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Transcranial Magnetic Stimulation in Alzheimer's Disease: A Review of Investigational and Therapeutic Findings

Stefano Pallanti[1-3]* and Anna Marras[3]

[1]UC Davis School of Medicine, Department of Psychiatry and Behavioral Sciences, Sacramento, CA, USA.
[2]Albert Einstein College of Medicine and Montefiore Medical Center, New York, USA.
[3]University of Florence, Department of Neuroscience, Florence, Italy

Abstract

Alzheimer's disease pathophysiology still remains unclear and current pharmacological strategies have limited effectiveness, so that the search for alternative and/or complementary therapeutic strategies is a compelling need, as well as a detailed characterization of the disease progression and its neurophysiological correlates. Transcranial Magnetic Stimulation (TMS),has been employed by a number of studies to physiologically characterize AD, investigating cortical reactivity, plasticity and functional connectivity. A few studies also investigated the therapeutic role of repetitive TMS to enhance cognitive functions in AD. Herein we review a total of thirty-two studies evaluating both investigational and therapeutic role of TMS. Although promising, therapeutic results are still very preliminary and need to be taken with caution, while insights have been provided by most investigational studies.

Keywords: Alzheimer's disease; Transcranial magnetic stimulation; Treatment; Diagnostics; Cortical reactivity; Cognitive functions

Introduction

Alzheimer's disease (AD) is neurodegenerative disease characterized by progressive neuronal loss, altered synaptic plasticity and disruptions in neurotransmitters levels, associated with episodic memory loss and decline in other cognitive domains (i.e., language comprehension, visuo-spatial orientation, word retrieval), as well as sensory and motor functions deterioration. Current available pharmacological treatments, such as acetylchol inesterase inhibitors (AchEI) and N-Methyl-D-aspartate receptor (NMDAR) antagonistsshowed limited effectiveness [1], and none can delay or stop the disease progression. Gene therapy (mainly viral vectors) has been proposed as an alternative to traditional strategies, with the aim of a "disease modification" [2], as well as other potential approaches such as methylene blue and osmolytes [3]. Albeit promising, results are still preliminary: therefore, the search for alternative and/or complementary therapeutic strategies is a compelling need, as well as a detailed characterization of the disease progression and its neurophysiological correlates.

In recent years, noninvasive neuromodulation techniques, such astranscranial magnetic stimulation (TMS) and deep brain stimulation (DBS),emerged as valuable tools in the diagnostic field and may represent candidate treatments for AD, given theirtherapeutic potential in psychiatric and neurologic disorders [4]. TMS is able to modulate cortical and subcortical function by the use of rapidly changing electromagnetic fields generated by a coil placed over the scalp. TMS may be used both with investigational and therapeutic purposes: single-pulse and paired-pulse protocols are generally employed to investigate cortical excitability and reactivity, while repetitive TMS (rTMS) is usually employed for treatment. Depending on the parameters of stimulation, rTMS can either decrease or increase cortical excitability in relatively focal areas, with low frequencies (<1 Hz) being usually inhibitory and high frequencies (>5 Hz) being usually excitatory [5,6]. rTMS is also known to induce synaptic plasticity effects on the brain, such as long-term potentiation (LTP) and long-term depression (LTD) [7]. DBS is a neurosurgical procedure that involves the implantation of a brain pacemaker, delivering electrical impulses via the implanted electrodes within specific areas of the brain to modulate the activity of dysfunctional circuits. DBS has been successfully employed in several neurodegenerative and neuropsychiatric disorders (Parkinson's disease, tremor, obsessive-compulsive disorder, major depression) [8-10]. Recently, its use in other neurodegenerative disorders, such as AD, is being considered. Compared to TMS, DBS represent an invasive neuromodulation technique, which requires careful patient selection and follow-up. Therefore, its use is restricted to a limited number of suitable candidates and the literature regarding its employ in AD is still preliminary. Herein, we provide a brief review of the most consistent neurophysiologic findings and preliminary therapeutic results obtained with TMS in AD.

TMS as an investigational tool

In the last two decades, TMS has been employed to investigate cortical reactivity, plasticity and functional connectivity: we reviewed a total of 25 studies [11-35], of which 22 focused on several cortical reactivity measures [11-22,24,25,27,28,30-34] and the remaining 3 focused on cortical plasticity and connectivity measures [23,26,28] (Table 1).

Cortical reactivity measures: The most consistent finding from reviewed studiesis a decreased resting motor threshold (RMT) in AD patients compared to controls, found in 15 of 24 studies assessing this measure [12-20,23,24,27,29,31,32,34]: RMT is the basic unit of transcranial magnetic stimulation dosing and it is thought to reflect membrane excitability of corticospinal neurons and interneurons projecting onto these neurons in the motor cortex [4]. Only one study [11] found increased RMT in AD patients, and the remaining 8 [15,21,25,26,28,30,33,35] found no significant differences: the overall results of a decreased RMT in AD seem to support the notion of a motor cortex hyper excitability in the disease.

***Corresponding author:** Stefano Pallanti, M.D., Ph.D., 3 Largo Brambilla, 50134 Firenze, Italy, Tel: 055 794 9707; Fax: 055 581051; E-mail: stefanopallanti@yahoo.it

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Study (Reference)	Number of patients	RMT	SAI	MEP	cSP	SICI	ICF	Cortical plasticity/connectivity
11	15	↑	-	N.S.	↓	-	-	-
12	14	↓	-	↑	-	-	-	-
13	17	↓	-	↑	-	N.S.	N.S.	-
14	21	↓	-	↑	↓	-	-	-
15	11	N.S.	-	-	N.S.	↓	N.S.	-
16	17	↓	-	N.S.	-	-	-	-
17	15	↓	↓	N.S.	N.S.	N.S.	N.S.	-
18	16	↓	-	-	-	-	-	-
19	20	↓	-	N.S.	N.S.	-	-	-
20	28	↓	↓	-	-	N.S.	-	-
21	12	N.S.	-	N.S.	-	↓	N.S.	-
22	20	-	↓	-	-	-	-	-
23	20	↓	-	N.S.	N.S.	-	-	5 Hz rTMS: lack of MEP ↑ N.S. [1 Hz]
24	20	↓	↓	-	-	-	-	-
25	13	N.S.	↓	-	N.S.	↓	N.S.	-
26	10	N.S.	-	N.S.	-	-	-	PAS: LTP-like plasticity ↓
27	10	↓	↓	N.S.	-	N.S.	-	-
28	12	N.S.	↓	-	-	-	-	-
29	5	↓	-	N.S.	-	-	-	EEG: TMS-evoked P30 ↓
30	8	N.S.	-	-	-	N.S.	N.S.	-
31	12	↓	↓	-	-	N.S.	-	-
32	11	↓	-	-	-	↓	N.S.	-
33	17	N.S.	↓	-	-	N.S.	N.S.	-
34	10	↓	↓	-	-	-	-	-
35	11	N.S.	-	-	-	↓	↓	-

Legend: RMT, resting motor threshold; SAI, short-latency afferent inhibition; MEP, motor evoked potential; cSP, cortical silent period; SICI, short-interval intracortical inhibition; ICF, intracortical facilitation; N.S., non significant; Hz, Hertz; rTMS, repetitive Transcranial Magnetic Stimulation; PAS, paired associative stimulation; LTP, long-term potentiation; EEG, electroencephalogram; ↑, increase; ↓, decrease.

Table 1: Findings from studies employing TMS as an investigational tool in AD: cortical reactivity, plasticity and connectivity results.

Another major findingis a significant decrease of short-latency afferent inhibition (SAI) in AD patients compared to controls, retrieved by all 10 studies assessing this measure [17,19,22,24,25,27,28,31,33,34] . SAI reflects an inhibitory effect, and it is considered a putative marker of central cholinergic activity [36]. Consequently, a decreased SAI is probably correlated with the broadly recognized reduced cholinergic activity characterizing AD. It is noteworthy that SAI appears to be normal in patients with mild cognitive impairment (MCI) –[28], so that it may not be useful to anticipate risk for development of AD, while it is helpful to differentiate AD from frontotemporal dementia [24] or vascular dementia [31].

Other cortical reactivity measures provided minor findings: the amplitude of motor evoked potentials (MEPs) has been found increased in 3 of 12 studies [12-14], while the remaining 9 [11,15-17,19,21,23,26,27,29] did not find significant differences in AD patients compared to controls. Abnormal MEPs may reflect dysfunctions at different levels in the corticospinal pathway, so that overall results suggest that the corticospinal tract is intact, at least in the early stages of the disease. Cortical silent period (cSP) and short-interval intracortical inhibition (SICI) are thought to reflect the excitability of inhibitory GABAergic cortical circuits. Only 2 of 7 studies [11,14] found a cSP reduction and 5 of 12 studies [15,21,25,32,35] found a significant reduction of SICI in AD patients, while most studies found no differences in these measures between AD patients and healthy controls, providing no support of GABAergic inhibition impairments in the disease.

Lastly, intracortical facilitation (ICF) has been found reduced in 1 study of 9 [35], while the other 8 [13,15,17,21,25,30, 32,33] did not find significant differences in ICF of AD patients compared to healthy controls. Since ICF is thought to reflect excitatory neurotransmission of the motor cortex, mediated by NMDARs, overall results suggest a normal NMDAR-dependent glutamate excitatory activity in AD.

Cortical plasticity and functional connectivity: Three studies assessed cortical plasticity [23,26] and connectivity [29] in AD, using two different TMS protocols: paired associative stimulation (PAS) and cortical responses to rTMS. The latter has been described above, while the former is a protocol of stimulation involving low frequency repetitive median nerve electric stimulation paired with timed TMS over the contralateral the motor cortex. Also, TMS and EEG are often combined and the real-time integration of these two provides more precise information on local and networks cortical excitability. Regarding cortical plasticity, arTMS study [23] employed suprathreshold high-frequency (5 Hz) rTMS to evaluate the effects of cortical motor areas modulation in AD patients and healthy controls: results showed normal MEPs that progressively increased in amplitude in controls, while patients exhibited decreasing MEPs after rTMS stimulation. This suggested the presence of facilitatory cortical plasticity disruptions in AD, while the cortical inhibitory circuits were found to be normal, as proved by an increase of cSP following rTMS in both groups. Moreover, a PAS study [26] compared corticomotor LTP-like plasticity in AD patients and healthy controls and found reduced PAS-induced plasticity in patients. These results suggest impaired

glutamatergic neurotransmission in AD, likely through NMDAR dysfunction.

In regard to functional connectivity, Julkunen et al. [29] assessed functional connectivity between motor cortex and other cortical regions. Using real-time integration of TMS and EEG, areduced reactivity and cortical connectivity between regions were found in patients with AD compared to both MCI subjects and healthy controls. The authors reported decreased TMS-evoked response at 30–50 ms in AD patients over widespread brain regions, especially in the ipsilateral parietal cortex and contralateral frontocentral areas, suggesting a large-scale sensorimotor networks dysfunction, possibly accompanied by a reduced synchronization of EEG activity in AD patients.

Normal cortical functioning in AD and progression of disease: A few cortical reactivity and connectivity measures appear to be non-pathological in AD, suggesting the integrity of specific brain structures and pathways. As previously mentioned, MEPs amplitude did not show significant differences between AD patients and healthy controls, as well as cSP, SICI and ICF. Moreover, central motor conduction time (CMCT) – whose amplitude alterations reflect demyelination or neuronal loss [4]–was also found to be unaffected in AD patients compared to controls [11,12,14,15,17,25,33]. Recent contributions also report a normal spinal cord motor conduction velocity (SCMCV), which reflect the integrity of the myelin sheath of pyramidal tract [37]. Taken together, these results suggest the integrity of the corticospinal tract in AD, and seem to provide further evidence of cholinergic system involvement as central in the disease process. In fact, Yang et al. [37] propose that the protection of motor neurons in motor cortex and corticospinal tract may be explained by the involvement of glutamic acid, instead of acetylcholine, as neurotransmitter in the corticospinal tract. Consequently, the high excitability of motor cortex and spinal cord may derive from the loss of acetylcholine control by inhibitory interneurons in the cerebral cortex and spinal cord, which determines a failure in the inhibition of motor cortex neurons and anterior horn cells of the spinal cord [37].

Regarding disease progression, from MCI to AD, several biomarkers have been proposed to identify a disease progression model. MCI represents an intermediate state of cognitive impairment that is greater than the level expected for a subject's education level and age [38] but does not meet criteria for dementia and does not compromise activities of daily living. MCI is often considered as a prodromal stage of AD, although not all cases of MCI progress to AD. The most reliable biomarkers of MCI progression to AD seem to be neuropsychological markers (episodic memory and semantic fluency) and some structural MRI makers (hippocampal atrophy, ventricular volume and whole brain atrophy) [39]. Also, cerebrospinal fluid (CSF) biomarkers, such as total tau, phosphorylated tau at the threonine 181 position (p-tau181p) and CSF amyloid beta 1 to 42 peptide (Aβ1–42), seem to carry information about disease pathology and represent promising markers for inclusion in clinical trials [40]. Quantitative EEG may also provide useful information regarding disease progression, as progressing MCI subjects show a reduced posterior alpha power at baseline, predicting cognitive decline and correlated with poorer cognitive function in psychometric tests [41]. Cortical reactivity and connectivity measures in MCI are still limited: as previously mentioned,SAI seems to represent a non-specific measure to discriminate between MCI and AD [28] and currently, cannot represent a reliable biomarker by itself [42]. RMT was also found to be normal in MCI subjects [28], suggesting a decrease during the later stages of disease [21].

TMS-evoked EEG responses may provide some useful insights: Julkunen et al. [29] reported P30 and P200 amplitudes of MCI group as halfway between the values of AD and control group, supporting the notion of MCI as a transition state from healthy aging to AD, while an increased activity in P30 GFP magnitude was found in MCI subjects. In a later study [43], the authors tested the sensitivity of TMS-EEG to discriminate between controls and MCI and AD subjects, and to evaluate the relationship between TMS-EEG response and cognitive decline. They found that the TMS-EEG response P30 amplitude correlated with cognitive decline, showing good specificity and sensitivity in differentiating healthy subjects from those with MCI or AD. Recently, decreased cholinergic activity was reported in vivo in MCI patients [44,45], supporting the cholinergic hypothesis also in the earlier stages of disease and suggesting cholinergic dysfunction as an early hallmark even before onset of dementia at the clinical stage of MCI.

TMS as a Therapeutic Tool

We reviewed a total of 7 studies [46-52], in which the major insights on the potential therapeutic effects of rTMS in AD come from the work of Cotelli et al. the research team conducted three consecutive studies assessing the effects of high-frequency rTMS on naming and language performance in AD subjects [46-48]. The first two crossover, sham-controlled, single-session studies [46,47] administered high-frequency (20 Hz) rTMS over the left and right dorsolateral prefrontal cortex (DLPFC) during the execution of naming tasks (on-line rTMS). While the first study [46] showed improved accuracy in action naming but not in object naming, in the second study [47] patients were distinguished on the basis of AD severity and differences between the two groups were found. Indeed, the results of previous study were replicated in mild AD patients (Mini Mental State Examination (MMSE) ≥ 17/30), while patients with moderate to severe AD (MMSE < 17/30), showed improvement in both action and object naming after rTMS treatment. In the latest study [48], Cotelli et al. investigated the effects on language production and comprehension of high-frequency (20 Hz) off-line rTMS over the left DLPFC in moderate AD patients. Results showed no significant effects of treatment on naming performance, but a significant effect on auditory sentence comprehension after 2 weeks of rTMS treatment was observed. Additional rTMS sessions (two weeks) led to no further improvements, yet benefits on auditory sentence comprehension persisted for 8 weeks after the end of treatment. It is noteworthy that no effects on memory and executive functions were detected: this seems to suggest that the obtained results were specific for the language network, and not due to a general, nonspecific effect on cognitive processing (Table 2).

A 2012 case report [49] showed cognitive improvement after one month of high-frequency (10 Hz) rTMS treatment over the left DLPFC in a 75-years old patient diagnosed with probable AD. rTMS was administered as adjunctive treatment to memantine and donepezil: improvements in episodic memory and speed processing tasks were observed after one month of rTMS treatment, and memory performance level was maintained at five-months follow-up.

rTMS has also been employed in combination with cognitive training (COG) to improve cognitive functions in AD. A recent study [50] evaluated the effects of high-frequency (10 Hz) rTMS interlaced with COG (rTMS-COG) over six different regions (Broca and Wernicke areas, right and left DLPFC and right and left parietal somatosensory association cortex). Two measures (ADAS-cog and CGIC) improved significantly after treatment, while MMSE, ADAS-ADL and HAM-D improved without statistical significance and NPI did not change. These results were replicated in a later randomized, double-blind,

Study	Number of patients	rTMS target	rTMS parameters	Number of sessions	Cognitive function improvement
46	15	L/R DLPFC	20 Hz, 90% MT	1	↑ Action naming
47	12 Mild 12 Moderate	L/R DLPFC	20 Hz, 90% MT	1	↑ Action naming (Mild); ↑ Action-object naming (Moderate)
48	5 real 5 sham	L DLPFC	20 Hz, 90% MT; sham	20	↑ Auditory comprehension
49	1	L/R DLPFC	10 Hz, 100% MT	10	↑ MMSE, MIS, Free and Cued Recall Test, IST, TMT
50	8	Broca's area; Wernicke's area; L/R DLPFC; L/R pSAC	10 Hz, 90-110% MT	54	↑ ADAS-COG, CGIC
51	15	Broca's area; Wernicke's area; L/R DLPFC; L/R pSAC	10 Hz, 90-110% MT	54	↑ ADAS-COG, CGIC
52	15 HF 15 LF 15 sham	L/R DLPFC	20 Hz, 90% MT; 1 Hz, 100% MT; sham	5	↑ MMSE, IALD, GDS (HF rTMS)

Legend: Hz, Hertz; rTMS, repetitive Transcranial Magnetic Stimulation; L, left; R, right; DLPFC, dorsolateral prefrontal cortex; pSAC, parietal somatosensory association cortex; MT, motor threshold; HF, high-frequency; LF, low-frequency; MMSE, Mini Mental State Examination; GDS, Geriatric Depression Scale; IALD, Instrumental Daily Living Activity; ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive; CGIC, Clinical Global Impression of Change; IST, Isaac's Set Test; TMT, Trail-Making Test; ↑, increase; ↓, decrease.

Table 2: Findings from studies employing TMS as a therapeutic tool in AD: cognitive functions results.

controlled study [51] examining the long-term "offline" improvement of cognitive functions after 6 weeks of intensive daily treatment and 3 months of bi-weekly maintenance treatment. Treatment parameters and target areas were the same of Bentwich et al. [50]: a significant improvement of ADAS-cog score for treatment group compared to placebo, sustained after 4.5 months of treatment was observed. Also, CGIC score improved significantly in the treatment group, while NPI showed a non-significant improvement. The authors also found superior results in ADAS-cog and CGIC scores after rTMS compared to usual pharmacological treatment (AchEI), suggesting that that the rTMS-COG technology provides an additional beneficial effect to that available with drugs.At last, the long-term efficacy of high- versus low-frequency bilateral rTMS over the DLPFC on cortical excitability and cognitive functions was investigated in AD patients [52]. Results showed a greater improvement on all rating scale (MMSE, Geriatric Depression Scale (GDS) and Instrumental Daily Living Activity Scale (IADL)) in the high-frequency group compared to the low-frequency and sham ones. These results are consistent with previous studies, all of which employed 10 or 20 Hz stimulation.

Conclusions

Most of the reviewed studies explored the role of TMS to physiologically characterize AD, providing new insights and supporting pre-existing knowledge about neurophysiologic and pathophysiologic aspects of AD. Among the most consistent findings using TMS as an investigational tool, a significant RMT and SAI reduction were found in AD patientscompared to controls. The former seems to reflect and support the notion of a cortical hyperactivity in the disease, while the latter seems to represent a putative marker of reduced central cholinergic activity. Cortical hyperexcitability has also been found as associated with reduced cortical thickness and reduced learning ability in older adults [53], consistently with previous neurophysiologic studies in AD patients reporting increased cortical excitability, brain atrophy and cognitive deficits. Cortical plasticity has been mainly investigated in motor areas, showing abnormalities in mechanisms supporting facilitatory cortical plasticity in AD [23]. Outside the motor cortex, cortical reactivity and plasticity have not been evaluated; yet functional connectivity between the motor cortex and other cortical regions has been showed reduced in AD patients compared to MCI subjects and healthy controls [29]. Taken together, these results seem to outline the usefulness of TMS to achieve a deeper understanding of cortical reactivity and plasticity changes in AD and to characterize motor system pathophysiology underlying the neurodegenerative processes in the disease.

Conversely, therapeutic effects of rTMS on cognitive deficits in AD are still to be confirmed. Results from the few studies [46-52] available are currently preliminary, yet they show considerable promise. Overall, high-frequency (10 Hz/20 Hz) rTMS stimulation over the left or right DLPFC resulted in significant improvements in action naming, language comprehension and few rating scales (e.g., MMSE, ADAS-Cog, CGIC) [46-52] and the conjunct use of rTMS and cognitive training showed promising results [50,51]. Also, high-frequency protocols proved to be more efficacious than low-frequency ones [52]. Although results are still preliminary, rTMS employ in AD is supported by far more studies compared to DBS. To our knowledge, a few recent trials and case reports have been conducted so far [54-56], with fornix as the target area of stimulation. The total number of AD patients who underwent DBS is 12 since, as Fontaine et al. [55] report, only a small proportion of AD patients seems to be interested in this approach and the acceptance of DBS by AD patients appears to be low, raising questions about the relevance of this approach to meet the expectations of these patients. Nevertheless, results from the latest contribution [56] suggest the potential of DBS to influence the natural course of brain atrophy in a neurodegenerative disease, in addition to modulating neural circuit activity.

The rationale for rTMS treatment in AD is the potential of rTMS to induce lasting changes in focal and non-focal neuroplasticity, as

LTD and LTP [57]. Most studies focused on DLPFC grounding on the evidence of increased activity of this brain area in MCI and AD [58]. rTMS may have the potential to modulate DLPFC hyperactivity, restoring the balance in MCI and AD patients and, consequently, improving memory function. Also, rTMS is capable to influence the activity of distant brain areas from those directly stimulated by the coil, presumably via cortico-cortical connections [46]. The mechanism underlying cognitive improvements observed in the afore-mentioned studies seems to be the ability of rTMS to help recruiting compensatory networks [59] or to determine a re-arrangement of synaptic efficiency in within the language network [46]. If further confirmed, these effects may be extremely promising within the search of interventions aimed at modifying disease progression.Nevertheless, most of the reviewed studies are characterized by short duration and the detected effects are often short-lived. The lack of an adequate follow-up period, the small sample sizes and the lack of strong evidence based studies coupled with the evidence of a presumably time-limited treatment effects, open the debate regarding the cost-effectiveness of rTMS treatment in AD. Although improvements have been observed in specific cognitive tasks, we are still far from speaking of a global cognitive enhancement: therefore, more solid investigation regarding long-term outcome are strongly needed to determine the potential therapeutic role of rTMS. Also, the neuropsychological assessment still lacks adequate standardization to ensure results comparison between studies: the heterogeneity of rating scales selection prevents from results generalization. Population variability represents another problematical point: age of onset, illness duration, pharmacological treatment and genetic burden represent variables that need to be taken in account, given their potential impact on outcome and treatment efficacy. Furthermore, a crucial question regards rTMS rationale for treating AD: since cortical hyperexcitability is one of the most robust findings in AD, the employ of high-frequency stimulation, known as aiming at a cortical excitability enhancement, may seem paradoxical. This re-opens the debate regarding the differential effects of high- versus low-frequency stimulation: the general assumption that high-frequency stimulation results in cortical excitability may be equivocal. It is more likely that rTMS effects depend on the state of activity of the brain at the time of stimulation [60]: this gives rise to the critical need of baseline cortical excitability evaluation before rTMS intervention. Also, the specific features of cortical plasticity disruptions in AD have still to be clarified, as well as the nature of neurotrophic factors levels alterations (e.g. brain derived neurotrophic factor – BDNF) – [61], in order to develop suitable rTMS stimulation protocols. Lastly, the disease progression is accompanied by the spread of deficits in multiple cognitive domains, thus future research might focus on interventions involving multiple stimulation areas,to target as many of cognitive deficits as possible.

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