Effects of repetitive transcranial magnetic stimulation on individual variability of resting-state functional connectivity in major depressive disorder

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Introduction

Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is an effective treatment for major depressive disorder (MDD). It can alter connectivity of networks, including the default mode network (DMN), frontoparietal network (FPN), and salience network (SN), that are important for emotion and affect regulation. A recent concurrent TMS-fMRI study showed that reduced connectivity across the brain predicted greater clinical improvement in patients with treatment-resistant depression. Despite the general effect of rTMS, the response rate remains around 50%. Major depressive disorder is a heterogeneous disorder, with patients showing individual differences in clinical profiles, resting-state functional connectivity (rs-fc), and illness trajectories. The conventional one-size-fits-all rTMS approach contributes to response heterogeneity, as patients may have individualized cortical targets owing to between-subject heterogeneity in functional network topography or different illness profiles. One proposed mechanism of rTMS is through indirect action on the subgenual anterior cingulate cortex (sgACC), with DLPFC target sites showing anti-correlation with the sgACC, representing potentially more efficacious rTMS targets. Recent work has shown that personalized approaches estimating the effects of rTMS related to cortical geometry via e-field modelling and individual functional connectivity predict a portion of clinical outcomes. Consequently, the study of individual variability may lead to a better understanding of the neurobiology of MDD and optimizing personalized target treatment interventions. While clinical heterogeneity is well acknowledged, only a small number of studies of MDD to date have explicitly considered neurobiological heterogeneity.

Background: Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD), but substantial heterogeneity in outcomes remains. We examined a potential mechanism of action of rTMS to normalize individual variability in resting-state functional connectivity (rs-fc) before and after a course of treatment. Methods: Variability in rs-fc was examined in healthy controls (baseline) and individuals with MDD (baseline and after 4–6 weeks of rTMS). Seed-based connectivity was calculated to 4 regions associated with MDD: left dorsolateral prefrontal cortex (DLPFC), right subgenual anterior cingulate cortex (sgACC), bilateral insula, and bilateral precuneus. Individual variability was quantified for each region by calculating the mean correlational distance of connectivity maps relative to the healthy controls; a higher variability score indicated a more atypical/diosyncratic connectivity pattern. Results: We included data from 66 healthy controls and 252 individuals with MDD in our analyses. Patients with MDD did not show significant differences in baseline variability of rs-fc compared with controls. Treatment with rTMS increased rs-fc variability from the right sgACC and precuneus, but the increased variability was not associated with clinical outcomes. Interestingly, higher baseline variability of the right sgACC was significantly associated with less clinical improvement (p = 0.037, uncorrected; did not survive false discovery rate correction). Limitations: The linear model was constructed separately for each region of interest. Conclusion: This was, to our knowledge, the first study to examine individual variability of rs-fc related to rTMS in individuals with MDD. In contrast to our hypotheses, we found that rTMS increased the individual variability of rs-fc. Our results suggest that individual variability of the right sgACC and bilateral precuneus connectivity may be a potential mechanism of rTMS.

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The neuroanatomical and functional architecture of the human brain is unique to each individual, arising from a combination of genetic and environmental factors. Individual differences in the pattern or magnitude of functional connectivity may be related to cognitive performance, symptom severity, and response to rTMS. Conventional group-wise analyses test individual variability as random noise, despite the fact that variability is a critical characteristic of individual-specific abnormality within a psychiatric disorder. Functional MRI studies using the individual approach have shown brain-wide variability in people with psychiatric disorders and healthy controls. Recent studies have identified increased variability in task-evoked fMRI activity, defined as deviation from the “normal” pattern, in both schizophrenia and autism spectrum disorder. In MDD, Pession and colleagues reported lower blood oxygen level-dependent signal (BOLD) variability in regions of the cerebellar and parietal cortex, while Hou and colleagues found higher variability of rs-fc between the DMN, SN, sensorimotor network (SMN), and cerebellar network (CN).

Previous evidence has shown that MDD is a heterogeneous disorder, with variability in response to rTMS, which is influenced by individual functional connectivity. Our prior study found that lower DLPFC target structural MCD in responders to rTMS, and recent work has also suggested individual variability in terms of deviation from group averages may represent a novel metric of brain function. The present study investigated individual variability of functional connectivity in response to rTMS in patients with MDD. We made use of data from a prior rTMS trial comparing 10 Hz rTMS with intermittent theta burst stimulation (iTBS), measuring individual variability of rs-fc as mean correlational distance (MCD), which is defined as the mean of the pairwise correlational difference from 1 participant to a group of others. It quantifies the extent to which each participant deviated from the average, normative pattern. Lower MCD scores suggest a typical brain pattern, and high MCD reflects an idsiosyncratic brain pattern. Therefore, MCD is a metric measuring the similarity of individual connectivity pattern to the group average, but allows for each individual to express a unique deviation from the norm.

Regions of interest were selected from the FPN, DMN, and SN as functional networks implicated in MDD and rTMS response. We examined seed connectivity from the rTMS target site in the DLPFC, part of the FPN; the sgACC, proposed as a potential indirect mechanism for rTMS; the bilateral precuneus as a marker of the DMN; and the bilateral insula of the SN. Baseline and post-rTMS functional connectivity in these regions has been suggested to be associated with clinical outcomes. We assessed group differences in MCD between patients with MDD and healthy controls at baseline. Given recent work showing greater individual variability of rs-fc across the brain in patients with MDD, and our work showing greater MCD in those with autism, schizophrenia, and bipolar disorder, we hypothesize that patients with MDD would show greater MCD than healthy controls. Second, individual variability was investigated as a potential biomarker of response in patients with MDD; we hypothesized that rTMS would reduce individual variability and that this reduction would be associated with clinical improvement. Finally, we explored the association between baseline MCD and clinical outcomes; we hypothesized that baseline MCD would be significantly associated with clinical outcomes. Owing to the exploratory aspect of this analysis, we did not hypothesize a specific direction for the association.

Methods

Sample and trial procedure

We examined fMRI data from a published randomized controlled noninferiority clinical trial (THREE-D). The inclusion criteria were reported in the published study. Briefly, participants were aged 16–65 years and had MDD diagnosed using the Mini-International Neuropsychiatric Interview. Of the 414 participants initially included in the THREE-D sample, the present study used neuroimaging data from the trial’s 2 Toronto sites (Centre for Addiction and Mental Health and Toronto Western Hospital) because all patients’ scans were acquired on the same MRI scanner at the Toronto Western Hospital (n = 372). Participants were randomized into 2 treatment groups: 20 Hz high-frequency left (HFL) rTMS stimulation, and iTBS to the left DLPFC with the same intensity at 120% resting motor threshold (RMT). Magnetic resonance image-guided neuronavigation with a visor neuronavigation system (ANT Neuro) targeted established Montreal Neurological Institute (MNI) coordinates (x = −38, y = 44, z = 26) to locate the left DLPFC. All participants went on to receive 20 rTMS sessions over a period of 4 weeks, with 5 sessions per week running from Monday to Friday. Participants who did not achieve remission after 4 weeks had the option to receive 2 more weeks of rTMS, for a total of 6 weeks of treatment. The 17-item Hamilton Rating Scale for Depression (HDRS) was used to evaluate the severity of depressive symptoms at baseline and after rTMS treatments. In addition, 76 healthy controls were also recruited as part of the THREE-D data set for comparison with the patients with MDD; healthy controls underwent a single (baseline) MRI.

MRI data acquisitions

Resting-state fMRI (rs-fMRI) scans were acquired before the rTMS treatment period and following rTMS, either at 4 or 6 weeks after baseline MRI. A single 3T GE HDx MRI scanner with an 8-channel phased-array head coil was used to collect all the MRI scans. During scanning, patients were instructed to lay flat and upright with their eyes closed without thinking about anything in particular. Whole-brain T1-weighted anatomic scans were collected (echo time [TE] 12 ms; inversion time [TI] 300 ms; flip angle 20°; 116 sagittal slices; slice thickness 1.5 mm, no gap; matrix 256 × 256; field of view [FOV] 240 mm), followed by 10 minutes of rs-fMRI (T1-weighted echo planar imaging; TE 30 ms; TR 2000 ms; flip angle 85°; 32 axial slices; slice thickness 5 mm, no gap; matrix 64 × 64 matrix; FOV 220 mm).
MRI and rs-fMRI data preprocessing

Standard fMRIPREP\textsuperscript{37} and CIFTIFY\textsuperscript{38} pipelines were used to preprocess the data; details can be found in Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.230135/tab-related-content. In short, anatomic T\textsubscript{1}-weighted MRI scans were run through FreeSurfer, and cortical surfaces and compartments were segmented. The fMRI data were preprocessed using fMRIPrep version 2.2.7\textsuperscript{37} Data were slice time–corrected, and a deformation field was applied to correct susceptibility distortions and was incorporated into composite realignments to correct for motion across scans. Functional MRI was registered to the T\textsubscript{1}-weighted anatomic scan, and a nonlinear warp was applied to transform into MNI152 space, which was then applied to the FreeSurfer cortical ribbon to extract cortical surface and transform into CIFTI surface space.\textsuperscript{38} Confound regression was performed using the 6 head-motion parameters (3 rotations and 3 translations), cerebrospinal fluid (CSF), white matter, and global signal, with the quadratic, temporal derivatives, and quadratic temporal derivatives terms included for all regressors. The data were further detrended using high- (0.01 Hz) and low-pass (0.1 Hz) filtering, and 6 mm surface smoothing was applied. The first 3 TRs were also dropped.

Seed map functional connectivity

Left DLPFC, bilateral insula, and precuneus connectivity maps were computed using the conventional seed-based approach. The 20 mm region of interest (ROI) in the left DLPFC was generated using the MNI coordinates from the rTMS treatment trial \((x = -38, y = 44, z = 26)\),\textsuperscript{28,39} whereas both the bilateral insula and precuneus ROIs were selected using ROIs from the Glasser atlas (Figure 1).\textsuperscript{40} For each participant, each ROI average time-series was Pearson correlated to the time series of all other vertices, resulting in the seed connectivity map.

Subgenual ACC seed map functional connectivity

The sgACC connectivity maps were calculated using a previously validated approach to improve the low signal-to-noise ratio (SNR) in the sgACC.\textsuperscript{10,28,41} We first constructed the right sgACC connectivity to whole brain using the Glasser atlas for each participant of the Human Connectome Project (HCP) data set (S1200 release, \(n = 1001\)). The average seed map was generated by averaging all of the right sgACC connectivity maps. To avoid any potential bias of rTMS at the target region in calculating right sgACC connectivity in our data, we removed the bilateral DLPFC according to regions within the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Schematic representation of the data analysis including functional connectivity and pairwise correlation distance matrix across 4 regions of interest (ROIs): (A) left dorsolateral prefrontal cortex (DLPFC), (B) bilateral insula, (C) bilateral precuneus, and (D) right subgenual anterior cingulate cortex (sgACC). Regions from the Human Connectome Project multi-modal atlas were used for the DLPFC, insula, and precuneus, while the estimated seed-map approach was used for the sgACC owing to low signal quality in that region (top row). Whole-cortex seed connectivity maps were calculated for those regions (middle row), and pairwise correlational distances were calculated (bottom row).}
\end{figure}
Glasser atlas (Appendix 1, Table 1) from the average seed map. The seed map without bilateral DLPFC was used as a weighted map to recreate the right sgACC time series, providing a more reliable signal quality than sgACC itself. Specifically, we weighted each vertex’s time series in our data by multiplying it by the corresponding vertex’s r values from the HCP average seed map, and the average of all weighted time series is an estimation of the right sgACC signal. We conducted Pearson correlation between the estimated right sgACC signal and all other vertices to generate individual right sgACC connectivity maps for pre- and posttreatment sessions.

Individual variability of rs-fc as MCD

Mean correlational distance provides a single value per participant, representing how similar that participant is to the normative group. In this regard, MCD is similar to a normative modelling approach. For each ROI, individual variability was analyzed separately for healthy controls and patients with MDD. In the control group, the seed connectivity maps were reshaped into 1-D spatial vectors and stacked together, creating a 2-D connectivity matrix (66 healthy controls by 59412 cortical vertices). A pairwise correlation distance (1 – [correlation]) was calculated for each pair of participants in the 2-D connectivity matrix, which resulted in the correlational distance matrix (66 × 66). Individual variability of rs-fc was quantified via MCD from 1 control to all others (Figure 1). Individual variability of each patient with MDD was calculated relative to the control sample instead of all other patients. By doing so, the individual variability of each patient with MDD is not inflated by greater variability in other patients with MDD or by rTMS treatment within the MDD group. Each MDD connectivity map was added to the 2-D connectivity matrix of the control group, and identical steps were followed as above to acquire the patient’s variability score. This process was repeated for 252 patients with MDD. As a result, a lower MCD reflects typical patterns of rs-fc relative to healthy controls, and a higher MCD suggests an idiosyncratic pattern of rs-fc. Both pre- and post-rTMS MCD scores were calculated in the MDD group separately for each of the 4 seed maps. The normality of MCD scores was assessed using a Shapiro–Wilk test (p < 0.05).

Statistical analysis

Since the MCD values were not normally distributed (Shapiro–Wilk test p < 0.001), case–control group differences at baseline were compared using the Mann–Whitney U test. The follow-up linear regression model was performed to adjust for age, sex, and motion covariates. Post hoc pairwise comparison was conducted using the Estimated Marginal Means (emmeans) package in R to show differences between groups, and the result was Bonferroni-corrected.

We conducted a linear mixed-effect model, with MCD as the dependent variable and scans as the independent variable, to evaluate pre-to-post changes in MCD from scans (scan1 = pre-treatment, scan2 = post-treatment) while accounting for treatment duration ([0] = 4-week; [1] = 6-week) and motion covariates. We also accounted for between-subject variability by adding a subject-specific random intercept in the model. To determine the directionality of MCD changes, post hoc pairwise comparison was conducted using the Satterthwaite approach. In the linear mixed-effects model, the effect size (Cohen d) of the changes in MCD from pre-to-post scan after accounting for the random effect was computed using the prior approach.

For each participant with MDD, clinical outcomes were defined by the percentage change of HDRS total scores, whereas changes in MCD were calculated by subtracting baseline MCD from posttreatment MCD. A linear regression model was conducted to predict clinical outcomes (dependent variable) by changes in MCD (independent variable) while adjusting for treatment duration ([0] = 4-week; [1] = 6-week) and average motion.

A linear model was used to assess the association between the baseline MCD and the percentage change of HDRS total scores while accounting for baseline HDRS total scores and average motion in the MDD sample.

All statistical analyses were conducted in R version 4.1.0. For each linear model, a statistical summary of the main predictors and covariates was reported using the car::Anova function in R. Models were constructed separately for each ROI, and the p values of main predictors were corrected for multiple group comparisons using false discovery rate (FDR) correction. If not otherwise specified, models met all the assumptions of linear regression by visualizing diagnostic plots in R. Analysis code has been made available on https://github.com/ThomasHMAC/THREE-D_Individual_Variability.

Results

Of the 448 participants (76 healthy controls, 372 patients with MDD), 105 patients with MDD were excluded because they did not receive pre- and posttreatment scans (Figure 2). A further 13 patients and 6 controls were excluded owing to scans of poor quality or that failed to pass fMRIPrep and CIFTIFY quality control (e.g., poor brain segmentation, normalization). Finally, 2 patients with MDD were excluded because of high motion (FD > 0.5) in either the pre- or posttreatment scan, and 4 controls were excluded owing to missing data (age and sex), leaving a final sample of 318 participants (66 healthy controls, 252 patients with MDD). The full sample characteristics are reported in Table 1. The MDD group was significantly older than the control group, and there were no group differences in sex. Patients with MDD showed moderate to severe depressive symptoms, which were significantly reduced compared with baseline after 4–6-weeks of treatment with rTMS (mean ± standard deviation [SD] 13.1 ± 7.6 v. 23.3 ± 4.26; t251 = -20.424, p < 0.001).

Patients with MDD did not show greater individual variability of rs-fc than healthy controls

In contrast to our expectation, patients with MDD did not show greater individual variability (i.e., MCD) of the left DLPFC, right sgACC, bilateral insula, or precuneus than
healthy controls (Figure 3). These results were not significant after FDR correction for multiple group comparison (left DLPFC: \( p = 0.66, p_{\text{corr}} = 0.92, d = 0.059 \); right sgACC: \( p = 0.08, p_{\text{corr}} = 0.32, d = 0.228 \); bilateral insula: \( p = 0.46, p_{\text{corr}} = 0.92, d = 0.096 \); bilateral precuneus: \( p = 0.16, p_{\text{corr}} = 0.49, d = 0.190 \)).

Pre/post changes in individual variability of rs-fc after rTMS were not associated with treatment outcomes

The analysis of the linear mixed-effect model showed that scan (pre- v. post-rTMS) was a significant predictor of individual variability of rs-fc for the right sgACC (\( b = 0.003, 95\% \) confidence interval [CI] \( 0.000 \) to \( 0.005, p = 0.025, p_{\text{corr}} = 0.05, d = 0.14 \)) and bilateral precuneus (\( b = 0.004, 95\% \) CI \( 0.001 \) to \( 0.007, p = 0.014, p_{\text{corr}} = 0.05, d = 0.16 \)) (Figure 4 and Table 2). This indicates that rTMS increased right sgACC and bilateral precuneus variability. It is also noteworthy that, contrary to our hypothesis, rTMS increased rather than decreased variability. Treatment duration was also a significant predictor of the variability of rs-fc for the bilateral precuneus; patients who received 6 weeks of treatment showed less of an increase in variability than those who received 4 weeks of treatment. No other significant results were observed for the left DLPFC (\( b = 0.00, 95\% \) CI \( -0.00 \) to \( 0.01, p = 0.49, p_{\text{corr}} = 0.49 \)) and bilateral insula (\( b = 0.002, 95\% \) CI \( -0.001 \) to \( 0.004, p = 0.20, p_{\text{corr}} = 0.27 \)) in the pre-to-post scan. Additional linear mixed-effects models were also computed separately for iTBS and HFL rTMS in the 4 ROIs (Appendix 1, Supplementary Table 2).

The changes in MCD did not differ between iTBS and HFL rTMS in the left DLPFC (\( U = 8073, p = 0.81, p_{\text{corr}} = 0.81 \)), right sgACC (\( U = 824, p = 0.59, p_{\text{corr}} = 0.79 \)), bilateral precuneus (\( U = 870, p = 0.18, p_{\text{corr}} = 0.53 \)), and bilateral insula (\( U = 857, p = 0.267, p_{\text{corr}} = 0.53 \)). There was also no significant association between the percentage change of HDRS total scores and changes in MCD separately for iTBS and HFL rTMS (Appendix 1, Supplementary Table 3), thus the treatment modality was not included in our analysis.
There was no significant association between changes in MCD and percentage change of HDRS total scores in the follow-up linear regression analysis adjusting for baseline HDRS total scores, treatment duration, and motion (Appendix 1, Supplementary Figure 1 and Supplementary Table 1).

**Discussion**

This study examined individual variability of rs-fc from regions belonging to functional networks implicated in MDD, in the context of rTMS treatment interventions. In contrast to a prior study showing greater variability of network connectivity in MDD, we did not find increased variability in MDD at baseline. While some results did not survive statistical correction, consistent patterns emerged with regard to the right sgACC: patients with MDD showed (nonsignificant) lower variability at baseline, rTMS increased variability toward that observed in healthy controls, and lower baseline variability was somewhat related to greater symptom reductions. The increased variability in both the right sgACC and bilateral precuneus connectivity was not significantly associated with greater clinical outcomes. While a consistent direction of effects was observed specifically in the sgACC, a region implicated in rTMS response, these did not survive multiple comparison corrections across the 4 ROIs. Thus, further work on the sgACC should confirm these results.
We did not observe greater variability in MDD, or decreased variability following rTMS. Contrary to our hypotheses, rTMS increased variability in seed-based connectivity from the sgACC and precuneus seeds. While the difference was nonsignificant, it is worth noting that mean MCD was lower in the MDD group, tentatively suggesting this increase in variability may have been a normalization of function, though this did not map onto reductions in depressive symptoms. While our prior work found higher variability in autism, schizophrenia, and bipolar disorder, it is worth noting that those studies made use of task fMRI activation during an N-back task, as opposed to rs-fc. Recent work also reported increased variability in functional connectivity in schizophrenia, with resting connectivity related to diagnosis but task-related connectivity driven by cognitive abilities. As our prior work made use of task-evoked activity or whole-brain resting patterns, we cannot presume the same patterns should be observed in this seed-based analysis in MDD. However, prior work with MCD has consistently found increased variability in psychiatric samples. Our analytic approach calculated functional connectivity using a seed-based approach compared with the whole-brain connectivity approach, which may have been too constrained for detecting other connectivity patterns beyond the selected ROIs.

Prior studies have reported inconsistent findings of connectivity in MDD using case–control group-level differences; group-averaging analytical approaches may be inadequate to preserve the substantial heterogeneity in symptoms and connectivity in MDD. Individual variability metrics such as MCD provide a unique way of analyzing brain functions of a specific system while allowing for unique differences in patients’ individual connectivity profiles, which may drive greater variability (i.e., MCD does not assume every patient shows the same pattern of deficits in sgACC connectivity to other brain regions). Notably, we found no evidence of an association between MCD and rTMS within the 4 ROIs. It is possible that MCD may not be an appropriate measure for assessing changes in individual rs-fc to rTMS treatment among patients with MDD; however, MCD may still have added value in other psychiatric disorders to detect heterogeneous differences that are not well captured by standard spatial group analyses.

Table 2: Linear mixed-effect models of pre-to-post changes in mean correlational distance for the 4 regions of interest

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Left DLFPC</th>
<th>Right sgACC</th>
<th>Bilateral insula</th>
<th>Bilateral precuneus</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>0.562</td>
<td>0.478</td>
<td>0.521</td>
<td>0.501</td>
</tr>
<tr>
<td>Scan [2]</td>
<td>0.001</td>
<td>0.003</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Treatment duration [1]</td>
<td>0.001</td>
<td>0.001</td>
<td>-0.000</td>
<td>-0.005</td>
</tr>
<tr>
<td>FWD</td>
<td>0.014</td>
<td>0.032</td>
<td>0.025</td>
<td>0.034</td>
</tr>
<tr>
<td>Random effects</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>$\tau_0$ STUDY_ID</td>
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<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>ICC</td>
<td>0.52</td>
<td>0.46</td>
<td>0.49</td>
<td>0.43</td>
</tr>
<tr>
<td>N</td>
<td>252 STUDY_ID</td>
<td>252 STUDY ID</td>
<td>504</td>
<td>504</td>
</tr>
<tr>
<td>Observations</td>
<td>504</td>
<td>504</td>
<td>504</td>
<td>504</td>
</tr>
<tr>
<td>Marginal $R^2$/conditional $R^2$</td>
<td>0.003/0.518</td>
<td>0.026/0.477</td>
<td>0.010/0.491</td>
<td>0.031/0.445</td>
</tr>
</tbody>
</table>

CI = confidence interval; DLPFC = dorsolateral prefrontal cortex; FWD = framewise displacement; ICC = intraclass correlation coefficient; rTMS = repetitive transcranial magnetic stimulation; sgACC = subgenual anterior cingulate cortex.

*Scan [1] = pre-rTMS treatments scan; Scan [2] = post-rTMS treatments scan; treatment duration [0] = 4 weeks of rTMS treatments or less than 6 weeks; treatment duration [1] = 6 weeks of rTMS treatment. Each model was conducted separately for each region of interest.
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Conclusion

Compared with the common group average analysis, the individual approach has the potential benefit of preserving the heterogeneity characteristics among psychiatric populations. Here, we provided preliminary evidence of rTMS in altering brain function via individual variability of rs-fc within the sgACC and precuneus, but this change was not significantly related to treatment outcomes. Further work with explicit focus on the sgACC and using new acquisition sequences (e.g., multiband, multi echo), or examination of task fMRI and/or whole-brain connectivity may shed further light on the role of rTMS in normalizing brain function.

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Contributors: Z.J. Daskalakis and C. Hawco designed the study. S. Nestor, F. Vila-Rodriguez, and D.M. Blumberger acquired the data, which V. Tan, J. Downar and Z.J. Daskalakis analyzed. V. Tan and C. Hawco wrote the article, which all authors reviewed. All authors approved the final version to be published and agreed to be accountable for the work.

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Figure 5: Association between percentage change in 17-item Hamilton Rating Scale for Depression (HDRS) total scores and baseline mean correlational distance (MCD) of resting-state functional connectivity (rs-fc) in the right subgenual anterior cingulate cortex (sgACC). At baseline, higher individual variability of rs-fc in the right sgACC was associated with less improvement in patients with major depressive disorder while adjusted for baseline HDRS total scores and motion. The Y-axis shows the percentage change of HDRS total scores; a negative value reflects a reduction in HDRS total scores.

Limitations

Several limitations of this study must be considered. The 10 minutes of fMRI was relatively short to have a reliable and stable signal. We constructed separate linear models for a series of prior ROIs known to be involved in MDD to investigate the association between variability and clinical outcomes; this may miss important and broader changes in network structure or organization, considering the brain is an integrated neural network. Future studies with more sophisticated models are needed to evaluate the cumulative effect of multiple ROIs in predicting treatment outcomes. We also did not assess specific depressive subscales because of concerns regarding the multiple comparison problems and lower reliability of specific symptom items. Although the weighted seed-map approach has been validated in estimating the sgACC signal, future studies could involve multi-echo sequences to improve the sgACC signal. Finally, to minimize multiple comparisons we selected a small set of regions related to rTMS treatment or networks implicated in depression, but other regions, such as the amygdala or limbic regions, may provide different results.
References


41. Westfall J, Kerney DA, Judd CM. Statistical power and optimal design in experiments in which samples of participants respond to samples of stimuli. J Exp Psychol Gen 2014;143:2020-45.


