Journal of Affective Disorders 217 (2017) 112–117

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

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

Santiago Tovar-Perdomo[a], Alexander McGirr[b], Frederique Van den Eynde[a], Nicole Rodrigues dos Santos[a], Marcelo T. Berlim[a,c,*]

[a] Neuromodulation Research Clinic, Douglas Mental Health University Institute and McGill University, Montréal, Québec, Canada
[b] Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada
[c] Depressive Disorders Program, Douglas Mental Health University Institute and McGill University, Montréal, Québec, Canada

ARTICLE INFO

Keywords:
Decision making
Impulse control
Major depressive disorder
Treatment resistant depression
Repetitive transcranial magnetic stimulation (rTMS)

ABSTRACT

Objectives: This open-label pilot study explored the effects of a course of accelerated high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) on two neurocognitive domains (decision-making and impulse control) in patients with major depressive disorder (MDD).
Methods: Participants with MDD and a treatment resistant major depressive episode (n = 24) underwent twice-daily HF-rTMS targeted at the left dorsolateral prefrontal cortex (lDLPFC) over two weeks. Psychopathology was assessed by clinician-administered and self-reported measures of depression and anxiety; decision-making was assessed by the Iowa Gambling Task, the Balloon Analog Risk Task and the Game of Dice Task; impulse control was assessed by the Stroop Color-Word Task, the Continuous Performance Task and the Stop-Signal Task.
Results: Depression and anxiety scores significantly improved from pre-post HF-rTMS treatment. However, none of the decision-making or impulse control variables of interest changed significantly from pre-post HF-rTMS. Moreover, there was no correlation between changes in psychopathological symptoms and in neurocognition.
Limitations: This is a moderately sized open label trial, and the confounds of ongoing psychotropics and illness chronicity can not be excluded in this treatment resistant sample.
Conclusions: There is dissociation between acute symptomatic benefit after a course of accelerated HF-rTMS applied to the lDLPFC in treatment resistant MDD and performance on tests of decision making and impulse control. Though rTMS appears cognitively safe, additional research is warranted to understand this potential dissociation and its putative clinical implications.

1. Background

High frequency repetitive transcranial magnetic stimulation (HF-rTMS) is a non-invasive neuromodulation technique that involves the electromagnetic induction of electrical currents within the cortex (Daskalakis et al., 2008). These electrical currents, in turn, are able to directly depolarize neuronal membranes located up to 1.5 cm in depth (Roth et al., 1994; Rothwell et al., 1999; Rudiak and Marg, 1994).

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 ≥10 daily sessions (Berlim et al., 2014), and we have recently reported clinical effectiveness of accelerated rTMS (McGirr et al., 2015) wherein treatments are provided over a condensed time course. Furthermore, growing evidence suggests the safety and tolerability of rTMS, including its neuropsychological profile (Guse et al., 2010; Moreines et al., 2011). This is especially relevant considering that cognitive dysfunction is a core feature of MDD (Rock et al., 2013; Snyder, 2013) that is usually associated with negative outcomes (Evans et al., 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,

Abbreviations: Rtms, Repetitive Transcranial Magnetic Stimulation; HF, High-Frequency; DLPFC, Dorsolateral Prefrontal Cortex; Hz, Hertz; EEG, Electroencephalogram; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; MINI, Mini International Neuropsychiatric Interview; QIDS, Quick Inventory of Depressive Symptomatology; BAI, Beck Anxiety Inventory; IGT, Iowa Gambling Task; BART, Balloon Analog Risk Task; GofD, Game of Dice Task; SCWT, Stroop Color-Word Task; CT, Continuous Performance Task; SST, Stop-Signal Task; SSD, stop signal delay; SSRT, stop-signal reaction time

* Corresponding author: Dr Marcelo T. Berlim, Douglas Mental Health University Institute, 6875 LaSalle Blvd., Montréal, Québec, Canada H4H 1R3.
E-mail address: nrc.douglas@me.com (M.T. Berlim).

http://dx.doi.org/10.1016/j.jad.2017.03.075
Received 14 January 2017; Accepted 30 March 2017
Available online 06 April 2017

and it might be even associated with improvements in 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 despite it being associated with clear parallel reductions in depressive symptomatology (Demirtas-Tatlidede et al., 2008; Huang et al., 2004; Isenberg et al., 2005; Kedzior et al., 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 positively affected by HF-rTMS and whether these putative improvements are directly related to changes in depressive symptomatology or, alternatively, are mood-independent.

Cognitive performance has been examined in conjunction with pharmacological management of MDD. Pharmacotherapy seems to be associated with improvements in cognition, however the effect sizes are small (Keefe et al., 2014; Rosenblat et al., 2015) and cognitive dysfunction can persist after clinical remission (Shilyansky et al., 2016). Yet, newer antidepressants are being more extensively investigated for their pro-cognitive potential (Mahableshwarkar et al., 2015; McIntyre et al., 2014), and there is likely to be heterogeneity between antidepressant agents that has not yet been fully explored. There is, however, data to suggest that among remitted patients, certain cognitive deficits improve after the discontinuation of antidepressants (Herrera-Guzman et al., 2010), raising the possibility of deleterious effects that could be circumvented with non-pharmacological interventions such as rTMS.

Therefore, we longitudinally assessed the effects of 20 sessions of HF-rTMS applied to the lDLPFC of depressed outpatients on measures of decision-making and impulse control - two domains that have been shown to be impaired in MDD (Lacerda et al., 2004; Must et al., 2013). We hypothesized that HF-rTMS would be associated with significant improvements in performance on the tasks assessing these domains, and that these longitudinal neurocognitive improvements would be significantly and inversely correlated with improvements in depressive symptomatology.

2. Methods

2.1. Design overview

This clinical trial was approved by the Douglas Mental Health University Institute's Ethics Review Board and has been registered at www.clinicaltrials.gov under identifier # NCT02125799. Eligible participants received HF-rTMS applied to the lDLPFC for 2 consecutive weeks. They performed a neurocognitive battery and were assessed in terms of their psychopathology at baseline and within 5 days after their last HF-rTMS session (week 3).

2.2. 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 MDD currently experiencing a major depressive episode (MDE) according to the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). They had to have failed to respond to at least 2 adequate courses (in terms of dose, duration and adherence) of antidepressants in the current MDE, as assessed by the Antidepressant Treatment History Form (Sackeim, 2001). 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 to 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 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.

2.3. 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 (F3 position (Herwig et al., 2003)). The resting motor threshold was determined weekly using the visualization method (Pridmore et al., 1998). Patients received 2 daily sessions of HF-rTMS (separated by a 45-min interval) for 2 weeks (20 total sessions). Stimulation was delivered at 10 Hz in 75 trains with a 26 s inter-train interval at 120% of the resting motor threshold (60,000 total pulses) (George et al., 2010; O'Reardon et al., 2007).

2.4. Psychopathology assessment

Patients were assessed 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 et al., 1988).

2.5. Neurocognitive assessment

The neurocognitive battery was composed of six computerized tasks presented in a pseudo-randomized sequence using Inquisit v4 (Millisecond Software, USA). Data were collected through a response pad (RB-540 model, Cedrus, USA), which offered 2–3 ms temporal fidelity. Subjects were seated at approximately 70 cm from the computer screen, which was positioned at the eye level. Participants were provided written instructions and conducted a brief practice session prior to commencement.

2.5.1. Decision-making

We used three tasks to tap into the decision-making construct: the Iowa Gambling Task (IGT) (Bechara et al., 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 half of the decks are disadvantageous (i.e., are associated with immediate gains but long-term losses) and half are advantageous (i.e., are associated with small immediate and long-term gains). Successful performance in the IGT 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. The net score is computed by subtracting disadvantageous draws from advantageous draws. Contrary to the IGT, the BART assesses risk taking without an explicit learning process. The BART requires participants to inflate 30 virtual balloons by repeatedly pressing a key on the response pad. Every ‘pump’ gives C$.05 added to a ‘temporary bank’ that the participant can transfer to a “permanent bank” at any time. Each balloon is programmed to pop