity between the cerebellum and motor areas, raising the hypothesis that NIBS techniques employing this frequency may facilitate interactions with the hippocampus, potentially yielding significant implications for the observed positive outcomes (De Zeeuw et al., 2008; Hoffmann et al., 2015; Koch et al., 2020; Spampinato et al., 2021). It is plausible to speculate that these connections between the cerebellum and hippocampus could be relevant in the context of MNS since subjects might leverage them as a valuable short-term memory repository for prediction and postdiction concerning action outcomes (Friston et al., 2016; Friston and Buzsáki, 2016). Indeed, memory is no longer regarded as a static information storage but rather as a dynamic process that facilitates the recollection of actions performed and the associated sensations. From this perspective, MNS could hold significance both for the encoding of memories (e.g. associating words with gestures that activate the corresponding motor representation) but also for retrieving, as recalling actions aligned with one's motor repertoire (overlapping with those already performed or observed) appears more effortless than unfamiliar ones (Dijkstra et al., 2007; Macedonia, 2014; Yee et al., 2013). In line with Rondi-Reig et al.'s proposition, it also appears that the hippocampus might provide contextual cues, such as recalling past actions, to the cerebellum, which could execute a learning mechanism based on model-free reinforcement learning driven by sensory predictions (Babayan et al., 2017; Rondi-Reig et al., 2022). This notion finds support in the pioneering work of Buzsáki, positing that the CNS gives meaning to actions by probing their sensory outcomes and encoding the resulting sensory-motor loop through a "chunking" process, namely by combining already existing neuron sequences (linked to familiar aspects of the experience) to novel activity combinations (Buzsáki, 2019). Crucially, in this context, the pivotal role of the hippocampus emerges, with the cerebellum potentially accessing these experiential segments, reasonably guided by sensory cues, suggesting it might have the

ability to combine them to explore the best pattern to achieve the outcome, ultimately minimising the disparity between predicted and actual results (Buzsáki and Tingley, 2018; Friston et al., 2016; Friston and Buzsáki, 2016). Therefore, drawing from this evidence, we propose that the MNs within the hippocampal circuitry provide the cerebellum with the mnestic fragments necessary to implement the mental representation of the motor programme during MI and that the cerebellum, in evaluating the incongruity between the anticipated and realised sensory outcomes in internal simulation, due to its close connection with fronto-parietal areas, implements adjustments by trying new combinations of hippocampal-encoded sequences. This mechanism may underscore the functional connectivity changes, enhancements in performance, and notably, the generalization of these enhancements, as the newly encoded segments from cerebellar simulation for optimizing performance become accessible for other tasks (during MI, AO, and execution because the AON shares these representations), solely through mental practice (Gentili et al., 2006; Ladda et al., 2021; Marins et al., 2019).

Moreover, of note, since the cerebellum-hippocampal connections appear to be fundamental for voluntarily recalling previous experiences but not for improving motor performance, this could justify why severe hippocampal lesions (e.g., the notorious H.M. patient) preclude voluntary recall of previous motor and non-motor experiences but do not obtaining the benefits associated with repeated practice, which instead depend more on the cortico-striatal-cerebellar circuitry (Behrendt, 2013; Krakauer and Shadmehr, 2006; Squire, 2009). Indeed, if memory traverses the realm of recorded experiences, then MI and predictive coding could be likened to exploration within the kingdom of potentialities. In both domains, the hippocampus and cerebellum appear pivotal.

Finally, additional support for this interpretation also arises from another pathological model, namely phantom limb pain (PLP), a condition in which the patient has undergone a traumatic or surgical amputation of a limb yet persists in experiencing pain from the territory of the removed body region. This phenomenon potentially stems from the brain's endeavor to retain the cortical territory associated with that body region, even in the absence of peripheral input, and such maladaptive plasticity often engenders severe and intractable pain (Antonioni et al., 2024b; Nikolajsen and Christensen, 2015). Once more, several studies have intriguingly revealed an alteration in the activity of the intra-cortical inhibitory circuit, akin to mechanisms previously discussed in stroke cases, which may facilitate cortical reorganisation (Candido Santos et al., 2020). Additionally, there appears to be an alteration in the circuitry of the MNS, as the internal simulation of actions involving the absent limb fails to align with reality, and this discrepancy between expected and actual outcomes might potentially give rise to severe pain in affected individuals (Antonioni et al., 2024b; Chen et al., 2013; Collins et al., 2018; Schwenkreis et al., 2000; Teixeira et al., 2021). This could also explain why many effective therapies for PLP, e.g. box-mirror therapy and AOT, are based on MNS activation: it is conceivable, indeed, that AO and MI activate the sensory-motor representations of the loop, which the subject, naturally, can no longer effectively utilise and, by mitigating this discrepancy, it may inhibit maladaptive plasticity and the ensuing pain (Beaumont et al., 2011; Kuffler, 2018; Suso-Martí et al., 2020). Importantly, several studies have documented significant cerebellar activation in the context of pain perception, likely linked to the processing of sensory information and the regulation of frequently provoked motor responses (Coombes and Misra, 2016; Moulton et al., 2010; Peyron et al., 2000). Consistently, recent research has shown that a cerebellar NIBS protocol can reduce pain symptoms in PLP patients (Bocci et al., 2019). Indeed, although the evidence is not yet conclusive, the application of cerebellar NIBS techniques appears to be a promising strategy for pain

modulation, both from the perceptual, motor-response preparation, and emotional-cognitive perspectives (Manto et al., 2022; Schmahmann, 2019). We speculate that this phenomenon occurs not solely due to the restoration of the excitation/inhibition balance in interconnected cortical areas, reducing maladaptive plasticity and enhancing the critical functioning of the MNS to alleviate pain, but also because cerebellar stimulation is likely to facilitate the updating of the internal model, thereby reducing the discrepancy between predicted and actual outcomes and, reasonably, correcting the sensory-motor representation of the lost effector in the vast network of the AON.

8.6.1 Neuroanatomical and neurophysiological underpinnings of cerebellar modulation on the MNS

Notably, while the cerebellar output is solely inhibitory to the DCNs, provided by the axons of Purkinje cells, the other cerebellar cells can exert a complex influence that may significantly modulate the overall response (D'Angelo, 2018). For instance, cerebellar inhibitory interneurons targeting Purkinje cells can modify their activity to enhance or reduce the inhibitory signal directed to the DCNs. Interestingly, a great deal of research highlighted distinct types of long-term neuroplastic changes within the cerebellar cortex, both in terms of potentiation (Long-Term Potentiation, LTP) and depression (Long-Term Depression, LTD) (D'Angelo, 2014). Of note, these changes depend on different molecular mechanisms and the specific cell types involved, and they have been linked to behavioral changes associated with learning (Cheron et al., 2016). This suggests that performance improvement derives from the possibility of finely modulating and adapting cerebellar computations at the molecular and cellular level.

It is also important to note that these LTP/D effects are considered the neurobiological correlates of modulations induced by NIBS techniques (Cirillo et al., 2017). Indeed, neuromodulation can induce long-term changes in neurophysiological measures and in various behavioral outcomes by acting on different molecular mechanisms, such as calcium signaling or neurotransmitter receptor activity (Huang et al., 2017). This is particularly relevant in the cerebellum, as LTP/D effects have been shown to underpin various forms of learning, and the numerous involved cell types allow for extremely complex and refined modulation (D'Angelo, 2014).

For example, although it is not associated with long-term neuroplastic changes, tACS is able to influence specific cell types through a frequency-specific "entrainment" effect, which is thought to depend on the intrinsic resonance frequency (i.e. the characteristic activity frequency) of the targeted cell (Elyamany et al., 2021). Consistently, several studies suggested that theta-tACS predominantly affects granule cells, while gamma-tACS (30-80 Hz) mainly influences Purkinje cells, with effects due to, reasonably, modulation of the computational activity performed by the specifically targeted cell type (Miyaguchi et al., 2018; Spampinato et al., 2021). Additionally, TBS involves triplets of pulses in the gamma-band interspersed at the theta rhythm, offering the potential for even more extensive and complex network effects, hypothetically reflecting the interaction between different cell types (Koch et al., 2008). This is crucial, as the cerebellum exhibits one of the broadest range of activity frequency in the CNS, from slower rhythms, such as delta (< 4 Hz), likely attributable to the inferior olivary nucleus and its climbing fibers, and theta, likely associated with granule cell activity, to faster ones, like beta, associated with Golgi cell activity, gamma, hypothetically linked to the network of Purkinje cells and molecular layer inhibitory interneurons, and even ultra-rapid frequencies, whose origin is not yet fully understood (De Zeeuw et al., 2008). Therefore, cerebellar NIBS techniques might be fundamental for modulating cerebellar output and, consequently, its complex influence on numerous targets within the CNS.

At the brain level, as shown in Figure 3, the DCNs modulate various target areas through a thalamic relay, primarily involving the complex fronto-parietal network, but also temporal regions (Baumann et al., 2015; Casula et al., 2016; Dum and Strick, 2003; Mukamel et al., 2010).

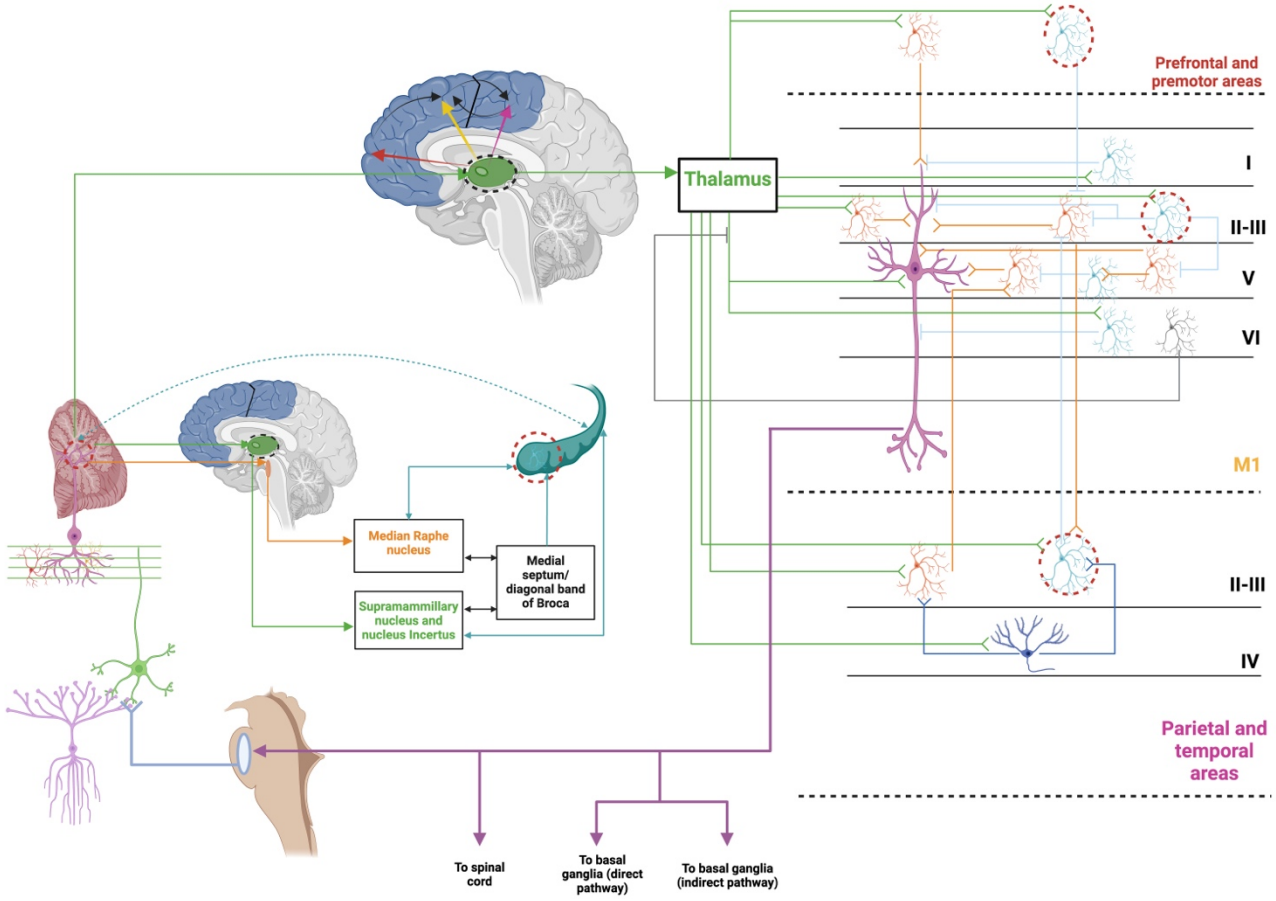


Figure 3. Schematic representation of the hypothetical model of the connections between the cerebellum and cortical/subcortical areas with inhibitory interneurons displaying mirror properties. On the left, an example of a cerebellar module is depicted (refer to Figure 1 for more details). The deep cerebellar nuclei project primarily to the thalamus (on the top), which in turn projects mainly to the primary motor area (M1) (on the right). This influence affects the output (i.e., the pyramidal neurons located in the cortical layer V) not only directly but also through excitatory (orange cells) and inhibitory cortical (blue cells) interneurons. Other inhibitory interneurons (grey cells located in cortical layer VI) provide a modulation on projections from the thalamus. Some of these interneurons reasonably display mirror properties (highlighted by a dashed red circle) and are responsible for the cerebellar influence on measures related to the Mirror Neuron System (MNS) activities, such as electroencephalographic measures (e.g., mu rhythm) and non-invasive brain stimulation techniques (e.g., short and long interval intracortical inhibition, SICI and LICI). These inhibitory interneurons are primarily found in cortical layers II and III in M1, where they can modulate the excitability of pyramidal neurons (and consequently the motor output) both directly and through a complex regulation of the excitation-inhibition balance involving other interneuronal circuits across various cortical layers. Notably, interneurons with similar properties and subject to cerebellar influence also appear to be present in prefrontal and premotor regions, as well as in associative parieto-temporal areas (on the right), justifying the cerebellum's participation and in

various aspects of MNS regulation. During the initial phases of learning, the cerebellum's influence on these interneurons may contribute to shaping the circuits by creating new visuo-motor (or audio-motor, depending on the specific areas) associations to optimize performance. When the discrepancy between predicted and actual outcomes is minimized, cerebellar influence becomes less relevant, and its activity diminishes. These interactions likely explain the performance improvements obtained not only by executing a task but also by merely observing it or listening to related significant stimuli. Furthermore, the cerebellum engages in bidirectional communication with the hippocampus (in the centre), both directly and through the thalamus and, to a lesser extent, the Median Raphe nucleus, a serotonergic brainsteam structure, which project to the medial septum and the nucleus of Broca's diagonal band, which provide access to the hippocampus. This allows the cerebellum to retrieve mnemonic traces during motor imagery (MI) to test the hypothetical sensory consequences of motor action (also using available information from cortical networks, which provide essential data on planning, strategy, multi-sensory associations, and a priori hypotheses from already established models), thereby refining interneuronal patterns to minimize discrepancies between predicted and expected outcomes. Conversely, once the models are optimized, the cerebellum strengthens hippocampal circuits that retain the optimized patterns, reasonably explaining the performance benefits associated with MI. Notably, these new internal models are available for other activities in which the MNS is involved, such as execution and AO, reasonably justifying the similar benefits derived from these different activities. Axons terminating bifidally indicate excitatory synapses, while those ending with a straight line indicate inhibitory ones. Based on (Bonini et al., 2022; Caligiore et al., 2017b; Casula et al., 2016; Daskalakis et al., 2004; Dum and Strick, 2003; Koch et al., 2008; Rolls, 2023; Rondi-Reig et al., 2022; Spampinato et al., 2023; Zeidler et al., 2020). Abbreviations: AO: action observation; LICI: long interval intracortical inhibition MI: motor imagery; MNS: Mirror Neuron System; M1: primary motor cortex; SICI: short interval intracortical inhibition. Figure created with BioRender.com.

Specifically, in M1, the thalamic projections modulated by the cerebellum influence not only the pyramidal neurons of layer V (i.e. the output of the motor cortex which forms the descending motor pathways) but also, notably, inhibitory interneurons, mainly located in cortical layers II and III (Opie et al., 2022; Rolls, 2023; Spampinato, 2020). Based on the discussed evidence, these interneurons could be the neurobiological substrate of EEG (i.e., mu rhythm) and NIBS (i.e., SICI/LICI) measures whose activity has been associated with the MNS and, therefore, justify the cerebellum's crucial modulation of this network (Cardellicchio et al., 2020; Casula et al., 2016; Farina et al., 2020; Ferroni et al., 2021; Nuara et al., 2023). Notably, the position of these inhibitory interneurons with mirror properties (dotted red circles in Figure 3) in M1 is critical, as it allows them not only to inhibit pyramidal neurons directly but also to finely modulate excitatory and inhibitory interneuronal circuits distributed across the different cortical layers (Chen, 2004; Yi et al., 2014). Indeed, these circuits likely enable increasingly accurate and precise motor outcomes by balancing excitation and inhibition to select the best motor patterns to achieve the desired motor outcome (Cardellicchio et al., 2018; Nuara et al., 2023). It is reasonable to hypothesize that cerebellar influence on these circuits is greater when there is a high disparity between predicted and actual outcomes, as seen in the early stages of learning. Conversely, as practice (whether actual or related to AO and MI) reduces this disparity, reflecting a proper shaping of visuomotor relationships, cerebellar activity diminishes, likely because the efference copy and peripheral signals do not report errors in internal models (Spampinato and Celnik, 2021).

However, as previously discussed, inhibitory interneurons displaying mirror properties have also been found in prefrontal, premotor, parietal, and to a lesser extent, temporal regions (Bonini et al., 2022). All these areas are strictly interconnected with M1, allowing for further modulation of its activity (Ferrer and De Marco García, 2022; Kinnischtzke et al., 2014; Rolls et al., 2023). Indeed, inhibitory interneurons with mirror properties in prefrontal and premotor areas might affect higher-order aspects of behavioral strategies and motor planning, where cerebellar modulation could play a critical role in selecting optimal activities based on specific goals (Balsters et al., 2010; Schmahmann, 2019; Tzvi et al., 2020). In contrast, cerebellar modulation of temporo-parietal areas, crucial for multisensory integration, might contribute by fine-tuning the action of inhibitory interneurons showing mirror properties that influence motor regions (Jakobs et al., 2012; Kohler et al., 2023). This process might leverage various sensory channels (i.e. visual and auditory), allowing learning not only through execution but also through AO or listening to meaningful stimuli, which represent a perspective with important clinical implications.

Crucially, the cerebellum is bidirectionally connected also with the hippocampus, both directly and, more importantly, indirectly, via other thalamic nuclei and brainstem structures, such as the Median Raphe nucleus (Rondi-Reig et al., 2022). Animal model studies have demonstrated that stimulation of this serotonergic brainstem nucleus leads to a motor inhibition associated with strong suppression of hippocampal theta rhythm (Bland et al., 2016). Considering the role of the cerebellum in motor inhibition and its extensive anatomic-functional connections (likely in the theta band) with the hippocampus, it is possible that these effects are also dependent on an interplay between the cerebellum and hippocampus mediated by this serotonergic system (Beliveau et al., 2015; Hoffmann and Berry, 2009; Peterburs and Desmond, 2016; Rondi-Reig et al., 2022). Both these thalamic nuclei (specifically, the supramammillary nucleus and nucleus incertus) and the Median Raphe nucleus access the hippocampus via the medial septum/diagonal band of Broca, a region that modulates various neurotransmitter systems, most crucially the GABAergic one (Damborsky and Yakel, 2021; Takeuchi et al., 2021). Therefore, it could represent a key gateway for the cerebellum to modulate hippocampal inhibitory interneurons displaying mirror properties (Kang et al., 2021). Reasonably, the hippocampus provides the cerebellum with memory traces to access context-dependent internal models (Mukamel et al., 2010; Zeidler et al., 2020). Furthermore, these connections might be crucial for enabling the cerebellum to test hypothetical sensory consequences and generate internal models in new contexts. This process is shaped by simulating actions within the AON and utilizing multisensory and strategic information from previous experiences stored in interconnected cortical networks (Caligiore et al., 2013; Yu and Krook-Magnuson, 2015). Since the hippocampus might provide memory traces to the cerebellum independently of available sensory stimuli, it is plausible to hypothesize that the refinement of internal models could occur solely through MI. Finally, since these connections are bidirectional, the cerebellum might strengthen hippocampal patterns matching to models minimizing the discrepancy between predicted and actual outcomes, likely modulating the activity of the same inhibitory interneurons that facilitate the recall of stored models during memory retrieval (Rondi-Reig et al., 2022). These patterns then become available for future use but might still be susceptible to modification if MI leads to the hypothesizing of different scenarios.

While these interactions are effective and optimized in healthy subjects, CNS lesions may impair these complex activities. For instance, direct cerebellar damage might impair the shaping of visuo-motor associations due to the loss of influence on cortical inhibitory interneurons, hindering learning and, consequently, performance optimization (Petrosini et al., 2003). Conversely, lesions in different brain areas could disrupt the

already discussed specific contributions to this complex computational model (Bonini et al., 2022). Importantly, in this context, NIBS techniques might be harnessed to promote recovery. Indeed, cerebellar neuromodulation techniques offer the opportunity to modify numerous aspects of cerebellar computation. This includes modulating membrane excitability in either an excitatory or inhibitory manner, such as through tDCS, or promoting the activation and synchronization of specific cell types using tACS by selecting the relevant frequencies (Ferrucci et al., 2015; Wessel et al., 2023). Moreover, other techniques, such as iTBS or cTBS, can induce long-lasting neuroplastic changes, like LTP/D effects, in various regions (depending on the application site) and in different cell types, based on the technique employed (Koch et al., 2008). All these modulations might help shift the cerebellar network effect, aiding in the recovery of compromised activities. For example, in pathologies characterized by abnormal cortical excitability, the inhibitory effect of the cerebellum on connected areas can be enhanced, and conversely in conditions where cortical excitability is reduced (Manto et al., 2022). Indeed, as previously discussed, the modulation of this balance between excitation and inhibition is crucial for performance optimization and this is likely attributable to the specific cerebellar influence on cortical inhibitory interneurons with mirror properties, potentially creating new visuomotor associations that enable the recovery of lost functions using available resources despite the damage (Vattikonda et al., 2016). Additionally, protocols combining cerebellar and cerebral neuromodulation might offer a crucial tool to bypass disrupted anatomical connections. Indeed, by leveraging rhythm-based coordination, these protocols could enable the cerebellum to create new visuo-motor associations to improve performance (Miyaguchi et al., 2018). Specifically, the gamma rhythm is thought to be essential for coordinating activities between spatially distant neuronal populations, and studies employing this rhythm have already demonstrated improved cerebellar-motor interactions and behavioral outcomes (Buzsáki and Schomburg, 2015; Miyaguchi et al., 2020). Crucially, it has been suggested that gamma rhythm arises from the activity of inhibitory interneurons, which enable fine regulation within functionally integrated circuits (Cardin, 2018). Therefore, it seems reasonable that protocols combining gamma-band cerebellar and brain stimulation modulate, on the one hand, the network formed by the Purkinje cells and the interneurons in the cerebellar molecular layer (De Zeeuw et al., 2008). On the other hand, they might influence the circuitry of cortical inhibitory interneurons, promoting the shaping of sensorimotor associations that are essential for learning and, notably, fundamental to the functioning of the MNS (Bonini et al., 2022; Miyaguchi et al., 2020; Nowak et al., 2018). Given the number of cell types involved in cerebellar computations, further studies will be fundamental to deepen their different contributions to these complex interactions.

Furthermore, despite the topographical organization of the cerebellum reflects the cerebellar-cortical loops from an input and output perspective, the horizontal extension of Purkinje cell dendritic arborizations and the collateral branches of mossy and climbing fibers allow communication between non-adjacent modules (Apps et al., 2018; Shinoda and Sugihara, 2022). This could be a useful tool for neuromodulating healthy areas to bypass lesioned sites because of various local and remote pathologies. Lastly, although our discussion has primarily focused on the relationship between the cerebellum, cortical networks, and the hippocampus, cerebellar output can also modulate the spinal cord and basal ganglia, providing additional benefits and likely exerting a highly complex influence on the MNS (Arber and Costa, 2022; Caligiore et al., 2017b). Further studies and future research will be needed to delve deeper into these influences.

8.6.2 Future clinical perspectives

Given the burden of neurological diseases and the expected increase in their prevalence in the coming years, interventions that enable effective recovery while reducing the burden on healthcare facilities are increasingly required (Feigin et al., 2020). Indeed, as recently highlighted by the COVID-19 pandemic, current diagnostic and therapeutic services depend critically on hospital admissions, increasing both direct and indirect medical costs and leading to significant risks, especially for the most vulnerable patients (Pujolar et al., 2022). In this context, there is a considerable interest in the potential for effective therapies that do not require hospital visits but can be administered directly at local facilities or even remotely (e.g. through video recordings or home-based NIBS treatments), enabling a safe and cost-effective treatment of patients (Caumo et al., 2023; Sale and Franceschini, 2012). Therefore, AOT might be a fundamental tool for improving the functional outcomes of patients with neurological disorders. Indeed, it could be systematically used not only in the acute phases of the disease, when patients often show motor deficits preventing the effective execution of exercises, but also in post-acute settings, thus integrating current clinical neurorehabilitation practices. As cerebellar NIBS enhances motor learning not only online but also through a priming effect for the retention of subsequently acquired skills, the combination of AOT and cerebellar neuromodulation might significantly improve clinical outcomes (Cantarero et al., 2015; Wessel et al., 2016). This is likely through a common modulation of the MNS, which might enrich patients' motor repertoire and, consequently, their daily autonomy.

Notably, the utility could extend beyond patients with motor deficits, including the large group of those suffering from various pain-related issues, which are extremely common in the general population (Rice et al., 2016). Indeed, as recently suggested, pain may also result from a mismatch between the sensory and motor information in the internal models due to different circuit alterations (Antonioni et al., 2024b). Therefore, remodulating the sensorimotor associations characterizing internal models could significantly improve patient's quality of life. This is particularly relevant when considering that pain therapy often requires the combination of numerous medications, which are burdened by significant adverse effects and frequently incomplete efficacy (Siebenhuener et al., 2017). Furthermore, it could represent an important therapeutic aid for patients who, due to their clinical conditions, often cannot undergo traditional rehabilitative treatments, such as those in palliative care. This is not only because of these techniques' safety and minimal invasiveness but also because they can be administered in any care setting (Chowdhury et al., 2020). Thus, combining cerebellar NIBS and AOT might be crucial in this respect. Considering the recent evidence on chronic pain syndromes post-COVID-19, these issues are expected to become even more relevant in the next years (Baroni et al., 2023). Hopefully, the evidence discussed in this review will provide insights for improving the complex management of various patient categories, leveraging the fundamental synergy between the cerebellum and cortical networks reasonably mediated by the MNS.

8.6.3 Limitations and possible alternative interpretations

Here, we have sought to gather and analyze the best evidence about the cerebellar involvement in the MNS. Although extensive research suggests a crucial role for cerebellar modulation in this context, there are relevant aspects to consider. Firstly, unfortunately, much of this evidence is indirect, as the cerebellum has not been adequately studied by older brain MRI protocols (Talairach and Tournoux, 1988). Indeed, this established atlas sets a standard for neuroimaging reporting, but it is tailored for the cerebral cortex and lacks validation for the cerebellum. Furthermore, most neuroimaging studies must choose between a larger spatial coverage or an

increased task sensitivity (i.e. a shorter acquisition time), leading researchers to favour a smaller field of view and, thus, to remove the cerebellum in many analysis protocols (Abdelgabar et al., 2019). Moreover, to support the involvement of the cerebellum in MNS activities, several meta-analyses have been included (Caspers et al., 2010; Hétu et al., 2013; Molenberghs et al., 2012; Van Overwalle et al., 2014). While they are important references in the literature due to their high quality, it is well known that meta-analyses can have several potentially significant limitations, chiefly the heterogeneity of the data collected in terms of sample size, data analysis techniques, study population, and potential confounding factors (e.g., age, gender, medication use) (Jennings and Van Horn, 2012; Müller et al., 2018). This is particularly relevant when considering that the evidence stems from healthy subjects and pathological contexts characterized by highly heterogeneous pathophysiology and various study designs, each characterized by its own advantages and disadvantages (Colditz, 2010). Furthermore, the data have been collected using different neuroimaging techniques, namely PET and fMRI. While the former is characterized by relatively low temporal resolution, the latter boasts excellent spatiotemporal definition but is often affected by artifacts and physiological variations (Wang et al., 2021). Moreover, the difference in the aspects investigated (i.e. brain metabolism versus blood flow variations) potentially complicates direct comparison (Jamadar et al., 2021). In addition to introducing considerable qualitative variability among the different studies, these aspects can lead to potential inconsistencies in the interpretation of results, which is crucial in meta-analysis of neuroimaging data (Metelli and Chaimani, 2020). In addition, there is often a publication bias in these contexts, as studies with significant results are more likely to be published than those with negative or inconclusive results, which could distort the reality of the available evidence (Page et al., 2021). Consistently, as previously discussed (see section 2), the results presented by the included meta-analyses are often conflicting. However, it is encouraging to observe that the most recent meta-analyses, compared to earlier ones, confirm significant cerebellar activity during AO and MI (Hétu et al., 2013; Van Overwalle et al., 2014). This suggests that, thanks to more recent evidence, with more up-to-date and higher quality data (also due to advancements in neuroimaging atlases), the cerebellum's role is emerging more clearly and consistently despite the aforementioned limitations.

Furthermore, a direct recording of the cerebellar rhythms, both in healthy controls and patients, is severely limited by numerous technical issues that have constrained the application of EEG in studying cerebellar activity. Indeed, the cerebellum is a deep structure and the distance between the EEG signal source and the recording electrode decreases the signal-to-noise ratio, reducing the reliability of the recorded data (Andersen et al., 2020). Moreover, the distance of the cerebellum from the main source of the EEG signal, the contamination caused by myogenic activity, and its architecture provide further limitations for EEG applications (Muthukumaraswamy, 2013; Samuelsson et al., 2020). However, emerging research indicates that, under specific conditions, cerebellar activity can be detected using EEG, and it is likely that much more neurophysiological data on its involvement in various functions will be available in the future (Andersen et al., 2020; Samuelsson et al., 2020).

Finally, although this review has compiled numerous pieces of evidence on the involvement of the cerebellum in the context of MNS activities, as previously highlighted, many of the discussed findings are indirect. Thus, the interpretations presented here require further research to confirm their correctness. Indeed, it is important to consider that the results on cerebellar activity during AO and MI allow for additional interpretative approaches. For example, the cerebellum is critically involved in motor coordination tasks and the fine-tuning of movements, so its activation during tasks related to MNS functioning may just reflect a motor coordination

aspect rather than a direct role in the imitation, MI or understanding of AO (Miall, 2022). Furthermore, as suggested by some authors, it is possible that the cerebellum merely encodes observed movements to make them more efficient and automatic, leaving the primary functions attributed to the AON in different brain areas (Balsters and Ramnani, 2011). It is also conceivable that the cerebellum's role is limited to processing data that supports the activities of cortical and subcortical regions (e.g., the basal ganglia), enhancing their computational capacity and, consequently, the subject's performance without being an integral part of the AON (Raymond and Medina, 2018). This might align with evidence showing increased cerebellar activation with general task complexity (Katz and Knops, 2016; van Dun et al., 2022). Additionally, the cerebellum might support high-level cognitive functions, such as attention and working memory, perhaps without a specific role in MNS activities (Schmahmann, 2019). However, studies demonstrating a strong correlation between AO, EEG biomarkers of MNS involvement (i.e. mu rhythm desynchronization), and cerebellar activation (as assessed through fMRI), together with evidence on the loss of observational learning due to AO following cerebellar lesions suggest a specific cerebellar role rather than mere co-activation or support to other key areas (Braadbaart et al., 2013; Petrosini et al., 2003). It is hoped that future studies will delve deeper into its precise contribution to this complex set of activities and clarify its specific interaction with other structures involved in shaping the significant effects of MNS-related activities (Caligiore et al., 2017b, 2013).

8.7 Conclusions

The evidence suggests that the cerebellum is critically involved in MNS activities, i.e. AO and MI, and that it may participate by modulating the activity of cortical inhibitory interneurons with mirror properties in visuomotor matching. During motor learning and movement observation, this phenomenon would reduce the discrepancy between what is expected and what is achieved. Indeed, it is reasonable to hypothesise that the cerebellum reinforces patterns that minimise, from a sensorimotor perspective, the difference between predicted and obtained outcomes, both during execution and during AO. Furthermore, through its connections with the hippocampus, it is reasonable that the cerebellum, during MI, participates in internal simulations of motor programmes, exploring numerous possibilities and reinforcing those most useful for achieving desired outcomes. However, further studies are needed to confirm this hypothesis. This aspect is innovative and crucial, as different NIBS techniques might also be used for therapeutic purposes, using cerebellar stimulation to promote motor recovery in patients. Consistently, cerebellar NIBS modulation appears to improve its impact on MNS activity by regulating the inhibitory circuitry of frontoparietal regions via the thalamus, and applications in neurorebilitative terms are steadily increasing. In conclusion, the MNS and the cerebellum seem to be strictly interconnected in their function, aimed at enhancing individual motor functioning, even in a pathological setting, a crucial point from a motor recovery perspective.

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Chapter 9. Elevating cerebellar theta oscillations boosts non-invasively induced motor plasticity

This chapter of the thesis delineates a study demonstrating—through five experiments initially conducted on healthy individuals and subsequently on patients with chronic stroke—that the modulation of the ongoing cerebellar oscillatory state during the administration of non-invasive brain stimulation (NIBS) is a critical factor in enhancing the efficacy of specific protocols. Specifically, the findings illustrate that modulation of the theta rhythm—which, according to converging literature, appears to be the frequency most strongly involved in mediating communication between the cerebellum and the cortical motor network—produces significant effects both at the neurophysiological level, as assessed within the circuitry of the primary motor cortex (M1), and in behavioral performance.

Indeed, entraining cerebellar theta rhythms through transcranial alternating current stimulation (tACS) during intermittent theta burst stimulation (iTBS) significantly improved neurophysiological plasticity and fine motor skills in humans. This approach further enhances the effects previously shown with cerebellar iTBS, which is known for inducing plasticity and neurophysiological changes in M1, as well as improving performance. Notably, these effects were both frequency- and site-specific: performance gains occurred when theta stimulation was applied over the cerebellum and gamma stimulation over M1, highlighting the importance of tailoring stimulation to each target's resonant frequency to maximize effectiveness and likely facilitate the recruitment of the neural pathways that mediate interactions between different brain regions. Thus, by aligning stimulation with the cerebellum's endogenous frequency, it becomes possible to selectively enhance circuit responsiveness and produce lasting, meaningful improvements in both healthy individuals and chronic stroke patients. This finding is highly relevant for advancing functional outcomes beyond the period of heightened post-stroke neuroplasticity.

The work presented here is currently under review in Science Advances.

9.1 Abstract

Matching brain stimulation to the brain's natural rhythms can drive plasticity, yet this principle has rarely been tested in humans. We targeted the cerebellum, a key hub for motor coordination and learning, using a rhythm-tuned protocol pairing theta-frequency transcranial alternating current stimulation with intermittent theta-burst stimulation to engage cerebello-cortical circuits. In young healthy adults, this pairing enhanced fine motor control and hand dexterity, with gains closely tracking physiological markers of cerebellar-driven plasticity. Applying the same approach in chronic stroke survivors yielded parallel behavioral and neural gains, demonstrating preserved rhythm–plasticity coupling despite injury. Control experiments confirmed frequency and site specificity, underscoring the mechanistic precision of the intervention. By linking cerebellar theta entrainment to circuit-level and functional outcomes, these findings establish a biologically grounded framework for targeted neurorehabilitation. Rhythm-specific cerebellar stimulation provides a scalable strategy to enhance plasticity and improve motor function across movement disorders and motor impairments.

9.2 Introduction

Frequency-tuned neuromodulation is a powerful yet underexplored strategy to enhance plasticity in subcortical brain circuits. The cerebellum, long recognized for its role in motor control and learning, is emerging as a key modulator of experience-dependent plasticity, but the mechanisms remain poorly understood. One candidate is intrinsic theta-band (4–8 Hz) activity, which organizes input–output transformations in cerebellar microcircuits and drives synaptic plasticity via spike-timing and N-methyl-D-aspartate/nitric oxide (NMDA/NO)-dependent mechanisms (De Zeeuw et al., 2008; Gandolfi et al., 2013; D. Popa et al., 2013).

While theoretical models highlight the importance of cerebellar theta dynamics, it remains unknown whether externally entraining these rhythms can directly modulate plasticity and behavior in humans. Aligning neuromodulation to intrinsic cerebellar activity offers a biologically grounded route to engage circuit-specific plasticity (Asan et al., 2020; Guerra et al., 2024; Spampinato et al., 2021; Thut et al., 2011), an especially promising approach in stroke, where cortical plasticity is often impaired but cerebellar–cortical pathways remain structurally intact and functionally responsive (Koch et al., 2019, 2008; T. Popa et al., 2013).

Cerebellar intermittent theta-burst stimulation (iTBS) has shown that the cerebellum is responsive to non-invasive neuromodulation and may facilitate motor recovery (Bonnì et al., 2014; Koch et al., 2019), but it does not directly target ongoing oscillatory activity. To address this, we introduce a dual-modality, resonance-based protocol combining 5 Hz transcranial alternating current stimulation (tACS) with cerebellar iTBS. Grounded in models of cerebellar resonance and circuit excitability (Courtemanche and Lamarre, 2005; D'Angelo et al., 2001; Mapelli et al., 2017), this approach is designed to entrain theta dynamics and amplify downstream motor plasticity.

Across experiments in young healthy adults and individuals with chronic stroke, we demonstrate that cerebellar-theta stimulation produces robust, frequency-specific enhancements in physiological plasticity and fine motor function. These findings establish cerebellar theta entrainment as a circuit-informed, translationally scalable strategy for restoring function in conditions marked by impaired cortical plasticity.

9.3 Results

We first tested whether combining cerebellar-theta tACS with iTBS (θtACS-iTBS) enhances motor plasticity in healthy individuals (Fig. 1). In Experiment 1, fourteen healthy young adults received cerebellar-targeted iTBS paired with tACS either at theta (5 Hz), gamma (50 Hz), or sham frequency (Fig. 1A). Biophysical modeling confirmed focal targeting of the lateral cerebellum, with peak intensities in the 35–45 V/m range (Fig. 1B), supporting the precision and efficacy of our targeting approach.

Corticospinal excitability, indexed by motor-evoked potentials (MEPs), served as a physiological proxy for cerebellar-motor plasticity. A repeated-measures ANOVA with SESSION (Theta, Gamma, Sham) and TIME (T0, T15, T30) revealed a significant main effect of SESSION ($F(2,26) = 5.411$, $p = 0.011$, $\eta^2_p = 0.294$). No significant main effect of TIME or SESSION × TIME interaction was observed. Post hoc comparisons showed that MEP amplitudes were significantly increased following θtACS-iTBS relative to sham ($p = 0.014$), with effects persisting through P30 (Fig. 2A). No significant change was observed following γtACS-iTBS (Fig. 2B). These enhancements are consistent with durable, circuit-level modulation of motor output. These findings suggest cerebellar theta entrainment primes local networks for synaptic potentiation, enabling iTBS to more effectively drive plastic change.

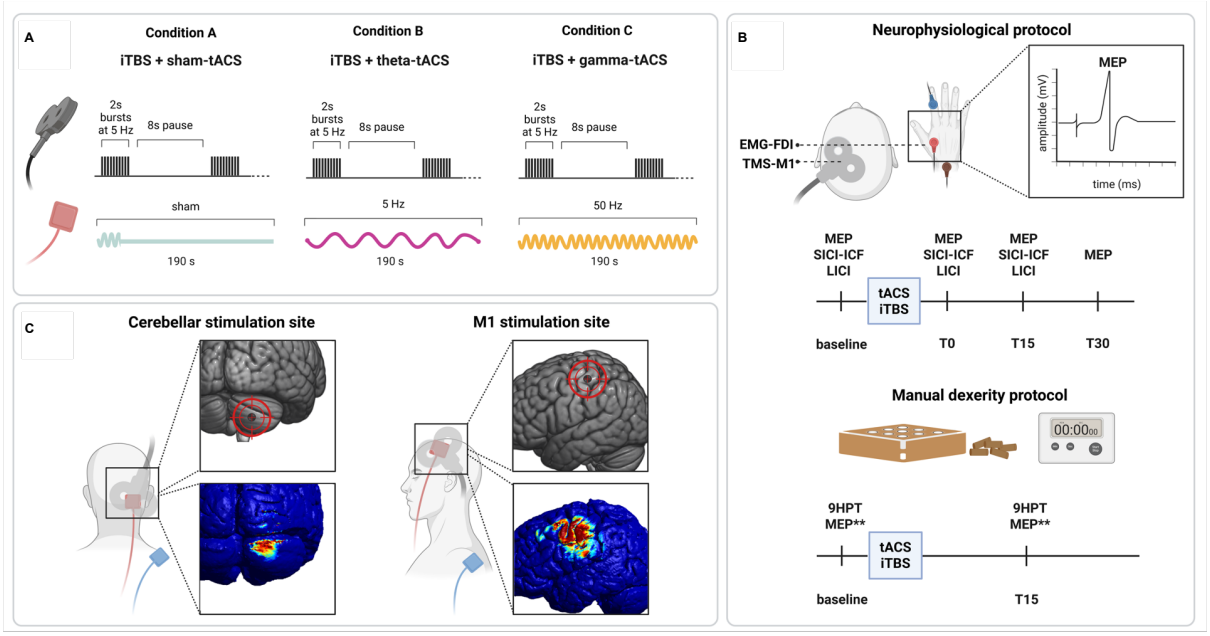


Figure 1. Experimental Conditions and Protocol Overview. (A) Each session involved intermittent theta burst stimulation (iTBS; 2-second bursts at 5 Hz repeated every 10 seconds, 80% AMT, 600 pulses total, 190 s) paired with transcranial alternating current stimulation (tACS; 2 mA). Three conditions were tested: sham-tACS, gamma-tACS (50 Hz), and theta-tACS (5 Hz). (B) Stimulation targeted either the lateral cerebellum (3 cm lateral and 1 cm inferior to the Inion) or the primary motor cortex (M1). In stroke participants, cerebellar stimulation was delivered contralesional to the affected hemisphere. Electric field simulations (bottom) depict induced field magnitude during tACS-iTBS at both targets, with a field strength range of 35–45 V/m for the cerebellum and 35–55 V/m for M1. (C) Neurophysiological outcomes included motor-evoked potentials (MEPs) to assess corticospinal excitability and paired-pulse protocols to evaluate short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and long-interval intracortical inhibition (LICI), recorded at baseline, and at 0 (T0), 15 (T15), and 30 (T30) minutes post-intervention. Manual dexterity was evaluated using the Nine-

Hole Peg Test (9HPT), performed before and 15 minutes after stimulation. ** MEP measures during 9HPT testing were acquired in healthy participants only. Figure created with BioRender.com.

To further characterize the physiological effects of stimulation, we assessed intracortical inhibition and facilitation using standard paired-pulse TMS protocols: short-interval intracortical inhibition (SICI, 2 ms), intracortical facilitation (ICF, 15 ms), and long-interval intracortical inhibition (LICI, 100 ms). A repeated-measures ANOVA with within-subject factors SESSION (Theta, Gamma, Sham) and TIME (Baseline, T0, T15) revealed a main effect of TIME for SICI ($F(2, 26) = 6.76$, $p = 0.004$), but no significant SESSION × TIME interaction ($p = 0.48$). Post hoc analyses within the theta condition showed that SICI was significantly reduced at 15 minutes post-stimulation compared to baseline ($t(13) = –2.82$, $p = 0.014$), consistent with a delayed disinhibitory effect (Fig. 2C). No significant differences were observed between baseline and T0 ($p = 0.16$) or between T0 and T15 ($p = 0.32$). No significant effects were found for ICF or LICI in any condition (all $p > 0.05$), nor were significant time effects observed in the gamma or sham sessions (Fig. 2C). These findings suggest that cerebellar θtACS-iTBS selectively reduces SICI over time, potentially facilitating cortical disinhibition and enabling downstream plasticity mechanisms.

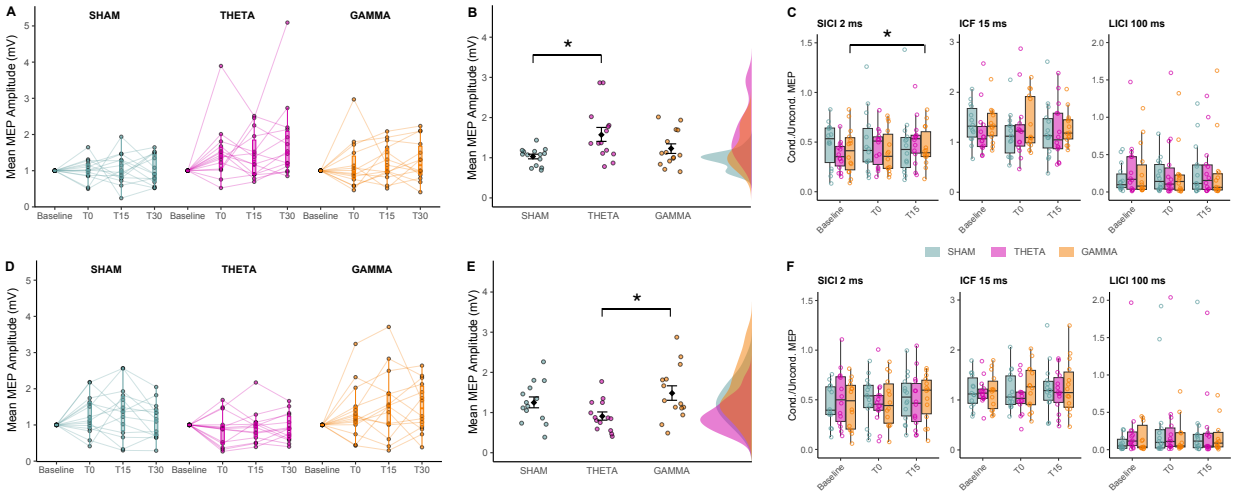


Figure 2. Cerebellar theta-tACS-iTBS selectively enhances corticospinal excitability through resonance-based plasticity. (A) Time course of normalized MEP amplitudes following cerebellar stimulation. Theta-tACS-iTBS produced a sustained increase in corticospinal excitability up to 30 minutes post-stimulation, while gamma and sham had no significant effect. (B) Group-level analysis shows significantly greater mean MEP amplitude following theta-tACS-iTBS compared to sham ($p = 0.014$), indicating frequency-specific enhancement Plots are shown as half-violin plus box plots to depict distribution and central tendency (C) Intracortical excitability assessed via paired-pulse TMS. Theta-tACS-iTBS significantly reduced SICI (2 ms) at 30 minutes post-stimulation compared to baseline, indicating reduced GABAergic inhibition. No significant effects were observed for ICF (15 ms) or LICI (100 ms). (D) MEP amplitudes over time following stimulation of the left primary motor cortex (M1). Gamma-tACS-iTBS increased MEP amplitudes over time, while theta stimulation failed to enhance, and sometimes suppressed, MEP responses. (E) Group-level analysis confirms significantly greater MEP amplitudes after gamma versus theta stimulation ($p < 0.05$), with no difference from sham. (F)

Paired-pulse measures following M1 stimulation showed no significant effects on SICI, ICF, or LICI across conditions. Error bars represent SEM. $p < 0.05$.

To formally assess the anatomical specificity of the observed effects, we pooled data from Experiments 1 and 2 and conducted a linear mixed-effects model with stimulation condition (Theta, Gamma, Sham) and stimulation site (Cerebellum, M1) as fixed factors. This analysis revealed a significant Condition × Site interaction for theta stimulation (β = –0.650, p = 0.047), indicating that the plasticity-enhancing effects of θtACS-iTBS were specific to cerebellar stimulation and did not extend to M1. These findings highlight the necessity of both anatomical and frequency precision in designing effective neuromodulation protocols.

We next asked whether these physiological changes translated into behavioral improvements. In Experiment 3, participants completed the 9HPT, a validated measure of fine motor control, before and after cerebellar θtACS-iTBS or sham stimulation (Fig. 3A). A paired-sample t-test revealed that movement times improved significantly following theta stimulation relative to sham ($t(17) = 1.67$, $p = 0.05$, $d = 0.394$) (Fig. 3B), suggesting enhanced manual dexterity. In the same individuals, a repeated-measures ANOVA revealed a significant main effect of TIME on MEP amplitude ($F(1,17) = 15.340$, $p = 0.001$, $\eta^2_p = 0.474$), but no significant SESSION or TIME × SESSION interaction effects (Fig. 3C), replicating the core physiological findings from Experiment 1 in an independent cohort. Importantly, only in the theta condition was the change in MEP amplitude significantly correlated with behavioral improvement ($r = 0.559$, $p = 0.024$) (Fig. 3D), while no such relationship was observed under sham. This brain–behavior link provides compelling evidence that cerebellar theta entrainment engages physiologically and functionally relevant plasticity mechanisms.

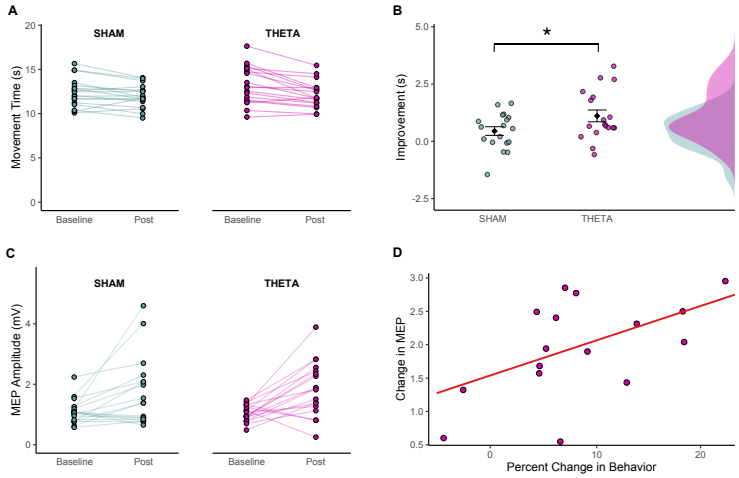


Figure 3. Cerebellar theta-tACS-iTBS improves manual dexterity and links plasticity to behavior. (A) Experimental timeline for assessing motor performance using the Nine-Hole Peg Test (9HPT) before (Baseline) and after stimulation (Post). (B) Theta-tACS-iTBS significantly reduced the time required to complete the dexterity task compared to sham (p = 0.05), indicating improved manual performance. (C) Motor-evoked potentials (MEPs) increased over time in both conditions, with no SESSION × TIME interaction. (D) Only in the theta condition was MEP enhancement significantly correlated with behavioral improvement (r = 0.559, p = 0.024), suggesting that cerebellar entrainment engages functionally relevant plasticity mechanisms. Error bars denote SEM. *p < 0.05.

Building on these findings, we tested whether cerebellar theta entrainment could re-engage spared plasticity pathways and promote recovery in individuals with chronic stroke. In Experiment 4, a randomized, sham-controlled, crossover study, stroke patients received θtACS-iTBS, γtACS-iTBS, and sham stimulation across three separate sessions, using a within-subject design that mirrored the healthy cohort. A repeated-measures ANOVA revealed a significant main effect of SESSION on corticospinal excitability ($F(2,26) = 4.34$, $p = 0.032$, $\eta^2_p = 0.250$) (Fig. 4A). Post hoc comparisons indicated significantly greater MEP amplitudes following theta compared to gamma stimulation ($p = 0.040$), while the difference between theta and sham did not reach statistical significance (Fig. 4B). Neither gamma nor sham stimulation produced significant changes, reinforcing the frequency-specific nature of the theta-induced enhancement. No significant main effects or interactions were found for SICI, ICF, or LICI across sessions or timepoints (all $p > 0.05$; see Fig. 4C).

To evaluate clinical relevance, Experiment 5 assessed upper limb function using the 9HPT in the same randomized, sham-controlled, crossover design (Fig. 4D). A paired-samples *t*-test revealed that movement times improved significantly following θtACS-iTBS compared to sham ($t(12) = 1.82$, $p = 0.047$, $d = 0.505$) (Fig. 4E), indicating that even a single session of frequency-matched stimulation can yield measurable functional gains in individuals with motor impairment. These gains, observed after a single 20-minute session, suggest this protocol may be viable for clinical interventions targeting impaired dexterity and recovery.

Together, these findings identify cerebellar θtACS-iTBS as a robust, frequency- and circuit-specific intervention for enhancing motor plasticity and behavior. Effects were consistent across healthy adults and individuals with chronic stroke. Figure 4F illustrates the anatomical diversity of stroke lesions, showing that benefits were observed even in patients with widespread cortical and subcortical damage. These findings identify cerebellar theta entrainment as a mechanistically precise and clinically actionable strategy for restoring motor function through resonance-based neuromodulation.

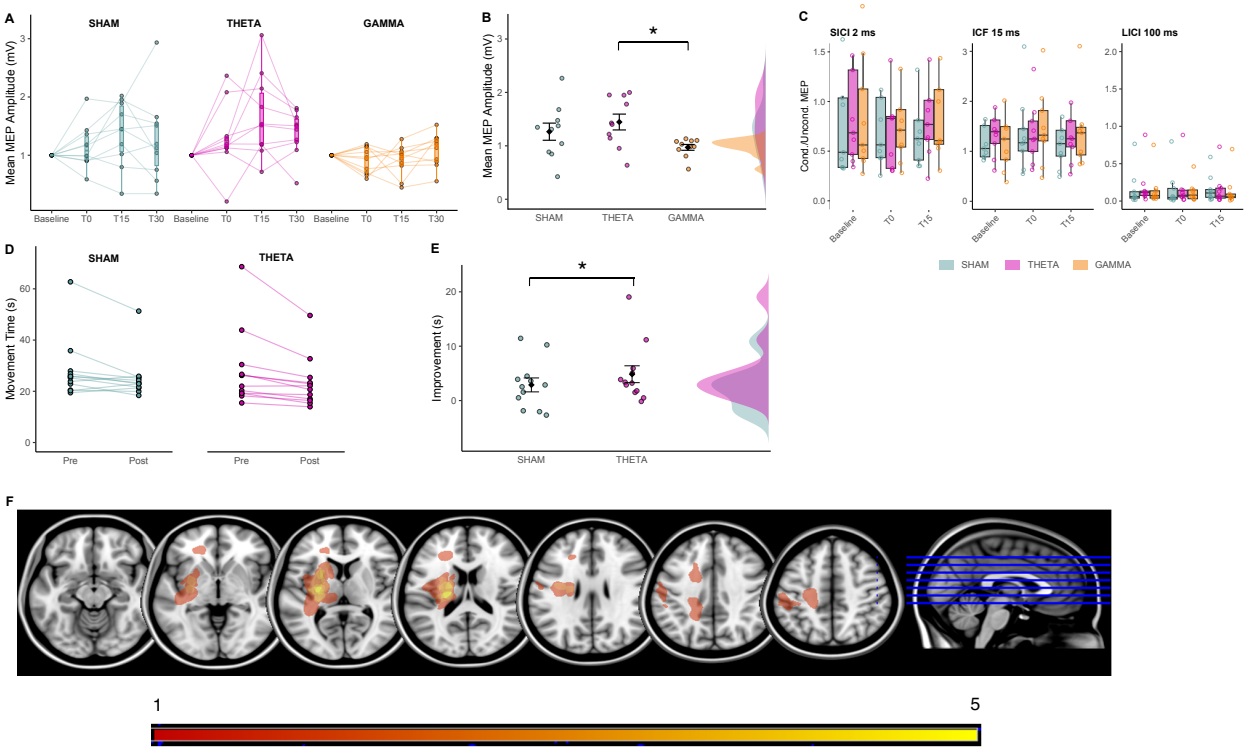


Figure 4. Cerebellar Theta-tACS-iTBS Selectively Enhances Plasticity and Motor Dexterity in Stroke Patients. (A) Time course of normalized MEP amplitudes across conditions. Theta-tACS-iTBS induced a sustained increase in corticospinal excitability, while gamma and sham stimulation had no effect. (B) Group-level comparison revealed significantly greater MEP enhancement following theta- versus gamma-tACS-iTBS ($p = 0.040$); the difference between theta and sham was not significant. (C) Intracortical excitability measures (SICI, ICF, LICI) showed no significant changes following any stimulation condition, indicating that effects were specific to corticospinal output. (D) Individual subject trajectories on the Nine-Hole Peg Test (9HPT), showing reduced movement times following cerebellar theta-tACS-iTBS relative to sham. (E) Group-level analysis confirmed a significant improvement in task completion time under theta stimulation ($p = 0.047$), consistent with enhanced manual dexterity. Error bars indicate SEM. *$p < 0.05$. (F) Lesion overlapping of stroke participants (n = 13), displayed on MNI template space. Lesions spanned both cortical (including primary motor and premotor cortices) and subcortical areas (e.g., internal capsule, basal ganglia).

9.4 Discussion

Theta-band oscillations are central to how the cerebellum orchestrates synaptic plasticity, refines sensorimotor integration, and supports fine motor control (Courtemanche et al., 2013; De Zeeuw et al., 2008; Gandolfi et al., 2013; Hartmann and Bower, 1998). These intrinsic rhythms provide a powerful temporal scaffold for experience-driven adaptation. Here, we demonstrate that entraining cerebellar theta rhythms via tACS significantly enhances neurophysiological plasticity and fine motor behavior in humans. By tuning stimulation to the cerebellum's endogenous frequency, we selectively amplified circuit responsiveness and induced durable, functionally meaningful improvements in both healthy individuals and stroke patients. These findings establish cerebellar theta entrainment as a precise, circuit-specific strategy for enhancing plasticity in the human motor system.

Our findings align with longstanding theories implicating cerebellar theta activity in spike-timing–dependent plasticity and error-based learning (Guerra et al., 2024; Huerta and Lisman, 1995; Koch et al., 2020; Mapelli et al., 2017; Thut et al., 2011). Although iTBS alone induces modest and variable effects (Hamada et al., 2013; Koch et al., 2019, 2008; T. Popa et al., 2013), pairing it with 5 Hz tACS entrains cerebellar networks at their resonance frequency, substantially enhancing their plastic potential. This synergy increased both the magnitude and persistence of plasticity, supporting θtACS as a biologically grounded priming mechanism.

We propose that this effect arises because θtACS-iTBS modulates neuronal excitability, shaping the temporal dynamics of responses to iTBS. Since iTBS depends on spike-timing–dependent mechanisms and is highly state-dependent (Suppa et al., 2016), theta entrainment may optimize the window of excitability within cerebellar microcircuits, particularly at mossy fiber–granule cell and parallel fiber–Purkinje cell synapses. Additionally, theta pacing may refine spike timing within Golgi–granule–Purkinje loops, enhancing temporal filtering and promoting the selective propagation of coherent bursts (Ankri et al., 2015; D'Angelo et al., 2013; Dugué et al., 2009; Lev-Ram et al., 1995). This coordinated state sharpens the precision of synaptic responses and broadens the population of neurons responsive to plasticity induction. Rather than acting additively, θtACS primes cerebellar microcircuits for plasticity through both temporal alignment and spatial recruitment.

Supporting this mechanism, the enhancement was both frequency- and site-specific. Stimulation of the cerebellum, but not M1, with 5 Hz tACS boosted corticospinal excitability and motor performance. Conversely, theta-tACS over M1 had no measurable effect, while gamma-tACS enhanced excitability at M1 but not in the cerebellum, consistent with prior studies (Guerra et al., 2018; Maiella et al., 2022). These results highlight the importance of tailoring stimulation to the resonance characteristics of the target circuit.

Importantly, only cerebellar θtACS-iTBS produced a significant correlation between MEP enhancement and behavioral improvement, demonstrating that oscillation-aligned stimulation engages plasticity mechanisms with both physiological and functional relevance. The rapid effects underscore its translational promise as a non-invasive intervention for restoring dexterity and motor function.

These changes in corticospinal excitability likely arise through modulation of cerebellar-thalamus-cortical pathways, particularly the dentate-thalamic projections to M1 (Middleton and Strick, 1997). Although stimulation was applied to the cerebellum, the downstream physiological effects (captured via MEPs) emerged cortically, suggesting that theta entrainment enhanced synaptic efficacy or excitability within these long-range circuits (Buckner et al., 2011; Koch et al., 2008; Spampinato and Celnik, 2018). Prior work has shown that the dentate nucleus projects to motor thalamic nuclei, which in turn influence pyramidal excitability in M1 (Daskalakis et al., 2004). Our results are consistent with the idea that cerebellar theta stimulation creates a temporally receptive state for activity-dependent plasticity along this pathway.

These findings have important implications for stroke rehabilitation. Stroke remains a leading cause of long-term disability (Krakauer, 2015; Veldema and Gharabaghi, 2022), often leaving individuals with persistent motor deficits. Current neuromodulation strategies typically target M1, which may be structurally damaged or functionally disconnected. The cerebellum, by contrast, is frequently spared and maintains extensive projections to motor and parietal regions (Kelly and Strick, 2003; Koch et al., 2019; Luft et al., 2008). Our results provide direct evidence that cerebellar theta entrainment can reactivate these intact pathways, restoring function even in chronic stages.

The observed gains likely reflect both short-term adaptation and longer-term recalibration of cerebellar-thalamus-cortical circuits that remain anatomically preserved after many cortical strokes (Middleton and Strick,

1997). This pattern aligns with prior studies implicating cerebellar mechanisms in adaptive motor learning and sustained recalibration (Coesmans et al., 2004; Dugué et al., 2009; Izawa et al., 2012; Koch et al., 2020; Spampinato and Celnik, 2018). Although our study focused on chronic stroke, resonance-based neuromodulation may be even more effective in the subacute phase, when plasticity is heightened and circuits are more responsive to intervention. By rhythmically engaging spared cerebellar networks, our protocol may reinstate adaptive learning processes in impaired systems.

Future work should address individual variability in response. Factors such as lesion location, cerebellar structure, and network connectivity likely shape stimulation outcomes. Combining this approach with neuroimaging or electrophysiological biomarkers could help identify responders and tailor stimulation to individual circuit dynamics. While these findings establish a causal link between cerebellar theta entrainment and motor plasticity, the study has limitations. The sample sizes were modest, and interventions were delivered in single sessions, which may constrain generalizability and underestimate potential cumulative effects. Follow-up investigations should examine multi-session protocols, evaluate efficacy during the subacute stage of stroke when plasticity is heightened, and leverage neuroimaging or electrophysiological biomarkers to personalize stimulation in real time. Such efforts will help define the optimal dosing, timing, and patient profiles for translating rhythm-tuned cerebellar stimulation into clinical practice.

More broadly, this work supports a principle of dynamic matching (Fries, 2015; Thut et al., 2011), where tuning stimulation to a circuit's endogenous frequency enhances, rather than overrides, intrinsic dynamics. Cerebellar θtACS-iTBS exemplifies this approach, offering a biologically informed framework for targeted neuromodulation and a generalizable model for rhythm-aligned circuit repair in neurologic disease.

In conclusion, cerebellar θtACS-iTBS introduces a novel, resonance-based strategy for enhancing motor plasticity in humans. This circuit-specific, frequency-matched, and scalable approach holds promise for restoring function in individuals with stroke or other movement disorders, and underscores the translational potential of rhythm-informed neuromodulation.

9.5 Materials and Methods

9.5.1 Study Design

This study was designed to evaluate whether cerebellar theta-frequency stimulation enhances motor plasticity and behavior in both healthy individuals and chronic stroke patients. We used a within-subject, randomized, sham-controlled, crossover design across five experiments. Phase 1 (Experiments 1–3) included healthy adult volunteers. Phase 2 (Experiments 4–5) involved chronic stroke patients with upper limb motor impairments. Demographic details are provided in Tables 1 and 2.

Sample sizes were determined a priori based on published effect sizes from cerebellar neuromodulation and transcranial magnetic stimulation (TMS) plasticity studies in both healthy individuals and stroke patients (Guerra et al., 2024; Koch et al., 2019; Spampinato et al., 2021). A formal power analysis ($\alpha = 0.05$, power = 0.80) indicated that $n = 14$ provides sufficient sensitivity to detect large effects (Cohen's $d \geq 0.81$), in line with established protocols. Data collection proceeded until all participants completed the full crossover protocol. No stopping rules were pre-specified.

All participants were recruited from the IRCCS Santa Lucia Foundation Hospital and Ferrara University. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the IRCCS Santa Lucia Foundation Hospital (CE-FSL, Protocol

CE/PROG.811, February 19, 2021) and of the Area Vasta Emilia Centro (CE-AVEC, Protocol 117/2023/Oss/AOUFe, February 15, 2023). The study adhered to established TMS safety guidelines (Rossi et al., 2021), and was recorded on Open Science Framework (OSF; https://osf.io/wemn9).

9.5.2 Eligibility Criteria

Healthy participants were eligible if they were aged 18–40 years, right-handed, with no history of neurological or psychiatric illness, no contraindications to noninvasive brain stimulation (e.g., history of seizures, metallic implants), and not currently using medications known to affect cortical excitability.

Stroke participants met the following inclusion criteria: age 18–80 years; chronic ischemic or hemorrhagic stroke (≥6 months prior to enrollment); unilateral lesion (left or right hemisphere); mild to moderate upper limb motor impairment; ability to complete the 9HPT with the paretic hand; and capacity to provide informed consent. Exclusion criteria included: severe spasticity (Modified Ashworth Scale >2); apraxia or neglect interfering with motor testing; history of epilepsy or unprovoked seizures; implanted metallic or electronic devices (e.g., pacemaker, cochlear implant); brain magnetic resonance imaging (MRI)-confirmed cerebellar lesion; or current use of medications that affect cortical excitability (e.g., benzodiazepines, antiepileptics).

9.5.3 Endpoints and Outcome Measures

The primary physiological endpoint was MEP amplitude, measured using single-pulse TMS. Secondary endpoints included measures of intracortical inhibition and facilitation, specifically short-interval intracortical inhibition (SICI, interstimulus interval [ISI] = 2 ms), intracortical facilitation (ICF, ISI = 15 ms), and long-interval intracortical inhibition (LICI, ISI = 100 ms), as well as behavioral performance on the 9HPT. All endpoints were prospectively defined. Bonferroni correction was applied to control for multiple comparisons across timepoints and stimulation conditions. No formal outlier removal was performed, and all valid data points were retained in the analyses.

The study followed a within-subject, sham-controlled, crossover design across five experiments. Experiments 1 and 2 involved three stimulation conditions (theta, gamma, and sham), while Experiments 3 and 5 included only theta and sham stimulation. Stimulation sessions were randomized, counterbalanced, and separated by a minimum of 72 hours to reduce carryover effects. All participants served as their own controls, allowing for repeated measures within individuals. Neurophysiological assessments included paired-pulse TMS protocols (SICI, ICF, LICI) performed at baseline, immediately post-stimulation (T0), and 15 minutes post-stimulation (T15). In addition, single-pulse MEPs were recorded at 30 minutes post-stimulation (T30) to assess the durability of plasticity effects. Behavioral assessments using the 9HPT were conducted before and after stimulation. For stroke participants, lesions were manually segmented from clinical MRI scans and normalized to Montreal Neurological Institute (MNI) space for group-level analysis.

The primary objective of the study was to determine whether cerebellar theta-frequency tACS paired with iTBS (θtACS-iTBS) enhances motor plasticity and behavior relative to sham or frequency-mismatched stimulation. Secondary aims included evaluating the frequency and anatomical specificity of stimulation effects, examining correlations between physiological and behavioral changes, and assessing translational feasibility in chronic stroke. To minimize bias, participants were blinded to stimulation conditions, and experimenters responsible for neurophysiological and behavioral assessments were blinded during data collection and analysis. Stimulation delivery was automated and coded to ensure blinding integrity.

9.5.4 Phase 1: Healthy Participants (Experiments 1–3)

Phase 1 assessed the effects of cerebellar θtACS-iTBS on physiological and behavioral outcomes in healthy adults. Participants were recruited from the IRCCS Santa Lucia Foundation and the University of Ferrara. All experiments employed a randomized, sham-controlled, double-blind, within-subject crossover design.

Experiment 1 investigated whether cerebellar theta-frequency stimulation enhances corticospinal excitability in a frequency-specific manner. Fourteen healthy participants (8 female; mean age = 30.8 years, SD = 3.8) underwent three stimulation sessions, each involving iTBS applied to the right cerebellar hemisphere (contralateral to the dominant hand), paired with either 5 Hz (theta), 50 Hz (gamma), or sham tACS. MEP amplitude was the primary outcome, with additional measurements of SICI, ICF, and LICI. Assessments were conducted at baseline, immediately post-stimulation (T0), 15 minutes post (T15), and for MEPs only, 30 minutes post (T30).

Experiment 2 tested the anatomical specificity of stimulation by delivering the same three stimulation conditions (theta, gamma, sham) over the left M1. Fourteen participants (10 female; mean age = 28.5 years, SD = 3.6) completed all sessions. Physiological outcomes mirrored those in Experiment 1 and were assessed at identical timepoints.

Experiment 3 evaluated whether cerebellar θtACS-iTBS improves manual dexterity. Eighteen participants (10 female; mean age = 27.2 years, SD = 3.2) received theta or sham stimulation over the right cerebellar hemisphere in a randomized crossover design. Behavioral performance on the 9HPT, performed with the dominant hand, was measured before and 15 minutes after stimulation. MEPs were also recorded pre- and post-stimulation to examine correlations between physiological and behavioral changes.

Demographic and stimulation parameters for healthy participants are provided in Table 1.

Participant	Exp	Age	Sex	Dominant Hand	AMT	iTBS E-field* (V/m)
I	1,2	34	M	Right	48	31
II	1,2,3	27	F	Right	63	40
III	1,2,3	29	M	Right	45	28
IV	1,2	26	F	Right	41	26
V	1,2	31	M	Left	69	45
VI	1,2	25	F	Right	50	34
VII	1,2	28	F	Right	59	38
VIII	1,2	25	F	Right	40	28
IX	1,2	32	M	Right	64	42
X	1,2	30	F	Right	41	27
XI	1,2	30	F	Right	49	33
XII	2	27	F	Right	55	36
XIII	2	26	M	Right	53	34
XIV	2	29	F	Right	51	33
XV	2	25	F	Right	54	34
XVI	3	24	F	Right	69	45
XVII	3	26	F	Right	43	27
XVIII	3	24	F	Right	64	42
XIX	3	27	M	Right	48	31
XX	3	34	M	Right	58	35
XXI	3	26	F	Right	53	34
XXII	3	27	F	Right	60	37
XXIII	3	21	F	Right	51	33
XXIV	3	25	M	Right	65	42
XXV	3	23	M	Right	55	36
XXVI	3	22	M	Right	50	34
XXVII	3	29	F	Right	58	35
XXVIII	3	34	F	Right	43	27
XXIX	3	25	M	Right	55	36
XXX	3	26	F	Right	53	34
XXXI	3	25	M	Right	71	44

Table 1. Demographic and stimulation parameters for healthy participants**.** Participants across Experiments 1–3 are listed with age, sex, handedness, motor threshold, and modeled electric field during iTBS. Active motor threshold (AMT) is reported as a percentage of maximum stimulator output. Electric field (E-field) estimates are based on individual stimulation intensities. *iTBS E-field was calculated using the individual TMS stimulation intensity via a computational model, tACS was delivered with a 0.08 mA/cm2 current density.

9.5.5 Phase 2: Stroke Participants (Experiments 4–5)

Phase 2 extended the findings to individuals with chronic stroke and upper limb motor impairment. Participants were recruited from the same sites and met predefined eligibility criteria. All stimulation was delivered over the cerebellar hemisphere contralateral to the lesioned cortex, using a randomized, double-blind, sham-controlled, within-subject crossover design.

Experiment 4 replicated the physiological protocol from Experiment 1 in a clinical sample. Fourteen individuals with chronic stroke were enrolled, and ten completed all three stimulation conditions (theta, gamma, sham). Single-pulse MEPs were recorded at baseline, T0, T15, and T30 to assess the effects of θtACS-iTBS on corticospinal excitability through spared cerebellar-thalamus-cortical pathways.

Experiment 5 assessed whether cerebellar theta stimulation improves motor performance in stroke. Thirteen participants completed both theta and sham sessions. The 9HPT was performed with the paretic hand before and 15 minutes after stimulation. MEPs were also recorded to evaluate neurophysiological correlates of behavioral change.

For all stroke participants, clinical MRI scans were used to segment lesions, which were then normalized to MNI space for group-level analysis. A lesion overlap map generated from 13 participants is presented in Figure 4E. Lesions affected cortical regions such as the M1 and premotor cortex and subcortical structures, including the internal capsule and basal ganglia; no participants had cerebellar damage.
Participant demographics and stimulation parameters for stroke participants are provided in Table 2.

Participant	Exp	Age	Sex	Dominant Hand	Lesion Site	Months from stroke onset	AMT	iTBS E-field* (V/m)
I	4	56	M	Right	Medial right midbrain	6	58	38
II	4,5	71	M	Right	Right fronto-parietal-temporal	66	38	28
III	4	77	M	Right	Left pons	7	47	31
IV	4	61	M	Right	Right parieto-temporal-insular region	6	61	41
V	4,5	49	F	Right	Right frontal and corona radiata	112	57	41
VI	4,5	62	M	Right	Right fronto-parietal-occipital	6	51	33
VII	4	74	M	Right	Left internal capsule	90	49	31
VIII	4	52	M	Right	Left occipital	22	66	44
IX	4	46	M	Right	Right fronto-parietal	52	50	34
X	4,5	74	M	Right	Left internal capsule	28	40	24
XI	5	54	M	Left	Right insular and capsular-lenticular	50	61	41
XII	5	52	M	Right	Right frontal-insular with deep capsular-lenticular-caudate extension	42	56	37
XIII	5	72	M	Right	Left bulbar	237	55	36
XIV	5	61	M	Right	Left capsular-lenticular	35	65	42
XV	5	54	F	Right	Right frontal-insular with deep capsular-lenticular-caudate extension	46	56	37
XVI	5	55	F	Right	Left capsular-lenticular with extension to corona radiata	168	68	45
XVII	5	51	M	Right	Left temporal-insular, corona radiata and centrum semiovale	23	49	33
XVIII	5	74	M	Right	Left lenticular and caudate nuclei	19	55	36
XIX	5	65	M	Right	Right capsular-thalamic	9	62	42

Table 2. Demographic and stimulation parameters for stroke participants. Stroke participants enrolled in Experiments 4 and 5. Lesion sites were confirmed via MRI. Active motor threshold (AMT) is expressed as a percentage of maximum stimulator output. Electric field (E-field) estimates were derived from individualized stimulation parameters using computational modeling.*iTBS E-field was calculated using the individual TMS stimulation intensity via a computational model, tACS was delivered with a 0.08 mA/cm2 current density.

9.5.6 tACS-iTBS Neuromodulation Protocol

The combined tACS-iTBS protocol was adapted from prior work (Guerra et al., 2018; Maiella et al., 2022). tACS was delivered via saline-soaked 5×5 cm sponge electrodes using a BrainStim stimulator (E.M.S., Bologna). θtACS (5 Hz) and γtACS (50 Hz) were applied at 2 mA. For cerebellar stimulation, the active electrode was placed 3 cm lateral to the inion. In healthy participants, stimulation was applied ipsilateral to the dominant hand, with the reference over the right shoulder. In stroke patients, the cerebellar hemisphere contralateral to the cortical lesion was targeted. For M1 stimulation, the active electrode was positioned over the left M1 hotspot. Sham stimulation involved a brief (5 s) ramp-up of γtACS.

iTBS was delivered using a Magstim Rapid2 with a figure-of-eight coil. The protocol consisted of 600 pulses delivered in 2-second trains (3 pulses at 50 Hz repeated at 5 Hz), at 80% of the active motor threshold (AMT). Stimulation lasted 190 seconds and was synchronized with tACS using BrainTrigger hardware and Signal software. The AMT was defined as the lowest intensity eliciting MEPs ≥ 200 μV during a voluntary contraction at 10% of the participant's maximal force, monitored via real-time visual feedback.

9.5.7 Neurophysiological Assessment

Neurophysiological assessments were conducted using TMS in combination with surface electromyography (EMG). EMG signals were recorded from the right first dorsal interosseous (FDI) muscle, amplified, and filtered using a Digitimer D360 amplifier (Digitimer Ltd, Welwyn Garden City, UK) with a band-pass filter ranging from 20 Hz to 2 kHz, and digitized at a sampling rate of 5 kHz. Data was stored on a personal computer for offline analysis using Signal software (version 6, Cambridge Electronic Design, UK).

Single-pulse TMS assessed corticospinal excitability; paired-pulse TMS assessed intracortical inhibition and facilitation using a Magstim 200^2 stimulator ($BiStim^2$ configuration) connected to a 70-mm figure-of-eight coil (Magstim Company Ltd, UK). The motor "hotspot" for the FDI muscle was defined as the scalp location over M1 that elicited the largest and most consistent MEPs. Stimulation intensity was individually calibrated and monitored throughout the experiment. The resting motor threshold (RMT) was defined as the minimum stimulus intensity required to evoke MEPs ≥ 50 μV in at least 5 out of 10 trials in the relaxed FDI muscle. Corticospinal excitability was assessed by recording 20 MEPs from the FDI hotspot in the left M1 (or from the affected M1 in stroke participants), using TMS intensity adjusted to produce responses of approximately 1 mV in amplitude (SI1mV). SICI and ICF were measured using paired-pulse TMS with a conditioning stimulus (CS) set at 70% of RMT and a test stimulus (TS) adjusted to elicit ~1 mV MEPs at rest (SI1mV). SICI was assessed with an interstimulus interval (ISI) of 2 ms; ICF was assessed with an ISI of 15 ms. LICI was evaluated using a suprathreshold CS at 120% of RMT and a TS set at SI1mV, with an ISI of 100 ms. For each protocol, 20 paired-pulse trials were recorded and averaged offline for analysis.

9.5.8 Behavioral Assessment

Hand dexterity was evaluated via a sensorized 9HPT (Mathiowetz et al., 1985). Participants placed and removed nine pegs from a 3×3 matrix with their dominant hand. Stroke patients used their paretic (affected) hand. Movement time was measured using a Hall-effect sensor (DRV5053, Texas Instruments). Five trials were performed pre- and post-stimulation, and the average completion time was used for analysis.

9.5.9 Statistical Analysis

All statistical analyses were conducted using SPSS (IBM SPSS Statistics, Version 24). To ensure baseline comparability across stimulation conditions, pre-stimulation MEP amplitudes were assessed using repeated-measures ANOVA (RM-ANOVA) for each experiment. Post-stimulation MEP amplitudes were then normalized to baseline (post/baseline ratio) and analyzed using RM-ANOVAs with the within-subject factors SESSION (Theta, Gamma, Sham) and TIME (Baseline, T0, T15, T30), enabling direct evaluation of SESSION × TIME interactions and assessment of frequency- and site-specific effects. Baseline corticospinal excitability was statistically equivalent across stimulation conditions in all experiments (Exp 1: $F(2, 26) = 0.275$, $p = 0.762$; Exp

2: $F(2, 26) = 1.54$, $p = 0.232$; Exp 3: $F(2, 18) = 0.576$, $p = 0.572$), justifying the use of normalized post/baseline MEP ratios in the main analyses.

For intracortical inhibition and facilitation measures, separate RM-ANOVAs were conducted for each protocol: SICI, ICF, and LICI. This approach preserves neurophysiological specificity and aligns with prior work indicating distinct underlying mechanisms (Fong et al., 2021; Kujirai et al., 1993). Behavioral performance on the 9HPT was evaluated using paired-sample t-tests comparing movement times between θtACS-iTBS and sham conditions. Pearson's correlation coefficients were calculated between normalized MEP amplitudes and 9HPT performance changes to assess brain–behavior relationships. To explore site- and frequency-specific effects, supplementary linear mixed-effects models (LMMs) were conducted, with fixed effects for GROUP (Theta, Gamma, Sham) and SITE (Cerebellum vs. M1), and random intercepts for SUBJECT. Statistical significance was set at $p < 0.05$. Bonferroni corrections were applied for post hoc comparisons to adjust for multiple testing. All tests were two-sided with alpha set at 0.05. Bonferroni correction was applied where appropriate. Data distributions were visually inspected and assessed for normality using the Shapiro–Wilk test. All outcome measures met criteria for approximate normality. No data were excluded as outliers, and no missing data were present for primary outcomes. All group-level outcomes are reported as mean ± standard error. Complete statistical details (test statistics, degrees of freedom, and effect sizes) are provided in the figure legends and the main text.

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Chapter 10. Frontotemporal dementia. How to deal with its diagnostic complexity?

In this Chapter, I introduce a complementary line of investigation that expands on the overall framework of cerebellar roles in brain function and dysfunction. While earlier sections focused on the cerebellum's role in post-stroke recovery and its modulation through non-invasive brain stimulation, this chapter shifts to the complex realm of frontotemporal dementia (FTD)—a neurodegenerative disease characterized by severe impairments in social cognition, executive functioning, language, and behavior. Also in this context, cerebellar involvement has been underexplored yet holds considerable potential. Indeed, the cerebellum, long regarded as a purely motor structure, is now recognized as a crucial contributor to higher-order cognitive and affective processes, many of which are severely disrupted in FTD. Given the cerebellum's dense connectivity with prefrontal and limbic cortices, and its role in predictive coding, social timing, and emotional regulation, its dysfunction could plausibly contribute to several hallmark features of the disorder.

Therefore, this Chapter provides an overview of the clinical complexity of FTD and explores emerging neurophysiological evidence related to its pathophysiology, which will be fundamental for understanding the cerebellum's contribution within the broader context of FTD—a topic that will be elaborated in Chapter 11.

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10.1 Abstract

Frontotemporal dementia (FTD) encompasses a group of heterogeneous neurodegenerative disorders. Aside from genetic cases, its diagnosis is challenging, particularly in the early stages when symptoms are ambiguous and structural neuroimaging does not reveal characteristic patterns. We performed a comprehensive literature search through MEDLINE, Scopus, and Web of Science databases to gather evidence to aid the diagnostic process for suspected FTD patients, particularly in early phases, even in sporadic cases, ranging from established to promising tools. Blood-based biomarkers might help identify very early neuropathological stages and guide further evaluations. Subsequently, neurophysiological measures reflecting functional changes in cortical excitatory/inhibitory circuits, along with functional neuroimaging assessing brain network, connectivity, metabolism, and perfusion alterations, could detect specific changes associated to FTD even decades before symptom onset. As the neuropathological process advances, cognitive-behavioural profiles and atrophy patterns emerge, distinguishing specific FTD subtypes. Emerging disease-modifying therapies require early patient enrollment. Therefore, a diagnostic paradigm shift is needed—from relying on typical cognitive and neuroimaging profiles of advanced cases to widely applicable biomarkers, primarily fluid biomarkers, and, subsequently, neurophysiological and functional neuroimaging biomarkers where appropriate. Additionally, exploring subjective complaints and behavioural changes detected by home-based technologies might be crucial for early diagnosis.

10.2 Introduction

Frontotemporal dementia (FTD) encompasses a group of progressive and heterogeneous neurodegenerative disorders from a clinical and neuropathological perspective (Antonioni et al., 2023b). Indeed, it can present with subtle personality changes, as well as executive dysfunctions, in its most common subtype, i.e. the behavioural variant (bvFTD) (Duignan et al., 2021; Rascovsky et al., 2011). Alternatively, it results in language impairments, characterising the primary progressive aphasias (PPAs), which are further classified into a semantic variant (svPPA) and a non-fluent variant (nfvPPA), depending on whether the deficits primarily involve comprehension or production skills, respectively (Gorno-Tempini et al., 2011). Additionally, a logopenic variant (lvPPA) has been described, which is generally associated with Alzheimer's disease (AD) pathology and thus classified within that spectrum (Conca et al., 2022). Interestingly, the right temporal variant (rtvFTD) was initially considered as svPPA with predominant right hemisphere involvement but it is now recognized for its distinct clinical features, such as behavioural changes, memory deficits, and prosopagnosia (Ulugut Erkoyun et al., 2020a). Moreover, the phenotypic spectrum includes patients with concomitant motor neuron disease or movement disorders, such as those with amyotrophic lateral sclerosis (FTD-ALS), corticobasal syndrome (CBS), or progressive supranuclear palsy (PSP) (Baizabal-Carvallo and Jankovic, 2016; Devenney et al., 2015). This highlights the significant variability in symptom manifestations within the FTD spectrum, particularly challenging to identify in its early stages when the changes are more subtle (Antonioni et al., 2023b).

Importantly, its clinical complexity is coupled with marked neuropathological heterogeneity, characterised by different pathological proteins accumulating in the brain, leading to neuronal loss, synaptic alterations,

microvacuolations, and gliosis, responsible for the characteristic symptoms of each FTD variant based on their specific locations and progressive spread (Walsh and Selkoe, 2016). Four main pathological groups have been identified: Tau protein (FTD-Tau), in 45% of cases; TAR DNA-binding protein 43 (FTD-TDP-43, with subtypes A, B, C, D, and E), involving about 50% of patients; TDP-43 negative, ubiquitin positive, and immunopositive for the fused in sarcoma protein (FTD-FUS) in 5% of cases; and very rare cases characterised by inclusions that label only for markers of the ubiquitin-proteasome system (FTD-UPS) or lacking inclusions (Mackenzie and Neumann, 2016). Except for svPPA, which frequently entails a TDP type C pathology, the correlation between clinical subtypes and neuropathology is weak, particularly for bvFTD, preventing a diagnostic confirmation in vivo (Rohrer et al., 2011; Spinelli et al., 2017).

While these considerations apply to sporadic cases, genetically linked cases represent an exception. Indeed, while genetic factors are important in other neurodegenerative diseases, including AD, FTD is distinguished by particularly high heritability (Bisceglia et al., 2022; Gossye et al., 2019; Greaves and Rohrer, 2019). In fact, 25-50% of patients have a positive family history, and 10-20% of cases are attributed to autosomal dominant mutations. Although these mutations show a weak correlation with the clinical phenotype, they provide an excellent prediction of the underlying neuropathology. Although numerous genes are actually known to be associated with familial forms of FTD, the most common mutations affect three genes: microtubule-associated protein tau (*MAPT*), granulin precursor (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*) (Antonioni et al., 2023b). Although *C9orf72* mutations are most commonly associated with a bvFTD clinical phenotype, there is considerable phenotypic variability. Furthermore, also *MAPT* mutations often lead to bvFTD clinical syndrome. Conversely, svPPA is rarely linked to genetic alterations and, in those cases, tends to be more frequently associated with *MAPT* mutations. *GRN*, on the other hand, can lead to heterogeneous phenotypes, including bvFTD, nfvPPA, bvFTD with atypical parkinsonism, and CBS (Filippi et al., 2016; Rohrer et al., 2009a). Moreover, intriguingly, certain *GRN* mutation carriers may present with distinctive language impairments, including unspecified PPA variants or even isolated cases resembling a lvPPA phenotype, along with consistent AD biomarkers (Chokesuwattanaskul et al., 2022; Samra et al., 2023). These findings significantly broaden the phenotypic spectrum associated with this genetic alteration and, thus, hinder its clinical identification. It is worth noting that a particularly young age at onset is a strong indicator of a *MAPT* mutation, whereas an older age is more likely to indicate a *GRN* mutation carrier (Beck et al., 2008; J L. Whitwell et al., 2009). Notably, these mutations are characterised by high penetrance, meaning that carriers will inevitably develop the disease. Thus, their presence, combined with supportive clinical-instrumental data, leads to diagnostic confirmation even in the absence of a neuropathological confirmation (Gossye et al., 2019). However, this possibility is limited to genetic forms, posing challenges in current clinical practice.

Consistently, although FTD is considered a rare disease, it is the second most common form of early-onset dementia (under 65 years) and has devastating consequences for patients and families due to its complex clinical management and high likelihood of genetic inheritance (Logroscino et al., 2023; Onyike and Diehl-Schmid, 2013). Indeed, its incidence is 3-4/100.000 people per year, while the prevalence in people aged 45 to 65 is 15-22/100.000 (Logroscino et al., 2023; Olney et al., 2017). As early-onset dementia is uncommon, it is often overlooked in favour of more common conditions in younger patients, particularly late-onset psychiatric disorders (Cipriani et al., 2020; Galimberti et al., 2015). This results in patients being referred for specialist assessment at a later stage, often leading to significant diagnostic delays that prevent the timely initiation of appropriate multidisciplinary management (Rosness et al., 2008). Moreover, the heterogeneity of symptoms

and lack of biomarkers for pre-mortem diagnosis (at least in sporadic cases) not only cause diagnostic uncertainty but also hinder patient inclusion in clinical trials for disease-modifying therapies, which require specific knowledge about the underlying neuropathology. This is even more difficult in the early stages when therapies might be most effective, but the clinical picture is not yet fully overt, making diagnosis particularly challenging (Shinagawa et al., 2006; Vissers et al., 2021). These uncertainties increase the burden on patients, caregivers, and clinicians as well as highlighting the need for biomarkers that can confirm the diagnosis before the clinical picture becomes fully apparent.

In this narrative review, we provide an overview of diagnostic tools, including both those well-established in clinical practice and some recently emerging, highly promising biomarkers whose clinical application still requires validation but which may assist in suspecting FTD from the earliest stages of the disease. Indeed, while currently validated methods allow diagnosis once clinical syndrome has manifested (at least in sporadic cases), they often miss pre-symptomatic stages where intervention could be more effective. Thus, beyond the actually established diagnostic tools, we also explore recent evidence that could enable earlier diagnosis according to the expected longitudinal profile of the onset of alterations. Specifically, we have outlined a progression that begins with the earliest changes, namely cerebrospinal fluid (CSF) and blood biomarkers and neurophysiological measures, followed by subsequent alterations in functional and, then, structural neuroimaging and, finally, the onset of clinical symptoms, which are often subtle and insidious but nonetheless indicative of the disease. We also compiled evidence describing the differential diagnoses of the FTD spectrum to guide clinicians from the first assessment of patients presenting with a possible FTD variant. We hope to provide useful elements not only to correctly suspect FTD but also to prompt categorising it to allow patients enrollment in clinical trials. We performed a comprehensive literature search using MEDLINE (via PubMed), Scopus, and Web of Science databases. Our search strategy combined a wide array of carefully chosen keywords (e.g., “behavioral variant”, “early-onset dementia”, “frontotemporal dementia”, “primary progressive aphasia”, “*GRN*”, “*C9orf72*”, and “*MAPT*”) and Boolean operators to maximize the retrieval of relevant publications. Additionally, to ensure the robustness of our search, we complemented the database queries by thoroughly examining the reference lists of all included studies, thereby minimizing the risk of overlooking any significant work. The selected studies were subjected to a detailed review and critical analysis to provide a comprehensive and up-to-date overview of the current knowledge on this complex and evolving topic.

10.3 FTD fluid biomarkers

Fluid biomarkers, typically evaluated on CSF and blood (including both plasma and serum), are objective indicators of biological processes occurring physiologically or pathologically. They can be used for diagnostic, staging (i.e., assessing the disease phase, which is particularly relevant for genetic forms often classified as presymptomatic, nearing symptom onset, or phenoconverted), or therapeutic purposes, such as evaluating their changes following pharmacological interventions (Swift et al., 2021). The characteristics of an ideal biomarker include being sensitive, specific, minimally invasive, cost-effective, and providing accurate and reproducible measurements (Shaw et al., 2007). Traditionally, CSF biomarkers are the most commonly used in the differential diagnosis of neurodegenerative diseases, particularly for ruling out other forms of dementia, especially AD, which is the most prevalent. Specifically, elevated CSF levels of tau protein (especially its phosphorylated isoforms [pTau], such as pTau181, 217, and 231) combined with reduced amyloid-beta 42

(Aβ42) levels are strongly indicative of AD patients. Conversely, a reduced Tau/Aβ42 ratio suggests an FTD variant (Leuzy et al., 2021; Llorens et al., 2016). However, exceptions to these rules have been reported, such as patients with *MAPT* R406W and V337M mutations, characterised by Tau pathology similar to AD (Swift et al., 2021). Indeed, only *MAPT* mutation carriers display alterations in plasma levels of pTau181 (Foiani et al., 2018). Furthermore, these biomarkers not only allow for the differential diagnosis but also suggest the underlying neuropathology in vivo. Consistently, compared to patients with Tau accumulations, those with TDP-43 are characterised by a reduction in the ratio of pTau181 to total Tau (Barbara Borroni et al., 2015; Hu et al., 2013). Another major challenge is differentiating FTD from other neurodegenerative diseases, as many biomarkers are non-specific and, therefore, do not allow the disease to be identified on an individual level (Holper et al., 2022). Moreover, lumbar puncture is an invasive procedure requiring specialised personnel, limiting its availability in all care settings. Therefore, there is growing interest in blood biomarkers, which are non-invasive and easier to obtain. In other pathological contexts, such as AD, blood biomarkers have already demonstrated the ability to accurately describe CSF status, and their clinical application in FTD is increasingly being explored (Antonioni et al., 2025, 2023a). However, currently, there is no biomarker that uniquely identifies the neuropathological process associated with sporadic FTD, leading to the exploration of various markers that, especially in combination, increase diagnostic accuracy. Therefore, an overview of some of the most relevant fluid biomarkers is now proposed, starting with the genetic cases, where some reliably identify patients in the FTD spectrum, in contrast to the sporadic cases.

10.3.1 FTD fluid biomarkers in genetic cases

- Progranulin: this is a ubiquitous growth factor crucial for tissue development, proliferation, and repair. Specifically, it is involved in various mechanisms, including stress response, TDP-43 aggregation, and synaptic function (Toh et al., 2011). Importantly, mutations in *GRN* often result in its haploinsufficiency, leading to reduced progranulin levels both in CSF and blood (L. H. H. Meeter et al., 2016; Swift et al., 2021). Consistently, *GRN* mutation carriers consistently show reduced plasma progranulin levels from an early age, with levels falling below the threshold by the late teens and remaining stable over time (Sellami et al., 2020). This is crucial because it suggests that plasma progranulin could be a cost-effective marker for detecting the mutation decades before disease onset, particularly in cases that are suggestive of familiar contexts, potentially obviating the need for expensive genetic sequencing. Additionally, alterations in its values might also predict the subsequent clinical phenotype. Specifically, reduced CSF progranulin level alterations are more relevant in TDP-43 pathologies, such as svPPA, rtvPPA, and bvFTD, compared to tauopathies (particularly nfvPPA) (Ulugut et al., 2021; Zetterberg et al., 2019). Interestingly, neuropathological differences are not only associated with differences in clinical manifestations but also in inflammation-related markers. In particular, CSF levels of some proinflammatory interleukin-17 (IL-17) and IL-23 are reduced, whereas some cytokines belonging to the tumor necrosis factor (TNF) family are increased in TDP-43 pathology in comparison to Tau pathology, suggesting different pathophysiological mechanisms (Hu et al., 2010). However, various genetic and non-genetic factors (including tumours, obesity, autoimmune, and metabolic diseases) can influence progranulin values. This, coupled with the sometimes weak association between CSF

and blood levels, currently limits its clinical utility (L. H. H. Meeter et al., 2016; Swift et al., 2021). Nevertheless, its potential has already been demonstrated from a therapeutic perspective. Consistently, an animal model study showed an increase in blood and CSF progranulin levels following the administration of a monoclonal antibody against sortilin, an endogenous progranulin modulator (Kurnellas et al., 2023). These findings suggest that, once more accurate cut-off values have been identified, progranulin might be useful for detecting FTD patients in the preclinical stages, particularly *GRN* mutation carriers.

- Dipeptide repeats: the hexanucleotide repeat expansion GGGGCC in the non-coding region of *C9orf72*, responsible for most familial FTD cases, particularly bvFTD and FTD-ALS, leads to the production of ribonucleic acid (RNA) fragments that are translated into several toxic dipeptide repeats, among which polyglutamine (poly(GP)) is the only one which is measurable (Mori et al., 2013). Although bvFTD and ALS patients typically present with hundreds or even thousands of repeats, the minimum number required to reach a pathological condition remains undefined (Woollacott and Rohrer, 2016). Importantly, their detection in the CSF allows a diagnostic confirmation with a specificity of 100% (Meeter et al., 2018a). Moreover, their levels are elevated regardless of phenotype and clinical stage, making them abnormal not only during symptomatic periods but also in presymptomatic phases (Gendron et al., 2017; Lehmer et al., 2017). Thus, similar to progranulin, they could be crucial for identifying mutation carriers without awaiting genetic screening and might also represent a marker of disease activity, as symptomatic mutation carriers display higher levels when compared to non-symptomatic ones (Zetterberg et al., 2019). Finally, this biomarker might also serve as an important potential outcome measure for trials utilising antisense oligonucleotides targeted against toxic RNAs (Tran et al., 2022).
- Glial fibrillary acidic protein (GFAP): this is an astrocytic marker reflecting glial inflammatory reaction against brain damage or during central nervous system (CNS) degeneration (Middeldorp and Hol, 2011). Given the key role of neuroinflammation in neurodegenerative diseases, the involvement of glial cells and related biomarkers is of increasing interest in this field (Kempuraj et al., 2016). However, while numerous elements of evidence are available in AD patients, data on FTD remain limited (Bright et al., 2019; Heneka et al., 2015). Of note, *GRN* mutation carriers show elevated GFAP plasma levels, particularly in symptomatic patients compared to presymptomatic ones (Ntymenou et al., 2021). Importantly, GFAP may also represent a useful staging tool, especially as its values increase immediately before the onset of the symptoms (Heller et al., 2020). However, GFAP levels are notably higher in AD patients compared to those with FTD, especially bvFTD, indicating distinct neuroinflammatory processes between the two conditions (Oeckl et al., 2022). Therefore, notably, serum GFAP might aid in the differential diagnosis between AD and FTD once more defined cut-off values are established.

While the above-discussed biomarkers have been extensively studied and have already clearly demonstrated their clinical utility in identifying patients carrying genetic mutations, additional evidence suggests that other biomarkers may hold great promise for identifying FTD patients from the earliest stages. Examples of such emerging biomarkers are presented below, although their validity in terms of clinical application still requires further real-world assessments:

- Neuronal pentraxins are a family of proteins involved in synaptic plasticity, and their utility in the context of genetic forms of FTD is increasingly recognised. Specifically, the neuronal pentraxin receptor is reduced in the CSF of symptomatic genetic FTD patients, along with neuronal pentraxin-2 (NPTX2) (van der Ende et al., 2020). Importantly, NPTX2 levels correlate with the disease stage and can indeed predict its clinical onset. Moreover, according to some recent biomarker-based disease models in familial FTD, it is the first CSF biomarker to show a detectable alteration before and around symptom onset (Van Der Ende et al., 2022). Finally, some research has reported a reduction of the neuronal pentraxin receptor also in sporadic bvFTD and PPAs, suggesting that their clinical application might be extended to these patient populations (Remnestål et al., 2020).
- Phosphorylated TDP-43 (pTDP-43): this specific isoform effectively distinguishes between genetic variants of bvFTD. Indeed, *GRN* and *C9orf72* mutation carriers exhibit higher levels compared to other bvFTD subtypes both in CSF and plasma, with a positive correlation between the two (Suárez-Calvet et al., 2014).

10.3.2 FTD fluid biomarkers in sporadic cases

Unlike genetic variants, sporadic cases present greater challenges for biomarker research due to the difficulty in identifying and tracking patients likely to develop the disease without known genetic risk factors. This complicates the characterisation of early biomarker profiles in sporadic cases. Indeed, pathological biomarkers like TDP-43, which aggregates in neurons and glial cells, leading to neuronal death, are available and result in elevated CSF levels (Steinacker et al., 2008). However, TDP-43 levels peak when neuronal damage is already advanced, reasonably well beyond the clinical onset period, limiting its utility for early disease diagnosis. Importantly, TDP-43 can be measured in both full-length, truncated, or phosphorylated forms, but no consensus exists on the most clinically useful isoform. Additionally, since TDP-43 is also produced in the periphery, refining measurement techniques to accurately identify the specific isoform is essential (Feneberg et al., 2018). Moreover, both TDP-43 and Tau are non-specific, as their levels do not reliably distinguish between FTD, different neurodegenerative diseases, and controls (Feneberg et al., 2018; Foiani et al., 2019). Nonetheless, some promising applications seem possible: for example, recent evidence suggests that early detection of TDP-43 in CSF is feasible due to its prion-like properties using Real-Time Quaking Induced Conversion (RT-QuIC) technology in FTD-ALS patients (Scialò et al., 2020). This highlights its potential for early identification, even before marker levels peak. Moreover, CSF TDP-43 levels are higher in ALS patients compared to those with bvFTD, a relevant aspect from a management and prognostic perspective (Junttila et al., 2016).

Additionally, although it is unclear at which clinical stage these alterations occur, certain biomarkers, particularly those linked to inflammation, can differentiate FTD patients from controls. For example, the protein triggering receptor expressed on myeloid cell 2 (TREM2, a microglial immunity receptor) and the plasma levels of the pro-inflammatory cytokine IL-6 are elevated in FTD patients compared to controls (Gibbons et al., 2015; Heywood et al., 2018). However, FTD patients also show increased levels of the anti-inflammatory cytokine IL-8, while the plasma levels of annexin-1, an inflammation resolution biomarker, are reduced in bvFTD compared to AD and controls (Fraga et al., 2019; Galimberti et al., 2006). These conflicting findings underscore

the complexity of neuroinflammation in FTD, likely influenced by the disease stage and underlying neuropathology. Consistently, several markers related to angiogenesis, which is strongly linked to inflammation, such as vascular endothelial growth factor (VEGF), placental growth factor, and angiogenin, as well as various isoforms of metalloproteinases, are elevated in FTD patients (Hansson et al., 2019; Janelidze et al., 2017; Morelli et al., 2020; Tuna et al., 2018). Furthermore, chitinase-3-like protein, a glycoprotein involved in extracellular matrix remodeling and inflammation, is elevated in the CSF of both genetic and sporadic FTD-ALS cases when compared to asymptomatic mutation carriers and controls, although the evidence remains limited (Oeckl et al., 2019). However, inflammation is a highly non-specific pathophysiological process (associated with almost any type of damage or alteration of homeostasis) (Glass et al., 2010). This suggests that, alongside other blood biomarkers—particularly if specific cut-off values are identified and validated—they could aid in characterizing each patient and potentially indicate which individuals may fall within the FTD spectrum, though without providing a definitive diagnosis in themselves.

Interestingly, many markers of altered synaptic functionality that show characteristic changes in AD patients (e.g., synaptosomal-associated protein, 25 kDa, and synaptotagmin) are normal in FTD patients, who instead show a specific reduction in CSF levels of Ras-related protein Rab3A, a presynaptic protein crucial for maintaining a reserve of vesicles (Clarke et al., 2019; Parakh et al., 2018; Swift et al., 2021). Similarly, neurogranin, a protein involved in calcium-dependent mechanisms that promote long-term potentiation (LTP) of synaptic connections, is reduced in plasma exosomes of FTD patients compared to controls (Goetzl et al., 2016). Finally, alterations in all neurotransmitter circuits (particularly the dopaminergic one), as well as combinations of circulating blood microRNAs (miRNAs), have allowed differentiation between FTD patients and controls (Engelborghs et al., 2008; Grasso et al., 2019; Janssens et al., 2018). The clinical application of these biomarkers requires additional studies in order to standardise the assessment methods, which are often heterogeneous, and understand the most appropriate stage of disease for application.

10.4 Promising FTD fluid biomarkers for early patient identification

In both genetic and sporadic variants, the neurofilament light chain (NfL), a specific type of intermediate filament that constitutes the axonal cytoskeleton in both the CNS and peripheral nervous systems, represents a promising biomarker. Indeed, NfL levels reflecting ongoing neurodegenerative processes, are particularly high in FTD patients when compared to different dementias, and are inversely correlated with survival time (Cajanus et al., 2020; Jong et al., 2007). Notably, NfL can also provide information on disease trajectory, as high NfL levels predict more aggressive cases, particularly in bvFTD and nfvPPA patients (Ljubenkov et al., 2018). Furthermore, NfL levels are altered from the earliest stages of the disease, even when patients are still asymptomatic, not only in mutation carriers (such as those with *GRN* and *C9orf72* mutations) but also significantly in sporadic cases (Katzeff et al., 2022; Panman et al., 2021; Rojas et al., 2021; van der Ende et al., 2019). Consistently, according to some studies, the interval between the onset of relevant pathophysiological changes and the appearance of symptoms in *GRN* mutation carriers is relatively short (approximately 2-4 years) (Jiskoot et al., 2018). This period is characterised by a significant (three- to fourfold) increase in serum NfL levels and an initial, subtle decline in cognitive performance, particularly in language, not only in the nfvPPA but also in bvFTD cases (L. H. Meeter et al., 2016; Panman et al., 2021). Consistently, NfL CSF values could be used to discriminate pre-symptomatic mutation carriers from patients and, therefore,

might represent a biomarker of phenoconversion (L. H. Meeter et al., 2016). However, it is noteworthy that more recent evidence has shown that, in all genetic FTD patients, an increase in NfL can be detected as early as 15 years before the clinical onset. Both NfL levels and their rates of increase were observed only in presymptomatic carriers who later converted to symptomatic disease but not in those who remained clinically stable during follow-up. This suggests that neuropathological changes might be detectable well in advance of clinical onset in patients known to be at risk (Wilke et al., 2022). Importantly, blood NfL accurately reflects CSF levels, allowing a non-invasive evaluation of the extent of the ongoing neuropathological process in the CNS, particularly when TDP-43 pathology is involved (Abu-Rumeileh et al., 2018; Wilke et al., 2016). Additionally, CSF NfL levels help identify patients with FTD-ALS, who exhibit markedly higher levels than those with different FTD subtypes (Gaetani et al., 2019). Therefore, NfL appears to be a highly promising marker for identifying FTD-ALS patients from the early (asymptomatic) stages, as has already been suggested for patients within the AD spectrum experiencing not only mild cognitive impairment (MCI) but also subjective cognitive complaints (SCC, i.e. subjective deficits not detected by neuropsychological assessments) (Giacomucci et al., 2022).

Moreover, although not specific on their own, as they are altered in all processes associated with neuronal degeneration, significantly elevated blood NfL levels have shown good discrimination between FTD (regardless of the clinical phenotype) and different neurodegenerative dementia and also, notably, non-neurodegenerative disorders, such as primary psychiatric diseases, which is a critical aspect in this context (Bolsewig et al., 2022; Ducharme et al., 2020; Meeter et al., 2018b; Rohrer et al., 2016; Wilke et al., 2016). Of note, their CSF and serum levels proved a strong correlation with cognitive impairment, suggesting that NfL accurately reflects the progression of neuropathological damage (Skillback et al., 2014; Steinacker et al., 2018). Although it has been less explored, also the phosphorylated isoform of the neurofilament heavy chain is elevated in the CSF of FTD patients compared to those with early-onset AD (Pijnenburg et al., 2007). Furthermore, recent evidence has suggested that this isoform, unlike its non-phosphorylated counterpart, increases in close proximity to clinical onset, suggesting that its alteration could aid patient stratification according to disease severity (Wilke et al., 2022).

Therefore, it would be reasonable to propose NfL levels as a useful screening tool for the early detection of neurodegenerative processes, even when not linked to a genetic cause, warranting patients' further characterisation with subsequent strategies. Indeed, although genetic cases exhibit certain biomarkers highly indicative of underlying FTD pathology (e.g., progranulin, dipeptide repeats), targeted testing for these may be most appropriate in the presence of a family history that raises suspicion of a specific genetic variant, thereby making them of relatively limited utility in the general population. In contrast, NfL levels, while inherently nonspecific, could help identify early neurodegenerative changes in both sporadic and genetic cases, thereby facilitating timely referral for further diagnostic evaluations essential for accurate assessment.

10.5 FTD neurophysiological biomarkers

Based on the evidence discussed in the following sections, neurophysiological biomarkers may prove highly useful in guiding diagnostic suspicion toward the FTD spectrum. However, while the actual findings are promising, it is essential to recognize that evidence in this area remains almost entirely limited to research settings. Larger, real-world studies will be needed to confirm their applicability to current clinical practice. As

such, these biomarkers are not yet part of routine diagnostics for patients with suspected FTD. Nevertheless, considering some advantages and their potential broad applicability, we suggest that they could become valuable tools in the diagnostic work-up for these patients in the future.

10.5.1 Noninvasive brain stimulation techniques

Noninvasive brain stimulation techniques (NIBS) encompass a wide range of methods involving the application of magnetic (transcranial magnetic stimulation, TMS) or electric stimuli (transcranial electrical stimulation) to the scalp to modulate the activity of underlying neuronal populations not only at the stimulation site but also in remote yet interconnected regions (Rossi et al., 2022). These techniques have significantly contributed to our understanding of neurophysiological mechanisms in healthy individuals and there is growing interest in their clinical application for diagnostic, prognostic, and therapeutic purposes across various patient populations (Antonioni et al., 2024c, 2024a; Baroni et al., 2024). In its basic form, TMS involves the application of a single magnetic pulse over the motor area (M1), which induces depolarisation of corticospinal and, subsequently, lower motor neurons located in the ventral horns of the spinal cord, leading to muscle contraction. This muscle activity could be recorded via an electromyographic (EMG) signal known as a motor-evoked potential (MEP), which has been instrumental in characterising changes in corticospinal excitability under physiological and pathological conditions (Spampinato et al., 2023). Furthermore, paired-pulse TMS protocols applied over M1 enable the assessment of neurophysiological measures reflecting the functional status of excitatory and inhibitory activity. Specifically, short- and long-interval intracortical inhibition (SICI and LICI, respectively) are thought to reflect ionophoric GABA-A and metabotropic GABA-B currents, which describe the activity of inhibitory cortical interneurons, while glutamatergic excitatory activity is assessed through intracortical facilitation (ICF), using specific intensities and inter-stimulus intervals tailored to the neuronal populations being evaluated (Cash et al., 2017). Indeed, the activity of inhibitory and excitatory interneurons modulates MEP amplitude, allowing for an assessment of the balance between excitation and inhibition in cortical circuits (Davila-Pérez et al., 2019).

Recently, NIBS techniques have also been applied to neurodegenerative diseases to characterise aspects related to plasticity, connectivity, and reactivity (Pini et al., 2019). These techniques have primarily been employed in AD patients, documenting alterations in neurophysiological measures, particularly those reflecting the status of the cholinergic system (i.e., the short latency afferent inhibition, SAI, a marker of sensorimotor integration), as well as in cortical plasticity (Boggio et al., 2011; Di Lorenzo et al., 2016). Notably, these neurophysiological alterations are specific biomarkers of AD patients. Indeed, SAI is strongly correlated with memory impairment and brain amyloid burden load, which are pivotal features of AD patients (Bonnì et al., 2017; Martorana et al., 2012). Building on these findings, which suggest that NIBS techniques allow the detection of alterations closely tied to the underlying neuropathology and, therefore, specific to the patient population, their diagnostic potential has also been explored within the FTD spectrum. Indeed, recent research has shown that FTD patients not only exhibit SAI within normal limits but has also proven significant impairment in SICI-ICF and partial impairment in LICI (Benussi et al., 2017). This evidence confirms that NIBS provides measures that accurately reflect the underlying neurophysiological processes (with SAI, linked to amyloid, unaffected as expected) and that, notably, it allows for non-invasive differentiation between patients with other

types of dementia, particularly AD. Indeed, FTD patients are characterised by a relative sparing of the cholinergic system and demonstrate no significant alterations in corticospinal excitability when compared to AD patients (Alberici et al., 2008; Di Lazzaro et al., 2006; Pierantozzi et al., 2004). Importantly, these findings seem to apply to both genetic (even in the presymptomatic phase, at more than 15 years before the clinical onset) and sporadic FTD cases and align with theories that attribute a crucial role to the dysregulation of the GABA-glutamate balance in its pathophysiology (Adams et al., 2021; Benussi et al., 2016, 2019a; Burrell et al., 2011).

Additionally, it is noteworthy that SICI-ICF alterations are evident from the earliest stages of the disease, thus providing safe, reliable, and cost-effective diagnostic support through a relatively short examination without excessively strict exclusion criteria (Benussi et al., 2017). Specifically, similar to what has been observed regarding fluid biomarkers, *GRN* and *C9orf72* mutation carriers exhibit characteristic neurophysiological alterations long before changes are detectable through structural neuroimaging or cognitive assessments. Indeed, these alterations follow a specific pattern, with glutamatergic disruptions occurring up to 30 years before the expected onset, followed by GABAergic alterations approximately two decades prior (Benussi et al., 2019b; Rohrer et al., 2015a). Subsequent research conducted exclusively on *GRN* mutation carriers has further validated this finding, demonstrating that both ICF and SICI alterations are characteristic of the early stages (Gazzina et al., 2018). This is crucial, as the balance between excitation and inhibition represents the cornerstone of the neuronal oscillations underlying cognitive processes (Schmidt et al., 2018). It is, therefore, plausible that these early disruptions represent the initial phase of the cognitive deficits that become manifest decades later—likely due to compensatory mechanisms—in these patients. Moreover, of note, the combination of alterations in neurophysiological markers reflecting peculiar neurodegenerative diseases allows patients to be differentiated not only between AD and FTD but also with other common differential diagnoses. Consistently, a seminal study showed that SICI-ICF was significantly impaired in FTD but also in dementia with Lewy bodies (DLB) patients, whereas LICI was rather specific to FTD, and SAI was impaired in both DLB and AD patients (Benussi et al., 2020b). These findings have encouraged further research into the potential of NIBS techniques for the differential diagnosis of patients from the earliest stages of cognitive decline. Indeed, while MCI due to AD-related pathology has been extensively characterised, MCI that may progress to FTD or DLB is more challenging to identify (Dubois et al., 2014; Gauthier et al., 2006; McKeith et al., 2020). This distinction is crucial not only for prognostic purposes but also for initiating the most appropriate therapeutic interventions as early as possible.

Of note, various studies have demonstrated, particularly in the context of AD, that NIBS can detect the presence of a neurodegenerative process when characteristic neurophysiological alterations are observed at the MCI stage (Di Lorenzo et al., 2020; Padovani et al., 2019, 2018). A recent study has highlighted that the combination of these neurophysiological measures—namely, SICI-ICF, LICI, and SAI—not only allows for the differentiation between healthy controls and patients with MCI but also categorises different forms of MCI, such as those associated with AD, FTD, or DLB (A Benussi et al., 2021). This categorisation is based on analysing specific neurotransmitter systems and circuits predominantly affected in these conditions, including the cholinergic system in AD and DLB, GABA-A and glutamate in FTD and DLB, and, to a lesser extent, GABA-B in FTD (Benussi et al., 2017; Di Lazzaro et al., 2002). Notably, the use of these measures has achieved a diagnostic accuracy which is only slightly lower than that of current gold standards, such as CSF biomarkers and functional imaging with Positron Emission Tomography (PET). Finally, once the disease has reached its

symptomatic stage, these techniques assist in defining the specific clinical subtype. Consistently, alterations are significantly more pronounced in bvFTD and nfvPPA patients compared to those with svPPA, particularly in terms of SICI (Benussi et al., 2020a). This may be attributed to a complex interplay of factors, including the type and regional distribution of pathological proteins, as well as the possible presence of genetic mutations. Notably, the severity of these neurophysiological abnormalities appears to predict functional decline over the following year, a challenge that other commonly used biomarkers struggle to address.

Finally, it is worth noting that ALS patients also show characteristic neurophysiological alterations, such as a pathological increase in motor excitability in the early phase (presumably compensating for ongoing damage) and, conversely, a decrease in the later phase, as well as changes in SICI particularly correlating with lower motor neuron dysfunction (Huynh et al., 2019). This is particularly relevant when considering that the differential diagnosis of early-stage motor neuron diseases is often complex, especially in cases with atypical presentations (Antonioni et al., 2020; Feldman et al., 2022). This evidence opens up intriguing possibilities for the clinical application of these measures, especially in the early stages of the disease, potentially reducing the need for more invasive and costly investigations.

10.5.2 Other neurophysiological biomarkers

Beyond NIBS techniques, other neurophysiological assessments provided profound insights into the distinct alterations observed within the FTD spectrum. Indeed, as previously mentioned, it is now well-established that all FTD phenotypes share deficits in emotion processing and empathy (Antonioni et al., 2023b; Couto et al., 2013). This is particularly relevant, as emotions involve not only cognitive components (such as the semantic categorization of experiences) but also, notably, somatic elements, including specific autonomic responses generated by the autonomic nervous system, which comprises a sympathetic and parasympathetic branch (Barrett, 2017). These responses allow the organism to adapt dynamically and contextually to daily circumstances, e.g. increasing heart and respiratory rates in situations requiring greater oxygen and nutrient availability to skeletal muscles to face potential threats, with the opposite occurring during relaxation. Thus, emotional awareness has been suggested to entail reciprocal feedback between somatic physiology and cognitive interpretation of these signals (Seth and Friston, 2016). Such autonomic responses can be assessed using neurophysiological techniques, including assessments of heart rate variability, respiratory rhythm, and galvanic skin conductance, which provide an objective correlate of emotional processing—often challenging to capture with standard neuropsychological evaluations, particularly in the presence of semantic deficits (as seen in many FTD patients) (Marshall et al., 2018a).

Numerous studies have demonstrated that these functions are mediated by a network of cortico-subcortical regions, specialized in comparing afferent information with predicted autonomic states and generating subcortical autonomic responses when there is a mismatch between expected and actual stimuli (Seth and Friston, 2016). Within this network, the insula is pivotal for integrating multimodal interoceptive signals, while various cortical areas (such as the anterior cingulate and orbitofrontal cortex) exert a top-down regulation, likely to integrate cognitive dimensions into autonomic response modulation (Craig, 2009; Critchley et al., 2011). Notably, all these regions are critically affected in the FTD spectrum, both in terms of atrophy and altered functional connectivity (see section 4), potentially resulting in aberrant processing of both afferent and efferent autonomic signals, which may underlie the altered emotional processing common among FTD patients

(Hua et al., 2023). Consistently, several studies have shown that bvFTD patients display altered baseline functioning of both the sympathetic (associated with greater emotional blunting) and parasympathetic systems (linked to reduced prosocial behavior), as well as decreased autonomic nervous system reactivity in response to stimuli with negative valence, which may underly their disrupted socio-emotional functioning (Guo et al., 2016; Hua et al., 2019; Sturm et al., 2018, 2013). Similarly, svPPA patients exhibit reduced parasympathetic (e.g., attenuated heart rate deceleration during emotion identification) and sympathetic reactivity (e.g., changes in skin conductance in response to emotional videos), along with reduced baseline autonomic function (Hua et al., 2023; Kumfor et al., 2019; Marshall et al., 2019). Interestingly, this finding has also been highlighted in rtvFTD patients, who exhibit much more pronounced autonomic alterations than svPPA ones, possibly explaining the more substantial interpersonal relationship impairments observed in the former group compared to the latter (Hua et al., 2023). Finally, nfvPPA patients also display, during emotion identification tasks, diminished cardiac sympathetic activity, as well as diminished respiration rate reactivity (Hua et al., 2020; Marshall et al., 2019). Moreover, nfvPPA patients are characterised by reduced pupil dilation (i.e., another common way to study autonomic nervous system activity) in response to sound and, notably, an altered EMG pattern in the facial muscles when looking at faces (Fletcher et al., 2015; Marshall et al., 2018b).

Indeed, EMG also provides a valuable tool for investigating abnormalities in emotion processing in these patients. In healthy subjects, the observation of faces expressing specific emotions rapidly and involuntarily engages the corresponding facial muscles in the observer, leading to a “motor mimicry” that facilitates the decoding of perceived emotions and thus enhances effective social interaction (Niedenthal, 2007; Wood et al., 2016). This process establishes a direct link between emotion observation, recognition, and mimesis. Notably, FTD patients exhibit distinct alterations in EMG activity during emotion observation depending on the phenotype, likely due to the differential involvement of cortico-subcortical networks responsible for these functions (Marshall et al., 2018b). For instance, bvFTD patients display a globally reduced facial muscle reactivity, while svPPA ones are marked by a disruption in the link between correct emotion identification and muscle response despite retaining overall muscle reactivity. Similarly, in line with the previously discussed autonomic response alterations, rtvFTD patients exhibit the most severe patterns, with both significantly reduced facial reactivity and an aberrant coupling between muscle response and emotion recognition.

These findings are particularly relevant, not only because they offer quantitative measures of emotional processing alterations (in terms of abnormal autonomic and/or EMG responses) but also because they aid the identification of the somatic correlates of the emotional experience disruptions in FTD patients, which has a somatic, not merely cognitive, component due to peculiar brain networks involvement in each patient groups. Although preliminary and requiring validation through larger studies (including pre-symptomatic individuals to assess any early onset of these alterations), these non-invasive and widely accessible evaluations hold significant potential for providing a more refined profiling of FTD patients.

10.6 FTD neuroimaging biomarkers

Traditionally, neuroimaging, particularly structural imaging, combined with CSF biomarkers, has been a cornerstone in the diagnosis of FTD. Indeed, it is typically characterised by atrophy primarily affecting the frontal and/or temporal lobes, with different patterns according to the specific subtype, especially in the early stages, as the atrophy becomes widespread in the advanced phases (Antonioni et al., 2023b). Importantly,

supportive neuroimaging is now required to move from a possible to a probable diagnosis of bvFTD (Rascovsky et al., 2011). Currently, structural imaging is performed first, followed by a functional imaging method for increased sensitivity and specificity. However, research conducted over the past decades has highlighted that functional imaging allows the detection of changes even before structural damage becomes evident (Minoshima et al., 2021). Therefore, although its application is currently limited to research settings, given its potential for future clinical applications, relevant findings about functional neuroimaging in this context will be discussed first.

10.6.1 Functional neuroimaging

10.6.1.1 Functional brain magnetic resonance imaging MRI (fMRI)

Resting-state fMRI, which assesses neural activity through time-dependent synchronised fluctuations in blood oxygenation level-dependent (BOLD) signals, allows the characterisation of brain networks formed by functionally connected areas that, although sometimes spatially separated, exhibit coordinated activities (Raimondo et al., 2021). Specifically, within the FTD spectrum, the most affected brain networks include the default mode network (DMN), consisting of the dorsal medial prefrontal, posterior cingulate cortex, precuneus, and angular gyrus and showing activity during wakeful rest (Menon, 2023); the language network, involving the left frontal operculum, M1, supplementary motor area, and inferior parietal lobule and responsible for the articulatory aspects of communication (Fedorenko et al., 2024); the semantic network, involved in linking multimodal sensory and symbolic data with meaning, includes the anterior, ventral, and inferior temporal regions, bilateral frontal cortex, left amygdala, hippocampus, caudate, and occipital regions, usually within the left hemisphere (Liuzzi et al., 2020); the salience network, which plays a key role in detecting and filtering salient stimuli and recruiting context-specific functional networks, mainly involves the frontal lobe, anterior cingulate, insula, ventral striatum, amygdala, and medial thalamus (Schimmelpfennig et al., 2023); and the executive control network, responsible for complex tasks such as problem-solving and sustained attention and encompassing the dorsolateral prefrontal and lateral posterior parietal regions (Witt et al., 2021).

BvFTD patients, characterised by typical impairments in interpreting the emotional valence of stimuli and preparing appropriate responses, show reduced connectivity in the salience network, particularly at the level of the left insula, whose alterations may predict their behavioural changes (Day et al., 2013). Interestingly, functional changes in the salience network may lead to a compensatory increase in connectivity in the DMN, although not all studies support this interpretation (Borroni et al., 2012; Farb et al., 2013; Filippi et al., 2013; St. Jacques et al., 2015; Zhou et al., 2010). Consistently, some authors suggest that reduced connectivity in the DMN may be the functional correlate of some deficits of bvFTD patients, such as impairments in autobiographical memory retrieval and in the ability to reflect on one's own mental state and infer that of others (i.e. so-called social cognition or theory of mind, which is one of the most specific aspects in these patients) (Bora et al., 2015; El Haj et al., 2024; Filippi et al., 2013; Lanata and Miller, 2016). Although evidence on the most affected networks and primary sites of neuropathological damage remains inconsistent, recent data bolster the theory of network-based atrophy in both sporadic and genetic bvFTD. This theory posits that atrophy progresses through network-specific connections (Shafiei et al., 2023). The underlying cause of this

vulnerability is still poorly understood but may relate to the unique molecular, genetic, or receptor characteristics of cells within a specific circuit (Kassubek et al., 2018; Zheng et al., 2019). As expected, svPPA and nfvPPA patients show reduced functional connectivity in the semantic network and the language and motor networks, respectively, as well as distinctive brain hub distributions when compared to healthy controls (Agosta et al., 2014; Guo et al., 2013; Seeley et al., 2009a; Tao et al., 2020).

In genetic cases, *MAPT* mutation carriers display reduced functional connectivity, as assessed through fMRI, within the DMN, while *C9orf72* expansion carriers are characterised by decreased connectivity in the DMN, salience, and sensorimotor networks (S. E. Lee et al., 2017; J. L. Whitwell et al., 2011). Finally, findings regarding asymptomatic *GRN* mutation carriers are often controversial, showing decreased connectivity in DMN and both increased and reduced connectivity in the salience network (Borroni et al., 2012; Dopper et al., 2014). Thus, further studies will be required to obtain conclusive data. Notably, fMRI has also been used to explore the correlates of specific tasks in asymptomatic *GRN* mutation carriers (Alexander et al., 2018). In addition to showing slower response latencies behaviourally, they have exhibited reduced functional activation in the anterior and posterior ventrolateral prefrontal cortex, effectively distinguishing them from non-carriers. This reduced activation was not attributable to structural differences between the two groups and was unrelated to the years until onset. This suggests that both resting-state and task-related data about the most vulnerable networks could be extremely helpful in identifying these patient categories.

10.6.1.2 18 fluorodeoxyglucose-PET (18F FDG-PET)

Another widely used technique for studying brain activity is 18F FDG-PET, which assesses metabolic activation patterns in neuronal populations under both physiological and pathological conditions (Mosconi, 2013). Indeed, altered metabolic regions observed through FDG-PET closely correlate with atrophic areas, making this technique particularly valuable for differentiating FTD from other neurodegenerative diseases like AD, and for identifying specific disease subtypes even before evidence of atrophy (Buhour et al., 2017; Davison and O'Brien, 2014; Rabinovici et al., 2011). Consistently, FDG-PET findings often overlap with those from fMRI, revealing in bvFTD patients a pattern of hypometabolism in the orbitofrontal, anterior cingulate, prefrontal cortex, and anterior temporal poles extending to the posterior fusiform gyrus (Bejanin et al., 2020; Franceschi et al., 2005; Verfaillie et al., 2015). However, other regions showing altered signals, such as the caudate, thalamus, and hippocampus, are reported less consistently across studies, likely due to variability in methodological aspects and disease severity (Franceschi et al., 2005; Gordon et al., 2016; Schroeter et al., 2007). Additionally, the PPA variants exhibit patterns consistent with their characteristic network disruptions, specifically in the left entorhinal and perirhinal cortex, inferior temporal regions, and amygdala in svPPA, and in the left inferior frontal and superior temporal regions in nfvPPA, respectively (Desgranges et al., 2007; Rabinovici et al., 2008). Nonetheless, unlike fMRI, FDG-PET requires the use of radioactive tracers, is expensive, and is not available in all healthcare settings. Furthermore, there are still several limitations in its current clinical application due to the frequent lack of uniform diagnostic standards and specific training in the interpretation of neurodegenerative diseases for many nuclear medicine clinicians (Foster, 2003). However, given FDG-PET's capability to detect synaptic dysfunction even in the early stages of the disease, its inclusion in the diagnostic work-up in the MCI stage appears justified to identify hypometabolic patterns indicative of FTD (Arbizu et al., 2018). Consistently, FDG-PET reliably identifies half of the bvFTD patients that remain

undetected by MRI (Kerklaan et al., 2014). Future studies in patients with possible FTD pathology in the presymptomatic phase should ideally examine FDG-PET patterns to better characterize the temporal progression of these changes, thereby identifying metabolic findings that may precede structural atrophy.

10.6.1.3 Other functional neuroimaging techniques

Arterial spin labeling (ASL) is a non-invasive and cost-effective technique that measures cerebral blood flow using magnetically labeled arterial blood water as an endogenous marker, without requiring radiation and with brief acquisition times (Telischak et al., 2015). Unfortunately, data on FTD patients using this method are limited, though some studies indicate its potential for differentiating AD. Specifically, bvFTD patients often show hypoperfusion in the bilateral frontal and anterior cingulate regions, while hypoperfusion in the posterior cingulate appears to be a key feature for distinguishing them from patients with early-stage AD (Shimizu et al., 2010; Steketee et al., 2016). Further research is needed to explore the characteristics of other clinical phenotypes to enable ASL use in clinical practice. Indeed, at present, ASL, as well as Single-photon emission computed tomography (SPECT), are outperformed by PET-FDG in detecting dementia at an early stage (Ceccarini et al., 2020; Duignan et al., 2021).

Other methods, such as PET using beta-amyloid tracers, are particularly useful for differentiating FTD from cognitive decline within the AD spectrum (Ward et al., 2023). Notably, only the lvPPA typically shows, as expected, a positive amyloid PET scan, whereas this finding is observed in only a small percentage of patients with other FTD clinical phenotypes (Conca et al., 2022; Rabinovici et al., 2008). However, it is worth mentioning that, as age advances, amyloid burden increases in both healthy elderly and, more significantly, in neurodegenerative dementias, often leading to its co-existence with other pathological protein accumulations (Haller et al., 2020; Sengupta and Kayed, 2022). Therefore, the role of amyloid PET is especially crucial in younger patients, while its contribution to differential diagnosis diminishes in older ones.

Recently, selective PET tracers for tau pathology have been developed, which are expected to be extremely useful for differential diagnosis, staging lesion burden, and evaluating otucomes of specific treatments (Kubota et al., 2024). There are significant technical challenges in obtaining the ideal tracer, since tau aggregates are intracellular, necessitating the crossing of both the blood-brain barrier and neuronal membranes to ensure effective binding. Additionally, the tracer should bind in a reversible, non-toxic manner with high affinity to tau, regardless of isoform and post-translational modifications (Gordon et al., 2016). However, 18F-flortaucipir PET already demonstrated high accuracy in differentiating AD from different neurodegenerative disorders, as well as in predicting clinical progression in cognitively unimpaired subjects (Groot et al., 2024; Ossenkoppele et al., 2022, 2018). Moreover, importantly, 18F-AV-1451 PET showed significant tracer retention in the frontotemporal region of *MAPT* mutation carriers a full three and a half years before symptom onset, suggesting its potential for early detection (Ghetti et al., 2015). Finally, new tau tracers, as well as ligands for different pathological proteins such as TDP-43 or techniques like proton magnetic resonance spectroscopy, are currently under development and might have important clinical applications in the coming decades (Beyer and Brendel, 2021; Chen and Kantarci, 2020a; Rao et al., 2021).

However, it is important to note that, while evidence from 18F FDG-PET and, to a lesser extent, fMRI, is relatively robust, with literature supporting their role in identifying patients within the FTD spectrum, the methods discussed in this subsection currently lack sufficient evidence for clinical applicability. Therefore, at

present, only 18F FDG-PET and fMRI could be considered for clinical use. In contrast, techniques such as ASL or PET with tau or TDP-43 tracers require studies on larger samples to demonstrate their utility beyond research settings.

10.6.2 Structural neuroimaging

10.6.2.1 Grey matter alterations

Volumetric brain MRI is traditionally used to map the patterns and distribution of brain lesions, often with a specific focus on grey matter. This is crucial for identifying the "signatures" specific to different subtypes of FTD and for differential diagnosis based on findings associated with other diseases, such as AD or cognitive decline due to cerebrovascular lesions (Gordon et al., 2016). Specifically, in bvFTD patients, even though there is significant individual variability in terms of hemispheric asymmetry, posterior cortical involvement, and predominant frontal or temporal lesion, the atrophy primarily affects the prefrontal and anterior temporal cortex, as well as the anterior cingulate, insula, striatum, and thalamus (Pan et al., 2012; Schroeter et al., 2014). Notably, the right hemisphere generally exhibits more pronounced atrophy than the left in the early stages (Perry et al., 2017). Consistently, the right insula and anterior cingulate cortex display a high concentration of von Economo neurons—large spindle-shaped neurons that facilitate faster communication between different brain regions (Allman et al., 2011). These neurons, prominently found in humans and great apes, are particularly susceptible to FTD neuropathological damage and their alterations might be the anatomical substrate for many of the characteristic symptoms of bvFTD (Gami-Patel et al., 2019; Kim et al., 2012). Based on the distinctive distribution of grey matter lesions, four subtypes have been identified, each likely reflecting different neuropathological mechanisms: a focal frontal-dominant subtype, a more distributed frontotemporal subtype, a focal temporal-dominant subtype, and a more widespread temporal-frontal-parietal subtype (Jennifer L. Whitwell et al., 2009; Whitwell et al., 2012). Importantly, one study has suggested that frontal and temporal subgroups reflect different pathophysiological processes rather than simply a distribution of damage over time (Ranasinghe et al., 2016). Moreover, the same authors identified an additional subtype consisting of patients with atrophy almost exclusively in subcortical regions (with minimal cortical involvement), characterised by the slowest progression among all patient groups. Although earlier observations had suggested a non-neurodegenerative nature for these forms (i.e., the so-called bvFTD-phenocopy), their patients still exhibited high rates of core symptoms and pathogenic mutations (Devenney et al., 2016). Notably, all of them had neuropathology consistent with the FTD diagnosis. This confirms that this subgroup falls within the spectrum, and it is reasonable that the symptoms were the result of disconnection syndromes between cortical areas due to thalamic and striatal involvement (Lee et al., 2014).

In contrast, svPPA is characterised by marked asymmetry, typically affecting the left hemisphere, particularly the anterior and inferior temporal regions, while forms predominantly involving the right hemisphere, as mentioned earlier, now represent a separate diagnostic category (Rohrer et al., 2009b). The earliest changes usually involve the temporal pole, inferior temporal cortex, fusiform gyrus, amygdala, parahippocampal, and entorhinal cortex (Rogalski et al., 2011; Schroeter et al., 2007). As the disease progresses, atrophy extends to anterior regions, affecting the insula, anterior cingulate, orbitofrontal cortex, and inferior frontal gyrus, as well as to posterior parietal-temporal regions and the homologous areas of the contralateral hemisphere (Rohrer

et al., 2009b). Even though nfvPPA also predominantly affects the left hemisphere, it specifically targets regions such as the pars orbicularis of the inferior frontal gyrus, the superior temporal gyrus, insula, and dorsolateral prefrontal cortex, useful in differentiating it from svPPA (Rogalski et al., 2011; Rohrer et al., 2009b). As the disease advances, the atrophy pattern expands to include anterior frontal (including M1 and premotor areas) and parietal regions, the lateral temporal areas of the left hemisphere, the contralateral prefrontal and temporal regions and the thalamus, and bilaterally the caudate and putamen (Gorno-Tempini et al., 2004; Rogalski et al., 2011). Generally, the atrophy is more severe in patients with bvFTD and svPPA than in those with nfvPPA (Planche et al., 2023). In summary, these patterns not only differentiate FTD subtypes but also show a strong correlation with typical cognitive and behavioural alterations (Antonioni et al., 2023b).

Notably, patients with genetic mutations display unique characteristics that set them apart from sporadic cases, with atrophy profiles that have allowed the identification of specific mutations on an individual level (Whitwell et al., 2012). For instance, *GRN* mutation carriers exhibit a markedly asymmetric involvement, especially of the parietal lobe, but also of the temporal and frontal regions (Rohrer et al., 2015b, 2010; Whitwell et al., 2012). One study showed an inverse correlation between SICI/ICF and superficial right insula surface area, an early affected region in the *GRN* subgroup, and indeed associated with their characteristic neurophysiological signature (Gazzina et al., 2018). In contrast, the *MAPT* mutation is associated with a peculiar focal and symmetrical involvement of the anteromedial temporal, anterior cingulate, and orbitofrontal regions, as well as of the insula and caudate (Ghetti et al., 2015). Similarly, *C9orf72* expansion carriers are characterised by a more symmetric and widespread pattern affecting the dorsolateral and medial frontal, anterior temporal, and orbitofrontal lobes, and to a lesser extent, the parietal and occipital lobes, as well as specific subcortical structures such as the thalamus and cerebellum (Mahoney et al., 2012; Sha et al., 2012). Specifically, the most striking atrophy pattern involves the frontal lobes, followed by the anterior temporal lobes in *C9orf72* expansion carriers (Whitwell et al., 2012). Consistently, temporal lobe involvement is less marked in the *C9orf72* group than in the *MAPT* and *GRN* ones, which are characterised by greater anteromedial and inferior involvement in this region, respectively. Based on these findings, the absence of frontal atrophy could reasonably seem to suggest a *MAPT* mutation, while striking dorsolateral frontal atrophy is more specific in sporadic FTD cases (Whitwell et al., 2012).

Unfortunately, evidence on rtvFTD is limited, largely because, until recently, this variant was categorised under svPPA cases or was often misdiagnosed within the AD spectrum due to complaints of episodic memory being reported (Ulugut et al., 2024). Therefore, it is possible that much of the knowledge concerning svPPA may partially pertain to this specific variant. Notably, a large retrospective study demonstrated that these patients exhibit predominantly right anterior temporal atrophy, as well as involvement of the left temporal and right ventral frontal areas (Ulugut Erkoyun et al., 2020a). Thus, the pattern of atrophy is essentially the mirror image of that typically observed in svPPA. Of note, damage to the temporal poles and the anterior fusiform gyrus, particularly on the left side, is associated with prosopagnosia, one of the distinguishing symptoms of rtvFTD.

Therefore, considering the variability of atrophy patterns (dependent, among other things, on disease stage, genetic mutations, and individual susceptibility to damage of specific brain networks), it is essential to integrate other types of information to correctly evaluate the structural alterations data, i.e., to identify the correct FTD subtype according to the clinical evolution and to associate it with the developmental stage of the damage as assessed by neuroimaging (Antonioni et al., 2023b; Seeley et al., 2009a).

10.6.2.2 White matter alterations

In addition to traditional structural imaging that primarily assesses gray matter atrophy, recent studies have also examined white matter alterations within the FTD spectrum. This research provides valuable data complementing the network dysfunctions discussed earlier as well as offering insights into the distribution patterns of pathological proteins across brain regions (Ayers et al., 2018). Diffusion tensor imaging (DTI) is an MRI technique that evaluates water diffusion patterns to determine the integrity of barriers, such as myelinated tracts, that influence its distribution in brain tissues. Specifically, DTI assesses the directionality (fractional anisotropy) and degree of diffusivity (mean, axial, and radial) of water in the brain (Assaf and Pasternak, 2008). For example, bvFTD is characterised by increased diffusivity (indicating damage to myelinated fibers) in the uncinate, inferior frontal-occipital, superior and inferior longitudinal fasciculi, the genu of the corpus callosum, and the cingulum—key structures that interconnect the frontal and temporal lobes (Agosta et al., 2012; Diehl-Schmid et al., 2006; Mahoney et al., 2015). Notably, patients with this phenotype and carrying the *MAPT* mutation show peculiar involvement of the cingulum and especially the uncinate fasciculus, with alterations detectable even in presymptomatic stages, indicating a selective vulnerability of this white matter tract (Dopper et al., 2014; Mahoney et al., 2014). Furthermore, *GRN* mutation carriers display a variable involvement in DTI assessments in the genu of the corpus callosum and the left inferior occipitofrontal and uncinate fasciculus, as well as in the internal capsule (Borroni et al., 2008; Jiskoot et al., 2018). It is noteworthy that DTI changes of the uncinate fasciculus were present in both *GRN* and *MAPT* mutation carriers two years prior to clinical onset (Jiskoot et al., 2019). Conversely, patients with *C9orf72* expansion, who often exhibit characteristic cerebellar atrophy, peculiar intracellular inclusions, and short neurites in the granule cells, show damage to the fibers of the superior cerebellar peduncle, highlighting the critical involvement of this subcortical structure (Boxer et al., 2011; Mahoney et al., 2012; Murray et al., 2011). Moreover, they often show white matter lesions in frontal and motor tracts, as well as in thalamic radiation and cingulum bundles (Bertrand et al., 2018; Floeter et al., 2018; S. E. Lee et al., 2017; Papma et al., 2017).

On the other hand, svPPA patients present with disruptions in the connections between key regions of the semantic network, particularly in the left uncinate and inferior longitudinal fasciculus tracts, as well as in the corpus callosum and cingulum (Galantucci et al., 2011; Tu et al., 2016). Meanwhile, nfvPPA patients are characterised by involvement of the left superior longitudinal fasciculus, cingulum, inferior frontal and parietal, anterior temporal, and orbitofrontal white matter bundles, along with the corpus callosum, reflecting selective damage within the language network (Agosta et al., 2012; Galantucci et al., 2011; Mahoney et al., 2013). Consistently, recent analyses, using global tractography analysis, have revealed alterations in connections in patients with svPPA from the temporal and occipital lobes also involving some specific nodes in the parietal and frontal inferior regions, more pronounced in the left hemisphere; in contrast, patients with nfvPPA characteristically show alterations in the frontal inferior cortex, premotor and motor regions, and basal ganglia (Reyes et al., 2019). Moreover, these pathological changes lead to a suboptimal topological organisation (Nigro et al., 2022). Importantly, alterations in connectivity precede gray matter atrophy and are detectable even in the earliest stages (Borroni et al., 2008; Dopper et al., 2014). This suggests that white matter anomalies could contribute to network dysfunctions and might serve as an additional tool for the early identification of patients, including sporadic ones.

While grey matter abnormalities are a cornerstone in FTD diagnosis, white matter alterations—gaining increasing importance in understanding the network-level involvement characteristic of each subtype—are currently mostly limited to research contexts. However, it is anticipated that once faster algorithms for analyzing connection pathways become available, the study of these abnormalities will see widespread adoption. Furthermore, it is noteworthy that certain white matter alterations also lead to more concrete implications in current clinical practice. White matter hyperintensities (WMH) are, in fact, a common finding in the general population, especially associated with vascular damage in patients with multiple cardiovascular risk factors, and are especially detectable through specific MRI sequences, such as flow-attenuated inversion recovery (FLAIR) (Prins and Scheltens, 2015). Importantly, several studies documented the presence of these abnormalities in patients within the FTD spectrum as well (Agosta et al., 2012; Xiao et al., 2024). Although the origin of WMH in FTD patients is not fully understood, evidence suggests that they likely arise not from vascular causes but from inflammatory changes due to microglial or astrocytic dysfunction (Sakae et al., 2019). Consistently, some studies indicate that bvFTD patients, regardless of cardiovascular risk, exhibit peculiar WMH distribution patterns distinct from those seen in AD, often mirroring cortical atrophy patterns (Huynh et al., 2021). Furthermore, bvFTD patients demonstrate a significantly higher WMH load compared to those with PPAs, highlighting a difference in susceptibility to WMH based on disease subtype. Interestingly, these alterations correlate with grey matter abnormalities and cognitive profiles, suggesting that a high white matter lesion load in patients without relevant cardiovascular risk factors to account for such damage could, when supported by clinical data, suggest a bvFTD subtype. Research on genetic mutation carriers has also revealed that WMH are present only in a subset of *GRN* mutation carriers, especially in frontal and occipital regions, with lesions initially periventricular and expanding over time to medial cortical areas (Sudre et al., 2019). This pattern implies a potential genetic basis for these abnormalities. Importantly, WMH burden in *GRN* carriers not only reflects disease severity but also increases significantly as symptom onset approaches, particularly in the occipital-parietal regions (Sudre et al., 2019). Thus, it is reasonable to propose that WMH assessment may aid in identifying primary neurodegeneration even in current clinical practice, particularly for bvFTD patients and/or *GRN* mutation carriers.

10.6.3 Longitudinal neuroimaging changes

The characterisation of longitudinal neuroimaging changes is becoming increasingly relevant in neurodegenerative diseases, as it provides valuable prognostic information and new insights into their complex pathophysiology (Gordon et al., 2016). Interestingly, one study has shown that FDG-PET is the most reliable biomarker for distinguishing MCI patients who remain stable or return to normal cognitive performance from those who progress to overt dementia, as well as for distinguishing between AD and non-AD cases (Caminiti et al., 2018). Moreover, rates of brain atrophy and ventricular expansion are significantly greater in the FTD spectrum compared to healthy controls (Gordon et al., 2010; Rohrer et al., 2012). Consistently, recent evidence suggests that the volume of the choroid plexus, now thought to play a crucial role in disease pathophysiology, may represent an extremely early marker for identifying various FTD subtypes (Assogna et al., 2023). Given the relative ease of obtaining this measure, it would be advantageous to explore its longitudinal profile further to assess changes and identify patients within this disease spectrum at an early stage.

Moreover, rates of annual global brain changes are also useful in distinguishing between the different FTD subtypes, as patients with PPAs show more homogeneous rates of change compared to those with bvFTD, predominantly localised in the left hemisphere, with more rapid changes in the temporal lobe for svPPA and in the frontal lobe for nfvPPA (Gordon et al., 2010; Rohrer et al., 2012). Specifically, the sensitivity in detecting pathology increases when assessing annual changes in atrophy in the temporal lobe for svPPA and in the precentral and supplementary motor areas for nfvPPA (Krueger et al., 2010; Whitwell et al., 2015). Regarding rtvFTD, as mentioned, the initial affected regions are the anterior temporal lobes, particularly on the right side, as well as the ipsilateral ventral frontal area (Ulugut Erkoyun et al., 2020a). Longitudinal studies have documented subsequent atrophy in the right orbitofrontal region, though other evidence has shown left temporal involvement that appears to mimic the typical pattern of svPPA (Brambati et al., 2009; Kumfor et al., 2016). Recent studies, however, suggest that rtvFTD and svPPA exhibit a mirror pattern of atrophy only in the early stages, with later stages showing a different distribution of atrophy between the two conditions (Ulugut Erkoyun et al., 2020b). Nevertheless, these observations remain limited, and further studies will be crucial to obtain conclusive data. Conversely, bvFTD patients exhibit more pronounced changes in the lateral orbitofrontal cortex, a relevant aspect for both identifying the disease subtype and differentiating it from AD (Frings et al., 2014; Möller et al., 2016).

Importantly, during disease progression, volume changes are outweighed by metabolic ones, which are globally more widespread at both early and late phases (Bejanin et al., 2020). A seminal study combined longitudinal data from different MRI databases in cohorts of sporadic FTD patients and showed that, while the cortical atrophy characteristic of each subtype appears late, the prodromal phase is characterised by significant changes in subcortical structures in both the behavioural and language networks (Planche et al., 2023). Indeed, subcortical MRI alterations last 8-10 years, and appear to be the most affected sites throughout the entire course of the disease. This is particularly relevant for the nucleus accumbens in all subtypes, which might represent the anatomical correlate of apathy and impulsivity typical of FTD patients (Basar et al., 2010). Specifically, early atrophy of the amygdala and striatum is characteristic of bvFTD, whereas bilateral amygdala atrophy identifies patients with svPPA. Finally, patients with atrophy affecting the left striatum generally progress to nfvPPA. This suggests that, while research has primarily focused on cortical atrophy patterns to differentiate FTD subtypes, subcortical structures may actually hold the key to early identification of the disease spectrum. This aligns with the proposed role of subcortical hubs in driving pathological spread in sporadic FTD, as atrophy patterns likely reflect the specific neural networks involved (Brown et al., 2019; Looi et al., 2014; Shafiei et al., 2023). It is hoped that future studies will confirm this and shed light on the specific trajectories of these patterns.

In genetic FTD cases, the annual changes in gray matter follow a gradient based on the specific mutation, being minimal in *C9orf72*, intermediate in *MAPT*, and maximal in *GRN* (Chen and Kantarci, 2020b; Mahoney et al., 2012; J.L. Whitwell et al., 2011). In these familial forms of the disease, although some studies have shown modest levels of atrophy before symptom onset, it was generally believed that this occurs in the context of or after the clinical onset (Borroni et al., 2008; Dopper et al., 2014; Rohrer et al., 2015a; Spina et al., 2008). In contrast, changes in structural and, especially, functional connectivity and metabolic activity seem to precede the clinically overt phase by significant intervals (Caroppo et al., 2015; Jacova et al., 2013). Indeed, *GRN* mutation carriers present with alterations in DTI already in the presymptomatic phase, particularly in the left uncinate and inferior frontal-occipital fasciculus, similar to *MAPT* mutation carriers, who show widespread

white matter anomalies in frontotemporal tracts (Borroni et al., 2008; Dopper et al., 2014). Notably, further research has confirmed that, in *GRN* mutation carriers, white matter changes, demonstrated by degeneration of the left anterior thalamic radiation on DTI, mark the early stages of the disease and correlate accurately not only with increases in NfL but also with deficits in executive functions that critically depend on the integrity of subcortical connections (Panman et al., 2021). These changes align with the observed thalamocortical hyperconnectivity—likely a compensatory mechanism— within the DMN, salience, language, and perirolandic networks during the presymptomatic stages of the disease in *GRN* mutation carriers, when cognitive performance and grey matter volume are similar to those of healthy controls (Lee et al., 2019). Importantly, the authors observed that thalamocortical connectivity increases as the clinical onset approaches, whereas symptomatic *GRN* mutation carriers display a reduction in this functional measure. This suggests the potential for non-invasive tracking of neuropathological progression.

However, fMRI data are often controversial, with some research showing reduced functional connectivity within the salience network of *GRN* presymptomatic mutation carriers, while others have not observed changes in functional connectivity or, conversely, an increase in this measure in prefrontal regions (Borroni et al., 2012; Dopper et al., 2014; Pievani et al., 2014). Similarly, *MAPT* mutation carriers have shown reduced connectivity in the lateral temporal and prefrontal regions in some studies, while different research has not observed changes in the presymptomatic phase (Dopper et al., 2014; J. L. Whitwell et al., 2011). In asymptomatic *C9orf72* expansion carriers, on the other hand, reduced connectivity in all functional brain networks involved in this FTD subtype has been documented, suggesting that network alterations (in terms of increases and decreases) are different depending on the pathophysiology of the disease, as well as FDG-PET hypometabolism up to 10 years prior to onset (S. E. Lee et al., 2017; Popuri et al., 2021). Importantly, these functional alterations in FDG-PET precede a significant increase in NfL levels in *C9orf72* expansion carriers, according to some studies (De Vocht et al., 2020). In addition, *C9orf72* familial cases are characterised by a reduction in cerebral blood flow, as assessed by means of ASL, about 12.5 years before the expected onset, and, notably, alterations are seen to be more marked in presymptomatic carriers closer to and beyond the expected onset age (Mutsaerts et al., 2019).

A large longitudinal cohort study has, however, recently evidenced significant alterations in cortical and subcortical regions distinguishing between presymptomatic carriers and non-carriers more than ten years before clinical onset, with patterns specific to the particular mutation (Rohrer et al., 2015a). Specifically, *MAPT* mutation carriers exhibited changes in the hippocampus and amygdala as early as 15 years before clinical onset, followed by alterations in the temporal regions and finally in the insula 10 and 5 years before symptom appearance, respectively. In contrast, *GRN* mutation carriers displayed a nearly opposite pattern, with initial changes in the insula, followed by alterations in the parietal-temporal regions, and finally in the striatum (the latter coinciding with the emergence of characteristic asymmetric abnormalities), 15, 10, and 5 years respectively prior to onset. Finally, *C9orf72* expansion carriers demonstrated a distinct pattern of neuroanatomical alterations, with abnormalities first appearing in the thalamus, insula, and posterior cortical regions as early as 25 years before the expected onset. Subsequently, the frontal and temporal lobes were affected, followed by the cerebellum, 20 and 10 years before onset, respectively. These alterations align with those documented in symptomatic carriers and suggest that it may be possible to identify familial cases even decades before the expected onset of symptoms, potentially inferring the genotype without genetic sequencing (Gordon et al., 2016). Further research has suggested that asymptomatic *MAPT* carriers are characterised by

an early and specific cortical temporal lobe involvement, the atrophy rate of which accelerates significantly with the onset of symptoms, followed by frontal and parietal lobe atrophy, with sparing of the occipital lobe (Chen et al., 2019). In addition, recent studies have not only confirmed the presence of specific patterns of atrophy in pre-symptomatic mutation carriers but have also shown that grey matter changes are associated with alterations in white matter, metabolism, and functional connectivity in a specific way to each subtype (McKenna et al., 2022). These data may be crucial in predicting specific phenotypes and timing of phenoconversion, as well as in tracking disease progression and optimising enrollment in clinical trials, as therapeutic efficacy is maximal during early disease stages in neurodegenerative disorders (Tabrizi et al., 2012). Moreover, it is worthy of note that these findings suggesting an early involvement of subcortical structures (especially the posterosuperior cerebellum and thalamus in *C9orf72* expansion carriers, but not exclusively), even in pre-symptomatic stages in patients with genetic variants are consistent with those already discussed in sporadic cases and suggest that future studies, especially longitudinal ones, should focus on these regions to identify changes specific to each FTD subtype (Bertrand et al., 2018; Bocchetta et al., 2021; Cash et al., 2018; Planche et al., 2023).

Interestingly, since pathogenic FTD mutations inevitably lead to brain atrophy at different ages, it has been suggested that the ability to maintain normal cognitive performance in carriers depends on the integrity of the functional brain network (Tsvetanov et al., 2021). Indeed, when comparing mutation carriers with non-carriers, the relationship between cognition and structure was found to be similar in both groups, whereas the relationship between cognition and function was stronger in pre-symptomatic carriers and became stronger approaching the age of clinical onset. Thus, it is within reason to say that the functional aspect predominates over the structural one, and network integrity plays a compensatory role in cognitive performance. This suggests that mutation carriers and potentially sporadic cases who maintain adequate network connectivity despite atrophy may remain asymptomatic or experience slower disease progression. Consequently, they might have a better prognosis and be less likely to seek specialist evaluation. Future studies should focus on this, particularly in patients with significant cognitive-structural dissociation—those with notable atrophy but borderline cognitive performance. These individuals may harbour an undiagnosed neurodegenerative process with strong functional compensation, which could greatly enhance our understanding of these disorders and have significant therapeutic implications, especially with the use of NIBS techniques. Ultimately, the combined use of various neuroimaging methods, particularly functional ones, could facilitate the identification of presymptomatic patients, offering a promising pathway for their inclusion in clinical trials. Although this evidence primarily stems from individual studies with highly selected patient cohorts, limiting the generalizability of these results to the general population, the advantage of longitudinal follow-up lies in its capacity to track disease trajectories over time. This suggests that, alongside the data discussed in previous sections, these findings could help refine diagnostic suspicion for FTD, perhaps even in a subtype-specific manner. While additional studies will be necessary to confirm their validity, it is hypothesized that this evidence will be invaluable for the early identification of patients within this complex disease spectrum.

10.7 FTD clinical features and neuropsychological assessments

As previously mentioned, each FTD subtype is characterised by specific cognitive-behavioral symptoms that allow for classification into one of the clinical phenotypes (Antonioni et al., 2023b). However, these

characteristic symptoms typically become apparent only at a later stage or emerge progressively, making early diagnostic classification challenging. Indeed, the initial manifestations, especially for bvFTD, are rather nonspecific and can resemble those observed in other common pathological conditions, particularly psychiatric disorders (Vismara et al., 2020). This explains the extended time interval often reported between the onset of symptoms and the conclusion of the diagnostic process, sometimes described as lasting several years (Rosness et al., 2008). This is even more problematic when considering, as discussed in previous sections, that the emergence of typical disease symptoms likely represents the final phase of a neuropathological process that reasonably begins decades earlier, at least in genetic mutation carriers (in sporadic cases, the available evidence suggests a similar progression, but longitudinal data remain quite limited). It is also possible that the current neuropsychological assessment tools are not sufficiently refined to detect subtle cognitive-behavioural changes that may be present when neuropathological damage begins to develop (Johnen and Bertoux, 2019). Consequently, patients may be classified as healthy even though an insidious decline in their performance or behaviour is starting to appear. For these reasons, waiting for the characteristic cognitive profile of the suspected FTD subtype to manifest does not seem to be the best strategy for appropriately diagnosing and, therefore, managing patients with this suspicion. Nevertheless, this section will attempt to describe not only the specific features of each clinical phenotype of FTD but also to offer some guidance on which symptoms might help direct diagnostic suspicion in the right direction as early as possible. Indeed, although any initial assessment must necessarily include a thorough history, from both the patient and a reliable informant, regarding information on onset, order, timing, and progression of symptoms, as well as comorbidities, educational level, and family history, and a neurological examination (both for differential diagnosis and to identify subtypes of FTD associated with movement disorders or motor neuron disease), some elements are quite specific to the different FTD clinical phenotypes (at least at onset, as the progressive spread of the neuropathological damage along large-scale neural networks leads bvFTD patients to develop PPA, and vice versa) (Seeley et al., 2009b).

10.7.1 bvFTD

As mentioned above, bvFTD is the most common FTD subtype, accounting for approximately 60% of cases, typically manifesting between the ages of 50 and 70, with a slight male predominance (Bang et al., 2015; Hogan et al., 2016). Being the most common phenotype, research and the literature have predominantly focused on this FTD subtype, and its clinical manifestations in the established stage have been studied and highlighted in the diagnostic criteria proposed in 2011 (Rascovsky et al., 2011). In particular, according to these criteria, the pivotal clinical characteristics of this FTD variant include: behavioural disinhibition (i.e., socially inappropriate behaviour, impulsivity, or loss of social decorum); apathy or inertia (i.e., a marked decrease in initiative or motivation); loss of sympathy or empathy (i.e., a reduced ability to understand or respond to others' feelings); perseverative, stereotyped or compulsive/ritualistic behaviour characterised by repetitive actions or routines; hyperorality and dietary changes with altered food preferences or abnormal eating behaviours; executive dysfunction with relative sparing of memory and visuospatial skills, leading to a significant impairment in planning, judgment, and complex decision-making (Rascovsky et al., 2011). According to the current diagnostic criteria, a diagnosis of possible bvFTD requires a flexible combination of at least three out

of these six clinical features and is thus based solely on the clinical syndrome. In contrast, a diagnosis of probable bvFTD requires, beyond defining the clinical syndrome, evidence of functional decline and supportive neuroimaging (see section 4.2) (Rascovsky et al., 2011). Another critical aspect that is often impaired in bvFTD is social cognition, affecting theory of mind, empathy, and emotion recognition. Consistently, patients often struggle to understand others' thoughts, intentions, and emotions, leading to inappropriate social behaviours and difficulty in maintaining relationships (Antonioni et al., 2023b; Eslinger et al., 2011; Harciarek and Cosentino, 2013). Several tests in clinical practice have been approved to assess the entity of social cognition impairment in bvFTD patients. Key tests include, for example:

- Reading the Mind in the Eyes Test (RMET), which assesses the ability to recognise emotions and mental states by interpreting facial expressions. Research indicates that bvFTD patients often score poorly on the RMET, reflecting their difficulty in understanding others' emotions and intentions (Baron-Cohen et al., 2001; Megías-Robles et al., 2020; Stafford et al., 2023).
- Faux Pas Test: this evaluates the ability to detect and understand socially inappropriate remarks or actions and the intent behind them. BvFTD patients have significant difficulty with this task, demonstrating their impaired social judgment and empathy (Delbeuck et al., 2022; Fernández-Modamio et al., 2018).
- Emotion Recognition Tasks: these involve identifying and labelling emotions from facial expressions or vocal cues. Tests like the Ekman 60 Faces Test assess the ability to recognise and interpret emotional expressions. BvFTD patients frequently show deficits in recognizing basic emotions, such as anger, fear, and sadness, due to atrophy in brain regions responsible for emotional processing (Diehl-Schmid et al., 2007; Gossink et al., 2018; Vismara et al., 2020).
- Theory of Mind Tasks: these tasks assess the ability to infer others' mental states, beliefs, and intentions. Tasks such as the Sally-Anne Test or the Strange Stories Test are commonly used (Nguyen and Gonzalez, 2022; Velloso et al., 2013).
- Social Norms and Behavior Rating Scales: the Cambridge Behavioural Inventory and the Neuropsychiatric Inventory are used to evaluate changes in behaviour, disinhibition, apathy, and compulsivity (Wedderburn et al., 2008; Yiannopoulou et al., 2019).
- Empathy Quotient is a self-report measure designed to assess empathy levels. While primarily used in research settings, it provides insight into the subjective experience of empathy and can be informative in understanding social cognitive deficits in bvFTD (Tafuri et al., 2023).

From a strictly neuropsychological perspective, bvFTD patients generally exhibit a predominant deficit in executive functions, including planning, set-shifting, working memory, sustained attention span, mental flexibility, problem-solving, and verbal fluency (Antonioni et al., 2023b; Poos et al., 2020). Among the various neuropsychological assessments useful in this sense, some are particularly sensitive measures of executive dysfunctions due to frontal pathology (Baddeley, 1992; Baddeley and Della Sala, 1996; Henry and Crawford, 2004; Kiselica and Benge, 2021; Weintraub et al., 2018). Additionally, these tests, if accurately selected, can aid in the differential diagnosis between bvFTD and AD, underlining an executive dysfunction due to frontal lobe damage (Kiselica and Benge, 2021; Possin et al., 2013). For example, the Trail Making Test Part B

(TMTB), letter fluency task, and backward number span are particularly useful in the evaluation of bvFTD patients, as they provide critical insights into executive dysfunction. Specifically, the TMTB evaluates cognitive flexibility and set-shifting abilities, while the letter fluency task assesses verbal fluency and cognitive control, reflecting the patients' ability to generate and organize verbal responses efficiently, and the backward number span test measures working memory and attention, highlighting deficits in the ability to manipulate and retain information over short periods (Kiselica and Benge, 2021; Weintraub et al., 2018). Moreover, inhibition can be assessed by the Stroop Test and frontal functions in general by the Frontal Assessment Battery. Figure copying may also be impaired due to poor organisation skills. However, visuo-spatial functions are generally spared.

Thus, the clinical profile, neuropsychological characteristics, and neuroimaging features observed in the advanced stages of bvFTD are well-established. However, identifying subtle early changes that could distinguish the disorder in its initial phase from other neurodegenerative and psychiatric conditions remains more complex. Therefore, recent research has increasingly focused on these specific aspects. Interestingly, as cognitive impairments generally follow behavioural ones, a prodromal phase called mild behavioural impairment (MBI) has been proposed in these patients (Ismail et al., 2016). Specifically, MBI is a late-life syndrome lasting at least six months, characterised by behavioural and psychiatric symptoms without major cognitive complaints and previous psychiatric illness. It can affect five areas: motivation, social cognition, impulse control, affective regulation, and perception or thought content. Since MBI prevalence is high in families displaying a history of dementia and it progresses to overt cognitive decline faster and more often than MCI, a specific checklist has been developed to detect it and thus identify possible neurodegenerative dementia at onset, such as bvFTD but also svPPA (Ismail et al., 2017; Taragano et al., 2018). However, detecting changes in behaviour may also vary according to cultural factors (Papatriantafyllou et al., 2009).

Some bvFTD patients present with episodic memory deficits similar to those of AD patients, and although this was thought to be due to their executive dysfunction, it has now been shown to be a specific feature, often from the early stages, in particular with storage and consolidation deficits characteristic of hippocampal involvement regardless of their executive function alterations in particular linked to TDP-43 neuropathology (Bertoux et al., 2016; Kril and Halliday, 2011; Pennington et al., 2011). It is important to note that, while FTD survival time generally lasts 2-11 years from clinical onset, bvFTD patients usually survive only 4 years due to the delay in diagnosis, but also to an increased risk of suicide, particularly in younger patients characterised by longer disease duration and high levels of anxiety and depression (Coyle-Gilchrist et al., 2016; J. S. Lee et al., 2017; Zucca et al., 2019). Notably, *C9orf72* expansion carriers often present with various neuropsychiatric phenotypes (such as mania and late-onset psychosis) even several years before the clinical onset of typical bvFTD symptoms (Ducharme et al., 2017). Moreover, there are cases of bvFTD phenotypes, particularly in males, characterised by relatively mild cognitive deficits that remain fairly stable over time and are referred to as “phenocopy” syndromes (Hornberger et al., 2009). Although they were previously thought to be non-degenerative in nature, as already pointed out, it is now hypothesised that they may depend on particularly slow patterns of subcortical damage (Devenney et al., 2016).

Thus, based on the above evidence, the complexity of the physician’s role in identifying the disorder at its onset is clear. Regarding these early stages of the disease, in 2022, Barker et al. proposed diagnostic criteria to enable an early and accurate diagnosis (Barker et al., 2022). Indeed, the authors identified clinical manifestations that can be observed in this phase (i.e., in subjects with Clinical Dementia Rating scale = 0 and preserved autonomy in daily life activities). Some of the initial manifestations mirror the diagnostic criteria for

overt bvFTD (Rascovsky et al., 2011). In particular, the most frequently reported features were apathy without moderate-to-severe dysphoria, behavioural disinhibition, irritability/agitation, reduced empathy/sympathy, repetitive behaviour (simple and/or complex), joviality/greediness, and altered appetite/hyperorality. Some differences can, however, be identified. Consistently, the criteria for prodromal bvFTD focus on identifying its early or preclinical stages and are, therefore, designed to capture the prodromal phase, which is characterised by subtle behavioural and cognitive changes that precede the overt clinical syndrome. Hence, key aspects include milder symptoms with emphasis on early and less severe behavioural and cognitive symptoms that are not yet disruptive enough to meet full bvFTD diagnostic criteria, as well as the incorporation of neuroimaging, genetic markers, and other biomarkers to support the diagnosis of prodromal bvFTD (Barker et al., 2022). Importantly, the functional decline, which is necessary when diagnosing dementia syndrome, is not present in MBI. From a neuropsychological point of view, the profile, also in the earliest stages of the disease, is that of executive dysfunction associated with alterations in social cognition and lack of insight (Snowden, 2023).

Moreover, the ability of cognitive assessments to differentiate between early stages of AD and bvFTD at initial clinical presentation is indeed challenging yet crucial for accurate diagnosis and intervention. A recent work critically analysed the different neuropsychological profiles between AD and bvFTD patients in the early stages of the disease (Reul et al., 2017). In particular, key elements to distinguish between the two conditions include verbal recall and verbal recognition, which are more impaired in AD patients, with the former being a relevant factor in distinguishing between AD and bvFTD; additionally, AD patients show more pronounced visuospatial impairments, particularly in figure copying, than those with bvFTD (Reul et al., 2017). Finally, the most prominent difference observed in this case is the divergent pattern of cognitive disturbance in the praxis domain. Indeed, AD patients generally have deficits in pantomime and imitation of limb gestures, while bvFTD patients display more significant disturbances in imitating facial postures (Reul et al., 2017). These results support previous research identifying distinct apraxia profiles for AD and bvFTD (Bertoux et al., 2012; Buhl et al., 2013; Johnen et al., 2015).

10.7.2 svPPA

This is an FTD subtype primarily characterised by loss of word and/or object meaning, decreased confrontation naming, surface dyslexia and dysgraphia, and progressive impairments in semantic memory. Pivotal characteristics are semantic memory deficits, with consequent significant difficulty with understanding and using word meanings, problems in naming objects, understanding complex sentences, and comprehending conversations (Antonioni et al., 2023b; Karageorgiou and Miller, 2014; Kertesz and Harciarek, 2014). Anomia is also frequent, with patients often struggling to name common objects and people. The speech, therefore, appears fluent but empty, and although patients may speak fluently with normal syntax and grammar, their speech can become devoid of meaning due to impaired comprehension and word-finding difficulties (Montembeault et al., 2018; Tippett, 2020). However, although the focus of research has been on the language domain (which is the dimension most obviously impaired in these patients), it is crucial to consider that the core deficit in svPPA is a specific transmodal agnosia, i.e. a condition in which the brain's ability to recognize and understand meaning across different sensory modalities is impaired (Macoir et al., 2020; Olofsson et al.,

2013). This fundamental deficit underlies the broader semantic impairments characteristic of the disease, affecting the patient's capacity to comprehend and assign meaning to concepts, words, and objects (Gorno-Tempini and Pressman, 2016). Non-linguistic cognitive abilities, such as executive function, visuospatial skills, and episodic memory, are often relatively preserved in the early stages compared to language functions (Montembeault et al., 2018). Notably, also svPPA patients may exhibit apathy, disinhibition, or changes in social behaviour (Fittipaldi et al., 2019). However, these changes are generally less pronounced than those seen in bvFTD. Deficits in social cognition have also been described in this PPA subtype.

Thus, the neuropsychological profile of these patients can be assessed by tests able to evaluate semantic memory (e.g., the Boston Naming Test or the Philadelphia Naming Test), which usually reveal significant impairments in object naming and word retrieval, and language abilities (e.g., the Token Test and the Pyramids and Palm Trees Test), which specifically assess semantic knowledge by asking patients to match related items or pictures. The overall profile is that of a fluent, grammatically correct speech that lacks meaning in the context of a global semantic knowledge impairment (de la Sablonnière et al., 2021; Iaccarino et al., 2015; Wilson et al., 2014). Verbal comprehension is impaired, especially in the early stages, for less commonly used terms in everyday language. However, syntactic comprehension is generally preserved. Calculation abilities remain intact, as do spatial orientation, memory skills for daily activities, and sometimes even executive functions (Snowden, 2023). Gestural praxis abilities are typically compromised due to the semantic deficit, as is object recognition, leading to associative agnosia (Snowden, 2023). Interestingly, figure-copying abilities generally remain intact in the early phases, even when the patient cannot recognise the depicted object due to a semantic deficit (Liu et al., 2019).

The diagnostic criteria for PPAs were established in 2011 (Gorno-Tempini et al., 2011). This classification involves a two-step process: firstly, patients must meet the basic criteria for PPA, i.e. aphasia is the most prominent deficit at the onset of symptoms and during the early stages of the disease; then, patients can be further sub-classified based on the specific characteristics of their aphasia. In the case of svPPA, the clinical picture is characterised by profound impairments in semantic memory, affecting the understanding and use of word meanings, but with relatively preserved fluency and grammar (Gorno-Tempini et al., 2011). Also in this context, it is important to identify the initial clinical manifestations that might suggest this PPA subtype rather than another in clinical practice. Importantly, according to the literature, early signs of svPPA may include anomia, difficulty in word-finding, and repetitive speech, while the initial behavioural symptoms often involve irritability and a sense of emotional detachment (Liu et al., 2019).

10.7.3 nfvPPA

Conversely, this PPA subtype is characterised by progressive language difficulties primarily affecting speech production and grammatical processing. Indeed, speech output is typically nonfluent, with patients struggling to construct sentences that are syntactically correct, often leading to simplified and telegraphic speech (Gorno-Tempini et al., 2011). Specifically, these alterations are collectively known as apraxia of speech, manifesting as difficulties in planning and coordinating movements necessary for speech, resulting in distorted speech sounds and abnormal prosody during the disease course (Botha and Josephs, 2019; Duffy et al., 2021). Consistently, from a clinical perspective, individuals with nfvPPA exhibit effortful, halting speech often

accompanied by agrammatism, which refers to the omission or incorrect use of grammatical elements such as articles, prepositions, and verb inflections (Antonioni et al., 2023b).

From a neuropsychological perspective, nfvPPA patients demonstrate relatively preserved comprehension of single words and simple sentences, but their ability to understand complex sentences, particularly those requiring syntactic parsing, is often impaired (Ash et al., 2013). Unlike svPPA, nfvPPA patients typically retain semantic knowledge and memory functions in the early stages, although these may decline as the disease progresses (Grossman, 2012). Regarding social cognition, individuals with nfvPPA may struggle with tasks that require complex social reasoning or emotional empathy, although this is less pronounced compared to other FTD subtypes. These difficulties are primarily related to their impaired ability to produce and comprehend grammatically correct sentences, affecting their capacity to engage in nuanced social interactions. For instance, effortful speech and agrammatism can lead to misinterpretations and challenges in maintaining effective communication, which can, in turn, impair their social relationships and interactions (Fittipaldi et al., 2019; Grossman, 2012). However, their fundamental understanding of social norms and their ability to interpret social cues may remain relatively intact early in the disease, though it can deteriorate as the condition progresses.

10.7.4 rtvFTD

As previously noted, while numerous authors have described cases of FTD primarily affecting the right temporal lobe, this recognition has emerged only relatively recently. Indeed, these cases were regarded as part of the svPPA spectrum, characterised by a predominantly right hemisphere neuropathological distribution, in contrast to the more typical presentations (Chan et al., 2009). It is now widely accepted that rtvFTD is primarily associated with symptoms mainly outside the language domain and a different prognosis from svPPA (Ulugut Erkoyun et al., 2020a). Consistently, a large multicenter retrospective study has frequently identified symptoms such as preoccupations and mental rigidity leading to complex repetitive behaviours (rather than mere stereotypies), disinhibition, prosopagnosia, and abnormal reactions to stimuli across various sensory modalities, particularly bodily sensations (Ulugut et al., 2024). However, their patients also exhibited difficulties with word finding (but not single-word comprehension, which is typical of svPPA patients), memory alterations, social cognition deficits, apathy, and loss of empathy. Notably, prosopagnosia, often considered one of the most characteristic signs of this clinical subtype, differs from that seen in other neurodegenerative conditions, as it does not only involve difficulties in visual recognition but also, for instance, in recognising voices and autobiographical information (Younes et al., 2022). Indeed, given the transmodal nature of agnosia, which extends beyond the visual domain (i.e., mere face recognition), there is a growing preference for the term cross-modal agnosia for familiar people (or person knowledge) over the more traditional prosopagnosia (Joubert et al., 2006). This term better emphasizes the inability to access person-specific semantic information required for identification, regardless of the modality of presentation. Nevertheless, the predominant involvement of the temporal lobes in both svPPA and rtvFTD (primarily affecting the left and right hemisphere, respectively, though modest contralateral damage is apparent even in the early stages), along with the shared presence of TDP-43 type C pathology and some overlapping symptoms, has led some to suggest that these conditions may not represent distinct diseases (Borghesani et al., 2020; Campos et al., 2022; Ulugut et al.,

2021). Rather, they may constitute the endpoints of a continuum that can be differentiated only in the early stages. In contrast, in more advanced stages, their distinctions converge, resulting in a clinical condition with many overlapping features. The debate on the appropriate classification of this variant remains active, and further research will be essential to reach a conclusive answer.

Furthermore, while bvFTD patients often display hyperorality or a preference for sweets, those with rtvFTD exhibit changes in eating habits and develop restricted preferences, allowing a distinction between the two categories (Antonioni et al., 2023b; Ulugut et al., 2024). In addition, although both groups are characterised by apathy and social cognition deficits, patients with bvFTD are more likely to have significant executive dysfunction, whereas those with rtvFTD have greater severity and frequency of depression (Everhart et al., 2015; Kamminga et al., 2015; Ulugut Erkoyun et al., 2020a). Interestingly, the preference for a limited range extends beyond food to include aesthetic and clothing preferences, likely reflecting the typical rumination, inflexibility, and rigid thinking of rtvFTD cases (Ulugut Erkoyun et al., 2020a; Younes et al., 2022). In addition, they typically lose enthusiasm for social activities but remain deeply concerned with activities performed in solitude (Ulugut et al., 2024). Moreover, a significant percentage present with memory deficits affecting episodic, semantic, and autobiographical domains, whose origin is still unclear in the absence of amyloid damage (Hornberger and Piguet, 2012; Ulugut Erkoyun et al., 2020a; Younes et al., 2022). This is particularly critical, given that the current FTD diagnostic criteria consider the presence of amnesia as an exclusion criterion, which could lead to a high risk of misdiagnosis (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Other symptoms, such as depression, mania, mood fluctuations, motor impairments, anxiety, and perceptual disturbances, have been observed less frequently (Ulugut et al., 2024). Finally, hyper-religiosity, visual hallucinations, getting lost, and cross-modal sensory experiences have also been described as particularly typical of these patients, albeit at different rates (Chan et al., 2009).

It is also noteworthy that some studies suggested a significant relationship between rtvFTD, parkinsonism, and motor neuron diseases, although the evidence is still inconclusive (Josephs et al., 2009; Miki et al., 2020). These complex and multifaceted symptomatic manifestations, along with the frequent presence of disturbances generally attributed initially to other diseases (such as memory disorders and psychiatric manifestations), make the diagnosis of rtvFTD extremely challenging. As awareness of this clinical phenotype grows, further longitudinal studies will be necessary to identify the earliest and most characteristic symptoms. However, as language performance is relatively less impaired initially in comparison to PPA patients, prosopagnosia, depression, episodic memory alterations, and behavioural complaints (including apathy, mental rigidity, and social cognition deficit) are currently considered the most prominent initial manifestations in these patients, together with evidence of right temporal lobe atrophy on brain MRI and a negative amyloid-PET scan (Ulugut Erkoyun et al., 2020a).

10.7.5 Clinical characteristics of FTD patients carrying genetic mutations

Among the genetic variants, *GRN* and *MAPT* mutations more frequently lead to language impairments, whereas *C9orf72* expansion carriers are generally characterised by alterations in verbal and visual episodic memory, dyscalculia, apraxia, and reduced spontaneous speech (Young et al., 2018). Furthermore, cognitive and neuropsychological assessments might aid the identification of specific mutation carriers within the bvFTD

phenotype (Poos et al., 2020). Specifically, an immediate and delayed memory recall impairment is rather specific for *MAPT* carriers, whereas attention, mental processing speed, and executive function deficits point to those with *GRN* mutation. Moreover, language alterations are more characteristic of *MAPT* and *C9orf72* mutations. Finally, while *C9orf72* carriers display a widespread (including attention, language, executive functions, and immediate recall alterations) and a rather stable cognitive profile over time, patients with *MAPT* and *GRN* are characterised by more rapid longitudinal alterations in confrontation naming, and attention and memory, respectively. Indeed, the onset in young adulthood and the relative stability over time of cognitive deficits in *C9orf72* expansion carriers have led some authors to suggest that this may be a neurodevelopmental disorder rather than a true neurodegeneration, but opinions are still conflicting (S. E. Lee et al., 2017). Importantly, *GRN* mutation carriers show alterations in mental processing speed and attention not only in the symptomatic but also in the presymptomatic phase, similar to memory recall deficit in *MAPT* ones (Jiskoot et al., 2018, 2016; Le Ber et al., 2008). Taken together, these results suggest that tests to assess attention may favour an early identification of *GRN* mutation patients, while memory recall deficits may be useful in those with *MAPT*. In contrast, there do not appear to be any neuropsychological features that can confidently identify *C9orf72* expansion carriers (Poos et al., 2020).

10.7.6 FTD severity assessment tools

Once the clinical diagnosis has been confirmed, assessing disease severity is crucial. Indeed, this step is essential both to establish the baseline severity—enabling tailored treatments based on specific symptoms and needs—and, more importantly, to monitor progression over time (Sapolsky et al., 2014). This includes tracking anticipated symptom worsening, documenting new symptoms, and assessing the effectiveness of pharmacological and behavioral therapies. Moreover, these evaluations play a key role in attempting to establish a clinical staging, a task complicated by the challenges of objectively measuring disease burden, the limited understanding of key pathophysiological milestones, and significant individual variability (Hardy et al., 2024). For AD, the widely used Clinical Dementia Rating Scale (CDR) is useful in both baseline assessments and clinical trials (Morris, 1997). Despite its proven reliability for AD pathology, it has limited applicability to the FTD spectrum. Indeed, its emphasis on memory deficits requires this domain for severity ratings above zero, even if other items (such as behavioral aspects) show alterations. Given that memory is often spared or only mildly affected in early-stage FTD, the CDR's usefulness in this context is limited (Miyagawa et al., 2020).
Thus, alternative scales have been developed to address these limitations and to more reliably assess clinical severity in early disease stages.
For instance, a modified CDR version, the Frontotemporal Lobar Degeneration (FTLD)-modified CDR, showed superiority over the standard CDR. However, it has not proven effective in distinguishing FTD subgroups or progression rates across variants (Knopman et al., 2008). Similarly, the CDR Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains (CDR plus NACC FTLD) includes behavioral and language evaluations to avoid an overemphasis on memory, as in the standard CDR (Miyagawa et al., 2020). It demonstrated excellent inter-rater reliability, relevant for clinical trials and research. Another promising tool, the Frontotemporal Dementia Rating Scale (FRS), highlighted the ability to identify six stages of clinical severity and to characterize each stage's features. Notably, the FRS has

consistently indicated a severity gradient across subtypes, adjusting for symptom duration. This gradient ranges from svPPA (least impaired), through nfvPPA (of intermediate severity, though some studies identify it as the least impaired), to bvFTD, which displays the greatest severity and fastest progression rate (Knopman et al., 2008; Mioshi et al., 2010). Notably, FRS scores correlate with functional decline over time but not with cognitive test scores, recognizing, for example, patients who remain functionally independent despite low cognitive test scores due to severe language impairments.

Importantly, given the complexity of language in FTD, several tools have been developed to assess disease severity in PPA subtypes. The Progressive Aphasia Severity Scale (PASS), adapted from the CDR language item, allows detailed assessment of impairment across specific language and speech domains (both at baseline and during follow-up) (Sapolsky et al., 2014). PASS integrates clinical evaluation, a caregiver questionnaire, and interviews with both patients and caregivers, providing a multidimensional assessment that values both clinical judgment and perceptions from patients and families. However, as FRS lacks granularity in communication function assessment and PASS does not consider non-language clinical features, the recent PPA-Squared Scale has been proposed to identify atypical progression trajectories and, importantly, to allow finer-grained staging of early and mild disease phases (Hardy et al., 2024). This scale focuses on early symptoms (e.g., hearing loss) and subtype-specific traits, both linguistic (e.g., vocabulary loss in svPPA and fluency alterations in public speaking in nfvPPA) and behavioral (e.g., appetite changes in svPPA and mental rigidity in nfvPPA). These tools are anticipated to play a significant role not only in new trials for disease-modifying therapies but also in clinical practice, enabling early identification of deficits in each patient and, thus, a personalized response to individual needs.

10.8 Differential diagnosis

A correct differential diagnosis from different neurodegenerative or non-degenerative diseases is crucial for the different medical, psychological, and social needs of patients and their caregivers, as well as for the implication in terms of disease progression, life expectancy, and, importantly, possible heritability (Musa et al., 2020). Many factors, including resources, culture, and stigma, may affect diagnostic speed and accuracy (Parra et al., 2018). Proper diagnosis relies on a careful personal and family history, including the progression of cognitive and behavioural alterations, as well as neuropsychological assessments and laboratory and neuroimaging evaluations (Bang et al., 2015). Indeed, psychiatric manifestations are the rule rather than the exception in numerous neurodegenerative disorders (Vismara et al., 2020). Consistently, FTD patients, in particular bvFTD ones, display a symptomatic overlap with several conditions, including major depression, obsessive-compulsive disorder, schizophrenia, bipolar, schizoid, antisocial personality, and autism spectrum disorders (Ducharme et al., 2015a). However, in PPAs, language impairments are significantly more prominent than psycho-behavioural disturbances, at least in the early stages (Antonioni et al., 2023b; Lanata and Miller, 2016). In contrast, in bvFTD, behavioural symptoms are almost invariably present from the onset, making differential diagnosis highly challenging, especially because many characteristic symptoms (e.g., apathy, disinhibition, loss of empathy) are also frequently observed in psychiatric disorders (Olney et al., 2017). Moreover, bvFTD presentations sometimes mimic forms of mania or obsessive-compulsive disorder (Ducharme et al., 2015b).

The complexity is further heightened as bvFTD patients often experience psychiatric disorders before the onset of dementia, while psychiatric pathology increases the risk of developing dementia (Papazacharias et al., 2017; Vismara et al., 2020). Moreover, the prevalence of psychosis reaches 50% in patients with FTD, with negative symptoms outweighing positive ones (Gossink et al., 2017; Hall and Finger, 2015). Importantly, as mentioned, personality changes in bvFTD may lead to criminal behaviours. Therefore, it is essential to consider this diagnosis not only in patients with cognitive decline but also in those facing legal issues due to newly emerging conduct disorders (Birkhoff et al., 2016). In addition, bvFTD patients are often initially assessed in a psychiatric setting and diagnosed with psychiatric disease in 50% of cases, limiting the caregivers' possibilities to seek proper support and management (Rasmussen et al., 2019; Woolley et al., 2011). This is particularly important when considering that, although cognitive deterioration is a hallmark symptom, it is often not detectable in the early stages, and the DSM-V criteria for diagnosing bvFTD rely almost exclusively on clinical phenotype, rather than genetic or instrumental aspects, which significantly increases the risk that these patients may never receive a correct diagnosis (Lanata and Miller, 2016). It is also relevant to recognise that the severity of cognitive impairment alone is not a reliable factor in distinguishing bvFTD from primary psychiatric disorders, as severe forms of the latter (e.g. major depression or schizophrenia) may present with cognitive deficits far more pronounced than those of the former in early or mild stages of the illness (B Borroni et al., 2015; Millan et al., 2012). This calls for great caution in the differential diagnosis, underscoring the importance of not rushing into a categorisation but rather thoroughly considering all available information before proposing the most likely diagnostic hypothesis.

However, some relevant clues might help clinicians differentiate between bvFTD and psychiatric patients (see Table 1).

Most likely psychiatric disorder diagnosis	**Most likely bvFTD diagnosis**
Acute/subacute onset	Late and insidious onset
Multiple mood episodes	Slow but steady progression
Partial or complete recovery between episodes	Family history of neurodegenerative diseases
Cognitive complaints only during mood episodes	Poor response to pharmacological treatment
Family history of mood disorders	Lack of insight (rarely complain of impairment, sadness, anxiety)
Psychiatric comorbidities (e.g., anxiety spectrum disorders, substance abuse)	Impulsivity without irritability
Suicidal ideation/attempt(s)	Aphasia/ verbal apraxia
Male gender	Apathy
Depression	Difficulties in abstract reasoning/ stereotypical thinking
Absence of stereotypies	Low rate of delusions and hallucinations (early stages)
Young onset (often during adolescence)	Onset rarely before the age of 35 years
Sometimes presentation with catatonia (fluctuating, responsive to treatments)	Rare presentation with catatonia (progressive and irreversible)

Table 1. Clinical features aiding the differential diagnosis between primary psychiatric illness and bvFTD. Based on (Dols et al., 2016; Ducharme et al., 2015b, 2015a; Ducharme and Dickerson, 2015; Galimberti et al., 2015; Gossink et al., 2017; Mendez et al., 2017; Reus et al., 2018; Vijverberg et al., 2017; Watanabe et al., 2018).

For example, while bvFTD cases are characterised by a progressive decline in frontal functions, psychiatric patients may improve over time and generally, as expected, exhibit globally better cognitive performance than those with FTD (Reus et al., 2018; Vijverberg et al., 2017). Furthermore, compared to schizophrenia, which

often enters into differential diagnosis, bvFTD patients more frequently exhibit stereotypical thinking and difficulties in abstract reasoning and, at least initially, a much lower rate of delusions and hallucinations (Gossink et al., 2017; Mendez et al., 2017). Importantly, while schizophrenia typically manifests in adolescence, bvFTD is rarely observed before the age of 35, which may further guide the diagnosis (Ducharme et al., 2015b). Of note, although catatonia is a rare presentation in FTD, some cases have been reported (Watanabe et al., 2018); however, it is associated with progressive and irreversible deterioration whereas, in psychiatric disorders, it is generally more fluctuating and may respond to treatments, such as benzodiazepines (Ducharme et al., 2015a). It is intriguing to consider that, according to some research, bipolar disorder may constitute a prodromal phase of bvFTD, as evidenced by their diagnostic association and shared genetic-environmental risk factors (Roman Meller et al., 2021; Vismara et al., 2020). Consistently, neuropsychiatric symptoms are particularly frequent among genetic mutation carriers, particularly those with *C9orf72* expansion (e.g. somatic delusions) (Erzurumluoglu et al., 2019; Sellami et al., 2018). Furthermore, common presentations among *GRN* mutation carriers include social withdrawal and apathy, as well as ritualistic behaviours and hallucinations, while those with *MAPT* mutations are characterised by lack of insight, disinhibition, mental rigidity, and obsessions (Cheran et al., 2019; Young et al., 2018). In fact, *C9orf72* expansion carriers show a very high frequency and severity of anxiety in the early phase, whereas hallucinations (both auditory and visual) are the most severe neuropsychiatric symptom in the intermediate phase (Alberto Benussi et al., 2021); on the other hand, *GRN* mutation carriers are characterised by significant depression and anxiety in both the early and late phases, whereas hallucinations (especially visual) and delusions are not frequent; finally, *MAPT* mutation carriers show extremely intense anxiety but no perception complaints. This suggests that, at least in certain cases, the boundary between psychiatric disorders and FTD is not so clear-cut, and further exploration of the complex relationship between these pathological spectra will be essential. Importantly, based on these observations, some authors have developed a checklist with a score that can predict the most likely diagnosis between bvFTD and psychiatric illness, albeit with some grey areas for intermediate scores (Ducharme et al., 2019). Some research suggests that social cognition is the only cognitive domain that can distinguish bvFTD patients from those with other neurodegenerative or psychiatric conditions and, indeed, it has been recommended that a specific test should be included in their standard assessment, although the data are not always consistent (Chiu et al., 2016; Ducharme et al., 2020; Gossink et al., 2018; Reus et al., 2018).

However, as bvFTD often presents with symptoms that overlap with various degenerative and non-degenerative conditions, a diagnosis based solely on clinical symptomatology may not always adequately distinguish between the two groups of patients. Moreover, aside from genetic cases, there are no fluid biomarkers that can accurately identify it. Thus, neuroimaging plays a crucial role in both the diagnostic process and differential diagnosis (Boeve et al., 2022; Ducharme et al., 2020; Krudop et al., 2017). This is particularly relevant when considering that a minority of bvFTD patients present with motor, visuospatial, and constitutional symptoms rather than behavioural ones, making the use of objective methods essential for their accurate classification (Ranasinghe et al., 2016). Importantly, as noted above, although detection of a suggestive atrophy pattern is rather specific, it is not very sensitive, particularly in the early stages, leading to misdiagnosis or delayed diagnosis (Vijverberg et al., 2016). Consistently, in the differential diagnosis between bvFTD and psychiatric disorders, it is essential to combine various neuroimaging methods to enhance diagnostic accuracy (Ward et al., 2023). Indeed, structural MRI alone is not as sensitive as FDG-PET, as evidenced by the absence of typical frontotemporal atrophy in 66% of carriers of a known genetic mutation, at least in the early stages of

the disease, i.e. when the pattern of structural changes characteristic of each FTD subtype has not yet emerged and, more often, there is a need for differential diagnosis with respect to a primary psychiatric disorder (Ward et al., 2023). Additionally, a significant percentage of patients with primary psychiatric disorders are mistakenly characterised as having FTD due to false-positive FDG-PET results, an important consideration given the frequent presence of non-specific abnormal findings in psychiatric patients (Duignan et al., 2021; Vijverberg et al., 2016). Nonetheless, as recently suggested, with the exception of certain genetic cases where hypometabolic patterns may not always match expected findings, FDG-PET can generally aid in ruling out bvFTD when results are normal (Ducharme et al., 2020; Levy et al., 2019). In addition, it is equally important to avoid over-interpreting non-specific regional metabolic abnormalities in psychiatric differential diagnosis to prevent diagnostic errors (Ducharme et al., 2020). Notably, in cases where diagnostic uncertainty persists, a follow-up PET scan (for instance, after a year) may be performed, which can be highly valuable in resolving ambiguities and refining the diagnostic categorization (Bergeron et al., 2016). Taken together, this evidence suggests that a single test alone does not provide a definitive answer and that a multidimensional, even longitudinal, assessment, taking into account all available clinical information and biomarkers, is recommended.

Similarly, while amyloid-PET has diagnostic value, particularly in atypical cases, to identify AD-related pathologies, a positive result does not definitively exclude an FTD subtype, whereas a negative result reliably rules out AD (Krishnadas et al., 2021; Langheinrich et al., 2021; Shi et al., 2020). Specifically, an assessment of amyloid burden pathology (whether via lumbar puncture or amyloid-PET) might be highly useful in the initial evaluation of rtvFTD patients, who often present with episodic memory impairments, to rule out an underlying amyloid pathology consistent with AD (Ulugut Erkoyun et al., 2020a). It is also important to note that recent studies have shown that certain blood biomarkers, particularly pTau217 and pTau181, demonstrate excellent diagnostic performance in distinguishing AD patients (including MCI subjects with amyloid pathology) from different neurodegenerative diseases, including FTD (Chouliaras et al., 2022; Thijssen et al., 2021). This represents an interesting opportunity for improving differential diagnosis by combining clinical data with blood-based biomarkers, thereby avoiding invasive and costly procedures such as amyloid-PET and lumbar puncture. However, these findings imply caution in interpreting individual tests and underscore the importance of completing the diagnostic process with multiple assessments before reaching a reliable conclusion.

Notably, the distinct patterns of brain atrophy can differentiate AD patients from those with FTD. Consistently, artificial intelligence (AI)-based techniques such as machine learning have demonstrated the ability to accurately categorise patients using data derived from brain MRI and predict the bvFTD phenotype in both sporadic and genetic cases (Bron et al., 2014; Falgàs et al., 2020; Manera et al., 2021). Furthermore, recent research has highlighted that these AI algorithms reliably distinguish between AD and FTD (including both bvFTD and PPAs) by using longitudinal data to train the classifier on the specific trajectories of brain atrophy, as well as predict the two-year follow-up diagnosis in patients with bvFTD, psychiatric disorders, and other neurological disorders (Pérez-Millan et al., 2023; Zhutovsky et al., 2019). In addition, to differentiate from patients with psychiatric illness, a right anterior temporal atrophy together with sparing of the left frontal lobe, as assessed by brain MRI, has specifically marked bvFTD patients with psychotic-like speech (Mendez et al., 2017). Notably, in genetic mutation carriers, it is possible to identify a correlation between atrophy in specific grey matter regions and the presence of neuropsychiatric symptoms. This suggests that alterations in genes involved in large-scale networks underpin these manifestations in both FTD patients and those with psychiatric

disorders (Sellami et al., 2018). While these methods hold promise for enhancing diagnostic accuracy, their main limitation is that they rely on atrophy patterns, identifying patients only after significant damage has occurred, thus hindering early detection. Additionally, in advanced stages, the severity of atrophy makes it difficult to differentiate between various pathologies. However, notably, the previously explored involvement of subcortical structures might be useful not only in identifying specific subtypes of FTD but also in distinguishing AD from bvFTD, which shows higher rates of atrophy in the thalamus and striatum (Landin-Romero et al., 2017). Importantly, recent research has shown that machine learning algorithms on neuropsychological data discriminate bvFTD patients from AD and healthy controls and that diagnostic accuracy increases when combined with MRI data, suggesting promising future applications (Bachli et al., 2020; Garcia-Gutierrez et al., 2022). Another aid in the differential diagnosis between bvFTD and AD arises from the assessment of functional impairment, which is more severe and more rapidly worsening in the former than in the latter, leading to a higher caregiver burden (Boutoleau-Bretonnière et al., 2008; Giebel et al., 2021; Riedijk et al., 2006).

Importantly, the first evaluation of suspected FTD patients also requires routine blood tests and a comprehensive metabolic panel, including kidney and liver function tests, vitamin levels, and thyroid studies, as well as assessments for potential toxic exposures (such as occupational use of heavy metals or substances of abuse), infectious diseases (including HIV and syphilis), and inflammatory conditions (autoimmune, paraneoplastic) (Bang et al., 2015). Indeed, risk factors for FTD have been identified, including diabetes mellitus, autoimmune diseases (which are particularly intriguing given the discovery of autoantibodies recognizing the GluA3 subunit of a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptor in the CSF of some FTD patients), and traumatic brain injuries, which can alter the FDG-PET pattern at the lesion sites (Ayubcha et al., 2021; Kalkonde et al., 2012; Palese et al., 2020; Rasmussen et al., 2018; Zamboni et al., 2024). These factors can lead to potentially misleading functional neuroimaging findings if not adequately contextualized within the patient's clinical history (Ward et al., 2023). This initial assessment is also essential for the correct differential diagnosis of WMH on brain MRI. While their presence often suggests cerebrovascular risk factors underlying vascular damage, certain indicators should prompt a shift towards suspecting primary neurodegeneration (Prins and Scheltens, 2015). These include WMH progression despite optimized management of common risk factors (e.g., hypertension, dyslipidemia, diabetes), absence of hemosiderin deposits in the same regions on susceptibility-weighted imaging (SWI), and a tendency for the lesions to expand from periventricular to more cortical regions, especially when aligned with relevant cognitive impairments (Huynh et al., 2021; Prins and Scheltens, 2015; Robinson and Bhuta, 2011; Sudre et al., 2019). Furthermore, a bvFTD phenotype is sometimes mimicked by normal pressure hydrocephalus or low intracranial pressure syndromes (Bang et al., 2015). Lumbar puncture may therefore be useful for assessing CSF pressure in addition to the biomarkers already described. Finally, it is important to investigate the possible presence of sleep disorders (e.g. Rem behavioural disorder, sleep apnoea), which may be risk factors for different neurodegenerative diseases, e.g. movement disorders characterised by alpha-synuclein accumulation, with which there is sometimes a symptomatic overlap (Antonioni et al., 2024b; Weihs et al., 2021).

10.9 Conclusions

This review has gathered evidence to aid the diagnostic pathway of patients with possible FTD neuropathology, particularly in early phases and even in sporadic cases, ranging from established to promising tools that could shape future clinical practice. Although this disease is exceptionally complex from both clinical and neuropathological perspectives, and a definitive diagnosis cannot be confirmed until post-mortem examination except in genetic cases, the data discussed suggest that the tools available for guiding accurate diagnosis are improving. Specifically, fluid biomarkers (in particular NfL) might play a key role in the identification of the initial stages of the neuropathological process, alongside neurophysiological investigations (i.e., SICI/ICF alterations) —which unfortunately remain underutilised—and functional neuroimaging, showing early networks, connectivity, perfusion, and metabolic alterations. This could be crucial not only for differential diagnosis but also for ensuring that the correct diagnosis is made before the disease reaches its advanced stages, marked by the typical clinical symptoms and patterns of atrophy associated with each FTD subtype. Indeed, although no disease-modifying therapies are currently approved, and treatment is limited to symptomatic medications (often off-label and associated with significant adverse effects) or non-pharmacological strategies (e.g., physiotherapy, speech therapy, caregiver training, and environmental adaptation), promising trials are currently underway, and there are great expectations for their therapeutic potential (Boxer et al., 2020; Panza et al., 2020). However, to maximize efficacy, it will be essential to enroll patients in the early stages rather than waiting for the later phases of the neuropathological process. Therefore, hopefully, this review will provide clinicians and researchers with valuable insights for the early identification of FTD patients, not only in genetic cases—where it is relatively easier—but also in sporadic ones to improve their outcomes and complex multidisciplinary management. Indeed, crucially, the similarities between sporadic and genetic bvFTD cases suggest the possibility of generalising novel biomarkers and clinical tools, but also therapies, in both patient groups (Heuer et al., 2020). Future longitudinal studies may support these observations and further aid in the early diagnosis of FTD patients.

10.10 Expert opinion

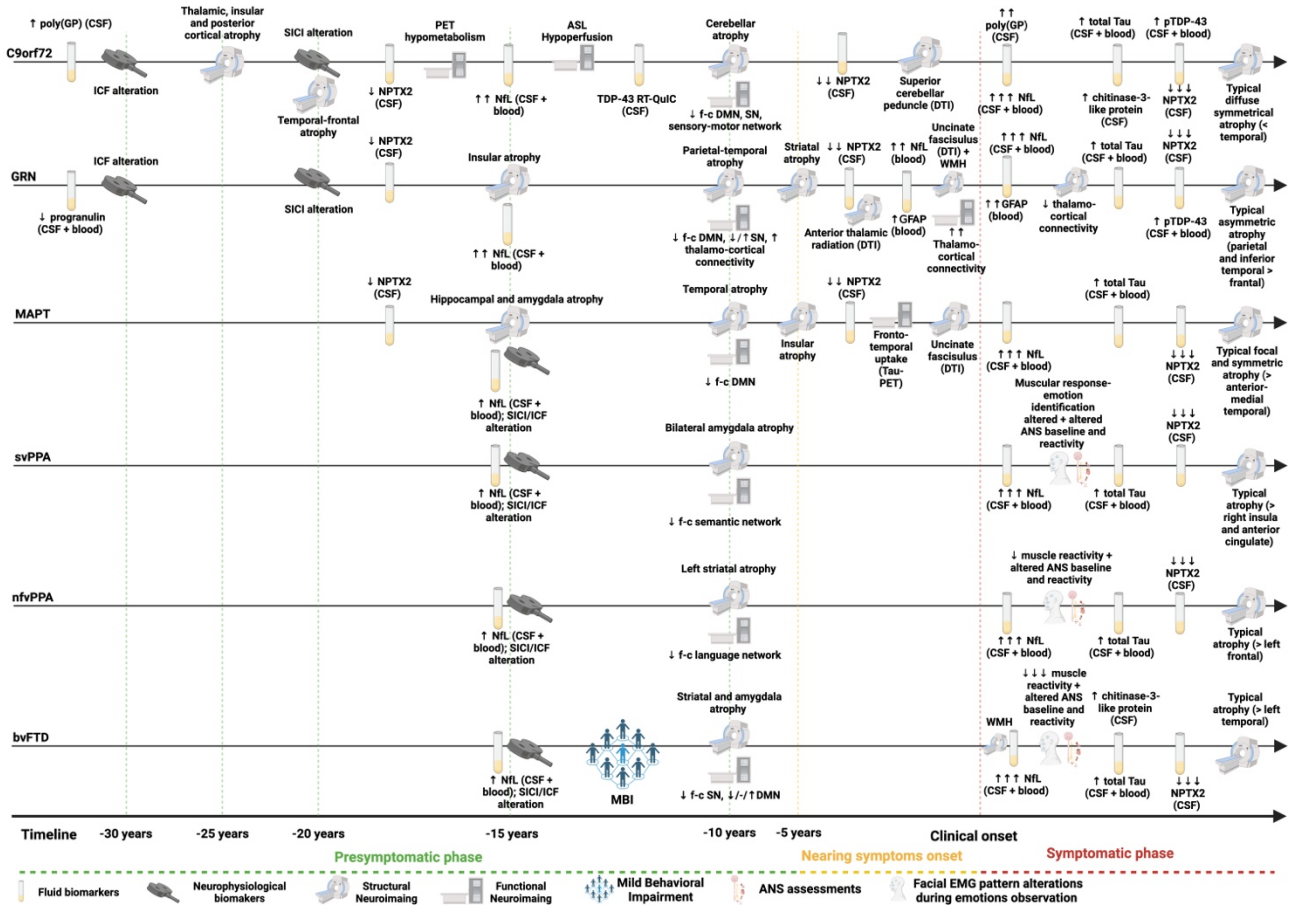


Figure 1. Pathological biomarkers in the spectrum of FTD. Hypothetical longitudinal profile of alterations in fluid, neurophysiological, structural and functional neuroimaging biomarkers, and behavioural profile in FTD patients, divided by genetic variants and, for sporadic cases, by clinical phenotype. Years refer to the interval before onset of symptoms. Abbreviations: ANS: Autonomic nervous system; ASL: arterial spin labeling; bvFTD: behavioural variant frontotemporal dementia; C9orf72: chromosome 9 open reading frame 72; CSF: cerebrospinal fluid; DMN: default mode network; DTI: Diffusion tensor imaging; EMG: electromyography; f-c: functional connectivity; GFAP: Glial Fibrillary Acidic Protein; GRN: granulin precursor; ICF: intracortical facilitation; MAPT: microtubule-associated protein tau; MBI: Mild Behavioral Impairment; NfL: neurofilament light chain; nfvPPA: non-fluent variant of primary progressive aphasia; NPTX2: neuronal pentraxin-2; PET: Positron Emission Tomography; poly(GP): polyglutamine; pTDP-43: Phosphorylated TDP-43; RT-QuIC: Real-Time Quaking Induced Conversion; SICI: short-interval intracortical inhibition; SN: salience network; svPPA: semantic variant of primary progressive aphasia; TDP-43: TAR DNA-binding protein 43; WMH: White matter hyperintensities. Created with BioRender.com.

In Figure 1, based on this extensive review of the literature, we have reconstructed the likely temporal progression of abnormalities in FTD patients, classified between genetic variants and clinical phenotypes in sporadic cases (Figure 1). With the partial exception of studies that provide specific temporal references on clinical onset, we acknowledge that the sequence in which abnormalities are presented may be subject to debate. This is particularly true given that the evidence is derived from patient populations that are not homogeneous as far as genetic background or clinical severity are concerned, and from assessment methodologies that vary widely depending on the laboratory and neuroimaging data acquisition techniques

employed. However, our intention here was not to perfectly delineate the chronological progression of alterations characterizing FTD patients according to the biomarkers in question—to the best of our knowledge, no definitive data currently exist that would make such a task feasible, and the diagnostic challenges would be significantly reduced if they did. Instead, our goal was to provide an overview, highlighting the tools available to clinicians and researchers that can assist in formulating an accurate diagnostic suspicion well before the typical cognitive-behavioural profile and the characteristic structural MRI atrophy patterns become evident. In patients with a family history of FTD, this task is relatively straightforward, as measuring specific biomarkers (e.g., progranulin and dipeptide repeats for *GRN* and *C9orf72* mutation carriers, respectively) facilitates confident identification without the need for costly genetic sequencing. As previously mentioned, this is crucial for identifying patients eligible for inclusion in new clinical trials, which are often designed to target the specific genetic abnormalities that characterise these individuals. Regrettably, beyond these genetic variants, the diagnostic challenges become significantly more pronounced, largely because the available tools are not yet fully integrated into current clinical practice.

Importantly, in many areas of modern medicine, particularly oncology, validated screening procedures exist that enable the early and highly sensitive identification of patients with potential tumours, allowing them to be promptly guided toward appropriate diagnostic and therapeutic pathways (Garcia et al., 2021). In the field of neurodegenerative diseases, however, such screening has historically been avoided due to ethical concerns arising from the lack of disease-modifying therapies available for affected patients (Hansson, 2021). Nonetheless, ongoing pharmacological research is transforming the prospects of these patients. Early identification also provides caregivers with crucial opportunities to obtain information and support in advance, as well as to assess the potential presence of hereditary factors. Therefore, it seems imperative to move beyond these traditional reservations and implement all necessary measures to identify patients who may be in the early stages of a neurodegenerative process. While some biomarkers, in the early stages (at least based on current knowledge), appear to be altered only in carriers of genetic mutations (e.g., NPTX2), studies consistently show that NfL levels rise early, even in the blood, in response to neuropathological damage (Meeter et al., 2018b; Wilke et al., 2022). We believe this blood biomarker could serve as a starting point for screening the general population, as it is relatively inexpensive, non-invasive, and highly sensitive. However, given its lack of specificity, any detected abnormalities would require further diagnostic evaluation. Of note, neurophysiology could play a critical role in this context. Indeed, NIBS techniques are relatively easy to administer, have minimal exclusion criteria, and offer excellent cost-effectiveness. Specifically, identifying characteristic neurophysiological alterations within this spectrum, such as changes in SICI/ICF, could represent a second step in the diagnostic process (Benussi et al., 2020b, 2019b). Only at this point might it be useful to perform a neuroimaging assessment, and among the available options, we believe that brain MRI is the best choice. Unlike PET-based methods, MRI does not require costly and invasive radioactive tracers, and it is a widely accessible tool that provides both structural data, useful for differential diagnosis (e.g., ruling out vascular or other lesions that might suggest an alternative diagnosis), and functional data that are particularly relevant for identifying FTD subtypes, even in presymptomatic stages (Dopper et al., 2014; Shafiei et al., 2023). It may seem controversial to reach this point without first conducting a specialist evaluation combined with a neuropsychological examination. However, it is important to recognise that these investigations are intended for patients in the presymptomatic phase, before the emergence of subtle and insidious cognitive-behavioural symptoms—symptoms that, according to some studies, may not appear until approximately five years before

the overt clinical onset and are often too subtle to be detected by current clinical assessments, which tend to rely on tools unable to capture such nuanced changes. On the other hand, patients who bypass this hypothetical screening phase would likely present with typical behavioural or cognitive symptoms, which would immediately draw medical attention (though not necessarily from a neurologist, as previously discussed), as is typically the case today. In other words, waiting for these manifestations results in a significant delay between the onset of neuropathological damage and the appearance of symptoms, and minimizing this delay is crucial for the reasons already outlined.

We acknowledge that implementing population screening based on biomarkers like NfL, NIBS techniques, and structural and functional brain MRI is a complex and challenging task at present when considering the limited economic and health resources and the unequal access to diagnostic services in different areas. While we believe it is essential to allocate resources toward establishing these pathways—especially since many expensive and limited-availability tests, such as FDG or amyloid PET, are often prescribed at stages of the disease where they offer less valuable or even redundant information—what steps can be taken to identify patients in the critical interval before clinical onset (Chételat et al., 2020)? As illustrated in Figure 1, while this interval (i.e., approaching symptom onset) has been extensively characterised in genetic variants, the available data for sporadic cases are currently scarce due to the difficulty in identifying at-risk individuals for longitudinal study within the general population. Although promising evidence suggests that findings from genetic patients might also apply to sporadic cases, there is not yet enough data to definitively confirm this hypothesis (Heuer et al., 2020). Therefore, it is proposed that we enhance the tools available for monitoring the general population, particularly those over 50 years of age, in a relatively cost-effective and non-invasive manner In this context, home-based technologies—such as tools for tracking daily activities and sleep patterns—are emerging as valuable instruments for the early detection of changes that may be associated with pathological alterations (Chen et al., 2022; Iqbal et al., 2016). Although the data remain somewhat limited, it is possible that these technologies could prove useful in identifying neurodegenerative processes that are on the verge of manifesting clinical symptoms (Cote et al., 2021). Similarly, SCC, once considered clinically irrelevant, is now recognised as potentially related to a pathological process, particularly within the AD spectrum, that may be too subtle to be detected by conventional neuropsychological assessments (Rabin et al., 2017). Indeed, recent evidence links this condition to network alterations, likely compensatory, suggesting that, as discussed in FTD patients, functional changes may precede structural ones (López-Sanz et al., 2017; Rodda et al., 2011; Tsvetanov et al., 2021). Therefore, we believe it is essential not only to be vigilant for any behavioural, personality, or social interaction changes that emerge in middle to older age without significant prior history (e.g., MBI) but also to monitor objective measures, such as a reduction in daily activities (possibly due to apathy or social withdrawal), an increase in nighttime activities, and alterations in dietary intake (Cote et al., 2021; Ismail et al., 2021). Given the large and complex datasets involved, AI-based data analysis techniques will likely provide critical support in this domain (Iaboni et al., 2022). Although these represent more advanced stages than those identifiable by the earlier discussed strategies, this period still spans several years, which could be crucial in avoiding the need to wait for more characteristic symptoms to emerge. It is also important to note that biomarker abnormalities tend to correlate with disease progression, making it likely that, by this stage, alterations in NfL levels, neurophysiology, and network functions will be even more marked, along with structural changes that may begin to display more distinctive patterns, as suggested by some studies (Benussi et al., 2020a; Hansson, 2021; Planche et al., 2021).

In summary, we advocate for a fundamental shift in the diagnostic approach in FTD patients, placing greater emphasis on early fluid, neurophysiological, and functional neuroimaging biomarkers, which are currently reserved for research purposes or used merely as confirmation in later stages. Greater attention should also be paid to subtle symptoms, particularly as the true clinical onset approaches. Furthermore, we underscore the importance of longitudinal studies to more precisely define the temporal profile of alterations in FTD patients, including sporadic cases. This will be vital for improving recruitment in clinical trials to demonstrate the efficacy of disease-modifying therapies, a crucial step in offering hope to patients affected by these conditions.

Abbreviation list

18F FDG-PET: 18 fluorodeoxyglucose-PET; Aβ42: amyloid-beta 42; AD: Alzheimer's disease;ALS: amyotrophic lateral sclerosis; ANS: Autonomic nervous system; ASL: arterial spin labeling; BOLD: blood oxygenation level-dependent; bvFTD: behavioural variant frontotemporal dementia; *C9orf72:* chromosome 9 open reading frame 72; CBS: corticobasal syndrome; CDR: Clinical Dementia Rating Scale; CDR plus NACC FTLD: CDR Dementia Staging Instrument plus National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains; CSF: cerebrospinal fluid; DLB: dementia with Lewy bodies; DMN: default mode network; DTI: Diffusion tensor imaging; EMG: electromyography; f-c: functional connectivity; fMRI: Functional brain magnetic resonance imaging; FRS: Frontotemporal Dementia Rating Scale; FTD: Frontotemporal dementia; FTD-ALS: Frontotemporal dementia - amyotrophic lateral sclerosis; FTLD: Frontotemporal Lobar Degeneration; FUS: fused in sarcoma; GABA: gamma-aminobutyric acid; GFAP: Glial Fibrillary Acidic Protein; *GRN:* granulin precursor; ICF: intracortical facilitation; IL: interleukin; LICI: long-interval intracortical; LTD/P: long-term depression/potentiation; lvPPA: logopenic variant of of primary progressive aphasia; M1: primary motor area; *MAPT:* microtubule-associated protein tau; MCI: mild cognitive impairment; MEP: motor-evoked potential; miRNAs: microRNAs; MBI: Mild Behavioral Impairment; NfL: neurofilament light chain; nfvPPA: non-fluent variant of primary progressive aphasia; NIBS: Noninvasive brain stimulation techniques; NPTX2: neuronal pentraxin-2; PASS: Progressive Aphasia Severity Scale; PET: Positron Emission Tomography; poly(GP): polyglutamine; PPAs: primary progressive aphasias; PSP: progressive supranuclear palsy; pTau: phosphorylated tau; pTDP-43: Phosphorylated TDP-43; RMET: Reading the Mind in the Eyes Test; RNA: ribonucleic acid; rtvFTD: right temporal variant of frontotemporal dementia; RT-QuIC: Real-Time Quaking Induced Conversion; SAI: short latency afferent inhibition; SCC: subjective cognitive complaints; SICI: short-interval intracortical inhibition; SN: salience network; SPECT: Single-photon emission computed tomography; svPPA: semantic variant of primary progressive aphasia; TNF: tumor necrosis factor; TDP-43: TAR DNA-binding protein 43; TMS: transcranial magnetic stimulation; TMTB: Trail Making Test Part B; TREM2: protein triggering receptor expressed on myeloid cell 2; UPS: ubiquitin-proteasome system; VEGF: vascular endothelial growth factor; WMH: White matter hyperintensities.

10.11 References

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Chapter 11. The cerebellum in frontotemporal dementia: From neglected bystander to potential neuromodulatory target.

In this chapter, I provide a narrative review that builds on neurophysiological insights from previous work on the cerebellar role in various brain functions, expanding those ideas into the area of neurodegenerative disease. Consistently, while the cerebellum's role in cognitive functions has gained growing recognition, its involvement in the pathophysiology and prospective treatment of frontotemporal dementia (FTD) remains largely underexplored. This review, therefore, aimed to synthesize current evidence on cerebellar structural and functional changes in FTD and to suggest the feasibility of targeting this region with non invasive brain stimulation (NIBS) protocols, also based on indirect evidence from different pathological contexts. By combining neuroanatomical, neurophysiological, and clinical data, evidence indicates that cerebellar circuits, especially those connected with the frontal and temporal lobes, may play a key role in major FTD symptoms, including language impairment, social-emotional dysfunction, and cognitive decline. Additionally, cerebellar neuromodulation, although rarely studied in this context, might be a promising therapeutic option.
This work supports one of the main messages of this Thesis: the cerebellum acts as a vital and adaptable core within both healthy and pathological brain networks. Finally, it serves as an effective target for NIBS interventions aimed at promoting functional recovery and cognitive enhancement across various neurological disorders.

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11.1 Abstract

Though cortical changes in frontotemporal dementia (FTD) are well-documented, the cerebellum's role, closely linked to these areas, remains unclear. To provide evidence on cerebellar involvement in FTD across clinical, genetic, imaging, neuropathological, and neurophysiological perspectives. Additionally, we sought evidence supporting the application of cerebellar non-invasive brain stimulation (NIBS) in FTD for both diagnostic and therapeutic purposes. We performed a literature review using MEDLINE (via PubMed), Scopus, and Web of Science databases. We emphasized the involvement of specific cerebellar regions which differentiate each FTD subtypes and may account for some of the characteristic symptoms. Furthermore, we highlighted peculiarities in FTD genetic alterations. Finally, we outlined neurophysiological evidence supporting a role for the cerebellum in FTD pathogenesis. The cerebellum is critically involved in the FTD spectrum. Moreover, it can be speculated that cerebellar modulation, as already shown in other neurodegenerative disorders, could restore the interneuronal intracortical circuits typically impaired in FTD patients, providing clinical improvements and fundamental outcome measures in clinical trials.

11.2 Introduction

11.2.1 Background on frontotemporal dementia

Frontotemporal dementia (FTD) is a neurodegenerative disease which represents one of the most common causes of primary dementia after Alzheimer's disease (AD) (Logroscino et al., 2023). Its clinical manifestations are heterogeneous, ranging from conduct and personality alterations, in the so-called behavioural variant of FTD (i.e., bvFTD), to speech disorders, characteristic of the semantic variant and agrammatic/non-fluent variant of primary progressive aphasia (i.e., svPPA and nfvPPA, respectively) (Antonioni et al., 2023). Recently, another diagnostic category has been identified, the right lobe variant of FTD (i.e., rtvFTD), which is characterised by a unique profile of cognitive, behavioural, and language alterations (González-Caballero et al., 2015). Since the clinical symptoms are variable and FTD often affects younger patients in comparison to the other neurodegenerative dementias (i.e., AD and dementia with Lewy bodies, DLB), diagnostic delays and misdiagnoses are frequent (Ducharme et al., 2020), preventing adequate and early care and therapeutic management (Besser and Galvin, 2020). Notably, this also entails concerns for patients' relatives, as FTD is characterised by a high heritability (Fenoglio et al., 2018; Greaves and Rohrer, 2019). Aside from known genetic cases with a possible correlation with neuropathology, predicting pathological proteins that cause brain damage in vivo is generally challenging (del Campo et al., 2022). Thus, there is currently no definite biomarker to confirm frontotemporal lobar degeneration (FTLD) pathological diagnosis before autopsy. Therefore, an important diagnostic aid comes from neuroimaging, in particular brain magnetic resonance imaging (MRI). Indeed, traditionally, FTD is associated with specific patterns of brain atrophy, particularly in the frontal and/or temporal regions, depending on the specific subtype and stage of disease progression (Chouliaras and O'Brien, 2023). However, several recent studies have actually shown that the amount of damaged brain regions in the FTD spectrum is much larger and includes areas such as the insula, the orbitofrontal cortex, the hippocampus, and subcortical structures (Chouliaras and O'Brien, 2023; Narayanan and Murray, 2016), which are key hubs of intrinsic functional connectivity networks, e.g. the so-called default mode network (DMN) and

salience network (SN), respectively active during relaxed waking phases without performing specific tasks and in the case of subjective salience (Goulden et al., 2014; Seeley et al., 2009). The crucial involvement of these networks allowed us to explore mechanisms associated with the propagation of pathological protein aggregates in the brain and to enhance our understanding of the multifaceted manifestations of FTD (Jaunmuktane and Brandner, 2020; Shafiei et al., 2023). Moreover, importantly, these studies gave us the opportunity to identify an often marked involvement of the cerebellum in numerous neurodegenerative diseases, including the FTD spectrum (Liang and Carlson, 2020).

11.2.2 Aims and scope of the present review

To date, attention on the correlations between cerebellar alterations and clinical features in the FTD spectrum has been limited (Ahmed et al., 2016; Kumfor et al., 2018a). Several studies have identified cerebellar alterations in FTD, but do not discuss or even report them in tabular form, making it difficult to detect their presence and analyse their implications (Rosen et al., 2002; Whitwell et al., 2010). Importantly, the seminal work of Chen et al. identified, through a meta-analysis of neuroimaging data, widespread involvement of both the cerebellar hemispheres bilaterally and various portions of the vermis in the FTD spectrum, showing its significant alteration in this context (Chen et al., 2019). Nevertheless, it is important to emphasise that their results were limited by the choice to collect data that were suitable to the specific analysis paradigm chosen (e.g. by excluding any negative results) and that patients with different disease durations, characterised by potentially very different neuropathological damage progression, were included in their study, limiting the generalisability of their results. Moreover, the presence of aberrant cerebellar gene expression, neuropathological changes at the cerebellar level, and cerebellar alterations not only in the grey but also in the white matter (i.e. of all three cerebellar peduncles, not only those afferent and efferent from the brain but also those connecting with the spinal cord and vestibular regions) has provided further support for its involvement in these pathological conditions (Belzil et al., 2013; Chen et al., 2020; Ferrer et al., 2015). However, in the complex landscape of neurodegenerative disorders that impact extensive interconnected networks, it is pertinent to inquire whether the cerebellar contribution to cognitive changes in FTD is driven by, or simply mediated by, disrupted cerebellar-cerebral connections. Importantly, a fundamental study underscored the cerebellar contribution to cognitive deficits even after controlling for brain atrophy, emphasising an independent cerebellar role in cognition within the FTD spectrum (Chen et al., 2018). Finally, of note, recent research not only showed pathology-specific patterns of cerebellar atrophy across major pathological subgroups of FTLD, even at early stages, but also that the degree of overall cerebral atrophy positively predicts the degree of cerebellar atrophy across all pathological subtypes (Chen et al., 2023). These findings suggest that cerebellar atrophy may be mediated by both pathological deposition and Wallerian degeneration and reinforce the idea that the cerebellum is not only compromised due to disconnection from cortical regions, but might be itself a primary and sometimes early site of neuropathological damage. Therefore, in light of recent evidence showing a specific vulnerability of the cerebellum within networks selectively involved in neurodegenerative disorders (Guo et al., 2016), we aim to synthesise data concerning the cerebellar role in the FTD spectrum. In particular, we will evaluate the role of the cerebellum in cognitive functions which are impaired in the FTD spectrum, as well as the clinical, neuropathological, neurophysiological, genetic, neuroimaging, and functional imaging data correlating FTD with cerebellar involvement and suggest, if possible, potential neuromodulation strategies by means of cerebellar non-invasive brain stimulation (NIBS) techniques, in order to propose possible future lines

of intervention. We performed a thorough literature review using MEDLINE (via PubMed), Scopus, and Web of Science databases to provide a comprehensive overview of the current understanding in this domain. Specifically, our search strategy involved a combination of keywords and subject headings, including terms such as FTD, cerebellum, bvFTD, and PPA. In addition, we examined the reference lists of included studies for additional pertinent sources. Finally, experts within our research group contributed suggestions for relevant research in this field.

11.2.3 The cognitive cerebellum

The cerebellum is located in the posterior cranial fossa and contains 70-80% of the neurons of the entire central nervous system (CNS) (Roostaei et al., 2014). Traditionally, the role of the cerebellum was thought to be limited to motor control, in particular to the coordination and correct sequencing of movements, which are typically altered in the case of cerebellar damage (Manto et al., 2012). Since such alterations do not characteristically occur in cognitive decline due to neurodegenerative dementias, this structure has been ignored in the vast majority of research works in this field, so much so that it was often used as a “reference” or as a “silent bystander” to study damage thought to be exclusive to cortical areas (Jacobs et al., 2018; Schmahmann, 2016; Toniolo et al., 2023). Consistently, in many studies using positron emission tomography (PET) or single photon emission scintigraphy (SPECT) to investigate CNS alterations, the cerebellum is used as the reference region and, even in recent times, has been considered as the least affected region in some neurodegenerative disorders, such as the FTD spectrum (Chen et al., 2019; Dukart et al., 2011). Moreover, the cerebellum is often excluded from neuroimaging analysis protocols, making it impossible to assess the implications of its possible involvement (Jiskoot et al., 2019). However, this view has been radically changed by an exponential amount of research that has been conducted to prove its involvement in numerous higher-order functions, including, among others, language, executive functions, visuospatial cognition, and affective-emotional aspects (Argyropoulos et al., 2020). Indeed, in higher-order apes and, especially, humans, the lateral cerebellum, defined as neocerebellum has undergone drastic expansion, in parallel with the extensive development of the neocortical areas with which it is richly interconnected (Schmahmann, 2019). In particular, the cerebellum includes an anterior portion, from lobules I to V, which, together with part of lobule VI and lobule VIII, connects with the spinal cord, through the spinocerebellar tracts and the inferior olivary nucleus complex, and with the motor cortices through the thalamus. On the other hand, the posterior cerebellar region is more involved and very relevant in cognitive aspects (Haines and Dietrichs, 2012). Specifically, part of lobule VI, the entire lobule VII (including both lobule VIIA in the vermis, which becomes crus I and II in the hemispheres, and lobule VIIB) and most of lobule IX, instead of connecting with the brainstem, the spinal cord or the primary cortical sensorimotor areas, project to regions essential in higher order behaviour, namely, the prefrontal cortex, the posterior parietal cortex, the superior temporal polymodal regions, the cingulate gyrus, and the posterior parahippocampal area (Schmahmann, 2019; Wagner and Luo, 2020). Importantly, crus I and II are considered the cerebellar counterparts of the DMN, while lobule VI belongs to the SN (Buckner et al., 2011). In particular, the dentate nucleus, which constitutes the only output of the cerebellar regions connected to these areas, projects to the ventral anterior and ventral lateral nucleus of the thalamus, which constitute a fundamental subcortical relay station for bidirectional communication with the neocortex (Pelzer et al., 2017). Indeed, the brain and cerebellum are bi-directionally connected and form closed-loop circuits, which allow feedback and feedforward information processing depending on the specific task (Habas, 2023). Although it is

still only partially understood how the complex neuronal circuitry of the cerebellum performs its function, it seems that it modulates brain activity through the creation of internal models that, in the event of an inconsistency between prediction and outcome, signal the error and allow corrective actions to be implemented, both in the motor and non-motor domains (Sokolov et al., 2017). Coherently, the cerebellar architecture is essentially uniform throughout, consisting of repeated modules which are characterised by a complex interaction among cells distributed between three layers, namely granules and Golgi cells, basket and stellate interneurons, and Purkinje cells, which constitute the only output from the cerebellar cortex directed towards the deep cerebellar nuclei, which, in turn, transmit to the other CNS structures (D'Angelo, 2018). Specifically, a cerebellar module consists of a set of inhibitory Purkinje cells, which topographically inhibit specific areas of the deep cerebellar nuclei that sequentially project to brain areas that send afferents to the cerebellum via the corticopontocerebellar pathway, which originates muscoid fibres that excite granule cells (Cerminara and Apps, 2011). These cells, in turn, emit axons (i.e. parallel fibres), which not only excite Purkinje cells, but also stellate and basket inhibitory interneurons, which inhibit Purkinje cells by means of a feed-forward mechanism. In addition, the inferior olive complex, which receives afferents from the spinal cord and various neural stations of the reticular formation, emits projections (i.e., climbing fibres) that further modulate the activity of Purkinje cells and deep cerebellar nuclei (D'Angelo, 2018). The cerebellar complexity is further increased, since its circuitry is also characterized by Golgi cells, Lugaro cells, and unipolar bush cells, which influence the activity of the granule cells and allow further integration of information from the CNS stations (Schilling et al., 2008). Thus, what makes the computation produced by cerebellar circuits specific is the topography of its afferent and efferent connections, and its action is fundamental to the proper performance of many complex functions performed by the cortical areas (D'Angelo, 2018).

11.2.4 The genetic contribution to cerebellar involvement in FTD

Three genes account for up to 30% of genetically determined FTD cases, namely microtubule-associated protein tau (*MAPT)*, progranulin (*GRN*) and, above all, large hexanucleotide (GGGCC) repeat expansion in the first intron of chromosome 9 open reading frame 72 (*C9orf72)* (Fenoglio et al., 2018). The latter also justifies varying degrees of motor impairments in FTD patients, ranging from almost clinically negligible to a full-blown motor neuron disease (MND, e.g. amyotrophic lateral sclerosis, ALS) (Beckers et al., 2021). Greater complexity is further provided by neuropathological variability. Indeed, molecular characteristics of neuronal inclusions of abnormal proteins allow FTD to be divided into four main categories: TAR-DNA-binding protein-43 (TDP-43), tau, FET (i.e. FUS, EWSR1 [Ewing sarcoma breakpoint region 1/EWS RNA binding protein 1], and TAF15 [TATA-box-binding protein-associated factor 15]) and rare variants of FTLD characterised by inclusions only labelling for markers of the ubiquitin/proteasome system (UPS) (Antonioni et al., 2023; Neumann and Mackenzie, 2019). Importantly, a recent study highlighted a more extensive and severe gray matter atrophy in patients characterised by genetic alterations in the FTD-MND spectrum disorders, in particular, among others, in the posterior cerebellar regions, which were absent in their sporadic counterparts (Spinelli et al., 2021). Although, in most cases, they are associated with the bvFTD phenotype, particularly for *C9orf72* expansion, alterations related to other subtypes have also been documented, underlining the complexity and multifactorial nature of these disorders (Kirola et al., 2022; Mol et al., 2021). Interestingly, however, it has been highlighted that, in neuropathologically healthy subjects, the highest expression of *C9orf72* occurs in the cerebellum (Renton et al., 2011). Indeed, studies in animal models have shown that it is present in the synapses of granule

cells, regulating synaptic transmission and autophagy (Kaliszewska et al., 2022; Xiao et al., 2019). Recent advances have allowed a better understanding of the pathophysiological mechanism involved. Specifically, in response to the aggregation of C9orf72 poly(gly-ala), TBK1 undergoes phosphorylation and becomes sequestered into inclusions. This process leads to a reduction in TBK1 activity, contributing to neurodegeneration. In mice, diminishing TBK1 activity worsened phenotypes induced by poly(gly-ala), such as heightened TDP43 pathology and the buildup of defective endosomes in neurons with poly(gly-ala) presence (Antonioni et al., 2023; Shao et al., 2022). This resulted in the distinctive segregation of TDP-43 and p62 proteinaceous inclusions, with the cerebellum showing the highest abundance, especially evident in the granular layer of the cerebellar cortex, although these observations are not unique to this particular genotype (Gami-Patel et al., 2021; Kaliszewska et al., 2022; Simón-Sánchez et al., 2012; Snowden et al., 2012; Troakes et al., 2012). Furthermore, in FTD-ALS patients carrying *C9orf72* expansion, toxic dipeptide protein repeats are often found in cerebellar regions, possibly contributing to the worsening of the disease (Gendron et al., 2015; Mori et al., 2013). On the other hand, in this case, the largest pathological ribonucleic acid (RNA) foci are found in Purkinje cells compared to all other regions of the brain, in absence of neuronal loss (DeJesus-Hernandez et al., 2017). It is therefore conceivable that the combination of toxic dipeptides and RNA foci, which can alter the synaptic functioning of both granule and Purkinje cells, is one of the main factors leading to the cerebellar involvement in FTD clinical manifestations (Kaliszewska et al., 2022). Indeed, the cerebellum is the region with the highest expression in the CNS of *C9orf72* and, when functional protein levels are reduced, p62 accumulates and its aggregation leads to tau hyperphosphorylation and axonopathy, leading to cerebellar alterations that are more common than in sporadic cases (Bieniek et al., 2013; Boeve et al., 2012; Chitiprolu et al., 2018; Devenney et al., 2014; Sha et al., 2012; Whitwell et al., 2012). Importantly, as mentioned above, *C9orf72* represents the most common genetic cause of ALS and, often, patients with FTD-ALS manifest a pattern of hypometabolism, as assessed by 18-fluorodeoxyglucose(FDG)-PET, in various brain regions, including the cerebellum (Rajagopalan and Pioro, 2023). Interestingly, however, these patients also sometimes manifest patterns of hypermetabolism in the same regions, which could be compensatory with respect to hypometabolism in other regions of the same networks, or reflect different phases in the disease course (Hinault et al., 2022; Rajagopalan and Pioro, 2023). Consistently, some studies suggest that evidence of cerebellar alterations is particularly evident in this group of patients, whereas, in *GRN* and *MAPT* mutation carriers, cerebellar alterations are much less prominent (Cash et al., 2018; Mahoney et al., 2012). In fact, from a comparison of genetic alteration groups, carriers of the *C9orf72* expansion have shown the smallest cerebellar volumes, particularly of lobule VIIa and crus I, and some models seem to identify these patients using the reduction in left cerebellum volume as an independent factor (Bocchetta et al., 2016; Whitwell et al., 2012). Crucially, these cerebellar regions are strictly associated with the thalamus, another critical area of atrophy in *C9orf72* carriers, which, in turn, projects to the prefrontal cortex, thus a relevant dysfunction in this cerebello-thalamic-cortical network could lead to many specific symptoms of this FTD subtype (Bocchetta et al., 2016; Downey et al., 2014; Palesi et al., 2015). Moreover, of note, Bussy et al. confirmed that patients with *C9orf72* expansion have extensive cerebellar involvement, specifically of crus I, crus II, IX, and X, which could correlate with specific behavioural features during the disease course, in particular with behavioural symptoms such as late psychiatric manifestations (Bussy et al., 2023). In addition, other evidence has also identified the involvement of cerebellar lobule V and vermis in the FTD-ALS spectrum, particularly with *C9orf72* expansion, which could justify typical symptoms of bvFTD (i.e. the most frequent in these patients) (McKenna et al., 2021;

Tan et al., 2015). Importantly, a study on individuals carrying FTD-related genetic variants without overt manifestations revealed that those with *C9orf72* expansions exhibited cerebellar atrophy a decade before the anticipated onset age predicted by the family's disease progression (Rohrer et al., 2015). Another study not only confirmed that carriers of the hexanucleotide expansion have more significantly diffuse cortical atrophy than non-carriers, but that white matter alterations have different characteristics between the two groups (McKenna et al., 2021). In addition, another study investigated white matter lesions in symptomatic *MAPT* mutation carriers (Corriveau-Lecavalier et al., 2024). While it did identify alterations in the superior cerebellar peduncle compared to controls, these differences did not reach statistical significance after multiple comparisons. This observation hints at the potential utility of assessing both grey and white matter involvement in distinguishing between various patient categories. However, the evidence in this case is still conflicting, as other studies have documented, as anticipated, that sporadic FTD patients show more pronounced cerebellar changes than *C9orf72* carriers even in earlier stages of the disease (Devenney et al., 2014; Irish et al., 2013; Lee et al., 2014). Finally, it is interesting to mention that, while it appears that *GRN* mutation carriers do not show any significant cerebellar alterations, those with *MAPT* pathology show a specific atrophy of the cerebellar vermis, which not only allows us to distinguish the pattern of atrophy from patients with *C9orf72* expansion, but could also justify the alteration of the limbic network underlying the behavioural and social conduct alterations typical of these patients (Bocchetta et al., 2016, 2015). Furthermore, it is noteworthy that recent studies have detected subtle early cerebellar atrophy also in *GRN* mutation carriers (Staffaroni et al., 2022). However, given the limited available evidence, further research is required to validate this observation and explore cerebellar involvement in this patient subgroup. These findings suggest not only that the cerebellum is critically involved in these genetic variants of pathology, but also that it may be one of the first areas where the disease is expressed considering that pathological aspects are particularly represented at this level (Bussy et al., 2023; Cash et al., 2018). Therefore, it is conceivable that studies on large case series will make it possible to assess the role of alterations in the cerebellum in the early identification of *C9orf72* expansion carriers, which is crucial for identifying candidates for gene therapies.

11.2.5 Non-invasive cerebellar stimulation techniques

Importantly, the involvement of the cerebellum and its circuits in higher-order functions has been greatly explored by means of NIBS techniques, given its anatomical position making it very easy to target. Indeed, in recent years, NIBS techniques have become widely used, as they allow cortical excitability and neuronal plasticity to be modulated by safely applying electrical or magnetic stimuli through the scalp (Rossi et al., 2022). Specifically, the application of a current (i.e. transcranial electrical stimulation, tES) or a magnetic stimulus (i.e. transcranial magnetic stimulation, TMS) induces ionic currents across neuronal membranes and, therefore, depolarises or hyperpolarises neuronal populations underlying the stimulation area, leading to their excitation or inhibition, respectively, based on the specific stimulation protocol used (Huang et al., 2017). Of note, some protocols allow for modifications that outlast the duration of the stimulation itself and may even last for tens of minutes, by means of long-term plasticity mechanisms in terms of both potentiation (LTP) and depression (LTD) that are based on, among others, calcium-dependent and receptor dynamics modulated by NIBS protocols (Cirillo et al., 2017). This evidence has encouraged the use of NIBS techniques as a therapeutic aid in numerous neurological and psychiatric disorders with very promising results and, although further research is needed to identify the most suitable protocols in each pathological condition, interest in the subject is steadily

increasing (Baroni et al., 2024; Hyde et al., 2022; Schulz et al., 2013). Moreover, importantly, the effects are not limited to the stimulated area, but also extend to other anatomically interconnected regions of the CNS and/or due to coordination between distant neuronal populations belonging to the same neural networks (Mencarelli et al., 2020; Nitsche et al., 2005). In this regard, it is not surprising that the cerebellum has been identified as a fundamental target of NIBS techniques, not only because it plays a crucial role in numerous physiological motor and non-motor functions, but also because its extensive connections with vast regions of the cerebral cortex, mediated through the dentate-thalamus-cortical pathway, allow their remote modulation, also when these are damaged or involved in pathological processes (Manto et al., 2022). Importantly, several studies have clarified the physiology of the cerebellar-thalamo-cortical pathway in the context of TMS protocols. Specifically, it has been hypothesized that magnetic stimulation on the cerebellum induces activation in the Purkinje cells of the superior cerebellum. This activation, in turn, leads to an inhibition of the dentate nucleus, which exerts a tonic facilitatory drive onto the contralateral motor cortex (M1) through synaptic relay in the ventral lateral thalamus (Dum and Strick, 2003). Therefore, the net effect is an inhibition of the contralateral motor area, due to a reduction in the dentato-thalamo-cortical facilitatory drive (Daskalakis et al., 2004; Pinto and Chen, 2001; Ugawa et al., 1997, 1994). Similarly, also cerebellar tES allow the connections between the dentate nucleus and motor areas to be modulated. For example, Spampinato et al. demonstrated that the application of a particular type of tES, i.e. transcranial alternating current (tACS) in the frequency range of the theta rhythm (i.e. 5 Hz), enhances the connections between the cerebellum and motor areas in healthy subjects (Spampinato et al., 2021). Crucially, cerebellar NIBS protocols exhibit effects that extend beyond neurophysiology, encompassing significant functional implications. For example, a recent systematic review and meta-analysis has confirmed that NIBS techniques applied to the cerebellum can modulate numerous cognitive processes (Pezzetta et al., 2024). Consistently, it has been suggested that cerebellar stimulation allows the modulation of complex interneuronal circuits within regions of the cerebral cortex connected to the cerebellum via the thalamic relay. Indeed, NIBS techniques make it possible to assess, by means of TMS protocols that involve the use of paired stimuli, neurophysiological measures that are believed to reflect the functional state of excitatory and inhibitory circuits in the cortex, generally studied at M1 due to its easy accessibility and the availability of neurophysiological indices to be used as outcome measures (Shirota et al., 2016). Specifically, short- and long-interval intracortical inhibition (SICI and LICI, respectively) appears to reflect ionophoric $GABA_A$ and metabotropic $GABA_B$ currents, respectively, and describes the inhibitory activity of cortical interneurons, while glutamatergic excitatory activity is assessed by means of intracortical facilitation (ICF), using specific intensity and inter-stimulus intervals of the coupled stimuli according to the neuronal populations to be assessed (Cash et al., 2017). These neurophysiological indices are assessed through a measure of M1 stimulation, namely motor evoked potentials (MEPs), whose amplitude is believed to reflect modulation by excitatory and inhibitory interneurons in the cortex (Davila-Pérez et al., 2019). Therefore, TMS protocols become very relevant to characterise cortical circuits in vivo not only in neurophysiological studies, but also in various categories of patients for both diagnostic and prognostic purposes (Comanducci et al., 2020; Kobayashi and Pascual-Leone, 2003; Kraus et al., 2019). Moreover, as rTMS protocols induce changes that outlast the duration of treatment, exploiting neuroplasticity mechanisms, their use is also spreading for therapeutic purposes with very promising results (Lefaucheur et al., 2020; Menardi et al., 2022). Importantly, it has not only been shown that cerebellar magnetic stimulation coupled, in a specific time interval (reflecting the conduction time of the dentate-thalamus-cortical pathway), to contralateral M1 consistently induces a decrease

in MEP amplitude (i.e. cerebellar-brain inhibition, CBI), but also the modulation of interneuron circuits (Fernandez et al., 2018). Indeed, particular cerebellar rTMS protocols, namely theta burst stimulation (TBS), can induce long-term changes in SICI, LICI, and, to a lesser extent, ICF, demonstrating that cerebellar modulation has direct consequences on M1 circuitry (Koch et al., 2008). Since, as shown below, these neurophysiological indices are altered in FTD patients, their remote modulation could have a fundamental clinical impact. Taken together, this evidence suggests a promising role for cerebellar modulation with NIBS techniques in numerous pathological conditions, and also FTD may fall into this group.

11.3 Cerebellar involvement in FTD subtypes

11.3.1 bvFTD

This is the most common FTD subtype and is characterised by the gradual onset of behavioural alterations (including apathy, stereotyped attitude, impaired executive functions, loss of empathy, disinhibition, and altered eating behaviour) that begin, on average, around the age of 50 (Piguet et al., 2011; Rascovsky et al., 2011; Seeley, 2019). Consistently, bvFTD patients typically manifest atrophy at the level of the bilateral medial prefrontal, right orbitofrontal, anterior insular, and anterior cingulate cortex on structural brain MRI, while functional neuroimaging highlights reduced functional connectivity in the SN, i.e. the frontal-insular-anterior cingulate gyrus, whose role in the higher-order functions typically impaired in these FTD subtypes is now well established (Friedman and Robbins, 2022; Molnar-Szakacs and Uddin, 2022; Narayanan and Murray, 2016; Olney et al., 2017; Rolls et al., 2022). Neuropathologically, this subtype is extremely heterogeneous, as it can present with almost all possible types of pathological inclusions reported for this spectrum (Josephs et al., 2006). Numerous studies have documented relevant cerebellar alterations in patients affected by bvFTD, even more prominent and widespread than in other FTD subtypes, such as svPPA and nfvPPA (Chen et al., 2018; McKenna et al., 2021). For example, an important paper by Ferrer et al. described two sisters born of consanguineous parents with a familial form of bvFTD, reporting marked deposits of abnormal tau also in cerebellar astrocytes and Bergmann's glia and loss of Purkinje cells and neurons in the dentate and inferior olivary nucleus, associated with reactive gliosis and marked microglial activation, reasonably due to a FUS mutation in both patients (Ferrer et al., 2015). Of note, the cerebellum, in particular its posterior regions and, specifically, lobule VII, has close connections with prefrontal regions and is, indeed, actively involved in the modulation of executive functions, social cognition, and theory of mind (i.e., that set of abilities that allows one to attribute mental states to others and predict their behaviour), eating behaviour and emotional-behavioural aspects (Kawabata et al., 2022; Koziol et al., 2012; Schmahmann, 2019; Schutter, 2022; Van Den Stock et al., 2019; Van Overwalle et al., 2020; Zhu and Wang, 2008). Indeed, these cerebellar regions are an integral part of fundamental brain networks, such as the DMN, the SN, and the executive control network (i.e. a network engaged in a cognitively demanding task that requires attention), as evidenced by their activation in the context of tasks that assess emotion processing, executive functions, and memory tasks (Balsters et al., 2014; Guo et al., 2016; Habas et al., 2009). Consistently, damage to the areas of the crus (and partly to the lobule VI) lead to, among others, neuropsychiatric, emotional, and executive domain disorders (Devenney et al., 2017; Kloeters et al., 2013; Kumfor et al., 2018a, 2018b; Laisney et al., 2009; Strenziok et al., 2011; Tan et al., 2015, 2014).

Importantly, two recent meta-analyses demonstrated a specific pattern of alterations in the cerebellum of these patients and, specifically, analysing only structural neuroimaging data, Gellersen et al. demonstrated multiple clusters of atrophy in crus I and II bilaterally (Gellersen et al., 2017). More recently, also considering functional neuroimaging data, Chen et al. confirmed an extensive cerebellar involvement in lobule VI, VIIb, VIIIb, most prominent at the level of the right lobule VII and crus II, highlighting that it is markedly altered especially in the posterior zone and in the right inferior region (Chen et al., 2019). Nevertheless, the data from a functional point of view were inconclusive, probably also due to the limitations already examined (see Section 1.2). Notably, a recent neuroimaging study has also confirmed that, in bvFTD patients, the atrophy has an asymmetrical pattern and is more pronounced in the right cerebellum (McKenna et al., 2021). However, previous evidence documented a greater alteration at the level of the left cerebellum, consistent, given the cross nature of the connections between cerebellum and brain cortical areas, with the presence of greater alterations at the level of the grey and white matter of the right insular region (Chen et al., 2020; Nguyen et al., 2013). Importantly, the right brain hemisphere is characterised by 30% more Von Economo neurons than the contralateral one, a particular class of nerve cells found almost exclusively in great apes and humans, that play a crucial role in the neocortical, limbic and paralimbic network that mediates human social cognition and that is selectively affected in bvFTD (Allman et al., 2011; Seeley et al., 2009, 2008). However, in some cases, the degeneration also appears to be symmetrical (Sokołowski et al., 2023; Whitwell et al., 2013). Therefore, the pathophysiological basis and functional implications of the prevalence of side in neurodegenerative damage are still largely unknown.

Furthermore, cerebellar alterations in the same regions have been documented in the context of attention and social cognition impairments, changes in eating behaviour, and lack of empathy, all of which are prominent features of bvFTD (Ahmed et al., 2016; Chen et al., 2018; Dermody et al., 2016; Kumfor et al., 2017; Synn et al., 2018; Wong et al., 2017), although a recent study failed to prove a correlation between lack of empathy and cerebellar alterations in these patients (Tafuri et al., 2023). Moreover, cerebellar crus I and II are functionally correlated with regions of the DMN crucial for social mentalisation and, indeed, recent work by Olivito et al. has shown an altered functional connectivity between these regions in patients with bvFTD, which correlates with performance on tests assessing the theory of mind (Bernard et al., 2012; Olivito et al., 2022). Interestingly, other studies have documented relevant alterations in patients with bvFTD at the level of lobule V, a region involved in emotional control, working memory, and rhythm processing (E et al., 2014; Tan et al., 2015). However, other research has documented that the involvement of the cerebellar vermis, which is also present in nfvPPA and ALS-FTD, reaches the most significant level in bvFTD (Chen et al., 2019; McKenna et al., 2021). This area is part of the so-called 'limbic cerebellum', as it is characterised by close connections with the limbic and paralimbic supratentorial regions and plays a key role in the regulation of emotional behaviour (E et al., 2014). Consistently, alterations at this level have been documented in the presence of numerous socially or emotionally inappropriate behaviours, such as disinhibition, aggression, and irritability, which are cardinal symptoms of bvFTD patients (Lupo et al., 2018; Tavano et al., 2007).

Furthermore, a recent study on patients with bvFTD has not only shown that cerebellar alterations are more pronounced in patients carrying the *C9orf72* expansion, highlighting the role played by genetic alterations also at the cerebellar level, but also that they are present at the level of specific thalamic nuclei (Bocchetta et al., 2022). In particular, both sporadic bvFTD and genetic cases showed a close correlation between behavioural symptoms and alterations of the ventral anterior and ventral lateral nuclei of the thalamus, whereas only

patients with the *C9orf72* expansion showed a correlation with abnormalities of the medio-dorsal nucleus. This demonstrates that the thalamus, as a sub-cortical station of connection between the cerebellum and cortical areas, could not only play a key role in contributing to the characteristic symptoms of bvFTD, which are also modulated by the presence of specific genetic abnormalities, but also that its alterations could corroborate the prion-like transmission of pathological proteins, providing important insights into the pathophysiology of these complex disorders (Bocchetta et al., 2020; McKenna et al., 2023). However, it is interesting to note that another study showed an opposite trend in the relationship between *C9orf72* and cerebellar alterations (Chen et al., 2022): specifically, even though the atrophy patterns were all overlapping in the bvFTD patients, the *C9orf72* positive group exhibited a more circumscribed yet more prominent cerebellar change, while the *C9orf72* negative group displayed a more widespread but comparatively milder alteration, as previous studies had already shown (Devenney et al., 2017; Schönecker et al., 2018). The authors hypothesise that this pattern of alterations, opposite to that expected, is partly due to the different disease duration of the groups, whereby *C9orf72* positive cases showed a delayed progression of cerebellar changes, evident by a heightened impact in the later disease stages compared to *C9orf72* negative ones (Chen et al., 2022). In contrast, at an early stage, cerebellar alterations do not differ between the two groups, thus it is possible, as already suggested by other research, that it is the thalamic involvement, and not the cerebellar one, that highlights *C9orf72* carriers in the FTD-ALS spectrum (Schönecker et al., 2018). However, similar to the cerebellar damage on the motor side, which prevents the patient from coordinating actions correctly and reducing the mismatch between prediction and outcome, it is possible that a damage to the cognitive cerebellar regions, together with the neurodegeneration in the prefrontal regions, with which it is closely interconnected, participates in leading to disinhibition and mood and behaviour disorders due to the inability to create correct internal models of reality (i.e. the so-called dysmetria of thought) (Antonioni et al., 2023; Schmahmann, 2023; Watson et al., 2014).

11.3.2 PPAs

PPAs are less frequent than bvFTD and are predominantly characterised by language impairment (Tastevin et al., 2021). As for the cerebellum, while its role in the articulatory aspects of language has for long been known, its involvement in perception and higher-order linguistic functions has been suggested much more recently (Ackermann et al., 2007; Mariën et al., 2014). Compatibly, also in this case, a dichotomy is evident between the anterior cerebellar regions, which are connected to the sensory-motor brain areas and regulate the motor aspects of verbal expression, and the posterior ones, which are more involved in the cognitive and conceptual aspects of language (Buckner et al., 2011; Habas et al., 2009). Importantly, this subdivision is also evident within the deep cerebellar nuclei, highlighting that functional topography is also maintained in the specific efferent pathways emerging from the cerebellum (Mariën et al., 2014). Indeed, the right posterior-lateral areas of lobules VI and VII connect to an extensive network of cortical areas, including the prefrontal, supplementary motor, superior temporal, and posterior parietal areas, limbic regions, and the cingulate and para-hippocampal gyri, which are crucial in mediating different aspects of verbal communication (De Smet et al., 2013). In fact, correlations have been shown between changes at the cerebellar level and alterations in language performance (Grossman et al., 2004). Interestingly, cerebellar damage in PPAs is considerably more focal than that observed in bvFTD and FTD-ALS, probably because the latter are often characterized by genetic alterations, in particular the *C9orf72* expansion, which may account for damage with different distributions, as already discussed (Chen et al., 2020, 2018; Tan et al., 2014). Moreover, a recent study, which unfortunately

did not subdivide patients according to FTD subtype, showed that cerebellar alterations, particularly at the level of crus I and II but also in numerous other regions involved in both articulatory and conceptual aspects of language (e.g. lobules IV, V, VI, VII, VIII, and IX), correlate with performance on phonemic verbal fluency tests, emphasising the crucial role of the cerebellum in language symptoms in this spectrum of disorders (Pizzarotti et al., 2020). Thus, although data on cerebellar involvement in PPAs are much less available than those on bvFTD, most likely due to their lower frequency, interest in the topic is growing and some studies have demonstrated rather specific patterns of cerebellar damage in these subtypes as well.

11.3.2.1 svPPA

svPPA begins around the age of 60 and its clinical course is slower as compared to bvFTD (Hodges et al., 2010). Its pivotal characteristic is a fluent language which is, however, lacking in substantial content, displaying semantic paraphases, circumlocutions, and anomie. This highlights a decline in the ability to grasp the meaning of words, initially affecting less commonly used terms and gradually extending to more frequently used ones. Syntactic and grammatical aspects of language are typically spared (Botha and Josephs, 2019). SvPPA has a very specific neuropathology, which in almost all cases is characterised by TDP type C protein inclusions (Bergeron et al., 2018; Spinelli et al., 2017; Whitwell and Josephs, 2012). In this case, brain MRI shows a pattern of atrophy mainly affecting the anterior temporal lobe bilaterally, usually asymmetrically and mainly on the left side, consistent with the hypometabolism highlighted by FDG-PET (Bejanin et al., 2020). Over time, the neuropathological process also spreads to involve the posterior temporal and inferior frontal lobes (Narayanan and Murray, 2016). Notably, Chen et al. showed a pattern of cerebellar atrophy at crus I and II and lobule VI in svPPA patients (Chen et al., 2019). Moreover, similar to what has already been discussed in bvFTD, also in svPPA a markedly lateralised pattern of atrophy has been demonstrated, with a clear predominance of the right hemisphere over the left, which again may depend on the crossed connections linking the right cerebellum to the left neocortical areas, which are generally much more impaired than the contralateral ones (Bede et al., 2018; Chen et al., 2018; E et al., 2014; McKenna et al., 2021; Omer et al., 2017). However, it is important to note that, depending on the method of analysis employed, different results have been documented, as evidenced by the finding of atrophy limited to the left crus I and II and lobule V in svPPA on morphometric investigations (Nasseroleslami et al., 2019). This underlines the importance of always comparing data provided by different complementary methods to describe the complex nature of cerebellar alterations.

11.3.2.2 nfvPPA

On the other hand, nfvPPA represents the second most common FTD subtype, accounting for about 25% of cases, and shows the most heterogenous clinical phenotype (Botha and Josephs, 2019; Butts et al., 2015). Patients mainly show apraxia of speech and agrammatism and, indeed, as the pathology progresses, their speech becomes progressively laboured, nonfluent, with reduced output and numerous phonemic errors (Harris et al., 2019). In nfvPPA, brain MRI and FDG-PET show an atrophy and hypometabolism pattern, respectively, in the anterior perisylvian region of the dominant hemisphere, specifically in the left frontal operculum and Broca's area (Narayanan and Murray, 2016; Olney et al., 2017). Consistently, regions affected in these FTD subtypes are critical nodes in the language network, which is extremely large, complex, and specialised, with a clear functional predominance of the left hemisphere in most cases (Friederici et al., 2017).

Concerning cerebellar involvement, although the damage is less significant than that of bvFTD, the cerebellar vermis is often involved and, given its relevant connections with limbic regions, this could justify the non-purely linguistic aspects, such as emotional and affective disorders, of these patients (E et al., 2014; McKenna et al., 2021; Rosen et al., 2006). Notably, similar to svPPA patients, the greatest proportion of atrophy is observed in the right cerebellum, consistent with the greatest neuropathological damage in the left brain hemisphere, reasonably because of the cerebrocerebellar connections already discussed (Chen et al., 2018; Gorno-Tempini et al., 2011; Leyton et al., 2011). Importantly, a comparison with healthy controls also identified some differences in the patterns of cerebellar atrophy between PPA subtypes, highlighting in particular a damage in lobules IV, V, and IX in svPPA and in crus I in nfvPPA patients, respectively (Guo et al., 2016).

11.3.3 rtvFTD

RtvFTD is a recently identified FTD subtype and diagnosistic criteria have only recently been proposed (Younes et al., 2022). As the atrophy specifically affects the right temporal cortex, these patients have often been regarded as variants of svPPA, but nowadays their manifestations at onset are considered to be quite specific, such as disinhibition, spatial orientation disturbances, obsessive traits, prosopagnosia (i.e. the inability to recognise people's faces, even familiar ones), and episodic memory impairments (Chan et al., 2009; Snowden et al., 2018). To the best of our knowledge, there is currently no specific evaluation of cerebellar involvement in this FTD subtype. However, as correctly noted by Chen et al., various studies that have investigated cerebellar changes in patients with svPPA have undifferentiated patients who had prominent right or left temporal atrophy, so it is possible that some of the available evidence for svPPA actually relates to this FTD variant (Chen et al., 2019). In fact, despite the recently introduced diagnostic criteria, it is still very complex to unambiguously diagnose rtvFTD, and its cognitive-behavioural alterations, initially different between svPPA and rtvFTD, tend to be superimposable in the more advanced stages of the disease even though the pattern of atrophy follows distinct pathways (Kumfor et al., 2016; Whitwell et al., 2017). However, based on the symptom profile and the partial overlap with the pattern documented at svPPA, it is possible to hypothesise an involvement, once again, of lobule VI and crus I and II, considering their role in spatial orientation, behavioural alterations, and episodic memory (Fliessbach et al., 2007; Schmahmann, 2019; Schutter, 2022). Interestingly, some reports also describe a cerebellar damage in patients affected by prosopagnosia, which is generally ascribed to damage of the fusiform gyrus of the right brain hemisphere, opening up the intriguing possibility that the cerebellum, specifically at the level of the superior vermis and the left posterior cerebellar hemisphere, may also contribute to this peculiar manifestation of symptoms in patients with rtvFTD (Barton et al., 2003; Sorger et al., 2007).

Table 1 summarizes the evidence on the characteristics of cerebellar involvement and the reasonably correlated symptoms in the different FTD subtypes, while Figure 1 shows the most affected cerebellar regions according to the specific FTD subtype.

FTD subtype	Assessment method	Involved cerebellar areas	Clinical findings	Author, year
bvFTD	Neuropathology	Dentate nucleus and inferior olive	Behavioural alterations, aprosodic speech	Ferrer et al., 2015
	Analysis of structural neuroimaging data	Crus I/II, lobule VII	Deficits in memory, language, executive, emotion and visuospatial domains	Gellersen et al., 2017
	Analysis of functional neuroimaging data	Cerebellar gray matter bilaterally; right lobule VI and crus regions	Behavioural and cognitive alterations, lack of insight, altered eating behaviour	Chen et al., 2019
	Brain MRI (structural imaging and DTI)	Lobule V, VI, VIIb, VIIIb	Alterations in verbal working memory, emotion and rhythm processing; irritability, disinhibition	McKenna et al., 2021
	Brain MRI (VBM)	Left cerebellum	Impairments in perspective taking	Dermody et al., 2016
	Structural and functional brain MRI	Crus I/II	Alterations in ToM	Olivito et al., 2022
	Brain MRI (VBM)	Right cerebellum	Alterations in eating behaviour	Ahmed et al., 2016
	Brain MRI (VBM)	Right cerebellum	Social source memory accuracy	Wong et al., 2017
	Brain MRI (VBM)	Lobules V-VII, vermis	Cognitive and neuropsychiatric decline; emotion dysfunction (right cerebellar hemisphere); cerebellar vermis (language dysfunction)	Tan et al., 2014
	Brain MRI (VBM)	Lobules I-IV, V	Alterations in ToM	Synn et al., 2018
	Brain MRI (structural and functional imaging)	Lobule VI	Not specified	Guo et al., 2016
	Brain MRI	Bilateral cerebellar atrophy	Alterations in cognition	Chen et al., 2022
	Brain MRI	Superior-posterior cerebellum	Not specified	Bocchetta et al., 2022
svPPA	Analysis of functional neuroimaging data	Right lobule VI, crus I	Language alterations	Chen et al., 2019
	Brain MRI (VBM)	Left crus I/II, lobule V	Language alterations	Nasseroleslami et al., 2019
	Brain MRI (VBM)	Right cerebellum	Alterations in eating behaviour	Ahmed et al., 2016
	Brain MRI (structural and functional imaging)	Lobules IV, V, IX	Language alterations	Guo et al., 2016
	Brain MRI (structural neuroimaging and DTI)	Crus I/II, lobule V (left-sided)	Language alterations	McKenna et al., 2021
nfvPPA	Analysis of functional neuroimaging data	Right lobule VI, crus I	Language alterations	Chen et al., 2019
	Brain MRI (structural and functional imaging)	Crus I	Language alterations	Guo et al., 2016
	Brain MRI (structural imaging and DTI)	Cerebellar vermis	Language alterations	McKenna et al., 2021
Genetic FTD	Brain MRI (whole-brain VBM)	Lobule VIIb and crus II (*C9orf72* hexanucleotide repeat expansions)	Alteration in modulation of emotions and social behaviours	Spinelli et al., 2021
	Brain MRI	Dentate nucleus and superior–posterior cerebellum (ALS-FTD)	Variable	Bocchetta et al., 2022
	Brain MRI (structural neuroimaging and DTI)	Crus I and lobule VIIa (*C9orf72*	Variable	McKenna et al., 2021

		hexanucleotide repeat expansions); vermis (*MAPT* mutation); lobules I–VI, crus and vermis (ALS-FTD)		

Table 1. Literature evidence on the characteristics of cerebellar involvement and the reasonably correlated symptoms in the different FTD subtypes. Abbreviations: ALS: amyotrophic lateral sclerosis; bvFTD: behavioural variant of FTD; *C9orf72*: chromosome 9 open reading frame 72; DTI: diffusion tensor imaging; FTD: frontotemporal dementia; *MAPT*: microtubule-associated protein tau; MRI: magnetic resonance imaging; nfvPPA: non-fluent variant of PPA; PPA: primary progressive aphasia; ToM: theory of mind; svPPA: semantic variant of PPA; VBM: voxel-based morphometry.

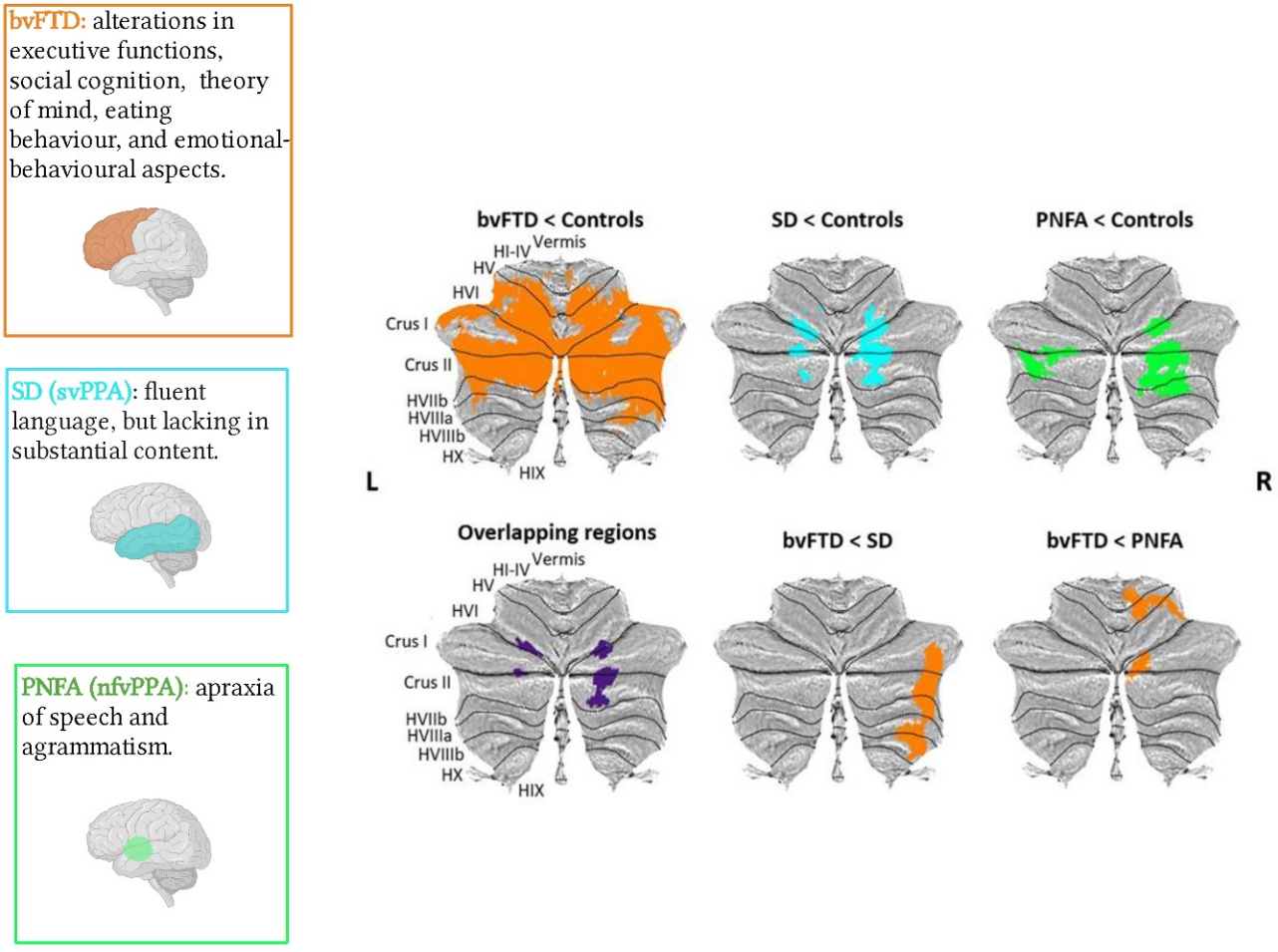


Figure 1. Main cerebellar and cortical areas involved in bvFTD, svPPA (SD), and nfvPPA (PNFA), and their clinical characteristics. Abbreviations: bvFTD: behavioural variant of fronto-temporal dementia; nfvPPA: non-fluent variant of primary progressive aphasia; PNFA: progressive non-fluent aphasia; SD: semantic dementia, svPPA: semantic variant of primary progressive aphasia. Adapted with permission from (Chen et al., 2018), 2018, © 2000-2024 by John Wiley & Sons.

11.4 The neurophysiology of FTD patients

Regarding FTD patients, quantitative electroencephalogram (EEG) data revealed not only that FTD patients are different from AD patients and healthy subjects, but also features that may differentiate specific FTD subtypes or genetic abnormalities have been documented (Lindau et al., 2003; Moretti et al., 2016; Nishida et al., 2011; Passant et al., 2005; Şalçini et al., 2020). These abnormalities have been attributed to damage of specific encephalic regions, particularly frontal and temporal ones, and of specific networks that contribute to the genesis of the peculiar rhythms and oscillations that characterise this type of patients (Chang and Chang, 2023; Lehnertz et al., 2021). Indeed, the dysfunction of cortical networks associated with cognitive functions is, in part, indicated by abnormal cortical neural synchronization mechanisms and impaired neuroplasticity in neural transmission, leading to the generation of pathological resting EEG rhythms (Babiloni et al., 2016). Although the abnormalities in brain rhythms observed in these studies were, consistently, most evident in the fronto-temporal regions, i.e. where the neuropathological damage is significant, various studies have confirmed that the genesis of abnormalities in EEG oscillatory activities depends not only on cortical regions, but also on numerous subcortical structures, among which the thalamus plays a prominent role (Feige et al., 2005; Shine, 2021). Indeed, in the so-called thalamic-cortical resonance, the thalamus and cortical regions interact synchronously to generate and maintain brain waves and the oscillations generated by the thalamus are then transmitted to various brain regions, influencing the frequency and amplitude of EEG rhythms in various physiological and pathological conditions (Steriade, 2000). Importantly, the cerebellum is one of the main modulators of thalamic activity and recent evidence has supported the hypothesis that altered cortico-thalamo-cerebellar network interactions may be associated with cognitive disturbances, for example, in psychiatric patients (Ha et al., 2023; Habas et al., 2019). Although further studies are needed, it seems plausible that the presence of neuropathological alterations in the cerebello-thalamic network, together with cortical damage, contributes to the characteristic EEG alterations and that the specificity of the connections between the neocortex and cerebellum determine, depending on the primary site of alteration, the clinical and neurophysiological peculiarities typical of each FTD subtype (D'Angelo, 2018). Of note, this interpretative framework is also supported by studies conducted in recent years using NIBS techniques. Indeed, importantly, a substantial amount of evidence has documented that FTD patients are characterised by alterations in glutamatergic and GABAergic circuits (i.e. a reduction in both SICI and ICF), whereas they do not manifest the cholinergic alterations typical of AD patients, namely an alteration of the short-latency afferent inhibition (SAI), crucial for sensorimotor integration (Di Lazzaro et al., 2021; Turco et al., 2018). Specifically, SICI and ICF alterations can identify mild cognitive impairment (MCI) patients evolving into FTD (Benussi et al., 2021, 2020a) and, in particular, impairment of ICF is more characteristic of the presymptomatic phase, especially of *GRN* mutation carriers, even fifteen years before clinical onset (Benussi et al., 2016). However, these neurophysiological indices are obtained from the motor areas (in particular by assessing the variation in MEP amplitude) and M1 is not the area most significantly involved in the FTD spectrum (although it can manifest alterations, especially in patients in the FTD-ALS spectrum). Thus, the finding of alterations in neurophysiological indices assessed at this level is thought to indicate a widespread and general alteration of cortical circuitry, probably much more relevant in the areas most affected by the disease (which are, unfortunately, not as easily assessed by commonly used neurophysiological investigation techniques), and/or

of disease-specific neurotransmitters (Antonioni et al., 2023; Gelon et al., 2022; Huey et al., 2006; Rawji et al., 2020). However, it is possible that thalamic damage, whether primitive or secondary to cerebellar lesions that modify its modulation on the thalamus, alter the regulation of interneuronal circuits at the level of the cortex and, consequently, the balance between excitation and inhibition that is believed to be fundamental in justifying the alterations discussed (Davila-Pérez et al., 2019; Habas et al., 2019; Taub et al., 2013). This could explain the presence of alterations in cortical areas (i.e. M1) other than those initially affected and, consequently, the early alteration of these neurophysiological measures. Another intriguing possibility is that the alterations in SICI and ICF circuits at M1 do not depend only on a widespread alteration of cortical interneurons, but reflect an abnormal modulation primarily dependent on cerebellar damage. Consistently, evidence has documented that the cerebellum has important and complex connections, mediated by the thalamic nuclei, with brain motor areas that play a fundamental role in the regulation of motor behaviour and recovery in various pathological conditions (Spampinato et al., 2023, 2020). Crucially, as previously mentioned, cerebellar TBS can induce long-term changes in SICI, LICI, and, to a lesser extent, ICF, showing that cerebellar stimulation has direct consequences on M1 circuitry (Koch et al., 2008). Of note, this evidence has been supported by research combining the TMS stimulus with the study of modifications in EEG activity, which allows the spatial and temporal resolution of the two methods to be combined to demonstrate that cerebellar NIBS induces changes in interconnected regions, particularly motor and parietal, most likely by acting on inhibitory interneuron circuits (Casula et al., 2016). Consistently, evidence from patients with exclusively cerebellar lesions has demonstrated an alteration of M1 GABAergic circuits in particular, confirming that modulation of the cerebellum mainly affects cortical inhibitory interneurons in various pathological contexts (Berardelli et al., 2008; Huynh et al., 2013; Tamburin et al., 2004). Finally, it is interesting to note that FTD patients with *GRN* mutation, i.e. those who show fewer cerebellar alterations (Cash et al., 2018; Mahoney et al., 2012), have early alterations in ICF, i.e. in the glutamatergic neurons (Benussi et al., 2016), and the evidence described above indicates that the cerebellum modulates M1 activity mainly by means of inhibitory interneurons (Casula et al., 2016), allowing us to hypothesise that the alterations observed in patients with *GRN* depend primarily on alterations other than cerebellar damage. Taken together, this evidence makes it possible to hypothesise that the cerebellum plays a fundamental role in the proper functioning of cortical areas and that its alterations may, with or without the mediation of possible alterations also in the thalamic nuclei, justify some of the evidence documented with EEG and NIBS techniques in FTD patients.

11.5 Cerebellar neuromodulation as a potential therapeutic aid for FTD patients

11.5.1 Cerebellar neuromodulation in other neurodegenerative disorders

Given its extensive connections with numerous neocortical areas already examined and its critical role in numerous motor and non-motor functions, it is not surprising that, in recent years, the cerebellum has become a neuromodulatory target in numerous pathological conditions, including, stroke, movement disorders, neuropsychiatric disorders, pain, multiple sclerosis, and neurodegenerative diseases (Benussi et al., 2020b; Billeri and Naro, 2021; Bocci et al., 2018; Koch et al., 2019; Manto et al., 2022; Tramontano et al., 2020). Of note, indeed, studies in other neurodegenerative diseases have confirmed that cerebellar stimulation induces changes in M1 interneuronal circuits and that, crucially, these neurophysiological changes are associated with clinical improvements. For example, in the context of Parkinson's disease (PD), it has been shown that CBI is

absent irrespective of therapy intake, and that the CBI alteration profile allows us to distinguish between PD, dystonia, healthy controls, and patients with suspected PD but normal dopaminergic SPECT investigations (Carrillo et al., 2013; Schirinzi et al., 2016). This suggests that, beyond the basal ganglia circuit, the cerebellum is also affected in PD. Consistently, specific alterations, such as accumulations of alpha-synuclein and morphological alterations of climbing fibres, have been noted in the cerebellum (Zhong et al., 2022). Importantly, Koch et al demonstrated that a cerebellar rTMS protocol in patients affected by advanced PD reduced SICI and increased LICI and that this reorganisation of M1 circuits was significantly associated with a reduction in levodopa-induced dyskinesias (Koch et al., 2009). This is particularly relevant since, although the cerebellum may not be the most prominently affected brain region in PD, evidence suggests its involvement in this spectrum of pathology as well, alongside the significant benefits of its noninvasive modulation. Indeed, reasonably, cerebellar neuromodulation might lead to a twofold benefit: on the one hand, it could indirectly modulate the brain circuits involved in the motor network through the dentate-thalamus-cortical connections, i.e. those eminently affected in these patients (Manto et al., 2022); on the other hand, it could also exert a site-specific effect, modulating the activity of cerebellar cells characterised by neuropathological alterations and promoting the restoration of their physiological activity (Aizenman et al., 1998; Chen et al., 2023; Popa et al., 2010). These insights might potentially apply to other neurodegenerative disorders, characterized by cerebellar involvement, even when the primary sites of damage are cortical regions. Indeed, even in pathologies where this region is not the most compromised, cerebellar stimulation represents a useful strategy to modulate altered circuits that may have fundamental clinical implications. Consistently, cerebellar stimulation also resulted in an improvement of global cognition and several cognitive domains in AD patients in a randomised clinical trial, by enhancing the cerebellar-cortical functional connectivity (Yao et al., 2022). These clinical and instrumental observations, coupled with the evidence of cerebellar-induced modulation of intracortical circuitry and motor cortex excitability, is highly significant, as it provides additional support for the cerebellum's role in neurodegenerative diseases. Coherently, previous work has not only confirmed that mechanisms of cerebellar-cortical plasticity are impaired in AD (Di Lorenzo et al., 2020), but also, importantly, that cerebellar TBS can modulate SAI in AD patients, reasonably by means of mechanisms engaging thalamic nuclei connected to cortical areas involved in sensorimotor integration (Di Lorenzo et al., 2013). Of note, SAI is a specific neurophysiological biomarker of AD patients, as demonstrated by its close correlation with cerebral amyloid burden load and memory performance (Bonnì et al., 2017; Martorana et al., 2012). All these findings in AD paved the way for a neurophysiological differentiation with FTD subjects.

11.5.2 Which role in FTD?

FTD is characterised by an impairment of non-cholinergic intracortical circuits, i.e. mainly those inhibitory circuits mediated by GABA (namely SICI) and, especially in early cases, glutamatergic ones (i.e. ICF) (Benussi et al., 2017). The presence of specific disease biomarkers, reflecting the dysregulation of excitation-inhibition balance within intracortical circuits and liable to neuromodulatory interventions, holds significant implications, particularly in the initial phases of cognitive disorders. Indeed, during this period, when clinical manifestations are not yet entirely overt and the differential diagnosis is more complex, such biomarkers could offer valuable insights for differential diagnosis (Benussi et al., 2017; Gossye et al., 2019). Furthermore, it seems reasonable that promptly detecting these distinctive alterations, particularly in ICF but also in SICI, could enable rapid intervention in these patients during the phase when all treatments appear most efficacious. Indeed,

consistently, research involving patients along the AD continuum has indicated that neuromodulatory interventions yield optimal outcomes when cognitive decline is at its early stages, reasonably because neuropathological damage is still limited, allowing for stronger therapeutic effects (Koch et al., 2022; Wang et al., 2021). Similarly, we suggest that, even in FTD patients, early disease stages might be the most suitable to start therapeutic protocols, including both NIBS and experimental pharmacological treatments. Notably, these therapeutic approaches could also have complementary and synergistic effects, as already shown in different pathological contexts (Perez et al., 2014; Spagnolo et al., 2020; Tao et al., 2024). For instance, while pharmaceutical interventions, such as monoclonal antibodies targeting tau protein accumulations, may primarily address the regions most impacted by neuropathological damage, such as the frontal and/or temporal brain areas, depending on the specific FTD variant, cerebellar NIBS techniques could facilitate the rebalancing of excitation and inhibition remotely, thereby fostering the restoration of normal function in intracortical circuits (Opie et al., 2022; VandeVrede et al., 2020). Moreover, the potential of cerebellar NIBS to modulate intra-cortical circuits might also hold a prognostic value, enabling the identification of patients more likely to respond to therapeutic interventions and, thus, potentially better suited for inclusion in experimental clinical trials. Indeed, in AD patients, modulation of SAI after a single dose of acetylcholinesterase inhibitors has been shown to identify good responders to long-term treatment (Lazzaro et al., 2005). Therefore, it seems reasonable to suggest that early modulation of ICF and SICI could identify FTD patients characterised by a better response to the innovative treatments currently under development in recent years (Benussi et al., 2017; Panza et al., 2020). Finally, crucially, NIBS techniques could emerge as a generally safe and well-tolerated therapeutic option for most patients, contrasting with drugs which, particularly in experimental contexts where safety profiles may not be fully established, could carry notable adverse effects and contraindications (Akhtar et al., 2021; Antal et al., 2017; Lefaucheur et al., 2020). Consistently, several studies have shown that NIBS techniques can be applied to FTD patients with promising results. For instance, excitatory rTMS protocols applied on the dorsolateral prefrontal cortex in bvFTD and PPA patients led to relevant improvement in cognitive performance (Antczak et al., 2018; Finocchiaro et al., 2006; Trebbastoni et al., 2013). Similarly, a transcranial direct current stimulation (tDCS) protocol applied to the same brain region demonstrated positive effects in both bvFTD and in PPA phenotypes, both in patients with a sporadic or genetic disease by improving cognitive performance and slowing disease progression, respectively (Benussi et al., 2020b).

Considering the existing evidence, what advantages might arise from cerebellar neuromodulation? A primary constraint of neuromodulation protocols lies in the significant intra- and inter-individual variability of outcomes, potentially influenced by a complex interplay of factors, including the ongoing activity within the targeted brain regions (Guerra et al., 2020). As previously mentioned, the cerebellum exhibits close connectivity with numerous neocortical regions pivotal in the FTD spectrum and demonstrates considerable neuronal plasticity (Manto et al., 2022). Emerging evidence suggests that cerebellar modulation selectively modulates the pathways of dentate-thalamo-cortical connections, ideally rendering these distant regions more prone to neuromodulatory interventions (Behrangrad et al., 2019; Guerra et al., 2024; Spampinato et al., 2021). Therefore, it is conceivable that cerebellar stimulation could be combined with brain stimulation, exploiting the former's ability to exert control over remote areas and the latter's ability to promote neuroplastic changes on cortical regions that are most impaired. Indeed, importantly, several studies have already shown the possibility of combining cerebellar and cerebral stimulation in the same protocol, leading to significant improvement in motor learning and visuomotor performance (Miyaguchi et al., 2020, 2018). Therefore, we suggest that

cerebellar neuromodulation could be a useful tool to improve NIBS protocols that have already demonstrated efficacy in FTD patients, reducing the variability that currently limits their applicability in clinical settings. However, cerebellar neuromodulation might also provide relevant effects not only when combined with stimulation targeting neocortical areas, but also on its own. Indeed, as previously mentioned, it is well-established that different FTD subtypes are associated not only with morphological alterations in specific brain regions, but also with large-scale network changes, whose functional breakdown leads to clinical symptoms (Pini et al., 2022; Seeley et al., 2009). For instance, bvFTD patients exhibit altered functional connectivity in the SN, whereas PPA patients show anomalies in temporal lobe connectivity (in svPPA) and frontal lobe connectivity (in nfvPPA) (Day et al., 2013; Mandelli et al., 2018; Reyes et al., 2018, 2019). Notably, these alterations are not nonspecific changes due to the neurodegenerative process, but instead characteristic of the FTD spectrum. Indeed, bvFTD patients exhibit reduced SN connectivity and DMN hyper-synchrony, whereas AD patients display an opposite pattern (Zhou et al., 2010). These findings have led to the hypothesis that abnormal network connectivity may represent a specific target for NIBS techniques in neurodegenerative diseases, and interest in their application is growing (Pini et al., 2022). Importantly, the cerebellum shows extensive connections with both fronto-parietal cerebral areas and medial brain regions, such as the cingulate gyrus and temporal cortex (Bostan et al., 2013). This is crucial, as it demonstrates that cerebellar connections might critically influence the activity of large-scale brain networks, particularly the SN, which is primarily anchored to the anterior insula and anterior cingulate, and the DMN, which primarily involves the precuneus/posterior cingulate cortex, lateral parietal cortex, and medial prefrontal cortex (Chiong et al., 2013). Consistently, numerous studies have already proved that cerebellar NIBS can modulate the activity of extensive cerebral networks, affecting both motor and cognitive functions (Behrangrad et al., 2019; Pezzetta et al., 2024). As various studies have already demonstrated that NIBS techniques, both tES and TMS, targeting specific networks in particular pathological contexts can not only promote the restoration of physiological functional connectivity, but also induce clinical improvement, it is reasonable to consider the cerebellum as a pivotal therapeutic target also in the context of FTD (Koch et al., 2022; Pini et al., 2022). Indeed, the cerebellum, a critical modulator of these networks, has significant connections with key hubs of these systems and evidence about the potential of cerebellar NIBS to restore physiology in altered networks is already available in various diseases (Habas et al., 2009; Kawabata et al., 2022; Koch et al., 2019; Manto et al., 2022; Potvin-Desrochers and Paquette, 2021). Thus, based on both neurophysiological and functional connectivity evidence, we suggest that cerebellar NIBS could also be a key therapeutic aid in patients with FTD.

Summarising, various neurodegenerative diseases (e.g. AD) are characterised by alterations in the cerebellar-thalamus-cortical pathway (Yao et al., 2022) and in specific neurophysiological indices (i.e. SAI) that correlate with cognitive performance, and a great deal of evidence suggests that non-invasive cerebellar stimulation, reasonably via the dentate nucleus-thalamus pathway, allows changes in the circuitry related to these neurophysiological measures and, in this way, a clinical improvement (Di Lorenzo et al., 2013). Since FTD patients are characterized by specific alterations in SICI and ICF (Benussi et al., 2017) and previous studies have pointed out that cerebellar rTMS protocols allow long-term modifications of these neurophysiological indices (Koch et al., 2008), we hypothesise that cerebellar NIBS will allow modulation of inhibitory interneuronal circuits and, thus, achieve clinical improvement in FTD patients as well. Consistently, studies on healthy subjects have already shown that the activity of cortical inhibitory circuits correlates with cognitive performance, even in higher-order cognitive tasks (e.g. executive control, attention tasks) and it is possible that their

modulation, through cerebellar NIBS, may also promote cognitive improvement in the FTD spectrum (Bolden et al., 2017; Loomes et al., 2023). Finally, crucially, modulation of SICI and ICF could become a future outcome measure in clinical trials, demonstrating specific changes of the most altered circuits in FTD after treatments. In fact, it is possible to hypothesise that FTD patients characterised by alterations in neurophysiological measures at baseline could show their restoration when therapies are effective, ideally with a dose-response relationship. Although the evidence in the FTD spectrum is still very limited, based on results from studies in other disease contexts we will try to suggest possible promising approaches for cerebellar NIBS in these patients. Indeed, as already mentioned, current studies in the treatment of FTD by means of NIBS techniques have employed cortical areas, particularly fronto-temporal ones, as targets, with generally encouraging results, for example, in language and theory of mind, whereas cerebellar stimulation in these patients, to the best of our knowledge, has not yet yielded evidence in the literature (Benussi et al., 2020b; Cotelli et al., 2018, 2016; Sanches et al., 2021; Teichmann et al., 2016; Tsapkini et al., 2018). However, data from other pathological contexts seem to suggest the potential usefulness of cerebellar NIBS in this context as well. For example, it has already been shown that cerebellar stimulation with both TMS and tES, particularly in the postero-lateral regions and especially on the right cerebellar hemisphere, depending on the specific protocol and the complexity of the task, can modulate performance in verbal working memory and, considering its alterations mainly in patients with bvFTD, it is conceivable that such protocols could represent a useful strategy (Antonioni et al., 2023; Boehringer et al., 2013; Pope and Miall, 2012). Similarly, tDCS on the right postero-lateral cerebellum increases verbal fluency, while postero-lateral cerebellum protocols of continuous TBS (cTBS, i.e. an inhibitory protocol) improves semantic associative priming, potentially very relevant aspects for nfvPPA and svPPA patients, respectively (Allen-Walker et al., 2018; Argyropoulos, 2011; Argyropoulos and Muggleton, 2013; Pope and Miall, 2012; Turkeltaub et al., 2016). Moreover, cerebellar NIBS also seems a promising treatment for emotional and behavioural disorders, which are crucial aspects especially in bvFTD, but also potentially in all FTD subtypes, which at various stages of the disease course often manifest these symptoms (Ciricugno et al., 2024; Manto et al., 2022; van Dun et al., 2022). Summarizing, in Table 2, drawing from evidence in healthy subjects and in other pathological contexts, we suggest which cerebellar neuromodulation techniques and sites might be most suitable depending on the symptoms and, consequently, the particular subtype of FTD.

HS/ patients population; function/symptoms	Cerebellar stimulation site	Cerebellar NIBS protocol	Most suitable FTD subtype(s)	Author, year
HS; working memory, attention and arithmetic capabilities	Right posterolateral	Cathodal tDCS	BvFTD	Pope and Miall, 2012
HS; rate and consistency in a verb-generation task	Right posterolateral	Cathodal tDCS	NfvPPA	
HS; phonemic fluency	Right posterolateral (lobule VII)	Anodal tDCS	NfvPPA	Turkeltaub et al., 2016
HS; lexical associative priming	Right posteromedial	cTBS	SvPPA, bvFTD	Argyropoulos, 2011
HS; semantic associative priming	Right posterolateral (lobule VII)	cTBS	SvPPA, bvFTD	Argyropoulos and Muggleton, 2013
HS; backward associative priming	Left posterolateral	cTBS	SvPPA, bvFTD	Allen-Walker et al., 2018
HS; speed advantage for predictable sentence items	Right posterolateral	Anodal tDCS	NfvPPA, bvFTD	Miall et al., 2016
HS; activation patterns and functional connectivity within whole-brain language networks	Right crus I-II	Anodal tDCS	SvPPA, nfvPPA	D'Mello et al., 2017
Chronic post-stroke aphasia; verb generation	Right posterolateral (lobule VII)	Cathodal tDCS	NfvPPA	Marangolo et al., 2018

Idiopathic late-onset cerebellar atrophy; speech (louder and clearer voice) and naming in dual-task conditions	Right posterolateral	Low-frequency rTMS	NfvPPA, bvFTD	Farzan et al., 2013
Progressive Supranuclear Palsy; dysarthria	Bilateral posterolateral	iTBS	NfvPPA	Brusa et al., 2014
Large bilateral chronic strokes; aphasia and anarthria	Right cerebellum	Anodal tDCS	SvPPA, nfvPPA	Sebastian et al., 2017
Obsessive-compulsive disorder	Right cerebellum	Anodal tDCS	BvFTD, rtvFTD, SvPPA	Bation et al., 2016
HS; recognition of emotional states as expressed by facial expressions	Medial cerebellum	Anodal and cathodal tDCS	BvFTD, rtvFTD, svPPA	Ferrucci et al., 2012
HS; recognition of emotional states as expressed by pictures of the eye region	Vermis (posterior region)	Anodal tDCS	BvFTD, rtvFTD, svPPA	Clausi et al., 2022
HS; emotional facial expressions recognition	Medial cerebellum	High-frequency rTMS	BvFTD, rtvFTD, svPPA	Schutter et al., 2009
HS; ability to infer and predict others' action intentions	Medial cerebellum	Anodal tDCS	BvFTD, rtvFTD, svPPA	Oldrati et al., 2021

Schizophrenia; motivation, social withdrawal, anhedonia	Medial cerebellum	iTBS	BvFTD	Garg et al., 2016
PD; recognition of negative emotional states	Medial cerebellum	Anodal tDCS	BvFTD, rtvFTD, svPPA	Ruggiero et al., 2022

Table 2. Literature evidence on cerebellar NIBS protocols used in healthy subjects or in disease contexts to improve functions or symptoms typically impaired in the FTD spectrum and, therefore, possible applications in the various FTD subtypes. Abbreviations: bvFTD: behavioural variant of FTD; c/iTBS: continuous/intermittent theta burst stimulation; FTD: frontotemporal dementia; HS: Healthy subjects; nfvPPA: non-fluent variant of PPA; NIBS: non-invasive brain stimulation; PD: Parkinson's disease; PPA: primary progressive aphasia; rtvFTD: right lobe variant of FTD; rTMS: repetitive transcranial magnetic stimulation; svPPA: semantic variant of PPA; tDCS: transcranial direct current stimulation.

Based on these results, it is possible to hypothesise which protocols and cerebellar stimulation sites may be most appropriate depending on the particular symptom in various FTD subtypes. Given that certain manifestations encompass multiple subtypes (e.g., alterations in theory of mind), it's plausible that certain NIBS protocols could yield improvements irrespective of the specific disease subtype, a prospect of considerable interest in this domain (Antonioni et al., 2023). Furthermore, as already mentioned, based on evidence from other neurodegenerative diseases, it seems reasonable that the optimal timing for implementing these interventions is in the early stages of the disease, particularly considering the demonstrated efficacy in both sporadic and genetic cases during the preclinical phase (Benussi et al., 2020b; Koch et al., 2022). However, it is important to acknowledge that, while supported by a wealth of neurophysiological and neuroimaging studies highlighting the cerebellum's involvement in different functions impaired in FTD patients, this evidence is still often indirect. Consistently, a great deal of findings arises from studies on healthy individuals or from diseases with markedly different pathophysiology. Hence, while targeting the cerebellum to ameliorate FTD symptoms appears plausible, dedicated research is imperative to yield conclusive evidence in this domain. Indeed, although evidence is growing on the efficacy of cerebellar neuromodulation for the treatment of numerous pathological conditions in addition to those already reviewed, it is important to point out that the precise mechanisms by which these techniques work is currently unknown. This is due both to the extreme inter-subjective variability that currently characterises almost all NIBS protocols, the reasons for which are only partly understood and which, in pathological contexts, are even more complicated, and to the complex circuitry of the cerebellar cortex (D'Angelo, 2018; Guerra et al., 2020). Indeed, it is possible that different NIBS techniques affect both Purkinje cells, stellate and basket interneurons, and granule cells, depending on the intensity and/or frequency of the stimulation used, which results in entrainment phenomena that stimulate mainly particular cell populations (Koch et al., 2008; Manto et al., 2022; Spampinato et al., 2021). Based on the overall effect, i.e. the population of neurons most stimulated, the effects on cerebellar output can potentially be very different and this could justify the sometimes opposite results obtained even with similar stimulation

paradigms (Manto et al., 2022). Thus, reasonably, multiple factors (e.g. stimulation protocol, underlying neuropathology, possible genetic alterations, disease duration) interact with each other in an extremely complex way to determine the effects of neuromodulation protocols. Further studies are therefore needed to demonstrate the efficacy of cerebellar NIBS in the spectrum of FTD as well, but the evidence discussed so far and the pathophysiological mechanisms seem to encourage its use also in this context. However, it is crucial to highlight that this evidence allows us to speculate that cerebellar stimulation might restore the impaired intracortical interneuronal circuits (i.e. SICI and ICF), and that neurophysiological indices could become outcome measures in clinical trials.

11.6 Conclusions

In this review, we have collected evidence demonstrating that the cerebellum is critically involved in FTD spectrum patients and that it may play a crucial role in determining many of the characteristic symptoms of these disorders. Indeed, although it has long been thought to be involved only in motor control, a great deal of recent evidence has shown, through clinical, genetic, neuropathological, and neuroimaging data, that it communicates with numerous cortical areas involved in cognitive tasks and that it is characterised by significant and even early alterations in different FTD subtypes. Moreover, it is possible to hypothesise that the information provided by the NIBS techniques, i.e. the alteration of neurophysiological indices representative of the circuitry of excitatory and inhibitory cortical interneurons, depends on, at least in part, the effects of cerebellar alterations, either directly or as a result of thalamic involvement. Furthermore, the long-term neuroplastic effects provided by specific cerebellar NIBS protocols have demonstrated benefits in numerous pathological conditions whose symptoms are also characteristic of FTD patients, and hopefully future studies could assess their therapeutic potential also in this complex and heterogeneous category of patients. Finally, it can be speculated that cerebellar modulation, as has already been demonstrated in other neurodegenerative disorders, could restore the intracortical circuits (namely SICI and ICF) typically impaired in FTD patients, providing not only clinical improvements but also fundamental outcome measures in clinical trials, which are still very difficult to identify. We hope that this summary will raise awareness of the importance of the cerebellar alterations in FTD spectrum as well as becoming a reference point for both clinical practitioners and researchers working in the field.

11.7 References

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Chapter 12. Cerebellar rhythms and theta-based neuromodulation: mechanisms and clinical frameworks

In this concluding Chapter of the Thesis, preceding the General Discussion and Conclusions, I provide a comprehensive review that expands upon the considerations developed in the previous Chapters concerning the role of the cerebellum within various large-scale brain networks and its oscillatory activity as a neurophysiological correlate of domain-specific functions. This Chapter reviews cerebellar circuitry and the neurobiological foundations of its various rhythmic activities, emphasizing evidence that connects these oscillations to functional outcomes at both neurophysiological and behavioral levels. Such associations are examined not only in healthy individuals but also in pathological conditions, where alterations in cerebellar rhythms—so-called “rhythmopathies”—emerge as hallmarks of disease with significant clinical implications.
The overarching aim is twofold: firstly, to emphasize the central role of cerebellar rhythms as a potential common substrate underlying the functional domains examined in the preceding Chapters; and second, to highlight the therapeutic potential of targeted, rhythm-informed neuromodulatory approaches. Indeed, the ability of non-invasive brain stimulation techniques to selectively target specific cerebellar oscillations may open new possibilities for treating various neurological conditions.

The work presented here is currently under review in Nature Reviews Neuroscience.

12.1 Abstract

Cerebellar rhythms are emerging as causal, frequency-specific mechanisms that support motor, cognitive, and affective function. These oscillations are not epiphenomenal, but dynamically regulated, spatially organized control signals that coordinate prediction, error correction, and internal model updating. As such, they represent biologically grounded targets for network-level diagnostics and therapeutic neuromodulation.

Beyond classical models centered on spike timing and long-term depression, the cerebellum is now understood as a frequency-organized structure. Theta, beta, gamma, and very high-frequency oscillations (VHFOs) arise from distinct microcircuit mechanisms and subserve separable behavioral functions. Theta rhythms, generated by inferior olive–Purkinje synchrony and granular layer pacemaking, provide a temporal scaffold for adaptive timing and sensorimotor prediction. Gamma and VHFOs enable high-fidelity spike coordination during movement execution. These oscillatory modes are differentially engaged across learning, planning, and feedback phases.

We synthesize evidence from invasive recordings, non-invasive electrophysiology, and brain stimulation to propose a frequency–function–modulation framework linking cerebellar rhythms to behavioral roles and interventional strategies. Emphasis is placed on theta-patterned stimulation protocols, including intermittent theta-burst stimulation (iTBS) and theta-frequency transcranial alternating current stimulation (tACS), which engage intrinsic mechanisms of cerebellar plasticity. These approaches have been shown to enhance motor adaptation, improve gait and balance, and suppress tremor, particularly in tasks that require precise timing or feedback-based adjustment.

Disruptions in cerebellar rhythmicity are increasingly implicated in essential tremor, Parkinson's disease, cerebellar ataxias, and neurodegenerative disorders. These conditions are marked by impaired cerebello-cortical coherence, abnormal frequency tuning, and loss of timing-specific modulation. Frequency-matched neuromodulation may restore synchrony within these networks and re-engage cerebellar contributions to adaptive control.

Among current approaches, co-stimulation with tACS and iTBS shows promise by combining oscillatory entrainment with synaptic plasticity induction. Next-generation strategies such as closed-loop stimulation, temporal interference, and anatomically informed current modeling offer new means of selectively engaging cerebellar microcircuits. We conclude by outlining a translational framework that links cerebellar circuit dynamics to state-dependent, biomarker-guided interventions. Theta-patterned stimulation protocols are exceptionally well-positioned to harness the cerebellum's endogenous timing architecture for therapeutic benefit across motor and cognitive domains.

12.2 Introduction

The cerebellum has long been recognized for its critical role in motor coordination, timing, and learning. Yet emerging evidence now places it at the center of a broader, frequency-organized network that extends beyond movement, encompassing cognitive, affective, and predictive control functions. As our understanding of cerebellar contributions has expanded, so has interest in the oscillatory dynamics that govern its interactions, both locally and across distributed cortico-cerebellar loops.

Until recently, cerebellar oscillations remained largely overlooked in humans due to technical challenges in non-invasive measurement. However, converging evidence from invasive recordings, computational models, and advanced electroencephalography and magnetoencephalography (EEG/MEG) source localization has

revealed a frequency-specific landscape of cerebellar rhythms. These oscillations span from low-frequency theta and beta bands, which support timing, prediction, and learning, to gamma and very high-frequency oscillations (VHFOs) that enable millisecond-scale spike timing and rapid sensorimotor coordination. Together, they form a dynamic substrate that supports both rapid error correction and longer-timescale learning.

Among these dynamics, theta-band oscillations (~4–8 Hz) stand out for their deep mechanistic ties to adaptive learning. As first proposed by Masao Ito, cerebellar long-term depression (LTD) depends on the precise timing of converging inputs, particularly climbing fiber and parallel fiber activation—whose coincidence is naturally structured by theta-frequency rhythms. These rhythms arise from electrotonic coupling in the inferior olive (IO) and intrinsic pacemaking in the cerebellar granular layer, providing a temporal scaffold for internal model updating, sensory prediction, and error-based correction.

Building on this foundation, theta-frequency stimulation protocols, including transcranial alternating current stimulation (tACS) and theta-burst transcranial magnetic stimulation (TBS), are increasingly used to engage cerebellar timing and plasticity mechanisms in both experimental and clinical settings. Although both operate in the theta range, they act through distinct mechanisms. TACS entrains ongoing oscillatory activity via weak sinusoidal electric fields, whereas TBS induces synaptic plasticity through high-frequency magnetic bursts nested within a theta rhythm. These complementary approaches offer distinct but converging routes for modulating cerebellar function.

Consistently, early studies using cerebellar tACS have shown frequency- and task-dependent effects on behavior and connectivity. These developments raise key questions about how cerebellar rhythms can be experimentally entrained, whether such modulation leads to measurable behavioral change, and how these insights can be translated into therapeutic interventions.

In this review, we propose a frequency–function–modulation framework to organize and interpret this emerging field. We synthesize evidence from animal models, human EEG/MEG, and cerebellar stimulation studies to examine how oscillations are generated, how they support distinct behavioral functions, and how they can be harnessed to restore function in clinical populations. We argue that cerebellar rhythms form a mechanistic bridge between local circuit dynamics and systems-level behavior, and that frequency-specific stimulation offers a principled approach to neuromodulation in motor and cognitive disorders.

12.3 Cerebellar Oscillations: Mechanisms, Functions, and Relevance for Modulation

Cerebellar circuits exhibit a wide range of intrinsic oscillatory dynamics, spanning low-frequency delta (1-4 Hz) and theta bands to very high-frequency activity. These rhythms are increasingly recognized as essential to cerebellar function. While classical models emphasized spike timing and error-driven plasticity, accumulating in vivo and in vitro evidence shows that cerebellar computation is also shaped by frequency-specific rhythmicity, governed by distinct cellular and network mechanisms (D’Angelo, 2018; De Zeeuw et al., 2008).

At the low-frequency end (1–8 Hz), delta and theta oscillations have been identified in both the IO and cerebellar granular layer. In the IO, these rhythms arise from electrotonic coupling via gap junctions, generating synchronized subthreshold oscillations that regulate the timing of complex spikes in Purkinje cells (Jacobson et al., 2009; Llinás and Yarom, 1986). This rhythmic input supports error correction and predictive modeling during motor adaptation (Ivry, 1996; T. Popa et al., 2013). In the granular layer, Golgi cells act as intrinsic theta-frequency pacemakers, shaping granule cell output through ionic conductances and synaptic integration

(D'Angelo et al., 2001). Together, these mechanisms provide a temporal framework for sensory processing and internal timing.

Beta-band activity (13–30 Hz), while less prominent, emerges during expectancy and attentionally demanding contexts. In the cerebellar cortex, beta power is modulated by task demands (Courtemanche et al., 2002) and may facilitate cortico-cerebellar communication during anticipatory motor control (Schnitzler and Gross, 2005). Furthermore, this cerebellar frequency band appears to play a crucial role in governing temporal processing, as evidenced by recent lesion studies (Andersen and Dalal, 2024; Antonioni et al., 2025a). These findings not only reinforce the cerebellum's well-known role in motor coordination but also highlight its wider involvement in timing functions across both motor and cognitive areas.

Higher-frequency oscillations—including gamma (30–80 Hz), high gamma (80–160 Hz), very fast oscillations (VFO, 80-160 Hz), and VHFOs (160-260 Hz)—are linked to synchronized firing of Purkinje cells and molecular layer interneurons (de Solages et al., 2008; Groth and Sahin, 2015). These fast oscillations enhance the precision and reliability of cerebellar output, particularly during rapid, high-demand motor actions. Time-locked spiking in the deep cerebellar nuclei (DCN) has been directly associated with these patterns (Person and Raman, 2011). Importantly, cerebellar neurons are susceptible to rhythmic entrainment by externally applied weak sinusoidal currents, especially in the high-gamma range, with frequency- and orientation-specific effects (Asan et al., 2020; Asan and Sahin, 2019). This provides physiological support for frequency-targeted neuromodulation.

These frequency-specific motifs offer a mechanistic foundation for neuromodulation. Theta-band activity (~4–8 Hz) likely coordinates IO–Purkinje cell timing during adaptive learning, while gamma rhythms (~45–70 Hz) reflect Purkinje–DCN synchrony critical for precise output. Asan et al. (Asan et al., 2020) further demonstrated that directional alternating current fields can entrain Purkinje cell activity in a frequency- and orientation-specific manner, confirming the cerebellum's intrinsic susceptibility to rhythmic modulation.

The IO–Purkinje–DCN functional complex serves as a central oscillator within cerebellar circuits. Theta-frequency activity from the IO synchronizes complex spikes in Purkinje cells, which in turn can entrain gamma and VHFOs in the DCN (Jacobson et al., 2009; Llinás and Yarom, 1986). This nested organization enables temporal prediction and precise motor coordination (Cheron et al., 2016).

Beyond coordinating spike timing, theta rhythms also regulate synaptic plasticity across cerebellar microcircuits. As originally proposed by Masao Ito, LTD at parallel fiber–Purkinje synapses depends on the timing of converging climbing and parallel fiber inputs—a coincidence naturally structured by theta-phase dynamics (Ito, 2006). Recent in vivo and computational studies suggest that theta-phase alignment enhances the likelihood of plasticity induction not only in Purkinje cells but also in the DCN, where spike-timing–dependent plasticity (STDP) is shaped by the timing of inhibitory inputs (Pugh and Raman, 2006; Suvrathan et al., 2016). Theta activity thus serves as both a temporal organizer and a dynamic regulator of plasticity thresholds.

Clinically, this plasticity framework provides a strong rationale for theta-patterned stimulation protocols, particularly intermittent TBS (iTBS), which emulates endogenous theta-phase–nested firing patterns to induce synaptic change. Consistently, iTBS has demonstrated promising effects on motor adaptation, gait stability, and cerebello-cortical connectivity in both healthy individuals and patient populations (Bonnì et al., 2014; Koch et al., 2019, 2008; Tramontano et al., 2020). While tACS can entrain oscillatory activity in a phase-specific

manner, iTBS more directly engages the mechanisms of activity-dependent plasticity intrinsic to cerebellar circuits.

Cerebellar oscillations are also spatially modular. Distinct cerebellar zones express characteristic frequency signatures, enabling parallel and functionally specialized processing (De Zeeuw et al., 2008). Popa et al. showed that the cerebellum modulates gamma-band coherence between sensory and motor cortices, and that cerebellar inactivation disrupts this long-range synchrony without affecting local cortical rhythms, demonstrating the cerebellum's role in coordinating distributed networks (D. Popa et al., 2013). This spatial–spectral organization of cerebellar rhythms across distinct microcircuits is summarized in Figure 1.

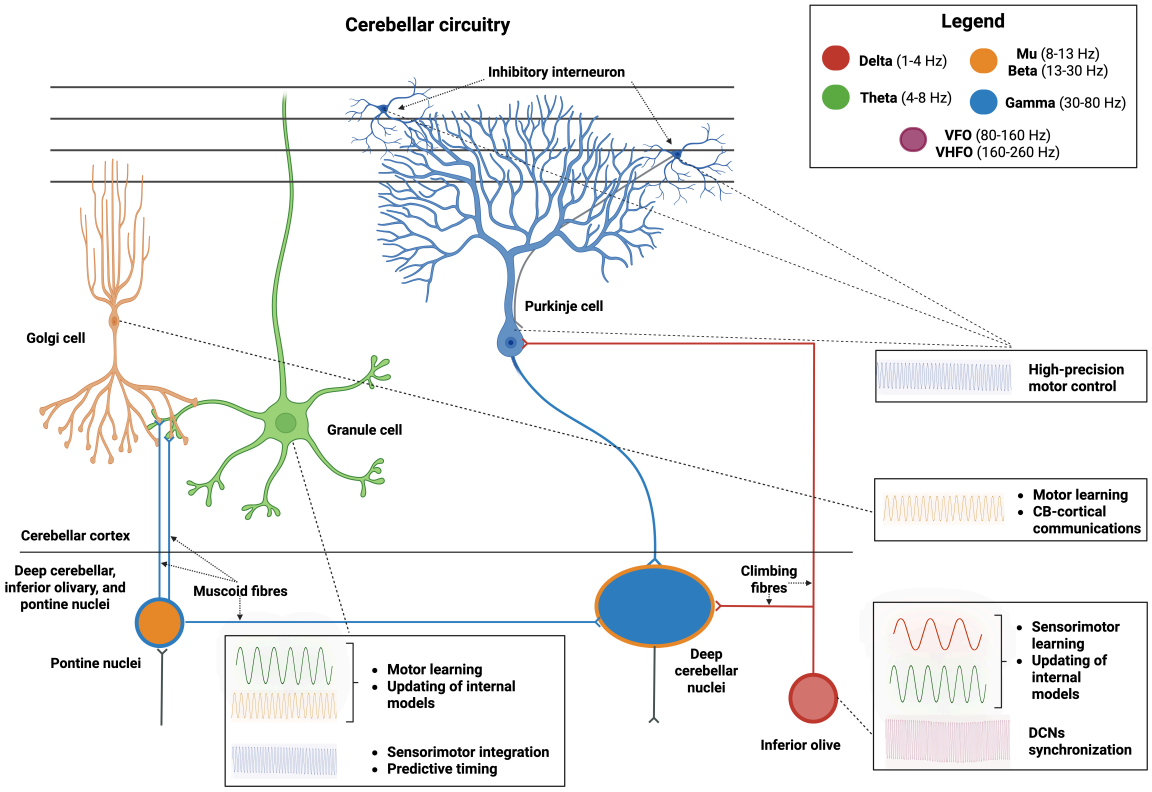


Figure 1. Schematic representation of key cerebellar circuits and their associated frequency bands. Theta oscillations (~4–8 Hz) originate in the inferior olive (IO) and cerebellar granular layer, where gap junction coupling and Golgi cell pacemaker activity, respectively, shape rhythmic output. Gamma (~30–80 Hz), high gamma (80–160 Hz), and very high-frequency oscillations (VHFOs; >160 Hz) emerge from synchronized firing in Purkinje cells, molecular layer interneurons, and deep cerebellar nuclei (DCN), supporting fast sensorimotor coordination. Distinct cerebellar modules exhibit characteristic frequency profiles, reflecting spatial–spectral specialization. These circuit-level rhythms form the basis for frequency-specific cerebellar computation and may serve as targets for entrainment-based plasticity and tailored neuromodulation strategies. Created with BioRender.com.

At the microcircuit level, the granular layer exhibits oscillations in both the 7–25 Hz and >30 Hz bands, shaped by Golgi cells and mossy fiber inputs (D'Angelo and De Zeeuw, 2009). These rhythms help align sensory inputs with motor output and facilitate the prediction of sensory consequences. Intrinsic oscillations can also scale to affect cortico-cerebellar synchrony during task engagement, as demonstrated by D'Angelo and colleagues (Gandolfi et al., 2013).

Although cerebellar rhythms have historically been complicated to detect noninvasively, due to their broadband nature and the tangential orientation of their sources, recent studies confirm their robustness. Dalal et al. synthesized evidence showing that cerebellar oscillations reliably emerge during feedback, adaptation, and learning, despite the limitations of scalp EEG (Dalal et al., 2013).

Disruptions in these rhythms may underlie the impaired timing, adaptation, and coordination observed in essential tremor, stroke, cerebellar ataxia, and increasingly, in non-motor disorders. Recent work has also implicated cerebellar dysfunction in frontotemporal dementia, suggesting that oscillatory disturbances may contribute to cognitive and affective symptoms and that the cerebellum may represent a viable neuromodulatory target in this context (Antonioni et al., 2025b).

Collectively, cerebellar oscillations act as mechanistic bridges between microcircuit dynamics and large-scale behavior. Their frequency specificity, responsiveness to entrainment, and task-dependent modulation make them compelling targets for precision neuromodulation across both motor and cognitive domains.

12.4 Oscillatory Dynamics in the Human Cerebellum: Insights from EEG/MEG and Non-Invasive Stimulation Studies

Detecting cerebellar oscillations in humans presents significant technical challenges due to the cerebellum's deep anatomical location, tightly folded structure, and the tangential orientation of many of its neural generators. These features limit the sensitivity of conventional EEG and MEG, which have historically been considered suboptimal for subcortical signal detection. However, innovations in source modeling and signal processing have increasingly challenged this assumption. Andersen et al. (2020) reviewed growing evidence that both EEG and MEG can reliably detect cerebellar activity, particularly when using high-density recordings and connectivity-based analyses in source space (Andersen et al., 2020). Although cerebellar signals are typically weaker and more spatially diffuse than cortical ones, they are accessible with appropriate methodological strategies.

Empirical studies support this conclusion. Seeber et al. (2019) used high-density EEG and source-space connectivity analyses to show that cerebellar oscillations are detectable during both rest and task states, contributing meaningfully to sensorimotor dynamics (Seeber et al., 2019). Similarly, Lin et al. (2019) demonstrated that optically pumped magnetometers can capture robust cerebellar responses to air-puff stimulation, with precise source localization and evoked components consistent with known cerebellar physiology (Lin et al., 2019). Their wearable MEG system overcomes many limitations of conventional cryogenic MEG arrays, including poor proximity to the posterior fossa and motion restrictions. Complementary modeling studies support these findings. Samuelsson et al. (2020) showed that, under realistic head geometries, both MEG and EEG can detect cerebellar sources using beamforming and anatomically constrained inverse solutions (Samuelsson et al., 2020). Similarly, Sadaghiani et al. (2010) demonstrated that integrating EEG with brain functional magnetic resonance imaging (fMRI)-derived priors improves subcortical source localization, including the cerebellum (Sadaghiani et al., 2010).

Beyond detection, cerebellar rhythms are now recognized as active participants in distributed brain networks. Wibral et al. (2011) applied transfer entropy analysis to MEG data and demonstrated directed information flow from the cerebellum to cortex during auditory working memory, suggesting a functional role in coordinating cognition (Wibral et al., 2011). Resting-state EEG studies have also revealed dynamic cortico-cerebellar connectivity. For instance, Mehrkanoon et al. (2016) found increased coherence in the mu (8–13 Hz) and beta

bands following motor learning, implying reorganization of cerebello-cortical communication during skill acquisition (Mehrkanoon et al., 2016). While spatial resolution remains a limitation, advances in beamforming and source-space analyses have improved the dissociation of cerebellar from cortical signals.

Despite these methodological improvements, non-invasive detection still relies on indirect inference, including inverse modeling, coherence metrics, and source reconstruction. Interpretations must therefore be cautious, particularly regarding contamination from nearby cortical activity. Nonetheless, the cumulative literature affirms the viability of high-resolution cerebellar electrophysiology and its integration into large-scale brain network models.

Building on these insights, non-invasive brain stimulation (tACS, iTBS) has been used to probe and modulate cerebellar rhythms in humans. Increasing evidence suggests that cerebellar excitability, connectivity, and behavior can be shaped in a frequency- and task-specific manner, and that stimulation can induce measurable changes in cerebello-cortical coupling as observed via EEG and MEG. These findings underscore both the mechanistic importance of cerebellar oscillations and their translational relevance for therapeutic intervention.

12.5 Intermittent Theta-Burst Stimulation: Inducing Plasticity Across Cerebello-Cortical Networks

iTBS is a patterned form of repetitive transcranial magnetic stimulation designed to mimic the intrinsic temporal structure of cerebellar theta rhythms. Unlike entrainment-based methods like tACS, iTBS induces lasting excitability changes, tapping into STDP mechanisms such as climbing fiber–parallel fiber coincidence in Purkinje cells. Its 50 Hz bursts, repeated at 5 Hz, align closely with the timing conditions that govern LTD and facilitate error-driven adaptation across cerebellar microcircuits. This mechanism is illustrated in Figure 2, where cerebellar iTBS is shown to engage gamma-sensitive circuit elements, including parallel fiber–Purkinje cell synapses and DCN, leading to LTD and downstream modulation of cerebello-cortical pathways.

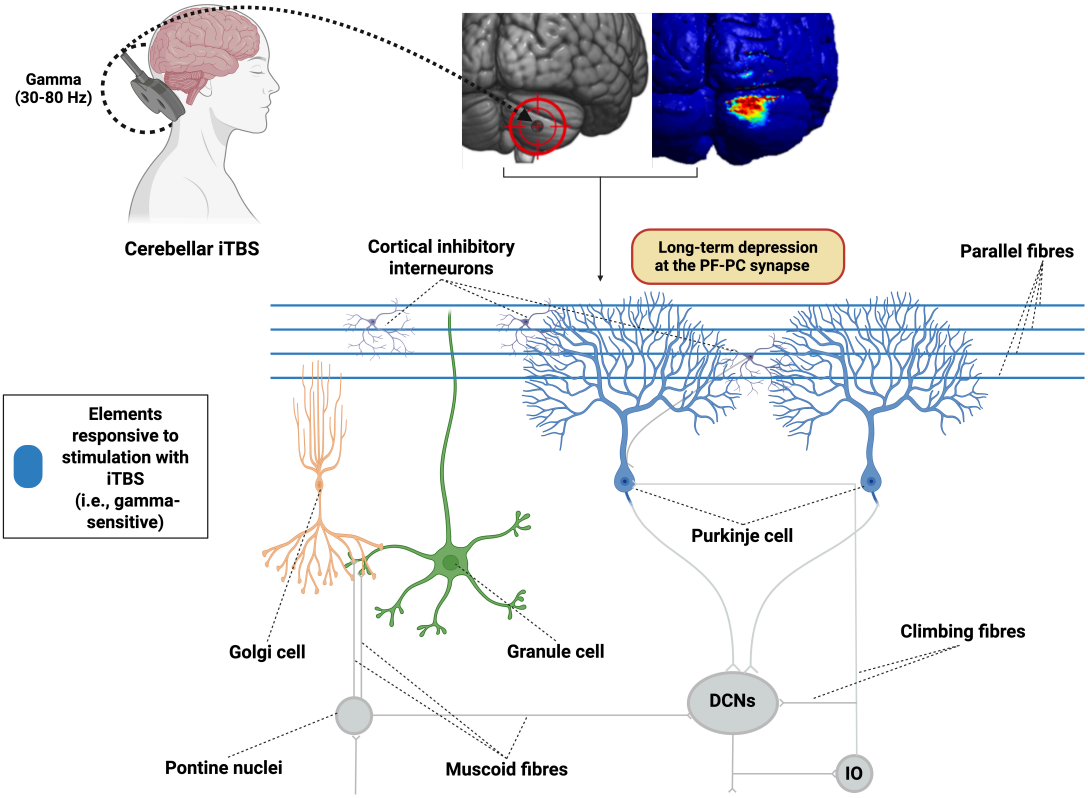


Figure 2. Cerebellar iTBS engages gamma-sensitive elements in the cerebellar cortex and nuclei, including Purkinje cells (PCs) and their parallel fiber (PF) inputs. This stimulation promotes long-term depression (LTD) at the PF–PC synapse through timing-dependent coincidence with climbing fiber activation. The figure highlights circuit components involved in this plasticity pathway, including granule cells, Golgi cells, climbing fibers from the inferior olive (IO), and deep cerebellar nuclei (DCNs). This activity-dependent plasticity is thought to underlie error correction, sensorimotor adaptation, and cerebello-cortical network modulation. Created with BioRender.com.

Several studies confirm the physiological and behavioral effects of cerebellar iTBS. Koch et al. (2008) demonstrated that cerebellar iTBS modulates intracortical circuits in the contralateral motor cortex, increasing motor-evoked potentials and reducing intracortical inhibition, suggesting enhanced cerebello-cortical excitability (Koch et al., 2008). Casula et al. (2016) extended this by showing that iTBS induces bidirectional modulation of both the primary motor area (M1) and posterior parietal cortex activity, altering beta-band oscillatory dynamics and evoked potentials in a temporally specific manner (Casula et al., 2016). These effects appear to depend on cerebellar–thalamic projections that selectively shape cortical excitability through gamma-aminobutyric acid (GABA)ergic pathways.

It should be noted that the modulation induced by iTBS is not confined solely to the neurophysiological domain but also bears significant functional implications. Consistently, in healthy individuals, cerebellar iTBS has been shown to facilitate visuomotor learning. Koch et al. found that iTBS applied to the cerebellum prior to a visuomotor adaptation task significantly accelerated error reduction during early learning and enhanced re-adaptation, indicating a priming of internal model updating (Koch et al., 2020). Concomitant transcranial magnetic stimulation (TMS)–EEG recordings revealed increased cortical excitability and desynchronization of evoked oscillations during task performance, pointing to a reorganization of cerebello-cortical networks that supports faster learning.

Crucally, iTBS has also shown promise in clinical populations. Koch et al. demonstrated improved gait and balance in chronic stroke patients when iTBS was combined with physiotherapy (Koch et al., 2019). Tramontano et al. (2020) replicated similar improvements in multiple sclerosis (Tramontano et al., 2020), while Bonnì et al. (2014) reported reduced ataxia symptoms in patients with cerebellar stroke following iTBS (Bonnì et al., 2014). Di Lorenzo et al. (2020) further demonstrated that cerebellar iTBS failed to induce LTP-like effects in the motor cortex of Alzheimer's disease (AD) patients, indicating impaired cerebello-cortical plasticity and suggesting a potential role for cerebellar stimulation in targeting cognitive dysfunction (Di Lorenzo et al., 2020).

At the network level, iTBS has been shown to modulate intrinsic connectivity. Halko et al. (2014) used connectivity-guided targeting to show that stimulation of Crus I/II increased functional connectivity within the default mode network (DMN), whereas stimulation of vermal lobule VII influenced the dorsal attention network (Halko et al., 2014). These findings demonstrate that cerebellar stimulation can selectively reorganize large-scale cortical networks depending on anatomical target and temporal pattern.

Together, these results position cerebellar iTBS as a physiologically grounded and functionally versatile tool that engages plasticity mechanisms across multiple spatial scales, from synaptic changes in Purkinje circuits to large-scale reorganization of cortical networks.

12.6 Frequency-Specific Modulation of the Human Cerebellum

Among frequency-targeted approaches, tACS offers a means to entrain ongoing neural oscillations and modulate cerebellar circuits in a rhythm-specific manner. tACS delivers weak sinusoidal currents that entrain ongoing neural activity, offering a mechanism to selectively target cerebellar circuits based on their intrinsic frequency dynamics. Across studies, the most robust behavioral and physiological effects occur when stimulation frequencies are matched to the cerebellum's functionally relevant rhythms.

Theta-band stimulation has been most consistently associated with predictive timing and adaptive motor control. Spampinato et al. (2021) showed that 5 Hz cerebellar tACS enhanced cerebellar–brain inhibition (CBI), a TMS-derived index of cerebellar output to motor cortex, without affecting global excitability, indicating selective entrainment of cerebellar output pathways (Spampinato et al., 2021). Similarly, Guerra et al. (2024) found that theta-tACS improved rhythmic motor synchronization (Guerra et al., 2024), supporting the idea that targeting theta rhythms can enhance cerebellar timing functions. This aligns with fMRI evidence from Tzvi et al. (2020), who showed that cerebellar-to-premotor connectivity is modulated during visuomotor adaptation, highlighting the functional role of cerebellar output in motor learning (Tzvi et al., 2020). However, the effects of theta stimulation appear to be task-dependent. Schellen et al. (2024), for example, reported no significant impact of theta-tACS on extinction learning (Schellen et al., 2023), suggesting that its efficacy may be limited to temporally structured, sensorimotor tasks where cerebellar timing functions are most engaged.

Alpha-band stimulation (8–12 Hz) has received comparatively less attention but may contribute to motor learning consolidation. Consistently, Schubert et al. (2021) showed that 10 Hz cerebellar tACS disrupted the typical post-learning decrease in premotor–cerebellar coherence, impairing the consolidation of motor sequences (Schubert et al., 2021). These findings suggest that alpha-range activity may support the reorganization or segregation of motor networks following encoding.

Beta- and gamma-band stimulation (13–80 Hz) has been explored more extensively due to its associations with excitability, precision control, and motor output. Figueroa-Taiba et al. (2024) applied gamma-tACS at 45 and 50 Hz during a visuomotor adaptation task and found that only 45 Hz stimulation accelerated early-phase learning, suggesting a frequency-specific resonance effect likely aligned with the intrinsic rhythmicity of Purkinje cells (Figueroa-Taiba et al., 2024). Herzog et al. (2022) reported that gamma-tACS increased corticospinal excitability and that this effect was modulated by individual differences in baseline cerebello-cortical connectivity (Herzog et al., 2022), highlighting the role of state-dependence in stimulation outcomes.

However, not all findings converge. Giustiniani et al. (2021) observed impaired implicit sequence learning following 50 Hz tACS (Giustiniani et al., 2021), while Wessel et al. (2020) found no benefit of gamma-tACS in a distinct motor learning paradigm (Wessel et al., 2020). These discrepancies may stem from differences in task structure, cognitive load, phase alignment, or the degree to which motor learning depends on cerebellar feedback. Supporting this, Miyaguchi et al. (2019) demonstrated that tACS was significantly more effective when stimulation was temporally aligned with motor output, underscoring the role of timing and phase synchrony in determining efficacy (Miyaguchi et al., 2019). Although beta stimulation has theoretical relevance for motor planning and temporal coordination, its effects remain inconsistent across studies, possibly due to anatomical and state-dependent factors.

Together, these findings support a functional organization of cerebellar oscillations, wherein distinct frequencies contribute to specific aspects of sensorimotor and cognitive processing. The effects of tACS appear to be shaped not only by stimulation frequency but also by temporal alignment, task context, and the individual's baseline network state. These observations underscore the need for a principled and personalized

approach to cerebellar neuromodulation. This emerging framework of frequency–function–modulation is illustrated in Figure 3.

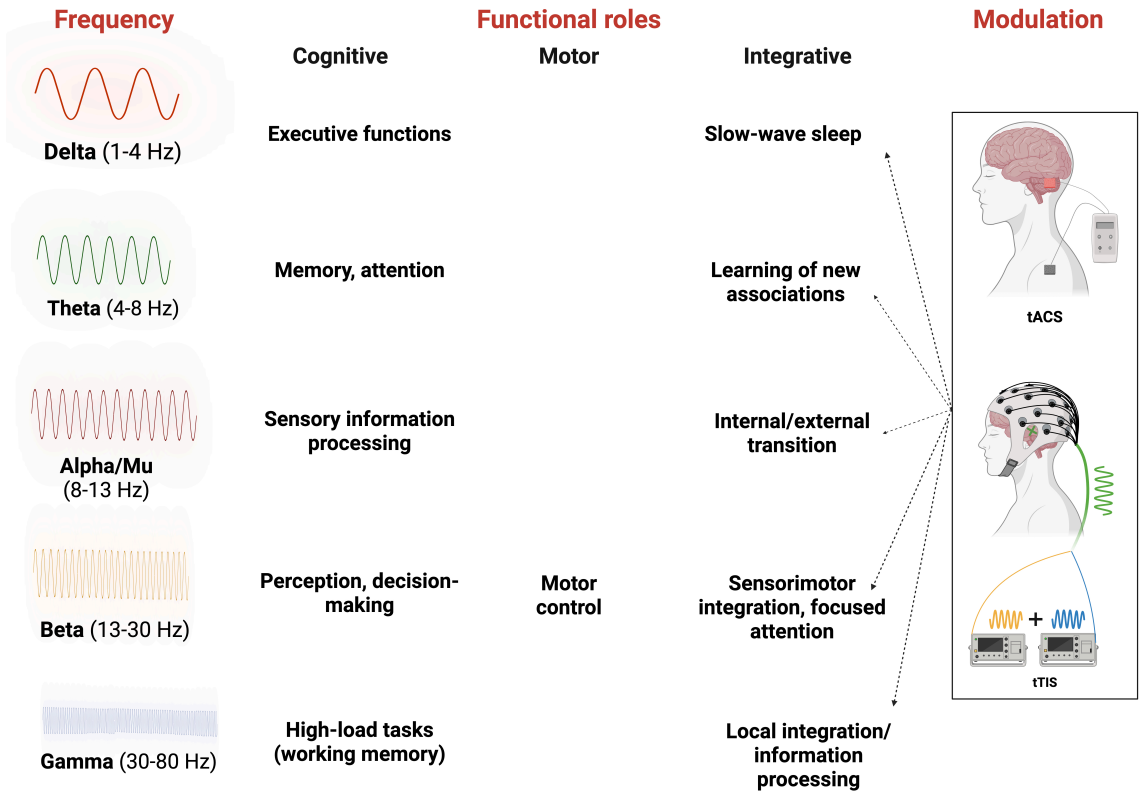


Figure 3. Schematic illustration of the frequency–function–modulation framework summarizing current evidence on cerebellar tACS. Different frequency bands are associated with distinct physiological and behavioral roles: delta (1–4 Hz) supports long-range integration and sleep-related processes; theta (4–8 Hz) is linked to memory, attention, and learning of new associations; beta (13–30 Hz) is classically associated with motor control, anticipation, and sensorimotor integration; and gamma (30–80 Hz) supports local excitability, working memory, and information processing. While beta is traditionally associated with motor control, emerging evidence suggests that cerebellar theta oscillations may also contribute to motor adaptation and plasticity, particularly in response to frequency-tuned neuromodulation. Modulatory outcomes depend not only on frequency selection but also on timing, task engagement, and individual network state. This framework emphasizes the need for personalized, state-aware stimulation protocols targeting cerebellar circuits involved in specific cognitive or motor processes. Created with BioRender.com.

12.7 Oscillatory Pathophysiology: Rhythm Disruption Across Disorders

Cerebellar dysfunction in neurological disease increasingly reflects not only degeneration or hypoactivity, but disruption in the oscillatory timing mechanisms that scaffold prediction, adaptation, and coordination. These “rhythmopathies” are now being identified across disorders, offering potential biomarkers and therapeutic targets (Figure 4).

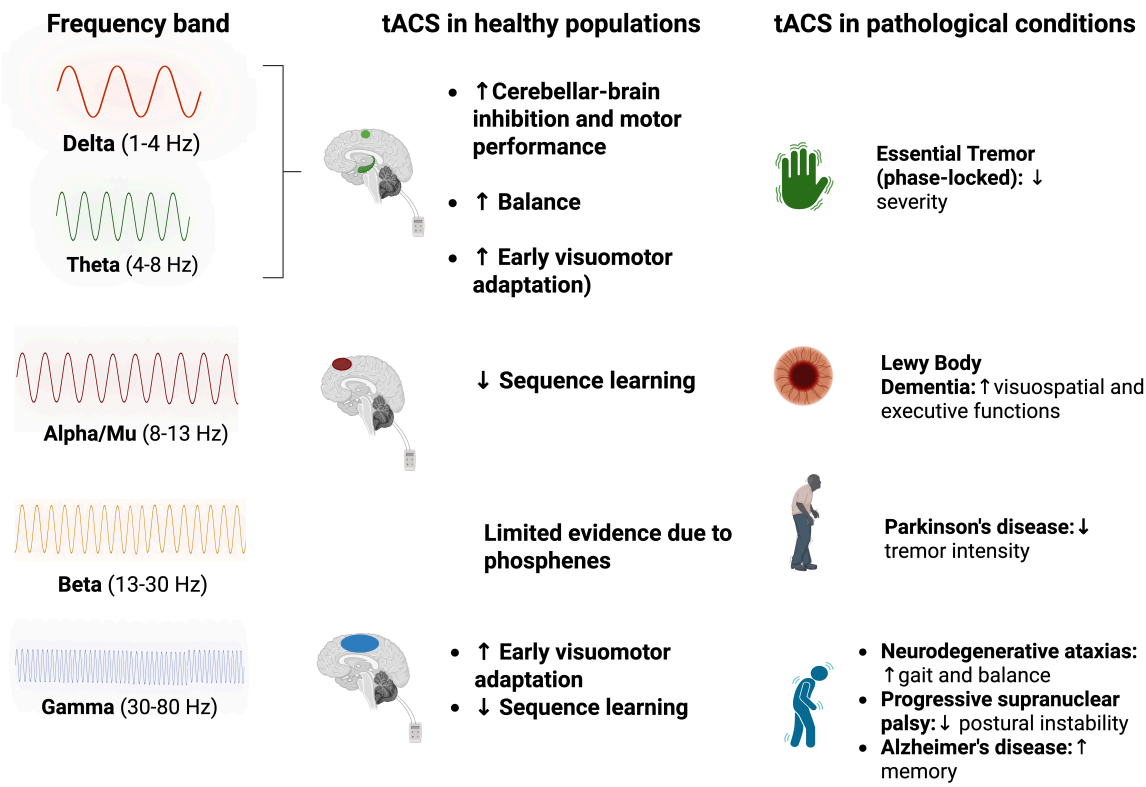


Figure 4. Summary of frequency-specific effects of cerebellar tACS in healthy individuals and neurological populations. Theta (4–8 Hz) stimulation enhances cerebellar–brain inhibition, improves balance, and facilitates early sensorimotor adaptation in healthy subjects, and reduces tremor severity in essential tremor when phase-locked to symptom onset. Gamma tACS has shown benefits for visuomotor adaptation and sequence learning, as well as improvements in gait, balance, and memory in disorders such as ataxia, progressive supranuclear palsy, and Alzheimer's disease. Alpha/mu and delta stimulation have shown preliminary or domain-specific effects. Beta-frequency tACS remains limited due to visual side effects (phosphenes), though beta-band dysfunction is implicated in Parkinsonian tremor. These findings highlight frequency-tuned tACS as a promising approach for circuit-specific neuromodulation in both motor and cognitive disorders. Created with BioRender.com.

In essential tremor (ET), aberrant cerebello–thalamo–cortical coupling results in excessive rhythmic activity in the theta and low-beta bands (~4–12 Hz). Steina et al. (2025) used simultaneous MEG and thalamic local field potential (LFP) recordings in ET patients with deep brain stimulation (DBS) implants and showed that tremor presence was associated with increased coherence between the ventral intermediate nucleus (Vim), cerebellum, and contralateral sensorimotor cortex at tremor frequency (Steina et al., 2025). Scherer et al. (2022) provided compelling cross-species evidence from both rodents and humans showing that tremor frequency is encoded by coherent population activity along the olivocerebellar axis. In ET patients with DBS implants, simultaneous recordings revealed that neuronal bursts in the ventral intermediate nucleus were phase-locked to tremor-band LFPs, with LFPs preceding spikes, suggesting entrainment by cerebellar output (Scherer et al., 2022). Notably, Schreglmann et al. (2021) showed that anti-phase theta-tACS applied over the cerebellum suppressed tremor amplitude in real time, with greater efficacy under closed-loop stimulation, highlighting the therapeutic relevance of frequency-specific entrainment (Schreglmann et al., 2021).

In Parkinson's disease (PD), excessive beta-band synchrony is a hallmark of motor impairment. Again, Scherer et al. (2022) showed that this synchrony originates from intrinsic bursting patterns in the subthalamic nucleus, linking single-neuron dynamics to the aggregate beta oscillations recorded with LFPs. While the cerebellum's role in PD remains less defined, emerging evidence suggests abnormal cerebellar oscillations contribute to both motor and non-motor symptoms (Scherer et al., 2022). For example, Bosch et al. (2022) reported elevated low-frequency activity in the cerebellum during rest and movement, while other studies have associated altered cerebello–cortical coherence with gait disturbances and postural instability (Bosch et al., 2022). Additional studies from the same group (Bosch et al., 2021b, 2021a) have linked altered cerebellar–cortical coherence to key motor symptoms such as freezing of gait and postural instability. These changes may reflect maladaptive or compensatory mechanisms in response to basal ganglia pathology, particularly in early stages.

In degenerative ataxias and progressive supranuclear palsy (PSP), cerebellar rhythms often exhibit desynchronization, poor phase-locking, or a loss of task-related modulation—disruptions that directly impair motor learning and coordination. In spinocerebellar ataxia type 3 (SCA3), Aoh et al. (2019) reported reduced beta-band event-related synchronization during movement, indicating deficient cortical activation linked to cerebellar dysfunction (Aoh et al., 2019). Similarly, Visani et al. (2019) observed impaired alpha and beta event-related desynchronization/synchronization responses in patients with spinocerebellar ataxia, consistent with abnormal cerebellar modulation of the motor cortex (Visani et al., 2019). Variability across genotypes may reflect distinct oscillatory signatures tied to differences in Purkinje cell vulnerability and network architecture.

In PSP, Shima et al. (2023) reported improvements in postural stability following backward gait training paired with cerebellar tACS (Shima et al., 2023). Though CBI was not directly measured, the clinical gains point to enhanced cerebellar timing and entrainment. Beyond ataxias, Song et al. (2020) conducted a sham-controlled repetitive TMS (rTMS)–EEG trial in patients with multiple system atrophy, demonstrating that cerebellar TBS improved balance and increased frontal connectivity, emphasizing the cerebellum's influence on broader motor system plasticity (Song et al., 2020).

Taken together, these findings support the view that cerebellar rhythmopathies are not merely downstream effects but core features of neurological dysfunction. Identifying frequency-specific disruptions may enable better patient stratification, for instance, distinguishing tremor-dominant from gait-dominant phenotypes, and inform precision stimulation strategies. As dynamic, state-dependent, and therapeutically accessible features of neural circuits, cerebellar oscillations provide a powerful framework for translational biomarker development and neuromodulation.

12.8 Individual Variability, Methodological Complexity, and Task Sensitivity

Despite increasing evidence for the functional impact of cerebellar tACS, considerable variability in outcomes has been observed across individuals and studies. This heterogeneity likely reflects a complex interplay of anatomical, physiological, and methodological factors that influence how effectively externally applied currents can entrain intrinsic cerebellar rhythms.

Brain state and network configuration emerge as key determinants of responsiveness. Herzog et al. (2022) reported that individuals with stronger baseline cerebello–cortical connectivity exhibited greater increases in corticospinal excitability following gamma-band tACS, suggesting that intrinsic network properties may gate stimulation effects (Herzog et al., 2022). Similarly, Miyaguchi et al. (2019) demonstrated that gamma-tACS

enhanced motor performance only when stimulation was temporally aligned with task execution, emphasizing the importance of phase synchrony between stimulation and ongoing neural dynamics (Miyaguchi et al., 2019). Study design can also significantly affect the detection and interpretation of tACS outcomes. Figueroa-Taiba et al. (2024) found that gamma-tACS accelerated early visuomotor adaptation in between-subjects designs but not in within-subject crossover trials. This discrepancy may stem from carryover effects, learning saturation, or interactions between task novelty and stimulation timing(30). These findings highlight the need to align design structure, frequency selection, and task demands when assessing stimulation efficacy.

Individual anatomical variability further complicates response prediction. Factors such as cerebellar foliation, cerebrospinal fluid distribution, and skull thickness can significantly influence current spread, focality, and effective field strength. Moreover, stimulation parameters, including electrode montage, intensity, frequency, and phase, interact nonlinearly with each participant's neurophysiological state, adding another layer of complexity (Guerra et al., 2020).

Emerging evidence increasingly supports the view that personalized tACS protocols are essential for optimizing neuromodulatory effects (Venugopal et al., 2025). Customizing stimulation based on pre-intervention EEG, MRI-derived current modeling, or individual connectivity profiles may enhance both spatial precision and functional outcomes. As summarized in Figure 5, stimulation responses are shaped by a hierarchy of interacting factors, including neuroanatomy, task context, and dynamic brain states.

The next frontier in this domain may lie in closed-loop cerebellar tACS, where stimulation is dynamically timed to the real-time phase or amplitude of intrinsic oscillations. Such adaptive systems could provide temporally precise, state-contingent neuromodulation, maximizing engagement with functional rhythms while minimizing off-target effects.

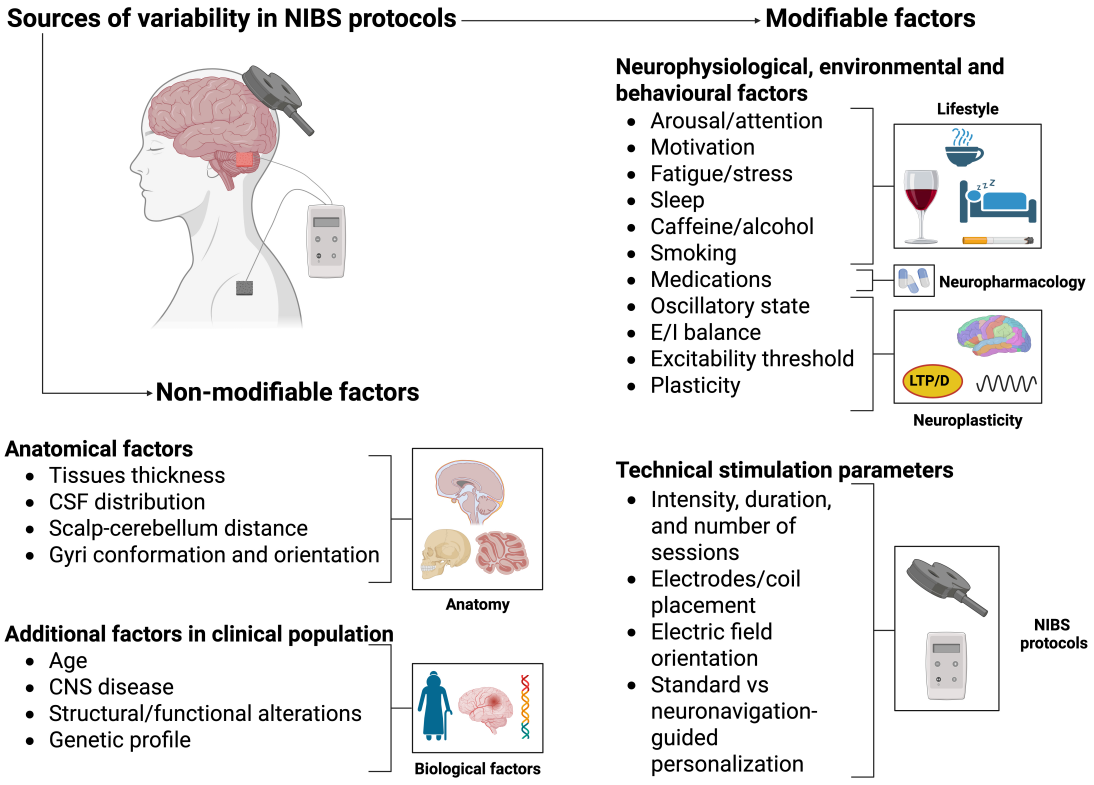


Figure 5. Overview of the interacting anatomical, physiological, technical, and contextual factors influencing cerebellar tACS outcomes. Response variability arises from modifiable elements such as brain state, cognitive

engagement, and behavioral context, as well as non-modifiable factors including skull thickness, cerebellar folding, and cerebrospinal fluid (CSF) distribution. Technical parameters (e.g., frequency, montage, timing) further interact with these intrinsic characteristics. Personalization strategies, including pre-stimulation EEG, MRI-based current flow modeling, and individualized connectivity profiles, may help optimize stimulation precision and efficacy. Closed-loop tACS, which adapts stimulation in real time to ongoing neural oscillations, represents a next-generation approach to targeted cerebellar neuromodulation and may reduce interindividual variability. Created with BioRender.com.

12.9 Behavioral and Clinical Extensions

The functional relevance of cerebellar tACS now extends beyond experimental paradigms, with growing evidence of behavioral and clinical benefit across both motor and non-motor domains. For instance, Sveva et al. (2025) found that cerebellar theta-tACS improved gait and postural stability during dynamic balance tasks in young adults, whereas gamma stimulation had no measurable effect (Sveva et al., 2025). Earlier studies by Mehta et al. (2014) and Khatoun et al. (2018) demonstrated that cerebellar tACS can entrain physiological tremor and modulate subthreshold rhythmic activity, thereby reinforcing the frequency-specific nature of cerebellar entrainment (Khatoun et al., 2018; Mehta et al., 2014).

In clinical populations, ET has emerged as a prominent target. Schreglmann et al. (2021) demonstrated that phase-locked theta-tACS over the cerebellum disrupted pathological synchrony within the cerebello–thalamo–cortical loop and transiently reduced tremor amplitude (Schreglmann et al., 2021). Olivier et al. (2023) observed similar improvements even in patients receiving thalamic DBS, suggesting that residual cerebellar oscillations remain therapeutically accessible (Olivier et al., 2023). Extending these findings, Nieuwhof et al. (2022) applied phase-specific transcranial electrical stimulation in dystonic tremor syndromes and found comparable tremor suppression, supporting cross-disorder applicability of cerebellar phase-specific stimulation in tremor syndromes (Nieuwhof et al., 2022).

In degenerative ataxias, repeated cerebellar tACS has shown promise in restoring motor coordination. Libri et al. (2024) reported that both tACS and transcranial direct current stimulation (tDCS) improved gait parameters and cerebellar–brain inhibition, with slightly larger improvements observed in the tDCS group (Libri et al., 2024). A parallel randomized trial by Liu et al. (2023) is currently investigating whether tACS can improve motor and non-motor symptoms, including fatigue and oculomotor control, using wearable sensors and electrophysiological readouts (Liu et al., 2022). In a single-case study, Shima et al. (2023) combined gait-synchronized tACS with backward walking in a patient with PSP, resulting in sustained postural improvements, which suggests synergistic effects between task-specific learning and oscillatory entrainment (Shima et al., 2023).

Beyond motor domains, cerebellar rhythms appear to modulate cognitive and affective functions. Theta and beta-frequency stimulation have been shown to influence episodic memory and semantic prediction (Dave et al., 2020), while cerebellar excitability correlates with perceived physical fatigue (Azzollini and Hayward, 2023; Casamento-Moran et al., 2023). Fronto-cerebellar alpha activity has been linked to attentional transitions and tonic alertness (Cebolla et al., 2016; Sadaghiani et al., 2010; Schutter and Honk, 2006). Other work has implicated the cerebellum in supporting spatial working memory via prefrontal–hippocampal theta interactions (Liu et al., 2022) and in ramping activity that underlies internal timing mechanisms (Parker, 2016).

Finally, closed-loop and adaptive stimulation systems are beginning to incorporate cerebellar targets. Stieve et al. (2023) demonstrated that cerebellar-directed stimulation could suppress seizures in a closed-loop framework (Stieve et al., 2023), while Wathen et al. (2018) used cerebellar neuromodulation to support post-stroke motor rehabilitation (Wathen et al., 2018). Together, these emerging approaches exemplify the broader potential of cerebellar tACS as a scalable, rhythm-tuned neuromodulatory platform for circuit-level intervention across diverse clinical populations.

12.10 Translational Perspectives and Future Directions

Cerebellar oscillations offer a mechanistic bridge from microcircuit physiology to system-level dysfunction and intervention. At the cellular level, Pan et al. (2020) demonstrated that tremor-related oscillations in essential tremor arise from disrupted synaptic pruning at climbing fiber–Purkinje cell synapses (Pan et al., 2020). These findings reinforce the view that developmental or degenerative alterations in intrinsic rhythm generators can directly shape pathological network dynamics. Far from being mere byproducts of dysfunction, cerebellar oscillations may represent core organizing principles of cerebellar computation.

Human studies build on this foundation, showing that cerebellar tACS can modulate motor output (e.g., motor-evoked potentials), plasticity (via CBI), and behavior (e.g., enhanced motor adaptation), often in a frequency-specific and state-dependent manner. Computational modeling supports the feasibility of cerebellar stimulation in modulating tremor-related activity in PD (Rahimi et al., 2023), providing a biophysically plausible translational pathway.

Translating these findings into clinical practice will require addressing three core challenges. First, personalization: protocols should be tailored to individual oscillatory profiles, anatomical constraints, functional connectivity, and task demands. Second, integration: combining tACS with concurrent neuroimaging, adaptive behavioral paradigms, or pharmacological priming may enhance both the precision and durability of effects. Third, scalability: future trials must move beyond early-phase feasibility to stratified, larger-scale studies that identify clinical effect sizes, optimal dosing schedules, and predictors of response.

If these hurdles are met, cerebellar tACS and related interventions could become powerful adjuncts to standard neurorehabilitation, enhancing gait, coordination, cognitive flexibility, and learning in stroke, ataxia, and movement disorders. The combination of frequency precision and behavioral specificity positions cerebellar oscillations as both a theoretical construct and an actionable therapeutic target.

As neuromodulation strategies become increasingly mechanistically informed, new approaches are targeting specific circuit properties and frequency profiles. One promising and testable direction involves co-stimulation with tACS and iTBS. In cortical studies, gamma-tACS combined with iTBS enhances and prolongs plasticity, likely through entrainment of gamma oscillations and modulation of GABA-A–ergic interneurons (Guerra et al., 2018; Maiella et al., 2022). Given the cerebellum's frequency sensitivity, inhibitory architecture, and dependence on spike-timing–dependent learning, this combined approach could synergistically engage resonant plasticity mechanisms. While untested in cerebellar targets, co-stimulation may allow rhythmic entrainment via tACS to align ongoing network activity with bursts of plasticity-inducing input from iTBS, providing a novel, physiologically grounded method for enhancing cerebellar learning.

12.10.1 Theta-Frequency Neuromodulation: Mechanism and Application

Among implicated frequency bands, theta activity is uniquely positioned at the intersection of physiology, plasticity, and intervention. Originating from electrotonic coupling in the IO and rhythmic pacing in the cerebellar granular layer, theta oscillations structure timing, error correction, and adaptive control. As originally detailed by Ito and confirmed experimentally, theta-phase alignment facilitates LTD at parallel fiber–Purkinje cell synapses and STDP in the DCN (Ito, 2006; Pugh and Raman, 2006; Suvrathan et al., 2016). These rhythms organize windows for coincidence detection and dynamically regulate plasticity thresholds across the circuit.

Clinically, theta-frequency neuromodulation has shown encouraging results. Cerebellar tACS at 5 Hz enhances CBI without increasing global excitability, suggesting selective entrainment of cerebellar output (Guerra et al., 2024; Spampinato et al., 2021). Other studies report improved rhythmic motor synchronization, postural control, and sensorimotor learning following theta-tACS, especially in temporally structured tasks (Guerra et al., 2024; Paparella et al., 2025; Schreglmann et al., 2021). These findings reinforce theta as a translationally relevant frequency for disorders marked by impaired timing and adaptation, such as essential tremor, cerebellar ataxia, dystonia, and early-stage PD.

Recent evidence also implicates theta-band oscillations in the pathophysiology of cervical dystonia. Leodori et al. (2025) reported increased theta-band intermuscular coherence between affected neck muscles in patients with torticollis, which was modulated by sensory tricks and correlated with symptom severity (Leodori et al., 2025). Interestingly, directionality analyses suggested a subcortical origin, consistent with a brainstem or cerebellar drive. These findings reinforce the translational significance of theta rhythms in motor timing disorders and support the rationale for using frequency-specific stimulation approaches in dystonia.

In parallel, iTBS provides another method for engaging cerebellar plasticity mechanisms (Koch et al., 2008). Mimicking naturally occurring theta-nested high-frequency bursts, iTBS has been used successfully in motor cortex plasticity studies and is now being extended to cerebellar targets(Koch, 2010). Early trials in cerebellar stroke and hemiparesis show improvements in gait, balance, spasticity, and cerebellar–frontal connectivity (Bonnì et al., 2014; Koch et al., 2019). These results suggest that theta-timed input can reshape cerebellar–cortical communication in functionally meaningful ways.

Importantly, tACS and TBS may offer complementary effects (Guerra et al., 2018; Maiella et al., 2022). While tACS promotes large-scale entrainment and phase synchrony, TBS induces LTP-like plasticity through patterned bursts. Together, they could be used in co-stimulation paradigms, where tACS primes cerebellar circuits through rhythmic phase alignment, enhancing the plasticity-inducing potential of iTBS. Recent findings from our group support this approach: in both healthy adults and individuals with stroke, a cerebellar theta-tACS–iTBS protocol enhanced M1 plasticity and improved motor performance (Spampinato et al., n.d.). Though untested in cerebellar contexts, this hypothesis represents a compelling direction for future intervention trials. This mechanistic concept is illustrated in Figure 6, comparing the localized and oscillation-dependent effects of iTBS alone with the broader, theta-entrained activation achieved through combined tACS–iTBS stimulation.

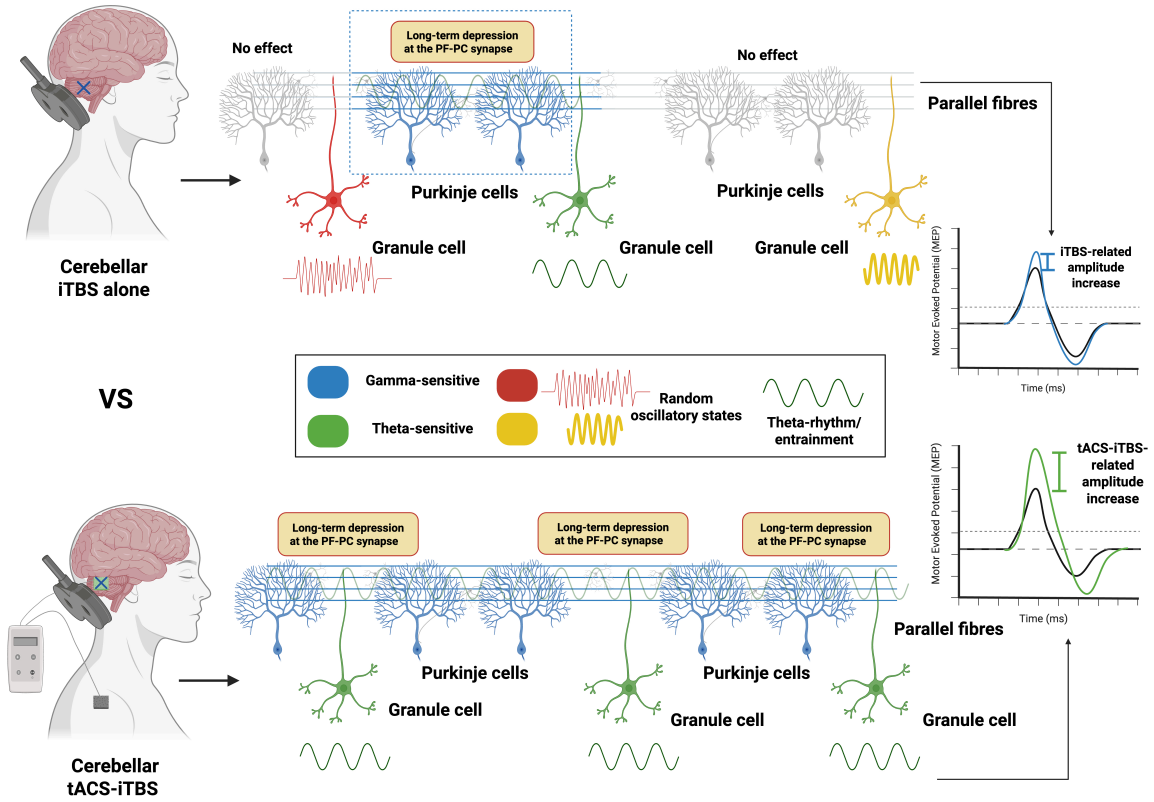


Figure 6. Synergistic effects of cerebellar co-stimulation with tACS and iTBS. The top panel illustrates the limited spatial engagement of cerebellar circuits following iTBS alone. Only granule cells and Purkinje cells tuned to gamma-frequency activity undergo LTD at the parallel fiber–Purkinje cell synapse, while neighboring circuits in non-entrained oscillatory states remain unaffected. In contrast, the lower panel shows that simultaneous application of theta-frequency tACS expands the number of granule–Purkinje units engaged in LTD by synchronizing their oscillatory activity, thereby enhancing the effectiveness of iTBS. This co-stimulation paradigm amplifies network-level entrainment and plasticity, resulting in stronger downstream motor-evoked potentials, as shown in the example traces on the right. This framework supports the hypothesis that the combination of tACS–iTBS can enhance cerebellar output and functional reorganization more robustly than either modality alone. Created with BioRender.com.

Beyond motor function, theta coherence extends into cognitive and affective regulation. Evidence supports cerebellar–prefrontal theta coupling during working memory, semantic prediction, and interval timing, suggesting broader applications of theta-frequency neuromodulation across motor and non-motor domains (Guell et al., 2018; Lesage et al., 2012).

Complementing these approaches, temporal interference stimulation (tTIS) offers a more speculative but potentially transformative method for targeting deep cerebellar structures. By using two high-frequency carrier waves with slightly offset frequencies, tTIS generates a low-frequency envelope at depth, potentially reaching the dentate nucleus or inferior olive (Vassiliadis et al., 2024). Though still in early stages, tTIS may eventually provide anatomically precise modulation of cerebellar generators involved in theta and VHFO rhythms.

In parallel, closed-loop stimulation is gaining traction. Rather than delivering static waveforms, these systems adapt stimulation in real time based on neural activity (e.g., EEG phase, LFPs, or behavioral events). While

explored in cortical and basal ganglia contexts, cerebellar-specific closed-loop applications for adaptive learning and seizure suppression are now emerging (Stieve et al., 2023).

Finally, longitudinal studies are expanding the scope of cerebellar stimulation. Multisession tACS has shown promise in enhancing working memory (Grover et al., 2022), hippocampal perfusion (Sprugnoli et al., 2021), and cognitive function in AD and dementia-related syndromes (Bréchet et al., 2021; Uehara et al., 2025). These trials emphasize the need to evaluate both acute and sustained effects.

Together, co-stimulation paradigms, closed-loop frameworks, and deeper targeting methods like tTIS represent a next-generation neuromodulatory toolkit. As device precision increases and multimodal integration becomes standard, these approaches offer increasingly refined means to engage the cerebellum's frequency-tuned architecture for clinical gain.

12.11 Conclusion and Outlook

Cerebellar oscillations are increasingly understood as foundational to the brain's timing, prediction, and adaptive control systems. Decades of animal and computational research have mapped how distinct frequency bands emerge from cerebellar microcircuits to support precise temporal coordination. These principles have now been extended to human neuroscience, with EEG, MEG, and source modeling revealing robust, frequency-specific cerebellar dynamics in both health and disease.

Building on this foundation, non-invasive neuromodulation, particularly tACS and iTBS, offers new tools to causally engage cerebellar rhythms. In both healthy individuals and clinical populations, frequency-specific stimulation has demonstrated promising effects on plasticity, motor learning, and network rebalancing across conditions such as essential tremor, PD, and cerebellar ataxia.

However, substantial variability in individual outcomes highlights the need for a more personalized, state-dependent approach. Adaptive stimulation protocols that account for anatomical variability, real-time brain state, and behavioral context are likely to enhance both efficacy and reliability. Emerging frameworks such as closed-loop control, multimodal integration, and biomarker-guided targeting are poised to advance the precision and impact of cerebellar neuromodulation.

By linking cerebellar circuit dynamics to functional behavior, frequency-specific stimulation strategies, such as tACS, tTIS, and co-stimulation paradigms (e.g., tACS–iTBS), offer a biologically grounded platform for next-generation neurorehabilitation. The challenge now lies in consolidating mechanistic insights, refining predictive models, and rigorously testing synergistic protocols to move from conceptual feasibility toward scalable clinical translation.

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Chapter 13. General Discussion and Conclusions

In this Thesis, I presented the results of both experimental studies and literature reviews aimed at deepening our understanding of the neurophysiological underpinnings of deficits observed in specific pathological conditions. The primary objective was to enhance our understanding of these dysfunctions and, more critically, to investigate their potential application in forecasting or improving functional recovery in neurological disorders.

The main focus of this work is stroke, a highly common condition worldwide, which—despite significant research efforts and clinical progress—remains a leading cause of long-term disability (Feigin et al., 2020, 2017; Lucas-Noll et al., 2023). Indeed, it is estimated that over half of stroke survivors experience long-term disabilities, most of which involve impairments in the upper limbs (Go et al., 2014). Given the crucial role of hand function in maintaining independence and daily life autonomy, this emphasizes an urgent need not only to refine and enhance existing rehabilitative strategies—especially since recovery is often incomplete and unsatisfactory in many cases—but also to develop objective tools to predict individual recovery profiles (Hatem et al., 2016; Stinear, 2017; Zhang et al., 2023). Consistently, considering the limited healthcare resources, it is essential to identify which patients are most likely to benefit from specific neurorehabilitation interventions and, ideally, to tailor treatment approaches based on the strategies that have the greatest potential to maximize recovery in each individual (Qiu et al., 2025; Reddy, 2025). Currently, many of these decisions still depend heavily on clinical judgment, which, although valuable, naturally involves some subjectivity and is influenced by the clinician's experience, expectations, and background knowledge—factors that can introduce significant bias in both patient selection and treatment planning (Cormier et al., 2016; Stinear, 2017; Stinear et al., 2019). This underscores the growing need to identify reliable biomarkers that can provide an objective and accurate prognosis and, ideally, track the effectiveness and progression of rehabilitation strategies over time. In this context, neurophysiological and kinematic methods—some of which are discussed in this Thesis, especially those related to electroencephalography (EEG) and kinematic analysis—show strong potential for improving precision rehabilitation and supporting more informed clinical decisions.

Specifically, the first two experimental studies presented in this Thesis describe neurophysiological biomarkers that may be crucial for characterizing motor recovery in stroke patients from the first weeks after the event. In particular, these kinematic and resting-state EEG parameters are associated with motor performance as early as the fourth week after a stroke. These findings suggest that early reorganization of brain regions, especially in the motor network, plays a key role in shaping recovery outcomes. Furthermore, they emphasize how interhemispheric dynamics contribute to compensatory mechanisms, where the brain tries to reorganize and support impaired functions. This reorganization is directly reflected in both movement quality and motor function, as assessed through widely used clinical rating scales.

These findings support a growing body of evidence suggesting that the neurophysiological reorganization of brain networks and motor patterns can serve as an objective measure of patient functional status from the early stages after a stroke (Milani et al., 2022; Motolese et al., 2023; Saes et al., 2022). Importantly, such biomarkers can help identify patients who are most likely to benefit from early rehabilitation interventions, especially during the critical window of increased neuroplasticity in the subacute phase, when properly timed therapy may work synergistically with spontaneous recovery processes (Kwakkel et al., 2023; Stinear et al., 2019).

Notably, a biomarker reflecting the activity of the Mirror Neuron System (MNS)—a network active during both the execution and observation of actions within a person's motor repertoire—may provide important data about the long-term recovery profile after stroke (Bonini et al., 2022). Specifically, our findings suggest that when the lesioned hemisphere shows early signs of reorganization and does not rely heavily on the contralesional hemisphere, especially in frontal regions—which are typically associated with increased cognitive load (Antonenko et al., 2010)—patients experience better long-term recovery trajectories. This emphasizes the key role of the MNS in post-stroke functional recovery and aligns with existing literature supporting its involvement in therapeutic approaches like action observation therapy and motor imagery training (Carvalho et al., 2013; Garrison et al., 2010; Mao et al., 2020; Yang et al., 2018).

Furthermore, Interestingly, our results may also indicate a potentially insightful dissociation between different neural dynamics, although further studies with larger samples and longer follow-up periods are needed to confirm this hypothesis. Indeed, the first study showed that during resting state, patients with better functional status exhibited greater compensatory activity in the contralesional hemisphere. In contrast, the second study found that during action observation (i.e., when the MNS is engaged), activity in the ipsilesional hemisphere predicted better long-term outcomes. Taken together, these insights suggest that multiple neural networks are involved in motor recovery, both during resting-state conditions and during task-related activity that engages motor and cognitive domains, such as the MNS. These findings are supported by a growing body of emerging evidence exploring oscillatory brain dynamics, which has revealed the involvement of multiple cerebral networks in the post-stroke reorganization process. Specifically, activities in the beta and alpha frequency bands, as well as dynamics within frontal, parietal, and temporo-parietal regions, have been consistently associated with motor recovery mechanisms (Cassidy et al., 2021). Furthermore, measures of functional and effective connectivity within the motor network highlight the complexity of neural interactions involved in recovery (Pirovano et al., 2022). These data suggest that a region-specific oscillatory contribution—both at rest and during task-related activation—plays a critical role in shaping the trajectory of post-stroke recovery (Milani et al., 2022; Zhang et al., 2018). The dynamic interaction between these networks reasonably supports compensatory processes and guides functional recovery over time, emphasizing the need to better understand and, when possible, regulate these oscillatory patterns to improve neurorehabilitation outcomes. Importantly, gaining a better understanding of how these networks interact could be vital for developing methods to target and modulate them, creating new opportunities to enhance recovery in stroke patients (Bonanno et al., 2025; Di Pino et al., 2014).

In this context, it is crucial to recognize that the cerebellum may play a pivotal role not only in deepening our understanding of the deficits observed in these patients but also in optimizing functional outcomes. Consistently, as extensively discussed in the previous Chapters, the cerebellum is intricately connected through multiple loops to a wide range of cortico-subcortical networks (Habas, 2023, 2021). Importantly, by modulating thalamic activity and regulating the excitation/inhibition balance at the cortical level, it can influence the activity—and thus the computations—of numerous brain regions involved in various tasks (Habas et al., 2019; Shine et al., 2023; Zhang et al., 2025). Furthermore, the cerebellum receives a wide array of information streams, including sensory inputs from the periphery, signals from regions that encode the current state of the body, and motor commands aimed at modulating the organism–environment interaction (e.g., corollary discharge) (Manzoni, 2005; Person, 2019; Rondi-Reig et al., 2014). This unique integration establishes the cerebellum as a central hub for building and refining internal models of sensorimotor relationships (Caligiore

et al., 2017; Spampinato and Celnik, 2021; Streng et al., 2022). It is plausible that the effectiveness of rehabilitation depends, at least in part, on the ability to establish new internal models adapted to the post-injury state of the nervous system (Kiper et al., 2016; Maier et al., 2019; Reinkensmeyer et al., 2016). The cerebellum's reciprocal interactions with other structures critically involved in motor learning—such as the basal ganglia (likely mediating reinforcement- or reward-based learning via dopaminergic mechanisms) and frontal-parietal networks (essential for the cognitive strategies underlying learning and for optimizing movement features according to sensory context)—further underscore its role as a key driver of functional gains following neurorehabilitation (Caligiore et al., 2017; Schmahmann, 2019; Yuan and Fathi, 2022).

Importantly, beyond its traditional sensorimotor functions, the cerebellum has also been demonstrated—both through existing literature and our data collected from acute stroke patients—to critically modulate the brain's capacity for processing temporal information (Breska and Ivry, 2018; Coelho et al., 2022; Ivry et al., 2002; Koch et al., 2009). Temporal processing is essential for adapting our interactions with the environment and is involved across nearly all functional systems of the central nervous system (CNS) (Akyürek, 2025; Finnerty et al., 2015; Golesorkhi et al., 2021; Mauk and Buonomano, 2004). This complex process likely contributes to enhancing our internal models, offering a novel approach to understand and use our understanding of post-stroke neurorehabilitation mechanisms. Notably, based on findings presented in the previous Chapter, temporal performance can be assessed using simple, bedside computer-based tasks, making them highly accessible for clinical use. Such assessments could be integrated into the evaluation of acute stroke patients, not only to characterize deficits but also to monitor the correlation of these abilities with rehabilitation responsiveness and their long-term progression regarding treatment effectiveness. Since effective motor performance relies heavily on the correct use of temporal information during interactions with the environment, it is reasonable to expect that improvements in processing deficits of temporal information during the acute stroke phases will occur alongside (likely with correlations to be explored through dedicated models) the recovery of motor function.

Similarly, we have explored a simple computer-based tool to evaluate motor learning ability in patients with chronic stroke, well beyond the early phase of increased neuroplasticity after stroke (Kwakkel et al., 2023). Findings suggest that, even at this stage, patients can still improve, and strategies like interlimb transfer (i.e., training the unaffected limb to boost the affected one) may provide promising options for intervention (Kuipers et al., 2025; Yadav and Mutha, 2020). Furthermore, numerous cognitive-affective factors influence these learning mechanisms (Maier et al., 2019; Subramanian et al., 2015); however, their contribution is often overlooked in research evaluating motor learning within these populations. Given its vital role in both motor learning and cognitive-affective functions performed by cortical areas, these results indicate the cerebellum's diverse influence across different domains and stages after stroke. They also emphasize the importance of utilizing cerebellar physiology to improve and tailor rehabilitation strategies. These considerations are especially relevant because optimizing motor learning strategies during the chronic phase of stroke is the main approach to improve functionality and, consequently, the quality of life in the affected individuals' population (Kal et al., 2016; Maier et al., 2019; Sampaio-Baptista et al., 2018). Having tools capable of assessing both the integrity and the functional capacity of learning mechanisms— even longitudinally, to track treatment-related effects— would be considered invaluable. These tools would enable more precise identification of patients who are most likely to benefit from recommended interventions and allow for a better understanding of potentially relevant contributing factors. This supports the improvement of rehabilitation strategies for this

often underrepresented patient group in current practice. However, importantly, because of their large numbers, one of the main challenges in rehabilitating patients with chronic stroke is the substantial resources required for their care, including intensive staffing and material needs that are often unavailable, especially in certain healthcare settings (Howard-Wilsher et al., 2016; Lucas-Noll et al., 2023; Rajsic et al., 2019). This reality highlights the urgent need to develop strategies that can maximize functional gains in these populations while being safe, efficient with time, and cost-effective, with benefits that can be objectively measured to determine the level of improvement.

Given its pivotal role in modulating complex brain networks, it is perhaps not surprising that non-invasive brain stimulation (NIBS) techniques are increasingly targeting the cerebellum for various purposes (Manto et al., 2022). Consistently, evidence has shown that cerebellar NIBS can significantly improve functional outcomes in stroke patients, including critical areas like walking and balance, which are vital for regaining independence (Hong-yu et al., 2023; Koch et al., 2019; Liu et al., 2024; Ntakou et al., 2022; Wessel and Hummel, 2018). Importantly, by also using protocols designed to investigate cerebellar–brain interactions, a substantial body of evidence, discussed in the previous Chapters of this thesis, has emerged demonstrating the cerebellum's capacity to critically modulate the activity of the MNS (Henschke and Pakan, 2023). This constitutes a significant finding, as previously discussed, given that the MNS is now regarded as a fundamental component in neurorehabilitation interventions that employ action observation and motor imagery of movements compromised by pathology within the patient's motor system repertoire (Carvalho et al., 2013; Garrison et al., 2010; Mao et al., 2020; Sale and Franceschini, 2012; Yang et al., 2018). This evidence suggests that NIBS could be used to modulate the MNS circuits influenced by the cerebellum, making them more receptive and thereby enhancing the therapeutic effects of these interventions.

However, several major limitations prevent the widespread clinical use of NIBS. Besides the costs of equipment and the need for highly trained staff to manage protocols, one of the most substantial challenges is the large variability in stimulation results, both within individuals and across different people (Guerra et al., 2020). While part of this variability—still only partially understood—can be attributed to anatomical factors (e.g., skull thickness, cortical folding variability), genetic predispositions, environmental conditions (e.g., time of day, prior night's sleep quality, nature of the interaction with the experimenter), and substance use (e.g., alcohol consumption, smoking), a significant portion is linked to the current brain activity at the time of stimulation (Davis, 2021; Guerra et al., 2020; López-Alonso et al., 2014; Miniussi and Bortoletto, 2025; Sasaki et al., 2021; Ziemann and Siebner, 2015). Indeed, this baseline oscillatory and network state can significantly affect both the magnitude and the direction (excitatory or inhibitory) of the stimulation's effects (Bergmann, 2018; Janssens and Sack, 2021). In pathological conditions, where neural network function is impaired, this variability may be greatly increased, raising the likelihood of inconsistent responses to the same intervention (Assenza et al., 2017; Krawinkel et al., 2015). Another major limitation is the brief duration of NIBS effects, which often last only a few minutes, significantly limiting their clinical usefulness (Goldsworthy et al., 2015). Furthermore, much of the current research has mainly focused on neurophysiological rather than behavioral outcomes, which makes it challenging to identify and characterize the functional benefits of the examined protocols (Desarkar et al., 2024).

In the study described, an effort was made to address the previously mentioned limitations by targeting the cerebellum, specifically by controlling the ongoing oscillatory state through entrainment of theta rhythms—a frequency likely representing the intrinsic resonance rhythm of granule cells (D'Angelo, 2022; D'Angelo et al.,

2001). Notably, its modulation at the cerebellar level has already been critically linked to regulating activity within regions of the brain motor network (Guerra et al., 2024; Paparella et al., 2025; Spampinato et al., 2021; Tzvi et al., 2022). Reasonably, by recruiting and synchronizing a greater number of these cells, it was possible to maximize the long-term neuroplastic effects in cortical motor regions that have previously been demonstrated following the cerebellar application of intermittent theta burst stimulation (iTBS) protocols (Koch et al., 2008). The reason is that rhythm-specific stimulation can modulate a larger population of Purkinje cells, which are the only output neurons of the cerebellar cortex, thereby increasing the responsiveness of the cerebellar–thalamus–cortical pathways to plasticity-inducing effects provided by iTBS. Notably, these effects were observed not only at a neurophysiological level—with a sustained increase in corticospinal excitability and modulation of intracortical inhibitory interneuronal circuitry, specifically in short latency intracortical inhibition (i.e., SICI)—but also in behavioral performance in healthy young adults. Consistently and remarkably, improvements were observed in a very simple and quick motor task like the Nine Hole Peg Test, where ceiling-level performance would otherwise be expected in this population (Wang et al., 2015). Importantly, similar effects were also observed in chronic stroke patients—long after the early post-injury period of increased neuroplasticity—both in neurophysiological measures and task performance, following just one stimulation session that lasted only a few minutes. This suggests that the neural pathways connecting the cerebellum and cortex, which are instrumental in inducing plasticity in the motor areas, can also be modulated within this timeframe of stroke through the application of NIBS protocols. Of note, these findings support numerous previous studies showing that cerebellar reserve and the structural and functional connectivity between the cerebellum and the motor network significantly shape motor recovery after stroke (Delion et al., 2025; Gopalakrishnan et al., 2022; Guder et al., 2023; Hanakawa et al., 2023; Yoo et al., 2025). They also support the well-established role of the cerebellum in reorganizing motor networks after cerebrovascular injury, especially by aiding the learning of new motor strategies to maximize the use of remaining effectors (Celnik, 2015; Luft et al., 2008, 2005). Notably, the cerebellum is often unaffected in many cerebral strokes, making it a promising therapeutic target to improve motor function in these complex patient populations through a treatment that is safe, well-tolerated, and efficient (Koch et al., 2019; Luft et al., 2008, 2005; Macdonell et al., 1987).

Furthermore, a key point, as outlined in the previous Chapters, is that while the cerebellum was traditionally seen as mainly involved in motor functions, it is now widely recognized to also play a vital role in a wide range of cognitive and emotional processes. These include executive functions, language, memory, and higher-order, multidomain abilities such as theory of mind and creativity (Adamaszek et al., 2022, 2017; De Smet et al., 2013; Marvel and Desmond, 2010; Olivito et al., 2023; Rondi-Reig et al., 2022; Schmahmann, 2019). Therefore, it is plausible that its influence on processes such as learning, interaction with the MNS, and the use of temporal information can be generalized well beyond strictly motor contexts. By leveraging its exceptional computational properties, the cerebellum can optimize internal models not only in the sensorimotor domain but also to minimize the mismatch between predicted and actual outcomes in diverse fields such as planning, social behavior, and the mental simulation of both past and future actions—likely supported by its interactions with the hippocampus and basal ganglia (Bastian, 2006; Caligiore et al., 2017; Leggio and Molinari, 2015; Popa and Ebner, 2019; Rondi-Reig et al., 2022). Consistently, in frontotemporal dementia—a highly complex neurodegenerative disorder primarily affecting the frontal and temporal brain networks—there is substantial evidence supporting significant cerebellar involvement in its pathophysiology and clinical

manifestations (Bocchetta et al., 2016; Chen et al., 2020, 2018; Schmahmann, 2016). In this context, as extensively discussed in the dedicated Chapter, the cerebellum could serve as a key neuromodulatory target: not only through its influence on interconnected cortical regions, which have historically been regarded as the primary sites of neuropathology, to alleviate symptoms linked to dysfunction in frontal and temporal brain regions, but also as a way to prevent or slow cerebellar damage from the early stages of the disease—an area that warrants significant future research (Cash et al., 2018).

Taken together, these points imply that modulating the cerebellum's computational dynamics could be a useful therapeutic and rehabilitative tool across various clinical scenarios. Indeed, given the cerebellum's wide range of oscillatory rhythms—many of which are only partially understood in terms of their functional roles—it would be possible to selectively target specific aspects of its computations based on the clinical outcome of interest (Courtemanche et al., 2013; De Zeeuw et al., 2008). For instance, as already mentioned, cerebellar theta rhythms appear most closely associated with sensory-motor cortical network interactions, whereas different oscillations seem involved in various brain functions (Dave et al., 2020; De Vico Fallani et al., 2017; Giustiniani et al., 2021; Guerra et al., 2024; McAfee et al., 2022; Popa et al., 2013; Schubert et al., 2021; Spampinato et al., 2021). This suggests a reasonable hypothesis that alternative, less-explored rhythms could play crucial roles across various functions, thus enabling significant applications in many pathological contexts, as discussed in the previous Chapter. These interventions can potentially be effective not only by directly influencing specific rhythms but also by decreasing the variability of the ongoing oscillatory state, thus increasing the susceptibility to interventions that utilize plasticity mechanisms through specific connectivity pathways, as demonstrated in the previous study.

Collectively, the studies within this thesis demonstrate that neurophysiological approaches possess considerable potential for patient profiling. These methods are particularly valuable in predicting recovery trajectories, characterizing deficits and performance at various timepoints following injury, and, most critically, in enhancing therapeutic and rehabilitative strategies across diverse patient populations. Such advancements are essential given the urgency of implementing effective interventions aimed at improving functional outcomes and, ultimately, the quality of life. In this context, the cerebellum is poised to become a key therapeutic target, and it is hoped that the results presented here will accelerate the adoption of more effective strategies for both neurological care and neurorehabilitation.

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Chapter 14. List of additional works conducted during the PhD Program not included in the Thesis

1. **Antonioni A**, Della Valle A, Leitner C, Raho EM, Cesnik E, Capone JG, Flacco ME, Casoni F, Proserpio P, Ferini-Strambi L, et al. Sleep Disturbances Across Dementias and Cognitive Decline: Study Protocol for a Systematic Review and Network Meta-Analysis of Polysomnographic Findings. Journal of Clinical Medicine. 2025; 14(20):7437. https://doi.org/10.3390/jcm14207437

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