Published in final edited form as:

Brain Stimul. 2017 ; 10(5): 919–925. doi:10.1016/j.brs.2017.07.002.

Functional Connectivity of the Left DLPFC to Striatum Predicts Treatment Response of Depression to TMS

Michael Avissar^{1,*}, Fon Powell^{b,*}, Irena Ilieva^{a,e}, Matteo Respino², Faith M. Gunning^{a,e}, Conor Liston^{a,c,d}, and Marc J. Dubin^{a,d}

^aDepartment of Psychiatry, Weill Cornell Medical College-New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, U.S

^bDepartment of Radiology, Weill Cornell Medical College-New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, U.S

^cSackler Institute for Developmental Psychobiology, Weill Cornell Medical College-New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, U.S

^dFeil Family Brain and Mind Research Institute, Weill Cornell Medical College-New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, U.S

^eInstitute of Geriatric Psychiatry, Weill Cornell Medical College-New York Presbyterian Hospital, 525 East 68th Street, New York, NY 10065, U.S

¹Division of Experimental Therapeutics, New York State Psychiatric Institute/Columbia University Medical Center, 1051 Riverside Drive, New York, NY 10032

²Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy

Abstract

Background—Repetitive transcranial magnetic stimulation (TMS) is a non-invasive, safe, and efficacious treatment for depression. TMS has been shown to normalize abnormal functional connectivity of cortico-cortical circuits in depression and baseline functional connectivity of these circuits predicts treatment response. Less is known about the relationship between functional connectivity of frontostriatal circuits and treatment response.

Objective/Hypothesis—We investigated whether baseline functional connectivity of distinct frontostriatal circuits predicted response to TMS.

Methods—Resting-state fMRI (rsfMRI) was acquired in 27 currently depressed subjects with treatment resistant depression and 27 healthy controls. Depressed subjects were treated with 5 weeks of daily TMS over the left dorsolateral prefrontal cortex (DLPFC). The functional

Address all correspondence to Marc Dubin at mrd9035@med.cornell.edu.

*Michael Avissar and Fon Powell contributed equally to this work

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

connectivity between limbic, executive, rostral motor, and caudal motor regions of frontal cortex and their corresponding striatal targets were determined at baseline using an existing atlas based on diffusion tensor imaging. TMS treatment response was measured by percent reduction in the 24-item Hamilton Depression Rating Scale (HAMD24). In an exploratory analysis, correlations were determined between baseline functional connectivity and TMS treatment response.

Results—Seven cortical clusters belonging to the executive and rostral motor frontostriatal projections had reduced functional connectivity in depression compared to healthy controls. No frontostriatal projections showed increased functional connectivity in depression (voxel-wise $p < 0.01$, familywise $\alpha < 0.01$). Only baseline functional connectivity between the left DLPFC and the striatum predicted TMS response. Higher baseline functional connectivity correlated with greater reductions in HAMD₂₄ (Pearson's $R = 0.58$, $p = 0.002$).

Conclusion(s)—In an exploratory analysis, higher functional connectivity between the DLPFC and striatum predicted better treatment response. Our findings suggest that the antidepressant mechanism of action of TMS may require connectivity from cortex proximal to the stimulation site to the striatum.

Keywords

TMS; treatment resistant depression; functional connectivity; fMRI; frontostriatal; brain stimulation

Introduction

Repetitive transcranial magnetic stimulation (TMS) is a non-invasive, safe, and efficacious treatment for depression [1–7]. Although the efficacy of TMS for depression is well established, we are only beginning to understand its mechanism of action, which patients are most likely to respond, and how to personalize treatment to individually target abnormal neural circuitry [8–10].

Depression is associated with increased functional connectivity of the default mode network (DMN), a frontoparietal cortical network which is active when an individual is at rest while his or her mind wanders freely [11–14]. This state of hyperconnectivity correlates with scores of rumination and is thought to reflect abnormal negative self-referential thinking in the depressed state [12,15]. TMS has been shown to normalize elevated functional connectivity of the default mode network in depression [9,10,16–18]. At baseline, elevated functional connectivity of the subgenual anterior cingulate cortex (sgACC) with structures in the DMN and central executive networks predicts TMS response [10,16,19], as does strength of functional connectivity between cortex within the DLPFC and the sgACC [8,20].

Although the sgACC is central to network dysfunction in depression, the predictive role of other structures trans-synaptically connected to the TMS stimulation site is relatively unexplored. The potential role of functional connectivity of the striatum in predicting TMS response is of particular interest for several reasons. First, there are robust connections between all cortical areas and the striatum [21–25] and these connections are structurally [26,27] and functionally [28–32] disrupted in depression. Second, TMS for depression typically targets the dorsolateral prefrontal cortex (DLPFC) and, thus, via trans-synaptic

activation, the ipsilateral rostral striatum [25]. Third, TMS over frontal cortex induces striatal dopamine release in animal models [33,34] and in normal humans [35]. Finally, TMS over the left DLPFC induces striatal dopamine release in depressed subjects [36,37], suggesting that the integrity of this frontostriatal connection may be important for successful treatment if dopamine release is a mediator of the antidepressant effect of TMS.

We conducted an open-label, exploratory study of 27 depressed subjects who received daily TMS 5 times weekly for 5 weeks and 27 healthy controls who received no treatment. First, we tested for differences in functional connectivity of distinct frontostriatal projections in depressed subjects compared to controls. Next, we tested whether baseline functional connectivity of these projections in depressed subjects predicted treatment response. Finally, we investigated TMS-related changes in functional connectivity of frontostriatal projections. We hypothesized that higher functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and its striatal target correlates with better response of depression to TMS.

Materials and methods

Subjects

27 currently depressed patients and 27 health controls participated in the study. Patients were eligible for inclusion if they met DSM-IV Text Revision criteria for a major depressive episode with a diagnosis of major depressive disorder (24 subjects) or bipolar II disorder (3 subjects) and if they also met criteria for treatment resistance, defined as a failure to respond to at least two previous antidepressant trials at adequate doses for 8 weeks during the current episode. Patients with a baseline HAMD₂₄ score < 16 were excluded. In addition, patients with a history of neurological disorder or seizures were excluded, as well as any patients with metal implants or devices precluding them from having an MRI. Patients were allowed to continue their current psychiatric medications as long as doses remained stable starting from 4 weeks prior to beginning of the treatment trial. Additional inclusion and exclusion criteria have been previously reported [38]. All aspects of our experimental protocol were approved by the Institutional Review Board of Weill Cornell Medical College and conducted in accordance with institutional guidelines.

TMS Protocol

All 27 patients completed 25 sessions of 10-Hz excitatory TMS (NeuroStar TMS Therapy System; Neuronetics, Inc, Malvern, Pennsylvania) over the left DLPFC, administered daily, 5 days per week, for a 5-week period. The stimulation protocol has been described in detail previously. 3000 pulses of 10 Hz TMS were delivered in 4 second trains with a 26 second inter-train interval. The standard “Figure 8” NeuroStar TMS coil was centered over the scalp via the Beam F3 method [39] using surface distances between the nasion, inion, tragus and vertex as landmarks. Resting motor threshold (MT) was defined as the stimulus strength over the thumb area of motor cortex that produced visually detectable thumb movement on 50% of trials. MT was measured prior to the first treatment and prior to every fifth treatment thereafter. We aimed to stimulate at 120% of the resting MT and applied intensities of 80–120% to all subjects except for two, whose stimulation intensity was limited by scalp discomfort.

We assessed treatment response using the 24-item Hamilton Depression Rating Scale (HAMD₂₄) at baseline (1 to 3 days prior to the first TMS treatment) and 1 to 3 days after completing treatment. Responders were defined as having a ≥30% reduction in HAMD [40].

Magnetic Resonance Imaging Data Acquisition and Preprocessing

Magnetic resonance imaging data (collected on a 3.0 Tesla Signa Excite MRI Scanner; General Electric Co., Fairfield, Connecticut) were obtained from patients in two sessions that occurred within 7 days prior to the first TMS treatment and within 3 days after the final TMS treatment and from controls in an individual session. Each session included a resting-state fMRI (rsfMRI) sequence (repetition time = 2 sec, 180 volumes) and a T1-weighted anatomical scan. Preprocessing of rs-fMRI data was conducted with the AFNI (<http://afni.nimh.nih.gov/afni/>) and FSL (<http://www.fmrib.ox.ac.uk/fsl/>) software packages and included motion correction (AFNI), spatial smoothing (6-mm full-width half-maximum Gaussian kernel; FSL), temporal band-pass filtering (0.005–0.1 Hz; AFNI), linear and quadratic detrending (AFNI), and removal of nuisance signals by regression on six motion parameters (roll, pitch, yaw, and translation in three dimensions) and signal time courses for white matter and cerebrospinal fluid (CSF) regions-of-interest (ROIs) determined on an individual basis using an automated segmentation algorithm (FSL). We did not use global signal regression [41].

Regions of interest

To fully partition frontostriatal connectivity, we used previously described regions that were generated by probabilistic diffusion tractography, and that were based on the structural connectivity between functionally distinct frontal cortical regions and striatum (Fig. 1). These fronto-cortical regions of interest and striatal regions of interest correspond to limbic, executive, rostral motor, and caudal motor circuits. Although defined by structural connectivity, striatal sub-divisions in this atlas show significant homogeneity of dopamine signaling, suggesting the atlas has significant functional validity. The cortical and striatal regions of interest are publicly available as part of the Oxford-GSK-Imanova Striatal Connectivity Atlas [25]. These four striatal ROIs were chosen from a larger set of seven striatal ROIs from the same study, which also included three ROIs which connected respectively to the temporal, parietal and occipital lobes. However, we limited our analysis to the frontal ROIs because of their greater relevance in the pathophysiology of depression. Original ROIs were resampled from 1 mm³ to 3 mm³ resolution using a nearest neighbor approach. Location and size of the striatal regions of interest projecting to the frontal lobe are reported in table 1.

Functional connectivity analysis

To identify frontal cortical clusters that were abnormally connected in depression compared to controls, we first performed a voxel-by-voxel Gosset (student) t-test restricted to only the cortical voxels within the seed's network, comparing the depressed group at baseline to the healthy control group using AFNI's 3dttest++ function with age and gender as covariates (gender coded as −1 for female and 1 for male). This generated a statistical map for each of the four striatal seeds. Next, a Monte Carlo simulation was performed for each map using

AFNI's 3dclustsim function to determine statistical thresholds for voxel cluster size needed to achieve a family-wise $\alpha < 0.01$ at voxel-wise $p < 0.01$. Cortical clusters meeting the statistical threshold were tested for in each of the four maps.

The spatial mean connectivity value (Z) of each cluster was extracted for each subject at baseline. This was used to perform a multiple linear regression using baseline functional connectivity at each frontal cluster abnormally connected in depression as a predictor variable and percent change in HAMD (where symptomatic improvement was scored as a positive change in HAMD-24: (pre-post)/pre). For any cluster that showed a significant beta coefficient in this multiple regression, the Pearson correlation between baseline functional connectivity and change in HAMD-24 from baseline to post-TMS and the Pearson correlation between change in functional connectivity and change in HAMD-24 was determined.

Results

Subject characterization

Twenty-seven outpatients meeting DSM-IV Text Revision criteria for a nonpsychotic major depressive episode and 27 controls participated in this study. The depressed subjects were older than healthy controls by a mean of 10.0 years (42.1 vs. 32.1, 95% CI 3.49 to 16.66) and contained a greater proportion of women, although gender difference was not statistically significant (18/27 vs 11/27, $p = 0.06$). For this reason, age and gender were used as covariates in statistical comparisons of functional connectivity between these two groups. A subset of 17 subjects from the depressed group were analyzed in a previous study and the 27 healthy controls in the present study constitute a subset of the 35 healthy controls used in the same previous study (Liston, et al, 2014).

TMS reduces depressive symptoms

HAMD₂₄ scores were obtained before and after treatment with TMS over left DLPFC in the 27 depressed patients (Fig. 2). HAMD₂₄ was reduced by a mean of 9.81 (95% CI 7.13 to 12.49). Using a 30% reduction to define treatment response, there were 15 responders (black-filled circles) representing a 56% response rate. Using the more conservative definition of response as a 50% reduction yields a response rate of 33% (9 out of 27 patients).

The executive and rostral motor divisions of the frontostriatal pathway are hypoconnected in depression

Seven clusters restricted to the executive division (4 clusters, Fig. 3) and rostral motor division (3 clusters, Fig. 4) showed reduced functional connectivity to the striatum in depressed subjects compared to controls. The 4 clusters in the executive division were within: (1) right DLPFC (2) left DLPFC, (3) left VMPFC, and (4) left dACC (Fig. 3A–C, Table 2). Of note, the left DLPFC cluster is in the same region as our stimulation site determined by the Beam F3 method. The 3 rostral motor clusters were in the (1) right supplementary motor area (SMA), (2) left SMA, and (3) right premotor cortex (Fig. 4A–C, Table 2). There were no abnormally connected clusters in the limbic or caudal motor

divisions in depressed subjects compared to controls. There were also no projections with greater functional connectivity in the depressed group compared to controls.

Baseline functional connectivity of the left DLPFC to the striatum predicts response to TMS

When treatment response (% change in HAMD-24) was predicted using a multiple linear regression, it was found that baseline functional connectivity between the left DLPFC region of significance and striatum was a significant predictor (Beta = 167.9, $p=0.037$) and baseline functional connectivity between the left SMA region of significance was a predictor at trend level (Beta = -88.6, $R=0.068$). Baseline functional connectivity between none of the other regions of significance and striatum were significant predictors of treatment response. The overall model fit was $R^2 = 0.48$ (Table 2). Treatment response correlated with baseline connectivity between the left DLPFC region of significance and striatum (Pearson's $R = 0.58$, $p = 0.002$, Fig. 5). Across all depressed subjects, treatment response correlated at a trend level with changes in functional connectivity between the left DLPFC cluster and its executive division striatal seed ($R = 0.328$, $p=0.095$). That is, a reduction in HAMD-24 score correlated with a reduction in functional connectivity.

Discussion

Abnormal frontostriatal connectivity in depression

We found several clusters of abnormal functional connectivity in the executive and rostral motor frontostriatal projections in depressed patients compared to healthy controls. Our study extends prior findings of reduced frontostriatal connectivity in depression [29–32]. Hypoconnectivity of executive and rostral motor frontostriatal projections could partially reflect a disorganization of circuits responsible for modulating cognitive control and motor action. Depressive symptoms such as cognitive slowing, reduced concentration, negative rumination, and psychomotor retardation may be explained by disruptions in these projections [42–47].

Limbic and caudal motor frontostriatal projections did not show differences in functional connectivity in our depressed sample relative to controls. Reduced functional connectivity has been reported previously in the limbic frontostriatal projection in depression [28–32] and has correlated with anhedonia and deficits in reward processing and emotion regulation [30,48]. Differences restricted to the dorsal, cognitive, frontostriatal projections from the bilateral ventrolateral prefrontal cortex to the dorsal striatum have also been observed between depressed individuals and controls [49]. To our knowledge, differences in functional connectivity of the caudal motor frontostriatal projection, consisting largely of the primary motor cortex, have not been previously reported, suggesting that this primary motor network may not be directly involved in the pathophysiology of depression.

Baseline frontostriatal connectivity as a biomarker for treatment response

The specific role of the left DLPFC-striatal connection may have several explanations. First, the left DLPFC has long been implicated in depression [50–53] and has been the most effective stimulation site studied [54,55]. Second, intact functional connectivity between

cortex proximal to the stimulation site and the striatum may enable enhancements in dopamine signaling which have been shown to be activated by TMS over ipsilateral DLPFC [35–37] and can lead to antidepressant effects [56,57].

Our study replicates and extends one previous report of frontostriatal connectivity of the TMS stimulation site in predicting response [14]. In this study, increased connectivity between the dorsomedial prefrontal cortical (DMPFC) stimulation site and sgACC predicted TMS response. However, DMPFC functional connectivity to the ventral striatum, a frontostriatal projection within the limbic division, was *inversely* correlated with TMS response. As the DLPFC-striatal projection in our study is part of the executive division, our study suggests that engagement of this division may be more important mechanistically than engagement of the limbic division. Taken together, both studies raise the possibility that baseline functional connectivity could be used to predict treatment response. Further, for patients with more globally reduced connectivity to deeper structures, direct stimulation of those structures with either deep TMS [58,59] or deep brain stimulation [60] may hold greater promise.

Effect of TMS on frontostriatal connectivity

Our trend-level finding that TMS reduces functional connectivity of the left DLPFC to the striatum -albeit preliminary and in need of replication - is consistent with another recently published report [61]. Decreasing functional connectivity of the subgenual cingulate cortex to the caudate over the course of TMS has also correlated with antidepressant treatment response [10]. These findings, in addition to others investigating the effect of TMS on default mode and central executive networks [10,16], support an antidepressant mechanism of action in which TMS normalizes both cortical and frontostriatal networks.

Study limitations and future directions

Several aspects of this study limit the interpretations of our findings. First, our study lacks a control arm receiving sham-TMS. We thus cannot be certain whether treatment response predictors are specific to active TMS or to placebo response. However, prior sham-controlled studies do provide strong evidence for an antidepressant effect of TMS beyond placebo [3], and our response rate was comparable to active TMS arms of prior studies [62,63]. Replication in a sham-controlled trial is warranted. Second, we examined the connectivity of functionally distinct frontostriatal projections that may correlate with separate symptom domains of depression. However, depressive symptoms and treatment response was assessed using the more general HAMD₂₄. Future work should incorporate scales that better delineate executive, motor, and affective symptom domains so that relationships with integrity of corresponding frontostriatal projections can be tracked. Third, the healthy controls are not matched with the depressed group for age and gender. Although we used age and gender as covariates in statistical comparisons of functional connectivity, age and gender may be confounded with depressive symptoms and thus this approach has the potential to remove variance of interest. Finally, the proximity of the region of significance in the left DLPFC to the stimulation site is not known as we did not measure the exact location of the stimulation site with respect to the subjects' MRI scans.

Conclusions

In an exploratory study, treatment-resistant depression was marked by hypoconnectivity of executive and rostral motor frontostriatal pathways, but normal connectivity of limbic and caudal motor frontostriatal pathways. Higher baseline functional connectivity of the left DLPFC to the executive division of the striatum in depressed patients correlated with treatment response to TMS over the left DLPFC, suggesting that an intact pathway from cortex proximal to the stimulation site to deeper structures may facilitate antidepressant effects. This raises the exciting possibility that baseline functional connectivity could be used as a biomarker for treatment response to TMS in depression.

Acknowledgments

The authors thank Rebecca Gordon and Jude Allen for technical assistance in administering transcranial magnetic stimulation and Rebecca Gordon for administering the Hamilton Rating Scales for Depression.

Funding

This work was supported by grants from the Brain and Behavior Research Foundation (National Alliance for Research on Schizophrenia and Depression Young Investigator Award) to MJD and by funds from the Pritzker Neuropsychiatric Disorders Research Consortium. CL was supported by grants from the National Institutes of Health (K99 MH097822) and the DeWitt Wallace Reader's Digest Foundation at Weill Cornell. FG was supported by a grant from the National Institutes of Health (R01 MH097735). MA received funding for this work from the American Psychiatric Association Resident Research Scholars Fellowship 2015–2016. FP was supported by a fellowship from the Ford Foundation.

Abbreviations

TMS	repetitive transcranial magnetic stimulation
TRD	treatment resistant depression
rsfMRI	resting-state fMRI
DLPFC	dorsolateral prefrontal cortex
HAMD	Hamilton Depression Rating Scale

References

1. Pascual-Leone A, Rubio B, Pallardó F, Catalá MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *The Lancet*. 1996; 348:233–37.
2. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multisite Randomized Controlled Trial. *Biol Psychiatry*. 2007; 62:1208–16. DOI: 10.1016/j.biopsych.2007.01.018 [PubMed: 17573044]
3. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010; 67:507–16. DOI: 10.1001/archgenpsychiatry.2010.46 [PubMed: 20439832]
4. George MS. Transcranial magnetic stimulation for the treatment of depression. *Expert Rev Neurother*. 2010; 10:1761–72. DOI: 10.1586/ern.10.95 [PubMed: 20977332]
5. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical

practice and research. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2009; 120:2008–39. DOI: 10.1016/j.clinph.2009.08.016

6. Slotema CW, Blom JD, Hoek HW, Sommer IEC. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry*. 2010; 71:873–84. DOI: 10.4088/JCP.08m04872gre [PubMed: 20361902]
7. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. TRANSCRANIAL MAGNETIC STIMULATION (TMS) FOR MAJOR DEPRESSION: A MULTISITE, NATURALISTIC, OBSERVATIONAL STUDY OF ACUTE TREATMENT OUTCOMES IN CLINICAL PRACTICE: Research Article: An Observational Study of TMS. *Depress Anxiety*. 2012; 29:587–96. DOI: 10.1002/da.21969 [PubMed: 22689344]
8. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biol Psychiatry*. 2012; 72:595–603. DOI: 10.1016/j.biopsych.2012.04.028 [PubMed: 22658708]
9. Salomons TV, Dunlop K, Kennedy SH, Flint A, Geraci J, Giacobbe P, et al. Resting-State Cortico-Thalamic-Striatal Connectivity Predicts Response to Dorsomedial Prefrontal rTMS in Major Depressive Disorder. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2014; 39:488–98. DOI: 10.1038/npp.2013.222
10. Liston C, Chen AC, Zebbley BD, Drysdale AT, Gordon R, Leuchter B, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol Psychiatry*. 2014; 76:517–26. DOI: 10.1016/j.biopsych.2014.01.023 [PubMed: 24629537]
11. Greicius MD, Flores BH, Menon V, Glover GH, Solvason HB, Kenna H, et al. Resting-State Functional Connectivity in Major Depression: Abnormally Increased Contributions from Subgenual Cingulate Cortex and Thalamus. *Biol Psychiatry*. 2007; 62:429–37. DOI: 10.1016/j.biopsych.2006.09.020 [PubMed: 17210143]
12. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, et al. The default mode network and self-referential processes in depression. *Proc Natl Acad Sci*. 2009; 106:1942–47. [PubMed: 19171889]
13. Sheline YI, Price JL, Yan Z, Mintun MA. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proc Natl Acad Sci*. 2010; 107:11020–5. DOI: 10.1073/pnas.1000446107 [PubMed: 20534464]
14. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJS. Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev*. 2009; 33:279–96. DOI: 10.1016/j.neubiorev.2008.09.002 [PubMed: 18824195]
15. Zhu X, Wang X, Xiao J, Liao J, Zhong M, Wang W, et al. Evidence of a Dissociation Pattern in Resting-State Default Mode Network Connectivity in First-Episode, Treatment-Naive Major Depression Patients. *Biol Psychiatry*. 2012; 71:611–7. DOI: 10.1016/j.biopsych.2011.10.035 [PubMed: 22177602]
16. Baeken C, Marinazzo D, Wu G-R, Van Schuerbeek P, De Mey J, Marchetti I, et al. Accelerated HF-rTMS in treatment-resistant unipolar depression: Insights from subgenual anterior cingulate functional connectivity. *World J Biol Psychiatry*. 2014; 15:286–97. DOI: 10.3109/15622975.2013.872295 [PubMed: 24447053]
17. Dichter GS, Gibbs D, Smoski MJ. A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. *J Affect Disord*. 2015; 172:8–17. DOI: 10.1016/j.jad.2014.09.028 [PubMed: 25451389]
18. Noda Y, Silverstein WK, Barr MS, Vila-Rodriguez F, Downar J, Rajji TK, et al. Neurobiological mechanisms of repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex in depression: a systematic review. *Psychol Med*. 2015; 45:3411–32. DOI: 10.1017/S0033291715001609 [PubMed: 26349810]
19. Silverstein WK, Noda Y, Barr MS, Vila-Rodriguez F, Rajji TK, Fitzgerald PB, et al. NEUROBIOLOGICAL PREDICTORS OF RESPONSE TO DORSOLATERAL PREFRONTAL CORTEX REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN DEPRESSION: A SYSTEMATIC REVIEW: Review: Biological Predictors of Response to rTMS. *Depress Anxiety*. 2015; 32:871–91. DOI: 10.1002/da.22424 [PubMed: 26382227]

20. Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. *NeuroImage*. 2012; 66C:151–60. DOI: 10.1016/j.neuroimage.2012.10.082
21. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci*. 1986; 9:357–81. [PubMed: 3085570]
22. Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat*. 2003; 26:317–30. DOI: 10.1016/j.jchemneu.2003.10.003 [PubMed: 14729134]
23. Leh SE, Ptito A, Chakravarty MM, Strafella AP. Fronto-striatal connections in the human brain: A probabilistic diffusion tractography study. *Neurosci Lett*. 2007; 419:113–8. DOI: 10.1016/j.neulet.2007.04.049 [PubMed: 17485168]
24. Di Martino A, Scheres A, Margulies DS, Kelly AMC, Uddin LQ, Shehzad Z, et al. Functional Connectivity of Human Striatum: A Resting State fMRI Study. *Cereb Cortex*. 2008; 18:2735–47. DOI: 10.1093/cercor/bhn041 [PubMed: 18400794]
25. Tziortzi AC, Haber SN, Searle GE, Tsoumpas C, Long CJ, Shotbolt P, et al. Connectivity-Based Functional Analysis of Dopamine Release in the Striatum Using Diffusion-Weighted MRI and Positron Emission Tomography. *Cereb Cortex*. 2014; 24:1165–77. DOI: 10.1093/cercor/bhs397 [PubMed: 23283687]
26. Krishnan KRR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, et al. Magnetic resonance imaging of the caudate nuclei in depression: preliminary observations. *Arch Gen Psychiatry*. 1992; 49:553–57. [PubMed: 1627046]
27. Bora E, Harrison BJ, Davey CG, Yücel M, Pantelis C. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychol Med*. 2012; 42:671–81. DOI: 10.1017/S0033291711001668 [PubMed: 21910935]
28. Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, et al. Activity and Connectivity of Brain Mood Regulating Circuit in Depression: A Functional Magnetic Resonance Study. *Biol Psychiatry*. 2005; 57:1079–88. DOI: 10.1016/j.biopsych.2005.02.021 [PubMed: 15866546]
29. Lui S, Wu Q, Qiu L, Yang X, Kuang W, Chan RCK, et al. Resting-state functional connectivity in treatment-resistant depression. *Am J Psychiatry*. 2011; 168:642–8. DOI: 10.1176/appi.ajp.2010.10101419 [PubMed: 21362744]
30. Furman DJ, Hamilton JP, Gotlib IH. Frontostriatal functional connectivity in major depressive disorder. *Biol Mood Anxiety Disord*. 2011; 1:1. [PubMed: 22738418]
31. Marchand WR, Lee JN, Suchy Y, Johnson S, Thatcher J, Gale P. Aberrant functional connectivity of cortico-basal ganglia circuits in major depression. *Neurosci Lett*. 2012; 514:86–90. DOI: 10.1016/j.neulet.2012.02.063 [PubMed: 22395089]
32. Marchand WR, Lee JN, Johnson S, Thatcher J, Gale P. Striatal circuit function is associated with prior self-harm in remitted major depression. *Neurosci Lett*. 2013; 557:154–8. DOI: 10.1016/j.neulet.2013.10.053 [PubMed: 24183891]
33. Keck ME, Sillaber I, Ebner K, Welt T, Toschi N, Kaehler ST, et al. Acute transcranial magnetic stimulation of frontal brain regions selectively modulates the release of vasopressin, biogenic amines and amino acids in the rat brain. *Eur J Neurosci*. 2000; 12:3713–20. [PubMed: 11029641]
34. Kanno M, Matsumoto M, Togashi H, Yoshioka M, Mano Y. Effects of acute repetitive transcranial magnetic stimulation on dopamine release in the rat dorsolateral striatum. *J Neurol Sci*. 2004; 217:73–81. DOI: 10.1016/j.jns.2003.08.013 [PubMed: 14675613]
35. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*. 2001; 21:1–4.
36. Pogarell O, Koch W, Popperl G, Tatsch K, Jakob F, Zwanzger P, et al. Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: Preliminary results of a dynamic [¹²³I] IBZM SPECT study. *J Psychiatr Res*. 2006; 40:307–14. DOI: 10.1016/j.jpsychires.2005.09.001 [PubMed: 16259998]
37. Pogarell O, Koch W, Popperl G, Tatsch K, Jakob F, Mulert C, et al. Acute prefrontal rTMS increases striatal dopamine to a similar degree as d-amphetamine. *Psychiatry Res Neuroimaging*. 2007; 156:251–5. DOI: 10.1016/j.pychresns.2007.05.002 [PubMed: 17993266]

38. Lan MJ, Chhetry BT, Liston C, Mann JJ, Dubin M. Transcranial Magnetic Stimulation of Left Dorsolateral Prefrontal Cortex Induces Brain Morphological Changes in Regions Associated with a Treatment Resistant Major Depressive Episode: An Exploratory Analysis. *Brain Stimulat.* 2016; 9:577–83. DOI: 10.1016/j.brs.2016.02.011
39. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulat.* 2009; 2:50–4. DOI: 10.1016/j.brs.2008.09.006
40. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology.* 2006; 31:1841–53. [PubMed: 16794566]
41. Chang C, Glover GH. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *NeuroImage.* 2009; 47:1448–59. DOI: 10.1016/j.neuroimage.2009.05.012 [PubMed: 19446646]
42. Sabbe B, Hulstijn W, van Hoof J, Tuynman-Qua HG, Zitman F. Retardation in depression: assessment by means of simple motor tasks. *J Affect Disord.* 1999; 55:39–44. [PubMed: 10512604]
43. Videbech P. PET measurements of brain glucose metabolism and blood flow in major depressive disorder: a critical review. *Acta Psychiatr Scand.* 2000; 101:11–20. [PubMed: 10674946]
44. Dunn RT, Kimbrell TA, Ketter TA, Frye MA, Willis MW, Luckenbaugh DA, et al. Principal components of the Beck Depression Inventory and regional cerebral metabolism in unipolar and bipolar depression. *Biol Psychiatry.* 2002; 51:387–399. [PubMed: 11904133]
45. Pier MPB, Hulstijn W, Sabbe BG. Differential patterns of psychomotor functioning in unmedicated melancholic and nonmelancholic depressed patients. *J Psychiatr Res.* 2004; 38:425–35. DOI: 10.1016/j.jpsychires.2003.11.008 [PubMed: 15203295]
46. Boecker H, Jankowski J, Ditter P, Scheef L. A role of the basal ganglia and midbrain nuclei for initiation of motor sequences. *NeuroImage.* 2008; 39:1356–69. DOI: 10.1016/j.neuroimage.2007.09.069 [PubMed: 18024158]
47. Gotlib IH, Joormann J. Cognition and Depression: Current Status and Future Directions. *Annu Rev Clin Psychol.* 2010; 6:285–312. DOI: 10.1146/annurev.clinpsy.121208.131305 [PubMed: 20192795]
48. Redlich R, Dohm K, Grotegerd D, Opel N, Zwitserlood P, Heindel W, et al. Reward processing in unipolar and bipolar depression: a functional MRI study. *Neuropsychopharmacology.* 2015
49. Kerestes R, Harrison BJ, Dandash O, Stephanou K, Whittle S, Pujol J, et al. Specific functional connectivity alterations of the dorsal striatum in young people with depression. *NeuroImage Clin.* 2015; 7:266–72. DOI: 10.1016/j.nicl.2014.12.017 [PubMed: 25610789]
50. Disner SG, Beevers CG, Haigh EAP, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci.* 2011; 12:467–77. DOI: 10.1038/nrn3027 [PubMed: 21731066]
51. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *Am J Psychiatry.* 2012
52. Fitzgerald PB, Oxley TJ, Laird AR, Kulkarni J, Egan GF, Daskalakis ZJ. An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. *Psychiatry Res Neuroimaging.* 2006; 148:33–45. DOI: 10.1016/j.psychresns.2006.04.006 [PubMed: 17029760]
53. Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp.* 2008; 29:683–95. DOI: 10.1002/hbm.20426 [PubMed: 17598168]
54. Fitzgerald PB, Maller JJ, Hoy KE, Thomson R, Daskalakis ZJ. Exploring the optimal site for the localization of dorsolateral prefrontal cortex in brain stimulation experiments. *Brain Stimulat.* 2009; 2:234–7. DOI: 10.1016/j.brs.2009.03.002
55. Johnson KA, Baig M, Ramsey D, Lisanby SH, Avery D, McDonald WM, et al. Prefrontal rTMS for treating depression: Location and intensity results from the OPT-TMS multi-site clinical trial. *Brain Stimulat.* 2013; 6:108–17. DOI: 10.1016/j.brs.2012.02.003

56. Tremblay LK, Naranjo CA, Graham SJ, Herrmann N, Mayberg HS, Hevenor S, et al. Functional neuroanatomical substrates of altered reward processing in major depressive disorder revealed by a dopaminergic probe. *Arch Gen Psychiatry*. 2005; 62:1228–36. [PubMed: 16275810]
57. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat Rev Neurosci*. 2016
58. Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*. 2015; 14:64–73. [PubMed: 25655160]
59. Kedzior KK, Gellersen HM, Brachetti AK, Berlim MT. Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: An exploratory systematic review and meta-analysis. *J Affect Disord*. 2015; 187:73–83. DOI: 10.1016/j.jad.2015.08.033 [PubMed: 26321258]
60. Morishita T, Fayad SM, Higuchi M, Nestor KA, Foote KD. Deep Brain Stimulation for Treatment-resistant Depression: Systematic Review of Clinical Outcomes. *Neurotherapeutics*. 2014; 11:475–84. DOI: 10.1007/s13311-014-0282-1 [PubMed: 24867326]
61. Kang J, Lee H, Jhung K, Kim R, An S, Yoon K, et al. Frontostriatal Connectivity Changes in Major Depressive Disorder After Repetitive Transcranial Magnetic Stimulation: A Randomized Sham-Controlled Study. *J Clin Psychiatry*. n.d; 77:e1137–43. [PubMed: 27379563]
62. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. 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. *Psychol Med*. 2014; 44:225–39. DOI: 10.1017/S0033291713000512 [PubMed: 23507264]
63. Kedzior KK, Reitz SK. Short-term efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression-reanalysis of data from meta-analyses up to 2010. *BMC Psychol*. 2014; 2:1.

Highlights

- Reduced frontostriatal functional connectivity was observed in depressed vs. healthy subjects.
- Higher DLPFC-striatal functional connectivity at baseline correlated with better TMS response.
- DLPFC-striatal functional connectivity is a candidate predictive biomarker for TMS response.

Figure 1.

Representation of striatal regions of interest or seeds (A and B) and the regions of frontal cortex with which they are most strongly connected (C and D). These regions were determined by a prior study using DTI probabilistic tractography to track white matter pathways from known functionally significant cortical regions to the striatum [25] (caudal motor: green, rostral motor: yellow, executive: red, limbic: blue. A and C: right hemisphere view, B and D: anterior view).

Figure 2. 24-item HAMD scores in depressed subjects before and after 5 weeks of open-label TMS. Response is defined as a > 30% reduction in HAMD. Horizontal line = mean. Error bars = SEM. Black-filled circles, responders. There was a statistically significant reduction in HAMD₂₄ after TMS (see text).

Figure 3.

Hypoconnectivity of the executive frontostriatal projection in depressed subjects vs. healthy controls. **A.** In the depressed group, four clusters in the executive cortex had lower functional connectivity to the executive division of the striatum. Clusters shown on 3D cutaway image of the brain represent statistically thresholded difference maps showing the difference in frontostriatal functional connectivity, Z , between depressed subjects and healthy controls in each abnormally connected cluster (family-wise $\alpha < 0.01$, voxel-wise $p < 0.01$). Clusters overlap the right DLPFC, left DLPFC, left VMPFC, and left dACC. **B.** Axial (top row) and sagittal (bottom row) images are 2-dimensional representations of the clusters in A. **C.** Bar graphs plot functional connectivity of the same clusters in depressed patients (blue) and controls (green).

Figure 4. Hypoconnectivity of the rostral motor frontostriatal projection in depressed subjects vs. healthy controls. **A.** In the depressed group, three clusters in the rostral motor cortex had lower functional connectivity to the rostral motor division of the striatum. 3D statistical map as in Fig. 3A. These clusters overlap the right Supplementary Motor Area, left Supplementary Motor Area, and right Premotor Cortex. **B.** Axial and sagittal images as in Figure 3B. **C.** Bar graphs as in Figure 3C.

Figure 5.

Baseline functional connectivity of left DLPFC to the executive region of the striatum predicts treatment response to TMS over the left DLPFC. Percent reduction in HAMD₂₄ is plotted on the vertical axis and baseline functional connectivity of the left DLPFC cluster to striatum on the horizontal axis. The solid black line is the linear regression with dashed lines depicting the 95% confidence interval. Reduction in HAMD₂₄ correlated with higher baseline functional connectivity.

Size (in 3mm³ voxels) of the bilateral extent of each striatal seed and the MNI coordinates of the center of mass of the left and right division each striatal seed.

Table 1

Region (of cluster)	Size (Voxels)	Right Center of Mass			Left Center of Mass		
		X	Y	Z	X	Y	Z
(MNI Coordinates)							
Caudal Motor	76	27	-6	6	-28	-5	6
Rostral Motor	47	26	1	9	-27	1	9
Executive	419	19	10	6	-18	10	5
Limbic	198	17	9	-6	-17	8	-7

Size (in 3mm³ voxels) and MNI coordinates of the center of mass of each cluster in the executive cortex and rostral motor cortex that have different frontostriatal functional connectivity in depressed subjects than in healthy controls. β -Coefficient of the multiple linear regression using baseline functional connectivity at each frontal cluster abnormally connected in depression as a predictor variable and percent change in HAMD (where symptomatic improvement was scored as a positive change in HAMD-24: (pre-post)/pre, *significant correlation). The overall model fit was $R^2 = 0.48$.

Table 2

Region (of cluster)	Size (Voxels)	X (MNI Coordinates)	Y (MNI Coordinates)	Z (MNI Coordinates)	β -Coefficient (Multiple Linear Regression)
Executive clusters					
R DLPFC	39	+44	+31	+22	$\beta = 7.4, p = 0.86$
L DLPFC	35	-45	+32	+22	$\beta = 167.9, p = 0.037^*$
L vmPFC	21	-40	+48	+6	$\beta = -3.0, p = 0.94$
L dorsal ACC	17	-4	+30	+36	$\beta = -51.2, p = 0.25$
Rostral motor clusters					
R SMA	64	+25	+7	+60	$\beta = 111.5, p = 0.22$
L SMA	41	-23	+5	+51	$\beta = -88.6, p = 0.068$
R premotor	16	+50	+5	+47	$\beta = -23.1, p = 0.67$