TMS by double-cone coil prefrontal stimulation for medication resistant chronic depression: A case report

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A double-cone coil with large angled windings has been developed to modulate deeper brain areas such as the anterior cingulate cortex (ACC). Abnormal resting state activity in the pregenual ACC (pgACC), dorsal ACC (dACC) and subgenual ACC (sgACC) has been observed in depression. A patient with medication resistant chronic depression received ten sessions of transcranial magnetic stimulation (TMS) (10 Hz, 2000 stimuli/session) using a double-cone coil placed over the supplementary motor area, targeting the anterior cingulate. Source localized EEG recordings were conducted pre- and post-TMS. The Beck Depression Inventory (BDI-II) improved by 27%, and the two subscales of the Hospital Anxiety Depression Scale (HADS), namely depression (40%) and anxiety (33%) improved as well. Along with the clinical improvement eletrophysiological resting state activity changed in the dACC and sgACC in this patient in comparison to a normative group. The results of this case report further support the involvement of pgACC, dACC and sgACC activity in the pathophysiology of depression and indicate that modulation of neural activity in this area by high frequency TMS with a double-cone coil might represent a new promising approach in the treatment of medication resistant chronic depression.

Keywords: Depression; Double-cone coil; TMS; Source localization.

INTRODUCTION

Depressive disorder is the most frequent psychiatric disorder and ranks among the top causes of worldwide disease burden and disability, with lifetime risk of 7–10% in men and 20–25% in women (Ressler and Mayberg, 2007). In many cases depression can be treated efficaciously by standard treatment involving pharmacotherapy and psychotherapy, but in 50–60% recovery is incomplete or patients experience significant side effects and 20% of patients fail to respond to standard interventions (Ressler and Mayberg, 2007). Brain imaging studies have shown structural and functional alterations of the anterior cingulate cortex (ACC) in depression (Mayberg, 1997; Mayberg et al., 1997; Mayberg et al., 2005). Under healthy conditions the ACC interacts with dorsal/cortical and ventral/limbic networks involved in the experience and regulation of emotion (Phillips et al., 2003). A subdivision of the ACC, the dorsal ACC (dACC) projects to the prefrontal cortex and plays...
a critical role in executive functions by influencing multiple cognitive processes (Bush et al., 2000). In contrast, the subgeneual ACC (sgACC), another subdivision of the ACC seems to be involved in emotion experience and processing (Ressler and Mayberg, 2007). Abnormal resting state activity in the dACC and sgACC has been observed in depression (Liotti et al., 2000; Mayberg et al., 1999) and also during induction of sad mood in healthy subjects (Liotti et al., 2000). The pregenual ACC (pgACC) has been implicated in hedonic processing in depression (Walter et al., 2009). Clinical response to treatment has been related to elevated pretreatment theta (4–7Hz) current density in the pgACC (Korb et al., 2008; Korb et al., 2009, 2011; Leuchter et al., 2009).

Improvement of depression is often associated with at least partial normalization of abnormal activation of the anterior cingulate (Holthoff et al., 2004; Mayberg et al., 1999). Over the last decade transcranial magnetic stimulation (TMS) received increasing attention as a potential therapeutic tool for the treatment of depression (Herbsman et al., 2009; Janicak et al., 2010). TMS is a non-invasive tool producing strong pulses of magnetic fields that induce an electrical current in the stimulated region of the brain through the intact scalp. TMS modulates the superficial cortical areas directly but has an indirect effect on remote areas functionally connected to the stimulated area. For the treatment of depression TMS is typically applied with a figure-of-eight coil at high frequencies over the left dorsolateral prefrontal cortex (Herbsman et al., 2009; Janicak et al., 2010). A recent study using positron emission tomography revealed that frontal TMS using a double-cone coil (DCC) can modulate deeper structures such as the dACC and sgACC as well as a number of more distal cortical areas (De Ridder et al., 2011; Hayward et al., 2007; Vanneste et al., 2011) (see Figure 1). In a case report from an alcohol dependent patient fMRI and source localized EEG data confirmed that anterior cingulate stimulation with the DCC TMS indeed modulates the dorsal and sgACC (De Ridder et al., 2011). Also a moderate transient improvement of tinnitus has been demonstrated after a single session of low frequency DCC TMS (Vanneste et al., 2011).

Given the involvement of ACC in depression (Liotti et al., 2000; Mayberg et al., 1999) modulation of ACC activity by frontal TMS with a double-cone coil could potentially represent a new treatment approach for depression. Hence, the aim of this case study is to determine the extent to which high frequency frontal TMS with a double-cone coil can modulate depression. Secondly, the objective of the present study was to verify the neurophysiological differences between pre-TMS and post-TMS using source localized resting state EEG recordings. Quantitative analysis of EEG is a low-cost and useful neurophysiological approach to the study of brain-related physiology and pathology (Babiloni et al., 2006). Cortical sources of the EEG rhythms were estimated by standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002). sLORETA is a functional imaging technique estimating maximally smoothed linear inverse solutions accounting for distributed EEG sources within MNI space (Pascual-Marqui, 2002). This feature is of special importance for the comparison of EEG results with those of most structural and functional neuroimaging studies.
CASE STUDY

A 46-year-old married man presented at the Brain neuromodulation clinic with a major depressive disorder since 1994. The diagnosis was confirmed by a psychiatrist and the Dutch version of the Beck Depression Inventory (BDI-II) (Beck et al., 1988; Bouman, 1985) revealed a score of 34. The patient did not report any co-morbidities. Multiple treatments have been attempted, but none of them resulted in longer lasting improvement. Behavioral treatment (outpatient individualized sessions and group sessions) and inpatient treatment in a general hospital as well as a specialized psychiatric hospital all yielded only a temporary improvement. The current pharmacotherapy consisted of paroxetine, tradonal, alprazolam. A large variety of different antidepressants has been used in the past without any improvement. During the rTMS treatment the patient’s jobs status (unemployed), as well as family life was relatively stable and no relevant life events occurred. The study has been approved by the Antwerp University Hospital IRB (“Comité voor medische ethiek”).

TMS has been performed by using a super rapid stimulator (Magstim Inc, Wales, UK) with a double-cone coil (DCC) (P/N 9902-00; Magstim Co. Ltd) placed over the medial frontal cortex (1.5 cm anterior to 1/3 of the distance from the nasion-inion) (Hayward et al., 2007). The motor threshold, assessed with a figure-of-eight coil was 65%. TMS was performed at a frequency of 10 Hz and with an intensity of 40% of the maximal machine output, because higher intensities were not tolerated. Ten sessions spread over two weeks were applied with 2000 stimuli/session (20 trains of 10 seconds duration and an inter-train interval of .5 seconds). During the TMS sessions the patient was not medicated and was requested not to seek any other kind of therapy during the interval between sessions. This was verified in the medical record of the patient as well as double checked by asking the patient.

Depressive symptoms were assessed before and after TMS treatment by using the validated Dutch versions of the Beck Depression Inventory (BDI-II) (Beck et al., 1988; Bouman, 1985). The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. Higher total scores indicate more severe depressive symptoms. The validation of the Dutch version revealed the following cutoffs: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Also the Hospital Anxiety Depression Scale (HADS) was assessed (McCue et al., 2006). The HADS is designed to provide a simple yet reliable tool in medical practice (Zigmond and Snaith, 1983) and is considered as a measure of general distress (Grulke et al., 2005; McCue et al., 2006; Robjant et al., 2009). This scale consists of 14 questions, 7 measuring anxiety (score from 0–21), and 7 measuring depression (score from 0–21). Each question was rated on a 4-point scale (0, 1, 2, 3). Furthermore, scores of 11 or more on either subscale are considered to be a significant “case” of psychological morbidity, while scores of 8–10 represent “borderline” and 0–7 “normal” (Zigmond and Snaith, 1983). We included the HADS next to the BDI-II to confirm the results for depression as well as have an additional measure for anxiety. In addition the Profile of Mood State (POMS) (Wald and Mellenbergh, 1990) was collected. The POMS consists of 32 items of mood descriptors (e.g. sad). The items are rated on a five-point scale starting from 0 indicating a low level (“not at all”) up to 4 indicating a high level (“extremely”) to evaluate the current feelings. It measures five co-varying mood-factors (depression-rejection, anger-hostility, fatigue-inertia, vigor-activity and tension-anxiety). These questionnaires were assessed immediately before and after the TMS sessions.

EEG recordings were obtained in a quiet and dimly lighted room with the patient sitting upright on a small but comfortable chair. The patient received a resting state EEG immediately before and after the TMS sessions. Each recording lasted approximately 5 minutes. The EEG was sampled with 19 electrodes (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1 O2) in the standard 10-20 International placement referenced to linked ears. Impedances were checked to remain below 5 kΩ. Data were collected eyes-closed (sampling rate = 1024Hz, band passed 0.15–200Hz). Data were resampled to 128 Hz, band-pass filtered (fast Fourier transform filter) to 2–44 Hz and subsequently transposed into Eureka! Software (Congedo, 2002), plotted and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movement, or ECG artifacts were removed from the stream of the EEG. Average Fourier cross-spectral matrices were computed. Standardized low-resolution brain electromagnetic tomography (sLORETA) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity.
in each of the eight frequency bands: delta (2–3.5 Hz), theta (4–7.5 Hz), alpha (8–12 Hz), beta1 (12.5–18 Hz), beta2 (18.5–21 Hz), beta3 (21.5–30 Hz) and gamma (30.5–50 Hz). sLORETA computes electric neuronal activity as current density (A/m²) without assuming a predefined number of active sources. The sLORETA solution space consists of 6,239 voxels (voxel size: 5 x 5 x 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. The sLORETA data were compared with an aged and gender-matched normative database of the Brain Research Laboratories (BRL), New York University. This normative database does not include people with psychiatric or neurological illness, a history of psychiatric disease (including drug/alcohol abuse) in a participant or any relative, current psychotropic/CNS active medications, a history of head injury (with loss of consciousness) or seizures, headache, physical disability. About 3–5 min of EEG was continuously recorded while the participant sat with the eyes closed on a comfortable chair in a quiet and dimly lighted room. EEG data were acquired at the 19 standard leads prescribed by the 10–20 international system (FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, O2) using both earlobes as reference and enabling a 60 Hz notch filter to suppress power line contamination. The resistance of all electrodes was kept below 5 kΩ. For consistency, we subsequently resampled the BRL database to 128 Hz using a natural cubic spline interpolation routine (Congedo, 2002). We removed from all data biological, instrumental and environmental artifacts, paying particular attention to biological artifacts generated by the eyes, the heart and the muscles of the neck, face and jaw. EEG recordings were visually inspected on a high-resolution screen and epochs containing visible artifacts were marked and ignored for ensuing analysis.

Standardized low-resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002) was used to estimate the intracerebral electrical sources that generated the scalp-recorded activity in each of the seven frequency bands. sLORETA computes electric neuronal activity as current density (A/m²) without assuming a predefined number of active sources. The sLORETA solution space consists of 6,239 voxels (voxel size: 5 x 5 x 5 mm) and is restricted to cortical gray matter and hippocampi, as defined by the digitized Montreal Neurological Institute probability atlas. To reduce confounds that have no regional specificity, such as total power inter-subject variability, a global normalization of the sLORETA images was carried out prior to statistical analyses. sLORETA was used to compare pre- and post-treatment EEG. Moreover a comparison was made between the patient and age/gender-matched subjects of the BRL both before and after rTMS treatment. The results are corrected for multiple comparisons.

**RESULTS**

The TMS treatment was well tolerated and no side effects were reported. A comparison of the different questionnaires showed a decrease after TMS on the BDI-II of 27%, and the two subscales of the HADS, namely depression (40%) and anxiety (33%). For the POMS, we found a decrease in the subscales tension of 45%, for depression 24%, and fatigue 44% after TMS in comparison to pre-TMS. We also found an increase in Power after TMS of 100%. Scores of all questionnaires before and after treatment are given in table 1.

The sLORETA comparison between pre- and post-TMS revealed a significant increase in alpha activity in the pgACC after treatment (see Figure 2). In comparison to the normative database alpha and gamma activity were significant decreased in the pgACC before TMS treatment (see Figure 3). Post-TMS this pattern normalized and an increase was noted in the dACC for alpha and gamma in comparison to the control group. Also a significant decrease was shown in the sgACC for beta activity in the patient in comparison to the control group.

**TABLE 1**

<table>
<thead>
<tr>
<th>Differences in Questionnaires Pre- and Post-TMS</th>
<th>Pre-TMS</th>
<th>Post-TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td>34</td>
<td>25</td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>POMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>Depression</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Anger</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Power</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 2. A comparison between the patient's source analyzed current densities before and after DCC TMS revealed a significant increase (p < .05) in alpha activity in the dorsal anterior cingulate cortex.

Figure 3. A comparison between the patient's source analyzed current densities for alpha, beta and gamma band activity and a control group (BRL normative database) before and after TMS. A significant decrease in activity was present Pre-TMS in the dorsal anterior cingulate cortex, both for alpha (Z = -8.47) and gamma (Z = -3.95) in the patient in comparison to the control group. Post-TMS a significant increase was revealed the dorsal anterior cingulate cortex for alpha (Z = 4.38) and gamma (Z = 4.51) for the patient in comparison to the control group. Also a significant decrease was shown in the subgenual anterior cingulate cortex for beta activity (Z = 5.32) in the patient in comparison to the control group.

DISCUSSION

The reported case suggests that DCC TMS placed over the medial frontal cortex can exert an antidepressant effect by modulating activity in the dACC and the pgACC. The antidepressant effect of DCC TMS treatment was reflected by meaningful and clinically relevant reductions of BDI-II, HADS and POMS scores after treatment. These improvements on the questionnaires suggest that the patient has an improvement due to benefit clinically from the DCC TMS treatment. EEG measurements before and after TMS revealed that during treatment the initially reduced alpha and gamma activity in the dACC increased and beta activity in the sgACC decreased. This was further confirmed by directly comparing pre- versus post-TMS. This latter analysis revealed a significant increase in alpha activity after TMS in the pgACC.

Our findings indicate an involvement of the subdivisions of the ACC (pgACC, dACC and sgACC) in this patient's depression and underscore the
relevance of these areas as targets for the treatment of depression. Previous studies already demonstrated that TMS with a figure-of-eight coil over the left dorsolateral prefrontal cortex (DLPFC) modulates the blood flow in the ACC (Paus and Barrett, 2004). Activity in the ACC has also been identified as a predictor for treatment response to high frequency TMS over the DLPFC (Langguth et al. 2007). Positron emission tomography (PET) in combination with left frontal TMS demonstrated that TMS at 1 Hz inhibits cortical excitability, whereas high frequency TMS (10 Hz) enhances cortical excitability (Speer et al., 2009; Speer et al., 2000). In our study ten sessions of high frequency TMS placed over the medial frontal cortex with a double-cone coil resulted in specific changes of brain activity in the dACC and in the sgACC. It is known that TMS can alter regional cerebral blood flow (rCBF) both in the directly stimulated brain areas and in functionally connected areas (Speer et al., 2000). It has been shown that there exists a functional connectivity between the dACC and sgACC (Margulies et al., 2007), permitting network changes induced by TMS. Deep brain stimulation targeting just below the subthalamic nucleus (Bejjani et al., 1999) is capable of improving treatment resistant depressive symptoms as well as an increasing activity in the dACC, while decreasing activity in the sgACC after stimulation as evaluated with PET (Mayberg et al., 2005). Even if direct comparison between brain activity changes detected with PET and EEG is difficult, our data suggest a comparable pattern of activity changes after DCC TMS placed over the medial frontal cortex. All results obtained were found in the alpha, beta and gamma frequency bands. Severe distress such as in post-traumatic stress disorder (i.e., the most serious TMS-related acute adverse effect) has been extremely rare, with most of the few new cases receiving TMS exceeding previous guidelines, often in patients under treatment with drugs which potentially lower the seizure threshold (Rossi et al., 2009). This report warrants further studies of DCC TMS for the treatment of depression.

In summary the clinical results in combination with the neuroimaging findings suggest that modulating pgACC, dACC and sgACC activity by DCC TMS placed over the medial frontal cortex might represent a new promising approach in the treatment of medication resistant chronic depression and warrant further exploration with placebo-controlled studies in larger samples. However, further long-term follow-up results are necessary to explore this approach as a promising treatment for depression.

The findings of this first case report suggest that DCC TMS might become a novel method for the treatment of depression. These findings corroborate with previous results that showed that a TMS with a figure-of-eight coil over the left dorsolateral prefrontal cortex was effective in treating major depression with minimal side effects reported (O’Reardon et al., 2007). In this case report the patient reported no side effects. Thousands of healthy subjects and patients with various neurological and psychiatric diseases have undergone TMS allowing a better assessment of relative risks. The occurrence of seizures (i.e., the most serious TMS-related acute adverse effect) has been extremely rare, with most of the few new cases receiving TMS exceeding previous guidelines, often in patients under treatment with drugs which potentially lower the seizure threshold (Rossi et al., 2009). This report warrants further studies of DCC TMS for the treatment of depression.
REFERENCES


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