RESEARCH PAPER

Transcranial magnetic stimulation predicts cognitive decline in patients with Alzheimer's disease

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ABSTRACT

Objective To determine the ability of transcranial magnetic stimulation (TMS) in detecting synaptic impairment in patients with Alzheimer's disease (AD) and predicting cognitive decline since the early phases of the disease.

Methods We used TMS-based parameters to evaluate long-term potentiation (LTP)-like cortical plasticity and cholinergic activity as measured by short afferent inhibition (SAI) in 60 newly diagnosed patients with AD and 30 healthy age-matched subjects (HS). Receiver operating characteristic (ROC) curves were used to assess TMS ability in discriminating patients with AD from HS. Regression analyses examined the association between TMS-based parameters and cognitive decline. Multivariable regression model revealed the best parameters able to predict disease progression.

Results Area under the ROC curve was 0.90 for LTP-like cortical plasticity, indicating an excellent accuracy of this parameter in detecting AD pathology. In contrast, area under the curve was only 0.64 for SAI, indicating a poor diagnostic accuracy. Notably, LTP-like cortical plasticity was a significant predictor of disease progression (p=0.02), while no other neurophysiological, neuropsychological and demographic parameters were associated with cognitive decline. Multivariable analysis then promoted LTP-like cortical plasticity as the best significant predictor of cognitive decline (p=0.01). Finally, LTP-like cortical plasticity was found to be strongly associated with the probability of rapid cognitive decline (delta Mini-Mental State Examination score ≤−4 points at 18 months) (p=0.04); patients with AD with lower LTP-like cortical plasticity values showed faster disease progression.

Conclusions TMS-based assessment of LTP-like cortical plasticity could be a viable biomarker to assess synaptic impairment and predict subsequent cognitive decline progression in patients with ADs.

INTRODUCTION

Alzheimer's disease (AD) is one of the most devastating conditions affecting elderly people in the Western world. Relatively well-defined criteria have been identified for the diagnosis of early AD, based on patients' clinical presentation and biomarkers, allowing the presence of beta-amyloid (Aβ) and tau pathology to be detected either by cerebrospinal fluid (CSF) examination or PET imaging.[1 2] However, there is still lack of sufficient accuracy in predicting disease progression even when considering CSF (ie, Aβ42, t-tau and p-tau)[3 4] and neuroimaging parameters such as hippocampal atrophy/whole brain volume.[5] Thus, efforts are underway to combine multiple biomarkers to achieve these aims,[6 7] with the major challenge of tracking the temporal evolution of each biomarker throughout the disease course.[8] Moreover, these biomarkers are based on invasive and/or high-cost procedures limiting their use in clinical practice. Several experimental studies have recently highlighted the concept that loss of synaptic density could be an early event preceding neuronal degeneration, suggesting that the impairment of synaptic plasticity mechanisms could play a key role in the pathogenesis of AD.[9 10] Notably, the loss of synaptic density has been put in relationship to the degree of cognitive impairment in AD.[11] Pathogenic role played by Aβ peptides and tau proteins has been shown to interfere with physiological mechanisms of neuronal synaptic plasticity in AD animal models,[12] with a detrimental effect on hippocampal long-term potentiation (LTP), the main neurophysiological correlates for learning and memory.[10 13]

Within this framework, novel neurophysiological techniques and in particular the transcranial magnetic stimulation (TMS) have been demonstrated to represent a valuable and reliable tool to identify and track synaptic impairment in humans. Several studies using TMS in experimental settings have claimed the detection of abnormalities in cholinergic transmission[14] and cortical reactivity[15] in patients with AD, showing differences between AD patients, those with other dementias and healthy elder individuals. Recent evidence suggests that, apart from cholinergic transmission,[14] LTP-like cortical plasticity is consistently impaired in patients with AD.[16–19] LTP can be assessed reliably and safely by means of intermittent theta burst stimulation (iTBS) protocol applied over the primary motor cortex (M1).[20]

Given its reliable ability in identifying cortical changes since early phases of the disease, here we aimed to evaluate the potential use of TMS in clinical/diagnostic pathway of AD. In particular, we investigated whether the assessment of synaptic impairment measured by TMS protocols could be related to cognitive domain dysfunction, as evaluated by means of neuropsychological tests, and to CSF biomarker profile.

Table 1 Clinical and electrophysiological data of patients with AD and the healthy control subjects

	AD (n=60)	HS (n=30)	P values
Age at baseline, years (mean±SD)	68.2±5.9	66.3±5.2	0.17
Female (%)	46%	54%	0.53
Disease duration, months (mean±SD)	13.5±3.9	–	
Education, years (mean±SD)	8.6±3.8	8.2±3.5	0.81
RMT (% mean±SD)†	36.8±6.8	43.2±4.3	<0.001*
Baseline MEP, mV (mean±SD)	1.21±0.42	1.19±0.35	0.66
SICI 3 ms (% mean±SD)‡	68.9±33.9	65.4±34.8	0.77
ICF 15 ms (% mean±SD)‡	115.1±37.0	116.0±47.6	0.93
SAI+4 ms (% mean±SD)‡	67.1±26.8	53.7±18.3	0.02*
LTP plasticity (% mean±SD)‡	80.7±25.4	129.0±26.4	<0.001*
CSF total-tau pg/mL (mean±SD)	674.4±368.9	–	
CSF p-tau pg/mL (mean±SD)	85.6±44.6	–	
CSF beta 1–42 pg/mL (mean±SD)	368.7±205.6	–	
APOE4 (%)	41%	–	

*Indicates p value <0.05.
†Is related to the maximal stimulator output.
‡Is related to the control MEP amplitude.
For SICI, ICF, SAI, LTP and LTD values, '%' are related to the control MEP amplitude.
AD, Alzheimer disease; CSF, cerebrospinal fluid; HS, healthy subjects; ICF, intracortical facilitation; LTP, long-term potentiation; MEP, motor evoked potential; RMT, resting motor threshold; SAI, short-latency afferent inhibition; SICI, short intracortical inhibition.

METHODS

Subjects

Sixty consecutive patients (range, 55–80 years; median, 69) were recruited at the memory clinic of the University Hospital Tor Vergata, admitted for complaining memory symptoms. Patients fulfilled the clinical criteria of dementia as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association.[21] Disease duration was calculated using standardised semistructured questions.[22] After the first visit to our centre, all patients underwent, for diagnostic purposes, a complete clinical investigation in a period not superior to 60 days, including medical history, neurological examination, Mini-Mental State Examination (MMSE), a complete blood screening and neuropsychological assessment including the following cognitive domains—general cognitive efficiency: MMSE; verbal episodic memory: Rey auditory verbal long-term memory (15-Word List Immediate and 15 min Delayed recall);[23–25] visuospatial abilities and visuospatial episodic memory: Rey's Complex Figure (RCF, copy and 10 min delayed recall);[26] executive functions: phonological word fluency;[27] analogic reasoning: Raven's Coloured Progressive Matrices.[27] Patients underwent also a neuropsychiatric evaluation, magnetic resonance or CT imaging, PET/CT and lumbar puncture for CSF analysis (table 1). Exclusion criteria were cognitive isolated deficits, clinically manifest acute stroke in the last 6 months showing a Hachinsky scale score >4 and a radiological evidence of ischaemic lesions, Ab1-42 CSF values >600 pg/mL.

Neurophysiological examinations were performed at the Santa Lucia Foundation within 30 days from CSF sampling. In the 90 days preceding TMS evaluation, none of the patients were treated with drugs that could have modulated cerebral cortex excitability such as acetylcholinesterase inhibitors, antidepressants or any other neuroactive drugs (ie, benzodiazepines, antiepileptic drugs or neuroleptics). After the neurophysiological assessment, all patients started treatment with rivastigmine patch (n=37) or donepezil (n=23) and were followed longitudinally with clinical assessments and MMSE testing at 6, 12 and 18 months. Thirty age-matched, sex-matched and education-matched HS (range, 58–73 years; median, 67) were recruited as controls. The study was performed according to the Declaration of Helsinki.

Biomarker collection and genotype analysis

The CSF was collected in a polypropylene tube, directly transported to the local laboratory for centrifugation at 2000*g* at +4°C for 10 min to eliminate cells and cellular debris and stored at −80°C pending biochemical analyses. CSF t-tau, p-tau phosphorylated at Thr181 and Aβ1–42 concentrations were determined using a sandwich ELISA (Innotest hTAU-Ag; Innogenetics, Gent, Belgium; Innotest β-amyloid; Innogenetics).[28] Genotyping for APOE were performed by allelic discrimination technology (TaqMan; Applied Biosystems).

TMS

A standard 70 mm TMS figure-of-eight coil connected to a monophasic Magstim Bistim2 system (Magstimo, Whitland, UK) was used for all TMS paradigms. Motor evoked potentials (MEPs) were recorded from the right first dorsal interosseous muscle during full muscle relaxation as previously reported.[17]

Resting motor threshold (RMT) was defined as the minimum stimulus intensity required to produce MEPs with a 50 mV amplitude in 50% of 10 consecutive trails.[29] The active motor threshold) was defined as the minimum stimulus intensity required to produce a minimal MEP (approximately 200 µV in 50% of 10 trials) during isometric contraction of the first dorsal interosseus (FDI) at around 10% of maximum force as measured through a manual transducer.

For the iTBS protocol, a second coil was connected to a biphasic Super Rapid Magstim stimulator (Magstim) and a 2 s train of TBS was repeated 20 times, every 10 s for a total of 190 s (600 pulses).[20] Twenty MEPs were collected and averaged at baseline. Then, over the same hotspot, 20 MEPs were recorded at 1–5, 6–10, 11–15, 16–20 and 21–25 min after iTBS and averaged.

Short-latency afferent inhibition (SAI) protocol consisted in the application of a conditioning stimuli (CS) of single pulses (200 µs) of electrical stimulation applied through bipolar electrodes to the right median nerve at the wrist with cathode positioned proximally.[30] Intensity of the CS was set at the lower level sufficient for evoking a visible twitch of the thenar muscles. The CS to the peripheral nerve preceded a magnetic test stimulus (TS) by different interstimulus intervals (ISIs), ranging from –4 to 18 ms from N20 in steps of 4 ms. TS was set to evoke an approximately 1 mV MEP in the relaxed FDI muscle. Ten paired stimuli CS–TS were delivered at each ISI with an intertrial interval of 5 s (±10%). The amplitude of the conditioned MEP at each ISI was expressed as a percentage of the amplitude size of the unconditioned test pulse in that block.

For short intracortical inhibition (SICI) and intracortical facilitation (ICF), we used a paired-pulse protocol with the CS preceding the TS by different ISIs: 1, 2, 3, 5 ms for SICI and 7, 10, 15 ms for ICF. For this protocol, the CS was set at 70% of the RMT.[15]

Statistics

We used the mean change of MEP amplitude (mean of MEP amplitudes recorded at 1–25 min after iTBS respect to baseline) as a surrogate of LTP-cortical plasticity. SAI was calculated as the individual amount of change at ISI=+4 ms because it has been already shown by using this specific ISI the capacity of SAI to detect the neurophysiological changes occurring in AD pathology.[17] Receiver operating characteristic (ROC) curve analyses and the area under the curve (AUC) were used to assess the ability (in terms of the sensitivity and specificity) of LTP, SAI and RMT in discriminating patients with AD from HS and, among patients with AD, those with faster disease progression. The method of Delong was used for the comparison of AUCs. The required sample sizes for each group of AD and HS for comparison of TMS measures on the same subjects were calculated with 80% power, a two-sided alpha level of 5% and an allocation ratio of 0.5 to detect an effect for LTP of 0.12.

Correction for multiple comparisons was used where appropriate. Data are presented as mean±SD. Only in patients with AD, Pearson *r* correlation coefficient or Wilcoxon/Kruskal-Wallis rank-sum test was used to explore any relationship between the individual amount of LTP-like cortical plasticity, demographics, cognition and AD-related biomarkers. Regression analyses were then performed to characterise the association between each clinical/neurophysiological parameter and clinical progression in patients with AD (delta MMSE score at 18 months respect to baseline). OR/beta coefficient (*beta*), SE, 95% CI and the variance explained (R^2) were reported. Finally, backward and forward multivariable regression analysis was performed to find the best explanatory variable for cognitive decline.

RESULTS

Demographic and clinical features of patients and controls are summarised in table 1.

LTP as neurophysiological biomarker able to discriminate AD from HS

Marked TMS abnormalities have been documented in patients with AD compared with HS. As compared with HS, patients with AD showed the expected reduction of motor thresholds (RMT) (AD 36.8±6.8; HS 43.2±4.3; p<0.001), a consistent alteration of SAI (AD 67.1±26.8; HS 53.7±18.3; p=0.02) and significant impairment of LTP-like cortical plasticity (AD 80.7±25.4; HS 129.0±26.4; p<0.001). Conversely, we did not find any difference for SICI and ICF between AD and HS groups (p>0.05 for comparisons) (see table 1). When performing ROC curve analysis, we found an AUC of 0.90 (SE 0.03; 95% CI 0.83 to 0.96) for LTP, indicating an excellent diagnostic accuracy of this parameter, but an AUC of only 0.64 (SE 0.06; 95% CI 0.52 to 0.77) for SAI and 0.76 (SE 0.05; 95% CI 0.66 to 0.87) for RMT (figure 1). ROC curve comparison confirmed LTP as the most accurate neurophysiological biomarker able to identify AD pathology (p<0.01 for both comparisons).

LTP-like cortical plasticity association with AD biomarkers

LTP plasticity was not significantly associated with sex ($z=0.89$, p=0.37), age ($r=-0.02$, p=0.75) or APOE genotype ($z=-0.81$, p=0.41). We confirm a significant association between LTP and both CSF t-tau ($r=-0.34$, p<0.01) and p-tau levels ($r=-0.26$, p=0.04), while no significant association was found for $A\beta_{1-42}$ ($r=-0.01$, p=0.89).

LTP-like cortical plasticity as predictor of disease progression

Higher values of LTP were associated with higher long-term verbal memory performances (California Verbal Learning Test (CVLT) delayed: $r=0.45$; p=0.002) (figure 2), while neither visual–spatial long-term memory (RCF delayed: $r=0.08$; p=0.53), general intelligence (Raven's Progressive Matrices test: $r=0.11$; p=0.45), executive functions (verbal fluency (FVF): $r=-0.13$; p=0.36) or visual–spatial abilities (RCF copy: $r=-0.08$; p=0.54) showed any association.

Moreover, in univariate linear regression analysis, LTP showed a significant association with disease progression (delta MMSE at 18 months respect to baseline) (*beta* 0.06; 95% CI 0.01 to 0.12; p=0.02; R^2 0.10), while no other AD neurophysiological, neuropsychological and demographic parameters were associated with cognitive decline, except for a trend regarding sex (*beta* −2.38; 95% CI −4.96 to 0.20; p=0.07; R^2 0.06), CVLT delayed (*beta* 0.49; 95% CI −0.04 to 1.02; p=0.07; R^2 0.09), CSF total-tau levels (*beta* 0.003; 95% CI −0.007 to 0.001; p=0.09; R^2 0.05) and RCF copy (*beta* −0.13; 95% CI −0.29 to 0.03; p=0.10; R^2 0.06) (table 2). We then used a stepwise, multivariable analysis including all variables with p value <0.10 at univariate analysis, and we found that LTP was the only variable retained in the

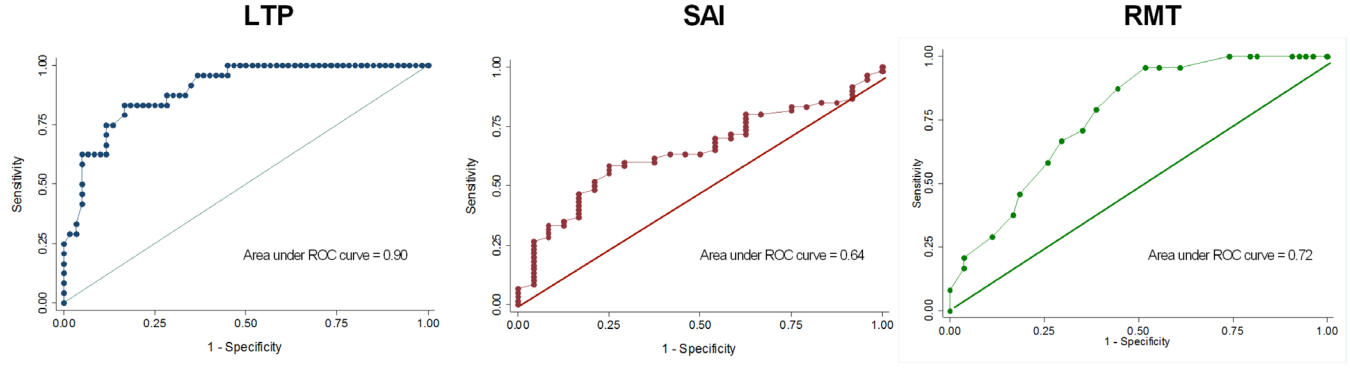

Figure 1 Receiver operating characteristic (ROC) curve analysis shows that long-term potentiation (LTP) has an excellent accuracy (area under the curve (AUC) 0.90) in discriminating patients with Alzheimer disease from healthy controls, respect to short-latency afferent inhibition (SAI) (AUC 0.64) and resting motor threshold (RMT) (AUC 0.72).

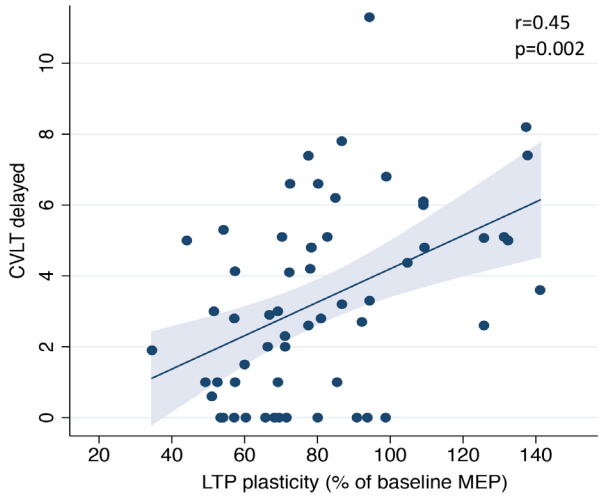

Figure 2 Long-term potentiation (LTP)-like cortical plasticity is significantly associated with delayed recall performances assessed by California Verbal Learning Test (CVLT). MEP, motor evoked potential.

model as significant predictor of cognitive decline (*beta* 0.07; 95% CI 0.01 to 0.12; p=0.01; R^2 0.14).

Finally, we performed a logistic regression analysis to assess the predictive value of LTP on the probability of rapid disease progression (evaluated as delta MMSE ≤−4 points at 18 months) and we observed a strong linear association (OR 0.97; 95% CI 0.94 to 0.99; p=0.04; R^2 0.07) in a way that a lower value of LTP plasticity was associated with higher probability of rapid cognitive decline (figure 3), confirming again a clear relationship between cortical plasticity impairment and disease progression in patients with AD.

Table 2 Univariate regression: predictors of disease progression (delta MMSE at 18 months respect to baseline)

	Coefficient	SE	P values	95% CI
LTP plasticity	0.06	0.03	0.02*	0.008 to 0.113
SAI	−0.004	0.02	0.85	−0.05 to 0.04
RMT	0.006	0.09	0.95	−0.19 to 0.20
CSF total-tau	−0.003	0.002	0.09	−0.007 to 0.001
CSF p-tau	−0.02	0.02	0.22	−0.05 to 0.01
CSF beta 1–42	0.001	0.003	0.54	−0.004 to 0.008
APOE4	−1.43	1.43	0.32	−4.32 to 1.46
Age	−0.08	0.11	0.43	−0.30 to 0.13
Female	−2.38	1.28	0.07	−4.96 to 0.20
Disease duration	0.05	0.19	0.78	−0.32 to 0.43
Education	0.21	0.17	0.24	−0.14 to 0.55
CVLT immediate	0.08	0.09	0.39	−0.10 to 0.26
CVLT delayed	0.49	0.26	0.07	−0.04 to 1.02
RCF immediate	−0.13	0.08	0.10	−0.29 to 0.03
RCF delayed	0.14	0.17	0.44	−0.21 to 0.48
RPM	−0.09	0.10	0.40	−0.30 to 0.12
Verbal fluency test	−0.06	0.06	0.28	−0.18 to 0.05

*Indicates p value <0.05.
CSF, cerebrospinal fluid; CVLT, California Verbal Learning Test; LTP, long-term potentiation; MMSE, Mini-Mental State Examination; RCF, Rey's Complex Figure; RMT, resting motor threshold; RPM, Raven's progressive matrices; SAI, short-latency afferent inhibition.

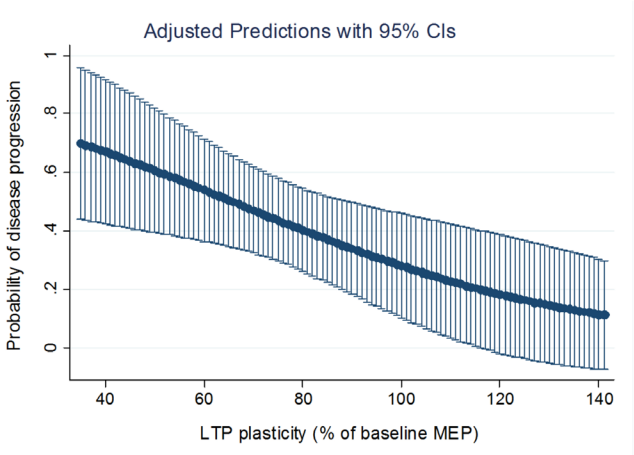

Figure 3 Probability of disease progression (delta Mini-Mental State Examination score ≤−4 at 18 months respect to baseline) according to long-term potentiation (LTP) measure. MEP, motor evoked potential.

DISCUSSION

We provide novel evidence that TMS is a viable biomarker useful to assess synaptic impairment and predict subsequent cognitive decline progression in patients with AD since the early phases of disease.

We found that patients with AD, as opposed to HS, are characterised by a weakened LTP-like cortical plasticity together with an impairment of SAI, putative biomarker of central cholinergic transmission[31] and a higher level of cortical excitability, consistent with previous findings.[15] On the other hand, consistent with the previous literature,[15 32] our findings do not show an impairment of SICI and ICF in patients with AD.

Remarkably, we found that LTP-like cortical plasticity is the most powerful TMS measurement in identifying patients with AD among all these neurophysiological parameters. This was not unexpected since we recently demonstrated that LTP-like cortical plasticity is severely dampened in patients with AD, independently from age of disease onset.[17] On the other hand, the dysfunction of cholinergic transmission investigated with SAI protocol was one of the first TMS findings in patients with AD with the ability to discriminate between different forms of dementia.[33–36] However, recent evidence showed an age-dependent alteration SAI circuits of both healthy subjects (HS) and patients with AD,[17] suggesting that cholinergic dysfunction represents more likely a marker of the interaction between physiological and pathological ageing. This could explain the poorer accuracy of SAI in discriminating patients with AD from cognitively normal age-matched individuals.

Apart from determining the diagnostic accuracy of TMS, our data show that LTP-like cortical plasticity is able to predict cognitive decline in patients with AD. As revealed by the logistic regression analysis, the probability of a faster cognitive decline increased with every point decrease of LTP-like cortical plasticity, suggesting that the level of cortical plasticity evaluated at early stages of the disease is strictly linked to the subsequent clinical worsening in these patients. This finding is supported by experimental works showing that synaptic loss is the strongest pathophysiological correlate of cognitive decline, pointing to synaptic degeneration as a central mechanism in the dementia.[11] Thus, the impairment of synaptic transmission due to toxic oligomeric species[9] could predict disease severity more precisely than neuronal loss, which is a more tardive event. Taken together, this evidence suggests that synaptic dysfunction could represent a key driver of AD-related

cognitive decline rather than a mere product of ongoing neurodegeneration. Translationally, we propose LTP-like cortical plasticity as a core neurophysiological marker of AD-related dysfunction, able to predict clinical progression.

Our results were also corroborated by the finding that a more impaired LTP-like cortical plasticity is associated to a less efficient verbal memory. The impairment of episodic memory recall is an almost universal early symptom of AD, and neuroimaging studies recently showed that verbal memory recall is associated in patients with AD with greater activity within frontal and frontoparietal cognitive control networks.[37]

Furthermore, more impaired LTP-like cortical plasticity was associated with higher t-tau but not 1–42 Aβ CSF levels. Aβ peptides exist in several soluble forms (oligomers) that can be released in the extracellular space where they may induce direct detrimental effects on neuronal transmission.[10] However, consistent with previous findings,[38 39] Aβ 1–42 fragments detected in the CSF of our patients with ADs did not correlate with measure of cortical plasticity.

It is interesting to note that the link between impaired cortical plasticity measures and CSF tau levels is clinically relevant when considering that patients with AD with very high CSF t-tau levels exhibit a faster disease progression[39] and higher mortality and that experimental studies have demonstrated that tau proteins can directly interfere with physiological mechanisms of neuronal synaptic plasticity in AD animal models.[13]

A limitation of the current work is that the data were collected from a relatively small sample size and need to be replicated in larger populations of patients with AD. The reliability of TBS (and other TMS techniques) is another critical point since the interindividual variability of a measure might reduce its sensitivity. However, several works of recent literature demonstrated that interindividual variability in patients with AD is very low respect to healthy individuals.[16 17 40] In particular, Fried and colleagues[40] investigated the reproducibility of single, paired-pulse TMS and patterned repetitive TMS, finding that measures of iTBS-induced LTP-like plasticity were the more reproducible among patients with AD, suggesting that the same pathological processes that cause certain measures to be abnormal in AD also exert a stabilising effect on TMS measures.[40] The relatively high reproducibility of LTP in AD would suggest validating its use as surrogate biomarker of AD cortical pathology. Moreover, further investigations are needed to study whether LTP-like cortical plasticity could be useful in discriminating between AD and other forms of dementia or could predict cognitive decline also in asymptomatic subjects at risk for AD.

CONCLUSIONS

The current advances in non-invasive brain stimulation techniques could provide the unique possibility to track and predict AD disease progression, by providing a reliable and well-characterised estimate of cortical synaptic activity, safely, with reduced costs.

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