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LTP-like cortical plasticity is associated with verbal memory impairment in Alzheimer's disease patients

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ABSTRACT

Background: Alzheimer's disease (AD) is characterized by a primary impairment of long-term declarative memory caused by deposition of misfolded protein aggregates. Experimental studies showed that AD neuropathological alterations impair synaptic plasticity and memory performance. Transcranial Magnetic Stimulation protocols have been recently introduced to investigate altered mechanisms of cortical plasticity in AD patients.
Aim: To investigate relationship between Long-Term Potentiation (LTP)-like cortical plasticity and patients' neuropsychological performance.
Methods: We applied intermittent theta burst stimulation and extensive neuropshycological battery in 75 newly diagnosed AD patients.
Results: We found that LTP-like cortical plasticity impairment is selectively associated to a less efficient verbal memory ($r = 0.45$; $p = 0.002$), but not to other cognitive functions, independently from biomarkers and other demographic and clinical factors.
Conclusion: These findings suggest that LTP-like cortical plasticity may represent a neurophysiological surrogate of memory in AD patients by evaluating the weight of pathological changes responsible for cognitive dysfunction.

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Introduction

Alzheimer's disease (AD) is a neurodegenerative process leading to dementia. The AD cognitive dysfunction's pattern is characterized by a prevalent impairment of declarative long-term memory, at least in early phases of the disease [1]. Tests assessing the free recall of verbal material demonstrated a greater sensitivity in predicting conversion to AD in Mild Cognitive Impairment subjects [2]. Memory formation has been linked to the continuous refinement of synaptic connections between pyramidal cells in cortical networks [3]. Synaptic activity can be recorded with electrophysiological tools in vitro by eliciting Long Term Potentiation (LTP), a neurophysiological phenomenon considered a cellular correlate of learning and memory [4]. In AD models extensive literature demonstrated that Aβ peptides and tau proteins disrupt synaptic terminals with harmful effects on LTP [5] and memory formation [6]. In AD patients LTP mechanisms can be investigated with Transcranial Magnetic Stimulation protocols such as Theta Burst Stimulation (TBS) [7], showing a clear impairment of LTP cortical-like plasticity [8,9] consistent with the AD murine models of altered plasticity [10]. Moreover, AD patients seem characterized by an impairment of Short-Afferent Inhibition (SAI) protocol [11], reflecting the central cholinergic impairment typical in AD. Here we aimed to assess correlations between measures of cortical plasticity, central cholinergic signaling and cognitive impairment in newly diagnosed AD patients.

Materials and methods

Seventy-five consecutive patients were recruited according previous studies' criteria [12]. The following cognitive domains

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were investigated: general cognitive efficiency: verbal episodic memory: Rey auditory verbal long-term (RAVLT) memory (15-Word List Immediate and 15-min Delayed recall) [13]; visuospatial abilities and visuospatial episodic memory: Complex Rey's Figure (RCF) (copy and 10-min Delayed recall) [14]; executive functions: phonological word fluency (FVF) [15]; analogic reasoning: Raven's Colored Progressive Matrices (RPM) [16]. Motor evoked potentials (MEPs) were recorded from right first dorsal interosseous muscle using Ag–AgCl surface cup electrodes. A monophasic Magstim 200 device was used to define the motor hotspot and to assess MEP size using a standard 70-mm figure-of-eight–shaped coil. The motor hotspot was defined as the location where TMS pulse produced the largest MEP size at 120% of resting motor threshold (RMT) in the target muscle [17]. A second coil was connected to a biphasic Super Rapid Magstim stimulator to deliver iTBS [7] (see supplementary materials for a detailed description of subject's recruitment and TMS protocols). We used the mean change of MEP amplitude (mean of MEP amplitudes recorded at 1–25 min after iTBS respect to baseline), as surrogate of LTP-like cortical plasticity. SAI was calculated as the individual amount of change at ISI = +4 ms. Spearman's correlation was used to assess associations between MEP amplitude mean change and all the neuropsychological tests. Using a multivariable regression analysis the relationship between neuropsychological tests (utilizing age- and education-corrected scores) and LTP-like cortical plasticity was investigated adjusting for AD-related biomarkers and demographical factors. We accepted as significant p values of less than 0.05 at cluster level.

Results

Higher values of LTP were associated with higher long-term verbal memory performances (RAVLT delayed: $r = 0.53$; $p = 0.002$), while neither visual-spatial long-term memory (RCF delayed: $r = 0.08$; $p = 0.53$), general intelligence (RPM: $r = 0.06$; $p = 0.45$), executive functions (FVF: $r = -0.11$; $p = 0.36$) or visual-spatial abilities (RCF copy: $r = -0.19$; $p = 0.54$) showed any association (Fig. 1-A). SAI did not correlate with any of the above-mentioned tests (RAVLT delayed: $r = -0.15$, $p = 0.42$; RCF delayed: $r = 0.03$, $p = 0.81$; RPM: $r = 0.16$, $p = 0.14$; FVF: $r = -0.11$; $p = 0.43$; RCF copy: $r = 0.13$, $p = 0.21$). The relationship between LTP and RAVLT remained significant in a combined model adjusting for AD-related biomarkers and demographical factors (beta = 0.05, $p = 0.001$, 95% CI: 0.02–0.08) (Fig. 1-B).

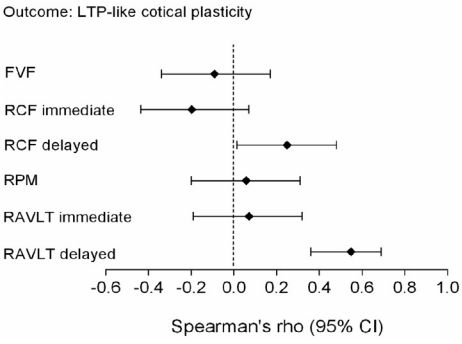
Discussion

Our results show that in AD patients a more impaired LTP-like cortical plasticity is associated to a less efficient long-term memory. This link could be explained by the deterioration of glutamatergic system occurring in AD [19], since studies on rodents [20,21] and humans [5] showed that generation of both iTBS aftereffects (in hippocampus [20] and neocortex [5,21]) and memory performances [22,23] are strictly related to NMDA receptors' activity. This explanation is further strengthened by the absence of correlation between verbal memory and SAI, that is a putative measure of central cholinergic activity [24] and memory [25].

We acknowledge that in young healthy subjects, evaluation of motor cortex plasticity shows an extreme inter-individual variability [26–28] due to changes in activation state [29–31] or genetic factors [32,33]. Nevertheless iTBS aftereffects seem the more reproducible in AD patients when compared to age-matched healthy controls, likely reflecting pathological rigidity of neurophysiological systems [34]. Consistent with our data a previous work showed that abnormal LTP-like cortical plasticity correlated with RAVLT performance in type-2 diabetes mellitus patients [35].

The impairment of episodic memory recall is a universal early symptom of AD congruous with the topographical distribution of the AD neuropathological abnormalities, involving precociously the hippocampus and the mesial–temporal lobe structures [36]. However, recent evidence suggests that this memory loss can be referred also to a dysfunction of large-scale networks underlying memory processes [37], caused by a disarrangement of cortico-cortical connections [38]. Notably, a recent neuroimaging study showed that verbal memory recall is associated in AD patients with impaired responses of fronto-parietal cognitive control networks [39]. Indeed, AD pathology does not involve only medial temporal lobe structures but spreads also to frontal regions [40] known to exert a cognitive control on memory functions [41]. Moreover, neuropathological studies in animals and humans have shown in the motor cortex a comparable burden of abnormalities in relation to other cortices generally considered more specific early targets for AD aggression [42]. Neurophysiological studies showed that changes in motor cortex physiology are associated with more general changes in brain function and plasticity, including cognitive function, in different clinical conditions [43–48]. More specifically in AD it has been extensively described a reduction of the resting motor threshold (that reflects neuronal membrane excitability) [49] resulting in cortical hyperexcitability and subclinical

A



B

	Coefficient	SE	*p* value	95%CI
LTP plasticity	0.051	0.014	<0.01	0.022 – 0.078
CSF total-tau	-0.001	0.001	0.43	-0.004 – 0.001
CSF p-tau	0.012	0.011	0.27	-0.009 – 0.033
CSF Beta 1-42	0.002	0.001	0.16	-0.009 – 0.005
APOE4	-0.147	0.672	0.83	-1.508 – 1.214
Female	-0.678	0.662	0.31	-2.019 – 0.664
Disease duration	-0.071	0.089	0.43	-0.251 – 0.110

Fig. 1. Spearman's rho values between LTP-like cortical plasticity and different cognitive tests. **1-A**: RAVLT: Tey-Auditory Verbal Learning Test; RCF: Rey Figure Copy; RPM: Raven's progressive matrices; FVF: Phonological verbal fluency; CI: Confidence Interval. **1-B** Multivariable adjusted model corrected for CSF t-tau, p-tau and Beta 1–42 levels, ApoE status, gender and disease duration. LTP-like plasticity is associated with memory performance also after adjusting for AD-related biomarkers and demographical factors. CI: Confidence Interval; SE: standard Error; LTP: Long Term Potentiation; CSF: cerebrospinal fluid.

motor cortical reorganization already evident from the early stages of the disease.

Thus, the altered cortico-motor plasticity induced by iTBS (that shows higher reproducibility in AD patients [34]) likely mirrors the brain-wide degeneration of neuroplasticity mechanisms, responsible for memory symptoms. Nonetheless, we suppose that other neurophysiological protocols, such as cortico-cortical paired associative stimulation (cc-PAS) [50,51], could better explore parietal function and its relations with other early AD clinical features, such as visuospatial deficits.

In conclusion, the correlation between episodic memory and LTP-like cortical plasticity suggests that in AD patients cortical plasticity impairment might cause memory deficits and reinforces the notion that LTP investigation may represent a valid and reliable tool to evaluate in vivo the weight of pathological changes responsible for cognitive dysfunction.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2018.10.009.

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