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Modulation of motor cortex excitability predicts antidepressant response to prefrontal cortex repetitive transcranial magnetic stimulation

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsolateral prefrontal cortex (DLPFC) is a treatment option for patients with medication-resistant major depressive disorder (MDD). However, antidepressant response is variable and there are currently no response predictors with sufficient accuracy for clinical use.
Objective: We report on results of an observational open-label study to determine whether the modulatory effect of 10 Hz motor cortex (MC) rTMS is predictive of the antidepressant effect of 10 Hz DLPFC rTMS.
Methods: Fifty-one medication-resistant MDD patients were enrolled for a 10-day treatment course of DLPFC rTMS and antidepressant response was assessed according to post-treatment reduction of the 17-item Hamilton Rating Scale for Depression score. Prior to treatment, we assessed the modulation of motor evoked potential (MEP) amplitude by MC rTMS. MEP's were induced with single TMS pulses and measured using surface electromyography. MEP modulation was calculated as the change of mean MEP amplitude after MC rTMS.
Results: MEP modulation proved to be a robust predictor of reduction of clinician-rated depression severity following the course of DLPFC rTMS: larger MC rTMS-induced increase of corticospinal excitability anticipated a better antidepressant response. This was found both in univariate analyses (Spearman regression: rho = 0.43, $p < 0.005$) and a multivariable linear regression model ($\beta = 0.25$, $p < 0.0001$) controlling for baseline depression severity, age and resting motor threshold.
Conclusions: These findings suggest that MC rTMS-induced modulation of corticospinal excitability warrants further evaluation as a potential predictive biomarker of antidepressant response to left DLPFC 10 Hz rTMS.

Introduction

Major depressive disorder (MDD) is a common disorder, frequently with a chronic and disabling course [1], and partial or non-response to first-line treatment options [2,3]. Transcranial magnetic stimulation (TMS), a technique based on electromagnetic induction, allows for focal non-invasive modulation of neural activity in discrete cortical regions [4]. Repetitive TMS (rTMS) has therapeutic effects in MDD when applied at high frequencies (10 or 20 Hz) to the left dorsolateral prefrontal cortex (DLPFC) [5–7], and

Abbreviations: APB, *abductor pollicis brevis* muscle; AUC, area under the curve; BDI-II, 21-item Beck Depression Inventory-II; DLPFC, dorsolateral prefrontal cortex; EMG, electromyography; HAM-D-17, 17-item Hamilton Rating Scale for Depression; MC, motor cortex; MDD, major depressive disorder; MEP, motor evoked potentials; RMT, resting motor threshold; ROC, receiver operating characteristic; rTMS, repetitive TMS; TMS, Transcranial Magnetic Stimulation.

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is useful in patients with medication-resistant MDD [8]. However, not all DLPFC rTMS candidates respond to treatment, with certain factors, such as age, medication resistance and episode duration [8–10], predicting poor antidepressant response, and others, such as psychomotor retardation and baseline sleep disturbance [9,11], predicting enhanced response. Unfortunately, while these factors predict antidepressant response to rTMS at a group level, they are not sufficiently accurate to guide decisions regarding individual patients (e.g., patient selection).

Variability in antidepressant efficacy of rTMS also depends on treatment parameters, namely stimulation intensity [12] and stimulation site [13], raising the possibility of individualizing such parameters in order to optimize antidepressant response [12,13]. To this end, definition of rTMS-related biomarkers will be instrumental for accurate identification of patients in need of parameter adjustment (i.e., those who would otherwise not improve with DLPFC rTMS) and for correct definition of individual parameter adjustments [14]. Intrinsic connectivity has been proposed as a biomarker for individualization of the stimulation target [15,16], but strategies to optimize rTMS stimulation intensity are lacking. Currently, in an attempt to balance treatment efficacy and safety, intensity is adjusted for each patient as a percentage of the resting motor threshold (RMT), i.e the minimum intensity needed to reliably produce an electromyographic (EMG) or movement response in a finger, when the contralateral motor cortex (MC) is stimulated [17]. RMT-adjustment of stimulation intensity for safety purposes is unquestioned [17]. However, the relationship of RMT with final antidepressant response is equivocal [10,18], possibly because rTMS intensity is associated with antidepressant response [19], and absolute intensity is defined according to RMT. Finally, other biomarkers proposed for rTMS intensity adjustment, namely coil-to-cortex distance, an indirect measure of cerebral atrophy, were of limited success [20].

It is thought that the therapeutic antidepressant effects of rTMS are mediated by modulation of prefrontal cortex excitability [5,21]. However, measurements of the relationship between rTMS-induced modulation of cortical excitability and clinical response to DLPFC rTMS have not been performed. Such studies could provide novel biomarkers for patient selection and individualization of treatment parameters and, in addition, contribute towards a better understanding of the mechanisms underlying rTMS efficacy. Here we examined whether modulation of motor cortex excitability by rTMS, measured prior to DLPFC rTMS treatment, is predictive of antidepressant treatment efficacy. Excitability modulation of the motor cortex, rather than the prefrontal cortex, was tested because it can be readily assessed by measures of corticospinal excitability, such as the amplitude of TMS-induced motor evoked potentials (MEP) [22]. We hypothesized that facilitatory modulation of corticospinal excitability would be related to an enhancement of antidepressant response.

Material and methods

Subjects

To address our hypothesis, an observational open-label study was conducted in medication-resistant outpatients, fulfilling DSM-IV criteria for the diagnosis of MDD, and who had failed at least three trials of adequate psychopharmacology treatment. Exclusion criteria were based on international safety guidelines for use of TMS [17]. Participants were selected from 73 patients referred to the Berenson-Allen Center for Noninvasive Brain Stimulation for rTMS for treatment of MDD (Fig. 1), 51 of who were eligible and consented to participate. In these participants, a stable antidepressant medication regimen was maintained 4 weeks prior to the trial and throughout rTMS treatment. Five participants did not complete the rTMS treatment protocol and one had missing data regarding primary and secondary outcomes. The study was carried out in accordance with the Declaration of Helsinki and approved by the Beth Israel Deaconess Medical Center's Internal Review Board. Informed consent for experimentation with human subjects was obtained from all subjects.

Clinical ratings and response classification

Severity of depression was assessed at baseline and after 2 weeks of rTMS treatment, with the clinician-rated 17-item Hamilton Rating Scale for Depression (HAM-D-17 [23,24]), administered by a board-certified psychiatrist, and the self-report 21-item Beck Depression Inventory-II (BDI-II [25,26]). Clinical response to rTMS was calculated as the percentage of score reduction after the second week of treatment, relative to baseline, on the HAM-D-17 (primary outcome measure: $HAM-D-17_{baseline} - \frac{HAM-D-17_{post-treatment}}{HAM-D-17_{baseline}} \times 100$) and BDI-II scores (secondary outcome measure: $\frac{BDI-II_{baseline} - BDI-II_{post-treatment}}{BDI-II_{baseline}} \times 100$). Positive values reflect a decrease in HAM-D-17 or BDI-II scores after treatment, representing improvement in depression symptoms after rTMS, while negative values denote worsening of severity of symptoms. Exploratory analyses were conducted on the number of patients responding to treatment (responders), defined according to a reduction of symptom severity of at least 50% after 2 weeks of treatment, as measured by HAM-D-17 total scores.

TMS procedures

TMS was performed using a Magstim SuperRapid Stimulator (Magstim Company Ltd., UK) equipped with a commercially available 70-mm figure-of-eight coil. Sites for TMS were marked on a tightly fitting swimming cap placed on each patient's head, to ensure accurate repositioning of the coil. For all procedures, the coil was held at approximately 45° to the midline and positioned tangentially to the skull with the handle pointing backward. Patients were seated in a comfortable chair with the elbow semi-flexed, and instructed to keep their hands as relaxed as possible. Resting motor threshold, established prior to all rTMS sessions, was defined using EMG techniques and according to international recommendations [27], as the lowest intensity of a single TMS pulse capable of eliciting at least 5 MEPs, with amplitude of at least 50 μV peak-to-peak, in a series of 10 consecutive single pulses delivered to the MC. Muscle activity was recorded with surface electrodes (Ag-AgCl, 10 mm diameter) overlying the right *abductor pollicis brevis* (APB) muscle, and surface EMG signals were amplified (×1000), filtered (20–1000 Hz) and sampled at 2000 Hz (PowerLab 4/25T, AD Instruments Ltd., Australia; Scope, version 4.0). The optimal scalp position over the MC to elicit maximal amplitude MEPs in the APB was identified (APB 'hotspot'), and pulses were delivered with an inter-stimulus interval of at least 7s.

In an initial rTMS session (day 0), we assessed the modulation of MC excitability by rTMS [22], in accordance with methods previously applied by Maeda and colleagues to obtain mostly, but not exclusively, MEP facilitation in a sample of healthy individuals [28]. For that purpose, MEPs were induced using single TMS pulses, delivered to the MC at an intensity of 120% of RMT, with a random stimulus interval of approximately 10 s (±1 s). Muscle relaxation was monitored through visual inspection of EMG signal, to ensure that single-pulses were delivered in the absence of active muscle contraction. MEP amplitude was measured peak-to-peak and averaged across 10 consecutive MEPs. Patients then received a single rTMS session over the APB 'hotspot' with the same