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Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: clinical experience

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Abstract Alzheimer's disease (AD) is the most common type of dementia among the elderly. Common treatments available and non-pharmacological interventions have their limitations, and new therapeutic approaches are critically needed. Transcranial magnetic stimulation (TMS) is a non-invasive technique that generates an electric current-inducing modulation in cortical excitability. The previous clinical trials showed that combinations of rTMS and cognitive training (rTMS-COG), as provided by the NeuroAD medical device system, offer a novel, safe, and effective method improving mild-to-moderate AD patients. In this article, we present our experience with rTMS-COG treatment, in clinical settings, of 30 mild-to-moderate AD patients that received rTMS-COG commercial treatments in two clinics for 1-h daily sessions, 5 days per week, for 6 weeks (30 sessions). Five patients returned for a second treatment. ADAS-Cog and MMSE scores were measured pre- and post-treatments. The main analyses were conducted on patients who received 1 treatment ($n = 30$). Data received from the five returning patients were analyzed separately. The effect of rTMS-COG treatment was statistically significant regarding both ADAS-Cog (-2.4 point improvement, PV <0.001) and MMSE ($+1.7$ points improvement, PV <0.001) scores. About 80 % of patients gained some cognitive improvement following NeuroAD treatment, with more than 60 % improving by more than two points, for a minimum of 9 months. The Neuronix NeuroAD System was shown to be a safe and effective non-invasive modality for cognitive improvement of Alzheimer patients, with measurable outcomes lasting, in some of them, for up to 1 year, following completion of the 6-week daily intervention course (a carryover effect).

Keywords rTMS · Alzheimer's disease · Cognitive training · Alzheimer's Disease Assessment Scale-cognitive · Dementia · Mini–mental state examination

Introduction

Alzheimer's disease (AD) is a well-known tragic and debilitating disease, the most common type of dementia among the elderly (Fargo et al. 2014).

Both the prevalence and financial burdens of AD are predicted to grow significantly in the near future. AD is already the sixth leading cause of death in the US today. Compared with the declining proportions of other leading causes of death (e.g., heart diseases, cancer), the proportion of AD deaths among the general population is continuously increasing (Hoyert and Xu 2012). In addition, as lifespan is prolonged with improvements in scientific, medical, social, and environmental conditions, so grows the number of AD patients (Grayson and Velkoff 2010). According to the World Health Organization (WHO) estimates, by 2030, the number of Americans with AD, aged 65 years and older, will reach 7.1 million, a 40 % increase from the 5 million currently affected (Hebert et al. 2013).

To add to the complexity of the management of AD, the average life expectancy of AD patients is 8–12 years, with 40 % of this time being at the severe stage of the disease (Fargo et al. 2014). As the number of AD patients and other types of dementia grows, the costs of the associated health

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care services will continue to increase, and are estimated to grow from $203 billion in 2013 to $1.2 trillion in 2050 in the US alone (Alzheimer's Association 2013; Gilligan et al. 2013a, b; Xie et al. 2008).

To date, the most widely used treatments for AD are approved pharmacological treatments, particularly acetyl-cholinesterase inhibitors (AChEIs)—donepezil, galan-tamine, and rivastigmine, which interfere with the breakdown of the neurotransmitter acetylcholine, a key factor in memory processes (Birks 2006).

However, it is well known that these medications are not effective for all patients and do not change the course of the disease (Fargo et al. 2014). In addition, according to the National Institutes of Health Report (NIH National Insti-tute on Aging 2015), these drugs may help only for a limited period of time and cause a range of side effects, such as nausea, vomiting, and diarrhea. For example, it has been claimed that on placebo-controlled clinical studies of AChEI, more patients left the active treatment groups due to adverse events compared with placebo (29 and 18 %, respectively) (Birks 2006).

ADAS-Cog is a validated scale for measuring changes in AD and remains the regulatory standard outcome for AD trials. However, consensus on the magnitude of change required to show a clinically meaningful change among patients with AD has still not been resolved.

In 2012, Schrag and Schott (2012) analyzed the ADAS-Cog results in a group of untreated Alzheimer patients, comparing them with the following tests: the Functional Activities Questionnaire (FAQ), the clinical dementia rat-ing (CDR) Scale, the severity score according to the CDRS, and a comprehensive neuropsychological battery of tests, including memory, naming and executive function within time (6 months and 1 year). They found that a minimum of three points decline in the ADAS-Cog score may be an appropriate value for evaluating achievements for a given treatment. However, they also wrote in the conclusions that further studies based on patient and caregiver reports should be included to determine the minimal clinically relevant difference between changes resulting from any treatment applied. In this respect, it is important to mention that in a previous randomized clinical study performed by our group (Rabey et al. 2013) with rTMS combined with cognitive training, we found an improvement of 3.57 in the average Clinical Global Impression of Change (CGIC) (after 6 weeks) and 3.67 (after 4.5 months) compared with 4.25 and 4.29 in the placebo groups (mild worsening) ($p = 0.05$ and $p = 0.05$, respectively).

Alongside the traditional treatments, a wide range of non-pharmacological interventions have been tested to treat, maintain, and improve the symptoms of AD. Such treatments include both cognitive and behavioral therapies,

sensory stimulation, and therapies involving reminiscing and validating past events. So far, efficacy results regarding treatment of behavioral symptoms of dementia are ambiguous (Sitzer et al. 2006; Olazarán et al. 2010; Reichman et al. 2010).

Hence, it is clear that due to lack of sufficient solutions and the growing unmet medical, financial, and social needs, new therapeutic approaches are critically needed.

One such approach may involve non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS). TMS is a neurostimulation and neu-romodulation method that uses electromagnetic induction of electric fields in the brain. While the technique is well described in the literature, its mechanism of action remains largely unknown. Nevertheless, the last 20 years have shown a rapid increase in applications of TMS, studying cognition, brain-behavior relations, and patho-physiology of various neurologic and psychiatric disorders (Rossi et al. 2009).

TMS works by passing a large, brief current through a wire coil placed on the scalp. The transient current pro-duces a large and changing magnetic field, which induces electric current in the underlying brain. The area activated is relatively focal, with a "figure of eight" or "butterfly" and more diffuse with a circular coil. The effect of TMS also depends on pulse waveform (monophasic vs biphasic) and on the direction of the induced current in the brain according to coil orientation (Kammer et al. 2001). This is likely due to the activation of various groups of cortical fibers (Di Lazzaro et al. 2004a, b).

The repetitive application of TMS (rTMS) causing long-lasting effects was used to study the influence on a variety of cerebral functions. High-frequency (>1HZ) rTMS is known to depolarize neurons and to indirectly affect areas are con-nected and related to behavior and emotions.

Enhanced synaptic plasticity has been suggested as a potential physiological mechanism that may account, at least in part, for the effect of TMS 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 the 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.

In 1999, Kimbrell et al. formulated a working hypoth-esis suggesting that high-frequency rTMS, similar to LTP, enhances the efficiency of synaptic cortical activity,

whereas low-frequency rTMS reduces it (see also Cotelli et al. 2011).

It has also been shown that rTMS elicits a localized elevation in regional cerebral blood flow in the area under the coil, whereas low-frequency rTMS (≤ 1 Hz) creates a localized reduction in cortical excitability, which persists beyond the duration of direct stimulation (Zheng 2000).

When applied repetitively, repetitive transcranial magnetic stimulation (rTMS) can modulate cortical excitability—decreasing or increasing it, depending on the parameters of stimulation (Rossi et al. 2009). rTMS, is a well-documented method that has be shown to facilitate cortical excitability for long-lasting effects. It has been studied on a variety of cerebral functions and there is evidence that it is also effective for many conditions, potentially including AD (Guse et al. 2010). rTMS has been approved by the U.S. Food and Drug Administration (in 2008) and other parts of the world for treatment of symptoms of depression.

Combination of high-frequency rTMS and cognitive training (rTMS-COG) as provided by the medical device NeuroAD System (Neuronix Ltd., Yokneam, Israel), offers a novel, safe, and effective method for treating mild-to-moderate AD. The system is based on Non-Invasive Cortical Enhancer (NICE^{TM}) technology, which was clinically studied in five trials: three trials at Assaf Harofeh Medical Center, Israel (Bentwich et al. 2011; Rabey et al. 2013; Internal data 2013, not published yet), one trial in Beth Israel Deaconess Medical Center (BIDMC), Harvard Medical School, Boston MA, USA (Brem et al. 2013), and one trial in Daejeon University Hospital, Korea (Lee et al. 2015).

Our previous open-label, proof-of-concept study and double-blind, randomized, controlled studies showed that rTMS-COG is a safe and effective treatment, with a synergistic, post-treatment effect for mild-to-moderate AD, as demonstrated by improvements of two crucial parameters: the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) and the Clinical Global Impression of Change (CGIC) scores. Not only did rTMS-COG show better results than either COG or TMS alone, the combination obtained superior results to those reported for AChEI (Birks 2006). Furthermore, rTMS-COG provides additional beneficial effect to patients already treated with AChEI, with no adverse effects or complications. Finally, when tested 2–6 weeks after treatment, improvements were sustained and compared with the placebo group, even grew further.

Following these successful clinical trials, a CE mark (0482, Medcert) was issued, signifying a legal designation that the manufacturer's product has met the requirements of all relevant Medical Device Directives in the EU,

followed by the Israeli Ministry of Health approval (AMAR No. 2439000 and 24390001).

Alongside marketing activities in Europe, two private clinics were established in Israel, offering commercial treatment for mild-to-moderate AD patients. The results of 30 patients from both clinics are reported here, including five patients who received a second treatment course, about 1 year following the first treatments.

The purpose of this publication is to present clinical experience with rTMS-COG in clinical settings with 30 mild-to-moderate AD patients in Israel over 6 weeks.

Methods

Subjects

Two private clinics offering commercial treatments with the NeuroAD System were opened in Israel in 2012. To assess patients' eligibility and the effect of treatment, medical screening was applied using two AD diagnostic tests [ADAS-Cog and the mini–mental status examination (MMSE)] by a trained physician, prior to and immediately following treatment. In addition, each individual patient underwent an MRI scan prior to treatment to localize regions-of-interest (ROI) individually.

Patients ($n = 30$) diagnosed with mild-to-moderate AD were treated for 1-h daily sessions, 5 days per week, for 6 weeks (30 sessions). Patients performed cognitive training, while the relevant brain region was stimulated by rTMS. Each daily session included the interlaced stimulation of three regions, using four different paradigms developed to match those same regions.

Thirty (30) subjects received one course of treatment; five returned for a second treatment; and a total of 35 treatment courses were analyzed. The main analyses were conducted on patients who received one treatment ($n = 30$). Data received from the five patients who underwent second treatments were analyzed separately, to exclude possible selection biases and dependencies in results derived from the two treatment courses.

Subjects' baseline characteristics are provided in Table 1.

Table 1 Baseline demographic characteristics of the patients

Characteristic	
N	30
N (%) female patients	13 (43)
ADAD-Cog score (pre-treatment)	20.5 (SD = 1.3)
MMSE score (pre-treatment)	22.2 (SD = 0.5)

Localization of treatment regions (ROI)

Six ROIs were targeted by the rTMS procedure concurrently with cognitive training: (1) left inferior frontal gyrus (Broca's area); (2) left superior temporal gyrus (Wernicke's area); (3, 4) left and right dorsolateral prefrontal cortices (DLPFCs); and (5, 6) left and right parietal somatosensory association cortices (R-PSAC and L-PSAC).

rTMS

The rTMS stimulations were guided by marked coordinates via an optical navigation system, and applied through rTMS eight-figure magnetic coils as follows: 20 trains, each lasting for 2 s, repetition of 10 Hz (totaling 400 pulses) for three out of four paradigms, and five trains for 2 s, repetition of 10 Hz (totaling 100 pulses) for the fourth paradigm. Each day, patients received 1300 TMS pulses to three selected brain regions.

To meet safety recommendations, an intensity calibration process was performed for each patient prior to each daily intervention and rTMS was set at 90–110 % of the patient motor threshold depending on the specific brain region.

Cognitive training

Cognitive training paradigms were designed to engage the six targeted ROIs. In conjunction with rTMS cortical stimulation, the patients performed the following tasks: syntax and grammar tasks designed to engage the Broca Region (Rogalsky et al. 2008); comprehension of lexical meaning and categorization tasks targeting the Wernicke Region (Harpaz et al. 2009); action naming, object naming, and spatial memory tasks (shapes, colors and letters) designed for the left and right DLPFCs (Bellgowan et al. 2009); and spatial attention tasks (shapes and letters) for left and right PSAC (Buck et al. 1997).

To keep patients challenged, the difficulty levels of all tasks were individually adjusted on a weekly basis, according to each patient's performance level.

Daily sessions included four different tasks for three of the six selected brain regions. Each region was coupled with a specific cognitive task. All cognitive tasks were presented on a computer touch screen and involved a "forced choice"—one of two alternative options.

Statistical methods

The ADAS-Cog is considered to be a gold standard test for AD and a clinical tool to evaluate the reliability and validity of cognitive changes following intervention. Up to 70 points can be scored, where lower scores stand for a better cognitive performance (Mohs et al. 1997). We used several versions of the ADAS-COG to avoid a learning effect.

The MMSE consists of 11 cognitive questions and requires 5–10 min to administer. Up to 30 points can be scored, where higher scores stand for a better cognitive performance (Folstein et al. 1975).

The main analyses consisted of the following:

Effect of a single treatment course ($n = 30$; all patients), with missing values imputed by multiple imputation (Missing Images–MI; SAS® Proc MI): sensitivity—for observed data only and for worst-case analysis ('worst-case' defined as no change on either of the two cognitive scales—all other analyses were based on observed data only).

Effect of repeated intervention by second treatment courses includes results of second treatment courses ($n = 5$); follow-up on the patients for the period between the first and second interventions (10 months on average); and comparison of changes in baseline cognitive scores between those returning for a second treatment course and those who did not.

Results

Safety

No severe side effects were reported. Transient mild cases—headaches and tiredness, were reported in some cases.

Efficacy

Cognitive measures

Table 1 presents baseline demographic characteristics of the patients and ADAS-Cog and MMSE scores (mean) of 30 patients before treatment. As demonstrated in Table 2, the ADAS-Cog scores were statistically significantly lower (better) post-treatment, compared with pre-treatment ($p < 0.001$).

Sensitivity analyses were conducted as described above. Results for both observed data only and worst-case analysis (missing value = no change) yielded statistically significant better post-treatment results compared with pre-treatment ($p < 0.001$).

Similarly, the MMSE results, as shown in Table 3, were statistically significant higher (better) post-treatment compared with pre-treatment ($p < 0.001$).

Tables 2, 3 show that the treatment has a statistically significant effect in improving patients' cognitive performance, when measuring on both ADAS-Cog and MMSE scales.

Table 2 ADAS-Cog scores pre- and post-treatment (6 weeks)

Parameter/measurement	Mean	SE	Min	Median	Max	N	p
ADAS-Cog							
Pre-treatment	20.5	1.3	10.6	18.8	37.3	30	
Post-treatment	18.1	1.4	8.3	16.2	33.6	30	
Difference	−2.4	0.6				30	<0.001

Missing data imputed by multiple imputation

p values calculated using the Wilcoxon Signed-Rank Test

SE standard error

Table 3 MMSE-Cog scores pre- and post-treatment (6 weeks)

Parameter/measurement	Mean	SE	Min	Median	Max	N	p
ADAS-Cog							
Pre-treatment	22.2	0.5	16.8	2.9	27.0	30	
Post-treatment	23.9	0.5	18.0	24.5	28.0	30	
Difference	1.7	0.3				30	<0.001

Missing data imputed by multiple imputation

P values calculated using the Wilcoxon Signed-Rank Test

SE standard error

Table 4 ADAS-Cog percentile improvement (%) per ADAS-Cog improvement points

ADAS-Cog improvement (points)	Patients' improvement percentile (%)
−5	21.4
−4	25.0
−3	42.9
−2	60.7
−1	71.4
0	78.6

Fig. 1 ADAS-Cog results for the first and second treatment course (5 patients)

Table 4 shows the improvement rates according to the ADAS-Cog scale. This enables the assessment of the percent of the population that could gain specific clinical improvement from this treatment. According to Table 4, approximately 80 % of patients gained some improvement in their cognitive abilities following neuroAD treatment, with more than 60 % of patients improving by at least two points on the ADAS-Cog scale.

Second treatment

Five (5) subjects returned for a second treatment course.

To study the prolonged effect of the first treatment courses, we compared the ADAS-Cog and MMSE scores between the first and second treatment courses. Fig 1 shows the ADAS-Cog scores for the first and second treatment courses.
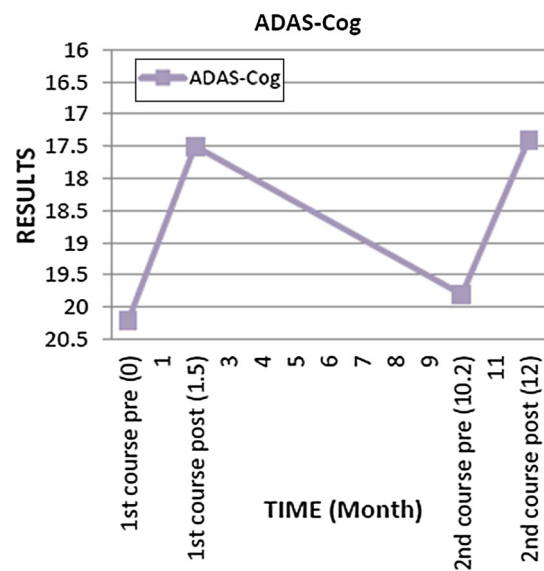
As shown in Fig. 1, the average of ADAS-Cog results of five patients at the beginning of treatment No.1 was 20.2, and after 6 weeks of the NeuroAD treatment, we measured an improvement of −2.7 point (going to 17.5). Then, following 10.2 months on average after the first treatment courses, the average ADAS-Cog result of the five patients was similar to and even better than that of their first treatment courses (19.9), hence showing that over a 10-month period, patients did not deteriorate on average.

Discussion

AD is an incurable, degenerative, and terminal disease and the most common type of dementia, posing also a huge financial burden. The NeuroAD System, developed by Neuronix, is an innovative, safe, and effective medical device for the treatment of AD.

Recently, Lefaucheur et al. (2014) published a paper with evidence-based guidelines on the therapeutic use of rTMS.

In the section concerning the application of TMS for AD, the main criticism is the low number of patients reported up till now. In addition to our work, they also mention a positive paper reported by Ahmed et al. (2012) applying rTMS in only one area, the left dorsolateral prefrontal cortex (like the treatment for depression), in multiple sessions (but without cognitive training like our protocol) with positive results in Alzheimer patients, but also a negative response when stimulating the right dorsolateral prefrontal cortex alone.

Very recently, Neuronix organized a randomized double-blind placebo-controlled study on treatment in an Alzheimer population (double sham versus double active treatment) in 120 cohorts from seven medical centers in USA. Results will be presented in the near future

Statistical analyses reveal significant results: an average improvement of -2.4 points was shown on the ADAS-Cog Scale ($p < 0.001$) (Table 2) and an average improvement of $+1.7$ points on MMSE ($p < 0.001$) (Table 3), following 6 weeks of daily sessions. In addition, approximately 80 % of patients gained some improvement in their cognitive abilities following NeuroAD treatment, with more than 60 % of patients improving by more than two points on the ADAS-Cog scale (Table 4).

The results presented suggest that repeated NeuroAD treatment (once a year) may be used to improve and preserve patients' cognitive status and maintain stability of improvement over time.

As Alzheimer is a neurodegenerative disease, it is estimated that patients will deteriorate by 5.5 points per year, depending on the severity of the disease (Ito et al. 2010).

The results shown here are encouraging. Yet, there are two main issues that should be further examined: increasing the number of the patients analyzed, as well as longer follow-up on patient progress for up to 2–3 years. Assuming that these results are maintained for larger populations and longer follow-up, Neuronix's neuroAD can be regarded as a proven device for effectively treating Alzheimer's patients, within time.

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