High frequency repetitive transcranial magnetic stimulation treatment for major depression: dissociated effects on psychopathology and neurocognition

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ABSTRACT

Objective: This open-label pilot study explored the potential effects of High frequency repetitive transcranial magnetic stimulation (HF-rTMS) on two neurocognitive domains (decision-making and impulse control) in adult patients diagnosed with Major Depressive Disorder (MDD).

Method: Subjects with a diagnosis of MDD (n=24) underwent HF-rTMS targeted at the left dorsolateral prefrontal cortex (lDLPFC) over the course of two weeks. Longitudinal changes in psychopathology were assessed by applying the Clinician-Administered Quick Inventory of Depressive Symptomatology (QIDS-C), the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR), and the Beck Anxiety Inventory (BAI) at baseline and after treatment completion; decision-making was assessed using the Iowa Gambling Task, the Balloon Analog Risk Task and the Game of Dice Task; impulse control was assessed using the Stroop Color-Word Task, the Continuous Performance Task and the Stop-Signal Task. The neurocognitive assessment was done at the same time-points as the psychopathology assessment.

Results: Depression and anxiety scores improved significantly between baseline and end of treatment. However, none of the decision-making or impulse control variables of interest changed significantly across time. Moreover, there was no significant correlation between change in symptomatology and decision-making or impulse control.

Conclusion: These preliminary findings suggest that HF-rTMS applied to the lDLPFC does not influence performance on decision-making or impulse control neurocognitive tasks in patients with MDD despite a significant reduction in depressive and anxious symptoms. Further studies with sham-controlled designs are warranted.

RÉSUMÉ

Objectif: Cet essai ouvert pilote a exploré les effets potentiels de la stimulation magnétique transcrânienne répétitive à haute fréquence (HF-rTMS, de l'anglais High-frequency repetitive transcranial magnetic stimulation) sur deux domaines neurocognitifs (prise de décision et contrôle de l'impulsivité) chez des patients adultes diagnostiqués avec un trouble dépressif majeur (MDD, de l'anglais Major Depressive Disorder).

Méthode: Participants ayant reçu un diagnostic de MDD (n = 24) ont subi HF-rTMS ciblant le cortex préfrontal dorsolatéral gauche (lDLPFC) pendant deux semaines. Les changements longitudinaux dans la psychopathologie ont été évalués avec le Clinician-Administered Quick Inventory of Depressive Symptomatology (QIDS-C), le Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR), et l'Inventaire d'anxiété de Beck (BAI, de l'anglais Beck Anxiety Inverntory) administrés avant le début du traitement et après la fin du traitement; la prise de décision a été évaluée en utilisant l'Iowa Gambling Task, le Balloon Analog Risk Task et le Game of Dice Task; le contrôle de l'impulsivité a été évalué en utilisant le Test Stroop Couleurs-Mots, le Continuous Performance Task et le Stop-Signal Task. L'évaluation neurocognitive a été effectuée aux mêmes moments que l'évaluation psychopathologique.

Résultats: Les scores de dépression et d'anxiété ont été améliorés de façon significative entre le début et la fin du traitement. Cependant, aucune des variables liées à la prise de décision ou au contrôle de l'impulsivité n'a considérablement changé à travers le temps. De plus, il n'y a pas de corrélation significative entre les changements de symptomatologie et la prise de décision ou le contrôle de l'impulsivité.

Conclusion: Ces résultats préliminaires suggèrent que la HF-rTMS appliquée au lDLPFC n'a pas d'influence sur la prise de décision ou les tâches neurocognitives liées au contrôle de l'impulsivité chez les patients ayant reçu un diagnostic de TDM, malgré une atténuation significative des symptômes dépressifs et anxieux. D'autres essais randomisés contrôlés sont nécessaires.

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PREFACE

This work presents a project aimed at assessing the effects on neurocognition produced by high-frequency transcranial magnetic stimulation, a neuromodulation technique used therapeutically for major depressive disorder. Data collection and handling for this project has been done by myself under the guidance and supervision of Dr. Marcelo T. Berlim and staff from the Neuromodulation Research Clinic of the Douglas Hospital Mental Health University Institute. The text in this work is original, and is the product of a collaborative work between myself and my supervisor.

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INTRODUCTION

High frequency repetitive transcranial magnetic stimulation (HF-rTMS) is a non-invasive neuromodulation technique that involves the painless induction of electrical currents within the cerebral cortex produced by rapidly changing magnetic fields (usually at 5-20 Hz) generated through a coil of wire placed near the scalp (Daskalakis, Levinson, & Fitzgerald, 2008). These electrical currents, in turn, are able to directly depolarize the membranes of neurons located down to a depth of ≈ 1.5 cm below the magnetic coil (Roth, Momen, & Turner, 1994; Rothwell et al., 1999; Rudiak & Marg, 1994) by opening voltage-sensitive ion channels (Wagner, Valero-Cabre, & Pascual-Leone, 2007).

HF-rTMS has been consistently shown to be effective for treating major depressive disorder (MDD) when applied to the left dorsolateral prefrontal cortex (lDLPFC) for over 10 or more daily sessions (Berlim, van den Eynde, Tovar-Perdomo, & Daskalakis, 2014). Furthermore, growing evidence suggests that this intervention is both safe and well tolerated, particularly with respect to its neuropsychological profile (Guse, Falkai, & Wobrock, 2010; Moreines, McClintock, & Holtzheimer, 2011). This is especially relevant considering that cognitive dysfunction is currently seen as a core feature of MDD (Rock, Roiser, Riedel, & Blackwell, 2013; Snyder, 2013) that is associated with negative psychosocial and quality of life outcomes (Evans, Iverson, Yatham, & Lam, 2014) even after symptomatic remission (Shimizu et al., 2013).

Overall, HF-rTMS does not seem to negatively affect neurocognitive performance within the treatment parameters commonly used in MDD, and it might be even associated with improvements in certain cognitive domains such as, e.g., verbal memory (Hausmann et al., 2004; Little et al., 2000), cognitive flexibility/conceptual tracking (Moser et al., 2002), and attention

(Martis et al., 2003; Shajahan et al., 2002). However, a number of studies have failed to demonstrate significant neurocognitive effects of HF-rTMS in MDD (e.g., in working memory, verbal fluency, response inhibition, cognitive flexibility) despite it being associated with clear parallel reductions in depressive symptomatology (Demirtas-Tatlidede et al., 2008; Huang, Su, Shan, & Wei, 2004; Isenberg et al., 2005; Kedzior, Rajput, Price, Lee, & Martin-Iverson, 2012; Speer et al., 2001; Wajdik et al., 2014). Although these heterogeneous findings may be partly explained by the use of different neuropsychological test batteries and/or stimulation parameters (Pallanti et al., 2012), it remains unclear whether HF-rTMS consistently improves neurocognitive performance in patients with MDD. More specifically, it is not yet known which specific cognitive domains are consistently and positively affected by HF-rTMS and whether these putative improvements are directly related to changes in depressive symptomatology or, alternatively, are mood-independent.

Therefore, in the present study, we assessed the longitudinal effects of 20 sessions of HF-rTMS applied to the lDLPFC of depressed outpatients on decision-making and impulse control - two key neurocognitive domains that have been shown to be dysfunctional in MDD (Lacerda et al., 2004; Must, Horvath, Nemeth, & Janka, 2013). We hypothesized that HF-rTMS would be associated with significant improvements in their performance on the tasks assessing decision-making (likely reflecting an amelioration of reward-learning processes and/or decreased risk-aversion) and impulse control (likely reflecting better inhibitory control), and that these longitudinal neurocognitive improvements would be significantly and inversely correlated with changes in psychopathology measures.

METHODS

Design Overview

This study was approved by the Douglas Mental Health University Institute's Ethics Review Board and has been registered at *www.clinicaltrials.gov* under identifier # *NCT0145015*. Eligible participants received HF-rTMS applied to the lDLPFC for 2 consecutive weeks, and were assessed at 2 time-points: at baseline and within 5 days after their last HF-rTMS session with a battery of computerized neurocognitive tasks on decision-making and impulse control as well as with questionnaires on depression and anxiety.

Subjects

A convenience sample of depressed outpatients was recruited from the Depressive Disorders Program at the Douglas Mental Health University Institute. Written informed consent was obtained from all eligible subjects before study enrolment. Outpatients were considered for the study if they were aged between 18 and 60 years and had a primary diagnosis of unipolar major depressive episode (MDE) according to the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Moreover, their current MDE had to be of at least moderate intensity as determined by a score ≥ 13 on the clinician-administered Quick Inventory of Depressive Symptomatology (QIDS-C) (Rush et al., 2003).

Subjects were not included in this study if they presented with any of the following: uncontrolled medical illnesses (e.g., cardiac, pulmonary), current psychotic features, lifetime history of any non-mood psychotic disorder, lifetime history of bipolar disorder types I or II, substance or alcohol abuse/dependence within the past 6 months, lifetime neurological disease

(e.g., Parkinson's, stroke), pregnancy and/or a contraindication for rTMS (e.g., personal history of epilepsy, metallic head implants).

Eligible participants were not withdrawn from their current medication regimen but the doses were required to remain stable in the 4 weeks preceding their enrolment and also for the duration of this study. The only exceptions were benzodiazepines (e.g., lorazepam ≤ 3 mg/day) or equivalent, which were allowed to be initiated or titrated for the management of insomnia.

rTMS Procedure

A Magstim Rapid2® magnetic stimulator (Magstim Company Ltd., U.K.) was used with a standard figure-of-eight coil placed over the lDLPFC (i.e., F3 position on the 10/20 EEG system (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003)). The resting motor threshold was determined weekly using the visualization method (Pridmore, Fernandes Filho, Nahas, Liberatos, & George, 1998). Patients received 2 daily sessions of HF-rTMS (separated by a 45-minute interval) for 2 weeks (i.e., 20 sessions in total). Stimulation was delivered at 10 Hz in 75 trains with a 26 second inter-train interval at 120% of the resting motor threshold (i.e., 60,000 pulses in total) (George et al., 2010; O'Reardon et al., 2007).

Psychopathology Assessment

Patients were assessed at baseline (week 0) and within five days of their last rTMS session (week 3) using the QIDS-C, the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR) (Rush et al., 2003), and the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988).

Neurocognitive Assessment

The neurocognitive assessment battery was also administered at baseline (week 0) and within five days of the last rTMS session (week 3). It was composed of six computerized tasks (three on decision-making and three on impulse control), and was presented in a pseudo-randomized sequence using Inquisit v. 4 (Millisecond Software, USA). Data were collected through a response pad (RB-540 model, Cedrus, USA), which offered a high reaction time resolution (i.e., 2-3 ms). Subjects were seated at approximately 70 cm from the computer screen, which was positioned at the eye level. A brief practice session was done before starting the actual neurocognitive assessment, and instructions for the tasks were written beforehand, assuring that all participants received the same information.

Decision-making

We used three tasks to tap into the decision-making construct: the Iowa Gambling Task (IGT) (Bechara, Damasio, Damasio, & Lee, 1999), the Balloon Analog Risk Task (BART) (Lejuez et al., 2002) and the Game of Dice Task (GofD) (Brand et al., 2005).

In the IGT, participants are asked to draw cards from four different decks with the goal of earning as much virtual money as possible. However, they are unaware that this task involves a total of 100 card draws, and that two of the decks (A and B) are disadvantageous in that they yield significant immediate gains but even greater long-term losses, whereas the two remaining decks (C and D) yield relatively small immediate and long-term gains. Successful performance in the IGT thus requires participants to implicitly and explicitly learn its underlying rules on frequencies and magnitude of wins and losses and to develop a long-term profitable monetary strategy

involving choosing progressively less disadvantageous card choices. The main variable of interest in the IGT is its "net score", which is the number of cards drawn from the advantageous decks minus the number of cards drawn from the disadvantageous decks.

The BART requires participants to inflate 30 virtual balloons by repeatedly pressing a key on the response pad. Each balloon is programmed to pop between 1 and 128 pumps, with an average breakpoint of 64 pumps. Specific information regarding the balloon breakpoint is not provided to participants, and every pump gives them C$ 0.05, which is gradually added to a "temporary bank". At any point during each trial, participants can stop pumping the balloon and click the "Collect $$$" button, which transfers the money accumulated from that trial into a "permanent bank" and produces a slot machine payoff sound. In contrast, when a balloon explodes, a "pop" sound is heard, the balloon disappears from the screen, the money in the "temporary bank" is lost, and the next trial begins. Hence, contrary to the IGT, the BART does not involve an explicit learning process as each balloon trial has a random outcome. The variable of interest in this task is the "average adjusted number of pumps" (i.e., the average number of pumps on each balloon prior to money collection).

The GofD requires participants to bet on either one or a combination of up to four numbers before throwing 18 virtual dices. They win or lose virtual money depending on whether their chosen number (or numbers) is part or not of each throw, and are aware that choosing a larger combination of numbers will increase their chances of having a winning bet but decrease the monetary sum earned. Thus, contrary to the IGT but similar to the BART, the GofD does not involve an explicit learning process. The variable of interest in this task is the "number of risky choices" (i.e., those associated with winning probabilities of less than 50%).

Impulse control

We used three tasks to examine the impulse control construct: the Stroop Color-Word Task (SCWT) (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006), the Continuous Performance Task (CPT) (Klee & Garfinkel, 1983), and the Stop-Signal Task (SST) (Logan, Cowan, & Davis, 1984).

In the SCWT, three different types of stimuli are presented to participants: coloured rectangles (neutral stimuli), color words written in the same ink as their meaning (e.g., the word "red" displayed in red ink; also known as congruent stimuli) as well as color words written in a discrepant ink relative to their meaning (e.g., the word "red" displayed in blue ink; also known as incongruent stimuli). They are asked to identify, as quickly and accurately as possible, the ink color of 84 randomly presented word-color stimuli by pressing the appropriate key on the response pad. Hence, successful performance in the SWCT requires participants to not only inhibit a planned response by disregarding distracting stimuli but to also effectively monitor the conflict between word reading vs. naming the word ink color. The main variable of interest in the SWCT is the "interference index", which measures the difference in response latencies (in milliseconds [ms]) between incongruent vs. congruent stimuli.

In the CPT, 620 letter stimuli flash consecutively in the screen. Participants are asked to press a specific key on the response pad whenever they see the letter "X" (65%). Every response to a letter other than "X" (35%) is identified as a "commission error" (which is indicative of "motor impulsivity"), and the total number of "commission errors" is the variable of interest in the CPT.

In the SST (Logan et al., 1984), participants are presented with both "go" and "stop" trials. On "go" trials, they are shown 192 "go" stimuli (i.e., consecutive arrows randomly pointing left

or right) and are required to press the matching key on the response pad (e.g., left arrow = left key). On "stop" trials, the "go" stimulus is immediately followed by a stop-signal sound (750 Hz, 75 ms), which indicates to participants that they must refrain from responding. Initially, the stop signal delay (SSD) is set at 250 ms after the presentation of the "go" stimulus, but afterwards it varies in a step-wise manner dependent on the previous response (i.e., it is decreased or increased by 50 ms after a successful or an unsuccessful "stop" trial, respectively). In total, there are 48 "stop" trials and 144 "go" trials, presented intermixed and counterbalanced for left and right arrows, in three separate blocks. The main variable of interest in the SST is the "stop-signal reaction time" (SSRT), which is estimated by subtracting the mean "go" reaction time from the mean SSD, and thus reflects the amount of time required by participants to prevent a planned motor response.

Statistical Analyses

Statistical analyses were performed using IBM SPSS v. 22 (IBM, Chicago, U.S.A.). Significance was set at $\alpha < 0.05$. Participant attrition was handled using the last-observation-carried-forward (LOCF) approach (Woolley, Cardoni, & Goethe, 2009). To investigate the effects of HF-rTMS on psychopathology, decision-making and impulse control we employed repeated measures analysis of variance (ANOVA) with time (i.e., pre-rTMS, post-rTMS) as the independent within-subjects variable, and the difference in pre-post scores on the depression/anxiety scales and the neurocognitive tasks as the dependent variable. Correlations between clinical and neurocognitive scores (deltas) were performed using Pearson's coefficients. Outliers were identified and removed using Tukey's boxplot method.

RESULTS

Subjects

Twenty four depressed outpatients were enrolled in this study. They had a mean age of 46.25 years (S.D. 11.47), were predominantly females (n= 18; 75%) and most suffered from a chronic MDE (46.22 months of duration; S.D. 54.90). Comorbidity with other Axis I disorders was common, particularly with generalized anxiety disorder (n= 17; 70.83%). The detailed socio-demographic and clinical characteristics of the enrolled subjects are described on **Table 1**.

Table 1. Baseline socio-demographic and clinical characteristics of the enrolled depressed individuals (n=24).

Variable	N (%) or M±SD
Age (Years)	46.25±11.47
Sex	Male = 6 (25.0%)
	Female = 18 (75.0%)
Education (years)	15.50±3.16
Duration of the current depressive episode (months)	46.22±54.90
Number of previous depression episodes	2.52±2.61
Age at onset of the depressive disorder (years)	30.21±13.33
Suicidality ǂ	7 (29.17%)
Axis I Comorbidity	
Generalized anxiety disorder	17 (70.83%)
Post-traumatic stress disorder	8 (33.33%)
Panic disorder	6 (25.00%)

Social phobia	6 (25.00%)
Agoraphobia	6 (25.00%)
Obsessive-compulsive disorder	5 (20.83%)
Eating disorder	2 (8.33%)

M: mean. SD: standard deviation.
ǂ Suicidality denotes patients who answered affirmatively to at least one of the questions assessing suicidal risk on the Mini International Neuropsychiatric Interview (MINI).

Psychopathology pre-post HF-rTMS

The repeated measures ANOVA showed a significant effect of time on the depression/anxiety scores (*Wilks' Lambda* = 0.21, $F(3,21) = 26.65$, $p < 0.0001$**)**. Please refer to Table 2 for more detailed information.

Table 2. Depressive and anxious symptoms pre-post HF-rTMS (n=24).

Measure	Mean ± SD at week 0	Mean ± SD at week 3	Statistics
QIDS-C	19.75 ± 5.33	10.38 ± 5.96	$MS = 1054.69$, $F(1) = 49.02$, $p < 0.0001$
QIDS-SR	21.13 ± 5.48	12.00 ± 6.43	$MS = 999.19$, $F(1) = 74.54$, $p < 0.0001$
BAI	26.75 ± 13.22	17.46 ± 11.49	$MS = 1036.02$, $F(1) = 29.18$, $p < 0.0001$

MS: mean square. SD: standard deviation.
BAI: Beck Anxiety Inventory. QIDS-C: Clinician-Administered Quick Inventory of Depressive Symptomatology. QIDS-SR: Quick Inventory of Depressive Symptomatology - Self-Report.

Decision-making and impulse control pre-post HF-rTMS

The repeated measures ANOVA did not show a significant effect of time on any of the neuropsychological variables of interest on decision-making and impulse control (*Wilks' Lambda* = 0.91, $F(7,14) = 0.19$, $p = 0.98$). In other words, HF-rTMS did not influence participants' performance on the neurocognitive tasks. Please refer to **Table 3** for more detailed information.

Table 3. Decision-making and impulse control pre-post HF-rTMS (n=21).

Variable measured	Mean ± SD at week 0	Mean ± SD at week 3	Statistics
IGT - Net score	11.43 ± 40.02	6.57 ± 44.36	$MS = 247.71$, $F(1) = 0.25$, $p = 0.62$
BART - Average number of pumps	22.83 ± 11.41	25.58 ± 13.57	$MS = 79.47$, $F(1) = 1.33$, $p = 0.26$
GofD - Number of risky choices	5.67 ± 5.46	5.76 ± 4.57	$MS = 0.09$, $F(1) = 0.01$, $p = 0.93$
SCWT – Interference index	354.06 ± 323.67	348.98 ± 351.36	$MS = 271.22$, $F(1) = 0.004$, $p = 0.95$
CPT – Number of commission errors	3.71 ± 3.50	4.14 ± 5.41	$MS = 1.93$, $F(1) = 0.22$, $p = 0.64$
SST – Stop-signal reaction time	266.15 ± 46.59	264.48 ± 68.19	$MS = 29.33$, $F(1) = 0.02$, $p = 0.90$

MS: mean square. SD: standard deviation.
BART: Balloon Analog Risk Task. CPT: Continuous Performance Task. GofD: Game of Dice Task. IGT: Iowa Gambling Task. SCWT: Stroop Color-Word Task. SST: Stop-Signal Task.

Correlation between psychopathology and neurocognition pre-post HF-rTMS

There was no significant correlation (deltas) between depressive/anxious symptoms and the variables of interest on decision-making and impulse control pre-post HF-rTMS (**Table 4**).

Table 4. Correlation between psychopathology and neurocognitive performance pre-post HF-rTMS (deltas).

Neuropsychological Task / Rating Scale	IGT - Net score	BART - Average number of pumps	GofD - Number of risky choices	SCWT – Interference index	CPT – Number of commission errors	SST – Stop-signal reaction time
	Pearson's *r*; p; n					
QIDS-SR score	.15; .48; 24	.18; .41; 24	.32; .14; 23	.30; .15; 24	.27; .22; 23	.15; .49; 23
QIDS-C score	.19; .38; 24	.15; .50; 24	.25; .25; 23	.16; .45; 24	.22; .32; 23	.15; .49; 23
BAI score	.13; .56; 24	.02; .92; 24	.35; .10; 23	.08; .70; 24	-.37; .09; 23	-.14; .52; 23

BAI: Beck Anxiety Inventory. BART: Balloon Analog Risk Task. CPT: Continuous Performance Task. GofD: Game of Dice Task. IGT: Iowa Gambling Task. QIDS-C: Clinician-Administered Quick Inventory of Depressive Symptomatology. QIDS-SR: Quick Inventory of Depressive Symptomatology - Self-Report. SCWT: Stroop Color-Word Task. SST: Stop-Signal Task.

DISCUSSION

To our knowledge, this is the first study investigating whether HF-rTMS applied over the lDLPFC of depressed individuals is able to improve their cognitive performance on decision-making and impulse control tasks. Contrary to the hypotheses, our findings suggest that 20 sessions of HF-rTMS administered twice daily for 10 days were not associated with improvements in these cognitive dimensions despite significant parallel reductions in depressive/anxious symptomatology from baseline to endpoint. Our results suggest that symptomatic improvement in MDD following this neuromodulation treatment seems to occur independently from any therapeutic effect on decision-making and impulse control – two key neurocognitive domains that have been shown to be altered in depressed individuals (Lacerda et al., 2004; Levasseur-Moreau & Fecteau, 2012; Must et al., 2013).

The rationale behind our hypotheses was based on converging lines of evidence highlighting the role of the DLPFC as a region which is (1) critically involved in neurocognition, notably in attentional and executive functions (Leh, Petrides, & Strafella, 2010) and as an integral part of the so-called "central executive" neural network by virtue of its consistent activation during events/tasks requiring attention to external stimuli and cognitive control (Miller & Cohen, 2001), (2) consistently linked to metabolic alterations and neurotransmitter abnormalities thought to underlie the pathogenesis/pathophysiology of MDD (Galynker et al., 1998; Snyder, 2013), (3) recruited during functional neuroimaging studies investigating cognitive reappraisal/suppression of stimuli and emotions of negative valence (Eippert et al., 2007; Ochsner, Bunge, Gross, &

Gabrieli, 2002; Ochsner et al., 2004) - a likely important strategy for mood and emotion regulation, and (4) rich in neuroanatomical connections with ventromedial prefrontal and orbital cortices, which are directly involved in decision-making and inhibitory control, respectively, and together with the DLPFC play a critical role in emotional and self-referential processing (Fuster, 2015; Pizzagalli, 2011).

Although the exact mechanism of action of HF-rTMS in MDD remains unclear, we initially hypothesized that its therapeutic effects on psychopathology would be directly related to parallel changes in cognition. However, our study did not support this assertion and a potential explanation could be related to our use of specific HF-rTMS parameters (such as coil positioning, stimulation frequency and treatment duration) that might not have been optimal to produce clear cognitive effects beyond the changes in core psychopathology. Most clinical studies on rTMS for MDD to date have involved high frequency protocols (≥ 5Hz) applied to the lDLPFC and the rationale for this is twofold: the lDLPFC has been consistently shown to be "hypoactivated" in depressed individuals (Baxter et al., 1989; Drevets et al., 1992), and HF-rTMS is believed to result in long-term potentiation-like (LTP) effects directly over the targeted tissue and indirectly over interconnected brain areas (Hoogendam & Ramakers, 2010). Our results could possibly reflect that the stimulation parameters employed in this study were not able to significantly modulate, directly or indirectly, the circuits underlying decision-making and impulse control to the extent necessary to allow detection by neuropsychological testing.

Previous investigations on the longitudinal association between symptomatic improvement and cognitive performance following lDLPFC HF-rTMS in MDD have produced conflicting results. For example, a sham-controlled randomized trial by Wadjik et al. (2014) including 65

participants found no evidence that HF-rTMS applied over the lDLPFC influenced attention, processing speed, global cognitive functioning or executive function despite it being associated with significant clinical improvement. Moreover, an open-label study (n=14) found no change in neuropsychological function in the domains of immediate memory, visuo-spatial processing, language, attention and delayed memory after HF-rTMS of the lDLPFC despite relatively high response and remission rates among individuals with MDD (Holtzheimer et al., 2010). Despite the afore-mentioned negative evidence, some studies have shown improvements in certain cognitive domains following HF-rTMS of the lDLPFC in depressed patients (Hoy, Segrave, Daskalakis, & Fitzgerald, 2012; Moser et al., 2002; Vanderhasselt, De Raedt, Leyman, & Baeken, 2009). In a recent systematic review, the authors proposed a grouping of cognitive domains into those consistently associated with improvement following rTMS (e.g., verbal learning, verbal memory, psychomotor speed) and those mostly unaffected by it (e.g., attention, verbal fluency, working memory) (Serafini et al., 2015). In this context, our results suggest that decision-making and impulse control likely belong to the latter category and, when viewed more broadly, seem to support the notion that the cognitive effects of HF-rTMS in MDD are contingent on the specific types of neuropsychological assessments and/or treatment parameters employed. Alternatively, it is possible that significant changes in cognition might only occur with more prolonged, or spaced, rTMS treatment protocols, as reported by Kedzior and colleagues (2012), who found a significant improvement in performance accuracy on a modified concept-shifting task on the last 10 days - but not on the first 10 - of a 20-day protocol of HF-rTMS applied over the lDLPFC of 10 depressed individuals. Similarly, changes in decision-making and impulse control might only occur *after* a certain period of time following the alleviation of the depressive/anxious symptoms.

LIMITATIONS

There are a number of limitations to this study that deserve to be mentioned. First, this was a moderately sized open-label trial and therefore it is subject to confound including treatment expectations on the part of patients and clinicians alike. Furthermore, because of its design, we could not estimate the significance of the placebo effect (although indirect evidence suggests that individuals with treatment-resistant depression are less prone to be influenced by it than those with uncomplicated MDD) (Dunner et al., 2006; Fekadu et al., 2009; Fournier et al., 2010). We also cannot exclude the possibility that the concomitant pharmacological treatment received by the participants might have been associated with neuropsychological effects of their own. Finally, although the neurocognitive battery employed in this study is well established in clinical research, none of the individual tasks allows for a detailed dissection of their underlying component processes/computations and this might have limited our ability to detect more subtle HF-rTMS-related cognitive changes.

CONCLUSION

The current study serves as a preliminary step towards a better understanding of the longitudinal effects (or lack thereof) of HF-rTMS applied over the lDLPFC of depressed individuals on decision-making and impulse control. Clearly, additional investigations with sham-controlled designs, larger samples, more sensitive neurocognitive tasks, and longer follow-up periods are needed to further explore this relevant issue.

REFERENCES

1. Baxter, L. R., Jr., Schwartz, J. M., Phelps, M. E., Mazziotta, J. C., Guze, B. H., Selin, C. E., . . . Sumida, R. M. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry, 46*(3), 243-250.

2. Bechara, A., Damasio, H., Damasio, A. R., & Lee, G. P. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci, 19*(13), 5473-5481.

3. Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol, 56*(6), 893-897.

4. Berlim, M. T., van den Eynde, F., Tovar-Perdomo, S., & Daskalakis, Z. J. (2014). Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychological ...*, 1-15. doi: 10.1017/S0033291713000512

5. Brand, M., Fujiwara, E., Borsutzky, S., Kalbe, E., Kessler, J., & Markowitsch, H. J. (2005). Decision-making deficits of korsakoff patients in a new gambling task with explicit rules: associations with executive functions. *Neuropsychology, 19*(3), 267-277. doi: 10.1037/0894-4105.19.3.267

6. Daskalakis, Z. J., Levinson, A. J., & Fitzgerald, P. B. (2008). Repetitive transcranial magnetic stimulation for major depressive disorder: a review. *Can J Psychiatry, 53*(9), 555-566.

7. Demirtas-Tatlidede, A., Mechanic-Hamilton, D., Press, D. Z., Pearlman, C., Stern, W. M., Thall, M., & Pascual-Leone, A. (2008). An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry, 69*(6), 930-934.

8. Drevets, W. C., Videen, T. O., Price, J. L., Preskorn, S. H., Carmichael, S. T., & Raichle, M. E. (1992). A functional anatomical study of unipolar depression. *J Neurosci, 12*(9), 3628-3641.

9. Dunner, D. L., Rush, A. J., Russell, J. M., Burke, M., Woodard, S., Wingard, P., & Allen, J. (2006). Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry, 67*(5), 688-695.

10. Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., & Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Hum Brain Mapp, 28*(5), 409-423. doi: 10.1002/hbm.20291

11. Evans, V. C., Iverson, G. L., Yatham, L. N., & Lam, R. W. (2014). The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. *J Clin Psychiatry, 75*(12), 1359-1370. doi: 10.4088/JCP.13r08939

12. Fekadu, A., Wooderson, S. C., Markopoulo, K., Donaldson, C., Papadopoulos, A., & Cleare, A. J. (2009). What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J Affect Disord, 116*(1-2), 4-11. doi: 10.1016/j.jad.2008.10.014

13. Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA, 303*(1), 47-53. doi: 10.1001/jama.2009.1943

14. Fuster, J. M. (2015). *The Prefrontal Cortex* (Fourth ed.): Academic Press London.

15. Galynker, II, Cai, J., Ongseng, F., Finestone, H., Dutta, E., & Serseni, D. (1998). Hypofrontality and negative symptoms in major depressive disorder. *J Nucl Med, 39*(4), 608-612.

16. George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., . . . Sackeim, H. A. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry, 67*(5), 507-516. doi: 67/5/507 [pii]

17. 10.1001/archgenpsychiatry.2010.46

18. Guse, B., Falkai, P., & Wobrock, T. (2010). Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *J Neural Transm, 117*(1), 105-122. doi: 10.1007/s00702-009-0333-7

19. Hausmann, A., Pascual-Leone, A., Kemmler, G., Rupp, C. I., Lechner-Schoner, T., Kramer-Reinstadler, K., . . . Weiss, E. M. (2004). No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *J Clin Psychiatry, 65*(6), 772-782.

20. Herwig, U., Satrapi, P., & Schonfeldt-Lecuona, C. (2003). Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation. *Brain Topogr, 16*(2), 95-99.

21. Holtzheimer, P. E., 3rd, McDonald, W. M., Mufti, M., Kelley, M. E., Quinn, S., Corso, G., & Epstein, C. M. (2010). Accelerated repetitive transcranial magnetic stimulation for treatment-resistant depression. *Depress Anxiety, 27*(10), 960-963. doi: 10.1002/da.20731

22. Hoogendam, J. M., & Ramakers, G. M. J. a. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimul, 3*(2), 95--118. doi: 10.1016/j.brs.2009.10.005

23. Hoy, K. E., Segrave, R. A., Daskalakis, Z. J., & Fitzgerald, P. B. (2012). Investigating the relationship between cognitive change and antidepressant response following rTMS: a large scale retrospective study. *Brain Stimul, 5*(4), 539-546. doi: 10.1016/j.brs.2011.08.010

24. Huang, C. C., Su, T. P., Shan, I. K., & Wei, I. H. (2004). Effect of 5 Hz repetitive transcranial magnetic stimulation on cognition during a Go/NoGo task. *J Psychiatr Res, 38*(5), 513-520. doi: 10.1016/j.jpsychires.2004.01.006

25. Isenberg, K., Downs, D., Pierce, K., Svarakic, D., Garcia, K., Jarvis, M., . . . Kormos, T. C. (2005). Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Ann Clin Psychiatry, 17*(3), 153-159.

26. Kedzior, K. K., Rajput, V., Price, G., Lee, J., & Martin-Iverson, M. (2012). Cognitive correlates of repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant depression--a pilot study. *BMC Psychiatry, 12*, 163. doi: 10.1186/1471-244x-12-163

27. Klee, S. H., & Garfinkel, B. D. (1983). The computerized continuous performance task: a new measure of inattention. *J Abnorm Child Psychol, 11*(4), 487-495.

28. Lacerda, A. L. T., Keshavan, M. S., Hardan, A. Y., Yorbik, O., Brambilla, P., Sassi, R. B., . . . Soares, J. C. (2004). Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. *Biol Psychiatry, 55*, 353-358. doi: 10.1016/j.biopsych.2003.08.021

29. Leh, S. E., Petrides, M., & Strafella, A. P. (2010). The neural circuitry of executive functions in healthy subjects and Parkinson's disease. *Neuropsychopharmacology, 35*(1), 70-85. doi: 10.1038/npp.2009.88

30. Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., . . . Brown, R. A. (2002). Evaluation of a behavioral measure of risk taking: the Balloon Analogue Risk Task (BART). *J Exp Psychol Appl, 8*(2), 75-84.

31. Levasseur-Moreau, J., & Fecteau, S. (2012). Translational application of neuromodulation of decision-making. *Brain Stimul, 5*, 77-83. doi: 10.1016/j.brs.2012.03.009

32. Little, J. T., Kimbrell, T. A., Wassermann, E. M., Grafman, J., Figueras, S., Dunn, R. T., . . . Post, R. M. (2000). Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol, 13*(2), 119-124.

33. Logan, G. D., Cowan, W. B., & Davis, K. A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and a method. *J Exp Psychol Hum Percept Perform, 10*(2), 276-291.

34. Martis, B., Alam, D., Dowd, S. M., Hill, S. K., Sharma, R. P., Rosen, C., . . . Janicak, P. G. (2003). Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin Neurophysiol, 114*(6), 1125-1132.

35. Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci, 24*, 167-202. doi: 10.1146/annurev.neuro.24.1.167

36. Moreines, J. L., McClintock, S. M., & Holtzheimer, P. E. (2011). Neuropsychologic effects of neuromodulation techniques for treatment-resistant depression: a review. *Brain Stimul, 4*(1), 17-27. doi: 10.1016/j.brs.2010.01.005

37. Moser, D. J., Jorge, R. E., Manes, F., Paradiso, S., Benjamin, M. L., & Robinson, R. G. (2002). Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology, 58*(8), 1288-1290.

38. Must, A., Horvath, S., Nemeth, V. L., & Janka, Z. (2013). The Iowa Gambling Task in depression - what have we learned about sub-optimal decision-making strategies? *Frontiers in psychology, 4*, 732. doi: 10.3389/fpsyg.2013.00732

39. O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., . . . Sackeim, H. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry, 62*(11), 1208-1216.

40. Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. (2002). Rethinking feelings: an FMRI study of the cognitive regulation of emotion. *J Cogn Neurosci, 14*(8), 1215-1229. doi: 10.1162/089892902760807212

41. Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *Neuroimage, 23*(2), 483-499. doi: 10.1016/j.neuroimage.2004.06.030

42. Pallanti, S., Di Rollo, A., Antonini, S., Cauli, G., Hollander, E., & Quercioli, L. (2012). Low-frequency rTMS over right dorsolateral prefrontal cortex in the treatment of resistant depression: cognitive improvement is independent from clinical response, resting motor threshold is related to clinical response. *Neuropsychobiology, 65*(4), 227-235. doi: 10.1159/000336999

43. Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology, 36*(1), 183-206. doi: 10.1038/npp.2010.166

44. Pridmore, S., Fernandes Filho, J. A., Nahas, Z., Liberatos, C., & George, M. S. (1998). Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J ECT, 14*(1), 25-27.

45. Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2013). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*, 1-12. doi: 10.1017/s0033291713002535

46. Roth, B. J., Momen, S., & Turner, R. (1994). Algorithm for the design of magnetic stimulation coils. *Med Biol Eng Comput, 32*(2), 214-216.

47. Rothwell, J. C., Hallett, M., Berardelli, A., Eisen, A., Rossini, P., & Paulus, W. (1999). Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl, 52*, 97-103.

48. Rudiak, D., & Marg, E. (1994). Finding the depth of magnetic brain stimulation: a re-evaluation. *Electroencephalogr Clin Neurophysiol, 93*(5), 358-371.

49. Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., . . . Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry, 54*(5), 573-583.

50. Serafini, G., Pompili, M., Belvederi Murri, M., Respino, M., Ghio, L., Girardi, P., . . . Amore, M. (2015). The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review. *Neuropsychobiology, 71*(3), 125-139. doi: 10.1159/000381351

51. Shajahan, P. M., Glabus, M. F., Steele, J. D., Doris, A. B., Anderson, K., Jenkins, J. A., . . . Ebmeier, K. P. (2002). Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. *Prog Neuropsychopharmacol Biol Psychiatry, 26*(5), 945-954.

52. Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., . . . Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

53. Shimizu, Y., Kitagawa, N., Mitsui, N., Fujii, Y., Toyomaki, A., Hashimoto, N., . . . Kusumi, I. (2013). Neurocognitive impairments and quality of life in unemployed patients with remitted major depressive disorder. *Psychiatry Res, 210*(3), 913-918. doi: 10.1016/j.psychres.2013.08.030

54. Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychol Bull, 139*, 81-132. doi: 10.1037/a0028727

55. Speer, A. M., Repella, J. D., Figueras, S., Demian, N. K., Kimbrell, T. A., Wasserman, E. M., & Post, R. M. (2001). Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive

transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *J ECT, 17*(4), 259-263.

56. Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2006). The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment, 13*(1), 62-79. doi: 10.1177/1073191105283427

57. Vanderhasselt, M. A., De Raedt, R., Leyman, L., & Baeken, C. (2009). Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. *J Psychiatry Neurosci, 34*(2), 119-126.

58. Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annu Rev Biomed Eng, 9*, 527-565. doi: 10.1146/annurev.bioeng.9.061206.133100

59. Wajdik, C., Claypoole, K. H., Fawaz, W., Holtzheimer, P. E., 3rd, Neumaier, J., Dunner, D. L., . . . Avery, D. H. (2014). No change in neuropsychological functioning after receiving repetitive transcranial magnetic stimulation treatment for major depression. *J ECT, 30*(4), 320-324. doi: 10.1097/yct.0000000000000096

60. Woolley, S. B., Cardoni, A. A., & Goethe, J. W. (2009). Last-observation-carried-forward imputation method in clinical efficacy trials: review of 352 antidepressant studies. *Pharmacotherapy, 29*(12), 1408-1416. doi: 10.1592/phco.29.12.1408