J Neural Transm
DOI 10.1007/s00702-012-0902-z



# Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study

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Received: 1 July 2012 / Accepted: 23 September 2012


**Abstract** Cortical excitability can be modulated using repetitive transcranial magnetic stimulation (rTMS). Previously, we showed that rTMS combined with cognitive training (rTMS-COG) has positive results in Alzheimer's disease (AD). The goal of this randomized double-blind, controlled study was to examine the safety and efficacy of rTMS-COG in AD. Fifteen AD patients received 1-h daily rTMS-COG or sham treatment (seven treated, eight placebo), five sessions/week for 6 weeks, followed by biweekly sessions for 3 months. The primary outcome was improvement of the cognitive score. The secondary outcome included improvement in the Clinical Global Impression of Change (CGIC) and Neuropsychiatric Inventory (NPI). There was an improvement in the average ADAS-cog score of 3.76 points after 6 weeks in the treatment group compared to 0.47 in the placebo group and 3.52 points after 4.5 months of treatment, compared to worsening of 0.38 in the placebo ($P = 0.04$ and $P = 0.05$, respectively). There was also an improvement in the average CGIC score of 3.57 (after 6 weeks) and 3.67 points (after 4.5 months), compared to 4.25 and 4.29 in the placebo group (mild worsening) ($P = 0.05$ and $P = 0.05$, respectively). NPI improved non-significantly. In summary, the NeuroAD system offers a novel, safe and effective therapy for improving cognitive function in AD.

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

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## Introduction

Alzheimer's disease (AD), the most prevalent cause of dementia in the elderly, is defined both by its clinical features and by its unique pathology. It increases dramatically in both prevalence and incidence after the age of 65, and doubles approximately every 5 years in individuals between 65 and 95 years of age (Rafii et al. 2009).

Based on pathological findings of loss of cholinergic transmission (Perry et al. 1977), AD is routinely treated with cholinesterase inhibitors (Birks 2006). A long-term study of the ability of donepezil to improve living disabilities showed that there was no significant benefit compared to the placebo for institutionalization or progression of disability (Courtney et al. 2004).

During the last years, supplemental or alternative therapies to pharmacological treatments have been tested in patients with AD. Person-to-person training (Spector et al. 2003) has been implemented, with results showing a lesser effect (Sitzer et al. 2006) compared with drug treatment (Birks 2006).

A recent review highlights the evidence that exercising the brain can prevent cognitive decline (Reichman et al. 2010). Specifically, Reichman et al. (2010) discussed the emerging commercial field of "brain fitness". However, despite the array of products and exercises being marketed, their effectiveness is not fully supported by scientific data.

Transcranial magnetic stimulation (TMS) is a non-invasive, painless technology that allows for discrete

Published online: 18 October 2012

modulation of cortical excitability and functions (Lisanby et al. 2000). TMS, if applied repetitively, produces an electromagnetic field in the brain that induces a modulation in brain cortical excitability (Rossi et al. 2009). Repetitive TMS (rTMS) can be applied as continuous low-frequency trains (1 Hz) or bursts of higher frequency (>5 Hz). In general, low-frequency rTMS is thought to reduce and high frequency to enhance excitability in the targeted cortical regions (Pascual-Leone et al. 1998). High-frequency rTMS has been increasingly utilized successfully for various psychiatric and neurological conditions (Mantovani and Lisanby 2004). It has been suggested that rTMS is involved in an increase in synaptic plasticity (Siebner and Rothwell 2003). TMS treatment is approved for the treatment of refractory depression worldwide. Moreover, enhancement or interference with cognitive performance can be observed, depending on the location and parameters of the stimulation and the physiological characteristics of the underlying cortical tissue (Grafman et al. 1994). A recent review on AD concluded that TMS can be useful in AD (Freitas et al. 2011). 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 improved during rTMS stimulation (relative to sham rTMS) (Cotelli et al. 2006).

In the present study, we wished to explore the long-term "offline" improvement in overall cognitive functions in patients with AD after repeated treatment using a combination of high-frequency rTMS and cognitive training (rTMS-COG), as provided by the NeuroAD system (Neuronix Ltd., Yokneam, Israel), compared to placebo-treated patients. A previous open, "proof of concept" study was published by our group that demonstrated a beneficial effect of rTMS-COG for the treatment of AD (Bentwich et al. 2011). The current study extrapolates on these results by examining the safety and efficacy of rTMS-COG for the treatment of AD in a randomized, double-blind, controlled protocol.

## Patients and methods

### Patients and study design

The current study was conducted at Assaf Harofeh Medical Center, Israel following protocol approval by the local ethics committee (Clinical Trials Government Number NCT01168245). Patients diagnosed with AD were treated 5 days/week for 6 weeks, followed by biweekly maintenance treatment for 3 months. rTMS-COG was applied to brain regions specifically activated during the performance of cognitive tasks. Various validated scoring tests were used to assess the effect of the treatment. Each test was applied prior to treatment, following intensive treatment (6 weeks), and following maintenance treatment (a further 3 months.) The scores from the tests were compared across these time points. Patients who participated in the trial understood and signed the informed written consent form.

### Inclusion criteria

Fifteen patients (seven treatment, eight placebo) with probable mild to moderate AD [diagnosed by DSM-IV diagnostic criteria, a Mini Mental Status Examination (MMSE) score of 18–24 and a Clinical Dementia Rating (CDR) score of 1] and no serious metabolic or cardiac diseases (main criteria) were included in the current study.

All patients participating in the study were required to have a caregiver (such as a family member, or professional caregiver) who would stay with the patient for a minimum of 10 h/week, in order to assess his/her performance. All patients participating in the study were required to have fluent Hebrew or Russian speaking skills as their first language and a brain MRI indicating cortical atrophy supporting the diagnosis of probable AD.

### Exclusion criteria

Excluded from the study (main criteria) were patients with a history of unstable medical conditions, lack of cooperation, severe agitation, epilepsy, alcohol/drug abuse, or consistent use of benzodiazepines or other hypnotics within 2 weeks prior to the start of the study. Patients taking tranquilizers were occasionally permitted to participate in the study. In addition, patients with severe visual disturbances were excluded as the capability to watch computer screens is needed for the training sessions. Patients receiving cholinesterase inhibitors and/or memantine therapy were allowed to participate provided the medication was taken for at least 2 months prior to the beginning of the study.

### NeuroAD treatment

#### *Mapping brain regions*

Before the study, each patient underwent a brain MRI scan (Avanto 1.5 T MRI Scanner, Siemens, Germany). A neuroradiologist evaluated the images to confirm the diagnosis of probable AD, and localized six cortical brain regions affected in AD on each MRI scan. The NeuroAD system (Neuronix Ltd., Yokneam, Israel) was used to superimpose the anatomical location of each brain area on the MRI scan images, such that the position of each cortical region could be identified for rTMS application. The six brain regions represent the location

of the primary centres that are involved in the manifestation of the clinical symptoms of AD, including the right and left dorsolateral prefrontal cortex (R-dlPFC and L-dlPFC, respectively; long-term memory, judgment, and executive functions); Broca and Wernicke (left frontal and left posterior region of the temporal lobe; language functions, respectively); and the right and left parietal somatosensory association cortex (R-pSAC and L-pSAC, respectively; spatial and topographical orientation and praxis). rTMS was applied to the above areas in conjunction with active cognitive training targeting these same brain regions.

## NeuroAD device

### *Stimuli*

The application of combined rTMS-COG was achieved using the NeuroAD system. The system is one unit and its components include a 47–86 mm diameter figure of eight magnetic coil attached to an electric stimulator (140 J/pulse maximum power), a controller, a user graphical display (for receiving user feedback and for computerized COG), and a couch seat.

### *TMS*

Prior to commencing each treatment, all patients underwent an intensity calibration procedure in order to abide by safety recommendation (Rossi et al. 2009). During this process, a motor threshold (MT) was established by aligning the magnetic coil over the motor cortex, and determining the minimum TMS energy needed to activate the patient's hand. The intensity for the TMS was adjusted to 90 % of the MT intensity at the Broca, R-dlPFC and L-dlPFC and up to 110 % of the MT intensity at the Wernicke, R-pSAC and L-pSAC, as long as there were no inconvenient eye twitches. Two brain regions were treated per day, for which 20 trains, consisting of 2 s of 10 Hz each (20 pulses/train) were administered per brain region, and a third region was treated with 25 trains, consisting of 2 s of 10 Hz each (20 pulses/train), totaling 1,300 pulses, which conforms to safety limitations of a maximum number of 1,500 pulses/day (Rossi et al. 2009). Treatment of the Broca, Wernicke and R-dlPFC brain regions occurred in one daily session (days 1, 3 and 5), while the L-dlPFC, R-pSAC and L-pSAC brain regions were treated the following days (days 2 and 4). The sham patients went through the same procedure using a sham coil.

### *Cognitive stimulation*

Activation of cortical brain regions was achieved using the NeuroAD system, which provided patients with specific COG paradigms. The cognitive tasks were prepared by neuro-psychologists for each of the six target brain areas. Patients performed these tasks in conjunction with the cortical stimulation by rTMS. Several paradigms were developed for the tasks including:

- Syntax and grammar tasks for the Broca region (Rogalsky et al. 2008).
- Comprehension of lexical meaning and categorization tasks for the Wernicke region (Harpaz et al. 2009).
- Action naming, object naming and spatial memory tasks (shapes, colors and letters) for the R-dlPFC and L-dlPFC brain regions (Bellgowan et al. 2009).
- Spatial attention tasks (shapes and letters) for the R-pSAC and L-pSAC brain regions (Buck et al. 1997).

The level of difficulty for the COG tasks was developed on a patient-to-patient basis, by controlling for task variables such as the time available to complete each task and the number of objects. The COG tasks were displayed on a touch screen, and the patients chose their answers by touching graphical buttons on the screen. For the sham treatment (placebo) patients, the touch screen showed nature movies (animals or landscapes).

## Treatment procedure

Patients were randomized to treatment or control group in a 1:1 ratio. During the intensive phase, patients in the active treatment group received daily treatment sessions (1 session/day, 5 days a week) over the course of 6 weeks. During the maintenance phase, participants received bi-weekly treatment sessions over the course of 3 months. Therefore, each participant received a total of 54 sessions [(5 sessions per week $\times$ 6 weeks = 30 sessions) + (2 sessions/week over 3 months = 24 sessions)]. Each single session was 45–60 min in duration, during which time three brain regions were stimulated separately. Twenty or 25 trains of rTMS (2 s of 10 Hz/train, 20 pulses/train), followed by 1–4 COG tasks over the course of 20–40 s was administered for each brain region. Given that there were 20 such repetitions, each brain region was stimulated with 400 or 500 pulses over the course of 7–15 min. The treatment was performed by a trained technician. Once a week, depending on each individual patient's progress and success in performing the cognitive tasks, the level of difficulty of the tasks was individually adjusted. Patients in the placebo group received sham treatment, with identical frequency and identical session length. The TMS device produced identical sounds and the coil was navigated to brain regions, but produced no magnetic stimulation even when varying the position of the coil.

### Assessment of cognitive functioning measures

A "pre-treatment evaluation" was performed for each participant within 3 weeks prior to commencement of the treatment. Follow-up assessments were performed 6 weeks after treatment began and 4.5 months after treatment began.

### Primary outcome measure

The primary outcome of the current study was the average performance using the Alzheimer Disease Assessment Scale, cognitive subsection (ADAS-cog) (Rosen et al. 1984).

The total score of this scale is 70. The ADAS-cog score was evaluated before and at 6 weeks and 4.5 months, and compared with the average performance prior to treatment ($P = 0.05$ and $P = 0.05$, respectively).

### Secondary outcome measures

Changes in the clinical status of the participants were evaluated based on the average result of the Clinical Global Impression of Change scale (CGIC) (Guy 1976) at 6 weeks and 4.5 months. In addition, the Neuropsychiatric Inventory (NPI) (Cummings et al. 1994) was also applied before and after 6 weeks and another 12 weeks of treatment.

All evaluations were performed by a trained neurologist from the clinical team. Each patient was evaluated by the same neurologist throughout the study who was blinded to the allocation of each participant (active or placebo group).

### Data analysis

All of the assessed measures (ADAS-cog and CGIC) were analyzed using repeated measures analysis of variances (ANOVA), run on IBM® SPSS® software (Version 15.0). The scores obtained for each measure were tested for the general effect of time. Measured scores from 6 weeks and 4.5 months were compared to those from the pre-treatment evaluation. Given that the CGIC is a comparative analysis, a score of "4" ("unchanged") was assigned to all participants at the "pre-treatment" time point. Thereafter, the same analysis that was performed for all other six measures was applied.

## Results

### Participants

Thirty-four patients were screened, 19 were found eligible. One of these 19 patients did not sign the informed consent, and the remaining 18 were recruited. All were diagnosed with probable AD. Two participants from the placebo group dropped out of the study, one due to a bladder infection and the other due to general weakness. One participant from the treatment group dropped out due to psychiatric symptoms that required medication. All dropouts, at different stages of the study, were unrelated to the device, as diagnosed by the principal investigator. Fifteen subjects (seven treatment and eight placebo) participated in this study. The baseline characteristics of the population were: the mean age of the participants in the treatment group was $72.6 \pm 8.9$ (mean $\pm$ SD), there was a male to female ratio of 5/2, Mini Mental State Examination (MMSE) score was $22 \pm 1.63$ and there were 6/7 medicated; while in the placebo group the mean age of the participants was $75.4 \pm 9.07$, the male to female ratio was 5/3, the MMSE score was $22 \pm 1.41$ and 7/8 were medicated. There were no statistically significant differences between the groups.

No side effects or adverse events were reported, and/or documented. All 15 participants remained in the study for the entire 4.5-month duration except one who changed medication after week 12 and hence was removed from the study, and his last observation was carried forward. For this patient, only the 6-week results were considered for the study result calculations.

### Primary outcome measure

#### *ADAS-Cog*

We included mild to moderate AD patients; baseline characteristics show patients were with a baseline ADAS-cog score between 12 and 31. The average ADAS-cog score in the treatment group changed from 24.09 at baseline to 20.33 at 6 weeks, and thus improved by 3.76 ($\pm$1.32SE) points compared to the placebo group, which changed by only 0.47 ($\pm$1.18SE) points at 6 weeks. Similarly, at 4.5 months, the treatment group improved by 3.52 points compared to a worsening in 0.38 in the placebo group (Fig. 1).

### Secondary outcome measures

#### *CGIC*

CGIC average scores obtained for the participants were: 3.57 for the treatment group at 6 weeks compared to 4.25 for the placebo group. Similarly, at 4.5 m, the score of the treatment group was 3.67 compared to 4.29 for the placebo ($P < 0.05$ for both).

#### *NPI*

NPI average scores decreased in the treatment group by 3.43 at 6 weeks (improvement) and increased by 1.38 in

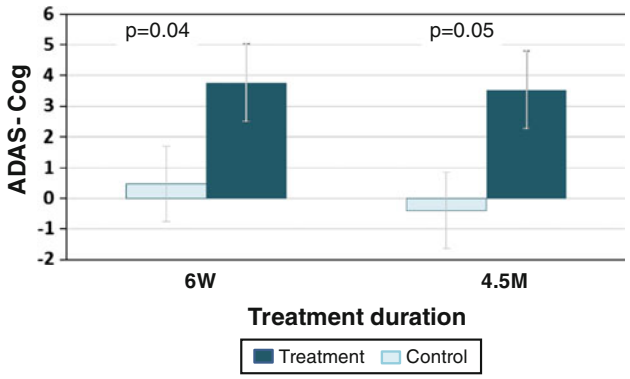


**Fig. 1** Clinical effect of treatment: efficacy of the treatment was tested with the Alzheimer Disease Assessment Scale, cognitive subsection (ADAS-cog) after 6 weeks of intensive treatment (5 days/week) and 4.5 months of maintenance (twice a week). Results of the treatment group compared with the placebo group were statistically significant. A positive change in this graph indicates reduction in the real ADAS-cog score, which represents an improvement

the placebo group (decline). However, there was no statistical significance.

*Compliance*

Patient compliance to treatment remained high throughout the study: participation in 90 % of the treatment sessions and 94 % of the sham sessions.

## Discussion

In our recently published study, we showed a synergistic, long-lasting, post-treatment effect of rTMS-COG for patients with mild to moderate AD (Bentwich et al. 2011). The current randomized, double-blind, controlled study evaluated the effect of rTMS-COG therapy for patients with mild to moderate AD, compared with a matched placebo group.

Regarding the primary objectives in our study, we found that following both 6 weeks of intensive daily treatment and an additional 3 months of maintenance treatment, there was a significant improvement in the ADAS-cog scores of the treatment group, as compared with the placebo group. Since the ADAS-cog range of the patients who were included in the study was on average 24 (±8) points in the treatment group, an improvement of about four points is both relatively and clinically significant (Rockwood et al. 2007). Considering the secondary objectives, the CGIC measure also demonstrated a clear improvement. The NPI also showed an improvement that did not reach significance.

Most of the pharmacological studies in clinical practice have been based on the evaluation of ADAS-cog and CGIC. For these two parameters, we obtained results that were superior to those reported for currently available medications (cholinesterase inhibitors) (Birks 2006). It is also important to note that the results obtained in our trial were in patients receiving medication during the trial (six of the seven active treatment patients were treated with cholinesterase inhibitors at the time of recruitment), which demonstrates that the rTMS-COG technology applied provides an additional beneficial effect to that available with drugs. These results suggest that rTMS-COG therapy may stimulate and exploit a "cognitive reserve" pool, which may remain intact in AD patients, in addition to the currently available therapy, which activates cholinergic systems.

Furthermore, our results demonstrate not only that rTMS-COG provides a significant improvement compared to currently available usual treatment, but also (given the reports in scientific literature) that rTMS-COG results are better than using COG or TMS alone (Ahmed et al. 2012; Nardone et al. 2012). The average improvement in the ADAS-cog score in this study was almost 4 points at both 6 weeks and 4·5 months. In comparison, Cotelli et al. (2011) reported a significant effect of rTMS on auditory sentence comprehension, but no significant effects on name performance or memory and executive functions, and in other studies, an average improvement of less than 2 points in ADAS-cog scores was recorded during treatment periods of a similar length utilizing COG alone [e.g. ADAS-cog recorded: 1.9 (Spector et al. 2003]. Moreover, a meta-analysis on publications summarizing the benefits of COG alone in AD (Reichman et al. 2010; Sitzer et al. 2006), showed that COG produced only a limited beneficial effect for several of the cognitive functions.

One of the interesting points still unresolved is the mechanism of action of rTMS on the brain of AD patients. rTMS can induce lasting modulation of brain activities in the targeted brain regions where it is applied and across brain networks through transcranial induction of electric currents in the brain (Wagner et al. 2007).

Enhanced synaptic plasticity has been suggested as a potential physiological mechanism that may account, at least in part, for the effect of rTMS on the brain (Grafman et al. 1994; Siebner and Rothwell 2003). Synchronous stimulation of two neurons results in long-term potentiation (LTP), a long-lasting enhancement interneuronal signal transmission. LTP is one of several events that form the basis of synaptic plasticity (the capability of synapses to alter their strength). LTP is regarded as one of the central cellular mechanisms of learning and memory, based on the fact that memories are encoded by changes in synaptic strength (Bliss and Collingridge 1993). Moreover, Hoogendam et al. (2010) recently presented a link between the after effects induced by rTMS and the induction of synaptic plasticity.

More than a decade ago, a working hypothesis was put forward, suggesting that high-frequency rTMS, similar to LTP, enhances the efficiency of synaptic cortical activity, whereas low-frequency rTMS reduces it (Kimbrell et al. 1999). A recent review detailed the growing potential of applying TMS in AD (Cotelli et al. 2006).

Concerning the hypothesis of a possible interaction between TMS and brain circulation, high-frequency TMS has been shown to elicit a localized elevation in regional cerebral blood flow in the area under the coil, whereas low-frequency rTMS ($\leq$1 Hz) creates a localized reduction in cortical excitability, which persists beyond the duration of direct stimulation (Zheng 2000).

Studies on animal models showed that rTMS modifies mechanisms that play a part in the formation of memories (Ahmed and Wieraszko 2006). Moreover, a very recent study has shown the benefit of rTMS for treating patients with AD (Nardone et al. 2012). Until our study, TMS has never been shown to have a lasting impact on cognitive functions, in particular for patients suffering from dementia. We believe that the mechanism of enhanced learning and memory, given learning under rTMS, may account, at least in part, for the beneficial results obtained in our current study.

The results of this study are promising, and provide a new non-pharmacological tool to treat AD patients in addition to the drugs presently available.

**Acknowledgments** We thank Dr. Ariela Alter (Neuronix Ltd., Yokneam, Israel) for her contribution to the manuscript and Dr. Innesa Bekerman for performing the MRI anatomical determinations.

**Conflict of interest** Neuronix Ltd, Yokneam, Israel financially supported this study through The Fund for Medical Research, Development of Infrastructure and Health Services—Assaf Harofeh Medical Center, Israel. The study sponsors supported the study by providing funds. The design, the collection, analysis and interpretation of the data, the writing of the report and the decision to submit the paper were the entire responsibility of the corresponding author and the co-authors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Prof. Rabey (the corresponding author) is a consultant for Neuronix Ltd.

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