

Accepted Manuscript

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Authors: Giacomo Koch, Alessandro Martorana, Carlo Caltagirone



PII: S0304-3940(19)30458-6
DOI: <https://doi.org/10.1016/j.neulet.2019.134355>
Article Number: 134355

Reference: NSL 134355

To appear in: *Neuroscience Letters*

Received date: 3 February 2019
Revised date: 22 June 2019
Accepted date: 26 June 2019

Please cite this article as: Koch G, Martorana A, Caltagirone C, Transcranial magnetic stimulation: emerging biomarkers and novel therapeutics in Alzheimer's disease, *Neuroscience Letters* (2019), <https://doi.org/10.1016/j.neulet.2019.134355>

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Transcranial magnetic stimulation: emerging biomarkers and novel therapeutics in Alzheimer's disease

Giacomo Koch^{1,2}, Alessandro Martorana² and Carlo Caltagirone¹

1. Non Invasive Brain Stimulation Unit/Department of Behavioral and Clinical Neurology, Santa Lucia Foundation IRCCS, Rome, Italy.

2. Department of Neuroscience, Tor Vergata Policlinic, Rome, Italy.

Correspondence to: Prof. Giacomo Koch, MD PhD, Non Invasive Brain Stimulation Unit, Neurologia Clinica e Comportamentale, IRCCS Fondazione S. Lucia, Via Ardeatina, 306- 00179-Rome, Italy. Phone number +39 0651501181. E-mail address: g.koch@hsantalucia.it

Highlights

- Transcranial magnetic stimulation (TMS) can be used to identify the early signatures of synaptic dysfunction characterizing the different forms of AD.
- -Neurophysiological information may be used as biomarkers for differential diagnosis, disease progression and response to therapy in dementia
- -We consider novel therapeutic approaches based on the clinical use of repetitive TMS.

Abstract

Alzheimer's disease (AD) is one of the most devastating conditions affecting elderly in Western World. Unfortunately, there are no effective treatments, and patients diagnosed with AD face an uncertain future, caused by the current inability to predict the course of the disease. This is mainly

due to the poor comprehension of AD pathophysiology and of patients' clinical heterogeneity. In recent years, several evidences supported the concept that loss of synaptic density could be an early event and precede neuronal degeneration, suggesting that the impairment of synaptic transmission should play a key role in the pathogenesis of different forms of dementia, including AD, frontotemporal dementia and Lewy body dementia. Despite this emerging background it has not been possible to quantify synaptic functioning (or dysfunction) directly in vivo in AD patients. Transcranial magnetic stimulation (TMS) has been recently introduced as a novel approach able to identify the early signatures of synaptic dysfunction characterizing the different forms of AD. We review the novel emerging neurophysiological signatures of AD and how this information may be used as biomarkers for differential diagnosis, disease progression and response to therapy. Finally, we also consider novel therapeutic approaches based on the clinical use of repetitive TMS.

Glossary: TMS=transcranial magnetic stimulation; LTP=long term depression; rTMS=repitive transcranial magnetic stimulation; AD=Alzheimer's disease; A β =amyloid- β ; DMN=default mode network; SAI=short afferent inhibition

Introduction

Alzheimer's disease (AD) is one of the most devastating conditions affecting elderly in Western World. It is considered as one of the most serious medical, economic and social emergencies faced by our society today and, even more extensively, over the next decades. Unfortunately, there are no effective treatments, and patients diagnosed with AD face an uncertain future, caused by the current inability to predict the course of the disease. The only approved treatment for AD is

indeed based on cholinergic and glutamatergic drugs, whose clinical efficacy is overall negligible. Nonetheless, recent clinical trials based on new 'putative' disease modifying drugs have failed in reaching their principal clinical outcome. So far, relatively well-defined criteria have been identified for the diagnosis of early AD, based on patients' clinical presentation and biomarkers' profile, such as beta-amyloid and tau proteins, detected either by CSF sampling or Positron Emission Tomography (PET) imaging [1]. Nonetheless, the clinical course of AD remains largely unpredictable at individual level. This is mainly due to the poor comprehension we currently have of AD pathophysiology and to patients' clinical heterogeneity. Crucially, the mechanisms determining the severity of AD progression, and those counteracting it, prevent any reliable prognostic prediction at individual patient level. As a consequence, the identification of appropriate interventional targets remains a challenging goal.

Synaptic dysfunction in AD

The aggregation and deposition of amyloid- β ($A\beta$) and tau proteins are two key factors known to be involved in AD pathogenesis. These pathological processes are estimated to begin years before the onset of cognitive impairment. However, the first signs of cognitive impairment only appear after significant neuronal and synaptic loss has occurred in vulnerable brain regions [2].

CSF concentrations of beta-amyloid 1-42, total tau (t-tau), and phosphorylated tau (p-tau) proteins have been recently put forward as a useful tool for AD diagnosis and phenotyping. Notably, AD patients with higher levels of CSF t-tau and p-tau have been reported to exhibit a more malignant disease course [3]. Recently, growing evidence has shown that the accumulation of tau pathology is highly associated to functional and structural deterioration of AD brains [4]. Additionally, it has been demonstrated that the accumulation of "tangles" correlates with patients' level of cognitive decline while beta-amyloid has been shown requiring the presence of tau proteins to explicate its

toxicity. Neuronal and synaptic loss reflects the cumulative outcome of different pathologic substrates in AD and, therefore, may provide the best surrogate for clinical and radiologic disease progression. However, it has to be considered that synaptic dysfunction is an early and prominent pathologic feature of AD that precedes frank neuronal loss in several brain regions. In basic science investigations, earlier studies into AD-related synaptic damages have mainly focused on the toxic effects of beta-amyloid. Only recently, an emerging role of tau was demonstrated [4], since tau overexpression is able to induce synaptic degeneration even in the absence of 'tangles'. This synaptic dysfunction is directly associated to the onset of early memory impairments observed in patients with AD [5]. Actually, although several AD biomarkers are widely applied and considered useful for diagnosis, sufficient accuracy still lacks in evaluating disease severity and predicting disease progression and response to therapy both considering CSF and neuroimaging parameters such as hippocampal atrophy/whole brain volume [6]. In particular, use of single biomarker provides insufficient information to capture the underlying severity of disease across its entire spectrum, from preclinical to clinical stages of AD. Moreover, AD biomarkers evaluation is routinely assessed by means of invasive and/or high-cost procedures, limiting their use in clinical practice. Indeed, the evidence provided by brain imaging methods is purely correlative, it is invaluable for identifying neural processes that may be targeted with causal manipulation methods. Thus, several efforts are underway to combine multiple biomarkers to predict the severity of AD, with the major difficulty in tracking the temporally different evolution of each biomarker throughout the disease course [6]

In recent years, several evidences supported the concept that loss of synaptic density could be an early event and precede neuronal degeneration, suggesting that the impairment of synaptic plasticity mechanisms should play a key role in the pathogenesis of AD [7] Notably, in various efforts to find semi-quantitative correlations between the progressive cognitive impairment and

brain pathological alterations, (i.e. burden of cortical amyloid plaques or neurofibrillary tangles), the strongest relationship has been found between the loss of synaptic density and the degree of cognitive impairment in AD. Thus, the impairment of synaptic transmission due to toxic oligomeric species [8], when significantly pronounced, could predict disease severity more precisely than neuronal loss, a more tardive event. These evidences find support on experimental studies showing that A β peptides and tau proteins can interfere with physiological mechanisms of neuronal synaptic plasticity in AD animal models. In particular, it has been demonstrated that these molecules influence hippocampal LTP [9].

These altered mechanisms have been related to spine shrinkage, neuronal network disarrangement, and cell death [10]. Moreover, in AD It is well known that abnormalities in terms of β -amyloid plaques and neurofibrillary tangles are paralleled by an initial disruption of medial fronto-parietal functional connectivity, as revealed by alterations of the so-called default mode network (DMN) [12]. AD typically presents with deficits in learning new information as well as in retrieving old memories [13]. This loss in long-term episodic memory has been referred not only to local damage of the medial temporal lobes, but also to a dysfunction of large-scale networks underlying memory processes. This disconnection precedes (and probably contributes to) the occurrence of regional brain atrophy, which becomes prominent at later disease stages [13]. Taken together, these evidences suggest that synaptic dysfunction occurring at different levels of brain activity could represent a key driver of AD-related cognitive decline.

Multimodal TMS-based methods

Transcranial magnetic stimulation (TMS) may represent a valid tool to overcome the problems limiting other imaging techniques to track dysfunction of synaptic activity in incipient dementia. It is based on the principle that brain stimulation can be induced by generating a brief, high-

intensity magnetic field by passing a brief electric current through a magnetic coil. When a substantial electrical current is induced in a stimulating coil, this is able to produce a transient time variable magnetic field. When a magnetic field of this sort and of sufficient strength is applied to the brain, it can induce an electrical current in the brain producing firing of groups of nerve cells. When stimulation of this sort is applied repeatedly, it will progressively change brain activity. The discovery and practical application of these basic techniques has led to the widespread use of rTMS in neuroscientific and clinical applications (Fitzgerald and Daskalakis, 2013).

Multimodal TMS-based methods are emerging as a unique approach providing the possibility to evaluate in real time the brain electrical activity in the healthy and pathological conditions. It is based on the principle that brain stimulation can be induced by generating a brief, high-intensity magnetic field by passing a brief electric current through a magnetic coil. Using TMS, the brain can be briefly activated or briefly inhibited; in fact, likely both occur with each stimulus in differing amounts and with different time courses. This effect can be used to localize brain functions in both space and time. Applications were first in the motor system but have now been used to map sensory processes and cognitive function [14]. Application of different TMS forms (i.e., single- or paired-pulse TMS, or short bursts of TMS) is able to focally induce bursts of action potentials in the stimulated neuronal population (approximately over a 2 cm squared brain area). Depending on the adopted protocol it is possible to test key physiological aspects of synaptic activity at different levels of local and global complexity. TMS allows to investigate in detail the properties of local interneuronal networks that are mediated by specific neurotransmitters [15], to determine the capability of specific areas of the brain to form cortical plasticity [16], to assess the ongoing oscillatory activity of a specific area or across broader and more distributed brain networks [17], and to establish causal relationships between stimulation and subsequent changes in cerebral function and behavioral outcome, by combining measurements of network-based neural activity

[18]. For instance, paired pulse TMS protocols applied over specific areas of the brain (i.e. the primary motor cortex) allows to evaluate in vivo the activity of different intracortical circuits such as short intracortical inhibition (SICI), reflecting GABAergic neurotransmission, and short afferent inhibition (SAI) probing cholinergic neurotransmission in AD patients [19; 20].

Repetitive TMS over the primary motor can be used to measure in vivo cortical plasticity mechanisms such as LTP, which is considered the main neurophysiological correlate for learning and memory [16; 21]. The combination of transcranial magnetic stimulation with electroencephalography (TMS-EEG) has provided an emergent method to directly probe local and widespread cortical dynamics, through the recording of TMS-evoked potentials (TEPs) [22]. TEPs have the great advantage to be highly reproducible, demonstrating consistency over time, but also to be extremely sensitive to changes in brain state. Moreover, TMS/EEG allows to investigate brain oscillatory activity within a specific areas and between anatomically distinct brain regions, which is relevant when considering AD as a disconnection syndrome (for a review, see [23]). TMS/EEG can indeed verify challenging aspect of the clinical assessment of brain disorders independently from patients' ability to interact with the external environment. Recently a novel theory-driven index of the level of global brain activity was introduced for the study of brain activity, called the perturbational complexity index (PCI) [24]. PCI is an empirical measure of brain complexity, which gauges the amount of information contained in the integrated response of the thalamocortical system to a direct perturbation. Additionally, simultaneous application of TMS pulses over different interconnected brain areas or during concurrent neuroimaging allows tests of how action potentials elicited in one brain area influence processing in interconnected areas in a top-down and/or context-sensitive manner (25; 26; 27; 28; 29); this makes it possible to study how brain networks dynamically operate at high temporal resolution and to stimulate deep cortical or subcortical areas indirectly via interconnected areas [30]. rTMS can also be applied to establish

causal relationships between stimulation and subsequent changes in cerebral function and behavioral outcome, for instance by combining fMRI measurements of network-based neural activity. In this scenario, trains of rTMS can be applied over a certain brain area, presumably a key node of a certain network and the induced changes in connectivity may be analyzed by means of resting state fMRI. These two complimentary tools can be combined to optimally study brain connectivity and manipulate distributed brain networks. Important clinical applications include using resting state fMRI to guide target selection for TMS and using TMS to modulate pathological network interactions identified with resting state fMRI. The combination of TMS and resting state fMRI has the potential to accelerate the translation of both techniques into the clinical realm and promises a new approach to the diagnosis and treatment of neurological and psychiatric diseases that demonstrate network pathology [18].

TMS-based biomarkers in AD

On the basis of this background, we and others recently introduced the notion that TMS can be considered a novel tool to shape early features of synaptic dysfunction at different levels of complexity in AD patients. We recently showed that a systematic TMS-based assessment of GABAergic and cholinergic neurotransmission reliably distinguishes AD patients from FTD and HC and therefore TMS could represent a sensible diagnostic tool for clinical practice [20]. We were among the first to demonstrate that LTP-like cortical plasticity is consistently impaired in AD patients as assessed with intermittent theta burst stimulation (iTBS) rTMS protocol applied over the primary motor cortex [21]. Cortical plasticity is regarded as the principal biological mechanism for learning and memory. In humans it can be assessed by non-invasive repetitive transcranial magnetic stimulation (rTMS) [16], in strict analogy with the hippocampal plasticity assessable in animal models. Works from our group and others revealed that AD patients show a remarkable

impairment of long-term potentiation (LTP)-like cortical plasticity [21; 31; 32; 33]. This condition was associated with a more aggressive AD clinical course and, importantly, in all of the cases associated to very high CSF levels of t-tau proteins [34]. Moreover, in the context of AD, we recently showed that innovative combined TMS/EEG protocols provide the possibility to directly measure cortical functional activity in cognitive-related areas such as the dorsolateral prefrontal cortex or the posterior parietal cortex (both involved in AD neurodegeneration) extending the potential role of TMS-based biomarkers in assessing the effects of therapies on cortical activity outside the primary motor cortex [35]. Thus the detection of novel TMS-EEG markers of synaptic dysfunction (in terms of cortical excitability, connectivity and oscillation), within the DMN might contribute to provide additional predictive biomarkers of response to therapies in AD.

In this complex picture, synaptic dysfunction is likely to be influenced also by genetic factors. For instance, there is a strong relationship between Apolipoprotein E (APOE) polymorphisms and cortical plasticity, since APOE is known to regulate both beta-amyloid clearance/aggregation and tau related microtubule stabilization, being strictly linked with altered mechanisms of synaptic plasticity [36]. In a recent work from our group, we observed that the presence of APOE polymorphisms imply different mechanisms of CSF tau-related dysfunction in AD patients [37]. Indeed, we found that high CSF tau levels are associated with impaired cortical plasticity and more aggressive disease progression only in AD patients carrying APOE4 but not APOE3 genotype. In parallel, we also found that CSF tau levels influence apoptosis in normal human astrocytes when incubated with CSF collected from AD patients with APOE4 but not APOE3 genotype. Taken together these findings reveal that CSF tau levels are linked to cortical plasticity, cognitive decline and astrocytes survival only when associated with APOE4 genotype [37].

Emerging TMS-based therapeutics in AD

To date, the mainstream treatment for AD patients is represented only by cholinergic and glutamatergic drugs. However, pharmacological treatments have limited efficacy and are accompanied by adverse side effects. For this, it is of great importance to develop alternative therapeutic approaches. Recently, different forms of non-invasive brain stimulation techniques (e.g., transcranial magnetic stimulation-TMS) have been applied to patients with AD in order to improve cognitive decline and behavioral disorders. In recent years, treatments based on multiple sessions of repetitive TMS have represented a promising tool for influencing cognition in people with neurodegenerative diseases [38]. This procedure is non-invasive and painless, and it does not require the use of anesthesia or pharmacological substances. The key principle of rTMS is based not only on regularly “repeated” stimulation of a focal cortical area but also on “accelerated” stimulation with multiple sessions and stimuli, leading to long lasting modulation of the brain plasticity. From a neurobiological perspective, rTMS could induce relevant clinical improvement by promoting changes in synaptic plasticity. Synaptic plasticity is the most important biological mechanism accounted for learning and memory; in particular, LTP is considered as a main neurophysiological correlate of these cognitive functions [39]. We recently demonstrated that AD patients show a disruption in LTP-like cortical plasticity since the early stages of the disease [40]. In this context, high-frequency rTMS could enhance LTP-like cortical plasticity, thus resulting in changes both, at local and network level as revealed by TMS/EGG and fMRI studies.

Until now, several studies have exclusively explored the effects of intensive treatments, lasting 2 weeks. Recently safety and efficacy of maintenance of rTMS treatment in early AD patients showed a long-term trend with less cognitive decline than would be expected [41]. Non-invasive brain stimulation methods have been recently proposed as a novel approach to improve cognitive functions in patients with dementia, targeting the prefrontal cortex as key area to be stimulated [42-45]. Moreover, novel interesting approaches are considering the possibility to stimulate in the

same patients more areas such as the right and left dorsolateral prefrontal cortex, Broca and Wernicke and the right and left parietal somatosensory association cortex in conjunction with active cognitive training targeting these same brain regions [46-47].

However, since the early stages of AD, prominent neuropathological abnormalities (i.e., β -amyloid plaques and neurofibrillary tangles) involve posterior cortical regions of the brain, including the precuneus (PC), the posterior cingulate, the retrosplenial, and lateral posterior parietal cortex (PPC) [48]. Moreover, there is an initial disruption of medial fronto-parietal functional connectivity. Specifically, AD patients show alterations of the so-called default mode network (DMN), for which the PC is a key node [12]. Interestingly, at early clinical stages of AD, disconnection of the PC precedes (and probably contributes to) the occurrence of regional brain atrophy, which becomes prominent at later disease stages [14]. This means that the PC is a vulnerable region for the transitional stage towards dementia, which may be targeted by tailored interventions [49]. Indeed, AD patients often show a reduction of PC cortical thickness accompanied by an abnormal activation during memory tasks and decreased functional connectivity [50]. This is especially relevant since the activity of the PC is considered necessary for episodic memory retrieval [51; 52], whose impairment represents the clinical onset of typical AD. Thus, the PC represents an ideal target for interventions aimed at slowing down and potentially counteracting memory decline in AD patients.

This hypothesis finds support in recent experimental work performed in healthy subjects showing that TMS applied to the PPC [53; 54] and PC [55; 56] is effective in modulating short and long-term memory functions. Following this line of evidence, we recently showed that 20-Hz rTMS is able to increase long-term memory performance potentiate the cortical activity of the PC, providing novel evidence that non-invasive treatment of network dysfunction, through stimulation of the PC, represents a potentially efficacious strategy to improve cognitive dysfunction in AD [35]. We

showed that high-frequency excitatory rTMS improves long-term memory in patients with AD, by modulating local neural activity the connections with parietal, frontal and temporal areas. However, the effects were only evaluated in a short-term course temporal window of two weeks. Sham controlled rTMS trials are needed to explore whether rTMS may have a clinical impact in modifying the course of AD when applied over clinically relevant periods of 6-12 months.

Conclusions

Transcranial magnetic stimulation is contributing to shape the characteristics of synaptic dysfunction in AD patients, helping to increase diagnostic accuracy and to provide relevant clinical information in terms of disease progression and response to therapy.

On the other hand, there is a great interest in developing novel rTMS protocols that may have the potential to improve cognitive functions in patients with mild dementia and eventually slow down cognitive decline if applied during a long term period of several months.

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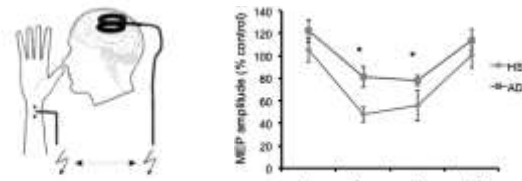
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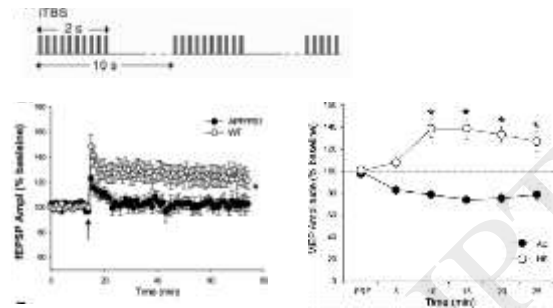
ACCEPTED MANUSCRIPT

Figure 1.

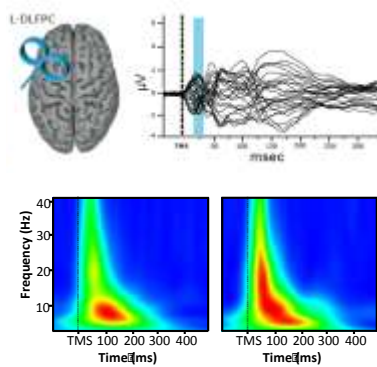
A) Short afferent inhibition
Cholinergic neurotransmission



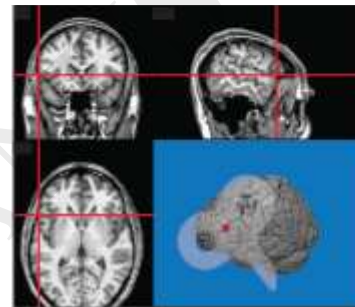
B) Theta burst stimulation
Cortical plasticity



C) TMS/EEG
Cortical oscillatory activity



C) Repetitive TMS
Therapeutic approach



Legend to figure 1.

Schematic representation of different TMS protocols. A) Short afferent inhibition protocol utilized to measure cholinergic neurotransmission; B) Intermittent theta burst stimulation (iTBS) protocol to measure LTP-like cortical plasticity; C) Combined TMS-EEG recordings allow measuring cortical oscillatory activity and related connectivity; D) repetitive TMS protocols with neuronavigation allow stimulating during several weeks the same cortical area.