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Review article

rTMS to improve cognitive function in Alzheimer's disease

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Abstract

***Background*: There have been carefully optimistic reports on the ability of repetitive Transcranial Magnetic Stimulation (rTMS) to improve cognitive function in Alzheimer's disease (AD). However due to inadequate data for analysis from randomized controlled trials (RCTs) uncertainties remain regarding dosing, potential additive effect with medication and duration of cognitive effects. *Methods*: A literature search was conducted to identify studies published between January 2015 and December 2018 on subjects with a diagnosis of AD without significant co-morbid psychiatric illness. *Results*: All of the 3 RCTs and 4 non-RCT studies identified utilised the Alzheimer's Disease Assessment Scale- Cognitive subscale (Adas-Cog) in their outcome measures on cognition. Although only one RCT demonstrated a significant improvement in cognition compared to sham treatment, all studies reported improvement compared to baseline measures. A few contributes noted this benefit to be particularly evident in the earlier stages of AD. Discussion: Although a large proportion of the evidence reviewed is limited by methodological weaknesses overall the evidence lends its support to the use of rTMS combined with cognitive tasks in AD. Further work is needed to distinguish the characteristics of those patients who are likely to benefit.**

KEYWORDS: rTMS, Alzheimer's disease, cognitive functions.

Introduction

Alzheimer's disease (AD) accounts for 60-80% of all dementia cases worldwide (1). The global prevalence of AD has been estimated to be as high as 24 million, and it is predicted to quadruple by the year 2050 (2). AD initially presents with memory loss however as the disease progresses all cognitive domains are affected, leading to a gradual loss of independence and inability to manage activities of daily life. Behavioural and personality changes are commonplace, causing distress not only to the affected person but also their family members, who often act as primary caregivers (3). Ultimately the disease is fatal, and as the elderly population increases, AD has become one of the greatest threats to public health in England (4).
It comes as no surprise therefore that dementia has been reported as the most feared condition amongst those over the age of 55 years (5).
Pharmacological treatments for AD are symptomatic and have no effect on the relentless progression of the disease, for which there is currently no cure or prevention.
The lack of definitively effective pharmacological treatment for Alzheimer's dementia is well recognized and has led to extensive global research to increase the understanding of the illness and to seek new treatment options. Established treatments for other mental health conditions are being evaluated for possible effect on AD, one such treatment being Transcranial magnetic stimulation (TMS); a neurophysiological technique currently approved for treatment of certain cases of severe depression in the UK (6).
TMS is a non-invasive technique in which a wired coil is placed on the scalp, producing a large magnetic field which induces an electric current in underlying cortical areas. When applied in a repetitive fashion (rTMS), cortical excitability can be modulated (decreased or increased) depending on the set parameters of stimulation (7). The last 20 years have seen an increase in the use of rTMS to study its potential in various psychiatric disorders such as depression, certain neurological conditions and cognition (8).
Several studies have confirmed the safety of the rTMS procedure (9, 10) and meta-analyses and systematic reviews alike have given carefully optimistic reports of rTMS's ability to improve cognitive function in mild to moderate AD (9-12). Lee, et al. (2016) reported remarkable effects especially on memory and language domains in subjects with mild AD, and ar-

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gued that the intervention is particularly useful in this subgroup of people. Whilst there appears the be a growing evidence base that rTMS is effective for the purpose of improving cognition in AD, there are contrary reports regarding the use of concurrent cognitive tasks. Some evidence suggests that combination therapy has added benefit to rTMS alone (12), whereas a more recent study found that AD patients without concurrent cognitive training displayed significant improvement in cognitive function (10). Whilst there appears to be an agreement in favour of high frequency stimulation procedure, researchers have called for further studies to determine the sustainability of the stimulation and increase the understanding of the changes in neural plasticity that follow rTMS treatment (12).

Other points which remain undetermined in relation to this treatment are potential additive effect of anti-dementia medication, duration of cognitive effect and optimal dosing amongst others, and there is a clear collective call for further well-designed controlled trials with larger sample sizes to produce more conclusive evidence. There is however a considerable amount of published non-RCT data which could aid in clarifying the above questions and assist our understanding of the effects of rTMS on cognition in AD, and this review considers the non-RCT evidence which has previously been excluded from the narrative in order to address whether rTMS combined with cognitive tasks is effective at improving cognitive function in patients with Alzheimer's disease.

Method

Literature Search: A search was conducted using Pubmed, Cochrane, Scopus, Trip, Modem, Webof-Science, ALOIS and MedNar databases using the following terms in isolation and in combination: "Alzheimer's disease", "alzheimer's dementia", "AD", transcranial magnetic stimulation", "repetitive transcranial magnetic stimulation", "TMS", "rTMS", "TBS", "theta burst stimulation", "cognition", "cognitive", "cognitive function". Studies published between January 2015 and December 2018 on subjects with a diagnosis of AD and no other significant co-morbid psychiatric illness were included. The original search was conducted in November 2017, and updated in September 2018.

Inclusion/Exclusion Criteria: We included studies conducted on human subjects of any age with diagnosis of Alzheimer dementia. We excluded studies utilizing transcranial Direct Current Stimulation as this are considered to be a slightly different procedures. Studies including Theta burst stimulation (TBS) were considered but none matched the criteria for inclusion in this review. Only papers relating to Alzheimer dementia were considered, and those in which psychiatric co-morbidities were described (such as moderate to severe depression, Bipolar Affective Disorder, Schizophrenia) were excluded. Those studies relating to people with Mild cognitive impairment rather than AD were also excluded. Two reviewers (AG and YK) were in agreement on the final articles selected for review.

Summary of the Study Characteristics

A total of 7 studies were identified and included in this review after application of the search criteria, and the baseline characteristics of these have been summarised in Table 1. 5 of the studies combined rTMS with cognitive tasks (rTMS+Cog) (8, 13-16), whilst 2 studies (17, 18) performed rTMS in isolation. Two randomized controlled trials (RCTs) from South Korea (13) and China (14) benefitted from similar study design and compared rTMS+Cog with sham. The third RCT by Wu, et al. also from China, focused primarily on the impact of rTMS on behavioural symptoms of AD, but nevertheless was included as authors also collected data on outcome measures for cognition. Zhao, et al. applied rTMS over P3/P4 and posterior temporal T5/T6 according to the electroencephalogram 10-20 system, whilst Wu, et al. targeted the left dorsolateral prefrontal cortex (dlfpc). Lee, et al. stimulated the right dlpfc, and in addition also Brocas, Wernicke's and parietal somatosensory association cortex. Alcala-Lozano, et al. targeted the same cortical areas as Lee, et al. in a longitudinal study on a Mexican single blinded sample, as did Rabey, et al. in their report of clinical experience from Israel. The dlpfc was also the focus of evaluation in a Canadian pilot study with a cross over design (15), whilst an open label study from France (16) administered rTMS+Cog to the prefrontal cortex, Brocas and Wernicke's areas

Baseline characteristics of patients

Probable AD (i.e. without histopathological evidence) was established in the majority of studies by clinical and neuropsychological examination. Age ranges of subjects varied slightly amongst those studies who reported them, with the highest variability in a study cohort being 57-86 years (15). Where reported, years in education varied drastically (from an average of 11.4 years (18), to an average of 4.9 years (14). Baseline and subgroup analyses was not available from the primary publication source for all of the studies (17)

How were subjects selected and divided into groups - mild AD vs moderate/severe AD

Whilst some studies did not make a distinction on the level of cognitive impairment in their participants (8,18), others separated subjects into subgroups to allow further subgroup analyses. MMSE scores between 21 and 26 were used to define "mild AD" and

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Table 1 - Characteristics of publications included in the review.

Author	Study type	Sample	Method	rTMS characteristics	Cognitive tasks	Outcome measures	Summary of results
Lee, et al. 2015	RCT rTMS vs sham	27 patients mild AD (MMSE 21-26) Moderate AD (MMSE <20)	rTMS+Cog to 6 cortical areas 1x5days/week Total 30 session Day 1,3,5: Brocas, Wernickes, right dlPFC treated Day 2 and 4: pSAC	90%-110% of motor threshold 10Hz 1 hour sessions	Difficulty assigned according to patients cognitive performance and adjusted according to prior results Cognitive tasks well described and tailored to cortical areas treated Sham group: no cognitive tasks	Adas-Cog (baseline, at completion and 6 weeks post-treatment) Secondary outcome measures: - MMSE - CGIC - GDS scores	Adas-Cog significantly improved in treatment group compared to baseline Results best for those with Mild AD, especially in domains of language and memory Effects unchanged 6 weeks posttreatment
Zhao, et al. 2016	RCT rTMS vs sham	30 patients Mild AD (MMSE 21-26) Moderate AD: (MMSE <20)	rTMS+Cog to Parietal P3/P4 and Posterior Temporal T5/T6 1x 5days/week Total 30 sessions	Motor threshold not specified 2Hz 1 hour sessions	Administered to treatment group only Cognitive tasks poorly described	Adas-Cog MMSE MoCA WHO-UCLA AVLT	Adas-Cog, MOCA and AVLT significantly improved in treatment group compared to baseline but not compared to sham Noted improvement especially in language and memory domains
Rutherford, et al. 2015	Stage 1: Cross-over RCT (pilot) Stage 2: Open-label study	Stage 1: 10 pts Stage 2: 6 pts "Early stage AD": Adas-Cog <25 "Advanced stage AD": Adas-Cog >30	Stage 1: Cognitive training +rTMS to dlPFC Total 13 sessions 4 week washout Stage 2: 2 week cycles every 2-7 months. Total 10-19 months	90-100% of motor threshold 20Hz	Object naming	Adas-Cog MoCA RMBC Costum-designed cognitive assessment	Significant improvement in MOCA for Mild AD group but not in other outcome measures Short-lasting effect of rTMS+Cog

To be continued

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Nguyen, et al. 2017	Open label study	10 patients	rTMS+Cog to Brocas, Wernickes and PFC 4x 5 days/week Total 25 sessions	Motor threshold not specified 10Hz	Difficulty assigned according to patients cognitive performance and adjusted according to prior results Cognitive tasks well described	Adas-Cog MMSE Dubois Score FAB Stroop colour test Tinetti score Apathy score Caregiver burden score Dependence score	Significant improvement in Adas-Cog, locomotor, apathy and dependence scores. Apathy and dependence scores improvements remained stable at 6 months
Rabey, et al. 2016	Open label study	30 patients Mild-moderate AD	1 session/day, 5 days/week Total of 30 sessions with 5 patient returning for additional course Brain areas stimulated: - Brocas - Wernickes - dlPFCbilat - parietal somatosensory association cortices bilaterally	10Hz 90-110% of motor threshold (depending on brain region) 1 hour sessions	Difficulty levels were individually adjusted based on previous performance Cognitive tasks well described	Adas-Cog MMSE	Significant improvement in Adas-Cog and MMSE compared to baseline
Alcala-Lozano, et al. 2017	Comparative study Longitudinal, single blind Comparison of 2 different rTMS modalities (Complex vs simple rTMS)	22 patients	2 groups; one received rTMS to dlPFC and the other one to 6 ROI (3 areas stimulated on each day: lpSAC, rpSAC, rDLPFC, and the other day Broca, Wernicke, iDLPFC) Both groups received rTMS for 3 weeks.		-	Changes in cognitive function using Adas-Cog Secondary outcome measure: - MMSE - Behavioural symptoms report (NPI) - GDS - IDDD functional	Both modalities improved cognitive, behavioural and functional measures equally Therefore appears to be no benefit to applying the complex stimulation modality

To be continued

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Wu, et al. 2015	RCT rTMS vs sham	54 patients	Total 20 sessions 1 session/day, 5days/week for 4 weeks Stimulation over left dlPFC	80% of motor threshold 20Hz	No cognitive tasks administered	Effect of rTMS on BPSD and cognitive function BEHAVE-AD ADAS-Cog MMSE	Adas-Cog: Significant results in memory and attention subscales post-treatment, and this was significantly different from sham group. No correlation between BEHAVE and ADAs scores.

Adas-Cog, Alzheimer's Disease Assessment Scale- Cognitive subscale; dlPFc, Dorsolateral prefrontal cortex; pSAC, Parietal somatosensory association cortex; PCF, Prefrontal cortex; ROI, region of interest; MMSE, Mini-mental state examination; MoCA, Montreal Cognitive assessment; WHO-UCLA AVLT, World health organisation/UCLA Auditory verbal learning test; RMBC, revised memory and behaviour problem checklist; FAB, Frontal assessment battery; GDS, Geriatric depression scale; IDDD, Interview for deterioration in daily living activities in dementia; CGI, Clinical global impression; BEHAVE, Behavioural pathology in Alhzheimer's disease rating scale.

scores below 20 to signify "moderate AD" in the studies by Lee, et al. and Zhao, et al. whilst Rutherford, et al. divided subjects into "early stage AD" and "advanced stage AD" based on Adas-Cog scores below 25 or above 30 respectively.

Nguyen, et al. based the division on clinical experience rather than cognitive scores, and divided patients according to number of impaired cognitive domains, where impairment in one domain corresponded to MCI, 2 impaired domains were compatible with early AD and all impairment in 3 domains was compatible with moderate-severe AD.

The Alzheimer disease assessment scale - cognitive subscale is a neuropsychological testing instrument commonly used in clinical trials to measure cognitive outcomes, and all the studies included in this review utilised Adas-Cog as an outcome measure.

Side effects and drop outs

Overall the treatment was well tolerated, and although reports of transient mild headaches and fatigue were reported across most studies, only one study reported a single drop out from the treatment group (18)

Cognitive tasks:

There was a notable difference in the approach taken to administration of cognitive tasks and whilst some studies reported in detail on a number of cognitive tasks tailored to area of cortical stimulation (8, 13, 16), one study (14) briefly stated that cognitive tasks were used but did not specify further. Cognitive tasks were not included in 2 of the studies (17, 18), and one study (15) used only simple object naming to keep the patient cognitively active during treatment.

Is rTMS effective at improving cognitive functioning amongst patients with Alzheimer's disease?

Adas-Cog results

All but one of the studies (15) reported significant improvement in Adas-Cog scores following rTMS treatment when compared to baseline, regardless of whether cognitive tasks were administered or not.

Two randomized controlled studies with similar designs and methodology (13, 14) both noted in subgroup analysis that those subjects with mild AD improved their scores the most, and the benefits were especially seen in the domains of language and memory. Whilst one of the studies (13) reported significant results compared to baseline measures only, the other (14) observed significant improvement compared to sham in the mild AD group.

Nguyen, et al. 2017 found significant improvement for tasks related to cognitive tasks administered during rTMS treatment, and for those Adas-Cog tasks corresponding to parietal and language areas.

Wu et al, 2015 studied a sample of patients with notably higher degree of baseline cognitive impairment compared to those of the other contributes, and inter-

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estingly demonstrated a between group (sham/treatment) difference in the improvement of scores on memory and attention subscales.

Results of remaining cognitive outcome measures

MMSE:

Whilst two studies found overall significant MMSE results compared to baseline (8, 17), other authors only found significant improvement in the mild AD group (13, 14). One study found no significant findings in their measurements but described significant improvement in locomotor, apathy and dependence scores (16).

MOCA

Two studies reported significant findings in the MOCA test in the mild AD group (14, 15)

Other Cognitive Outcome Measures

No notable findings were reported from the observer-rated CGIC or the GDS (13), whereas AVLT scores were found to improve significantly from baseline (14).

How long do effects of rTMS last?

4 of the 7 studies included in the review measured cognitive outcomes beyond date of completion of rTMS (13, 14, 16, 17). Two of them (13, 14) found that cognitive test results remained steady or were further enhanced at 6 weeks post-treatment compared to completion of treatment course. One study (13) reported the improvement in Adas-Cog score to be on average 1.11 points compare to post-treatment measurements and 0.5 points for the MMSE scores. Subjects with mild AD were found to display a greater improvement from baseline measures compared with those subjects in the moderate AD group, and these findings were statistically significant in a comparison between baseline and 6 weeks post-treatment. However, these results were not reflected in the CGIC score, which at 6 weeks post-treatment was found to have deteriorated compared to start of treatment measures.

Zhao, et al. 2016 found overall significant findings for all cognitive batteries used for the mild AD group, but reported that whilst language and cognitive domains continued to improve at 6 weeks post-treatment, executive function did not.

Alcala-Lozano, et al. 2017 used a slightly shorter follow-up period, and found that clinically significant improvement on cognitive measures was maintained at 4 weeks post-treatment in both primary and secondary outcome measures.

An open label study (16) applied a longer follow-up period of 6 months for repeat measurements, and reported that whilst Adas-Cog scores had returned to baseline on average in the entire series of patients, the best responders at completion of treatment remained significantly improved at 6 months (and these finding were also true for apathy score and dependence score), suggesting that the best responders could benefit from a single NeuroAd procedure for a prolonged time beyond the time of stimulation

Discussion

This review found trends to support that rTMS combined with cognitive tasks or rTMS administered in isolation improved cognitive function amongst AD patients and this improvement was particularly evident for patients with mild AD. Interestingly, all but one of the studies reported that rTMS alone improved cognitive function measured by the Adas-Cog regardless of whether cognitive tasks were administered or not.

The findings from this review corroborate existing evidence in support of rTMS as a treatment to improve cognitive function amongst Alzheimer's patients (9-12). This is particularly promising given that rTMS is a non-invasive procedure, with minimal side effects.

Given the heterogeneity across the studies, which are discussed in depth below, it is difficult to draw direct comparisons across the studies. Furthermore, variability in the site and duration of stimulation make it difficult to identify which site(s) of stimulation are associated with the greatest benefit to cognitive function. Although the precise mechanism of rTMS is unknown (19), there is evidence based on this review that multisite rTMS is beneficial to cognitive scores. Such a finding has also been echoed in the wider literature (20).

Despite the variations across the studies, a trend for an improvement in Adas-Cog scores following on from the administration of rTMS was apparent and there is evidence from 2 of the studies (13, 14) that this effect was sustained as far as 6 weeks after the delivery of rTMS. Given that both of these studies delivered rTMS across a total of 30 sessions, it may be the case that patients presenting with Mild AD experience the most beneficial effects on their cognitive function, if they receive regular intervals of rTMS at least every 6 weeks. However, implications from the results should be drawn cautiously due to the following limitations with the studies.

Limitations with the Studies

There are several methodological issues that may limit the conclusions drawn from the studies reviewed. As with many reviews, the studies were highly heterogeneous and variations in stimulation protocols, neuropsychological testing and cognitive tasks administered, unknown status of concomitant medication and differences in administered cognitive tasks complicate interpretation of results. Although the remit of the review was to include non-RCT studies, these studies are susceptible to the introduction of bias and so the 'true' effect of rTMS is difficult to decipher. Potential confounding factors within the studies include and are not limited to qualities of the study participants and recruitment; randomization and

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blinding; medication and comorbidities.

Sufficient descriptions of the study participants and the recruitment process was missing from the narrative and only a selection of studies reported on important demographic information such as education (13, 14, 18) and mean duration of illness (16, 18), opening the studies up to bias and potentially weakening external validity.

Although 5 of the studies utilized a blinded randomized design (13-15, 17, 18), additional detail on the process and allocation concealment would have provided a more transparent description. Although one study described the use of a random numbers table (18), it is unclear whether the random sequence was implemented without knowledge of the next treatment assignment, and whether the implementer can be considered as unbiased.

Whilst blinding of participants and cognitive assessors was confirmed in some cases (13, 14, 18), blinding status of participant's carers and other study personnel remains unclear.

A cross-over trial (15) reported being unable to blind all their cognitive assessors, and described "very compelling results" only for the unblinded outcomes. The second phase open-label phase of the same study may also have introduced further bias through complete unblinding.

Nevertheless where blinding was implemented steps were taken to maintain it, either through recorded sounds imitating the rTMS treatment sound (13, 14) or through turning of the coil to severely reduce the magnetic field penetrating the brain in order to weaken the magnetic field (18).

The majority of the studies stressed the maintenance of steady medication doses as central to the inclusion criteria, though few studies specified when anti-dementia medication such as Donepezil was used (13, 14, 18) and an account of participants medical comorbidities and other regular medication was absent. This is of some concern to study validity as a number of medications can interact with the effects of rTMS, and rTMS may itself affect neurotransmitters and neuromodulators (21). Furthermore, unexpected enhancing or suppressing effects on transcranial stimulation by concomitant psychotropic medication have been described (22) and certain antidepressants are thought to interact with non-invasive transcranial treatment procedures (23). This underpins the need for a full description of medication, especially as baseline GDS scores (13) point towards a varying degree of depression in the participants and the well-established effectiveness of rTMS in treating depression (6). In a similar vein, a record of concomitant functional mental illness and physical co-morbidities could have been identified as important confounding variables.

It may have been a possibility that some of the samples in the studies reviewed were taking herbal remedies as these are commonly used, especially amongst the elderly populations of East Asian countries which constitute a significant part of the participants across the studies in this review. Results for the efficacy of Ginko Biloba on cognition in dementia has been inconclusive (25). Interestingly however, cognitive improvement measured by the Adas-Cog scale and MMSE for up to 12 weeks following initiation of Ginseng has been reported (26). These results are by no means decisive, but demonstrate the potential confounding effect of herbal remedies.

Conclusion

Despite the limitations within and across the studies reviewed, the use of rTMS is associated with an improved level of cognitive function, which is particularly promising for patients presenting with mild AD. The concurrent administration of cognitive tasks may not further enhance the benefits of rTMS and given the promising results of rTMS, it is crucial to conduct further research in this field with methodologically robust studies including larger sample sizes and minimizing the potential for bias. Furthermore, the subjective experience of the patient has not been well reported and further insight into the perspective of the patient would also acknowledge quality of life during and after the delivery of rTMS.

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