

# Benefits of Deep Transcranial Magnetic Stimulation in Alzheimer Disease

## Case Series

Keren Avirame, PhD,\* Jimmy Stehberg, PhD,† and Doron Todder, MD, PhD\*‡§

**Background:** Patients diagnosed with Alzheimer disease (AD) show severe cognitive deficits. Decline in memory, language, and executive function have repeatedly been reported. Although AD affects 60% to 80% of demented elderly patients, there is currently no cure and limited treatment alternatives.

**Objectives:** The aim of the study was to evaluate the feasibility of stimulating prefrontal cortex (PFC) with deep transcranial magnetic stimulation (dTMS) to ameliorate cognitive deficits in patients suffering from AD.

**Methods:** Eleven patients (6 males; mean [SD] age, 76 [7] years) in moderate to severe stages of AD received dTMS over the PFC for 20 sessions. Computerized battery (Mindstreams [MS]) and neuropsychological testing (Addenbrooke Cognitive Examination [ACE]) were used to assess cognitive performance before and after treatment.

**Results:** Compared with baseline, 60% of patients performed better on the MS battery and 77% of patients performed better on the ACE testing at the end of dTMS treatment. None of the patients performed worse on both tests at the end of treatment. The DTMS effects on the group mean in ACE and MS approached significance ( $P = 0.065$  and  $P = 0.086$ , respectively). A dTMS-induced improvement in the ACE was significant ( $P = 0.001$ ) on patients in more progressed stage ( $n = 6$ ). Change in ACE negatively correlated with score at baseline.

**Conclusions:** In sum, the current report of this novel technique indicates that deep stimulation might lead to preservation and even improvement of cognitive functions, at least during the time of treatment. Further examinations should report of long-term effects of this technique.

**Key Words:** transcranial magnetic stimulation, Alzheimer, plasticity, cognition

(*JECT* 2016;32: 127–133)

Alzheimer disease (AD) is an irreversible condition that affects a significant portion of the elderly population worldwide.<sup>1,2</sup> It is characterized by cognitive and behavioral disturbances varying as a function of time since the onset of the degeneration process.<sup>3</sup> To date, the etiology of AD remains unknown. Genetic<sup>4</sup> and vascular factors<sup>5</sup> are argued to play a critical role in the involvement of the observed cognitive decline and neurodegeneration in this illness. Alzheimer disease commonly begins with a gradual deterioration in memory and increased confusion. Cognitive deficits are also manifested in domains such as executive function and language. The pathology has been associated with structural changes (for review, see Frisoni et al<sup>6</sup>), abnormal protein deposits (for review, see Huang and Mucke<sup>7</sup>), and loss of cholinergic

neurotransmission.<sup>8</sup> Neurophysiological studies have consistently reported of impaired plasticity,<sup>9,10</sup> which has been interpreted as a sign of reduced neuronal communication.<sup>11</sup> Functional disconnections in AD were also observed in resting-state functional magnetic resonance imaging (MRI) studies indicating loss of large-scale connectivity<sup>12</sup> and disruption in functional networks critical for memory.<sup>13</sup> Presently, the possibilities for therapy are very limited. Patients normally receive pharmacological treatments in the mild to moderate stages with the aim to decelerate the progression of cognitive deterioration.<sup>14</sup> Given that age is currently the strongest risk factor for AD and that the population is aging, it is necessary to explore novel avenues of treatment.

So far, only a handful of studies have investigated whether the use of noninvasive brain stimulation techniques might lead to cognitive gains in AD (for review, see Hansen<sup>15</sup>). These studies are based on the assumption that modulating cortical activity in a target region or network leads to more efficient processing.<sup>16</sup> This cortical modulation could be achieved by transcranial magnetic stimulation (TMS), which has been long used to enhance performance on tasks involved in attention, memory, and language.<sup>17</sup> Decades of research about TMS provide a substantial amount of knowledge about its underlying neurophysiological mechanisms.<sup>18,19</sup> In clinical contexts, TMS is often used in a repetitive mode (rTMS), in which trains of suprathreshold pulses are delivered in high frequency over target regions during multiple sessions.<sup>20</sup>

Most rTMS studies on patients with AD stimulate with high frequency (10-20 Hz) the dorsolateral prefrontal cortex (DLPFC) to improve cognitive functions.<sup>21,22</sup> For example, Coteli et al<sup>23</sup> reported improved naming performance in the group receiving rTMS compared with the control group. Recent functional MRI study showed that 4 sessions of rTMS over the left DLPFC enhanced naming abilities and increased activation in Broca's area.<sup>24</sup> Other studies examined the effects of concurrent cognitive training and rTMS over multiple brain regions to take full advantage of neuroplasticity.<sup>25,26</sup> The authors observed a significant improvement on the Alzheimer Disease Assessment Scale (ADAS-cog) both after 6 weeks and 4.5 months, pointing to a long-lasting benefit. In fact, even an occasional use of rTMS for long-term maintenance (10-19 months) resulted in slower progression of the disease.<sup>27</sup>

Deep TMS (dTMS) is a new interventional technology approved by the Food and Drug Administration for the treatment of medication-refractory depression and the stimulation of peripheral nerves.<sup>28,29</sup> This noninvasive technique uses special coils (H-coils) capable of stimulating deep cortical regions critical for reducing symptoms in a range of neuropsychiatric disorders (for review, see Bersani et al<sup>30</sup>). Roth et al<sup>31</sup> reported that the H2-coil induces direct stimulation in both lateral and medial parts of the PFC in depths of up to 3 cm using low power, thus overcoming the depth limitations of the common rTMS with figure-8 coils. In such a way, dTMS might activate bilateral hubs in the lateral PFC potentially involved in language, executive, and attentional functional networks.<sup>32</sup> In addition, stimulating the medial PFC

From the \*Neuroclinic Health Center, Ramat Gan, Israel; †Laboratorio de Neurobiología, Centro de Investigaciones Biomédicas, Universidad Andres Bello, Santiago, Chile; ‡Beersheva Mental Health Center and §Zlotovsky Center for Neuroscience, Ben-Gurion University, Beersheva, Israel.

Received for publication May 7, 2015; accepted October 15, 2015.

Reprints: Keren Avirame, PhD, Neuroclinic Health Center, Menachem Begin Rd 7, Ramat Gan 5268102, Israel (e-mail keren.avirame@gmail.com).

The authors have no conflicts of interest or financial disclosures to report.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

DOI: 10.1097/YCT.0000000000000286

could be advantageous because it is part of the default-mode network, which is important for memory functions.<sup>13,33</sup> Here, we summarize changes in cognitive performance in 11 patients who received 20 sessions of high-frequency dTMS over the PFC in our clinic.

## METHODS

### Patients

Eleven patients diagnosed with AD (6 males; mean [SD] age, 76 [7] years) received dTMS treatment. Patients received the dTMS treatment as coadjutant to pharmacological treatment, which remained unchanged throughout treatment. All patients are treated with acetylcholinesterase inhibitors for at least 6 months before dTMS treatment. Table 1 details demographic and medical information about the patients. Two additional patients did not complete the treatment procedure because of deterioration in medical condition, which is unrelated to AD, and therefore are not included in the case series.

### Deep TMS

The H-coil has been reported to induce robust and persistent effects<sup>34</sup> while being safe for use at high frequencies.<sup>35</sup> In the current report, all patients were treated with the H2-coil, which is designed to stimulate deep prefrontal brain regions bilaterally (for technical details, see Roth et al<sup>31</sup>). The dTMS stimuli were delivered by a Magstim Super Rapid stimulator (Magstim Company, Ltd, Carmarthen, Wales, UK). In the beginning of the first session, the optimal spot on the scalp corresponding to the site of the left primary motor cortex (C3 in electroencephalogram 10-20 system) was localized. This was conducted by delivering single pulses at 60% stimulator output to elicit involuntary contraction of the right abductor pollicis brevis muscle. The motor threshold (MT) for each patient was then determined by gradually decreasing the intensity of single pulses delivered in an interval of 5 seconds. The MT was defined as the lowest intensity of stimulation able to produce muscle movement in 5 of 10 times. After the identification of MT, the coil is moved forward 6 cm anterior from the motor cortex to the site of stimulation, the bilateral PFC.

During the sessions, patients had earplugs to reduce any possible adverse effects on hearing. To prepare the patient for the treatment protocol, trains of 10 Hz were delivered at a gradually growing intensity (100%–120% in a step of 10% of MT). Devi et al<sup>24</sup> reported of no observable difference between frequencies higher than 10 Hz. Each TMS session consisted of 42 trains of 10 Hz given for 2 seconds, every 20 seconds, and lasted for approximately 20 minutes. The treatment protocol consisted of 20 dTMS sessions delivered 2 to 3 times a week with a minimum interval of 1 day between sessions.

### Cognitive Assessments

#### Mindstreams

Mindstreams (MS; NeuroTrax Corp., Bellaire, Tex) is a battery of computerized tests assessing cognitive functions, which are commonly affected by aging. These tests were found to be valid and reliable<sup>36</sup> and have been used in studies of genetic factors in normal aging,<sup>37</sup> neurodegenerative disorders such as mild cognitive impairment,<sup>38</sup> and association between cognition and brain structure.<sup>39</sup> Furthermore, the MS was found to be suitable for longitudinal studies because of high reliability coefficients.<sup>36</sup> The tests measure accuracy and latency to evaluate memory (verbal and nonverbal immediate and delayed recognition), executive function (go–no go task, stroop task, and catch game), attention (go–no go task and stroop task), and visual spatial perception (for detailed descriptions, see Dwoletzky et al<sup>40</sup>). Scores for each of these 4 domains are calculated separately as deviation from the standardized performance and summed together to give the global score. The entire test is administered in 40 to 60 minutes. The MS battery was administered twice including the same tasks in the same order but with different stimuli.

#### Addenbrooke Cognitive Examination

Addenbrooke Cognitive Examination (ACE<sup>41</sup>) is a 100-point screening tool that assesses the following 5 cognitive domains: attention (18 points), memory (26 points), verbal fluency (14 points), language (26 points), and visuospatial ability (16 points). The ACE is a brief and sensitive battery, which has been validated in many

TABLE 1. Patients Description

| Patient | Age, y | Sex | Education, y | Concomitant Pathologies  | Medication   | MT, % |
|---------|--------|-----|--------------|--|--|-------|
| P1      | 75     | M   | 15           | Polycythemia vera, pancreatic tumor  | Hydroxyurea, Coumadin, aspirin, Exelon                                   | 58    |
| P2      | 77     | M   | 15           | Cholesterol, thrombophilia   | Tevapirin, Litorva, Exelon   | 35    |
| P3      | 73     | F   | 12           | Hypertension, cholesterol  | Amlo, aspirin, Lipitor, Exelon, Memox                                    | 56    |
| P4      | 81     | F   | 12           | Peptic ulcer, cholesterol, insomnia, anxiety   | Lansoprazole, Normalol, Simvaxon, Remotiv, Vaben, Stinlox                | 62    |
| P5      | 87     | M   | 15           | Hypotension, atherosclerosis   | Disothiazide, Ebixa, Exelon  | 53    |
| P6      | 61     | M   | 17           | Benign prostatic hyperplasia   | Tamsulin, Memorit, Wellbutrin  | 33    |
| P7      | 76     | F   | 12           | Peptic ulcer, osteoporosis, hypertension, hypercholesterolemia, atherosclerosis, angina pectoris | Fosalan, Plavix, Mopral, Simvastatin, Cardiloc, Nitroderm, Ebixa, Exelon | 57    |
| P8      | 81     | M   | 18           |  | Ebixa, Exelon  | 38    |
| P9      | 76     | F   | 22           |  | Ebixa, Exelon  | 54    |
| P10     | 70     | M   | 17           | Hypercholesterolemia, diabetes, thrombophilia  | Aspirin, Glucomin, Simvastatin, Ebixa, Exelon                            | 61    |
| P11     | 81     | F   | 12           | Atrial fibrillation, hypercholesterolemia, hypothyroidism  | Coumadin, Lipitor, Eltroxin, Tambocor, Memorit, Memox                    | 40    |

Demographic and medical information of patients with AD.

F indicates female; M, male; MT, motor threshold; P1-P11, patients.

languages, including Hebrew and has been used to diagnose cognitive deterioration in elderly patients because it extends the mini-mental state examination (MMSE<sup>42</sup>). Furthermore, it was found to obtain high reliability coefficients.<sup>43</sup> The memory test measures both episodic and semantic memory. The language part comprises naming, comprehension, oral repetition of words and sentences, writing complex sentences, reading regular and irregular words, and verbal fluency. Visuospatial testing consists of copying overlapping pentagons and a wire cube and drawing a clock. Scores for each of the 6 domains are calculated separately and summed together to give the total ACE score. The entire test is administered in 20 to 30 minutes.

**Treatment Procedure**

All patients arrived to the clinic after being diagnosed with AD by an expert neurologist. At the clinic, patients were examined by an expert psychiatrist who confirmed their diagnosis, assessed their medical state, and controlled exclusion criteria according to safety guidance.<sup>44</sup> The exclusion criteria included a history of seizures or epilepsy, previous head injury, the presence of metallic implants in the cephalic region, neurostimulators, surgical clips, or other electronic equipment, the presence of an acute or chronic cardiac disease, deafness or hearing loss, metabolic or systemic diseases, and comorbidity with some neurological disorders: increased intracranial pressure, space occupying lesion, history of stroke or transient ischemic attack, brain aneurysm. At the second day, patients filled in personal and medical questionnaires and signed a consent form to undergo the treatment. Patients also received a full explanation on the possible adverse effects, such as scalp discomfort, migraine, dizziness, and tiredness. Patients were also informed about the rare occurrence of epileptic seizures. Once the informed consent form was signed, cognitive evaluations were administered by trained psychologists. Evaluations were performed at baseline (before beginning of treatment) and at the end of the 20 dTMS sessions. Before each session, patients were asked about possible adverse effects resulting from the previous session. This questionnaire included symptoms such as tiredness, dizziness, nausea, headache, and mood, as well as sleep disturbance,

agitation, loss of appetite, and irritability. Patients were under the direct supervision of a physician throughout the treatment and any adverse effect or subjective disturbance was immediately recorded and responded to. The treatment was conducted in accordance with the guidelines approved by the Ministry of Health for dTMS treatment of AD. The records of 11 patients with AD treated in our clinic between January and December 2014 were retrospectively reviewed.

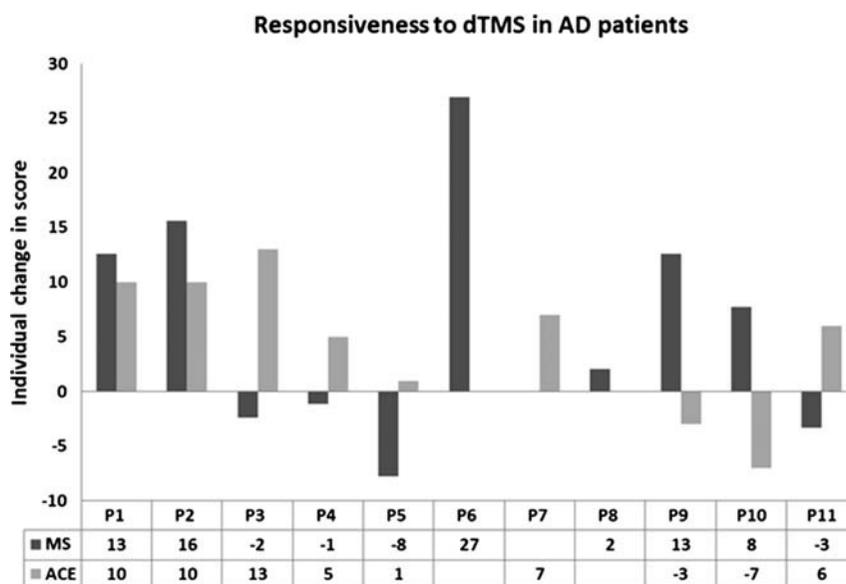
**Statistics**

Statistical analyses were carried out using SPSS, Version 18. Kolmogorov-Smirnov test was used to test for normality before data analysis. Paired sampled *t* tests were employed to compare cognitive scores before and after dTMS treatment. Pearson correlation coefficients were used to probe associations between cognitive scores at baseline and changes in cognitive scores. All statistical tests were considered significant at a *P* value of less than 0.05.

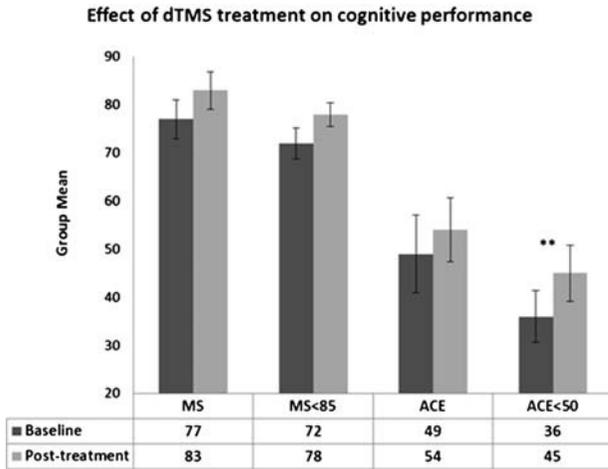
**RESULTS**

Change in cognitive scores was calculated separately for MS and ACE ( $\Delta = [after - before]$ ). Sixty percent of patients performed better on the MS battery and 77% of patients performed better on the ACE neuropsychological testing after dTMS treatment. Figure 1 details the cognitive scores in ACE and MS for each patient. Patient 7 could not complete MS because of poor computer skills. Patients 6 and 8 started the treatment before ACE was in use in the clinic. Of note, none of the 11 patients who were included in the data analysis performed worse on both tests at the end of treatment. This finding suggests that evident decline in cognition was not detected during the treatment period.

Paired samples *t* test was used to test the effect of dTMS treatment on cognitive performance in the current group of patients with AD (Fig. 2). Pre-treatment and post-treatment comparisons revealed that the increase in ACE ( $t_8 = 2.141; P = 0.065$ ) and in MS scores ( $t_9 = 1.858; P = 0.086$ ) approached significance. Furthermore, patients who initially scored low in the ACE testing (<50) performed significantly better at the end of treatment



**FIGURE 1.** Responsiveness to dTMS in patients with AD. Individual change ( $\Delta = [after - before]$ ) in MS and ACE scores. The ACE scores are missing for P6 and P8 and MS score is missing for P7. P1 to P11 indicates patients included in the case-series.



**FIGURE 2.** Effect of dTMS treatment on cognitive performance in patients with AD. Paired *t* test compared the mean test score before and after the dTMS treatment. ACE < 50 indicates patients with scores lower than 50, denoting severe stage (n = 6); MS < 85, patients with scores lower than 85, denoting pathological decline in cognition (n = 8).

(*t*<sub>6</sub> = 6.902; *P* = 0.001). However, when taking into account only patients who performed at baseline lower than the norm on the MS battery (<85), no significant improvement was observed (*t*<sub>8</sub> = 6.02; *P* = 0.192).

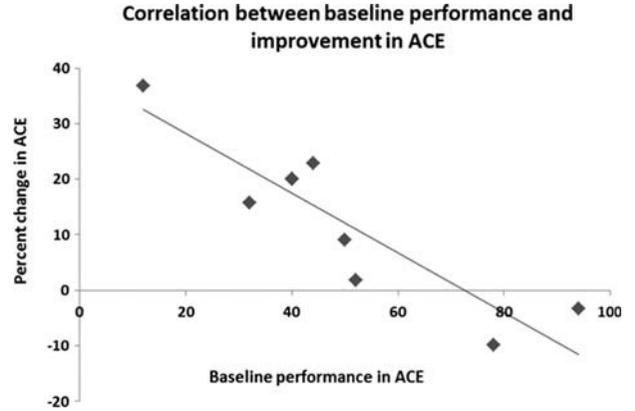
In an exploratory approach, comparisons between pre-treatment and post-treatment revealed the cognitive functions for which the treatment was most beneficial (Table 2). Improvement in visuospatial abilities in ACE ( $\Delta = 1.89 [0.54]$ ) was found to be highly significant (*t*<sub>8</sub> = 3.51; *P* = 0.008). Performance on MS tasks of executive functions and attention approached significance (*t*<sub>9</sub> = 1.96; *P* = 0.085; *t*<sub>9</sub> = 1.93; *P* = 0.089, respectively).

Percent change was also calculated separately for MS and ACE (% change = [(1 - before / after) × 100]). Pearson correlational analyses also revealed that baseline performance on the ACE neuropsychological testing negatively correlated with percent change of ACE (*r* = -0.897; *P* = 0.001). This correlation indicates that the effect of dTMS treatment increases depending on the baseline state of deterioration, with higher effect on patients with poorer cognitive abilities (Fig. 3). Although baseline performance on the MS battery was not significantly correlated with percent change of MS (*r* = -0.495; *P* = 0.167), it showed the same

**TABLE 2.** Exploratory Analyses of dTMS Effects on Different Cognitive Functions

| Test        | Function           | Change in Score Mean (SD) | <i>t</i> | <i>P</i> (2 tails) |
|-------------|--------------------|---------------------------|----------|--------------------|
| MS (n = 9)  | Memory             | 3.63 (2.11)               | 1.713    | 0.121              |
|             | Executive function | 9.91 (5.04)               | 1.963    | 0.085              |
|             | Attention          | 16.46 (8.52)              | 1.933    | 0.089              |
|             | Visuospatial       | 1.53 (6.97)               | 0.219    | 0.831              |
| ACE (n = 8) | Memory             | 0.77 (0.91)               | 0.855    | 0.417              |
|             | Attention          | 0.44 (0.99)               | 0.450    | 0.665              |
|             | Fluency            | 0.00 (0.70)               | 0.000    | 1.000              |
|             | Language           | 0.44 (1.27)               | 0.350    | 0.736              |
|             | Visuospatial       | 1.89 (0.54)               | 3.51     | 0.008              |

Neuropsychological assessments of patients with AD.



**FIGURE 3.** Correlation between baseline performance and improvement in ACE in patients with AD. Percent change ( $\Delta = [after - before]$ ) in ACE was negatively correlated with baseline ACE score (*r* = -0.897; *P* = 0.001).

trend toward a negative relationship, suggesting a more robust change in cases of poor baseline performance.

As for safety, the treatment was well tolerated, with minimal adverse effects that included light headache and occasional tiredness, mainly after the first sessions. Even those patients who had a high MT and received higher stimulation intensities did not complain about uneasiness or painful sensations.

**DISCUSSION**

The current study aimed at presenting for the first time a series of cases in which patients with moderate to severe AD were treated with high-frequency dTMS over the bilateral PFC. Treatment with dTMS was tolerable with very few minor adverse effects such as light headache after the first treatment. Improvements in cognitive abilities were found in the present cohort of patients after 20 dTMS sessions, as indicated by change in scores in 2 neuropsychological batteries, MS and ACE. Our report is congruent with previous studies applying rTMS over the PFC to improve cognitive abilities in patients with AD. Most of these studies focused on the DLPFC and some used specific language tasks to measure cognitive change,<sup>23</sup> whereas others applied a more comprehensive battery. For example, Ahmed et al<sup>45</sup> revealed that 5 days of high-frequency rTMS over the left and then right DLPFC (ie, consecutively) improved score on the MMSE, which is incorporated within the ACE. Furthermore, rTMS was found to shorten the duration of transcallosal inhibition, suggesting more efficient communication between hemispheres and possibly increased activity in functional networks. In fact, the use of H-coil permitted not only to reduce the duration of each TMS session, because stimulation over the left and right PFC was simultaneous, but also to stimulate both prefrontal cortices, which might be more efficient for improving cognitive functions.

Our results also emphasize the importance of using different assessment tools in a group of patients with AD to have a more comprehensive view of the possible changes induced by dTMS. One reason could be related to the large variance in demographic factors such as education and expert computer use, as well as pathological factors including the extent of cognitive loss. In a recent paper,<sup>27</sup> the cognitive gains of rTMS treatment were observed in one test (Montreal Cognitive Assessment) but not in others (ADAS-cog), raising the question about the consistency of these tools. This might suggest that general cognitive skills are improved during treatment, but the effect may not be equally detected by all the tests in use. In other words, even if the batteries included similar

functions, task-related factors such as demands, setup, and difficulty, determine how the cognitive function is measured. Here, we applied one manual testing, the ACE, which incorporates the MMSE, one of the most frequent assessment tools to measure cognitive performance in elderly patients and neuropsychiatric disorders.<sup>46</sup> We also applied a computerized battery, the MS, which contains more complex tasks such as stroop, go–no go, motor planning, spatial perception, and a variety of memory tests. However, despite the advantage of a computerized battery with standardized score, the challenge of using a computer in aging population emphasizes the importance of a manual test that is administered by a trained psychologist and is adapted to the pace of each patient.

Despite the obvious goal to improve memory functions in AD, exploratory analyses revealed that the larger effects were observed in attention, visuospatial, and executive functions. Increased excitability in the PFC might have activated hubs of functional networks related to attention and executive function, which are located in the PFC.<sup>47</sup> Furthermore, Wang et al<sup>12</sup> proposed that increased functional connectivity of the PFC in AD is probably a compensatory mechanism for reduced temporal connectivity as a result of structural changes. Indeed, memory impairment in AD is thought to stem from atrophy, cellular pathology, and cell loss in medial temporal structures.<sup>48</sup> On the other hand, improved cognition may rely on activation of frontal “cognitive reserve.”<sup>49</sup> It is therefore possible to assume that TMS-induced plasticity cannot compensate for structural losses.

Importantly, Ahmed et al<sup>45</sup> observed cognitive improvement only in mild to moderate but not in patients with severe AD, pointing to the importance of cognitive reserve and neuroplasticity, both of which significantly diminish with aging.<sup>48</sup> Rutherford et al<sup>27</sup> reported that 2 weeks of rTMS over the DLPFC increased Montreal Cognitive Assessment scores only in early stage of AD. However, in the present study, correlational analyses between baseline performance and percent change in the ACE test indicate that greater effects of dTMS are found in patients who had poorer baseline performance. The difference in the results might stem from the intervention technique, because dTMS stimulates more deeply and widely, which might be particularly effective for more severe cases.

Of note, TMS as a therapeutic tool is often applied on a daily basis with the assumption that intensive stimulation is necessary for modifying brain activity in a specific area or network.<sup>50</sup> Here, we limited the amount of sessions received each week for 2 reasons: first, not to burden patients who had difficulties to come to the clinic because of their physical and mental condition and, secondly, by applying less sessions per week, we overall extended the duration of the treatment, which might be gainful in AD because of continuous necessity to decelerate cognitive decline. Indeed, none of the patients performed worse on both assessments at the end of the treatment period, suggesting that dTMS may allow maintenance of cognitive abilities during the period it is being applied. In the context of rapid degeneration occurring in moderate to severe stages of AD, a 3-month long period of cognitive improvement or preservation is clinically significant. This is in line with preliminary evidence from a recent open-label study on 6 patients receiving a single session of rTMS every 2 months for cognitive protection in a long-term maintenance phase, in which the authors claimed that occasional application of rTMS may reduce the expected decline rate associated with AD.<sup>27</sup> In the present study, there was no placebo control group. Thus, there is no way of measuring what the expected cognitive decline of this cohort of patients with AD should have been if there was no treatment. However, the lack of cognitive decline suggests a potential reduction that should be tested in a placebo-controlled trial. Further research is also needed to determine how the amount of

sessions and the interval between them may affect the magnitude and duration of the induced improvement, leading eventually to an optimized stimulation protocol.

Although the current observations are encouraging, particularly given the lack of optimal treatments that target core symptoms of AD, these findings require validation via a placebo-controlled, double-blind clinical trial for dTMS in AD. Beyond the obvious limitations of this case series, such as including a small cohort and no control condition, the lack of follow-up assessments prevents us from making conclusions regarding the duration and strength of the effect. In addition, the interpretation of the effects of dTMS on this group of patients with AD is limited because of the possible mediation of mood. Indeed, mood improvements by antidepressants can have beneficial effects on cognition in patients with depression<sup>51</sup> and schizophrenia.<sup>52</sup> However, despite the fact that AD has a high comorbidity of depression,<sup>53</sup> there is currently no sufficient evidence for efficacy of antidepressants in improving cognitive symptoms of patients with AD.<sup>54</sup> Because in the present study depressive symptoms were not measured before and after treatment, a contribution from antidepressant effects of dTMS in the observed cognitive improvements cannot be ruled out. Notwithstanding, in a study using traditional 8-coil rTMS with high-frequency bilateral stimulation of PFC in patients with AD, cognitive improvements were obtained in patients with and without depressive symptoms,<sup>27</sup> suggesting that the effects of rTMS on AD’s cognitive decline may be independent of subjacent depression. As with most studies that use the same evaluation before and after treatment to examine interventional gains, it is plausible that at least part of the observed improvement attributed to treatment may result from practice (having performed the task more than once). In the present study, the scales used have been previously reported to be highly reliable after repetition.<sup>36,43</sup> Nonetheless, to still reduce further risk for a practice effect, the interval between the baseline and posttreatment testing was set to 3 months, which is particularly long for patients with AD, which is essentially characterized by memory deficits. Clearly, many questions regarding the physiological and neuronal mechanisms of this reported improvement remain unclear because no methods were used in the present study to measure potential plasticity changes as a result of treatment. Lack of such measurements prevents us from proposing explanations about the possible neurogenesis mechanisms that might have led to such gains. In the future, connectivity measurements using electrophysiology and imaging could disclose the underlying mechanisms for modulating pathological networks and functional activity by TMS.<sup>55</sup>

## ACKNOWLEDGMENTS

*We would like to thank the patients who gave us their confidence and let us examine their minds and all the therapists in the clinic who helped treating the patients and performed the cognitive testing. We would also like to thank BRAINSWAY for their technical support.*

## REFERENCES

1. Hebert LE, Scherr PA, Bienias JL, et al. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol.* 2003;60:1119–1122.
2. Brookmeyer R, Johnson E, Ziegler-Graham K, et al. Forecasting the global burden of Alzheimer’s disease. *Alzheimers Dement.* 2007;3:186–191.
3. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat Rev Neurol.* 2011;7:137–152.
4. Bekris LM, Yu C-E, Bird TD, et al. Review article: genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol.* 2010;23:213–227.

5. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci.* 2004;5:347–360.
6. Frisoni GB, Fox NC, Jack CR, et al. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol.* 2010;6:67–77.
7. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell.* 2012;148:1204–1222.
8. Francis PT, Palmer AM, Snape M, et al. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry.* 1999;66:137–147.
9. Battaglia F, Wang H-Y, Ghilardi MF, et al. Cortical plasticity in Alzheimer's disease in humans and rodents. *Biol Psychiatry.* 2007;62:1405–1412.
10. Koch G, Di Lorenzo F, Bonni S, et al. Impaired LTP-but not LTD-like cortical plasticity in Alzheimer's disease patients. *J Alzheimers Dis.* 2012;31:593–599.
11. Freitas C, Perez J, Knobel M, et al. Changes in cortical plasticity across the lifespan. *Front Aging Neurosci.* 2011;3:5.
12. Wang L, Zang Y, He Y, et al. Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *Neuroimage.* 2006;31:496–504.
13. Greicius MD, Srivastava G, Reiss AL, et al. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A.* 2004;101:4637–4642.
14. Mangialasche F, Solomon A, Winblad B, et al. Alzheimer's disease: clinical trials and drug development. *Lancet Neurol.* 2010;9:702–716.
15. Hansen N. Brain stimulation for combating Alzheimer's disease. *Front Neurol.* 2014;5:60.
16. Freitas C, Mondragón-Llorca H, Pascual-Leone A. Noninvasive brain stimulation in Alzheimer's disease: systematic review and perspectives for the future. *Exp Gerontol.* 2011;46:611–627.
17. Luber B, Lisanby SH. Enhancement of human cognitive performance using transcranial magnetic stimulation (TMS). *Neuroimage.* 2014;85:961–970.
18. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature.* 2000;406:147–150.
19. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurol.* 2003;2:145–156.
20. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol.* 2001;112:1367–1377.
21. Guse B, Falkai P, Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J Neural Transm.* 2010;117:105–122.
22. Nardone R, Bergmann J, Christova M, et al. Effect of transcranial brain stimulation for the treatment of Alzheimer disease: a review. *Int J Alzheimers Dis.* 2012;2012:687909.
23. Cotelli M, Manenti R, Cappa SF, et al. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *Eur J Neurol.* 2008;15:1286–1292.
24. Devi G, Voss HU, Levine D, et al. Open-label, short-term, repetitive transcranial magnetic stimulation in patients with Alzheimer's Disease with functional imaging correlates and literature review. *Am J Alzheimers Dis Other Demen.* 2014;29:248–255.
25. Bentwich J, Dobronevsky E, Aichenbaum S, et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. *J Neural Transm.* 2011;118:463–471.
26. Nardone R, Tezzon F, Höller Y, et al. Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease. *Acta Neurol Scand.* 2014;129:351–366.
27. Rutherford G, Lithgow B, Moussavi Z. Short and Long-term effects of rTMS treatment on alzheimer's disease at different stages: a pilot study. *J Exp Neurosci.* 2015;9:43–51.
28. Roth Y, Zangen A, Hallett M. A coil design for transcranial magnetic stimulation of deep brain regions. *J Clin Neurophysiol.* 2002;19:361–370.
29. Roth Y, Pell GS, Chistyakov AV, et al. Motor cortex activation by H-coil and figure-8 coil at different depths. Combined motor threshold and electric field distribution study. *Clin Neurophysiol.* 2014;125:336–343.
30. Bersani FS, Minichino A, Enticott PG, et al. Deep transcranial magnetic stimulation as a treatment for psychiatric disorders: a comprehensive review. *Eur Psychiatry.* 2013;28:30–39.
31. Roth Y, Amir A, Levkovitz Y, et al. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *J Clin Neurophysiol.* 2007;24:31–38.
32. Fox MD, Snyder AZ, Vincent JL, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A.* 2005;102:9673–9678.
33. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol.* 2008;21:424–430.
34. Zangen A, Roth Y, Voller B, et al. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol.* 2005;116:775–779.
35. Levkovitz Y, Roth Y, Harel EV, et al. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. *Clin Neurophysiol.* 2007;118:2730–2744.
36. Schweiger A, Doniger GM, Dwolatzky T, et al. Reliability of a novel computerized neuropsychological battery for mild cognitive impairment. *Acta Neuropsychol.* 2003;1:407–413.
37. Thaler A, Mirelman A, Helmich RC, et al. Neural correlates of executive functions in healthy G2019S LRRK2 mutation carriers. *Cortex.* 2013;49:2501–2511.
38. Doniger GM, Dwolatzky T, Zucker DM, et al. Computerized cognitive testing battery identifies mild cognitive impairment and mild dementia even in the presence of depressive symptoms. *Am J Alzheimers Dis Other Demen.* 2006;21:28–36.
39. Sasson E, Doniger GM, Pasternak O, et al. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci.* 2013;7:32.
40. Dwolatzky T, Whitehead V, Doniger GM, et al. Validity of the Mindstreams™ computerized cognitive battery for mild cognitive impairment. *J Mol Neurosci.* 2004;24:33–44.
41. Mioshi E, Dawson K, Mitchell J, et al. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry.* 2006;21:1078–1085.
42. Mathuranath PS, Nestor PJ, Berrios GE, et al. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology.* 2000;55:1613–1620.
43. Yoshida H, Terada S, Honda H, et al. Validation of Addenbrooke's cognitive examination for detecting early dementia in a Japanese population. *Psychiatry Res.* 2011;185:211–214.
44. Rossi S, Hallett M, Group S of TC, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009;120:2008–2039.
45. Ahmed MA, Darwish ES, Khedr EM, et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol.* 2012;259:83–92.
46. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. *QJM.* 2007;100:469–484.
47. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci.* 2007;8:700–711.

48. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron*. 2004;44:195–208.
49. Stern Y. Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20:112–117.
50. Thut G, Pascual-Leone A. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. *Brain Topogr*. 2010;22:219–232.
51. Rosenblat JD, Kakar R, McIntyre RS. The Cognitive Effects of Antidepressants in Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Int J Neuropsychopharmacol*. 2015;pyv082.
52. Singh SP, Singh V, Kar N, et al. Efficacy of antidepressants in treating the negative symptoms of chronic schizophrenia: meta-analysis. *Br J Psychiatry*. 2010;197:174–179.
53. Chi S, Wang C, Jiang T, et al. The prevalence of depression in Alzheimer's disease: a systematic review and meta-analysis. *Curr Alzheimer Res*. 2015;12:189–198.
54. Sepehry AA, Lee PE, Hsiung GY, et al. Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression. *Drugs Aging*. 2012;29:793–806.
55. Fox MD, Halko MA, Eldaief MC, et al. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). *Neuroimage*. 2012;62:2232–2243.