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Transcranial Magnetic Stimulation in Alzheimer's disease: are we ready?

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Transcranial Magnetic Stimulation in Alzheimer's disease: are we ready?

ABSTRACT

Transcranial magnetic stimulation (TMS) is among a growing family of non-invasive brain stimulation techniques being developed to treat multiple neurocognitive disorders, including Alzheimer's disease (AD). Although small clinical trials in AD have reported positive effects on cognitive outcome measures, significant knowledge gaps remain, and little attention has been directed at examining the potential influence of TMS on AD pathogenesis. Our review briefly outlines some of the proposed neurobiological mechanisms of TMS benefits in AD, with particular emphasis on modulatory effects on excitatory/inhibitory balance. On the basis of converging evidence from multiple fields, we caution that TMS therapeutic protocols established in young adults may have unexpected detrimental effects in older individuals, or in the brain compromised by AD pathology. Our review surveys clinical studies of TMS in AD alongside basic research as a guide for moving this important area of work forward toward effective treatment development.

Significance Statement

There is an urgent need for the development of new, effective strategies in the battle against Alzheimer's disease (AD). Transcranial magnetic stimulation (TMS) has emerged as a promising possibility, but evidence regarding long-term efficacy and mechanism of action is limited. Among the major unresolved issues, findings linking the effects of TMS on excitatory/inhibitory balance with mechanisms of AD pathogenesis merit careful consideration. Our survey of clinical TMS studies in AD alongside basic research aims to move the area forward toward effective treatment development using non-invasive brain stimulation.

1. The Need for Novel Approaches to AD Treatment

Alzheimer's disease (AD), the most common form of dementia, is characterized by progressive memory impairment and associated decline in multiple cognitive domains, ultimately leaving patients incapacitated. Inexorably eroding the lifetime of memories that define us, AD robs patients of their unique identity. The neuropathological hallmarks of AD prominently include microscopic foci of degenerating neurites and extracellular amyloid β-protein (Aβ) deposition, together with intracellular aggregates of hyperphosphorylated tau protein that disrupt microtubule organization (Selkoe, 2001). The single greatest risk for AD is aging. The ε4 allele of the apolipoprotein E (APOE) gene is present in approximately 40% of cases and is the strongest genetic risk for the sporadic, late-onset form of AD (Farrer et al., 1997; Heffernan et al., 2016). In the absence of effective interventions for disease prevention or slowing, the projected burden of AD represents a looming healthcare crisis as the population of most industrialized countries continues to grow older.

Currently approved pharmacological treatments for AD offer limited symptomatic relief for some patients, and none alter the underlying progression of disease. While the search for new drugs with improved clinical efficacy is ongoing, increasing attention is focused on disease modifying strategies, aimed at bending the trajectory of aging toward healthy neurocognitive outcomes. Ideally, intervention would be initiated in at-risk individuals before the clinical expression of disease, during the decades-long prodromal phase thought to precede AD diagnosis. Non-invasive brain stimulation (NIBS) has generated considerable interest in this context. Prominently including Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS), this family of related technologies shares a generally well-

tolerated safety profile in healthy young adults, and is currently under investigation for treating a growing list of potential indications (Rossi et al., 2009; Guo et al., 2017).

Among the various types of NIBS, TMS has received the greatest attention in clinical research on neuropsychiatric disorders. The mechanistic basis of TMS benefits is poorly understood, but there is general agreement that cortical excitability can be persistently modified by the repetitive delivery of a high intensity magnetic field, generated by passing electrical current through an inductive coil. Repetitive TMS (rTMS), delivered in daily hour-long sessions over the course of several weeks was approved by the U.S. Food and Drug Administration for the treatment of pharmacologically refractory depression in 2008. In general, trials of rTMS treatment vs. sham showed significant improvement in depression scores and lower rates of remission with rTMS (Health Quality Ontario, 2016; Pohar and Farrah, 2019), benefits that can be enhanced when rTMS is combined with antidepressant medication (Wei et al., 2017). In the ensuing years, the range of potential clinical applications under investigation has increased dramatically, including a number of relatively small trials in AD (**Table 1**).

2. Therapeutic effects of rTMS in AD

Developing NIBS as a potential intervention for any clinical indication critically involves the choice of an appropriate stimulation protocol. Generally, rTMS protocols are operationally classified as 'low-' or 'high-frequency', and 'conventional' or 'patterned'. Low-frequency typically refers to stimulation rates ≤ 1 Hz, whereas rates ≥ 3 Hz are considered high-frequency (including the 10 and 20 Hz frequencies most commonly used in AD trials). In conventional protocols, single TMS pulses are applied in a regular rhythm; in patterned rTMS, short, high-frequency bursts are interleaved with brief periods of no stimulation. Some

examples of patterned rTMS include stimulation mimicking theta activity, wherein short bursts of high frequency pulses repeated at 5 Hz (theta burst stimulation; TBS) are delivered as continuous (cTBS) or intermittent TBS (iTBS) pulses. Perhaps most important with respect to the clinical effects of stimulation, low-frequency rTMS protocols are understood to result in cortical suppression and inhibition, whereas high-frequency stimulation increases cortical facilitation and excitability (Huang et al., 2005). Beyond stimulation frequency, a wide variety of generally untested factors are likely to influence the outcome of rTMS, including coil shape, coil-cortex distance, motor threshold normalization, area of stimulation, use of concomitant medication, machine output, among others (Lang et al., 2006; Kar, 2019).

Initial studies of rTMS effects in AD focused on high-frequency protocols almost exclusively (see **Table 1** for procedural details of available rTMS trials). For example, in research examining language function, mild and moderate AD participants received 20Hz unilateral TMS over the dorsolateral prefrontal cortex (dlPFC) (Cotelli et al., 2006; Cotelli et al., 2008). Object naming ability improved during stimulation, and the endurance of these effects, immediately after and 8 weeks following treatment, was assessed in subsequent work (Cotelli et al., 2011). The duration of intervention was also manipulated, with one group receiving a 4-week course of rTMS, while a second underwent 2 weeks of sham treatment followed by 2 weeks of rTMS. Auditory sentence comprehension improved in both groups, and although the previously reported effect on naming was not confirmed, comprehension benefits persisted for 8 weeks. Other outcome measures were unaffected, including activities of daily living and global cognition. In a more recent study, episodic memory improved in comparison with pre-treatment scores in AD patients who received 20Hz stimulation over the precuneus, whereas no difference was detected after sham stimulation (Koch et al., 2018). A related

investigation tested 10Hz dlPFC stimulation in a mild cognitive impairment (MCI) sample (Drumond Marra et al., 2015) and reported significant benefit relative to sham on tests of everyday memory, with effects persisting up to one month. However, in this case sham group scores for logical memory, executive function and language also varied over the observation period. Improvements in performance when assessment is repeated over time, or "practice effects", although controllable with appropriate experimental design, are a frequent confound and complicate interpretation in this area of research. Generally similar results have been reported in other small trials (Eliasova et al., 2014; Rutherford et al., 2015; Zhao et al., 2017) as detailed in **Table 1**.

Studies directly comparing cognitive outcomes following high vs. low frequency stimulation in AD were first reported in 2012. In one investigation, 20 Hz or 1 Hz rTMS was delivered bilaterally over the dlPFC in participants with mild or severe dementia (Ahmed et al., 2012). High frequency stimulation in the mild dementia group was more effective than 1 Hz relative to pre-treatment scores as measured by all clinical assessments (i.e., the Mini Mental State Examination; MMSE, Instrumental Activities of Daily Living Scale; IADL, and in the Global Deterioration Scale; GDS), and the benefits persisted at all test intervals (i.e., up to 3 months). In contrast, participants with severe dementia showed no improvement, regardless of stimulation protocol. A second study also examined the effects of dlPFC stimulation, but in this case, while healthy controls received either unilateral iTBS or 1 Hz rTMS, participants with MCI received only unilateral 1Hz stimulation (Turriziani et al., 2012). Recognition memory improved in both cognitively healthy and MCI subjects following low frequency stimulation of the right dlPFC compared to sham. Intriguingly, high frequency TMS over the same site in controls impaired recognition memory, raising the possibility that the cognitive response to

TMS is dependent on stimulation frequency and/or the baseline status of memory. Unfortunately, the effects of iTBS in memory-impaired participants, with MCI, were not reported (Turriziani et al., 2012).

Encouraged by this background, together with the much larger literature of experimental studies in normal participants (Iriarte and George, 2018), stimulation protocols specifically intended for clinical application in mild to moderate AD are under active development. Using high-frequency rTMS in conjunction with concurrent cognitive training (rTMS-COG), one current strategy involves an intensive phase of 10 Hz stimulation at 6 different cortical sites (bilateral dlPFC, parietal somatosensory association cortices, and Broca's and Wernicke's areas), nominally 3 regions/day, 5 days/week for 6 weeks. Alongside rTMS, in this regimen patients receive cognitive training overlapping with TMS delivery, specifically tailored to engage the brain regions targeted for electromagnetic stimulation. A maintenance phase has been included in some studies, comprised of two subsequent sessions/week for 3 months. In the first study examining the effects of rTMS-COG (Bentwich et al., 2011), improvement in the AD Assessment Scale-cognitive subscale (ADAS-Cog) was observed at 6 weeks and 4.5 months relative to pretreatment scores. Similar findings in other studies include improved ADAS-Cog and MMSE scores 6 weeks post-treatment (Rabey and Dobronevsky, 2016), and increased ADAS-Cog and Clinical Global Impression of Change (CGIC) scores at 6 weeks, 3 months, and 4.5 months (Rabey et al., 2013) compared to placebo stimulation.

Complementing these findings, rTMS-COG in a group of probable AD cases reportedly produced statistically significant or numerical improvement relative to baseline as assessed by a variety of standard measures (e.g., CGIC, MMSE or ADAS-Cog), either

immediately or 6 weeks after the intervention protocol (Lee et al., 2016). Effects were most robust among mild AD participants and were not detected in those with more advanced cognitive deficits. Notably, however, scores also improved in a parallel sham condition, and accordingly, interactions between treatment condition and assessment episode were not statistically significant. The endurance of potential treatment benefit in AD remains to be fully documented, but in a recent study (Nguyen et al., 2017) improved ADAS-Cog scores seen 45 days after rTMS-COG reverted to pre-treatment baseline at 6 months after intervention. The lack of a sham control that might have detected worse decline without treatment complicates the interpretation of this work (Nguyen et al., 2017).

3. Toward an Approved TMS Therapy for AD

Important issues remain to be addressed in the potential clinical application of rTMS in AD. A recent FDA review for approval of a commercial TMS system for AD treatment identified a number of deficiencies that need to be addressed, including uncertainty around the reporting of adverse events, concern that current evidence fails to demonstrate a clinically meaningful TMS benefit in AD, and agreement that there is insufficient data documenting that the benefits of the proposed therapy outweigh its health risks (see www.fda.gov, March 21, 2019, Neurological Devices Panel of the Medical Devices Advisory Committee: De Novo DEN160053). The following sections briefly consider some of the experimental design challenges in this area of research, and then turn to evidence concerning the neurobiological mechanisms that might mediate the effects of TMS. A comprehensive mechanistic review is available elsewhere (Keck, 2003; Pell et al., 2010). The perspective here is more targeted, suggesting on the basis of converging evidence that NIBS protocols with established safety in healthy young adults may have different effects in the context of AD

pathogenesis. Finally, we outline key issues that will need to be resolved in order to advance the rational application of rTMS and related technologies for the prevention, symptomatic relief or disease modifying treatment of AD.

4. Challenges in Assessing rTMS Effects in AD

As noted earlier, TMS is approved for the treatment of medication-resistant depression (McClintock et al., 2018; Kaster et al., 2019). Accordingly, in AD trials it is important to control for the possibility that patients might benefit from TMS secondary to stimulation effects on comorbid depressive symptoms (Cotelli et al., 2006; Cotelli et al., 2008). The prevalence of depression in AD may be as high as 50% (Rutherford et al., 2013), and even mild depressive symptoms are associated with significant functional impairment (Starkstein et al., 2005). Many of the stimulation protocols tested for the treatment of AD are similar to those used in depression, including a prominent focus on the dlPFC. Although some studies have explicitly excluded patients with depression (Cotelli et al., 2006; Cotelli et al., 2008; Cotelli et al., 2011; Turriziani et al., 2012; Drumond Marra et al., 2015), others have not reported mood disorders as an exclusion criterion (Ahmed et al., 2012; Rabey et al., 2013; Eliasova et al., 2014; Rabey and Dobronevsky, 2016; Nguyen et al., 2017). The degree to which cognitive improvement following TMS in AD results from alleviating depressive symptoms is therefore difficult to judge, but it is notable in this context that treated patients sometimes also exhibit elevated mood, scoring better on depression and apathy scales (Ahmed et al., 2012; Lee et al., 2016; Nguyen et al., 2017; Padala et al., 2018).

Other experimental controls have also been lacking at times in this area of work. In a number of reports, potential improvements in performance simply as a consequence of repeating cognitive assessment across multiple occasions (i.e., practice effects) were not

considered. Studies examining rTMS-COG protocols have generally lacked groups receiving either rTMS alone, or cognitive assessment without stimulation (recent preliminary findings are an exception (Alcala-Lozano et al., 2017)), and in such cases the individual and interactive contributions of training and TMS are unknown. Whether they are independent, competitive or synergistic, there is considerable precedent for the idea that the effects of rTMS are 'state-dependent' and critically modulated by concurrent functional engagement of the neural circuitry targeted by stimulation (Silvanto et al., 2008). The precise schedule of cognitive training relative to epochs of rTMS delivery, however, has not been systematically manipulated in AD trials. Small sample size is another limitation, and in many investigations, groups of a dozen or fewer participants are not uncommon. Much larger samples, offering increased statistical power, are needed to accurately estimate effect size and enhance reproducibility (Button et al., 2013). As noted in the FDA review cited earlier and previous reports (Buss et al., 2019; Koch et al., 2019), properly designed, larger and longer trials are needed to address unresolved issues in the use of rTMS as a therapeutic treatment for AD.

Studies reporting positive TMS effects in mild AD have failed to find reliable benefit in more advanced cases (Ahmed et al., 2012; Rutherford et al., 2015; Lee et al., 2016; Zhao et al., 2017), suggesting that treatment efficacy may be dependent on disease stage. As proposed for other interventions, rTMS might be most effective early in the course of the disease, before neuronal loss has disrupted critical cortical circuitry beyond rescue. The accuracy of early disease diagnosis and staging is an endemic challenge in clinical research on AD, and estimates are that nearly 20% of cases are misdiagnosed (Witte et al., 2014). Thus, important goals for future clinical trials of rTMS include an increased focus on participants qualified on the basis of neuroimaging or biomarker results, and cognitively normal samples at

increased risk for development of disease (e.g., on the basis of APOE genotype or polygenic risk). To date, no longitudinal clinical trial has investigated the response to rTMS-COG in prodromal or asymptomatic AD, when arresting or reversing neuronal dysfunction may have the greatest prospects of success.

5. Potential Mechanisms of rTMS Benefits

The rTMS protocols tested most frequently as potential interventions for AD were selected partly on the basis of the persistent enhancement in cortical excitability observed following repetitive high frequency stimulation (Huang et al., 2005; Potter-Nerger et al., 2009). Such facilitation is thought to involve Long-Term Potentiation (LTP)-like changes in synaptic strength that are widely presumed to be a key cellular mechanism of learning and memory. LTP induced by high frequency magnetic stimulation (100 Hz) has been directly documented in rat hippocampal slices (Tokay et al., 2009), and related synaptic enhancement has been reported in both other slice preparations and primary cortical cell cultures following 10 and 20 Hz magnetic stimulation (Vlachos et al., 2012; Banerjee et al., 2017). Neuronal activity and LTP regulate the expression of plasticity-related neurotrophins such as brain-derived neurotrophic factor (BDNF), which declines in the AD hippocampus (Phillips et al., 1991), and animal studies confirm that high frequency rTMS can significantly upregulate BDNF levels (Makowiecki et al., 2014). The speculation based on these findings is that rTMS might result in clinical benefit by correcting or blunting the impaired LTP-like plasticity and associated signaling defects observed in AD (Kumar et al., 2017).

In parallel with these findings, recent advances have also identified rTMS as a modifier of inhibitory neuron function. Studies in hippocampal slice cultures demonstrate that 10 Hz stimulation reduces GABAergic synaptic strength on principal neurons, supporting a

model in which mechanisms involving GABAergic synapses modulate overall inhibitory/excitatory balance (Lenz et al., 2016). Findings based on immunocytochemical analysis in animals (Trippe et al., 2009; Mix et al., 2010; Benali et al., 2011) and magnetic resonance spectroscopy in humans (Stagg et al., 2009) show that TMS can lead to temporally graded changes in a variety of inhibitory neuronal markers, lasting at least a week. In preclinical animal research, such alterations generally comprise increases in GABAergic synthesizing enzymes and transporter after low frequency stimulation (Trippe et al., 2009; Mix et al., 2010) (i.e., changes that might promote a net increase in inhibitory drive), and decreases in the number of immunocytochemically-identified inhibitory cells after high frequency stimulation (Benali et al., 2011; Jazmati et al., 2018).

Other mechanisms implicated in the pathogenesis of AD that might contribute to the cognitive effects of rTMS in AD include neurochemical modulation (Michael et al., 2003; Strafella et al., 2003), epigenetic modification of gene transcription (Etievant et al., 2015), and modulatory effects on neural network dynamics in vulnerable circuitry (Marron et al., 2018). The effect of TMS on these and other potential mechanisms, however, has received limited attention. In the following section we focus on a particularly illuminating example, suggesting a potential link between the modulatory influence of rTMS on excitatory/inhibitory balance with mechanisms of AD pathogenesis.

6. Excitatory/Inhibitory Balance in AD: A Challenging Opportunity

Growing interest centers on the possibility that increases in neuronal activity levels directly contribute to AD pathogenesis (Palop et al., 2006). Overexpression of Aβ causes epileptiform activity within entorhinal-hippocampal circuitry that, together with homeostatic responses to aberrant firing, may contribute to memory dysfunction in transgenic mouse

models and humans with AD (Palop et al., 2007). Soluble oligomeric Aβ assemblies also increase neuronal excitability and impair hippocampal function by inducing an imbalance between glutamatergic/GABAergic transmission (Lei et al., 2016). The strongest known genetic risk for sporadic AD, the APOE ε4 allele, disrupts GABAergic inhibitory networks, influencing both Aβ aggregation and the clearance of soluble Aβ. In AD mouse models, APOE ε4 knock-in leads to a decrease in GABAergic interneurons in the hilar region of the dentate gyrus that correlates with learning and memory impairment (Li et al., 2009; Huang and Mucke, 2012). This effect, in turn, is reversible with hilar transplantation of inhibitory interneurons (Tong et al., 2014). Relative to non-carriers, the ε4 positive genotype in young adult humans is associated with both hippocampal hyperactivity during memory encoding and increased resting-state connectivity, many decades before clinical or neurophysiological expression of neurodegenerative processes (Filippini et al., 2009). Basic research points to a potential feed forward effect, demonstrating that neuronal stimulation in hippocampal slice preparations induces amyloid precursor protein release (Nitsch et al., 1993), and that stimulating entorhinal cortex projections to the hippocampus increases interstitial Aβ in AD mice (Kamenetz et al., 2003). Thus, together the available findings strongly suggest that neuronal activity is linked to Aβ processing and release, specifically in circuitry known to be affected early in the course of AD (Jagust and Mormino, 2011).

Prompted by the failure of recent clinical trials aimed at slowing or stopping the progression of AD, attention has turned to novel approaches targeting earlier, preclinical abnormalities. Whereas the direction of effect between disrupted neural network activity and AD pathogenesis may vary across brain regions and stages of disease, the emerging consensus is that distributed changes in neuronal excitability are an early signature conferring increased

risk for AD (Palop and Mucke, 2010). In this context, therapies aimed at normalizing the balance between excitatory and inhibitory drive in vulnerable circuitry represent a potentially powerful approach to modifying the course of AD. Preliminary support includes evidence that GABA receptor agonist administration in AD transgenic (Shao et al., 2014) and aged mice (Yamamoto et al., 2015), as well as in humans (Chung et al., 2016) lowers Aβ burden and attenuates Aβ-induced neurotoxicity. Other treatments, including the use of growth hormone-releasing hormone in healthy elderly and MCI subjects, increase cortical GABA levels in association with improved cognition (Friedman et al., 2013). In perhaps the most direct test of targeting excess neuronal activity, low dose treatment with the antiepileptic levetiracetam improves memory in both aged rats (Koh et al., 2010) and amnestic MCI (Bakker et al., 2012), together with a reduction in hippocampal hyperactivity. Whether this approach, implemented early, is sufficient to alter the fundamental trajectory of disease is under active investigation.

7. Frontiers in AD Management and Treatment Using TMS: a Path Forward

The possibility that a safe, non-invasive, and relatively low-cost treatment such as TMS might prove effective in the battle against AD has generated understandable excitement (https://www.scientificamerican.com/article/could-magnetic-brain-stimulation-help-people-with-alzheimer-rsquo-s/). However, the available evidence regarding clinical efficacy and mechanism of action is limited. The view developed here is that defining the neurobiological substrates responsible for the effects of TMS and other NIBS modalities will be critical for maximizing their efficacy and safety. We encourage a constructive, dispassionate evaluation of the evidence, aimed at establishing an informed platform for moving TMS and related strategies forward toward clinical application in AD.

The evidence summarized in this review highlights at least three conceptually distinct targets for TMS intervention in AD. **Figure 1** schematically represents the hypothetical relationships between these targets (red text), together with an exemplar outcome for each (blue text), and how they might vary with low versus high frequency TMS. The majority of extant research in this area has examined stimulation effects on cognitive and neuropsychological symptoms of disease, with the primary outcome of interest comprising improved clinical outcome. The effects of high frequency stimulation have been tested most often, with positive studies reporting a variable degree of cognitive benefit, at least in mild AD. Insufficient attention has been directed at tracking the influence of TMS on AD pathogenesis or biomarkers, i.e., proxies of the underlying disease process (see, for example (Marron et al., 2018)). Nonetheless, substantial evidence indicates that neuronal activity promotes amyloid deposition, raising the possibility that the same high frequency stimulation that leads to improved clinical symptoms might also accelerate underlying AD pathogenesis. Conversely, low frequency rTMS reportedly decreases amyloid burden in the brains of AD transgenic mice (Huang et al., 2017), while preserving the reported cognitive benefit of high frequency stimulation. Finally, perhaps the most hopeful target of TMS in AD - that intervening before symptom onset might correct contributing mechanisms or block seed events in the initiation of the disease process – remains largely untested. Disrupted excitatory/inhibitory balance is thought to comprise an early driver of AD pathogenesis, and based on its presumed mechanism of action, TMS may be ideally positioned as a disease-modifying intervention against this target.

The need for effective strategies in the battle against AD grows ever more urgent. The disappointing outcome of recent clinical trials encourages consideration of fresh

perspectives, and in this context, NIBS has emerged as a novel alternative to pharmacological therapeutics and other interventions. The exciting potential of this approach, however, should not overshadow the important questions that remain unanswered. Among them, the safety profile established for other indications merits reconsideration in the context of neurobiological changes associated with AD, including hyperexcitability and epileptic activity, consistent with current safety guidelines (Rossi et al., 2009). Studies aimed at directly tracking pathological progression by *in vivo* imaging in patients receiving TMS are also needed. Efficacy in appropriately controlled, well-powered trials remains to be confirmed, and longer-term cognitive outcomes established. At what stage in the progression of AD pathology will TMS be most effective? If TMS is used to target excitatory/inhibitory balance, at what frequency and in which brain regions, recognizing that such effects may be brain-region specific (Banuelos et al., 2014)? Indeed, given the prominent regional vulnerability of AD, it will be important to consider that TMS aimed at correcting excitatory/inhibitory balance in one target area may well have unanticipated or negative secondary effects in other, distally connected networks. Basic research, designed in alignment with the priorities of clinical research, can provide helpful guidance and yield much needed insight into the neurobiological mechanisms responsible for the clinical effects of NIBS (Tang et al., 2017) The challenges are great, but a path forward toward the rational application of rTMS and related modalities in AD has begun to emerge.

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624 **Table 1**: Summary characteristics of clinical studies using rTMS to treat AD.

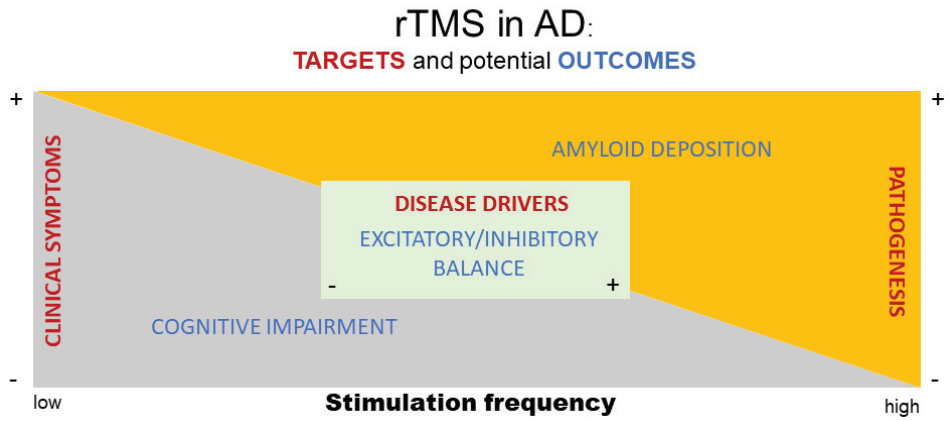
Authors	Sample	Exclusion/ Inclusion criteria	Methods	Stimulation site	Cognitive outcome variable	Assessment schedule	Summary results	Author conclusions
Cotelli *et al*., 2006	15 mild to moderate AD patients	Exclusion of patients with major depression	One session of 20Hz rTMS during cognitive stimulation. No sham group	Unilateral dlPFC and sham region	Action naming and Object naming	Baseline and during stimulation	Patients improved action naming accuracy during stimulation with rTMS applied to either the right or left dlPFC.	High frequency TMS could represent a potential treatment for language deficits in AD patients.
Cotelli *et al*., 2008	12 mild AD, 12 moderate to severe AD patients	Exclusion of patients with major depression	One session of 20Hz rTMS during cognitive stimulus. No sham group	Unilateral dlPFC and sham region	Action naming and Object naming	Baseline and during stimulation	Mild AD improved action naming accuracy during stimulation with rTMS applied to either the right or left DLPFC. Moderate to severe AD improved action and object naming accuracy with rTMS applied to either the right or left DLPFC.	High frequency TMS could represent a potential treatment for language deficits not only in the early phase of AD, but also in more advanced stages.
Cotelli *et al*., 2011	10 moderate AD patients	Exclusion of patients with major depression	Two groups: a 4-week stimulation group, and 2-week placebo treatment + 2 weeks of stimulation. 20Hz rTMS, for 25 min/day, 5 days/week. No sham group	dlPFC (hemisphere not specified)	MMSE, ADL, IADL, Picture naming, SC-BADA, Aachener Aphasia Test, Serial curve position, Cognitive estimation test	Baseline, 2, 4 and 12 weeks after stimulation onset	The 4-week stimulation group improved on SC-BADA after the first 2 weeks of stimulation. The placebo+real stimulation group only improved on SC-BADA after the 2 weeks of stimulation. Effects lasted for 8 weeks in both groups.	High frequency TMS has long lasting effects on auditory sentence comprehension performance in moderate AD patients.
Drumond Marra *et al*., 2011	34 MCI subjects	Exclusion of patients with psychiatric disorders	Sham and stimulation groups. 10Hz for 5s, 25s intertrain interval 20 minutes/day for 5 days/week for 2 weeks	Left dlPFC	IQCODE, B-ADL, MMSE, RBMT, Logical memory I and II, RAVLT, Letter-number sequencing test, Digit span, TMT A/B, Verbal fluency tests, Victoria Stroop Test	Baseline, end of treatment and 30 days after end of treatment	MCI improved RBMT scores after 10Hz stimulation, lasting up for 30 days. MCI improved TMT-B 30 days after treatment. Sham improved Logical memory, letter-number sequencing and TMT-B after treatment. Effects on the Logical memory lasted up for 30 days. Sham improved verbal fluency 30 days after treatment.	High frequency rTMS may represent an effective intervention for MCI and could delay further decline.
Bentwich *et al*., 2011	7 mild or moderate AD patients	Inclusion of 2 patients with depression and 4 patients with depression in remission	No sham groups. rTMS-COG. Intensive + maintenance phase (4.5 months of stimulation total). 10Hz for 2s, 20 trains	Broca, right/left dlPFC, Wernicke, right/left pSAC	ADAS-cog, CGIC, MMSE, ADAS-ADL, HAMILTON, NPI	Baseline, after intensive phase, and after maintenance phase	Improved ADAS-cog scores after 6 weeks and 4.5 months of treatment. No significant changes on other tests.	High frequency TMS combined with cognitive training may have a synergistic effect and improve cognition for up to 4.5 months.

Ahmed *et al.*, 2012	32 mild to moderate AD, 13 severe AD patients	N/A	Sham, 20Hz and 1Hz groups. 20Hz: 5s, 20 trains. 1Hz: 2 trains of 1000s, 30s intertrain interval. 5 days	Bilateral dlPFC	MMSE, IADL, GDS	Baseline, end of treatment, 1 and 3 months after treatment	Mild to moderate AD improved in all tests after 20Hz up to 3 months compared to 1Hz and sham. Mild to moderate AD improved in IADL after 1Hz compared to sham. There was no improvement in severe AD.	High frequency TMS has long lasting effects in mild to moderate AD and is more effective than low-frequency stimulation.
Turriziani *et al.*, 2012	100 healthy controls, 8 MCI subjects	Exclusion of MCI subjects with history of psychiatric disorders	Sham and stimulation groups. One session of 1Hz and iTBS applied in controls, 1Hz applied in MCI. iTBS: 20 trains, three 50-Hz pulses (a burst) repeated at 5 Hz for 2s. 1 Hz: 600 pulses	Unilateral dlPFC for healthy controls and bilateral dlPFC for MCI (interval of 3 weeks)	Recognition memory for faces, buildings and words.	Immediately after stimulation	Recognition memory improved in controls and MCI after 1Hz stimulation over the right dlPFC. iTBS over right dlPFC impaired non-verbal recognition memory in healthy controls. iTBS over left dlPFC had no effect in healthy controls.	Low frequency TMS over the right dlPFC improves recognition memory when applied during encoding in MCI and healthy controls.
Rabey *et al.*, 2013	15 mild to moderate AD patients	N/A	Sham and stimulation groups. rTMS-COG. Intensive phase + maintenance phase (4.5 months in total). 10Hz, 20 trains, for 2s.	Broca, right/left dlPFC, Wernicke, right/left pSAC	ADAS-cog, CGIC, NPI	Baseline, after intensive phase and after maintenance phase	AD patients improved on ADAS-cog and CGIC scores at the end of intensive phase. Effects lasted up for 4.5 months.	rTMS-COG treatment significantly improves cognition, is superior to currently available medications, and better than COG or TMS alone.
Eliasova *et al.*, 2014	3 MCI and 7 mild AD patients	N/A	Sham-controlled study with a crossover design. 2 sessions of 10 Hz, 45 trains of 4.9 second duration with an interval of 25 s, resulting in 2250 pulses/session. One-day interval between each session	Right inferior frontal gyrus and right superior temporal gyrus (active rTMS), and vertex (sham rTMS)	TMT, Stroop test, complex visual scene encoding task test	Baseline and immediately after each stimulation	Stimulation over the inferior frontal gyrus induced significant improvement in the TMT A and B. No significant difference in the Stroop test or in the CVSET after the rTMS of the right inferior frontal gyrus.	Modulating the inferior frontal gyrus excitability with rTMS may lead to clinically relevant improvement in attentional task performance in early AD patients.
Rutherford *et al.*, 2015	Stage 1: 10 mild to moderate AD patients; Stage 2: 6 mild to moderate AD patients	Exclusion of patients with moderate or severe depression. Inclusion of one patient with mild depression	4-week block of double-blind treatment with sham condition (Stage 1) followed by 2 weeks of open-label maintenance treatment repeated every 3 months (Stage 2). 20 Hz (40 pulses per burst) with 5-second inter-train intervals during cognitive task. 2000 pulses to each side	Both the left and right DLPFC per session	ADAS-cog, RMBC, MoCA	Stage 1: baseline and 4 weeks after the treatment. Stage 2: a few days after the treatment. MoCA was assessed every week in both stages	Stage 1: no statistically significant changes on ADAS-cog or RMBC scores comparing treated vs sham. Treated patients scored higher on MoCA in 2 and 3 weeks after start of treatment compared to baseline. Stage 2: with the exception of the ADAS-cog scores for 2 patients, all decline rates were better than the expected.	rTMS can be an effective tool for improving the cognitive abilities of patients with early to moderate stages of AD. However, the positive effects of rTMS may persist for only up to a few weeks. Specific skills being practiced during rTMS treatment may retain their improvement for longer periods.

Rabey & Dobronevsky, 2016	30 mild to moderate AD patients	N/A	No sham groups. rTMS-COG. Intensive phase only (6 weeks). 10Hz, 20 trains for 2s	Broca, right/left dlPFC, Wernicke, right/left pSAC	ADAS-cog, MMSE	Baseline and end of treatment	AD patients improved on ADAS-cog and MMSE scores at the end of treatment.	Repeated rTMS-COG treatment might be used to improve patients' cognitive status and maintain improvement over time.
Lee *et al.*, 2016	19 mild AD, 7 moderate AD patients	Exclusion of patients who had taken psychoactive medications within a month of the study	Sham and stimulation groups. rTMS-COG. Intensive phase (6 weeks). 10Hz, 20 trains for 2s	Broca, right/left dlPFC, Wernicke, right/left pSAC	ADAS-cog, CGIC, MMSE, GDS	Baseline, end of treatment and 6 weeks after end of treatment	Mild AD patients improved in ADAS-cog after treatment and remained for 6 weeks, but no different than the sham group. The mild AD group also improved in MMSE 6 weeks after end of treatment. Sham group improved in GDS scores at the end of the treatment.	rTMS-COG is a useful adjuvant therapy with currently available medication for AD, especially during the mild stage of the disease.
Nguyen *et al.*, 2017	2 MCI, 1 mild AD, and 4 moderate-to-severe AD patients	N/A	No sham group. rTMS-COG. Intensive phase + maintenance phase (4.5 months in total). 10Hz, 20 trains, for 2s	Broca, right/left dlPFC, Wernicke, right/left pSAC	ADAS-cog, MMSE, Dubois score, Frontal Assessment battery, Stroop color test, locomotor score, apathy score, caregiver burden interview and dependence score	Baseline, after intensive phase and 6 months after end of treatment	Patients improved on ADAS-cog, locomotor, apathy and dependence scores after intensive phase. Scores returned to baseline 6 months after treatment.	AD patients can benefit from rTMS-COG in terms of cognitive performance, apathy and independence. The duration of the benefit suggests that the repetition of a full course of stimulation every six months might be sufficient to produce a sustained clinical effect.
Zhao *et al*., 2017	30 mild to moderate AD patients	Exclusion of patients with a history of alcohol abuse or who had taken psychoactive medications within the past month	Sham and stimulation groups. 20 Hz, 20s intermediate/train. 1 session/day, 5 days/week for 6 weeks	Parietal P3/P4 and posterior temporal T5/T6 according to electroephalogram system	ADAS-cog, MMSE, MoCA, WHO-UCLA AVLT	Baseline, end of treatment and 6 weeks after the end of treatment	Patients improved on ADAS-cog, MMSE, MoCA and WHO-UCLA AVLT after the treatment. 6 weeks following treatment, patients further improved on ADAS-cog and WHO-UCLA AVLT remained higher. The sham group also improved on ADAS-cog compared to pre-treatment.	rTMS improves cognitive level, memory and language of AD patients, especially in the mild stage. Thus, rTMS can be recommended as a promising adjuvant therapy combined with cholinesterase inhibitors at the mild stage of AD patients.
Koch *et al*., 2018	14 mild AD	AD confirmed by cerebrospinal fluid protein levels	Sham and stimulation groups (cross-over design). Two weeks of 20Hz stimulation (40 trains, for 2s, 1600 pulses/day)	Precuneus	RAVLT, DSST, MMSE and FAB	Baseline and end of treatment	Patients improved on the Delayed Recall of RAVLT at the end of treatment. No significant effects after sham stimulation.	High frequency rTMS is a promising treatment for memory impairment in patients at early stages of AD.

Notes: AD: Alzheimer's Disease; ADAS-ADL: Alzheimer Disease Assessment Scale-Activities of Daily Living subscale; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; ADL: Activities of Daily Living; B-ADL: The Bayer Activities of Daily Living Scale; CGIC: Clinical Global Impression of Change; dlPFC: dorsolateral prefrontal cortex; DSST: Digit Symbol Substitution Test; FAB: Frontal Assessment Battery; GDS: Global Deterioration Scale; HAMILTON: Hamilton Depression Scale; IADL: Instrumental Activities of Daily Living Scale; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; iTBS: intermittent Theta Burst Stimulation; MCI: Mild Cognitive Impairment; MMSE: Mini Mental State Examination; MoCA: Montreal Cognitive Assessment; NPI: Neuropsychiatric Inventory; pSAC: parietal somatosensory association cortex; RAVLT: Rey Auditory Verbal Learning Test; RMBC: Revised Memory and

Behavior Checklist; RBMT: Rivermead Behavioral Memory Test; rTMS: repetitive Transcranial Magnetic Stimulation; SC-BADA: Battery for Analysis of Aphasic Deficits; TMT A/B: Trail Making test A and B; WHO-UCLA AVLT: World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test.



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636 **Fig. 1**: Schematic representation of target areas (red text) and potential outcome measures (blue

637 text) to test rTMS as an intervention for AD. See text for further description.

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