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Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study

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Abstract The current drug treatment for Alzheimer's disease (AD) is only partially and temporary effective. Transcranial magnetic stimulation (TMS) is a non-invasive technique that generates an electric current inducing modulation in cortical excitability. In addition, cognitive training (COG) may improve cognitive functions in AD. Our aim was to treat AD patients combining high-frequency repetitive TMS interlaced with COG (rTMS-COG). Eight patients with probable AD, treated for more than 2 months with cholinesterase inhibitors, were subjected to daily rTMS-COG sessions (5/week) for 6 weeks, followed by maintenance sessions (2/week) for an additional 3 months. Six brain regions, located individually by MRI, were stimulated. COG tasks were developed to fit these regions. Primary objectives were average improvement of Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) and Clinical Global Impression of Change (CGIC) (after 6 weeks and 4.5 months, compared to baseline). Secondary objectives were average improvement of MMSE, ADAS-ADL, Hamilton Depression Scale (HAMILTON) and Neuropsychiatric Inventory (NPI). One patient abandoned the study after 2 months (severe urinary sepsis). ADAS-cog (average) improved by approximately 4 points after both 6 weeks and 4.5 months of treatment ($P < 0.01$ and $P < 0.05$) and CGIC by 1.0 and 1.6 points, respectively. MMSE, ADAS-ADL and HAMILTON improved, but without statistical significance. NPI did not change. No side effects were recorded. In this study, rTMS-COG (provided by Neuronix Ltd., Yokneam, Israel) seems a promising effective and safe modality for AD treatment, possibly as good as cholinesterase inhibitors. A European double blind study is underway.

Keywords rTMS · Alzheimer's disease · Cognitive training · ADAS-cog · ADAS-ADL

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Introduction

Alzheimer's disease (AD), the most common form of dementia in elderly people (van Duijn 1996; Fratiglioni et al. 2000; Plassman et al. 2007) is manifested by cognitive and behavioral derangements that markedly interfere with occupational and social functioning (Hyman et al. 1989). AD affects millions of people (Hebert et al. 2003; Brookmeyer et al. 2007) and the numbers keep rising due to the aging of the population.

Currently, we do not know the etiology of AD and as a consequence there is no cure for AD. However, considering that AD is characterized by a loss of cholinergic neurotransmission (Perry et al. 1977; Giacobini 1990; Beach et al. 2000), cholinesterase inhibitors have become the mainstream treatment for patients with mild to moderate AD. The medications from this group available today for AD patients include donepezil, rivastigmine, and galantamine (Rogers and Friedhoff 1996; Birks 2006; Birks et al. 2009).

Another type of medication, memantine, based on *N*-methyl-D-aspartate receptor blocker properties (Robinson and Keating 2006; Mecocci et al. 2009), has also been used in patients with advanced AD as a complement to cholinesterase inhibitors.

Non- pharmacological strategies for delaying the progression of cognitive deficits and resulting functional impairment in AD have produced mixed results. Alternative or supplemental treatments added to pharmacological interventions include psychosocial treatment and targeting cognition or cognitive training (COG) (also known as cognitive stimulation therapy) for AD in the mild to moderate stages of the disease in the form of person-to-person training [i.e. one-on-one or group training (Spector et al. 2003; Onder et al. 2005; Foerster et al. 2009)] or computer-based training (Tárraga et al. 2006). Overall, a lesser effect is considered to be obtained with COG (Sitzer et al. 2006) compared with drug treatment (Birks et al. 2009).

A recent meta-analysis of publications dealing with the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive functions (Guse et al. 2010) found convincing data supporting improvement in some cognitive functions (including executive, learning, memory and attention).

Transcranial magnetic stimulation (TMS) is a relatively new, non-invasive and painless technology that allows for discrete non-invasive probing and modulation of cortical excitability and functions (Lisanby et al. 2000). TMS uses alternating magnetic fields to induce a modulation in electric currents on cortical tissue in specific brain regions. Depending on the stimulation parameters, cortical excitability may be increased or decreased, and the changes may be transmitted, possibly lasting for weeks. In addition, depending on the location and parameters of the stimulation and the physiology of the underlying cortical tissue, varying changes in behavior may be seen, including enhancement of or interference with cognitive performance (Grafman et al. 1994; Boroojerdi et al. 2001). TMS, if applied repetitively, produces an electromagnetic field in the brain that induces a modulation in brain cortical excitability (Rossi et al. 2009). High-frequency rTMS has been increasingly utilized successfully for various psychiatric and neurological conditions such as depression, mania, obsessive–compulsive disorder, posttraumatic stress disorder, schizophrenia, and Parkinson' disease (Mantovani and Lisanby 2004; George et al. 2010).

Some studies have also reported that TMS can modify brain cortical excitability as well as regional cerebral blood flow (Bohning et al. 1999, 2000; Zheng 2000). In another study, high-frequency rTMS (>1 Hz) produced a local increase in regional cerebral blood flow (e.g. in the area under the coil), while low-frequency rTMS (e.g. ≤1 Hz) produced a local decrease in cortical excitability that lasted after the stimulation had terminated (Nakamura et al. 1997).

Although the exact biological mechanism explaining the effects of rTMS on the brain is still unknown, it has been suggested to involve an increase in synaptic plasticity (Siebner and Rothwell 2003; Thickbroom 2007).

Animal models have been instrumental in demonstrating lasting effects of rTMS on brain cortical tissue. Specifically, numerous studies have demonstrated similarities between the effects of rTMS and those of electroconvulsive shock in animal models of depression (Belmaker and Grisaru 1998; Fleischmann et al. 1999). Belmaker and Grisaru (1998) described that rTMS led to an enhancement of apomorphine-induced stereotypy, a reduction of immobility time in the Porsolt swim test, and an increase in the seizure threshold for subsequent stimulation. They also showed evidence that rTMS led to a reduction in beta-adrenergic receptor density in cortical areas, but not in the hippocampus.

Long-term potentiation (LTP) is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying synaptic plasticity, the ability of chemical synapses to change their strength (Cooke and Bliss 2006). As memories are thought to be encoded by modifications of synaptic strength, LTP is widely considered one of the major cellular mechanisms that underlie learning and memory (Bliss and Collingridge 1993).

Kimbrell et al. (1999) presented a working hypothesis suggesting that high-frequency rTMS, like LTP, increases synaptic cortical efficacy, while low-frequency rTMS reduces it. Consistent with this speculation was their finding of a differential antidepressant response to rTMS as a function of baseline glucose metabolism. Pretreatment global hypometabolism was associated with a positive clinical response to 10-Hz rTMS applied to the left dorsolateral prefrontal cortex, and pretreatment global hypermetabolism was associated with a response to 1-Hz rTMS at this same site. Concerning the influence of TMS on the LTP phenomenon, we still lack robust proof of this hypothesis.

Moreover, a recent meta-analysis of publications searching for the effects of rTMS on cognitive functions (Guse et al. 2010) found convincing data supporting improvement in some cognitive functions (including: executive, learning, memory and attention).

Another study supporting the use of TMS in mild AD was published recently by Julkunen et al. (2008).

Consequently, and based on the information available, we hypothesized that a treatment combining COG with rTMS might result in some synergistic effect that might be more significant than that obtained by applying either COG or

rTMS separately. Indeed, an "online" cognitive improvement was observed in AD patients subjected to both COG (performing an action naming task) and rTMS (applied to the left and right dorsolateral prefrontal cortex), simultaneously. In that study, patient performance was recorded during rTMS stimulation and was found to improve (relative to sham rTMS) (Cotelli et al. 2006). Nonetheless, no study has searched for a long-term "offline" improvement in cognitive functions in patients with AD after repeated treatment with rTMS combined with COG.

In this study, we aimed to obtain a synergistic "offline" effect of rTMS interlaced with cognitive training (rTMS-COG) (system provided by Neuronix Ltd., Israel) in patients with AD. For this purpose, we recruited mild to moderate AD patients, to whom 6 weeks of daily (i.e. intensive) treatments, followed by 3 months of bi-weekly (i.e. maintenance) treatments were applied. During the treatments, rTMS-COG was applied to brain regions known to be activated during the performance of cognitive tasks. For evaluation of the effect of the treatment we utilized a total of seven validated scoring tests for each participant. Patients were assessed before treatment (pre-rTMS-COG), post intensive treatment (post int-rTMS-COG) and post maintenance treatment (post maint-rTMS-COG) and the seven scores obtained were then compared between time points.

Patients and methods

The study was conducted at the Memory Clinic at Assaf Harofeh Medical Center, Israel, during 2009, following protocol approval by the local ethical committee. All participants understood and signed the content of the informed written consent form, and agreed to participate in the trial, which lasted 4.5 months.

Inclusion criteria

Only patients (males and females, aged 55–85 years; mean age 75.4 $\pm$ 4.4) with a diagnosis of probable early or moderate AD, according to the DSM-IV criteria, a Mini Mental Status Examination (MMSE) score of 18–24, a Clinical Dementia Rating (CDR) score of 1, and no serious cardiac or metabolic disease, as confirmed by medical history and examination, clinical laboratory results and EKG were included in the study. Patients suffering from mild depression controlled by medication were included.

All the patients needed to have a caregiver (e.g. spouse, family member or a professional caregiver) who agreed to be responsible for the participation of the patient throughout the study and would stay with the patient for at least 10 h/week.

In addition, all those included in the study needed to speak Hebrew fluently and have a brain MRI showing cortical atrophy supporting the diagnosis of probable AD.

Exclusion criteria

- Patients with a history of epilepsy, severe agitation, lack of cooperation, unstable medical conditions, alcoholism and/or drug abuse, or regular use of benzodiazepines or other hypnotics (up until 2 weeks before the beginning of the study) were excluded from the study.
- Patients taking occasional tranquilizers were allowed to participate in the study. Patients treated with cholinesterase inhibitors or memantine were allowed to participate only if the were taking the medication for more than 2 months before this trial.

Mapping brain regions

A brain MRI scan (*Avanto 1.5 tesla* MRI Scanner, Siemens, Germany) was performed for each patient prior to the beginning of the study. After confirming that MRIs were compatible with probable AD (scan images were evaluated by a senior neuroradiologist), six cortical brain regions, known to be affected in AD, were localized on each MRI scan. The MRI scan images, along with the anatomical location of each brain region identified, were superimposed utilizing the Neuronix System, so that the position of each cortical area could be easily identified for rTMS stimulation during the trial. The six brain regions were selected according to the location of the main centers that are considered to be the basis of the clinical symptoms in AD, and rTMS was applied to these areas: Broca and Wernicke (in the left frontal and left posterior part of the temporal lobe) (language functions); right and left dorsolateral prefrontal cortex (R-dlPFC and L-dlPFC, respectively) (judgment, executive functions and long-term memory); and right and left parietal somatosensory association cortex (R-pSAC and L-pSAC, respectively) (spatial and topographical orientation and praxias).

Stimuli

The Neuronix System was used for applying rTMS-COG. This system includes an rTMS figure-of-eight magnetic coil (diameter 47–86 mm) connected to an electric stimulator (maximum power 140 Joules per pulse), a stereotactic camera (Brainsight^{TM}, Magstim, UK), connected to a stereotactic system, a controller, a user graphical display (for computerized COG and for receiving user feedback), and a couch seat. The Neuronix System controller keeps

the different components (including the rTMS pulsation electronics and the user graphical interface) highly synchronized.

TMS

In order to meet safety recommendations (Wassermann et al. 1996; Rossi et al. 2009), an intensity calibration process was performed for each patient prior to the start of each treatment. In this process, a motor threshold (MT) was determined by pointing the magnetic coil on top of the motor cortex and determining the TMS minimal energy required for activating the patient's hand. The TMS treatment intensity was set to 90% of the MT intensity at the frontal cortex (Broca, R-dlPFC and L-dlPFC) because of inconvenient eye twitches and 110% of the MT intensity at the other regions (Wernicke, R-pSAC and L-pSAC).

In addition, in order to meet safety limitations of up to 1,500 pulses a day (Rossi et al. 2009), the protocol was designed such that three brain areas were treated each day, for which 20 trains, composed of 2 s of 10 Hz each (i.e., each train was composed of 20 pulses) were administrated per brain area. This resulted in three brain areas $\times$ 20 trains $\times$ 20 pulses per train $=$ 1,200 pulses per day per patient.

Last, to further ensure safe TMS treatment, according to safety recommendations (Rossi et al., 2009), the brain regions that were treated each day were at a distance of at least 50 mm from one another. This resulted in treating the Broca, Wernicke and R-dlPFC brain regions at one daily session, while the L-dlPFC, R-pSAC and L-pSAC brain regions were treated on the following day.

COG

The Neuronix System provides the patient with COG paradigms targeted to activate various cortical brain areas known to be affected by AD. Based on functional MRI (fMRI) and TMS studies for each of the six target brain areas, experts from Neuronix prepared specific cognitive tasks (involving those same brain regions), which were performed by the patients in parallel to the cortical stimulation by rTMS.

The paradigms included

- Syntax and grammar tasks for the Broca area (Grossman and Rhee 2001; Nixon et al. 2004; Rogalsky et al. 2008)
- Comprehension of lexical meaning and categorization tasks for the Wernicke area (Grossman et al. 2002; Harpaz et al. 2009).
- Action naming, object naming and spatial memory (of shapes, colors and letters) tasks for both the R-dlPFC and the L-dlPFC brain areas (Bellgowan et al. 2009; Braun et al. 2008; Hamidi et al. 2008; Berlingeri et al. 2008).
- Spatial attention (for shapes and letters) tasks for both the R-pSAC and L-pSAC brain areas (Buck et al. 1997; Hao et al. 2005).

The COG tasks were developed with a scale of difficulty levels that was applied individually for each patient. The difficulty levels were developed by controlling for task variables (e.g. number of objects, time available to complete the task, etc.).

The COG tasks were presented on a 22″computer touch screen (Elo-Touch, USA) which is part of the Neuronix System, located about 50 cm from the patient. The participants selected their answers by touching graphical buttons on the touch screen.

Procedure

All patients were subjected to an intensive (int-rTMS-COG) treatment phase in which daily treatment sessions (i.e. one session per day, 5 days a week) were applied for 6 weeks. The intensive phase was then followed by a maintenance phase (maint-rTMS-COG) in which bi-weekly treatment sessions were applied during the following 3 months. This potentially added up to 54 sessions in total [5 sessions per week $\times$ 6 weeks (=30 sessions), $+$ 2 sessions per week over 3 months (=24 sessions)].

Each daily treatment session lasted about 45 min. In each session, three brain areas were separately stimulated as described above. For each brain area, the treatment consisted of 20 trains of rTMS (2 s of 10 Hz each train, 20 pulses per train), followed by 1–4 COG tasks, during a period of 20–40 s. Since there were 20 such repetitions, each area was stimulated with 400 pulses, during a period of 7–15 min. Difficulty levels of the cognitive tasks were individually adjusted once a week, for each patient, in accordance with the patient's progress and success in performing the tasks.

The treatment was administered by a trained EEG technician.

Assessment of cognitive functioning measures

All the participants were assessed within 3 weeks prior to the start of the treatment ("pre-treatment evaluation"), 6 weeks after treatment started ("6w") and 4.5 months after treatment started ("4.5m"). The assessment included patient performance on the structured tests selected (see next paragraph).

Primary objectives

One primary objective of the trial was to evaluate the average performance of the patients as assessed by the

Table 1 Patient characteristics

Name	Gender/ age (years)	Education (years)	Disease duration (years)	Comorbidities	Cholinesterase inhibitors	Other medications
DI	M/77	8	3	Hypertension, S/P CVA, depression (in remission), anxiety	Rivastigmine (patch 10)	Enalapril, disothiazide, alprazolam, olanzapine
EM	M/71	12	2	Depression (in remission), hypertension		Escitalopram
NN	M/76	10	3	S/P hemicholectomy, (for Ca of colon)	Rivastigmine	Aspirin, atenolol, enalapril, doxazosin
SD	F/80	10	3	Depression (in remission), hyperlipidemia, hypothyroidism	Rivastigmine	Simvastatin, thyroxine, Aspirin, bezafibrate, sertraline
TC	M/69	12	1.5	Depression (in remission), hyperlipidemia, hypertension		Simvastatin, aspirin, atenolol, amlodipine, Ramipril/hydrochlorothiazide, escitalopram
LE	M/72	13	3	Hyperlipidemia, S/P melanoma excision (left arm)	Rivastigmine, memantine	Simvastatin
NP	M/79	8	3	Depression, osteoporosis	Donepezil	Alendronate, escitalopram
KR	M/80	14	2.5	Depression, hyperlipidemia, Parkinsonism	Rivastigmine, memantine	Simvastatin, levodopa, paroxetine

Alzheimer Disease Assessment Scale-Cognitive (ADAS-cog) (Rosen et al. 1984) at 6w and 4.5m, both compared with the mean performance of the AD group before treatment.

Another primary objective of the trial was the evaluation of the average result of the Clinical Global Impression of Change scale (CGIC; Guy 1976) at 6w and 4m.

Secondary objectives

The secondary objectives of the trial were to analyze the mean performance of the patients applying the MMSE (Folstein et al. 1975) at both 6w and 4.5m in comparison with the mean performance of the AD group before treatment. In addition, we evaluated the activities of daily living, depression and caregiver evaluation by applying the Alzheimer Disease Assessment Scale-Activities of Daily Living (ADAS-ADL) (Rosen et al. 1984); the Hamilton Rating Scale for Depression (HAMILTON) (Hamilton 1980); and the Neuropsychiatric Inventory test (NPI) (Cummings et al. 1994), respectively.

All assessments were performed by either a trained neurologist or a psychologist from our team.

Data analysis

We used IBM® SPSS® software (Version 15.0) to run repeated measures analysis of variances (ANOVA) for all of the assessed measures (ADAS-cog, CGI, MMSE, ADAS-ADL, HAMILTON, and NPI). General effect of time was tested for the scores obtained for each measure. Measure scores obtained at 6w and at 4.5m were compared to those obtained at pre-treatment evaluation.

Since CGIC was a comparative test, we assigned the score "4" (i.e. "unchanged") for all participants at the time point "pre-treatment". Thereafter, we applied the same analysis as that performed for all other six measures.

Results

Participants

Eight subjects (2 women and 6 men) were recruited for this pilot study. All were diagnosed with probable AD. However, 2 months after the beginning of the treatments, one of the participants suffered from sepsis due to a urinary tract infection and was therefore excluded from the study. Thus, the results obtained for this participant are not included in the evaluation after 4.5 months of treatment.

Five of the patients included in this trial were treated with AD drugs for more than 2 months prior to the beginning of the study and continued their drug treatment throughout the study (see Table 1 for patient clinical characteristics) without any change in the dose.

Apart from some minor tiredness, no side effects were reported. In addition, no adverse events were recorded except for the patient with urinary sepsis (unrelated to the trial).

All the patients (except 1) remained in the study during the entire 4.5 months.

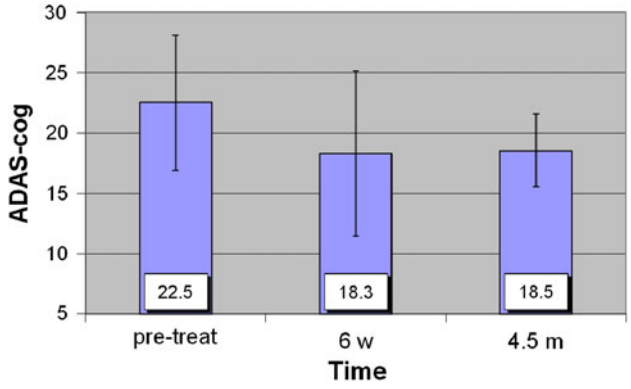

Fig. 1 ADAS-cog results

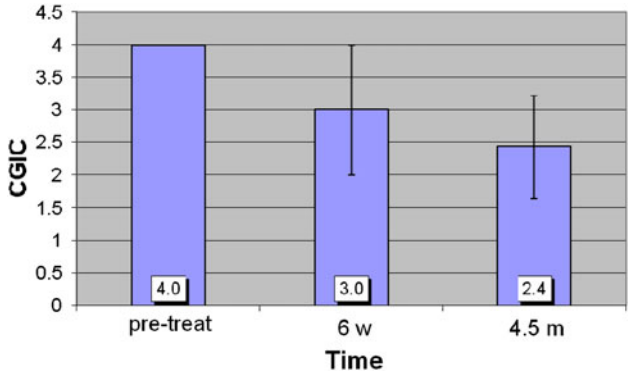

Fig. 2 CGIC-COG results

Primary objectives

ADAS-cog

ADAS-cog average scores (±STD) obtained for the participants were 22.5 (±5.6) at pre-treatment, 18.3 (±6.8) at 6w ($n = 8$) and 18.5 (±3.8) at 4.5m ($n = 7$) (Fig. 1). A statistically significant improvement was demonstrated at 6w and 4.5m, compared with pre-treatment evaluation ($P = 0.007$ and 0.040, respectively).

CGIC

CGIC average scores (±STD) obtained for the participants were 3.0 (±1.0) at 6w and 2.4 (±0.7) at 4.5m (Fig. 2). Hence, improvement was demonstrated at 6w and at 4.5 months, compared with pre-treatment. However, due to the small sample size, no statistical analysis was available.

Secondary objectives

MMSE

MMSE average scores obtained for the participants were 22.9 (±1.7), 24.1 (±2.2) and 22.1 (±2.1), at pre-treatment evaluation, 6w and 4.5m, respectively. Statistically significant improvement was demonstrated at 6w compared with pre-treatment ($P = 0.049$). No significant change was demonstrated at 4.5m compared with pre-treatment.

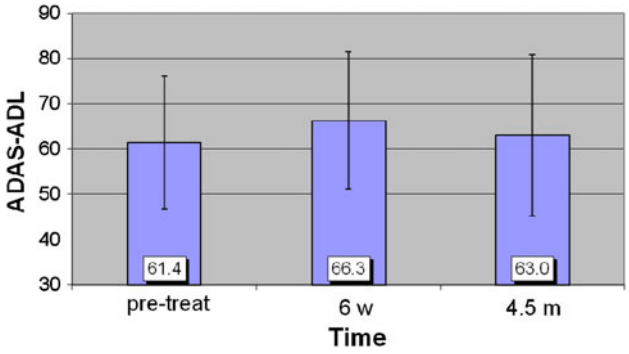

Fig. 3 ADAS-ADL results

ADAS-ADL

ADAS-ADL average scores obtained for the participants were 61.4 (±14.6), 66.3 (±15.1) and 63.0 (±17.8), at pre-treatment evaluation, 6w and 4.5m, respectively (Fig. 3). A statistically significant improvement was demonstrated at 6w ($n = 8$) compared with pre-treatment evaluation ($P = 0.01$).

HAMILTON

Some patients suffered from a *dysthymic* disorder (DSM IV TR criteria), successfully treated with medication at the time of recruitment for the study. As a consequence, the basic Hamilton score was low. Average HAMILTON scores were 9.7 (±4.2), 5.6 (±1.8) and 8.3 (±2.7), at pre-treatment, 6w and 4.5m, respectively. Although a near-significant improvement was demonstrated at 6w compared with pre-treatment evaluation ($P = 0.053$), the results lacked clinical significance.

NPI

NPI average scores were 5.2 (±7.8), 3.8 (±8.9) and 7.1 (±10.0), at pre-treatment, 6w and 4.5m, respectively. However, due to the data distribution and standard deviation values, no significant results were obtained for the NPI measure.

Discussion

COG, on its own, has been shown to produce some benefits in AD patients. On the other hand, rTMS produces changes

in cognition and behavior. The present theories suggest that its effects may be produced by changes in focal cortical circulation, an increase in synaptic connectivity (possibly modifying the LTP phenomenon) or modulation of the cognitive reserve.

In this study, we checked for a possible synergistic lasting after-treatment effect of rTMS-COG for patients with mild to moderate AD. For this purpose, eight AD patients were recruited (seven completed the trial) and received treatment (intensive for 6 weeks and maintenance for a further 3 months).

Overall results showed significant improvement for the ADAS-cog scores, after 6 weeks of intensive daily treatments and also after 4.5m. The CGIC measure also demonstrated a clear improvement, but without statistical power due to the small sample. Both Hamilton and ADAS-ADL also showed improvement at 4.5m compared with pre-treatment evaluation, but with no statistical power.

Most of the pharmacological studies in clinical practice have been based on the evaluation of ADAS-cog, ADAS-ADL and CGIC. For these three parameters we obtained good results.

It is also important to note that the results recorded with the method applied were obtained in addition to medication (while 5 of the patients were treated with cholinesterase inhibitors), which demonstrates that the rTMS-COG technology applied here seems to provide an additional beneficial effect to that available with drugs. These results may suggest that rTMS-COG treatment stimulates and hence exploits some "cognitive reserve" (Stern 2002), which AD patients may still possess, in addition to the activation of cholinergic pathways by medication.

Considering our study, one may question the role of COG rTMS. While the average improvement in the ADAS-cog score in this study was approximately 4 points at both 6w and 4.5m, an average improvement of less than 2.6 points in ADAS-cog scores was recorded during treatment periods of similar length in studies utilizing COG alone [e.g. ADAS-cog recorded: −2.54 (Tárraga et al. 2006), −1.9 (Onder et al. 2005), −1.9 (Spector et al. 2003), −1.9 (Orrell et al. 2005)].

Moreover, a recent meta-analysis on publications summarizing the benefits of COG alone in AD patients (Sitzer et al. 2006), showed that COG produced only a limited beneficial effect for several of the cognitive functions. Therefore, a comparison of the results obtained for the ADAS-cog score in our study and those obtained in studies that applied COG alone indicates quite clearly an additional effect of rTMS-COG.

The present study has some limitations of which we are fully aware. First, the study was performed prospectively in a single center with a small number of patients, which limits the extent of the conclusions. An improvement of about 4 points in the ADAS-cog scores was demonstrated after 6 weeks of intensive daily treatment, compared with the pre-treatment evaluation and lasted for at least an additional 3 months, during which time the patients were submitted to maintenance therapy (2 sessions/week). Bearing in mind the small sample group, we would nevertheless like to point out that average improvements recorded for the currently approved drugs for the treatment of AD are usually in the region of 2.7 ADAS-cog points for a similar time range post treatment (Birks et al. 2009) and 1 for memantine (Mecocci et al. 2009). However, we are aware of the fact that these studies were double blind and ours was an open study.

We wish to emphasize that rTMS-COG is a safe non-invasive technique and as such is advantageous when compared with anticholinsterase drugs [which are known to cause several possible side-effects, such as: headaches, nausea, vomiting and diarrhea; (Birks et al. 2009)]. In addition, it should be noted that although the treatment applied in this study was time consuming for the patients and required daily visits to the hospital, normally with the escort of the caregiver, none of the participants dropped out due to these inconveniences and their participation remained high throughout the entire trial.

More research is required to confirm our data. Indeed, a double-blinded, (active treatment versus placebo), multi-site, European study is under way and is expected to be concluded by 2011.

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Conflict of interest Neuronix Ltd, Yokneam, Israel, financially supported this study through the Department of Research of Assaf-Harofeh Medical Center, Israel. Prof. Rabey is a consultant for Neruronix Ltd. He is also Chairman of the Steering Committee for the European multi-center research sponsored by Neuronix Ltd. Jonathan Bentwich was an employee of Neuronix Ltd.

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