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ORIGINAL COMMUNICATION

Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia

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Abstract The aim of the study was to compare the long-term efficacy of high versus low frequency repetitive transcranial magnetic stimulation (rTMS), applied bilaterally over the dorsolateral prefrontal cortex (DLPFC), on cognitive function and cortical excitability of patients with Alzheimer's disease (AD). Forty-five AD patients were randomly classified into three groups. The first two groups received real rTMS over the DLPFC (20 and 1 Hz, respectively) while the third group received sham stimulation. All patients received one session daily for five consecutive days. In each session, rTMS was applied first over the right DLPFC, immediately followed by rTMS over the left DLPFC. Mini Mental State Examination (MMSE), Instrumental Daily Living Activity (IADL) scale and the Geriatric Depression Scale (GDS) were assessed before, after the last (fifth) session, and then followed up at 1 and 3 months. Neurophysiological evaluations included resting and active motor threshold (rMT and aMT), and the duration of transcallosal inhibition (TI) before and after the end of the treatment sessions. At base line assessment there were no significant differences between groups in any of the rating scales. The high frequency rTMS group improved significantly more than the low frequency and sham groups in all rating scales (MMSE, IADL, and GDS) and at all time points after treatment. Measures of cortical excitability immediately after the last treatment session showed that treatment with 20 Hz rTMS reduced TI duration. These results confirm that five daily sessions of high frequency rTMS over the left and then the right DLPFC improves cognitive function in patients with mild to moderate degree of AD. This improvement was maintained for 3 months. High frequency rTMS may be a useful addition to therapy for the treatment of AD.

Keywords Repetitive transcranial magnetic stimulation · Cortical excitability · Cognitive function · Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in older adults, and manifests initially with a decline in explicit memory [45]. At the age of 60 years, the risk of developing AD is estimated to be 1%, doubling every 5 years to reach 30–50% by the age of 85 years [16].

Repetitive transcranial magnetic stimulation (rTMS) can be used to explore the role of brain areas and circuits in a variety of different ways. If applied over an area that is causally engaged in that task being executed, short bursts of rTMS can interfere with function for brief periods and transiently change behavioral performance. This is sometimes referred to as on-line interference. Used in this way, rTMS has confirmed the involvement of the dorsolateral prefrontal cortex (DLPFC) in various aspects of cognitive control. In some cases (e.g., memory), rTMS can interfere with task performance, inducing an increase in the number of errors [33]. In other cases (e.g., naming), even with comparable stimulation parameters, performance can actually be facilitated [3–5, 49]. In a recent study recorded by Cotelli et al. [5], the authors stimulated left or right DLPFCs

for 500 ms during object and action naming in a group of AD patients. Action naming performance was improved in all subjects during high frequency stimulation of both left and right DLPFC compared with sham stimulation.

For therapeutic purposes, rTMS is usually given for much longer periods, applying several hundred or thousand stimuli. This generates long lasting effects on excitability that persist after the end of stimulation, and may, therefore, be of therapeutic use ("off-line" effects of rTMS). High (>5 Hz) and low (<1 Hz) frequency rTMS have been employed, with the rationale that the former has mainly an excitatory net effect and the latter has mainly an inhibitory net effect [28]. For example, recent studies report improved ability to name pictures after administration of long lasting low frequency rTMS in order to suppress activity in the anterior portion of the right homologue of Broca's area in patients with non-fluent aphasia [30, 35, 36]. In contrast, higher frequency rTMS has been applied over the motor cortex of the stroke hemisphere in order to improve recovery of the paretic arm in patients after stroke [20, 21]. Nevertheless, several studies have demonstrated that both types of stimulation (high and low frequency) may have similar, positive effects in selected pathological conditions, depending on the site of stimulation [11]. It is also important to note that the effects of (particularly long lasting) rTMS spread from the directly targeted brain region to anatomically connected distant cortical and subcortical regions [34, 37]. Therefore, it is possible by using rTMS at one point in a circuit to modulate activity in specific neural networks, using cortical targets as "entry ports" [15].

To our knowledge there has been only one off-line therapeutic rTMS study in patients with AD. Cotelli et al. [7] applied daily high frequency rTMS over the left DLPFC of patients with AD for 2–4 weeks. They found that real rTMS improved performance in cognitive tests relative to sham for up to 8 weeks after the end of treatment. There have been no studies of the long-term effect of rTMS to either the right DLPFC, or to both hemispheres consecutively. The latter is of particular interest since functional neuroimaging and rTMS studies have shown that older adults tend to recruit regions of the contralateral hemisphere in addition to regions of the specialized hemisphere used by younger adults when performing cognitive tasks [2, 7, 9, 17, 18, 26, 29, 43, 47, 56]. There are also no studies that compare the effects of low and high frequency stimulation.

The mechanism of action of rTMS over DLPFC in AD is unknown. It is possible that rTMS over DLPFC improves dementia by a direct effect on DLPFC and connected circuits. In addition, rTMS can also have effects on neurotransmitter function. Dopamine is an important regulator of the status of the networks centred on the prefrontal cortex [44]. A combined rTMS/positron emission tomography (PET) study reported elevations in extracellular dopamine concentration in the caudate nucleus following 10 Hz rTMS administered to the DLPFC [48]. Such reasoning has led several groups to explore the possible use of rTMS as a therapeutic tool to induce changes in synaptic function in patients with depression [11] or movement disorders [22], or dementia [5].

In the present study we have compared the long-term efficacy (off-line) of high versus low frequency rTMS applied bilaterally over the left and right DLPFC daily for 5 days on MMSE, IADL and GDS, as well as measures of motor cortical excitability including transcallosal inhibition (TI) in an attempt to understand the effects of rTMS in patients with AD. Given its effects on cognition in younger individuals noted above, together with the effects on dopaminergic transmission, we hypothesized that high frequency stimulation of both DLPFC would improve cognitive function more than low frequency or sham rTMS.

Patients and methods

Fifty-two consecutive patients with a diagnosis of probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [32] were included in this study. In all patients, computed tomography scans (CT) or magnetic resonance imaging (MRI) showed diffuse brain atrophy. Exclusion criteria were the following: previous history of stroke, metabolic disturbance, other major medical illnesses or epilepsy. Patients with metallic objects in the body, or subjected to a craniotomy in the past, were also excluded. Three cases declined to participate in the study and four cases were excluded, two of them had metallic pace makers and the other two had a history of convulsions [40].

Forty-five patients (29 females and 16 men) mean age 68.4 years, (range 60–82 years) were included in the trial. At the time of recruitment, none of the patients were taking cholinomimetics, antidepressants, or neuroleptic, sedative-hypnotic drugs for at least 2 weeks before the assessment. All participants or their caregivers gave informed consent before participation in the test and after full explanation of the study protocol. The local ethical committee of Assiut University Hospital approved the study protocol.

The stage of dementia was evaluated by means of the Mini Mental State Examination (MMSE) [13]. Assessment of daily activity was made using the Instrumental daily living activity (IADL) scale [23] and depression was assessed using the geriatric depression scale (GDS) [39].

The mean (SD) total MMSE score of AD patients was 14.84 (±5.5) ranging from 6 to 21; 32 had mild to moderate dementia, and 13 had severe dementia. Each patient received the following neurophysiological assessments of left hemisphere.

Experimental protocol

Subjects sat in a comfortable chair. Electromyographic (EMG) recordings from the first dorsal interosseous muscle (FDI) of both hands were acquired with silver–silver chloride surface electrodes, using a muscle belly-tendon set-up, and a 3 cm diameter circular ground electrode placed on the wrist. A Nihon Kohden Machine model 9400 (Japan) was used to collect the signal. EMG parameters included a bandpass of 20–1,000 Hz and a recording time window of 200 ms. TMS was performed with a commercially available 90 mm figure of eight coil connected to a Magstim super rapid magnetic stimulator (UK).

Determination of motor thresholds

First we determined the optimal scalp location of both hemispheres from which TMS evoked motor potentials of greatest amplitude in the FDI. We used a constant suprathreshold stimulus intensity and moved the figure-of-eight coil systematically in 1 cm steps to determine the scalp position from where TMS evoked motor potentials of maximum peak to peak amplitude in the target muscle were evoked. The coil was positioned tangentially to the scalp and oriented so that the induced electrical currents would flow approximately perpendicular to the central sulcus, at a 45° angle from the mid-sagittal line. Single pulse TMS was then delivered to the optimal location starting at suprathreshold intensity and decreasing in steps of 1% of the stimulator output. Relaxation and EMG signals were monitored for 200 ms prior to stimulation. The rMT was defined as the minimal intensity required eliciting motor evoked potentials of 50 μV peak to peak amplitude in five out of ten consecutive trials [41]. AMT was determined in the same way while subjects made a mild contraction of about 10% maximum. AMT was defined as the minimal intensity required to elicit an MEP larger than 200 μV in five of ten consecutive trials. Both the rMT and the aMT were expressed as a percentage of the magnetic stimulator maximal output (equal to 100%). Resting and active MTs were measured in both hemispheres in order to adjust rTMS stimulus intensities (see below). Measures were made before the first and after the last treatment session.

Transcallosal inhibition (TI)

Approximately 5 s prior to each stimulus, subjects were instructed to make an isometric (approximately 50% maximal contraction) contraction of the left FDI and to maintain it for a similar period after the stimulus. The degree of muscle activation was monitored by an oscilloscope. Stimulation intensity was 150% RMT of the left hemisphere. If RMT was above 65% of maximum stimulator output then maximum stimulation intensity was used. The onset and offset of TI were defined as the points where the EMG trace fell persistently below and where it returned persistently above the base line. The TI duration is calculated as the time of offset of TI minus the onset [12].

RTMS performed with a commercially available 70 mm figure-of-eight coil connected to a Magstim rapid stimulator with the centre of the coil placed over the optimal position for the DLPFC (right then left hemisphere consecutively where 2,000 pulses were applied for each hemisphere for all groups of patients). The examiner was blind to the degree of dementia.

The patients were randomly classified into one of the three groups using closed envelopes; the first and second groups received real rTMS over the DLPFC (20 and 1 Hz, respectively), and the third group received sham stimulation over the DLPFC but with the coil elevated away from the head. All patients received treatment every day for five consecutive days. The DLPFC stimulation site was defined as being 5 cm rostral in the same sagittal plane as the optimal site for motor threshold production in the first dorsal interosseous for each hemisphere [41].

During rTMS, all patients wore earplugs. Group 1 included 15 patients who received real rTMS with 20 Hz, 5 s, 20 trains, 25 s interstimulus interval, with total 2,000 pulses at 90% of RMT (nearly 10 min for each hemisphere and 10 min between hemispheres). Group 2 included 15 patients who received real continuous 1 Hz rTMS with total of 2,000 pulses at 100% of RMT divided into two trains with an interstimulus interval 30 s (33 min). Group 3 included 15 patients who received sham rTMS with the same parameters as the first group but the sessions were applied with the coil angled away from the head to reproduce the noise of the stimulation as well as some local sensation. In each session, rTMS was applied first over the right DLPFC immediately followed by rTMS over the left DLPFC. The decision to apply right rTMS before left rTMS was arbitrary since we had no a priori information that would suggest any effect of order. Thus, we gave all patients the same treatment.

We followed up the patients clinically at the end of sessions then at 1 and 3 months after the end of treatment. Evaluations using MMSE, GDS, and IADL scales were performed blindly by a neurologist who was unaware of the type of rTMS each patient had received.

Data analysis

All data were analyzed with the aid of the SPSS ver. 16 (http://www.spss.com). The results were expressed as mean ± SD. Each group was subdivided into two subgroups (mild to moderate dementia and severe dementia) using MMSE. Statistical analysis of the scores in each test

was done with a repeated measures ANOVA with time points (pre- and post-fifth session, and then at 1 and 3 months follow up) as the within subject factor, and patient subgroups (mild to moderate vs. severe dementia) as well as type of treatment (high, or low, or sham stimulation) as the between subject measure. Greenhouse-Geisser degree of freedom corrections were applied to correct for non-sphericity of the data. The effects rTMS on RMT and AMT were evaluated using one-way ANOVA with time before and after rTMS. $P > 0.05$ was considered significant for all statistical analysis.

Results

All the patients tolerated rTMS well without any adverse effects. There were no significant differences between the studied groups regarding the baseline demographic and clinical assessment of different scales (MMSE, IADL, and GDS), details of the examined patients are illustrated in Table 1.

Table 1 Demographic and clinical data

	Group 1 (15 patients received 20 Hz)	Group 2 (15 patients received 1 Hz)	Group 3 (15 patients received sham)	*P* value
Age (years): mean ± SD	65.9 ± 5.9	68.6 ± 6.7	68.3 ± 4.9	NS
Range	60–80	60–82	65–80	
Sex: male/females	5/10	6/9	5/10	NS
Residence urban/rural	4/11	5/10	3/12	NS
Education:				
Literate	7 (46.7%)	6 (40%)	7 (46.7%)	NS
≤6	4 (26.7%)	3 (20%)	4 (26.7%)	
>6	3 (20%)	3 (20%)	3 (20%)	
Illiterate	8 (53.3%)	9 (60%)	8 (53.3%)	
Duration of illness: mean ± SD	3.9 ± 2.3	4.1 ± 2.3	4.4 ± 2.5	NS
Range (years)	0.9–10	1–10	2–10	
MMSE: mean ± SD	14.7 ± 3.7	12.7 ± 3.9	13.9 ± 3.9	NS
Range	8–19	6–21	7–20	
IADL: mean ± SD	16.2 ± 4.8	14.2 ± 3.7	15.3 ± 3.7	NS
Range	10–23	10–21	10–23	
GDS: mean ± SD	7.1 ± 3.9	5.9 ± 6.0	6.0 ± 4.0	NS
Range	2–14	1–15	1–11	

The data presented as mean ± standard deviation (SD)

NS nonsignificant, *MMSE* Mini Mental State Examination, *IADL* Insturmental Daily Living Activity scale, *GDS* Geriatric Depression Scale

Effect of rTMS on clinical rating scale

Two factor ANOVA with repeated measures analysis for each treatment subgroup versus sham with time (pre-, post-sessions, 1 and 3 months after the end of sessions) and group (20 Hz and sham; 1 Hz and sham) as main factors were recorded.

There was a significant Time X Group interaction for the comparison of 20 Hz versus Sham in all three scales MMSE, IADL, and GDS [$F = 21.6$, $df = 1.9$ (51.9) and $P = 0.0001$, $F = 18.1$, $df = 2.5$ (72.4) and $P = 0.0001$ and $F = 15.5$, $df = 1.6$ (44.5) and $P = 0.0001$, respectively], which was due to the fact that the 20 Hz treatment group tended to improve more across the four assessment times than the sham group. There were no significant interaction terms for the 1 Hz group versus sham in the rating scales although there was a significant improvement in IADL rating scale in comparison to the sham group [$F = 5.9$, $df = 1.9$ (53) and $P = 0.005$].

We next compared the effect of 20 versus 1 Hz groups: there were significant interactions of Time X Group in all the measures [MMSE, IADL, and GDS $F = 5.5$, $df = 1.6$ (43) and $P = 0.049$, $F = 3.4$, $df = 2.1$ (59.7) and $P = 0.03$, and $F = 4.1$, $df = 1.3$ (35) and $P = 0.04$, respectively] indicating that the 20 Hz treatment group tended to improve more than the 1 Hz group in all rating scales across the four times of assessment.

Subgroup analysis of behavioural effects

The analyses above have combined data from all patients in each treatment group. However, it was possible to split each group into subgroups of mild/moderate versus severe dementia. Interestingly, in the first treatment group (20 Hz); patients with mild/moderate dementia improved significantly in all rating scales ($P = 0.0001$ for each scale) while no such improvement in severe dementia. In the second treatment group (1 Hz) there was significant improvement in IADL (0.005) in mild/moderate dementia only with no significant changes in the other rating scales nor in the sham group (Table 2, 3, 4 as well as Figs. 1, 2, 3).

There were no significant changes in rMT or aMT between pre-post rTMS in any group either for mild/moderate or severe dementia. However, there was a significant ($P = 0.001$) changes in the duration of TI which was due to the fact that TI duration was shorter after 20 Hz rTMS in mild to moderate dementia but not in severe dementia. However, there were no such changes were after

Table 2 Changes in MMSE before and after treatment

Groups	Before first session	After last session	1 month follow up	3 months follow up	*P* value One way ANOVA (main factor time) for each subgroup	*P* value Paired *t* test (post vs. 3 months) for each subgroup	*P* value two factor ANOVA interaction (time X subgroup) (mild to moderate versus severe dementia
First group (20 Hz)							
Mild to moderate dementia (10 patients)	18.4 ± 2.7	21.4 ± 3.2	22.3 ± 2.0	22.6 ± 1.5	**0.0001**	**0.032**	**0.001**
Severe dementia (5 patients)	10.4 ± 1.7	11.00 ± 1.9	10.4 ± 1.7	11.2 ± 1.9	0.89	1.00	
Second group (1 Hz)							
Mild to moderate dementia (11 patients)	15.5 ± 3.5	15.7 ± 4.0	16.7 ± 4.4	16.8 ± 4.1	0.104	0.25	0.16
Severe dementia (4 patients)	10.2 ± 1.8	10.2 ± 1.9	8.4 ± 1.8	8.8 ± 2.3	0.51	0.58	
Third group (sham)							
Mild to moderate dementia (11 patients)	15.4 ± 2.8	15.6 ± 2.6	14.9 ± 2.8	14.4 ± 3.2	0.08	0.26	0.66
Severe dementia (4 patients)	8.0 ± 1.7	8.3 ± 2.3	8.0 ± 1.0	8.0 ± 1.0	0.58	0.74	

Table 3 Changes in IADL before and after treatment

Groups	Before first session	After last session	1 month follow up	3 months follow up	*P* value One way ANOVA (main factor time) for each subgroup	*P* value Paired *t* test (post vs. 3 month) for each subgroup	*P* value two factor ANOVA interaction (time X subgroup) (mild to moderate versus severe dementia
First group (20 Hz)							
Mild to moderate dementia (10 patients)	20.1 ± 2.6	21.9 ± 2.6	23.7 ± 2.5	24.7 ± 2.2	**0.0001**	**0.001**	**0.023**
Severe dementia (5 patients)	11.6 ± 1.4	13.0 ± 3.3	12.4 ± 2.5	12.2 ± 2.9	0.18	0.184	
Second group (1 Hz)							
Mild to moderate dementia (11 patients)	15.9 ± 3.4	17.3 ± 4.6	18.2 ± 4.8	19.0 ± 5.1	**0.005**	0.023	0.09
Severe dementia (4 patients)	11.1 ± 1.4	11.2 ± 1.6	11.0 ± 1.8	11.6 ± 2.2	0.307	0.178	
Third group (sham)							
Mild to moderate dementia (11 patients)	16.4 ± 3.2	16.3 ± 3.4	16.0 ± 3.7	17.0 ± 3.2	0.08	0.13	0.16
Severe dementia (4 patients)	10.7 ± 1.2	10.3 ± 0.6	10.3 ± 0.6	10.0 ± 1.0	0.90	0.42	

1 Hz or sham treatment either in mild to moderate nor in severe dementia (Table 5).

Discussion

Given the limited effectiveness of pharmacological treatments, non-pharmacological interventions in AD (e.g., rTMS, behavioral and cognitive training) have gained attention in recent years [4–7, 42, 53]. The capability of rTMS to interact with the intrinsic ability of the brain to restore or compensate for damaged function makes it a promising method to investigate for potential benefits in AD. In the present study, we measured the effect of rTMS on MMSE and IADL as well as GDS scales. The results show that high frequency rTMS applied bilaterally to the DLPFC improves scores on the three rating scales in patients with AD. As we argue below, the mechanism

Table 4 Changes in GDS before and after treatment

Groups	Before first session	After last session	1 month follow up	3 months follow up	*P* value One way ANOVA (main factor time) for each subgroup	*P* value Paired *t* test (post vs. 3 month) for each subgroup	*P* value Two factor ANOVA interaction (time X subgroup) (mild to moderate versus severe dementia
First group (20 Hz)							
Mild to moderate dementia (10 patients)	5.9 ± 3.4	4.2 ± 3.2	2.3 ± 2.0	2.6 ± 1.5	**0.0001**	**0.01**	**0.023**
Severe dementia (5 patients)	4.1 ± 1.4	3.00 ± 2.3	2.4 ± 2.5	2.2 ± 2.9	0.057	0.09	
Second group (1 Hz)							
Mild to moderate dementia (11 patients)	6.6 ± 6.4	5.1 ± 4.9	3.9 ± 4.7	3.9 ± 4.7	0.059	0.053	0.40
Severe dementia (4 patients)	3.6 ± 6.5	3.2 ± 5.6	2.8 ± 4.7	2.6 ± 4.2	0.37	0.16	
Third group (sham)							
Mild to moderate dementia (11 patients)	6.2 ± 4.4	6.4 ± 4.7	6.1 ± 4.4	6.1 ± 4.3	0.46	0.56	0.12
Severe dementia (4 patients)	3.6 ± 6.5	3.3 ± 3.5	2.9 ± 4.0	2.5 ± 3.5	0.19	0.82	

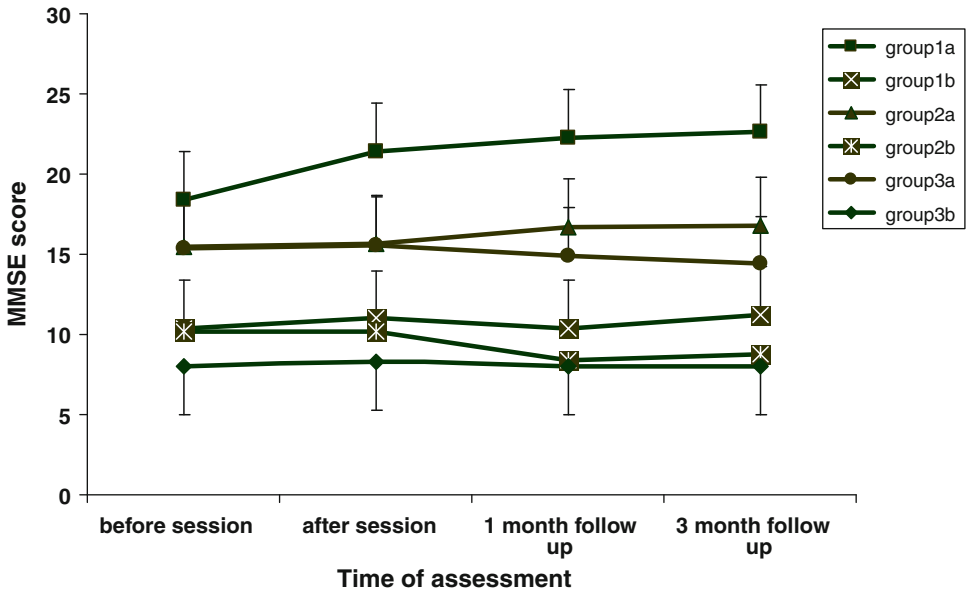

Fig. 1 Changes in mean (± SD) of MMSE at the four assessment points in the six subgroups of patients (group 1a = mild to moderate dementia of 20 Hz, group 1b = severe dementia of 20 Hz group, group 2a = mild to moderate dementia of 1 Hz, group 2b = severe dementia of 1 Hz group and group 3a = mild to moderate dementia of sham stimulation, and group 3b = severe dementia of sham group). The first assessment was immediately before commencing repetitive transcranial magnetic stimulation (rTMS) treatment, the second assessment was immediately after the last session of rTMS, the third and the fourth assessment were 1 and 3 months later. Data from the Mini Mental State Examination (MMSE). There was significant improvement in the MMSE among the subgroup of mild to moderate dementia of the 20 Hz group along the course of the treatment ($P = 0.0001$). This improvement was persistent after the end of sessions (post-session vs. 3 months after sessions with $P = 0.03$), while no significant changes among all other subgroups

most likely relates to the known effect of rTMS to the DLFPC and its interconnected circuits on cognitive function in healthy subjects [14]. Interestingly in the 20 Hz treatment group, patients who had mild to moderate dementia improved significantly in scores of MMSE and IADL, while the group of patients with severe dementia did not respond at all to either the 1 or 20 Hz treatment.

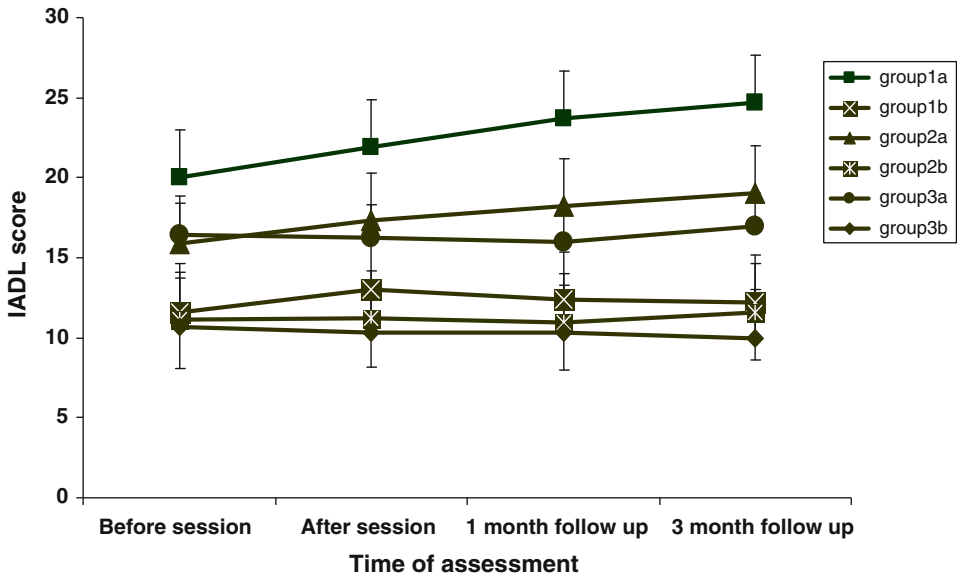

Fig. 2 Changes in mean (±SD) of Instrumental Daily Living Activities (IADL) at the previous four assessment points in the six subgroups of patients. Improvement were significantly recorded among mild-moderate subgroups of 20 and 1 Hz groups in IADL. This improvement was persistent after the end of sessions (post-session vs. 3 months after sessions) for both subgroups, while no significant changes among all other subgroups

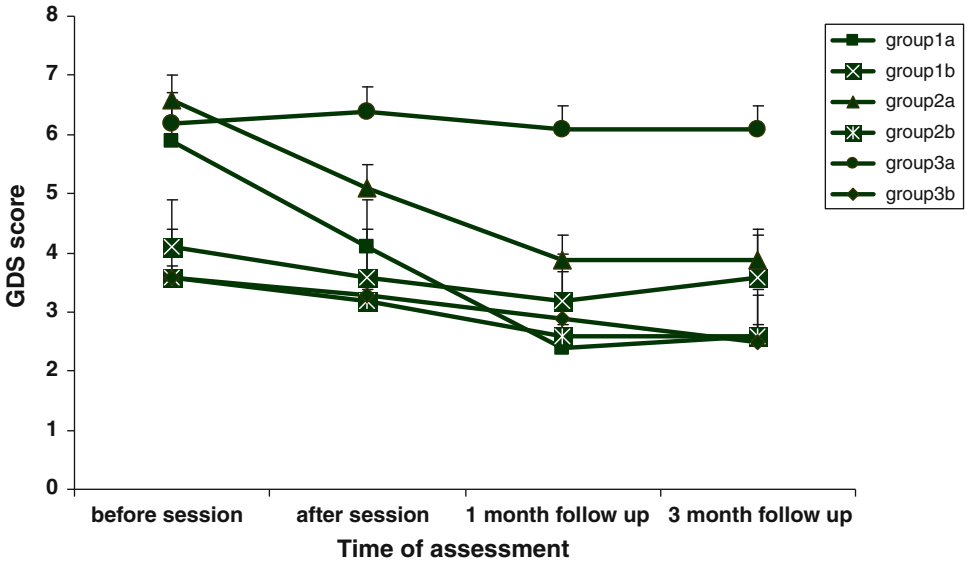

Fig. 3 Changes in mean (±SD) of Geriatric Depression Scale (GDS) at the four assessment points in the six subgroups of patients. There was significant improvement in the GDS among the subgroup of mild to moderate dementia of the 20 Hz group along the course of the treatment ($P = 0.0001$). This improvement was persistent after the end of sessions (post-session vs. 3 months after sessions with $P = 0.01$), while no significant changes among all other subgroups

A slight concern is that in scores on MMSE and IADL were highest in the 20 Hz group even before the application of rTMS. However, a larger data sample would be needed to assess the potential effects of this on the response to rTMS.

To our knowledge few studies [7] have assessed the off-line therapeutic effects of rTMS on cognitive function in AD patients. They noted that sentence comprehension improved for 2 months after either 2 or 4 weeks rTMS over the left DLPFC, which is similar to the duration of effects in the present study. A few studies have evaluated the effect of rTMS on memory in normal subjects [27], and a few published data on the effects of rTMS on memory performance [46] in patients with memory impairment. A positive effect on executive dysfunction has been reported in patients with cerebrovascular disease [38]. A general improvement of cognitive function after stimulation of the DLPFC also has been reported in depressed patients [25, 31]. Vanderhasselt et al. [52] stimulated the left dorsolateral prefrontal cortex (DLPFC) in depressed patients and had them perform a switching task that required the control of attention between visual and auditory cues. It was found patients that received active stimulation had improved reaction times, whereas those that received sham stimulation showed no improvement.

The improvement of both cognitive function and depression may be related to rTMS effects on dopamine (AD) release. A combined rTMS/positron emission

Table 5 Resting, active motor threshold and transcallosal inhibition of dominant hemisphere before and after treatment

Groups	Resting motor threshold			Active motor threshold			Duration of transcallosal inhibition		
	Before first session	After last session	Paired *t* test *P* value	Before first session	After last session	Paired *t* test *P* value	Before first session	After last session	Paired *t* test *P* value
First group (20 Hz)									
Mild to moderate dementia (10 patients)	39.4 ± 4.8	41.6 ± 3.9	0.30	30.3 ± 4.3	33.0 ± 4.2	0.134	26.3 ± 4.8	22.7 ± 3.4	**0.028**
Severe dementia (5 patients)	31.7 + 4.8	33.0 + 1.4	0.60	24.7 + 4.0	26.2 + 2.1	0.28	25.5 + 4.1	25.9 + 4.4	0.199
Second group (1 Hz)									
Mild to moderate dementia (11 patients)	33.2 ± 7.1	37.2 ± 6.1	0.04	27.3 ± 4.8	29.7 ± 5.3	0.098	26.6 ± 4.6	25.5 ± 4.9	0.43
Severe dementia (4 patients)	31.79 + 5.1	32.1 + 4.1	0.88	23.6 + 5.2	24.4 + 4.3	0.47	29.5 + 2.3	29.9 + 6.4	0.96
Third group (sham)									
Mild to moderate dementia (11 patients)	36.7 ± 7.7	36.9 ± 7.1	0.33	28.1 ± 6.8	29.1 ± 6.1	0.08	27.3 ± 6.0	26.5 ± 4.1	0.79
Severe dementia (4 patients)	33.75 + 5.2	32.0 + 2.1	0.55	25.6 + 3.2	24.0 + 1.8	0.268	27.3 + 1.3	28.4 + 1.7	0.115

tomography (PET) study reported elevations in DA concentration in the caudate nucleus following 10 Hz rTMS administered to the DLPFC [48]. Circuits involving connections between prefrontal cortex and basal ganglia are known to be important in many cognitive functions [44] so that changing the status of the network by changing dopamine concentrations could also be relevant for the potential effects that we observed on AD. Depressive symptoms are common in AD, occurring in approximately 40% of patients, although major depressive episodes and suicide are notably rare [1, 8, 50, 54]. The striking effect that was recorded on the GDS in the present study could account for the changes in the MMSE and IADL scales. Thus, part of the improvement we saw in our AD patients could potentially be via a similar mechanism as previously reported in other studies [1, 8, 50, 54].

In the present study there were no changes in different rating scales in patients who received low frequency or sham stimulation. Others have reported that low frequency stimulation (1 Hz) seems to worsen rather than improve cognitive functioning. One study done by Trojano et al. [51] found a selective deterioration of function directly and after 10 min of 1 Hz stimulation. In comparison with studies using 1 Hz stimulation, high-frequency studies seem to be superior for improving cognitive outcome. Interestingly, there were no disease progression recorded in the sham group which may be partially related to the small sample size and the short period of time.

The absence of changes in RMT and AMT after low and high frequency rTMS in the present study suggest that the improvement in MMSE scale observed after high frequency rTMS was not caused by changes in membrane excitability. However, the improvement was associated with shortening of the duration of transcallosal inhibition. The improvement in the MMSS, IADL and GDS with the absence of changes in RMT and AMT may therefore result from changes in network activity and synaptic efficiency (functional plasticity). An important point is that in AD, there is degeneration of the parent layer III pyramidal neurons [24] whose axons form the corpus callosum, and presumably this is responsible for the degeneration that is seen anatomically [55, 57]. The principal function of CC is to allow the exchange of information between the hemispheres, so that its degeneration may be responsible for the occurrence in some patients of a disconnection syndrome similar in nature to that demonstrated by split-brain subjects. Thus, improved cognitive function could be partially related to the changes in TI that we observed in the 20 Hz group.

In agreement of the absence of effects on RMT and AMT, Zarkowski et al. [58], did not find a significant effect of treatment with rTMS on RMT using a stimulation intensity of 120% rMT and 3,000 stimuli per day. Inghilleri et al. [19], in their study of elderly patients with mild to moderate AD and healthy subjects, found that 1 Hz-rTMS-induced response was similar in the two groups studied with no change on resting and active MT or MEP amplitude post stimulation. Daskalakis et al. [10], exploring the effects of both 10 and 20 Hz and showed no effects on RMT or MEP amplitude.

Conclusion

In our study we demonstrated that high frequency rTMS could improve cognitive function and activity of daily living in patients with mild to moderate AD. Together with previous studies this suggests that rTMS may be a suitable add-on therapy for treatment of AD patients.

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Conflict of interest None.

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