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Title: The impact of high frequency repetitive Transcranial Magnetic Stimulation on fine motor functions in medication resistant major depression

Running head: Impact of HF-rTMS on fine motor functions in MDD

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Abstract:

Objectives: Whereas high frequency-repetitive Transcranial Magnetic Stimulation (HF-rTMS) over the left dorsolateral prefrontal cortex (DLPFC) has been reported to improve mood symptoms in Major Depression (MDD), research on its impact on psychomotor symptoms is scarce. This study assessed the psychomotor effects of respectively one and ten sessions of HF-rTMS over the left DLPFC.

Methods: Ten HF-rTMS sessions were applied in 21 medication-free MDD patients over a 2 week-period. At the beginning, one placebo (sham) -controlled rTMS session was also applied in a crossover, single-blind design. Psychomotor variables were digitally recorded during completion of a Fitts task, at baseline, after the first and second real/sham session, and at endpoint.

Results: The total 10 session-treatment period resulted in a decrease of depression severity. One HF-rTMS-session resulted in improvements on the Fitts task, however without a difference between active and sham stimulation. No further improvements occurred from session 2 to 10.

Conclusions: No evidence was provided to link the observed psychomotor improvements to HF-rTMS stimulation, as a practice effect could have impacted the significant psychomotor outcomes.

Key words: transcranial magnetic stimulation, HF-rTMS, psychomotor symptoms, retardation, major depressive disorder

Introduction

Last years, studies investigating the therapeutic efficacy of repetitive Transcranial Magnetic Stimulation (rTMS) for Major Depressive Disorder (MDD) have exponentially increased [1-3]. A growing body of evidence has been published indicating that depressed patients can be successfully treated with high-frequency (HF)-rTMS when administered on the left prefrontal cortex [4-6]. Recent meta-analytic studies support the antidepressant efficacy of this technique in treatment-resistant depressed patients when stimulation periods are long enough (e.g. >2 weeks) [2-3]. Besides the treatment duration, frequency and side of stimulation should also be taken into account when evaluating the efficacy of rTMS [3].

Most rTMS studies focussed on the reduction in mood symptoms in MDD, whereas effects of rTMS on psychomotor functioning have been rarely explored.

Notwithstanding, cognitive dysfunctions and psychomotor retardation have also been determined as core features of a major depressive episode [7-9]. Psychomotor slowing appears to be a strong diagnostic marker for MDD with melancholic features. As psychomotor retardation is one of the key symptoms of the melancholic subtype of depression, a cohort of melancholic patients would be very appropriate to investigate psychomotor changes following rTMS treatment. From a neurobiological perspective, psychomotor retardation in major depression -and especially the melancholic subtype- has been linked to a hypodopaminergic state [7,9]. Moreover, prefrontal rTMS has been found to influence striatal dopaminergic activity [10-11]. Furthermore, a higher level of psychomotor retardation has been associated with reduced metabolic activities in the left dorsolateral prefrontal cortex (DLPFC) suggesting an important role of this cortical area on psychomotor functioning [9]. Therefore, given the possible neurobiological and clinical implications, a thorough investigation of the psychomotor effects of rTMS in MDD is warranted.

A limited number of studies already examined the neurocognitive effects of rTMS in MDD [12-13], but even fewer studies examined the impact of rTMS on psychomotor performance in MDD. Applying the Motor Agitation and Retardation Scale (MARS), Hoeppner et al. [14] observed a reduction in psychomotor retardation following 10 HF-rTMS sessions over the left dorsolateral prefrontal cortex, whereas the same authors [15] could only demonstrate a trend in the reduction of psychomotor agitation but not for retardation in MDD following 15 left prefrontal HF-rTMS sessions. Finally, Baeken et al. [16] demonstrated a positive effect of 10 sessions of HF-rTMS on psychomotor slowing as measured by means of the Salpêtrière Retardation Rating Scale (SRRS).

Given the limited number of studies on this subject and their divergent results, the current study further investigated the psychomotor effects of HF-rTMS in MDD, applying the Fitts' task. This computerized task is an objective and reliable method to assess fine motor activity, and is generally considered to be a rater-independent and more objective measurement method than the more subjective rating scales [9]. The Fitts' task has been widely used in the research into psychomotor symptoms in MDD [17-19]. This fine motor task requires a precise sensori-motor programming, initiation and execution of the muscle commands [17-19] and one HF-rTMS session with parameters comparable to rTMS treatment for depression has been reported to affect this psychomotor functioning in healthy subjects [20].

Consequently, the present study aims to further explore the psychomotor effects of HF-rTMS over the left DLPFC in a sample of medication resistant MDD patients, applying the Fitts' task. To evaluate the effect of a single stimulation on psychomotor functioning, we assessed the effects of one sham-controlled session of HF-rTMS delivered on the left DLPFC, in a single blind placebo controlled crossover design. To examine the effect of HF-rTMS treatment, the effect on the Fitts' task was assessed after10 such sessions spread over a period of 2 weeks of treatment. To ascertain that the melancholic depressed patients displayed

decreased psychomotor speed, their baseline Fitts' measurements were compared to an age and gender matched control group.

As mentioned above, few studies on psychomotor effects in MDD have been executed up to now, psychomotor retardation has been associated with DLPFC hypofunction and a hypodopaminergic state, and rTMS has been supposed to exert an impact on the dopaminergic system. Together with the limited existing evidence mentioned above, all these findings make us hypothesize that an improvement in psychomotor functioning could be expected after HF-rTMS treatment especially in our treatment responder group.

1. Methods

2.1. Patients

Our group consisted of twenty-one medication-free unipolar depressed patients of the melancholic subtype (female:male =13:8; age 44.7 ± 10.3 years). Psychiatric disorders were assessed using the Mini-International Neuropsychiatric Interview (MINI) [21]. Because concomitant personality disorders were not part of the exclusion criteria no formal diagnostic screening on axis II diagnosis was performed. Severity of depression was assessed with the 21-item Beck Depression Inventory (BDI) [22] and the 17-item Hamilton Depression scale (HDRS) [23]. The HDRS was administered by an experienced psychiatrist, not related to the study. Eleven participants were current in-patients during HF-rTMS treatment. Treatment resistance was assessed with the Thase and Rush criteria [24]. All were right-handed and considered at least stage III treatment resistant: they had had a minimum of two unsuccessful trials of SSRI/NSRI treatment and one failed trial with tricyclic antidepressants (TCA) as described by Rush et al. [25]. Because concomitant antidepressant treatment can confound outcome results, all patients went through a two week antidepressant washout before entering the study (3 weeks if they were on fluoxetine). Where necessary, patients were kept on a steady dose of their ‘somatic’ medications. During the washout period patients had contact with their physicians on a regular basis. Only habitual benzodiazepine agents were allowed: one subject took alprazolam (1mg), one clonazepam (0.5mg), one flunitrazepam (1mg), and one took alprazolam (1mg) and flurazepam (27mg). During our stimulation protocol, all psychopharmacological changes were considered as drop-out from the study. Additionally, no changes of habitual somatic treatment were allowed. All subjects underwent physical, neurological (MRI, EEG) and psychiatric examinations.

Exclusion criteria were current or past history of epilepsy, neurosurgery, having metal or magnetic objects in the brain, and being pregnant. Patients with suicide attempts during the current depressive episode or alcohol/drug dependence and/or abuse, were not included.
A group of 28 healthy controls (mean age: 40.82 +/- 6.93; male:female ratio= 11/17) was included matched for sex and age with the patient group (p=0.20 and p=0.77, respectively). These controls were recruited in the context of a previous research project on psychomotor functioning in major depression [26]. This study was part of a larger project investigating the influence of HF-rTMS on different neuro-cognitive markers. The study was carried out consistent with the latest version of the Helsinki Declaration and was approved by the ethics committee of the University Hospital (UZBrussel) of the Vrije Universiteit Brussel (VUB). All subjects gave written informed consent.

2.2. Psychomotor assessments

For the objective psychomotor measurement, all participants carried out a Fitts' task (see Figure 1) using a pressure-sensitive inking ballpoint pen on sheets of paper placed on a digitizer that was connected to a personal computer. The Fitts task is a computerized fine motor task that has been designed especially to evaluate sensorimotor programming, initiation and execution of the muscle commands, without requiring higher-order cognitive processes [17-19]. In this task subjects had to connect two vertically placed circles, depicted on a normal sheet of paper, by drawing a line of about one cm. They were instructed to start in the middle of the top circle and to end in the middle of the lower circle. Per trial six lines had to be drawn. The accuracy of movement was varied by changing the circle diameter from 0.50 cm in trials 1 and 4 (Figure 1, upper part) to 0.25 cm in trials 2 and 3 (Figure 1, lower part). Movement time (MT) was recorded, i.e. the time between the start and the completion of each

separate line drawing movement. The movement times of inaccurate line drawings, i.e. when the line was drawn from the lower to the upper circle and/or when the start/endpoint of the connecting line was situated outside the circle diameter, were not included in the analyses.

In addition, visual analogue scales (VAS) were used to examine subjective mood changes: subjects were asked to rate their mood on five horizontal 100 mm VAS in order to detect subtle changes in feelings of ‘depression’, ‘fatigue’, ‘tension’, ‘anger’ and ‘vigor’ . The minimum score on each VAS subscale is 0 and the maximum score is 100. Right-handedness was assessed with the Van Strien Questionnaire [27].

--Insert Figure 1 about here--

2.3. Design and rTMS procedure

Patients underwent 10 sessions of HF-rTMS on the left DLPFC within a period of 2 weeks. At the beginning of this open treatment trial, each subject received also one placebo (sham) HF-rTMS stimulation session, separated 1 day from the first active stimulation session. This phase was a placebo-controlled crossover, single-blind design allowing examination of a single session, specific rTMS effects in MDD patients.

Potential mood changes were assessed before (Tpre), immediately after (Tpost) and 30 min after (Tpost30) terminating the first rTMS (real/sham) session, using VAS scales. Antidepressant effects of 2 weeks of rTMS treatment were investigated by assessing the HDRS and BDI at baseline and endpoint, i.e. after the eleventh stimulation session (of which one was a placebo session). The Fitts task was applied before (Tpre: before the first session real or sham) and immediately after (Tpost) terminating the first and second rTMS (real and sham) session, and at the end of the rTMS treatment period (Tpost-treatment: after the last session).

Because this study is part of a larger project investigating the influence of HF-rTMS on different neuro-cognitive markers, additional tasks were also administered that were not used for the purposes of the present study. All measures were always presented in the same order for all participants.

Patients were kept unaware of the type of stimulation; they wore earplugs and were blindfolded. Importantly, all patients were stimulated on all occasion within the same time schedule, i.e. between 10 am and noon.

For the application of rTMS we used a Magstim high-speed magnetic stimulator (Magstim Company Limited, Wales, UK), connected to a figure-of-eight-shaped coil. Before each application, the motor threshold (MT) of each individual was determined using electromyography (EMG). A stimulation intensity of 110 % of the subject's motor threshold of the right abductor pollicis brevis muscle was used. In order to accurately target the left dorsolateral prefrontal cortex (Brodmann area 9/46), the precise stimulation site and position of the coil were determined using MRI non-stereotactic guidance (Philips Intera, Best, The Netherlands). Perpendicular to this point, the precise stimulation site on the skull was marked and stimulated [28]. In each high-frequency (10 Hz) stimulation session, subjects received forty trains of 3,9 s duration, separated by an intertrain interval of 26.1 s. Each session, therefore, lasted 20 minutes (1560 pulses per session). For the sham condition, the coil was held at an angle of 90°, with one edge only resting on the scalp. The International Society of Transcranial Magnetic Stimulation (ISTS) safety guidelines were followed [29-30].

2.4. Statistics

All results were analysed using the SPSS for Windows 16.0 software package. Statistical analyses were performed using ANOVA's. The significance level was set at $p<0.05$ for all analyses. Baseline and endpoint psychomotor outcomes in the patient group were compared

with the outcomes of an age- and gender-matched control group that participated in a previous research project in which psychomotor measurements were registered [26]. Separate analyses were conducted to investigate the single session effect (1 active/sham session) and the treatment effect (10 active sessions) of HF-rTMS.

Regarding the single session effects, we used separate 3X2 ANOVA's with the VAS mood scales as dependent variables and Session (Tpre, Tpost, Tpost30) and Stimulation (active or sham) as within-subject factors. With regard to the analyses for the single session effects on the Fitts task, a 2X2X2 factorial design was used with Stimulation (active, sham), Session (Tpre, Tpost) and Complexity [small vs. large circles] as within-subject factors.

Subsequently, overall improvement in HDRS and BDI-scores between the baseline and final assessment were analysed using paired t-tests over the whole group. Clinical response was defined as a 50% reduction of the baseline HDRS score.

A similar 2X2X2 design was applied for the psychomotor outcomes related to the 10 session treatment with Session (Tpre, Tpost-treatment) and Complexity (small vs. large circles) as within-subject factors, and Treatment Response (responders, non-responders) as between-group factor.

2. Results

2.1.Baseline psychomotor outcomes

A comparison of the baseline Fitts outcomes of the patient group with those of an age- and gender-matched control group (mean RT: 255 msec; SD: 0.25) pointed to a significantly slower performance of the patients (mean RT: 321 msec; SD: 0.12; $t=2.21$, $p<0.05$).

2.2. Single session effects

Mood

VAS analyses were conducted on 20 patients because one subject had numerous missing values. The separate ANOVAs did not reveal any significant effect, neither for the main effect of Stimulation [all F-values <1.33] or Session [all F-values<2.45], nor for the Stimulation by Session interaction [all F-values<1.09]. The only exception was the VAS depression subscale that showed a main effect of Session [$F(2,18)=8.38$, $p<0.01$] with the scores slightly decreasing from Tpre (6.46) over Tpost (5.12) to Tpost30 (5.74), however without a significant Stimulation by Session interaction [$F<1$].

Psychomotor variables

As demonstrated in previous studies, a smaller diameter of the circles resulted in significantly higher MTs [$F(1,20)=94.6$, $p<0.001$]. Moreover, a significant main effect of Session was found with the MTs improving from pre to post-stimulation [$F(1,20)=5.68$, $p<0.05$; Tpre: 309 ms, Tpost: 284 ms]. However, neither the Stimulation by Session interaction nor any of the other interactions were significant [all Fs<1], with the exception of the Complexity by Session interaction [$F(1,20)=3.91$, $p<0.1$]. These results indicate that the first rTMS session did improve fine motor performance but no difference could be demonstrated between active (T pre: 306msec; T post: 279msec) or sham (T pre: 311msec; T post: 287msec) stimulation

within that time frame. It should be noted that patients remained slower than healthy controls after the first stimulation session ($F=3.14$, $p<0.1$).

2.3.Treatment effects

Mood

Mean HDRS scores before entering the study were 25.24 (*SD*= 3.9) and mean BDI scores were 33.82 (*SD*= 12.19), indicating severe depression. The overall patient group demonstrated a significant improvement in HDRS and BDI-scores between the baseline and final assessment [final HDRS: 15.35, $t=5.61$, $p<0.001$; final BDI: 25.27, $t=2.76$, $p<0.05$]. Eleven patients (52%) were considered as clinical non-responders, and the other ten (48%) as clinical responders.

Psychomotor variables

A significant psychomotor improvement was observed from baseline to endpoint [Tpre: 321ms, Tpost-treatment: 276ms; $F(1,19)=4.22$, $p<0.05$], as well as the well known effect of Complexity [$F(1,19)=80.88$, $p<0.001$]. Neither the main effect of nor any interactions with Treatment Response were significant [$Fs<2.12$].

A comparison of the endpoint Fitts outcomes of the patient group (mean RT: 276 msec) with the baseline data of the control group (mean RT: 255 msec) did not reveal any significant differences in psychomotor performance anymore ($t=0.78$, $p=0.44$).

Note that no further substantial psychomotor improvements occurred between session 2 (which was an HF-rTMS or a Sham session) and session 10 (last HF-rTMS session): $F<1$, $p=0.36$. This could implicate that the observed psychomotor improvements are obtained between the first and the second psychomotor assessment (following 1 sham/rTMS stimulation), which further underscores the previously mentioned impact of a practice effect.

Additional correlational analyses were conducted to further investigate the association between the clinical and psychomotor variables. No significant correlations could be observed neither between the absolute difference of the baseline and endpoint rTMS psychomotor variable and the absolute difference in HDRS/BDI scores, nor between the proportional changes of mentioned variables (all r values <0.34, all p values >0.15). In this context, it should also be mentioned that the Fitts outcomes at baseline and endpoint did not correlate with the duration of the current episode or the stage of treatment resistance (all r-values < 0.19, all p values >0.4).

3. Discussion

The current study explored the clinical and psychomotor effects of respectively one sham-controlled and ten active HF-rTMS sessions in treatment resistant major depression applying clinical rating scales and an objective psychomotor assessment method, i.e. the Fitts' task.
At baseline MDD patients performed significantly slower than an age- and gender-matched control group, which has also been demonstrated repeatedly in previous studies from our research group [9].The total patient sample manifested a clear improvement in depression severity following 10 active rTMS sessions with approximately half of the patient sample manifesting a clear clinical response, as determined with a 50% decrease of the initial HDRS scores, which is in line with previous HF-rTMS treatment studies in MDD [31]. Regarding the VAS, one HF-rTMS session did decrease the depression subscale scores, however irrespective of the stimulation type (active or sham). Scores on the other VAS subscales did not significantly change following one session.
Focussing on the effects of one HF-rTMS-session, psychomotor improvements were observed on the Fitts' task, however without revealing a difference between active and sham stimulation. The analyses investigating the total treatment period of 10 HF-rTMS sessions did point to a better endpoint performance on the Fitts' task, but these psychomotor improvements are likely due to a practice effect on the task. Indeed, the psychomotor improvements observed after session one emerged irrespective of sham or active HF-rTMS stimulation, and no further improvements occurred from session 2 to session 10.
Notwithstanding, it should be mentioned that for every assessment session patients were given the opportunity to practice with and get used to the task, before the proper recordings started. Besides the mentioned practice effect, it might be possible that due to certain non-specific aspects related to the rTMS procedure such as its impressive name, its discomfort, and its sophisticated-looking equipment a placebo effect could have influenced the one session

outcomes [32]. In addition, we cannot totally rule out a possible impact of our sham control condition: although this sham condition was performed at a 90° angle, ensuring minimal stimulation of the DLPFC, it still could be possible that a partially active placebo was used [33].

Whereas the current study mainly focused on fine motor performance, it would also be interesting to obtain more knowledge on the effects of rTMS on gross motor performance. However, the relationship between gross and fine motor performance in MDD has not yet been elucidated and it is not clear whether MDD patients with fine motor dysfunction are affected to the same degree in their gross motor performance [9]. Therefore, in order to investigate the impact of rTMS on gross motor performance, a similar rTMS design should be executed with assessment methods of gross motor activity such as actometric measurements. In addition, most previous studies have examined the psychomotor effects of rTMS treatment applying clinical rating scales. Hoeppner and colleagues reported a significant improvement of baseline MARS-rated psychomotor retardation after 10 HF-rTMS sessions spread over 2 weeks for both a group treated with 20Hz HF-rTMS as a group treated with 1Hz HF-rTMS, whereas a sham group did not manifest any psychomotor improvement [14]. In another study however, Hoeppner et al. could not demonstrate a beneficial effect of left prefrontal 10Hz HF-rTMS treatment during 15 days on MARS assessed psychomotor retardation [15]. Instead, they found nearly significant reductions in the agitation symptoms. Very recently, Baeken et al. reported a decrease in SRRS scores after 10 sessions of 10 Hz HF-rTMS over the left DLPFC [16]. In this context, it needs to be mentioned that rating scales and the applied psychomotor assessment method substantially differ in their duration of observation: rating scales are based on prolonged clinical observations whereas experimental tasks just capture fine motor performance during task execution [9]. Moreover, rating scales can be rater-dependent whereas the currently used assessment method does not depend on the rater [9].

A limitation of the current study could be the number of HF-rTMS sessions. In spite that rTMS treatment parameters are quite intense, the duration of two weeks might be considered as rather short. Indeed, current HF-rTMS treatment protocols stimulate patients three to six weeks daily [6, 34]. Further, as a higher level of treatment resistance in the current depressive episode might be inversely related to clinical outcome, this might to some extent have impacted our fine motor task results [35].

A major strength of the present study is that all patients had a sufficient washout period from their antidepressants, whereas in several other studies patients were still taking their current psychotropic medication. Moreover, during the stimulation protocol, no changes to the patients' habitual somatic treatment were allowed. On the other hand, although all included patients in our analysis continued with exactly the same benzodiazepine concentrations, the use of benzodiazepines in our sample might have been a confounding variable [19].

Future studies might do well to further objectively investigate fine motor functioning in depressed samples in association with rTMS treatment. More intensive placebo-controlled rTMS studies are needed to further disentangle the effect of HF-rTMS on the psychomotor system as clinical improvement with these kinds of techniques are reported.

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Conflicts of interest:

None to declare.

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Figures:

Figure 1: Fitts task

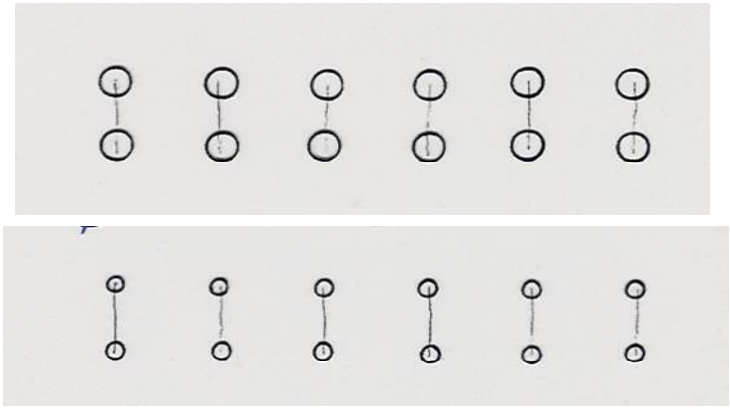

Figure 2: Mean movement times (in msec) of the patient group from baseline to endpoint for the Fitt's task