Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression

Jonathan Downar, Joseph Geraci, Tim V. Salomons, Katharine Dunlop, Sarah Wheeler, Mary Pat McAndrews, Nathan Bakker, Daniel M. Blumberger, Zafiris J. Daskalakis, Sidney H. Kennedy, Alastair J. Flint, and Peter Giacobbe

Background: Depression is a heterogeneous mental illness. Neurostimulation treatments, by targeting specific nodes within the brain's emotion-regulation network, may be useful both as therapies and as probes for identifying clinically relevant depression subtypes.

Methods: Here, we applied 20 sessions of magnetic resonance imaging-guided repetitive transcranial magnetic stimulation (rTMS) to the dorsomedial prefrontal cortex in 47 unipolar or bipolar patients with a medication-resistant major depressive episode.

Results: Treatment response was strongly bimodal, with individual patients showing either minimal or marked improvement. Compared with responders, nonresponders showed markedly higher baseline anhedonia symptomatology (including pessimism, loss of pleasure, and loss of interest in previously enjoyed activities) on item-by-item examination of Beck Depression Inventory-II and Quick Inventory of Depressive Symptomatology ratings. Congruently, on baseline functional magnetic resonance imaging, nonresponders showed significantly lower connectivity through a classical reward pathway comprising ventral tegmental area, striatum, and a region in ventromedial prefrontal cortex. Responders and nonresponders also showed opposite patterns of hemispheric lateralization in the connectivity of dorsomedial and dorsolateral regions to this same ventromedial region.

Conclusions: The results suggest distinct depression subtypes, one with preserved hedonic function and responsive to dorsomedial rTMS and another with disrupted hedonic function, abnormally lateralized connectivity through ventromedial prefrontal cortex, and unresponsive to dorsomedial rTMS. Future research directly comparing the effects of rTMS at different targets, guided by neuroimaging and clinical presentation, may clarify whether hedonia/reward circuit integrity is a reliable marker for optimizing rTMS target selection.

Key Words: Anhedonia, betweenness, depression, dorsomedial, fMRI, graph theory, prefrontal, rTMS, stimulation, subtype

Major depression is heterogeneous in its course, symptomatology, and responsiveness to treatment. A variety of clinical features or biomarkers have been proposed to reliably parse this heterogeneity into subtypes useful for prognosis or treatment selection. Examples include Leonhard's (1) original distinction between unipolar and bipolar illness, as well as later proposed distinctions between melancholic and atypical depression (2), responsiveness to the dexamethasone suppression test (3), and the presence of agitation or mixed features (4). However, the utility of most such clinical features in guiding treatment selection remains controversial.

From the MRI-Guided rTMS Clinic (JD, TVS, PG), Toronto Western Hospital; Department of Psychiatry (JD, JG, TVS, SHK, AJF, PG), University Health Network; Toronto Western Research Institute (SW, MPM), University Health Network; Department of Psychiatry (JD, JG, TVS, DMB, ZJD, SHK, AJF, PG), Faculty of Arts and Sciences (KD), and Institute of Medical Sciences (JD, MPM, NB, ZJD, SHK), University of Toronto; and Temerty Centre for Therapeutic Brain Intervention (DMB, ZJD), Centre for Addiction and Mental Health, Toronto, Canada.

Address correspondence to Jonathan Downar, M.D., Ph.D., F.R.C.P.C., University Health Network, Department of Psychiatry, MRI-Guided rTMS Clinic, 399 Bathurst Street 7M-415, Toronto, Ontario M5T 2S8, Canada; E-mail: jonathan.downar@uhn.ca.

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Anhedonia is a core symptom of depression in the DSM-IV diagnostic criteria and is drawing increasing attention as a key feature of the illness (5,6). Overall, studies using behavioral, pharmacologic, and neuroimaging methods suggest a disruption of the appetitive and consummatory aspects of reward in depression (7–11). However, its potential relevance to treatment selection and outcome prediction has received relatively little attention to date.

Current neuroimaging-based models of depression posit network-level changes in the interactions between emotion-regulating regions, including dorsomedial prefrontal cortex (DMPFC) and ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex, and dorsal and ventral anterior cingulate cortex (ACC), as well as amygdala, hippocampus, and brainstem monoaminergic nuclei (12–17). The implications of this model are twofold: first, that different clinical subtypes of depressive illness could arise from different patterns of network disruption, and second, that different treatment modalities could target this network at different points, thus addressing specific subtypes of illness.

Neuromodulation techniques, such as deep brain stimulation (DBS) or repetitive transcranial magnetic stimulation (rTMS), are neuroanatomically specific in their effects on brain activity. Any putative network-level subtypes of depression might therefore be most readily apparent with these treatment modalities. Deep brain stimulation and rTMS may therefore be useful not only as therapies but also as tools for parsing the heterogeneity of depression in ways that are intrinsically relevant to treatment selection.

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In depression, the conventional rTMS target is the DLPFC (18,19). However, convergent evidence from lesion, stimulation, and neuroimaging studies (20) suggests that the DMPFC may also play a central role in depression. Dorsomedial prefrontal cortex lesions confer a strong risk of depressive symptoms (21,22). Inadvertent deactivation of DMPFC via DBS can precipitate immediate depressive symptomatology (23). The DMPFC also shows consistent gray matter reduction in volumetric studies of depression (24). Resting-state functional magnetic resonance imaging (fMRI) studies have characterized the DMPFC as a dorsal nexus region where networks for cognitive control, default-mode rumination, and somatic marker generation converge in depressed patients but not healthy control subjects (16). The DMPFC may therefore present a promising target for excitatory rTMS in depression (20), as suggested by a recent case report (25).

Aside from the dorsal nexus, other regions could potentially contribute to the heterogeneity of depression. The mathematical tools of graph theory, which enables detailed analysis of complex network topology (26), are now being used to identify pathologic patterns of brain activity in Alzheimer dementia, schizophrenia, autism, and mood disorders (27–30). A particular network parameter, known as betweenness centrality (BC), measures the number of shortest paths between all other points A and B that pass through a given node. Nodes with high BC act as chokepoints that can be particularly damaging to network traffic if they are disrupted.

Betweenness centrality maps have been used to identify vulnerable points in energy transmission networks (31), critical proteins in biochemical pathways for therapeutic targeting in neurodegenerative disease (32,33), and abnormal patterns of whole-brain functional connectivity in Alzheimer dementia (34). Betweenness centrality has also recently been applied to resting-state fMRI series to distinguish patients with depression from healthy control subjects (35). However, to our knowledge, this approach has never previously been used to distinguish responders from nonresponders to a given treatment.

In the present study, we first sought to employ DMPFC-rTMS as a probe, as well as a treatment, to test the hypothesis that this intervention would reveal discrete subtypes of patients (as opposed to a unimodal continuum of response) within a heterogeneous sample of patients with treatment-refractory depression. Since virtually no studies of DMPFC-rTMS have been performed to date, we then adopted a more descriptive approach, examining pretreatment clinical and fMRI data to characterize the subtypes in greater detail, both in terms of symptomatology and BC maps of brain activity. Finally, we assessed the congruency of the clinical-symptom outcome predictors with the neural activity outcome predictors.

Methods and Materials

Design Overview

This study investigated the effects of 20 sessions of open-label, add-on bilateral magnetic resonance imaging (MRI)-guided rTMS of the DMPFC in a series of patients meeting DSM-IV criteria for unipolar or bipolar disorder and a current major depressive episode resistant to medication. Following initial clinical assessment, patients underwent MRI and a baseline symptom assessment before motor threshold testing, then began treatment 3 days later. During treatment, patients completed daily self-assessment questionnaires and weekly clinician-rated assessments as described below. Patients achieving response but not remission criteria were offered an additional 10 sessions (2 weeks) of treatment. Patients then underwent clinical assessments at 2, 4, 6, 12, and 26 weeks posttreatment to assess clinical response. Supplement 1 provides a more detailed description of all methods used.

Subjects

Subjects were a series of 47 consecutive patients (20 male patients, 27 female patients, age 42.2 ± 12.7 years), with either unipolar ($n = 38$) or bipolar ($n = 9$) illness referred to the University Health Network's MRI-Guided rTMS Clinic for the treatment of a major depressive episode. All patients had a clinical history of resistance to at least two adequate medication trials (discontinuation of a medication trial due to adverse effects also being included in this count), including at least one trial in the current episode. Baseline symptom severity was a mean 22.7 ± SD 6.8 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) and 32.6 ± SD 10.6 on the Beck Depression Inventory-II (BDI-II). Major depressive episode duration was a mean 40.6 months ± SD 55.7. The total number of previous medication trials (including antidepressants and add-on mood stabilizers, antipsychotics, or psychostimulants, discontinued due to either intolerance or inefficacy) ranged from 2 to 25 (mean 6.7 ± SD 4.3). Seven patients had also previously failed to respond to electroconvulsive therapy.

Regarding exclusion criteria, no patients with active substance use or psychotic disorders participated in the study. Patients with potential contraindications to rTMS or MRI, including a history of seizures, implanted devices, foreign metal bodies, cardiac arrhythmia, unstable medical conditions, or pregnancy, were excluded from treatment. All patients had maintained a stable regimen of medications for ≥4 weeks before treatment, with no changes throughout the course of treatment. All patients provided informed consent to treatment, and the study was approved by the Research Ethics Board of the University Health Network.

rTMS Treatment Parameters

Repetitive transcranial magnetic stimulation was delivered using a MagPro R30 rTMS device (MagVenture, Farum, Denmark) via a Cool-DB80 stimulation coil. The coil vertex was placed over the DMPFC under MRI guidance using the Visor 2.0 system (Advanced Neuro Technologies, Enschede, The Netherlands). The details of MRI acquisition, neuronavigation, and motor threshold procedures are described in Supplement 1. Stimulation was delivered at 120% of resting motor threshold, at 10 Hz, with a duty cycle of 5 seconds on and 10 seconds off, for a total of 3000 pulses in 60 trains per hemisphere per session. Preferential stimulation of each hemisphere was accomplished by lateral coil orientation (36,37) (Figure 1A).

Clinical Assessments

In the week before treatment, before motor threshold testing, patients underwent a baseline clinical assessment incorporating the HAMD-17 as the primary outcome measure (38). Patients also completed a battery of self-report BDI-II (39), Beck Anxiety Inventory (40), 16-item self-rated Quick Inventory of Depressive Symptomatology (QIDS) (41), Sheehan Disability Scale (42), Quality of Life Enjoyment and Satisfaction Questionnaire (43), and Warwick-Edinburgh Mental Well-Being Scale (44). This set of clinician-rated and self-report assessments was repeated after each five sessions of treatment, with follow-up assessments scheduled 2, 4, 6, 12, and 26 weeks posttreatment. The Clinical Global Impression of severity was also obtained before and after treatment and the Clinical Global Impression-Improvement measure was collected posttreatment.