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ORIGINAL ARTICLE

Changes in Functional Connectivity Predict Outcome of Repetitive Transcranial Magnetic Stimulation Treatment of Major Depressive Disorder

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD) is associated with changes in brain functional connectivity (FC). These changes may be related to the mechanism of action of rTMS and explain the variability in clinical outcome. We examined changes in electroencephalographic FC during the first rTMS treatment in 109 subjects treated with 10 Hz stimulation to left dorsolateral prefrontal cortex. All subjects subsequently received 30 treatments and clinical response was defined as ≥40% improvement in the inventory of depressive symptomatology-30 SR score at treatment 30. Connectivity change was assessed with coherence, envelope correlation, and a novel measure, alpha spectral correlation (αSC). Machine learning was used to develop predictive models of outcome for each connectivity measure, which were compared with prediction based upon early clinical improvement. Significant connectivity changes were associated with clinical outcome ($P < 0.001$). Machine learning models based on αSC yielded the most accurate prediction (area under the curve, AUC = 0.83), and performance improved when combined with early clinical improvement measures (AUC = 0.91). The initial rTMS treatment session produced robust changes in FC, which were significant predictors of clinical outcome of a full course of treatment for MDD.

Key words: repetitive transcranial magnetic stimulation (rTMS), depression, functional connectivity, machine learning, electroencephalogram (EEG)

Introduction

Major depressive disorder (MDD) is increasingly conceptualized as a disorder of brain networks (Fornito and Bullmore 2015; Kaiser et al. 2015). Network dysregulation has been reported in the fronto-parietal control, dorsal attention, and default mode networks, with both increased and decreased resting-state functional connectivity (rsFC) reported in comparisons of MDD and healthy control subjects (Kaiser et al. 2015; Philip et al.

2018). MDD appears to be associated with altered cortico-thalamic connectivity, which plays a role in regulating cognitive processes and circadian processes (Llinas et al. 2005). Dysregulation of these connections may result in a syndrome of thalamocortical dysrhythmia (Llinás et al. 1999; Vanneste et al. 2018).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique that has well-established clinical efficacy for MDD (Burt et al. 2002; George et al. 2010; Carpenter et al. 2017). rTMS modulates brain activity not only at the stimulation target, but also has network-wide effects that may be facilitatory or inhibitory (Fox, Halko, et al. 2012; To et al., 2018). The therapeutic benefit of rTMS may in part be based upon resetting thalamocortical connectivity (Peters et al. 2016; To et al., 2018).

Both the clinical benefits of rTMS (Mutz et al. 2018) and the effects of rTMS on rsFC are quite variable (Fischer et al. 2016; Tik et al. 2017). Variability in pre-treatment rsFC measured with functional magnetic resonance imaging (fMRI; Fox, Buckner, et al. 2012; Ge et al. 2017; Fettes et al. 2018) as well as treatment-emergent changes measured with electroencephalography (EEG) or magnetoencephalography (Pathak et al. 2016; Kito et al. 2017) are related to differences in treatment outcome. These findings suggest that changes in FC may be related to the mechanism of action of rTMS and may serve as biomarkers of outcome (Fidalgo et al. 2014; Leuchter et al. 2015; Leuchter and Corlier 2018).

EEG measures have been proposed as practical and reliable biomarkers for treatment outcomes in MDD (Fidalgo et al. 2014; Leuchter et al. 2015; Leuchter and Corlier 2018). Previously examined EEG biomarkers include motor cortex excitability (Fitzgerald et al. 2004; Oliveira-Maia et al. 2017), ERPs (Price et al. 2008; Arns et al. 2012), EEG band power (Micoulaud-Franchi et al. 2012; 2013; Woźniak-Kwaśniewska et al. 2015; Bailey et al. 2017), individual alpha frequency (IAF; Price et al. 2008; Arns et al. 2012), local frontal midline connectivity (Bailey et al. 2017), asymmetry (Price et al. 2008), cordance (Arns et al. 2012), and EEG complexity measures (Arns et al. 2014). Results with some of these methods have been promising, but many have been examined in small samples without cross-validation, limiting their clinical generalizability (Widge et al. 2013; Krepel et al. 2018).

Treatment-emergent TMS-EEG measures (Fischer et al. 2016; Sun et al. 2016; Tik et al. 2017) is a promising method that can measure the responsivity of brain networks to therapeutic stimulation, and which may capture more specific associations with outcome than pre-treatment measures alone (Leuchter et al. 2014). We performed this study with two goals: (1) to utilize TMS-EEG to measure changes in connectivity during the first rTMS treatment, and (2) to utilize these changes to construct predictive models of clinical outcome from a full course of treatment. We applied machine learning with rigorous training and testing performance to construct models to predict response to a course of 30 rTMS treatments based upon TMS-EEG data recorded in the first rTMS session. We focused on the alpha (α) frequency band because it comprises the rTMS stimulation frequency and represents the best characterized thalamocortical rhythm, and compared the performance of three neurophysiologic connectivity measures: coherence, envelope correlation, and a novel measure of spectral correlation in the alpha frequency band (αSC). We examined a large sample of patients undergoing rTMS treatment for MDD (n = 109) as well as a more homogeneous subsample receiving predominantly unilateral left (UL) rTMS treatment (n = 68). We also compared the performance of these neurophysiologic predictors with the accuracy of prediction based upon early changes in depressive symptoms during rTMS treatment.

Methods

Subjects

Subjects were 121 individuals (mean age 47.0, SD = 15.3, female = 59) with a primary diagnosis of MDD confirmed by the MINI International Diagnostic Interview (for details, see the Supplementary Information). The research protocol was approved by the UCLA IRB and all subjects provided informed consent prior to any procedures being performed. Subjects continued to receive previously prescribed psychotropic medication concurrent with rTMS and underwent medical clearance before receiving rTMS treatment. Twelve subjects were excluded from the study because of technical difficulties with EEG recording or dropout before treatment 15, yielding a final sample of 109.

Clinical Outcome

Outcome was based upon the percentage change in the 30-item inventory of depressive symptomatology—self-rated (IDS-30 SR; Trivedi et al. 2004) score from pre-treatment baseline to immediately following treatment 30, with clinical response defined as a decrease of ≥40%. This criterion was more clinically meaningful in this sample of highly medication-resistant MDD subjects than the 50% decrease employed in many pharmacotherapy studies, and yielded roughly balanced cell sizes of responders and non-responders.

rTMS Procedures

rTMS treatments were performed with either the Magstim Super Rapid Plus 1 stimulator with a 70-mm Double Air Film coil (Magstim, Whitland, South Wales, UK) or the Neuronetics Neurostar treatment system (Neuronetics, Malvern, PA, USA). Active motor threshold (MT) determination was performed using electromyography monitoring prior to the first treatment. The initial treatment session consisted of 3000 pulses delivered to the left DLPFC target (defined using the Beam F3 method; Beam et al. 2009) at a frequency of 10 Hz using 40-pulse trains, a 26-s inter-train interval, and an intensity of up to 120% MT. Sixty eight subjects continued to receive unilateral left (UL) treatment for the majority of their treatments (>15/30 sessions), while 41 subjects, who did not tolerate or respond to UL stimulation, were changed to sequential bilateral treatment for the majority of treatments (10 Hz at left DLPFC, followed by 1-Hz stimulation at the right DLPFC target). See Supplementary Information for further details on rTMS methods and the clinical treatment paradigm.

EEG Recording

Sixty-four-channel EEG data were recorded at 2000-Hz sampling rate during the first treatment using the ANT Neuro TMS-compatible EEG system (Advanced Neuro Technology [ANT]; Enschede, the Netherlands) and converted to a common average reference offline for analysis. All recordings included at least 5 min of baseline resting-state EEG, the full treatment, and at least 5 min of post-treatment recording.

EEG Data Processing

Preprocessing

Semi-automated EEG preprocessing for artifact detection was performed using the ICA-based FASTER algorithm (Nolan et al. 2010). Data then were visually inspected to reject any epochs containing residual artifact.

Individual Alpha Frequency Determination

A dominant alpha frequency peak was determined for each subject. This peak, a highly stable and reproducible measure within-subjects over time (Grandy et al. 2013) was defined as the highest spectral peak within the 7–13 Hz alpha range (Klimesch et al. 2003) that surpassed a 95% confidence interval of the mean spectral power in the same range derived from a 2000-samples bootstrapped distribution. This alpha peak was used to form the center of a 4-Hz IAF band (peak ± 2 Hz) calculated per subject. If the subject had no alpha peak, the alpha range centered at 10 Hz was chosen for further analysis.

Data Pipeline and Analysis

Neurophysiologic Connectivity Measures

We compared three measures that reflected different aspects of changes in neurophysiologic connectivity in the IAF band in response to rTMS stimulation: (a) coherence, (b) envelope correlation, and (c) a novel measure, αSC. Coherence is the correlation of amplitude and phase, envelope is the correlation of the amplitude only, and αSC is the similarity of the spectral waveform of the alpha band across regions and which may represent the transmissibility of alpha power through a distributed area after TMS. Because αSC examines shared activity between two electrodes, it has face validity as another indicator of FC. See Fig. 1B and Supplementary Information for details on calculation and comparison of all connectivity metrics.

For each of the three neurophysiologic measures, the change in connectivity from pre-treatment baseline to immediately after the first rTMS session was calculated for seeds in left and right DLPFC and all other channels. We defined the seed regions as the channels at/around stimulation site because this is where rTMS-induced changes in connectivity originate. This resulted in a total of 783 features for each predictor (Fig. 1A, left frontal seeds marked in yellow, right frontal seeds marked in blue). See Supplementary Information for detailed calculation of connection numbers (Supplementary Table 1). Additionally, we performed a correlational analysis to evaluate the content similarity of the three measures (see Supplementary Information and Supplementary Figure 1).

Statistics

To determine whether depression severity was predictive of treatment outcome, a *t*-test was used to compare baseline IDS-SR 30 scores for responders versus non-responders. To evaluate whether any medication was over-represented in responder or non-responder groups, we examined differences in response for subjects receiving each of the five most common categories of medication (antidepressants, anxiolytics and sedative hypnotics, antipsychotics, stimulants, and anticonvulsant mood stabilizers) using ANOVA with each medication as a between-subjects factor. We examined differences in FC between responders and nonresponders at pre-treatment baseline by computing 783 pairwise Wilcoxon sum ranking tests comparing each feature. A non-parametric test was used because normal distribution was not assumed, and P-values were corrected for multiple comparisons using false discovery rate. For the post-rTMS condition, we examined effect sizes (Cohen's *d*) of the overall (average) feature distributions for responders and non-responders.

Elastic Net Model Analysis

We built predictive outcome models using the elastic net (EN) method (Zou and Hastie 2005), which assessed 783 features simultaneously to identify those that were most predictive of clinical response. EN combines the most discriminative features, excludes the least significant, and optimizes classification accuracy by shrinking coefficients of correlated predictors towards each. The EN algorithm for selection of the most informative variables minimizes the problem of overfitting that is common with other approaches to stepwise feature selection. EN models were developed first for the entire sample ($N = 109$), partitioning the sample into 70% for training purposes using 10-fold cross-validation and 30% for testing (predictions); this procedure was repeated 100 times (Fig. 1C) (see Supplemental Information for additional machine learning methods). The top 10 features most consistently selected across the 100 trained models were analyzed in terms of their topography (Fig. 1D). Subsequently, separate models also were built for UL group ($n = 68$). Model performance was evaluated using calculations of receiver operating characteristic (ROC) area under the curve (AUC), as well as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and classification accuracy. This procedure was applied to all three connectivity metrics separately.

Finally, logistic regression was used to compare the predictive performance of connectivity biomarkers with that of early response to treatment. IDS-30 SR score at baseline as well as percent change in IDS score at 1 week and 2 weeks were used alone and in combination with the connectivity measure to determine the best classifier. EN models were created both for the entire sample and the separate UL cohort using the strongest predictor.

Results

Clinical Response

rTMS treatment was significantly associated with clinical improvement measured by the percent change in the IDS-30 SR ($n = 109$, *t*-statistic = −9.44, $P < 0.001$), and 45% of subjects met response criteria. There was no significant difference between responders and non-responders in terms of age (46 ± 15.2 vs. 48.9 ± 15.3), gender (49% male vs. 58% male), or severity of baseline depression (44.3 ± 9.5 vs. 41.3 ± 12.2, respectively) (Supplementary Table S2). There was no effect of the five classes of concomitant medication on clinical outcome ($P = 0.11$).

Relationship Between Neurophysiologic Measures and Treatment Outcome

Wilcoxon rank sum tests assessing the difference in FC between responders and non-responders at baseline did not yield any significant results after correction for multiple comparison, with significant overlap in pre-treatment connectivity distributions of the two groups (Fig. 2, top row). In contrast, treatment-emergent changes in connectivity showed a clear separation of distributions (Fig. 2, bottom row), with medium effect sizes for coherence and envelope correlation (left and middle columns) and a large effect size for αSC (right column) (Cohen's $d = 0.84$, 1.22, and 1.52, respectively). On average, non-

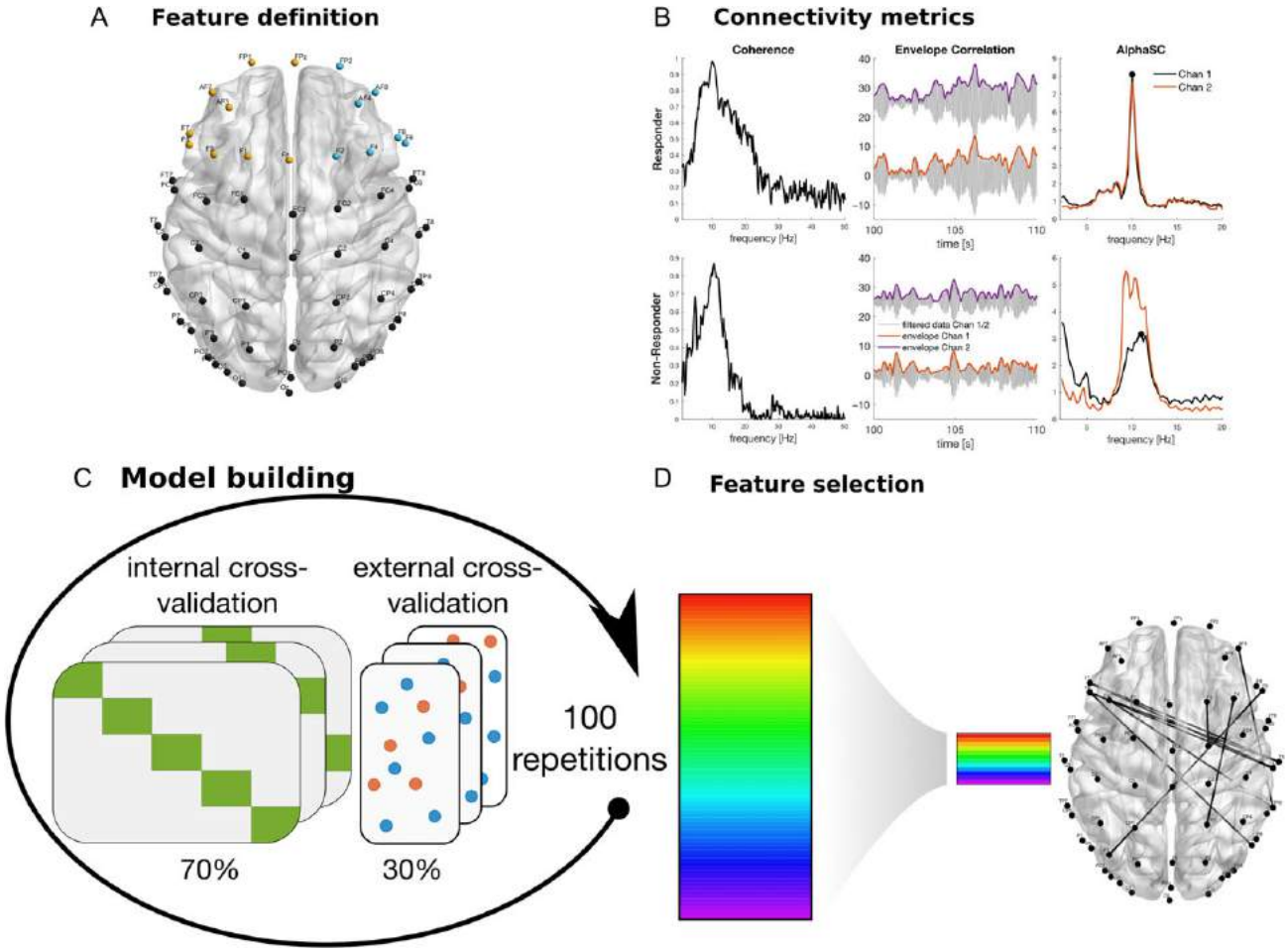

Figure 1. Illustration of the analysis pipeline. (A) Locations of seed electrode locations for connectivity analyses, with the nine left prefrontal seeds shown in yellow (Fpz, Fp1, AF3, AF7, Fz, F1, F3, F5, F7) and the seven right prefrontal seeds shown in blue (Fp2, AF4, AF6, F2, F4, F6, F8). All electrode locations (N = 61) were utilized as connectivity nodes. Connectivity pairings of selected left and right seeds with all other electrodes yielded a total of 783 connectivity features per subject. (B) Examples of the three connectivity metrics of coherence, envelope correlation, and αSC for one responder (upper row) and one non-responder (bottom row). Magnitude squared coherence takes amplitude and phase information into account. Envelope correlation is an amplitude-amplitude coupling measure. αSC is the similarity of the spectral waveform between two channels, which was found to be more similar for responders than non-responders. (C) Elastic net regularization was used to build a model for each neurophysiologic measure that distinguished between responders and non-responders. Models were subjected to training and testing cross-validation repeated 100 times to minimize overfitting and spurious classification due to random sampling effects. For each repetition, the full sample (N = 109) was divided into 70% training and 30% testing sets. For each run, training cross-validation consisted of splitting the training set 10-fold, training the model on 9/10-folds and using the 10th-fold to make predictions. This procedure was repeated 10 times, so that each fold served as both a training and testing set. Testing validation consisted of applying the model obtained from training to make predictions about the test data set. (D) For each neurophysiologic measure, the connections that most reliably predicted outcome in validation were identified. These consisted of the 10 features most consistently selected in all training models across 100 repetitions compared among the predictors. These features then were plotted topographically (right panel).

responders had higher connectivity values than responders in coherence (average 0.015 vs. 0.004) and envelope correlation (average 0.00 vs. −0.022), while non-responders showed lower αSC values (average −0.04 vs. 0.01).

Classification of Responders/Non-responders

EN models showed that αSC yielded more accurate and reproducible classification than either coherence or envelope correlation. While AUCs of training performance were only marginally larger for αSC than for coherence and envelope correlation (83.2, 82.5, and 82, respectively), testing performance showed that αSC classification was notably more stable and reproducible (66.1, 52.7, and 57.8, respectively; Fig. 3A; Table 1). The αSC classifier also had notably higher sensitivity and NPV than did either coherence or envelope correlation, although somewhat lower specificity on testing performance (Table 1).

The topography of the top 10 connections comprising each classifier across 100 trained models differed notably among the three measures (Fig. 3B). EN for coherence (left panel) and envelope correlation (middle panel) were comprised of connections from frontal to temporo-parietal nodes, while for αSC (right panel) was comprised primarily of connections between left frontal seeds (near the stimulation site) and contralateral fronto-temporal locations. The connections included in the EN models, and the percentage of cross-validation runs in which they were selected, varied across the three measures (Supplementary Table 3). In general, the numeric values for coherence and envelope connections were higher among non-responders than responders, while the opposite was true for αSC (Supplementary Fig. 2). This indicated

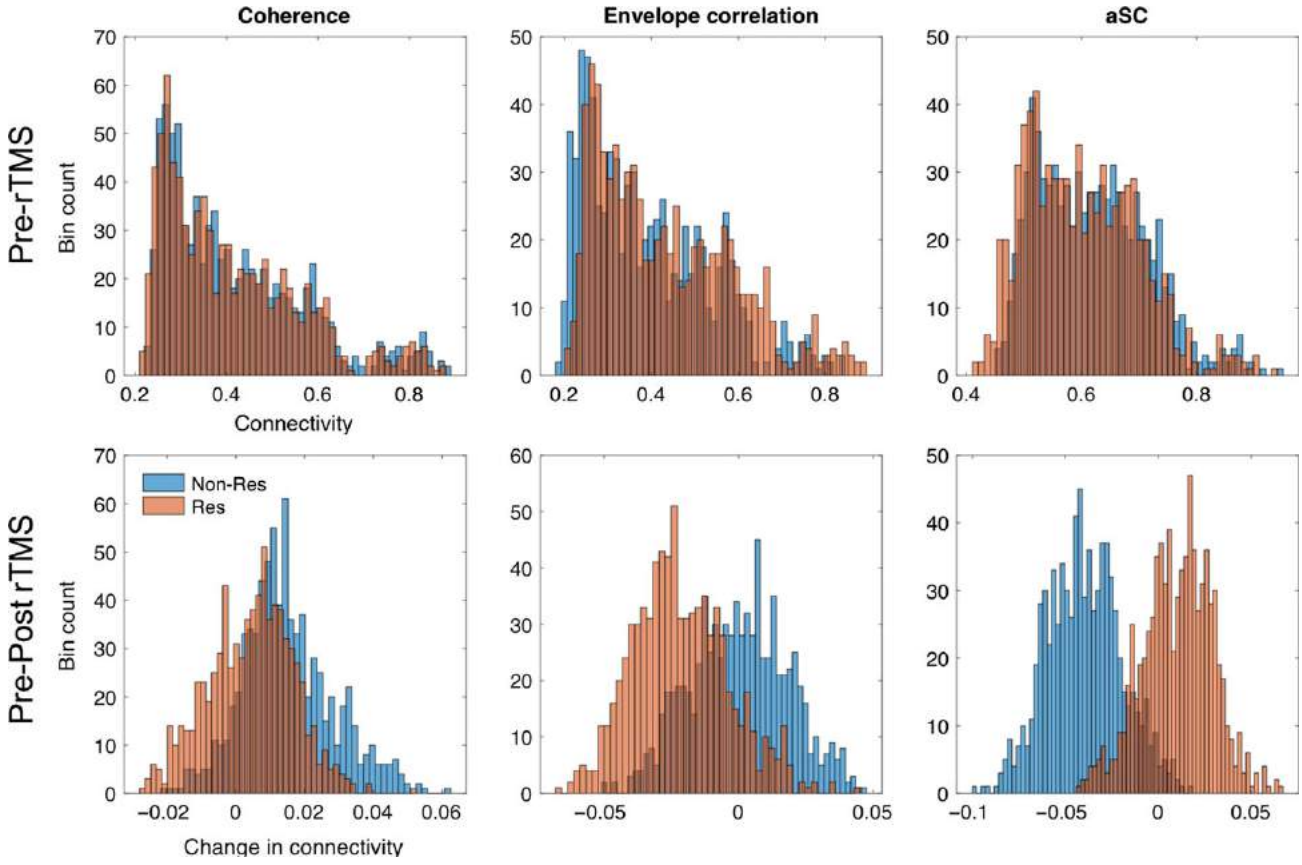

Figure 2. Treatment-emergent connectivity differences. Top row: histograms of mean values for all features for responders (red) and non-responders (blue) before the first rTMS treatment. None of the features differed significantly between groups. Bottom row shows differences in treatment-induced connectivity changes, where group separation is more apparent. Coherence and envelope correlation (left and middle column) showed smaller group separation than αSC (right column) (respective effect sizes Cohen's $d = 0.84$; 1.22; 1.52). For coherence and envelope correlation, non-responders had on average greater connectivity changes than responders. Inversely, change in αSC was on average greater for responders.

that eventual treatment response was associated with a decrease in coherence and envelope correlation and an increase in αSC in the initial rTMS treatment session.

Logistic regression using 2-week IDS-30 SR percent change showed AUCs of 74.4 and 72.7 (training and testing performance, respectively; Fig. 3C). Further analyses were performed using αSC because of its stronger association with outcome than either envelope correlation or coherence. Logistic regression combining αSC and early clinical response improved classification accuracy with AUCs of 85.2 and 75.6 (Fig. 3D), while neither baseline nor Week 1 change in IDS-30 SR significantly improved classification accuracy based upon αSC features alone (Supplementary Table S4). EN modeling performed on the UL treatment sample showed increased classification accuracy in subjects who received the more homogeneous left-sided treatment. Classification of responders versus non-responders to UL treatment showed AUCs of 87.5 and 75.6 when using αSC only, 79.2 and 79.1 for IDS-30 SR only, and 91 and 81.8 in combination of αSC with early symptom change (Table 2).

Discussion

We examined changes in neurophysiologic connectivity resulting from the first rTMS treatment session using three complementary neurophysiologic connectivity measures. Rigorous machine learning methods using training and testing cross-validation demonstrated that changes in all connectivity measures were significant predictors of outcome. A novel measure, αSC, yielded more accurate and reproducible prediction of response than traditional connectivity measures of coherence or envelope correlation. In a subset of subjects receiving UL treatment, a combination of the αSC biomarker and early symptom change during treatment resulted in a classification accuracy of 91% training and 82% testing performance. Connectivity among electrode locations overlying the bilateral DLPFC and the fronto-temporal and supramarginal regions had the strongest association with treatment outcome. This study is an important extension of previous fMRI studies, demonstrating for the first time that TMS-EEG measures can detect treatment-emergent connectivity changes after a single rTMS treatment. The fact that outcome could be predicted based on very early connectivity changes could be highly useful, and suggests that αSC changes may constitute a reliable biomarker for early prediction of response to rTMS treatment in MDD.

The three metrics examined here capture different aspects of connectivity: coherence measures phase and amplitude covariance of two signals based upon frequency bins; envelope correlation evaluates the covariance of amplitudes of two time series; and αSC indicates the similarity of two frequency spectra averaged over time. The finding that both αSC and envelope correlation produced predictive models that were superior to coherence suggests that phase and temporal information inherent in coherence are less robust for characterizing the therapeutic effects of rTMS. Such information may be non-

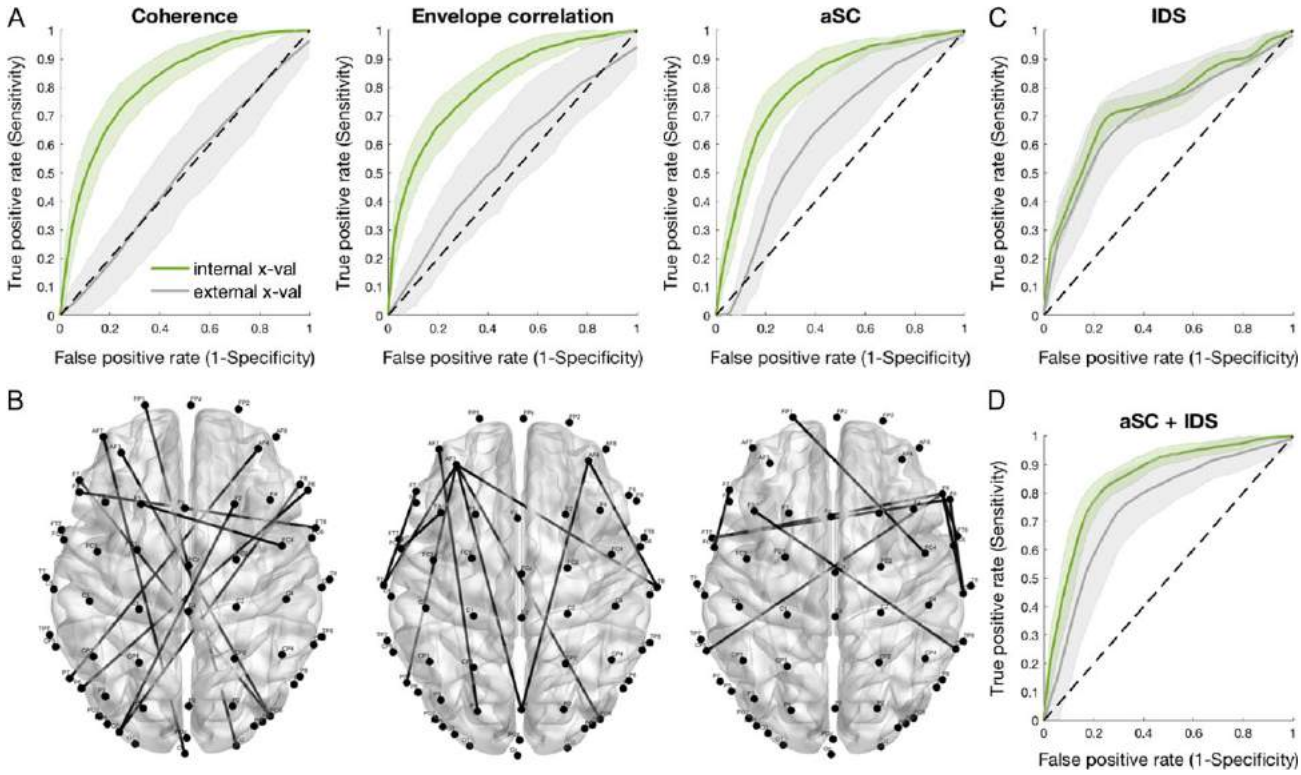

Figure 3. AUCs and feature topography for all EN models. (A) AUCs for all three predictors for training (green) and testing performance (gray) averaged over 100 repetitions. Coherence (training and testing): 82.5 and 52.7; Envelope correlation: 82 and 57.8; αSC: 83.2 and 66.1, with highest AUCs for αSC. (B) The corresponding top 10 selected features per predictor across all 100 trained models. EN models for coherence and envelope correlation showed a diffuse coupling pattern, while αSC showed a more focal connectivity. (C) AUCs for a logistic regression model using solely the early clinical response to rTMS treatment: 74.4 and 72.7. (D) AUCs for a logistic regression model combining the top αSC features and the early clinical response: 85.4 and 77.8, which represented the overall best predictive model.

Table 1 Summary of training and testing EN model performance for the total sample for all three neurophysiologic measures. AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value. Numbers represent mean and (SD) values across the 100 repetitions

	Coherence		Envelope correlation		αSC		IDS-30 SR only		αSC with IDS-30 SR	
	Training	Testing	Training	Testing	Training	Testing	Training	Testing	Training	Testing
AUC	82.5 (3.6)	52.7 (8.5)	82.0 (4.0)	57.8 (9.8)	83.2 (3.3)	66.1 (6.8)	74.4 (3.3)	72.7 (8.1)	85.4 (2.6)	77.8 (6.8)
Accuracy	78.1 (3.6)	61.8 (5.4)	77.4 (3.5)	64.8 (5.3)	79.2 (3.4)	69.3 (6.0)	74.3 (2.6)	75.1 (6.0)	82.3 (2.6)	79.2 (6.0)
Sensitivity	73.5 (10.3)	34.8 (27.1)	69.6 (11.5)	44.4 (25.7)	76.9 (8.4)	67.1 (19.2)	68.0 (5.1)	64.1 (16.5)	80.0 (5.8)	75.7 (13.3)
Specificity	81.9 (8.4)	82.7 (16.9)	83.9 (8.7)	80.8 (15.6)	81.1 (7.7)	70.9 (13.3)	79.6 (3.5)	83.6 (9.6)	84.2 (5.1)	81.9 (9.5)
PPV	78.2 (6.8)	58.2 (31.3)	79.7 (7.5)	67.7 (21.3)	78.1 (6.3)	64.9 (10.3)	73.7 (3.5)	77.2 (10.2)	81.2 (4.6)	77.6 (8.4)
NPV	79.4 (5.5)	63.8 (7.4)	77.5 (5.4)	67.2 (8.4)	81.3 (4.7)	75.6 (9.5)	75.0 (3.0)	76.0 (7.4)	83.7 (3.6)	82.2 (7.7)

Table 2 Summary of EN model performance for the UL treatment subgroup. AUC, area under receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value. Numbers represent mean and SD values across the 100 repetitions

	αSC		IDS-30 SR		αSC + IDS-30 SR	
	Training	Testing	Training	Testing	Training	Testing
AUC	85.2 (2.9)	75.6 (8.9)	79.2 (3.1)	79.1 (7.6)	91.0 (2.7)	81.8 (8.7)
Accuracy	82.4 (3.0)	77.1 (6.5)	80.2 (3.1)	80.7 (6.9)	86.5 (2.9)	81.4 (7.2)
Sensitivity	79.5 (7.1)	71.6 (14.2)	75.3 (5.2)	77.5 (10.9)	87.7 (5.9)	81.0 (11.6)
Specificity	84.7 (5.2)	81.3 (11.0)	86.4 (4.3)	84.6 (10.5)	84.8 (6.4)	81.8 (12.3)
PPV	81.7 (4.7)	76.6 (9.9)	87.8 (3.4)	86.7 (7.9)	88.4 (4.0)	85.5 (9.0)
NPV	83.6 (4.4)	79.5 (7.6)	73.4 (4.1)	76.5 (9.1)	85.0 (6.0)	79.3 (10.6)

stationary and actually obscure the predictive information contained in the frequency signal. The relatively strong prediction based upon spectral similarity is consistent with the observation that frequency spectrum coupling shapes brain network connectivity (To et al., 2018). rTMS stimulation may entrain brain activity in a manner similar to that of sensory input (Thut et al. 2011; Herrmann et al. 2016), for which frequency coupling is an essential component of information transfer.

Higher αSC among responders suggests that increased similarity in the power spectrum induced by the first rTMS session reflects a form of increased functional coupling or entrained resonance between cortical sites. Conversely, lower coherence and envelope correlation among responders may indicate that rTMS stimulation induces strong non-stationary changes in both amplitude and phase synchronization, resulting in the appearance of lower average coupling over the span of minutes. Further investigation of temporal fluctuations would be necessary to further elucidate the nature of the rTMS-induced physiological changes.

αSC EN models most consistently included connections among electrodes overlying bilateral middle and inferior frontal, superior temporal, postcentral, and supramarginal cortices. These regions can be seen as parts of multiple networks known to be dysregulated in MDD, including the fronto-parietal control network, default mode network and also the salience network (Kaiser et al. 2015; Downar et al. 2016; Fischer et al. 2016). It is challenging to assign these regions to one specific network exclusively. Interestingly, the distribution of these connections corresponds most closely to an rTMS-responsive network detected with resting-state fMRI that included the dorsal cingulate and posterior dorso-medial prefrontal cortices, DLPFC, inferior parietal lobule, inferior frontal cortex, and posterior temporal lobes described by Tik and colleagues (Tik et al. 2017). These authors suggested that this represents a cognitive control network linking default mode and attention network components at the nodes of ACC and the inferior parietal lobules, all of which have been reported to be dysregulated in mood and anxiety disorders (Williams 2016; Tik et al. 2017).

In contrast, the coherence and envelope correlation EN models emphasized connections among electrodes overlying the superior frontal locations and the middle temporal and superior occipital cortices. These locations coincide with nodes that fall into the fronto-parietal control and the dorsal attention networks. While these networks have been reported to show decreased connectivity in resting-state fMRI studies of MDD (Kaiser et al. 2015), similar regions have been shown to have higher theta and alpha frequency FC measured with coherence (Leuchter et al. 2012). It is not entirely clear why rTMS response was associated with a decrease rather than increase in these connections. Future studies should aim to elucidate the relationships among EEG and fMRI connectivity measures.

We showed that treatment-emergent changes in connectivity allow for a better separation of responders and non-responders than based solely on the pre-rTMS connectivity. The accuracy of this biomarker compares favorably with pre-treatment predictors previously reported (Widge et al. 2013). We propose that discriminative features are related to the brain networks' ability to respond to stimulation. These may be carry-forward effects of rTMS stimulation into the post-stimulation period that may last 30 minutes or longer following the cessation of stimulation and they may be of non-stationary nature (Rosanova et al. 2009; Thut and Pascual-Leone 2010; Vernet et al. 2012; Valero-Cabré et al. 2017). Average differences between responders and non-responders in the persistence of these effects in the first five minutes following cessation of stimulation probably is the basis for the findings that we report. A future investigation should address the temporal scale of rTMS-induced aftereffects and their potential non-stationary nature in more detail.

Classification accuracy was further enhanced by including measurement of changes in mood after 2 weeks, but not after 1 week or prior to treatment. While the EEG features have the desirable advantage of being available right after the first treatment, symptoms-change predictors can provide complementary information to enhance accuracy and further guide clinical decision-making along the treatment course.

The present results are consistent with previous findings showing that neurophysiological measures have significant potential to serve as translational biomarkers of rTMS treatment outcome (Farzan et al. 2016; Sun et al. 2016; Voineskos et al. 2018). If the usefulness of the αSC TMS-EEG biomarker is confirmed by future studies, it could help to guide administration of rTMS. In particular, it could be used to identify those patients most likely to benefit from a particular rTMS treatment approach in the initial treatment session, and potentially optimize treatment parameters such as stimulation site or frequency for subsequent treatment sessions. The fact that classification accuracy was higher in the subject group receiving more homogeneous primarily left-sided treatment suggests that the physiological connectivity profiles of patients who benefit from left-sided rTMS may differ from those who improve with sequential bilateral treatment. A follow-up study should examine the connectivity features that would be indicative of whether a patient would experience a better outcome with UL, sequential bilateral, or other forms of treatment, to assist the clinician in treatment planning. Additionally, an examination of effects of 10 Hz stimulation on other frequencies outside the alpha band should complement the current hypothesis-driven approach.

The results of the current study should be interpreted in the context of certain limitations. First, while this was a large study, it was comprised of patients treated in a clinical setting. Several rTMS treatment parameters were adjusted based upon a clinical decision-making paradigm related to tolerability and response. Because these treatment parameters were not randomly assigned, we cannot precisely determine the role that adjustments in parameters may have had on outcome and the biomarker results. Second, the great majority of subjects received concomitant pharmacological treatment. It is possible that medication effects contributed to some of the findings here. Additionally, in any classification study there is some risk of overfitting the data. However, we have guarded against it by limiting the number selected features and reporting testing performance. The fact that accurate and stable predictors of outcome were identified suggests that the results of this study may be generalizable, and that the biomarkers identified here would be useful in clinical practice. Independent replication studies prospectively validating this biomarker are necessary to for more conclusive evidence.

Conclusions

Neurophysiologic connectivity changed significantly during the initial rTMS treatment session, and these changes were significant predictors of outcome of a full course of treatment. A novel measure of connectivity, αSC, detected connectivity changes that were more accurate and reproducible than other neurophysiologic measures, indicating that EEG features

relevant to rTMS outcome were most strongly coded by frequency composition, rather than phase, amplitude, or temporal dynamics. As a future direction, it would be important to evaluate the functional differences between these connectivity metrics using a computational or neural modeling approach. Predictive accuracy was further increased when αSC was combined with a measure of early (2-week) clinical response, which may be valuable to refine the clinical decision process along the treatment course. Future research should aim to replicate these findings in independent patient samples.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Notes

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References

Arns M, Cerquera A, Gutiérrez RM, Hasselman F, Freund JA. 2014. Non-linear EEG predict non-response to rTMS treatment in major depressive disorder. Clin Neurophysiol. 125: 1392–1399.

Arns M, Drinkenburg WH, Fitzgerald PB, Kenemans JL. 2012. Neurophysiological predictors of non-response to rTMS in depression. Brain Stimul. 5:569–576.

Bailey NW, Hoy KE, Rogasch NC, Thomson RH, McQueen S, Elliot D, Sullivan CM, Fulcher BD, Daskalakis ZJ, Fitzgerald PB. 2017. Responders to rTMS for depression show increased fronto-midline theta and theta connectivity compared to non-responders. Brain Stimul. 11:190–203.

Beam W, Borckardt JJ, Reeves ST, George MS. 2009. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. Brain Stimul. 2:50–54.

Burt T, Lisanby SH, Sackeim HA. 2002. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 5:73–103.

Carpenter LL, Aaronson ST, Clarke GN, Holtzheimer PE, Johnson CW, McDonald WM, Stannard EL, Schneider MB. 2017. rTMS with a two-coil array: safety and efficacy for treatment resistant major depressive disorder. Brain Stimul. 10:926–933.

Downar J, Blumberger DM, Daskalakis ZJ. 2016. The neural crossroads of psychiatric illness: an emerging target for brain stimulation. Trends Cogn Sci. 20:107–120.

Farzan F, Vernet M, Shafi MMD, Rotenberg A, Daskalakis ZJ, Pascual-Leone A. 2016. Characterizing and modulating brain circuitry through transcranial magnetic stimulation combined with electroencephalography. Front Neural Circuits. 10:73.

Fettes PW, Moayedi M, Dunlop K, Mansouri F, Vila-Rodriguez F, Giacobbe P, Davis KD, Lam RW, Kennedy SH, Daskalakis ZJ, et al. 2018. Abnormal functional connectivity of frontopolar subregions in treatment-nonresponsive major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 3: 337–347.

Fidalgo TM, Morales-Quezada JL, Muzy GSC, Chiavetta NM, Mendonca ME, Santana MVB, Goncalves OF, Brunoni AR, Fregni F. 2014. Biological markers in noninvasive brain stimulation trials in major depressive disorder: a systematic review. J ECT. 30:47–61.

Fischer AS, Keller CJ, Etkin A. 2016. The Clinical Applicability of Functional Connectivity in Depression: Pathways Toward More Targeted Intervention. Biol Psychiatry Cogn Neurosci Neuroimaging. 1:262–270.

Fitzgerald PB, Brown TL, Marston NAU, Daskalakis ZJ, de Castella A, Bradshaw JL, Kulkarni J. 2004. Motor cortical excitability and clinical response to rTMS in depression. J Affect Disord. 82:71–76.

Fornito A, Bullmore ET. 2015. Connectomics: a new paradigm for understanding brain disease. Eur Neuropsychopharmacol. 25: 733–748.

Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. 2012. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry. 72:595–603.

Fox MD, Halko MA, Eldaief MC, Pascual-Leone A. 2012. Measuring and manipulating brain connectivity with resting state functional connectivity magnetic resonance imaging (fcMRI) and transcranial magnetic stimulation (TMS). Neuroimage. 62:2232–2243.

Ge R, Blumberger DM, Downar J, Daskalakis ZJ, Dipinto AA, Tham JCW, Lam R, Vila-Rodriguez F. 2017. Abnormal functional connectivity within resting-state networks is related to rTMS-based therapy effects of treatment resistant depression—a pilot study. J Affect Disord. 218:75–81.

George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, et al. 2010. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 67:507–516.

Grandy TH, Werkle-Bergner M, Chicherio C, Schmiedek F, Lövdén M, Lindenberger U. 2013. Peak individual alpha frequency qualifies as a stable neurophysiological trait marker in healthy younger and older adults. Psychophysiology. 50: 570–582.

Herrmann CS, Strüber D, Helfrich RF, Engel AK. 2016. EEG oscillations: from correlation to causality. Int J Psychophysiol. 103:12–21.

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. 2015. Large-scale network dysfunction in major depressive disorder. JAMA Psychiatry. 72:603–609.

Kito S, Hasegawa T, Takamiya A, Noda T, Nakagome K, Higuchi T, Koga Y. 2017. Transcranial magnetic stimulation modulates resting EEG functional connectivity between the left dorsolateral prefrontal cortex and limbic regions in medicated patients with treatment-resistant depression. J Neuropsychiatry Clin Neurosci. 29:155–159.

Klimesch W, Sauseng P, Gerloff C. 2003. Enhancing cognitive performance with repetitive transcranial magnetic stimulation at human individual alpha frequency. Eur J Neurosci. 17:1129–1133.

Krepel N, Sack AT, Kenemans JL, Fitzgerald PB, Drinkenburg WH, Arns M. 2018. Non-replication of neurophysiological predictors of non-response to rTMS in depression and neurophysiological data-sharing proposal. Brain Stimul. 11: 639–641.

Leuchter AF, Cook IA, Hunter AM, Cai C, Horvath S. 2012. Resting-state quantitative electroencephalography reveals increased neurophysiologic connectivity in depression. PLoS One. 7:e32508–e32513.

Leuchter AF, Corlier J. 2018. A precision medicine approach to repetitive Transcranial Magnetic Stimulation (rTMS). Brain Stimul. 11:463–464.

Leuchter AF, Hunter AM, Krantz DE, Cook IA. 2014. Intermediate phenotypes and biomarkers of treatment outcome in major depressive disorder. Dialogues Clin Neurosci. 16:525–537.

Leuchter AF, Hunter AM, Krantz DE, Cook IA. 2015. Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. Ann N Y Acad Sci. 1344:78–91.

Llinas R, Urbano FJ, Leznik E, Ramírez RR, van Marle HJF. 2005. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci. 28: 325–333.

Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. 1999. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci USA. 96:15222–15227.

Micoulaud-Franchi JA, Richieri R, Boyer L, Lançon C, Vion-Dury J, Guedj E. 2013. Combining neurophysiological and functional neuroimaging biomarkers to predict rTMS non-response in depression. Brain Stimul. 6:461–463.

Micoulaud-Franchi J-A, Richieri R, Cermolacce M, Loundou A, Lancon C, Vion-Dury J. 2012. Parieto-temporal alpha EEG band power at baseline as a predictor of antidepressant treatment response with repetitive transcranial magnetic stimulation: a preliminary study. J Affect Disord. 137:156–160.

Mutz J, Edgcumbe DR, Brunoni AR, Fu CHY. 2018. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression—a systematic review and meta-analysis of randomised sham-controlled trials. Neurosci Biobehav Rev. 92:291–303.

Nolan H, Whelan R, Reilly RB. 2010. FASTER: fully automated statistical thresholding for EEG artifact rejection. J Neurosci Methods. 192:152–162.

Oliveira-Maia AJ, Press D, Pascual-Leone A. 2017. Modulation of motor cortex excitability predicts antidepressant response to prefrontal cortex repetitive transcranial magnetic stimulation. Brain Stimul. 10:787–794.

Pathak Y, Salami O, Baillet S, Li Z, Butson CR. 2016. Longitudinal changes in depressive circuitry in response to neuromodulation therapy. Front Neural Circuits. 10:50.

Peters SK, Dunlop K, Downar J. 2016. Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. Front Syst Neurosci. 10:104.

Philip NS, Barredo J, Aiken E, Carpenter LL. 2018. Neuroimaging mechanisms of therapeutic transcranial magnetic stimulation for major depressive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 3:211–222.

Price GW, Lee JW, Garvey C, Gibson N. 2008. Appraisal of sessional EEG features as a correlate of clinical changes in an rTMS treatment of depression. Clin EEG Neurosci. 39:131–138.

Rosanova M, Casali A, Bellina V, Resta F, Mariotti M, Massimini M. 2009. Natural frequencies of human corticothalamic circuits. J Neurosci. 29:7679–7685.

Sun Y, Farzan F, Mulsant BH, Rajji TK, Fitzgerald PB, Barr MS, Downar J, Wong W, Blumberger DM, Daskalakis ZJ. 2016. Indicators for remission of suicidal ideation following magnetic seizure therapy in patients with treatment-resistant depression. JAMA Psychiatry. 73:337–339.

Thut G, Pascual-Leone A. 2010. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topogr. 22:219–232.

Thut G, Veniero D, Romei V, Miniussi C, Schyns P, Gross J. 2011. Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr Biol. 21:1176–1185.

Tik M, Hoffmann A, Sladky R, Tomova L, Hummer A, de Lara LN, Bukowski H, Pripfl J, Biswal B, Lamm C, et al. 2017. Towards understanding rTMS mechanism of action: stimulation of the DLPFC causes network-specific increase in functional connectivity. Human Brain Mapping. Journal. 162: 289–296.

To WT, De Ridder D, Hart J, Vanneste S. 2018. Changing brain networks through non-invasive neuromodulation. Front Hum Neurosci. 12:128. doi:10.3389/fnhum.2018.00128.

Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, Crismon ML, Shores-Wilson K, Toprac MG, Dennehy EB, et al. 2004. The inventory of depressive symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the quick inventory of depressive symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med. 34:73–82.

Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. 2017. Transcranial magnetic stimulation in basic and clinical neuroscience: a comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev. 83:381–404.

Vanneste S, Song J-J, De Ridder D. 2018. Thalamocortical dysrhythmia detected by machine learning. Nat Commun. 9:1103.

Vernet M, Bashir S, Yoo W-K, Perez JM, Najib U, Pascual-Leone A. 2012. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. Eur J Neurosci. 37:598–606.

Voineskos D, Blumberger DM, Zomorrodi R, Rogasch NC, Farzan F, Foussias G, et al. 2019. Altered transcranial magnetic stimulation-electroencephalographic markers of inhibition and excitation in the dorsolateral prefrontal cortex in major depressive disorder. Biol Psychiatry. 85:477–86. doi:10.1016/j.biopsych.2018.09.032.

Widge AS, Avery DH, Zarkowski P. 2013. Baseline and treatment-emergent eeg biomarkers of antidepressant medication response do not predict response to repetitive transcranial magnetic stimulation. Brain Stimul. 6:929–931.

Williams LM. 2016. Precision psychiatry: a neural circuit taxonomy for depression and anxiety. Lancet Psychiatry. 3:472–480.

Woźniak-Kwaśniewska A, Szekely D, Harquel S, Bougerol T, David O. 2015. Resting electroencephalographic correlates of the clinical response to repetitive transcranial magnetic stimulation: a preliminary comparison between unipolar and bipolar depression. J Affect Disord. 183:15–21.

Zou H, Hastie T. 2005. Regularization and variable selection via the elastic net. J R Stat Soc: Series B (Stat Methodol.) 67:301–20. doi:10.1111/j.1467-9868.2005.00503.x.