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Effects of Palmitoylethanolamide Combined with Luteoline on Frontal Lobe Functions, High Frequency Oscillations, and GABAergic Transmission in Patients with Frontotemporal Dementia

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Abstract.
Background: Frontotemporal dementia (FTD) is a presenile neurodegenerative disease for which there is no effective pharmacological treatment. Recently, a link has been proposed between neuroinflammation and FTD.
Objective: Here, we aim to investigate the effects of palmitoylethanolamide (PEA) combined with luteoline (PEA-LUT), an endocannabinoid with anti-inflammatory and neuroprotective effects, on behavior, cognition, and cortical activity in a sample of FTD patients.
Methods: Seventeen patients with a diagnosis of probable FTD were enrolled. Cognitive and neurophysiological evaluations were performed at baseline and after 4 weeks of PEA-LUT 700 mg×2/day. Cognitive effects were assessed by Neuropsychiatric Inventory (NPI), Mini-Mental State Examination, Frontal Assessment Battery (FAB), Screening for Aphasia in Neurodegeneration, Activities of Daily Living-Instrumental Activities of Daily Living, and Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating scale. To investigate *in vivo* neurophysiological effects of PEA-LUT, we used repetitive and paired-pulse transcranial magnetic stimulation (TMS) protocols assessing LTP-like cortical plasticity, short-interval intracortical inhibition, long-interval intracortical inhibition (LICI), and short-latency afferent inhibition. Moreover, we used TMS combined with EEG to evaluate the effects on frontal lobe cortical oscillatory activity.

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Results: Treatment with PEA-LUT was associated with an improvement in NPI and FAB scores. Neurophysiological evaluation showed a restoration of LICI, in particular at ISI 100 ms, suggesting a modulation of GABA(B) activity. TMS-EEG showed a remarkable increase of TMS-evoked frontal lobe activity and of high-frequency oscillations in the beta/gamma range.

Conclusion: PEA-LUT could reduce behavioral disturbances and improve frontal lobe functions in FTD patients through the modulation of cortical oscillatory activity and GABA(B)ergic transmission.

Keywords: Brain inflammation, behavioral symptoms, EEG, executive functions, frontotemporal dementia, GABA activity, transcranial magnetic stimulation

INTRODUCTION

Frontotemporal dementia (FTD) is a presenile neurodegenerative disorder characterized by neuronal loss and gliosis of the frontal and temporal lobes. Although FTD is the second most common form of presenile degenerative dementia [1], there is still no approved treatment to slow the progression of the disease [2], which leads to a decline in patient functioning, caregiver dependency, and death for complications in a few years after the first symptoms onset [3].

As for other neurodegenerative diseases, recent findings suggest an important and active contribution of neuroinflammation in the pathogenic process of FTD, and a possible link between immune-mediate mechanism and the progression of the disease since the early phases [4]. The role of neuroinflammatory response dysregulation in FTD is supported by recent studies showing that genes mutation related to microglial activation, including the gene encoding progranulin (GNR) and triggering receptor expressed on myeloid cells 2 (TREM 2), are responsible or risk factors, respectively, for FTD [5–7]. Furthermore, cerebrospinal fluid, blood, and serum of FTD patients showed a dysregulated expression of several biomarkers of inflammation, such as elevated cytokines, e.g., tumor necrosis factor-α, with increased production of pro-inflammatory markers [8]. Finally, a link between FTD and several autoimmune diseases has been demonstrated [9]. Along the same lines, *in vivo* positron emission tomography studies with Translocator Protein (TSPO)-ligands ^{11}C-PK11195, a specific marker to detect active microglia, found higher level of inflammatory microglial activation in frontal and temporal lobes of patients with FTD [10, 11].

Although further studies are needed to understand the exact role played by inflammatory cells in FTD progression, all these findings support the idea that targeting and modulating neuroinflammation pathways seems to be a promising field to slow down the progression of FTD. Recent evidences have shown that palmitoylethanolamide (PEA), a saturated N–acylethanolamide belonging to the family of endocannabinoids, can exert anti-inflammatory and neuroprotective effects preserving memory function in rodent models of Alzheimer's disease and reducing central nervous system (CNS) inflammation [12]. The beneficial effects of PEA-LUT is thought to partially depend on its action on microglial cells, emerging as a potential intervention for neuroinflammation in CNS disorders [13]. In addition, a recent study found an effective effect of PEA on muscle function conservation of patients with amyotrophic lateral sclerosis, a disease that presents a pathophysiological and clinical profile similar to FTD [14]. Finally, a previously unrecognized function of PEA in enhancing GABA neurotransmission, through the modulation of the release of the endocannabinoid 2-AG, has been recently identified [15]. This is relevant since GABA transmission is impaired in FTD, as demonstrated by the loss in upper cortical layers in GABAergic bind calbindin- D28k local-circuit non-pyramidal neurons [16]. Finally, GABAergic inhibitory neurons play also a key role in the regulation of cortical oscillatory rhythms, in particular in the generation of gamma oscillations [17, 18] that were found to be reduced in the frontal lobes of FTD patients [19]. On these premises, PEA fulfills the criteria for a favorable candidate as an adjunctive therapeutic agent for neurodegenerative disorders such as FTD, having a modulatory effect both on neuroinflammation and on GABAergic neurotransmission.

The aim of this study was to investigate cognitive and behavioral impact of the administration of ultra-micronized PEA combined with luteoline (PEA-LUT), for four weeks, in FTD patients. To non-invasively investigate the *in vivo* neurophysiological effects of PEA-LUT on both GABAergic neurotransmission and cortical oscillations, we used ad-hoc protocols based on transcranial magnetic

stimulation (TMS). First, as already done in other studies from our group [20, 21], we adopted different paired-pulse TMS protocols such as intracortical facilitation (ICF), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and short-latency afferent inhibition (SAI), able to investigate interneuronal activity mediated by different neurotransmitters, respectively glutamate, GABA(A), GABA(B), and acetylcholine. Second, we combined TMS with electroencephalography (EEG) to test cortical activity and cortical oscillations on the left dorsolateral prefrontal cortex (DLPFC), an area that is particularly impaired in FTD neuropathology, and on the posterior parietal cortex (PPC) of the same hemisphere, as a control area.

MATERIALS AND METHODS

Patients

We enrolled 17 consecutive patients with a diagnosis of probable FTD, including the behavioral variant (bvFTD) and primary progressive aphasia (PPA)based on the current clinical diagnostic criteria [22, 23]. All patients initially underwent a clinical screening comprising medical history, neurological examination, neuropsychological and neuropsychiatric assessment, a complete blood screening, PET imaging, and brain MRI scanning [24]. Inclusion criteria were: age between 50 to 85 years; a FTLD-modified Clinical Dementia Rating (FTLD-CDR) scale total score of $\leq$2; evidence of frontotemporal hypometabolism at PET imaging. Exclusion criteria: treatment with drugs modulating brain excitability, such as antidepressants, benzodiazepines, antiepileptic drugs, or neuroleptics in the three months before entering this study; other significant CNS neurodegenerative disorders, psychiatric illnesses, and signs of concomitant cerebrovascular disease on MRI scans. All participants signed a written informed consent. The current study was performed according to the Declaration of Helsinki and it was approved by the Ethics Committee of Santa Lucia Foundation.

Experimental design

Patients who agreed to participate (N = 17; age: 62.3 ± 9.4; 11 females; see Table 1 for clinical and demographical details) started a 4-weeks treatment consisting of administration of ultramicronized PEA combined with luteolin (PEA-LUT) at the oral dosage of 700 mg$\times$2 daily. All participants underwent a neuropsychological and neurophysiological assessment the day before ("pre-treatment evaluation") and after 4 weeks ("post-treatment evaluation") of PEA-LUT administration.

Table 1
Demographic, clinical, and neurophysiological information

Age (y)	62.35 ± 9.43
Sex (m/f)	(6/11)
Education (y)	12.47 ± 3.41
Clinical variant (PPA/bvFTD)	9/8
Disease duration (y)	2.61 ± 1.29
MMSE	16.65 ± 10.14
NPI	22.82 ± 15.09
FAB	6.65 ± 3.92
FTLD-CDR SoB	8.41 ± 4.22
ADL	5.35 ± 0.93
IADL	3.65 ± 2.5
SAND	51.75 ± 21
RMT monophasic (%MSO)	53.00 ± 11.58
RMT biphafasic (%MSO)	61.81 ± 12.78

The table shows the mean $\pm$ standard deviation average values of our sample. PPA, primary progressive aphasia; bvFTD, behavioral variant FTD; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; FAB, Frontal Assessment Battery; FTLD-CDR SoB, FTLD-modified Clinical Dementia Rating scale Sum of Boxes; ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SAND, Screening for Aphasia in Neurodegeneration; RMT, resting motor threshold; MSO, percentage of maximum stimulator output.

Cognitive and behavioral assessment

Cognitive and behavioral assessment consisted of Neuropsychiatric Inventory (NPI), to evaluate the behavioral disturbances in dementia [25]; Mini-Mental State Examination (MMSE), to evaluate the global cognitive status [26]; Frontal Assessment Battery (FAB), to evaluate global executive functions [27]; Screening for Aphasia in Neurodegeneration (SAND), to evaluate language domain [28]; Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (ADL/IADL), for functional disability measurement [29]; FTLD-CDR, to evaluate the clinical severity of the disease [30].

Corticospinal evaluation

The position of the coil on the scalp was defined as the M1 site in which TMS evoked the largest MEPs in the relaxed first dorsal interosseous (FDI) muscle of the hand contralateral to the stimulation. The coil was placed tangentially to the scalp at about 45° angle away from the midline, thus inducing a posterior-anterior current in the brain. The intensity of stimulation for single-pulse TMS was adjusted

to evoke a MEP of ∼1 mV peak-to-peak amplitude. Intensity of paired-pulse TMS was based on the resting motor threshold (RMT), defined as the lowest intensity that produced MEPs > 50 μV in at least five out of ten trials in the relaxed FDI of the right hand [31]. Intensity of theta burst stimulation (TBS) was based on the active motor threshold (AMT), defined as the lowest intensity that produced MEPs > 200 μV in at least five out of ten trials during 10% of maximum contraction of the same muscle [32].

Paired-pulse TMS protocols consisted of 1) SICI/ICF, in which a conditioning stimulus (CS) delivered at 90% of AMT preceded a test stimulus (TS) delivered at 1 mV MEP intensity over M1 by 1, 2, 3, 5, 7, 10, and 15 ms [33, 34]; 2) LICI, in which a CS delivered at 110% of RMT preceded a TS delivered at 1 mV MEP intensity over M1 by 50, 100 and 150 ms. Ten TMS paired pulses were delivered for each ISI [35]; 3) SAI, in which an electrical CS (200 μs), applied through bipolar electrodes to the right median nerve at the wrist (cathode proximal), preceded a TS delivered at 1 mV MEP intensity over M1 by 16, 20, 24, and 28 ms. The intensity of the electrical CS was set at just over motor threshold for evoking a visible twitch of the thenar muscles. To measure intracortical facilitation or inhibition circuits, we considered the mean peak-to-peak amplitude of the conditioned MEP at each ISI expressed as a percentage of the mean peak-to-peak amplitude of the unconditioned MEP in that block. TBS protocol consisted of 3 pulses at 50 Hz, repeated every 200 ms (5 Hz) [33]. For intermittent TBS (iTBS), a 2 s train of TBS was repeated 20 times, every 10 s, for a total of 190 s (600 pulses) [36]. To measure LTP, we considered the mean peak-to-peak amplitude of 20 MEPs collected with single-pulse TMS before and after 1, 10, and 20 min after iTBS.

TMS-EEG cortical evaluation

Cortical evaluation was performed with TMS-EEG. Intensity of stimulation was set at 90% of RMT, tested on contralateral FDI muscle at rest (see previous paragraph). Each session consisted of 80 TMS single-pulses applied at a random ISI of 2–4 s over left DLPFC and PPC, targeted using a neuronavigation system. The order of stimulation of the two areas was counterbalanced across patients. Each participant wore in-ear plugs which continuously played a white noise that reproduced the specific time-varying frequencies of the TMS click [37]. TMS-evoked EEG activity was recorded from the scalp with a TMS-compatible DC amplifier (BrainAmp, Brain Products GmbH, Munich, Germany). The EEG was continuously recorded from 61 scalp sites positioned according to the 10–20 International System, using TMS-compatible Ag/AgCl pellet electrodes mounted on an elastic cap. EEG signals were digitized at a sampling rate of 5 kHz. Skin/electrode impedance was maintained below 5 kΩ. Horizontal and vertical eye movements were detected by recording the electrooculogram (EOG) to off-line reject the trials with ocular artifacts. MS-EEG data were pre-processed offline with Brain Vision Analyzer (Brain Products GmbH, Munich, Germany). Physiological and TMS-related artefactual components were detected using INFOMAX-ICA and removed basing on their scalp distribution, frequency, timing, and amplitude [38].

To evaluate the effects of the PEA-LUT treatment, the single-pulse TMS-evoked responses over each stimulation site were first evaluated in the spatio/temporal-domain analysis. Spatio/temporal-domain analysis was conducted on a time window lasting from 100 ms before to 500 ms after single-pulse TMS. To assess the TMS-evoked global cortical response, over DLPFC and PPC, we computed the global mean field power (GMFP) as:

$$GMFP\,(t) = \sqrt{\frac{\left[\sum_i^k \left(V_i\,(t) - V_{mean}\,(t)\right)^2\right]}{K}}$$

where t is time, K the number of channels, V the voltage in channel i averaged across patients and V_mean is the mean of the voltage in all the channels [39]. For each patient and each stimulation site, the first three peaks (P1, P2, P3) of the GMFP waveform were detected within the 300 ms following the TMS pulse.

To evaluate changes in the oscillatory domain, we performed a time/frequency decomposition based on Morlet wavelet (parameters $c = 3$; 41 linear 1 Hz steps from 4 to 45 Hz), and then we computed TMS-related spectral perturbation (TRSP; [37]). TRSP is a measure of event-related changes in spectral power over time in a certain frequency range computed as:

$$TRSP\,(f, t) = \frac{1}{n}\sum_{k=1}^{n} |F_k\,(f, t)|^2$$

where, for n trials, the spectral estimate F was computed at trial k, at frequency f and time t. Spectral power was subsequently extracted for the theta (4–7 Hz), alpha (8–13 Hz), beta (14–30 Hz), and gamma band (31–45 Hz) and averaged in a time window lasting from 20 to 300 ms after TMS [40, 41].

Oscillatory activity was assessed at global level by averaging the spectral power of all channels for each session. Oscillatory activity was assessed at global level by averaging the spectral power of all channels for each session [42].

Statistical analysis

All data were analyzed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Prior to undergoing ANOVA procedures, normal distribution of neuropsychological and neurophysiological data was assessed by means of Shapiro-Wilk test. When data were not normally distributed, they were analyzed with non-parametric Wilcoxon test. Level of significance was set at $\alpha = 0.05$. Sphericity of the data was tested with Mauchly's test; when sphericity was violated (i.e., Mauchly's test < 0.05) the Huynh–Feldt ε correction was used. Pairwise comparisons were performed with paired *t*-test corrected by the Bonferroni method. To assess the effect of PEA-LUT on patients' neuropsychological evaluation, we used Wilcoxon non-parametric test comparing the performance before the treatment ("pre-treatment") and right after it ("post-treatment"), separately for each test. We used a Kruskal-Wallis non-parametric test with the clinical subtype (PPA and bvFTD) as a between-subjects factor to assess if the effects on neuropsychological evaluation was driven by a single clinical subtype. To evaluate the effect of PEA-LUT on corticospinal excitability, we used a paired *t*-test comparing the RMTs tested before the treatment ("pre-treatment") and right after it ("post-treatment"). The analysis of the other corticospinal measures, i.e., intracortical inhibitory/facilitatory circuits and LTP, were performed using a repeated-measures ANOVA (rmANOVA). Specifically, for intracortical measures, rmANOVA was performed with within-subject factor "treatment" (pre versus post-treatment) and "ISI" (1, 2, 3, 5, 7, 10, and 15 ms for SICI/ICF; 50, 100, and 150 ms for LICI; 16, 20, 24, and 28 ms for SAI). For LTP evaluation we used an rmANOVA with within-subject factor "treatment" and "time" (1, 10, and 20 min after iTBS). To assess the effect of PEA-LUT on cortical measures, i.e., GMFP and TRSP, we used an rmANOVA. Specifically, for GMFP, rmANOVA was performed with within-subject factor "treatment" and "peak" (P1, P2, and P3). For ERSP, rmANOVA was performed with within-subject factor "treatment", separately for the two frequency ranges, i.e., theta/alpha and beta/gamma.

RESULTS

Seventeen patients with FTD took part in the study, which was conducted between June 2018 and August 2019. They all had a good treatment compliance, as reported by their caregivers, and completed all the cognitive and behavioral assessments. PEA-LUT treatment and TMS procedures were well tolerated with no significant side effects. TMS was not tolerated in two patients.

Cognitive and behavioral evaluation

Figure 1 depicts the results of the cognitive and behavioral evaluation. After 4 weeks of PEA-LUT treatment, we observed a significant improvement in the NPI score post-treatment, as compared to the pre-treatment evaluation (pre: 22.82 ± 3.65, post: 19.41 ± 3.63) ($Z = 21.500$; $p = 0.028$). The analysis of NPI sub-items did not show any significant difference.

We also found an improvement in the FAB score post-treatment, compared to the pre-treatment evaluation (pre: 6.64 ± 0.95, post: 7.58 ± 1.06) ($Z = 40.500$; $p = 0.031$). We did not find any significant difference between the improvement of the two different clinical subtypes (bvFTD and PPA) for NPI and FAB score.

We did not observe any difference in the ADL/IADL, MMSE, SAND, and FTLD-CDR scores (all $p > 0.05$).

Corticospinal evaluation

Figure 2 depicts the results of the corticospinal evaluation. Analysis of RMT (reported in Table 1) did not show any difference between the pre- and post-treatment evaluation [$t(14) = 0.731$; $p = 0.477$) (pre: 53.00 ± 11.58, post: 51.78 ± 11.68). Analysis of LICI showed a significant effect of treatment × ISI interaction [$F(2,26) = 5.283$; $p = 0.012$; $\varepsilon = 0.289$]. *Post-hoc* analysis showed a lower corticospinal excitability at an ISI of 100 in the post-treatment evaluation compared to the same ISI in the pre-treatment evaluation (pre: 99.6 ± 29.3, post: 52.1 ± 12.7) (*post-hoc* $p = 0.038$). Analysis of SICI/ICF, SAI, and LTP did not show any significant difference between the pre- and post-treatment evaluation in any of the ISIs.

Cortical evaluation

Figure 3 (A, C) depicts the results of the cortical activity evaluation, as assessed by GMFP. TMS

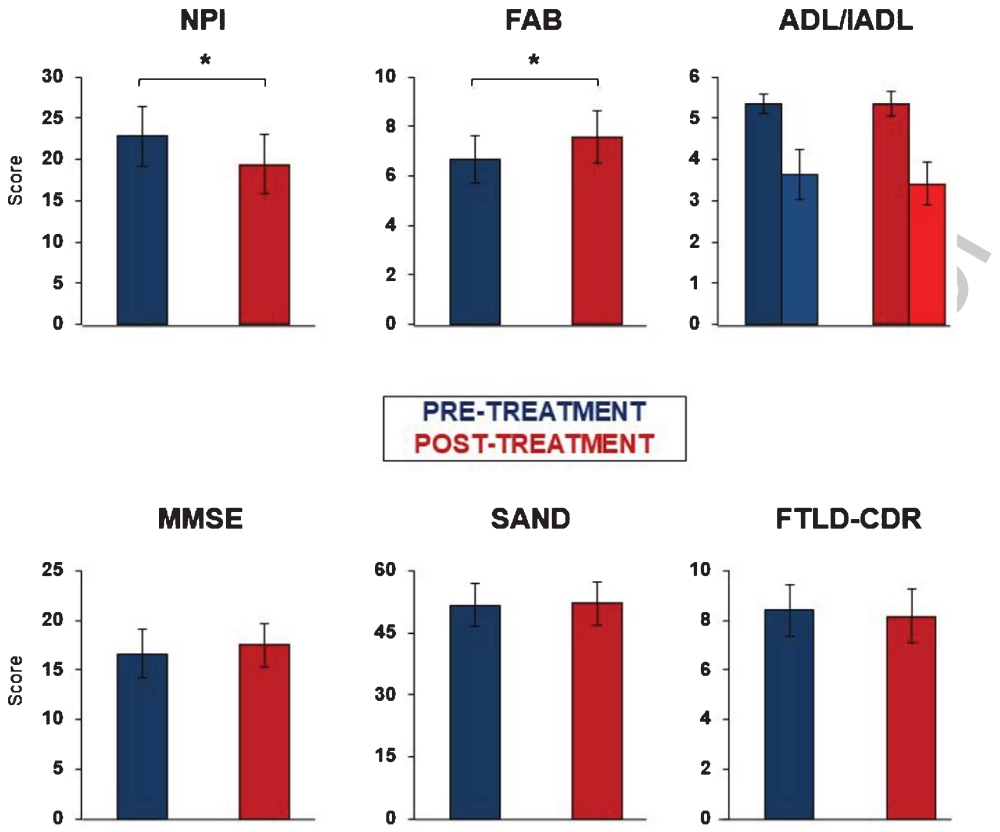

Fig. 1. Cognitive and behavioral evaluation results. Each plot depicts the grand-average score (17 patients) at Neuropsychiatric Inventory (NPI), Frontal Assessment Battery (FAB), Activities of Daily Living and Instrumental Activities of Daily Living (ADL/IADL), Mini-Mental State Examination (MMSE), Screening for Aphasia in Neurodegeneration (SAND), and FTLD-modified Clinical Dementia Rating (FTLD-CDR) scale. Blue bars indicate pre-treatment condition; red bars indicate post-treatment condition. Error bars indicate standard error. $^{*}p < 0.05$.

of left DLPFC evoked a sustained activity lasting about 300 ms with three main time windows of activity 15–70 ms (P1), 71–140 ms (P2), and 141–300 ms (P3) after TMS [43]. A similar activation was observable after TMS of left PPC with three main time windows of activity at 15–45 ms (P1), 46–130 (P2), and 131–300 ms (P3). Analysis of left DLPFC-GMFP revealed a significant treatment effect [$F(1,14) = 8.006$; $p = 0.013$; $\varepsilon = 0.364$] showing an higher left DLPFC cortical activity in the post-treatment evaluation compared to the pre-treatment evaluation with no effect on specific GMFP peaks (pre: 1.37 ± 0.163, post: 1.63 ± 0.120). Analysis of PPC-GMFP did not reveal any significant effect. Figure 3 (B, D) depicts the results of the cortical oscillations evaluation, as assessed by ERSP. TMS evoked a sustained oscillatory activity lasting about 350 ms. A first spot of activity in the beta and gamma frequency was observable between about 20 and 70 ms after TMS; a second spot of activity in the theta and alpha frequency was observable between about 70 and 350 ms. Analysis of left DLPFC-TRSP in the gamma and beta frequency showed a significant effect of treatment [$F(1,14) = 5.521$; $p = 0.034$; $\varepsilon = 0.283$], revealing an increase of gamma and beta oscillatory activity in the post-treatment evaluation compared to pre-treatment (gamma/beta: pre: 0.028 ± 0.004, post: 0.044 ± 0.007). Analysis of left PPC-TRSP did not reveal any significant difference between the pre- and post-treatment evaluation for any of the frequency bands analyzed.

DISCUSSION

Our work was designed to evaluate the potential cognitive and neurophysiological effects of the administration of PEA-LUT in a group of FTD

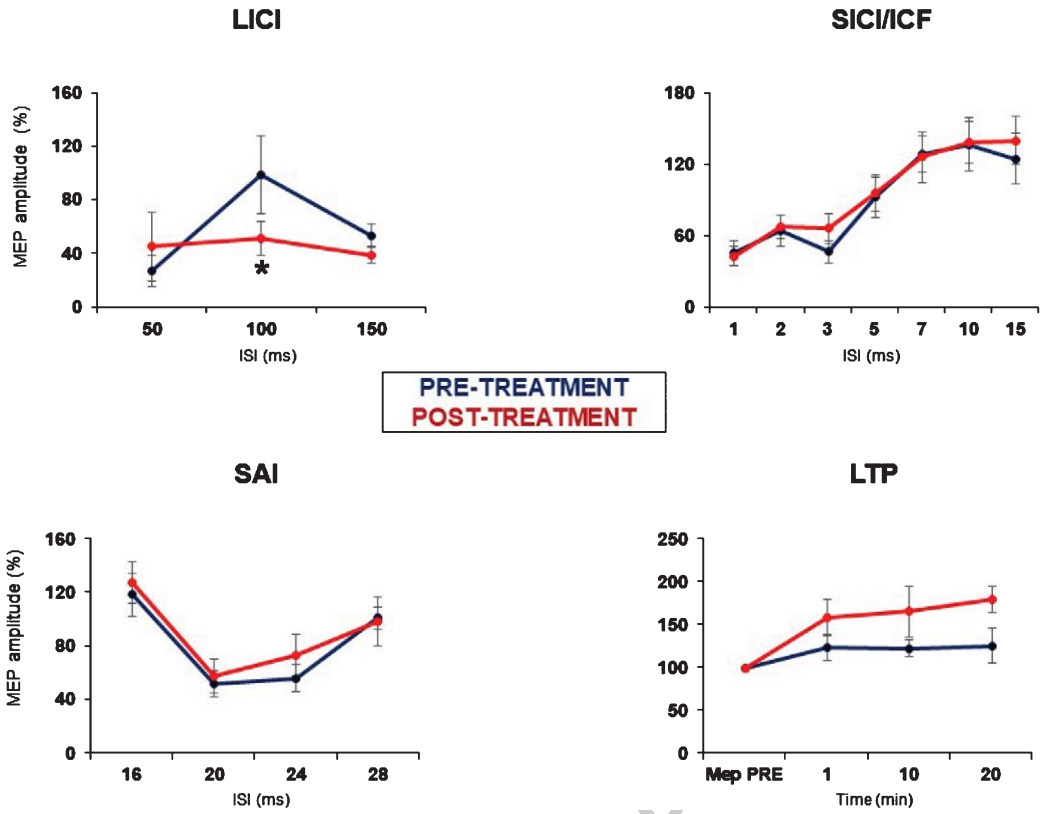

Fig. 2. Corticospinal evaluation results. Each plot depicts the grand-average rate (15 patients) of long-interval cortical inhibition (LICI), short-interval cortical inhibition and intracortical facilitation (SICF/IFC), short-latency afferent inhibition (SAI), and long-term potentiation (LTP). Blue lines indicate pre-treatment condition, red lines indicate post-treatment condition. Error bars indicate standard error. $*p < 0.05$.

patients. Although the progression of symptoms can vary by individual and inconstantly across different clinical variants, FTD brings to an inevitable decline in functioning, especially in planning or organizing activities; behaving appropriately in social or work contexts; communicating with others or relating to loved ones. At present, there are not reliable treatments to cure FTD, nor even to slow the progression of its symptoms. For instance, cholinesterase inhibitors have been tested in FTD patients, although they do not show signs of cholinergic loss, with some disappointing results [44], thus their routine use is not recommended. Antipsychotics have long been used to control behavioral disturbances, but evidence for their use in FTD comes mainly from case reports and uncontrolled series [45–48]. Furthermore, antipsychotic drugs may increase the risk of extrapyramidal side effects, to which FTD patients are particularly vulnerable [49]. A general trend in current therapies for FTD, includes the use of selective serotonin reuptake inhibitors (SSRIs; [50]), considering that these patients show a profound presynaptic serotoninergic deficit [44]. Use of SSRIs in FTD may be associated with some variable improvement in total NPI scores [50–53].

We found that after 4 weeks of PEA-LUT treatment FTD patients showed an improvement in frontal lobe functions, as measured by FAB, and a decrease in behavioral disturbance, as measured by NPI. In this framework, the current results could indicate that the modulation of neuroinflammation by means of PEA-LUT could be a novel strategy with a potential important clinical impact in slowing down decline of cognition and reducing behavioral disturbances in FTD patients. Importantly, in terms of safety PEA-LUT treatment was well-tolerated since all patients concluded the 4 weeks of treatment with no major side effect reported. Clearly further randomized placebo-controlled trials eventually taking in account specific FTD clinical variants are required to confirm our hypothesis and to validate our results in order to candidate PEA-LUT as a potential effective therapy in FTD patients. In particular, whether longer periods of treatment with PEA-LUT might lead to

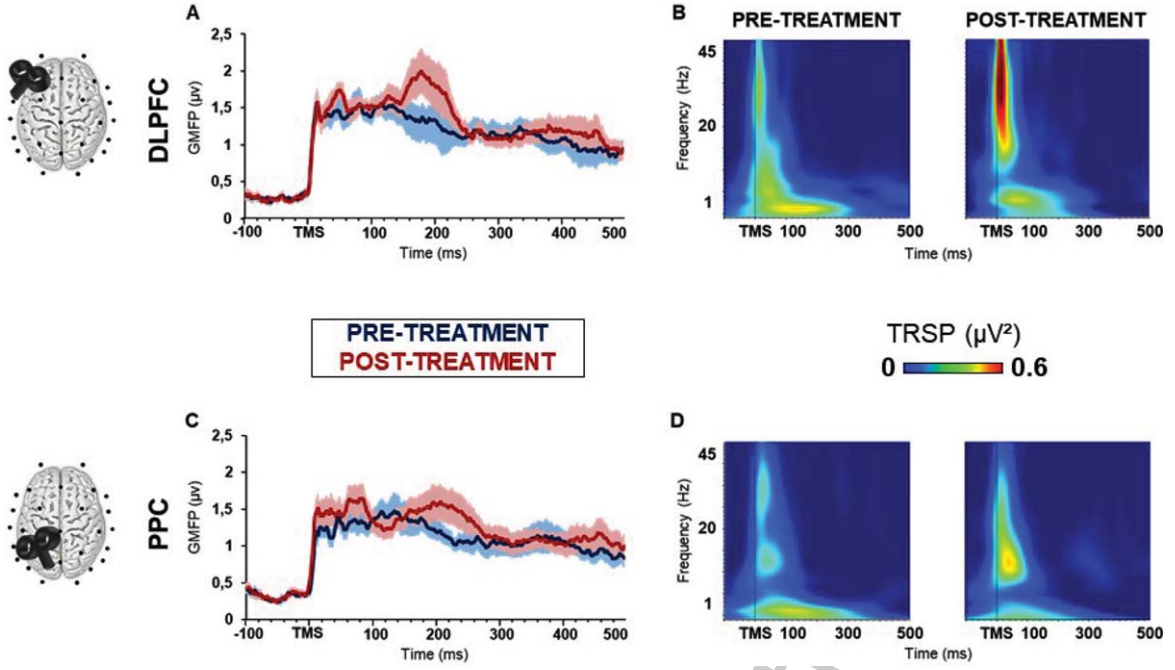

Fig. 3. Cortical evaluation results. Plots depict the global mean field power evoked from stimulation of the dorsolateral prefrontal cortex (DLPFC, A) and of the posterior parietal cortex (PPC, C). Blue lines indicate pre-treatment condition; red lines indicate post-treatment condition. Error bars indicate standard error. Panel B depicts the TMS-related spectral perturbation evoked from stimulation of the DLPFC and panel D of the PPC in the pre-treatment and post-treatment condition.

a long-lasting clinical effect is still unknown, since in the current study FTD patients were treated for 4 weeks, thus future randomized controlled trials might evaluate the effects of longer PEA-LUT treatments.

As reported by recent studies, our neurophysiological results confirm that FTD patients are characterized by an impaired LICI [54, 55], a well-known marker of post-synaptic inhibition mediated trough GABA(B) activity at an interneurons level [35]. We observed that our PEA-LUT treatment induced a remarkable restoration of the decreased LICI at ISI of 100 ms, which usually shows the maximum inhibition of MEPs due to intracortical inhibitory mechanism mediated by GABA(B) [35]. These results were specific since we did not find any difference for other TMS paired-pulse protocols assessing GABA(A)-ergic activity (SICI), glutamatergic activity (ICF), and cholinergic activity (SAI) [33, 56, 57]. We also observed a significant increase in left DLPFC TMS-evoked oscillations, in particular for high-frequency oscillations in beta and gamma bands. Consistently with this hypothesis, TMS-EEG results revealed a significant increase in left DLPFC cortical activity and in particular in later TEP components that are likely originated from GABA(B) inhibitory mechanisms following the TMS pulse [58, 59], which can be either modulated by the administration of GABA(B) agonists [60]. Anomalies in these frequencies between frontal regions and the interconnected network underlie behavioral symptoms in FTD patients [19], potentially being a target of intervention to improve those disturbances. GABAergic interneurons, expressing the Ca2+-binding protein parvalbumin, exert an inhibitory activity on pyramidal cells through a negative feedback system [61] and play a well-established crucial role in the generation and the coordination of neocortical gamma oscillations [17]. Gamma synchronization is considered to be essential for several cognitive functions, including working memory [62] and attention-dependent stimulus selection [63] in which FTD are defective [64–66]. To additionally support our findings, dysfunction in neural synchrony in gamma bands has been suggested from previous work as a possible responsible for the cognitive impairment in schizophrenia patients [18, 67], a disorder that presents a phenotypic similar to FTD, as well as dysfunction of similar brain networks and pathways [68]. Furthermore, GABA levels correlates with gamma power at rest and during

cognitive processes among all regions in the DLPFC and their impairment may contribute to cognitive decline in FTD. By investigating the topographical reorganization of oscillatory dynamics in our population, we provided a new insight into the precise neurophysiological signature of clinical and behavioral improvements. Our neurophysiological results suggested that the amelioration in behavioral and executive functions in our cohort of FTD patients might reflect the modulation of cortical excitability and GABAergic transmission exerted by PEA-LUT.

Several preclinical *in vitro* and *in vivo* studies have demonstrated that PEA can induce its biological effects by acting on several molecular targets in both central and peripheral nervous systems [69–71]. It has been initially suggested that PEA can directly activate at least two different receptors: the peroxisome proliferator-activated receptor-alpha (PPAR-α) [72] and the orphan GPCR 55 (GPR55) [73]. PPAR-α actually seems to be the main molecular target involved in the anti(neuro)inflammatory effects of PEA [74, 75]. Moreover, other data suggest that the beneficial anti-neuroinflammatory effects of PEA might be mediated, at least in part, by GPR55 activation [76]. In addition, other evidence indicates that PEA could produce several indirect receptor-mediated actions, through the so-called entourage effect [70, 77]. In particular, PEA may indirectly activate cannabinoids receptors CB1 and CB2 by acting as a false substrate for fatty acid amide hydrolase, the enzyme involved in the degradation of the endocannabinoid AEA [70, 78]. PEA can also indirectly activate the transient receptor potential vanilloid type 1 (TRPV1) channel, which is also a target for the endocannabinoids [79], via different mechanisms. Taken together, the above findings strongly suggest that PEA could play protective roles in contrasting neuroinflammation and neurodegeneration. The ability of PEA to synergistically interact via several mechanisms is attributed to the compound's quite unique properties in respect to the traditional anti-inflammatory drugs. In the case of FTD, these mechanisms have not directly investigated. However, our findings are consistent with previous works on animals models, indicating that PEA-LUT seems in fact to have an anti-inflammatory action in physiological and pathological conditions regulating microglial cells activity through the enhancement of GABA(B)ergic transmission [15]. It is thus possible that such an interaction may have also occurred in the current study. Further *in vivo* imaging studies using molecular ligands for microglial activity such as TSPO-ligands 11C-PK11195 [10, 11] could help to further deepen these complex interactions. Our study presents some limitations. First, the relatively small sample size did not allow us to have a completely homogeneous group of patients from a clinical point of view. Patients with FTD classically have frontal and temporal atrophy and hypometabolism which is often asymmetrical, with different patterns of grey matter atrophy for different clinical variants, mutations, and subtypes [80, 81]. In this extremely variable framework, further studies are needed to determine whether our current clinical and neurophysiological findings may vary depending on the pattern of atrophy in FTD patients and on the main clinical variants (bvFTD, svPPA, avPPA). In addition, we are aware of the fact that our conclusions are limited by the absence of a placebo control group. However, it is important to consider that we used several control protocols in our experimental design. Indeed, our results were specific for LICI, a well-known measure of GABA(B)-ergic neurotransmission, and not for the other protocols testing activity of other interneuronal populations. Along the same lines, our conclusions are supported by specific effects on beta/gamma frequencies, which are known to be mediate by GABAergic interneurons [17, 18]. Finally, we also tested the activity of a control area (PPC), which did not present any change after the treatment.

To conclude, our work suggests for the first time that PEA-LUT by acting on neuroinflammation could reduce behavioral disturbances and improve executive function in FTD patients through the modulation of cortical excitability and the restoration of the impaired GABAergic neurotransmission. Considering the lack of FDA-approved disease-modifying treatment for FTD [2], the cognitive and behavioral symptoms strongly affecting patients and caregivers' quality of life, and the limited efficacy of symptomatic drugs [82], our results could indicate that PEA-LUT and more in general drugs acting on neuroinflammation may be considered as potential effective targets to improve FTD management.

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