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Desirée Spronk, Martijn Arns, Aukje Bootsma,  
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## Key Words

Depression

Dorsolateral Prefrontal Cortex

Event-Related Potential

QEEG

Repetitive Transcranial Magnetic Stimulation

Treatment

## ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) treatment for depression has been under investigation in many controlled studies over the last 20 years. Little is known about the neurobiological action of rTMS in patients. We therefore investigated pre- and post-treatment effects on QEEG, ERP's and behavior (BDI and NEO-FFI).

rTMS treatment was applied in 8 subjects for an average of 21 sessions to the left Dorsolateral Prefrontal Cortex (left DLPFC). Clients were assessed on a QEEG and Oddball ERP evaluation pre- and post-treatment. Clients were stimulated over the left DLPFC with 10 Hz rTMS (100% MT). Furthermore, rTMS treatment was complimented by psychotherapy.

All subjects showed full remission within 20 sessions and there was a significant reduction in depressive symptomatology (BDI score) after 10 and 15 sessions and a clear decrease in the Neuroticism and an increase on the extraversion scale of the NEO-FFI personality questionnaire. Pre- and post-QEEG measurements did not reveal treatment specific effects, but only an indirect right frontal increase in delta power. On the other hand, ERP measures did reveal treatment specific effects by showing an increased positivity in the post-treatment ERP's specifically left frontal. The P2 amplitude demonstrated a significant left frontal increase in amplitude, whereas for the negative N1 and N2 a significant decrease in amplitude was observed.

The results of this pilot study demonstrate that rTMS can be a safe and efficacious treatment modality for depression. Furthermore, a specific left frontal increase in positivity for the ERP's was found (increased P2 and decreased N1 and N2 components) most likely related to the rTMS over the left DLPFC. Furthermore, there was no change in the alpha asymmetry lending support to the fact that frontal alpha asymmetry can be considered a trait marker for depression. The findings from this pilot study require future replication with larger sample sizes.

## INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method to stimulate the brain.<sup>1</sup> A growing body of research on its therapeutic effects has demonstrated that rTMS can be seen as an effective and safe new treatment in depression.<sup>2-4</sup> Despite this extensive body of research demonstrating the clinical effectiveness of rTMS treatment for depression, neurophysiological correlates of outcomes related to rTMS treatment have rarely been investigated.

Application of rTMS in depressed patients usually employs one of two different protocols; either the patients receive high frequency (>5 Hz) stimulation on the left dorsolateral prefrontal cortex (DLPFC) or receive low frequency ( $\leq 1$  Hz) over the right DLPFC.<sup>5</sup> Imaging studies have demonstrated deviant activation/ perfusion in the left dorsolateral cortex in depression<sup>6</sup> as well as changes in right DLPFC<sup>7</sup> which explains the rationale behind the reported stimulation sites. Evidence from human neuroimaging studies shows that rTMS stimulation induces metabolic alterations at the site of stimulation<sup>8,9</sup> and also at additional other regions in the brain.<sup>10</sup>

Electroencephalography (EEG) is a well known and widely used technique for the visualization of brain activity. It has been suggested that the EEG power spectrum might be used as a neurophysiological measure in examining the effects of a specific stimulation protocol as well as for evaluating the physiological outcomes of stimulation protocols.<sup>11</sup> A small number of studies have been performed that examined the effect of rTMS on EEG power measures with differing results.<sup>12,13</sup> However, these studies examined transient changes in the EEG power spectra following one rTMS session and did not take into account long-term treatment effects on the EEG.

In this study a different approach has been taken. Instead of examining short-term effects of rTMS treatment, long-term neurobiological manifestations in the EEG power spectra were examined. It was demonstrated that increased cerebral perfusion correlates with increased EEG power in the higher beta frequency bands.<sup>14</sup> Since it has been shown that rTMS induces an increase in cerebral perfusion<sup>8</sup> and assuming that successful treatment of depression manifests itself in a normalization of the frequently reported hypoperfusion of the left frontal cortex in depression, we predicted that high frequency rTMS stimulation at the left DLPFC would cause an increase in the EEG beta power and a decrease in the alpha power band relative to the pretreatment assessment. This hypothesis is also in line with studies demonstrating increased left frontal alpha relative to the right frontal cortex<sup>15,16</sup> in depression.

In addition to neuropsychological test measures, event-related potentials (ERPs) are often reported as neurophysiological reflections of cognitive functioning. ERPs measure the response of the brain to a particular stimulus. They are obtained by averaging EEG activity on the basis of a time locked recurring event, such as an auditory stimulus a subject has to respond to while ignoring other stimuli. The most frequently reported ERP component in psychiatric research is the P3, which is a positive potential with an amplitude of around 10 to 20 mV and

From Brainclinics Diagnostics B.V. (D. Spronk, M. Arns); Brainclinics Treatment B.V. (M. Arns, A. Bootsma, R. van Ruth), Nijmegen, The Netherlands; and Alfred Psychiatry Research Centre, The Alfred and Monash University School of Psychology, Psychiatry and Psychological Medicine (P. B. Fitzgerald), Melbourne, Australia.

Address requests for reprints to Drs. Desirée Spronk, Brainclinics Diagnostics B.V., Toernooiveld 100, 6525 EC Nijmegen, The Netherlands.

Email: [desiree@brainclinics.com](mailto:desiree@brainclinics.com)

a latency of about 300 ms.<sup>17</sup> The P3 (often also referred to as P300) is often associated with learning processes.<sup>18</sup> In particular, the P3 *latency* possibly reflects the time needed to determine the significance of a certain stimulus, while the P3 *amplitude* is correlated with psychological variables such as expectancy, attention and meaning of the stimulus.<sup>19</sup>

Deviations in the P3 also seem to be specifically associated with depression.<sup>20,21</sup> Many studies have reported a smaller P300 *amplitude*<sup>22</sup> in patients with depression while others have reported a prolonged P300 *latency* in depression.<sup>23,22</sup> Himani et al.<sup>23</sup> found a delayed P300 response in patients with major depression as compared to normal controls. In contrast, in a study by Vandooleaghe<sup>21</sup> a higher P2 amplitude was found in a group of major depressed subjects as compared to normal volunteers. The current study was also designed to obtain pre- and post-rTMS treatment measures of the P3 and P2. From the studies above it was expected that after completion of the treatment, patients would demonstrate more normalized ERP measures; e.g., the P3 latency will be shortened and the P3 and P2 amplitude will be increased relative to the pre-treatment assessment. More specifically, because patients will receive a left-sided stimulation protocol, these effects are expected to predominantly occur in the left frontal hemisphere. Because of the exploratory nature of this study the results of the N1 and N2 amplitude and latency will be analyzed as well.

## METHODS

### Design

This study was based on a naturalistic ongoing study and we report data from the first eight patients undergoing rTMS treatment in our program under this protocol. Patients' individual EEGs were screened for the presence of focal beta spindles at F3 (beta spindles exceeding 20  $\mu$ V peak-to-peak amplitude<sup>17</sup>) or the presence of paroxysmal EEG activity which served as exclusion criteria. Patients received left frontal rTMS at 10 Hz.

### Participants

Participants were 8 patients (5 male, mean age 42.6 yrs., range 28-50 yrs) with a diagnosis of major depressive disorder (MDD). Patients were screened for major depression by a clinical psychologist using the Beck Depression Inventory (BDI) and a structured interview (M.I.N.I. Plus Dutch version 5.0.0, sections Depressive episode, Dysthymia, Suicide, Manic episode, Alcohol Dependence & Abuse and Mixed Anxiety/Depressive disorder) during intake. Three clients were on medication and 1 client was using St. Johns Worth during the course of treatment and 4 patients were free of medication during the course of treatment.

All participants were asked to refrain from caffeine or nicotine intake for at least 2 hours prior to testing. All patients signed a written informed consent form prior to testing.

### Pre- and post-assessments: QEEG, ERPs and NEO-FFI personality questionnaire

Participants were seated in a sound and light attenuated room, controlled at an ambient temperature of 22°C. EEG data were acquired from 26 channels: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz and O2 (Quikcap; NuAmps; 10-20 electrode international system). Data were referenced to averaged mastoids with a ground at Fpz. Horizontal eye movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow and 1.5cm below the middle of the left bottom eyelid. Skin resistance was < 5 K Ohms and above 1K Ohm

for all electrodes. A continuous acquisition system was employed and EEG data were EOG corrected offline. The sampling rate of all channels was 500 Hz. A low pass filter with attenuation of 40dB per decade above 100 Hz was employed prior to digitization.

The auditory event-related potential was measured during an auditory oddball task. During EEG recording patients were exposed to a series of high and low pitched tones. They were asked to press a button with their left and right index finger in response to the high pitched tone, while keeping their eyes fixed on a red dot presented on a computer screen in front of them. Subjects were asked to sit quietly. In this study we are interested in the N1, P2, N2 and P3. Additionally clients also filled out a NEO FFI personality<sup>24</sup> questionnaire prior to the QEEG assessment.

### rTMS Treatment

rTMS sessions were administered using a Magstim Rapid<sup>2</sup> (Magstim Company, Spring Gardens, UK) stimulator with a figure-of-8 coil (70 mm diameter). Patients received magnetic stimulation at 10 Hz over the left dorsolateral prefrontal cortex 5 cm anterior to the motor cortex area of the musculus abductor pollicis brevis at 100% of the motor threshold (20 trains of 5 second duration separated by 40 s). Furthermore, rTMS treatment was complimented by cognitive behavior psychotherapy by a skilled psychologist. Becks Depression Inventory (BDI) scores were assessed during intake and after every fifth session, to track progress of treatment. The total number of sessions was determined by the clinical course of the patient and varied from 15 to 25 sessions. The decision rule to stop treatment was 1) a minimum of 15 sessions, 2) a >50% decrease of depressive symptoms on the BDI for 5 consecutive sessions which was considered a positive response after which treatment was terminated.

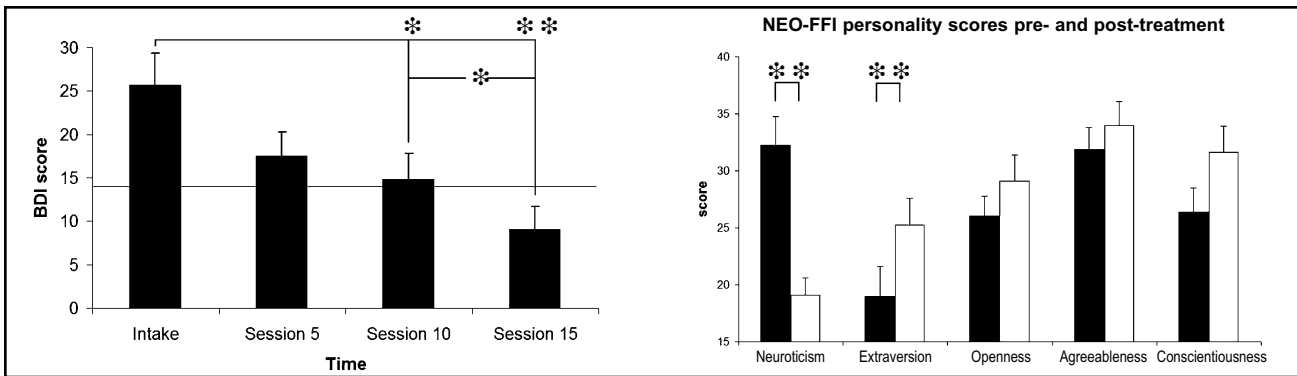
### Data analysis

ERP analysis: The single-trial epochs to target and background stimuli from the auditory oddball paradigms were filtered with a low-pass Tukey (cosine taper) filter function that attenuated frequencies above 25 Hz. These epochs were then averaged to form conventional ERPs. In this study only ERPs to target stimuli were investigated. The amplitude and latency of the, N1, P2, N2 and P3 component were identified. Missing values were replaced by values of the average of two nearby frontal electrodes. When these were also missing, the subject was excluded from analyses of this component.

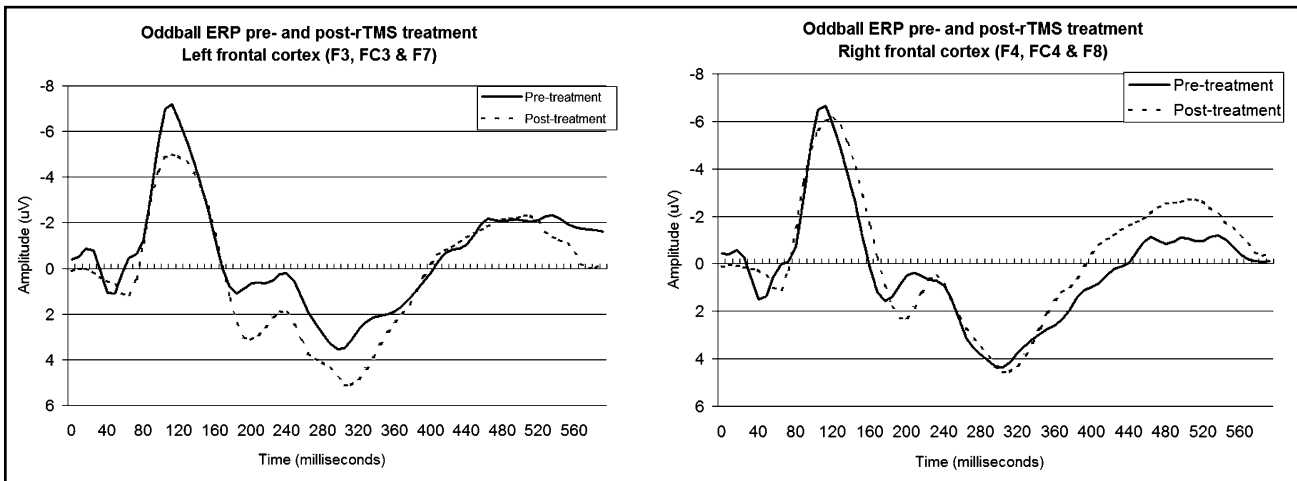
Average power spectra were computed for the eyes open and eyes closed paradigms. The 2 minutes of EEG in each paradigm were first divided into adjacent intervals of 4 seconds. Power spectral analysis was performed on each 4 second interval by first applying a Welch window to the data and then performing a Fast Fourier Transformation (FFT). The resulting power spectra were then averaged for each electrode position in each of the two paradigms over the following frequency bands: alpha 1 (8-11 Hz), alpha 2 (11-13 Hz), beta 1 (14.5-20 Hz), beta 2 (20-25 Hz), beta 3(25-30 Hz), theta 1 (4-5 Hz), theta 2 (5-7.5 Hz) and delta (1.5-3.5 Hz) band. This data was then square-root transformed to approximate the normal distributional assumptions required by parametric statistical methods.

### Statistical analysis

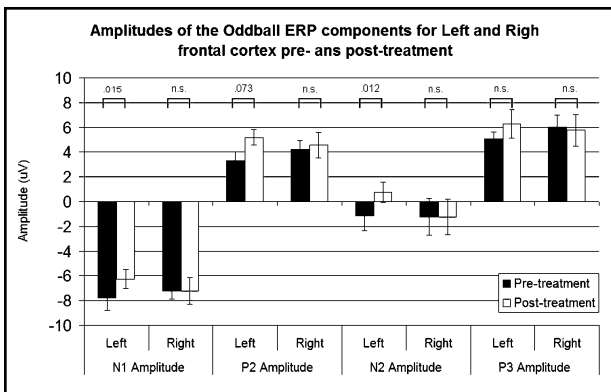
Differences between the BDI scores over sessions, the NEO-FFI questionnaire as well as differences between pre- and post-assessment and left and right hemisphere on ERP and EEG power variables were analyzed using the Statistical Package for Social Science (SPSS v. 16). For the BDI scores, a repeated measures ANOVA was computed with Time (4 levels) as within subject factor.



**Figure 1.** Mean BDI scores administered at intake, session 5, session 10 and session 15 (left) and mean scores on the Neo-FFI personality questionnaire administered pre- (black) and post- (white)-treatment. The displayed personality traits are Neuroticism, Extraversion, Openness, Agreeableness and Conscientiousness. Error bars represent SEM and the horizontal line at 13 indicates the cut-off point of the BDI scale (\*:  $p < .01$ ; \*\*:  $p < .001$ ).



**Figure 2.** This figure shows the average raw ERP waveforms for the left frontal cortex (F3, FC3 and F7) and the right frontal cortex (F4, FC4 and F8) for pre- and post-treatment. Note the specific increased positivity in the P2, N2 and P3 components for the left frontal cortex only.

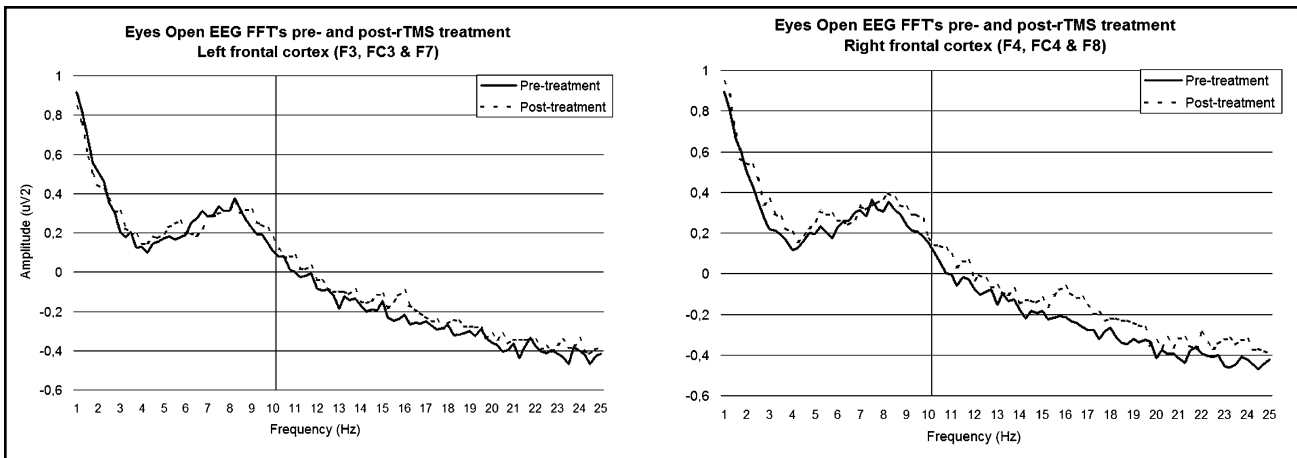


**Figure 3.** This figure shows the different ERP component amplitudes for the right and left hemisphere and the pre- and post-treatment changes. Note that consistently for the left frontal sites there are pre- and post-treatment changes (increased positivity) whereas for the right ERPs amplitudes are more comparable. Error bars represent SEM, numbers indicate p-value and n.s. = not significant.

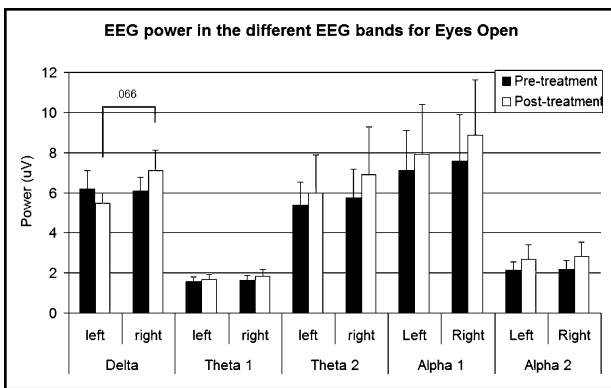
Post-hoc paired t-tests were performed in case of significant main effect. Each subscale of the NEO-FFI questionnaire was separately analyzed by means of a paired t-test.

For analyses on the amplitudes and latencies of the selected ERP components and the EEG power measures repeated measures ANOVAs were computed separately for each component and frequency band. Time (pretest/post) and hemisphere (left/right) were taken as a within-subject factor in each of the analyses. For the ERP components and EEG power measures the left – right comparisons were performed by means of averaging across three frontal electrode sites. Analyses on the left hemisphere were based on including F3, FC3 and F7. Analyses on the right hemisphere were based on including F4, FC4 and F8. The left-sided selected electrodes represent the area of stimulation since using the 5-cm anterior rule the site of stimulation is mostly posterior to F3, hence in the triangle of electrodes F3, F7 and FC3. The right-sided electrodes are their ipsilateral counterparts.

Given the small number of patients in this study and the exploratory nature of this study significances of  $p < 0.1$  will be reported together with the partial eta-squared value.



**Figure 4.** This figure shows the EEG FFT waveforms for eyes open for the left and right frontal cortex. Note the slight increase in the alpha 2 power band for both sides. The vertical line depicts the 10 Hz frequency as a frame of reference. Also note that for both sides and both pre- and post-treatment the alpha peak frequency is rather slow (normally the alpha peak should be around 10 Hz).



**Figure 5.** This figure shows the EEG power changes between pre- and post-treatment for both right and left frontal areas during eyes open. Note the non-specific overall change in theta and alpha power for both right and left frontal cortex further evidenced by a lack of significant interaction effects. Also note the post-treatment increased right-frontal delta power ( $p=.066$ ).

**RESULTS**

**Behavioral data**

Figure 1 shows the mean depression score (BDI) at each point of administration and the pre- and post-treatment differences on the NEO FFI personality questionnaire. BDI scores are only reported up-to session 15, since all patients filled out the BDI to session 15, and only few on sessions 20 and 25 which would otherwise bias the results. The repeated measures ANOVA on the BDI scores yielded a significant effect of time ( $F(3,5) = 10.093, p < 0.015$ ). Post-hoc paired t-test showed that patients demonstrated a significant improvement from intake to session 10 ( $t = 3.876, p < .006$ ), from intake to session 15 ( $t = 5.959, p < .001$ ) and from session 10 to session 15 ( $t = 4.004, p < .005$ ). All clients showed full remission at the end of therapy with BDI scores lower than 13 with an average 20.88 of sessions (range 16 to 25 sessions).

Paired t-tests on each of the NEO-FFI personality traits showed that patients had a significant decrease on the neuroticism scale ( $t =$

5.115,  $p = .001$ ) and a significant increase on the extraversion scale ( $t = -4.944, p = .002$ ) after treatment.

**Event-related potentials**

The grand average ERPs at left frontal and right frontal sites pre- and post-treatment are shown in Figure 2 and the differences in pre- and post-treatment ERP amplitudes can be found in Figure 3.

The repeated measures on the N1 amplitude revealed a significant interaction effect of time and hemisphere ( $F(1,7) = 5.893, p = .046$ , partial eta squared = .457). In the left hemisphere, the N1 amplitude at the pre-assessment was larger compared to the post-assessment (-7.813 vs. -6.261  $\mu V, t = -3.190, p = .015$ ), whereas at the right hemisphere the difference between N1 amplitude at the pre- and post-assessment were not significant (-7.216 vs. -7.224  $\mu V$ ). For the N1 latencies no significant effects were found.

For the P2 amplitude there was a marginal significant hemisphere x time interaction effect ( $F(1,7) = 4.719, p = .066$ , partial eta squared = .403). Within the left hemisphere the P2 amplitude at the post-condition is significant larger as compared to the pre-condition (3.304 vs. 5.191  $\mu V, t = -2.111, p < .073$ ), whereas within the right hemisphere there are no significant differences between pre- and post-assessment to be seen (4.241 vs. 4.566  $\mu V$ ). No significant interaction effect at P2 latencies was found.

Analyses on the N2 amplitude also revealed a significant hemisphere x time interaction ( $F(1,7) = 8.835, p = .021$ , partial eta squared = .558). Within the left hemisphere there was a relatively big difference between N2 amplitude pre- and post-treatment ( $t = -3.393, p = .012$ ). N2 amplitudes at pre-treatment were much more negative compared to the N2 at post-treatment (-1.161 vs. 0.742  $\mu V$ ). But within the right hemisphere the N2 amplitude was comparable (-1.237 vs. -1.246  $\mu V$ ). Again, no significant interaction on N2 latencies could be demonstrated.

The repeated measures ANOVA on the P3 amplitude also revealed a marginal significant interaction effect between time and hemisphere ( $F(1,7) = 4.409, p = 0.074$ , partial eta squared = .386). A similar effect as for the P2 amplitude was found, the P3 amplitude within the left hemisphere was larger post-treatment compared to pre-treatment, while this effect for the right hemisphere was absent. However, post-

hoc test did not reveal any significant effects. Also, no significant interactions between hemisphere and time was found for P3 latency.

#### EEG measures

Separate repeated measures ANOVAs were computed for each of the predetermined frequency bands for the eyes open as well as for the eyes closed condition. Figure 4 displays the EEG power spectra for Eyes Open for both right and left frontal cortex. For the EEG beta bands no significant differences were found and are hence not reported. The slight increase seen in Figure 4 was mainly due to 1 subject exhibiting more EMG on the post-assessment.

In the alpha 1 band a marginal significant effect was observed for hemisphere ( $F(1,7) = 4.293, p = .077$ , partial eta squared = .380). Overall the alpha 1 power at the right frontal hemisphere was higher in comparison to the left frontal side. The analyses on the alpha 2 band yielded a marginal significant increase of alpha 2 power at the post-treatment assessment ( $F(1,7) = 3.737, p = .094$ , partial eta squared = .348). No significant time x hemisphere interactions were observed for the alpha eyes open measures.

Marginal significant effects were also observed for hemisphere at the theta1 frequency band eyes open as displayed in Figure 4. Theta 1 power was higher at the right hemisphere as compared to the left ( $F(1,7) = 4.140, p = .081$ , partial eta squared = .372). Again, no significant interaction effects were found. No significant effects were found for the theta 2 band.

For the delta band in the eyes open condition, we found a trend towards a significant interaction effect between hemisphere and time ( $F(1,7) = 4.119, p = .082$ , partial eta squared = .370, see Figure 5). Delta power measures between left and right hemisphere at pre-treatment did not differ ( $t = .513, p = .624$ ) while within the post-treatment measures the delta power was increased in the right hemisphere as compared to the left hemisphere ( $t = -2.175, p = .066$ ).

For the eyes closed condition alpha 1, alpha 2, theta 1, theta 2 and delta power measures were analyzed by means of a repeated measures ANOVA as well. For the alpha 1 and alpha 2, theta 2 and delta power measures, no significant effects on each of variables, nor interaction effects were observed. Theta 1 power measure post-treatment was significant lower as compared to pre-treatment  $F(1,7) = 4.673, p = .067$ , partial eta squared = .400). No significant interaction effect were found at the theta 1 band.

## DISCUSSION

### Behavioral data

This study demonstrates that 10 Hz left-sided rTMS therapy combined with psychotherapy results in highly significant improved clinical outcomes as evidenced by the BDI and the NEO-FFI. The eight patients showed a significant gradual improvement over time in depressive symptomatology as measured with the BDI, with all patients showing full remission within 21 sessions. Furthermore, this group did show a significant reduction in neuroticism and an increase on the extraversion scale of the big five personality questionnaire (NEO-FFI).

Since clients were treated using a combination of rTMS and psychotherapy it is hard to differentiate between the clinical effects from the psychotherapy versus the rTMS. Given the very beneficial response of full remission within 20 sessions and previous studies reporting clear antidepressive effects of left frontal rTMS<sup>2,5,4</sup> together with the specific normalization of the oddball ERP's in only the left frontal cortex, it is very likely that rTMS had a significant contribution to these clinical effects. In comparison, common reported remission rates for psychotherapy with or without the combination of medication are in

the range of 30-50%.<sup>25</sup> The investigated patients in this study are the first 8 patients who were treated with the exact same parameters and are part of ongoing treatment in our clinic. Future analysis on more of our clients and 6-month follow-up is needed to demonstrate that this effect is sustained over time and whether these high remission rates are a coincidence or real effects.

The physiological measures pre- and post-treatment, discussed below, try to provide more insight into the neurophysiological treatment effects.

### ERP data

To our knowledge, this is the first study that compared the effects of rTMS treatment in depression on pre- and post-treatment ERP assessments. In the present study we found clear interaction effects between hemisphere and time for the N1, P2 and P3 amplitudes. Although these effects were frequently not significant at a  $p < 0.05$  level, the N1, N2, P2 and P3 amplitudes consistently demonstrated differences between the pre- and post-assessment within the left hemisphere, but not within the right hemisphere. As can be seen clearly in Figure 2 this can be explained by an increased positivity for these components for left frontal sites only. Given their consistency, these effects would seem to be likely to reach significance given a larger sample size.

For the N1 and N2 a decrease, whereas for the P2 and P3 components an increase in amplitude was observed. From the examined ERP components, deviations of the P3 in depression have been most extensively examined.<sup>23,22</sup> They uniformly demonstrate a decreased P3 and P2 amplitude and a prolonged P3 latency measured in depression as compared to controls. To the author's knowledge only one study has examined the effect of rTMS treatment on P3 amplitude and latency,<sup>26</sup> in which it was reported that left frontal rTMS treatment was associated with a significant increase in the P3 amplitude and latency. With regard to P3, there was a tendency towards a site specific effect on the P3 amplitude within the left hemisphere. Moreover, the fact that this effect was observed at the left hemisphere indicates that it was likely caused by the rTMS stimulation. However, post-hoc t-tests could not demonstrate a significant effect which illustrates the need for further studies with larger sample sizes. No differences were found on P3 latency. For the P2 amplitude on the other hand, an increased P2 amplitude at the post-treatment assessment was observed which is in contrast with previous published literature<sup>21</sup> in which depression was associated with an increased P2 amplitude. The relation between the N1, N2, components and depression is less clear and is therefore difficult to relate to previous studies. It can also be questioned whether an interpretation based on ERP components is valid, given that these effects can be better explained by an increased positivity for all components (hence reduced N components and increased P components) in terms of Slow Cortical Potentials (SCPs). In these terms increased positivity could reflect a state of low excitability<sup>27-29</sup> or a reflection of inhibitory processes.<sup>29</sup> Hence the site specific increase at the left hemisphere suggests that the obtained effect was caused by rTMS treatment. Further research is needed to replicate and to further explain the observed effects either in ERP terms or in SCP terms.

### EEG power

The rTMS treatment did not seem to have a treatment specific effect on the selected alpha and beta power measures. For beta power no effects were found. A general increase in alpha 2 measure post-treatment as compared to pre-treatment was observed. This finding contradicts the finding that depression is characterized by an increase

of frontal alpha.<sup>30</sup> More specifically, depressive patients show excessive left frontal alpha power as has been reported in several studies.<sup>31,16</sup> Our hypotheses suggested that remission of depression would be characterized by a *decrease* in alpha. Since all patients received left frontal 10 Hz stimulation, it was expected to obtain a hemisphere by time interaction effect in this frequency band. The observation that such an effect failed to happen, requires further elucidation by for example including additional parameters such as the alpha peak frequency or alpha coherence. On the other hand, some authors have proposed that the frontal alpha asymmetry is a trait marker for depression and found that frontal alpha asymmetry was still observable in formerly depressed patients and remained even after successful treatment.<sup>32,33</sup> In this light, the lack of findings on hemisphere specific alpha power would be understandable and considered a trait marker for depression.

In the *eyes closed* condition, the theta 1 power measure post-treatment was lower compared to pre-treatment. This finding is consistent with studies utilizing eyes-closed QEEGs that have shown elevated theta activity in MDD patients when compared with healthy controls.<sup>34,35</sup> In addition, a comparison between a group of depressives and a group of patients in remission revealed less theta power in the bilateral frontal regions in the remission group.<sup>36</sup> These studies demonstrate an association between elevated theta power and depression, and maybe in line with the alpha asymmetry, theta power might then be considered a state marker, whereas alpha asymmetry could be considered a trait marker for depression.

A clear increase in the delta band was observed post- as compared to pre-treatment in the *eyes open* condition. This effect was solely observed within the right hemisphere and not within the left hemisphere. It has been reported before that patients demonstrate lower delta power as compared to normals.<sup>37</sup> Our findings show that at the post-treatment assessment delta power is elevated in the right hemisphere, which could indicate the improvement in depressive symptomatology. Many authors have suggested that magnetic stimulation at one location leads to a cascade of effects throughout the brain which can also be measured at more locations,<sup>10</sup> also

demonstrated by Ilmoniemi et al.<sup>38</sup> who showed that TMS on the left side also spreads to the ipsilateral side of the brain. Hence, it could be speculated that the right-sided increase in delta power is also related — indirectly — to the left frontal stimulation.

Our study has several limitations. The study is limited by the small number of patients, and its open-label design. Another limitation is the adjunctive use of pharmacotherapy in some of the patients and the heterogeneity of the patient group. Also, the behavioral measures are limited to the use of the BDI. Future studies would benefit from including an additional measurement of depression.

Despite these limitations, our results suggest that QEEG can be used to better understand the effects of rTMS treatment in patients with depression. The outcomes of the ERP and QEEG measures suggest that frontal alpha may be a trait marker for depression which is not affected by rTMS treatment. Normalization of ERP components — specifically in the stimulated area — as well as a normalization of the EEG in the delta and theta bands suggests that these measures might be considered state markers.

Future research with larger subject numbers and also including other rTMS protocols (i.e., 1 Hz TMS over right dorsolateral prefrontal cortex) are needed to clarify these effects further.

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#### DISCLOSURE AND CONFLICT OF INTEREST

Paul B. Fitzgerald has received external funding through Neuronetics Inc. for participation in an rTMS multi-site trial. Desirée Spronk, Martijn Arns, Aukje Bootman and Rosalinde van Ruth have no conflicts of interest in relation to this article.

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