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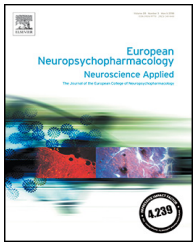

Baseline effective connectivity predicts response to repetitive transcranial magnetic stimulation in patients with treatment-resistant depression

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Abstract
Repetitive transcranial magnetic stimulation (rTMS) has become a popular treatment option for treatment-resistant depression (TRD). However, suboptimal response rates highlight the need for improved efficacy through optimisation of treatment protocol and patient selection. We investigate whether the limbic salience network and its connectivity with prefrontal stimulation sites predict immediate and longer-term responsiveness to rTMS. Twenty-seven patients with TRD were randomly allocated to receive 16 sessions of either conventional rTMS or intermittent theta-burst (iTBS) over 4 weeks; delivered using connectivity profiling and neuronavigation to target person-specific dorsolateral prefrontal cortex (DLPFC). At baseline and 3-month

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follow-up, patients underwent clinical assessment and scanning session, and 1-month clinical follow-up. Resting-state fMRI data were entered into seed-based functional and effective connectivity analyses between right anterior insula (rAI) and DLPFC target, and independent components analysis to extract resting-state networks. Cerebral blood flow (CBF) was also assessed in the rAI. All brain measures were compared between baseline and follow-up, and related to treatment response at 1- and 3-months. Baseline fronto-insular effective connectivity and salience network connectivity were significantly positively correlated, while baseline rAI CBF was negatively correlated, with early (1-month) response to rTMS treatment but not sustained response (3-months), suggesting persistence of therapeutic response is not associated with baseline features. Connectivity or CBF measures did not change between the two time points. We demonstrate that fronto-insular and salience-network interactions can predict early response to rTMS in TRD, suggesting that these network nodes may be key regions toward developing rTMS response biomarkers.

1. Introduction

The identification of biomarkers for various health conditions such as heart disease and cancer have been crucial for the transformative impact on treatment and management of these illnesses. However, the same cannot be said for mental illness where the identification for diagnostic and prognostic markers have been far more challenging, especially in depression where symptoms and response to treatments are highly variable. Furthermore, clinical subtypes do not have distinct neurobiology which hinders attempts for treatment stratification. In order to optimise treatments, it may therefore be more useful to identify distinct biotypes that can predict whether a patient will be more likely to respond to a specific treatment.

Functional abnormalities are now well documented in depression, with particular dysfunctions in the core networks of the default mode (DMN), central executive (CEN) and salience (SN) networks (for review see Brakowski et al., 2017), and there is consensus that treating symptoms requires the normalisation of these aberrancies (Hamilton et al., 2013) . Repetitive TMS (rTMS) is a treatment option that is thought to correct network abnormalities and has become increasingly popular for the treatment of depression, especially in those whom first-line treatment is not effective. However, response rates are moderate at best and there is a clear need for optimising rTMS treatment as well as stratifying care. Like other treatment approaches, rTMS can be highly effective for some patients, while not for others, suggesting that certain neurobiological patterns might allow greater responsiveness to neurostimulation approaches. Numerous neuroimaging studies have identified potential brain biomarkers for predicting treatment response in depression (Avissar et al., 2017; Downar et al., 2014; Drysdale et al., 2017; Gong et al., 2011; Liston et al., 2014; McGrath et al., 2013). For example, using a canonical correlation analysis method in a large dataset, recent work has elegantly demonstrated that there are specific biotypes within depression that are derived from shared dysfunction in brain connectivity across the whole brain (Drysdale et al., 2017). Interestingly, one specific biotype was highly responsive to rTMS treatment and importantly, the predictive power of brain connectivity measures far outperformed clinical measures alone, illustrating that subtyping patients based on clinical measures alone has limited value toward treatment selection.

While there is some evidence for prefrontal rTMS-induced changes on connectivity metrics in both healthy controls (Chen et al., 2013; Gratton et al., 2013; Iwabuchi et al., 2017; Mastropasqua et al., 2014; Tik et al., 2017) and patients with depression (Li et al., 2004; Liston et al., 2014), there is still limited work linking the underlying mechanisms of rTMS on brain connectivity and therapeutic effect. For instance, Liston et al. (2014) demonstrated a normalisation of subgenual cingulate connectivity dysfunction following rTMS treatment, and this region's connectivity at baseline was predictive of response to rTMS. However, the association between the functional change and clinical response was not reported. More recently, Weigand et al. (2018) reported that the functional connectivity of the subgenual cingulate with the dorsolateral prefrontal cortex (DLPFC) target site predicted clinical improvement following rTMS. In addition, Avissar et al. (2017) showed dorsolateral prefrontal cortex (DLPFC) to striatum connectivity was predictive of response to rTMS with a trend association between the connectivity change and depression score change.

In our previous work, we demonstrated that targeted theta-burst rTMS modulates the fronto-insular (TMS target to salience) network in healthy controls after a single session (Iwabuchi et al., 2017). Here, we extend this study to include depressed patients seeking rTMS. We investigated the effects of facilitatory rTMS treatment (conventional rTMS-based protocol and theta-burst protocol) on both fronto-insular networks, as well as other large-scale resting-state networks known to be affected in depression, and how these effects relate to immediate and longer-term therapeutic response. Specifically, we assessed net outflow of the right anterior insula (rAI) to the DLPFC as measured by Granger causality to index the bidirectional interactions with the DLPFC target site; the major resting state networks (CEN, DMN and SN) were explored via independent components analysis. Based on prior observations indicating the primacy of insula in moderating treatment response to depression (e.g. McGrath et al., 2013), we hypothesise that the connectivity and regional cerebral blood flow (CBF) of the salience network (centred around the key anterior

Table 1 Patient demographics for all available data ($N = 27$).

	Mean (SD)
Age	49.85 (10.88)
Sex	15 Males/12 Females
Age of illness onset (years)	25.3 (10.58)
Duration of current episode (months)	23.5 (31.5)
Thase/Rush score	2.89 (1.01)
BDI score	
Baseline	31.93 (11.2)
1 month	20 (13.6)
3 months	18.11 (13.35)
HAMD score	
Baseline	20.48 (7.4)
1 month	9.41 (6.24)
3 months	10.11 (6.3)

insula hub) will predict the degree of response to rTMS treatment.

2. Experimental procedures

2.1. Participants

A total of 27 patients with treatment-resistant depression were recruited for the study. The trial (www.clinicaltrials.gov registered: NCT02016456) was conducted in a secondary care setting (Nottinghamshire Healthcare NHS Foundation Trust) and participants were referred by their clinician to the Nottingham Neuromodulation Unit and screened for eligibility to the trial. Patients were eligible if they had a diagnosis of depressive disorder with a treatment resistance of at least stage 1 (as defined by Thase and Rush (1997)) and were aged between 18 and 70 years. Patient demographics are summarised in Table 1. Patients were excluded if they had a history of bipolar disorder, neurological condition, contraindications to MRI, pregnant, major unstable medical illness, or change in medication in the two weeks preceding the start of TMS treatment, and current substance dependence. A member of the research team informed the participant of all aspects pertaining to participation in the study before obtaining the patient's consent (the study was approved by NRES Committee East Midlands). Given the treatment resistance of patients, the majority were already prescribed antidepressants, antipsychotics or anxiolytics or receiving psychological support therefore we requested patients to maintain the same treatment regimen during their participation. However, if a change in treatment was deemed necessary by the referring clinician, this was left to his/her discretion. A list of medications is provided in the supplementary materials.

2.2. Study intervention and rTMS administration

All patients underwent an initial assessment of clinical symptoms (Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), Beck Depression Inventory (BDI) (Beck et al., 1996), cognitive (Montreal Cognitive Assessment (Nasreddine et al., 2005), Digit Symbol Substitution Test), functional status and current and past treatments/medications. Patients then underwent an MRI scan that lasted approximately one hour in total. Patients were randomised to either the conventional rTMS protocol or the iTBS protocol using a web-based online allocation system (Sealed Envelope, www.sealedenvelope.com). Both patient and clinician completing assessment were blind to the intervention throughout the 12 weeks of participation in the trial. Following the location of the TMS target region based on Granger Causal Analysis (GCA) seeded from the rAI (MNI coordinate 30, 24, −14) to find the region of greatest influence within the left prefrontal cortex (see (Iwabuchi et al., 2017) for detailed methodology), TMS treatment commenced at the beginning of the following week. We used a 70 mm Double Air Film Coil (Magstim, Whitland, Dyfed, UK) connected to a Magstim Super $Rapid_2$ $Plus_1$ stimulator. On day one, resting motor threshold was determined using a single pulse over the right motor cortex, and was defined as the minimum required intensity for generating a visually detectable movement in the left hand in a minimum of three out of five pulses. The TMS wand was then positioned using Visor2 (www.ant-neuro.com) to the patient's individual DLPFC coordinate. The position was marked and measured using fiducial landmarks to enable accurate repositioning without neuronavigation for the following treatment days. Individuals assigned to iTBS received 10 bursts of 3 pulses (80% motor threshold) at 50 Hz applied at a frequency of 5 Hz (i.e., every 200 ms) (Huang et al., 2005). The pulses were repeated for a total of 5 runs of 600 pulses each, with 5 min rest intervals between runs. Individuals assigned to the conventional rTMS protocol received 75 trains of 10 Hz pulses (4 s per train) interspersed by 26 s intertrain intervals. Our protocol differed from other iTBS trials in depression (see Supplementary Table 2), in that we matched the total number of pulses delivered per day between the standard rTMS and iTBS (3000 pulses per day for 16 days). All TMS treatments were provided 4 days a week for 4 weeks. At the end of the 4 weeks, patients underwent clinical and cognitive assessment by the same clinician. At 12 weeks, patients returned for a final assessment (by the same clinician) and MRI scan. Clinical response to rTMS treatment was defined as >50% decrease in HAMD score. At the end of the follow-up visit, the treatment assignment was revealed to the patient.

2.3. MRI acquisition

All subjects underwent MRI at 3T (Discovery MR750, GE Healthcare) using a 32-channel head coil. For BOLD resting-state fMRI data, 160 single-echo-planar (EPI) volumes were acquired over 5 min 20 s (TE/TR=32/2000 ms, interleaved acquisition, slice thickness=3.6 mm, 35 axial slices parallel to anterior-posterior commissure plane, flip angle=90°, matrix=64 × 64, field of view=240, voxel size=3.75 × 3.75 mm). A T1-weighted anatomical image was also acquired using a 3D fast spoiled gradient echo (FSPGR) sequence acquired in sagittal orientation (TE/TR=3.192/8.224 ms, TI=900 ms, slice gap=1 mm, matrix=256 × 256, flip angle=8°, voxel size= 1 × 1 mm). We also acquired arterial spin labelling (ASL) data, which were acquired using a pulsed-continuous ASL (pCASL) labelling sequence (TE/TR=10.5/4844 ms, labelling duration=1450 ms, post-labelling delay=2025 ms, FOV=240 mm, slice thickness=4 mm, slice gap=4 mm, number of slices=36, echo train length=1, number of excitations = 3, matrix=128 × 128, flip angle=111°) (Dai et al., 2008). Data will be made available as per the conditions of research ethics approval and sponsoring institutions (Nottinghamshire Healthcare NHS Trust and the University of Nottingham). Reasonable requests for access to the data should be directed to the corresponding author.

2.4. MRI analysis

2.4.1. Preprocessing

For quality control, we used the MRI Quality Control Tool (MRIQC) to rigorously assess data image quality (Esteban et al., 2017). Three

datasets from baseline scans and one patient datasets from the follow-up scans were excluded due to excessive motion, excessive noise and/or imaging artefacts identified within the quality reports of MRI data (i.e., >0.3 mm average FD; DVARS outliers; artefacts in timeseries heatmap (Power, 2017)). MRIQC output report for the dataset is available in the supplementary materials. This resulted in a total of 24 patients at baseline, 17 patients at follow-up (16 patients in total with both baseline and follow-up scans). Image preprocessing was carried out using FSL 5.0.10 (FMRIB software library). Steps included high-pass temporal filtering (0.01-Hz cutoff), interleaved slice-timing correction, motion correction (Jenkinson et al., 2002), brain extraction and spatial smoothing (5 mm FWHM). Functional images were registered to the T1-weighted anatomical image and the Montreal Neurological Institute (MNI) standard template (12 degrees of freedom (DOF)) using FLIRT (FMRIB's Linear Image Registration Tool) (Jenkinson et al., 2002; Jenkinson and Smith, 2001), and was denoised using independent component analysis ICA-AROMA (ICA-based Automatic Removal Of Motion Artifacts) (Pruim et al., 2015). CSF and WM timeseries were also regressed out from each subject's data using FMRIB's Automated Segmentation Tool (FAST) to tissue segment the T1-weighted images. The CSF and WM maps were transformed into functional space and volume thresholded to retain the top 20 cm^3 (CSF) and 198 cm^3 (WM) to keep partial volume and global demeaning effects to a minimum (Chai et al., 2012). Mean CSF and WM timeseries were regressed out of each subject's data for all subsequent analyses. CBF maps (ml/100 g/min) were reconstructed using the methods reported in Zaharchuk et al. (2010). The cerebral blood flow maps from ASL were first brain-extracted and registered to the MNI template using FSL's FLIRT (12 DOF) and smoothed at 8 mm FWHM in FSL.

2.4.2. Functional and effective connectivity between rAI and DLPFC target

Functional connectivity (FC) is a measure of correlation of activity between two given regions, while Granger causality provides a measure of directed effective connectivity where neuronal activity of a certain region can be predicted by the activity occurring in another region. FC analyses were conducted using FSL 5.0.10 and GCA was run using REST software (Song et al., 2011). For both FC and GCA, a 6 mm radius sphere centred on the rAI (MNI coordinates: 30, 24, −14 used in a previous study (Iwabuchi et al., 2017) based on findings of McGrath et al. (2013)) was used as a seed region. Reverse GCA was also run from the individualised DLPFC TMS targets (6 mm sphere) back to the rAI to understand the reciprocal effective connectivity between these regions. In addition, we provided a measure of the net outflow of the rAI to the DLPFC target to quantify the bidirectional interaction, which was calculated by subtracting the rAI-DLPFC Granger coefficient from the DLPFC-rAI Granger coefficient. All seed masks were back registered to functional space so that all connectivity analyses were conducted in subject space. The resulting FC and *x*-to-*y* GCA maps were Fisher *r*–*z* transformed to extract mean FC coefficients from the DLPFC to determine rAI-DLPFC FC, and mean Granger coefficients from both DLPFC and rAI to determine rAI-DLPFC and DLPFC-rAI effective connectivity. Detailed analysis procedures for GCA are reported in previous publication (Iwabuchi et al., 2014).

2.4.3. Gross network connectivity

We were also interested in observing gross network changes. Therefore, we ran group ICA (using FSL Melodic 3.15) with multi-session temporal concatenation (restricted to 15 components to avoid smaller sub-networks) on all baseline data to extract the three major resting state networks: DMN, CEN and SN. These maps were used to create subject-specific versions of the spatial maps, and associated timeseries, using dual regression (Filippini et al., 2009). The group-average set of spatial maps is regressed into the subject's 4D space-time dataset which generates a set of subject-specific timeseries. These timeseries are then regressed into the same 4D dataset, resulting in a set of subject-specific spatial maps to be entered into a permutation test.

2.4.4. Cerebral blood flow

We extracted mean CBF of the rAI from the preprocessed maps using a spherical mask of 10 mm radius and used for further statistical analysis.

2.5. Statistical analysis

2.5.1. Therapeutic response to rTMS

We entered the HAMD scores into a repeated measures ANOVA with protocol as a covariate, to determine symptom improvement at one month follow-up and 3-month follow-up. All statistical analyses were performed in SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) and used an α level of $p<.05$. Data included for each comparison consist only of patients who had baseline and one or both follow-up observations.

2.5.2. Pre-post rTMS-induced changes

As we were interested in the neurobiology of TMS treatment effects irrespective of the stimulation protocol, we collapsed the two active TMS protocols for the statistical analysis and used the protocol type as a covariate. We entered FC, EC and CBF measures into a repeated measure ANOVA to determine changes between baseline and 3-month follow-up. These statistical analyses were performed in SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) and used an α level of $p<.05$. For the three resting-state networks from the ICA analysis, pre-post rTMS differences were tested using FSL's randomise permutation-testing tool (5000 permutations).

2.5.3. Baseline connectivity and blood flow related to response

To look for relationships between HAMD change and brain measures, we first controlled for protocol by regressing out the effect of protocol from each of the connectivity and blood flow measures (in order to collapse the groups). These were then entered into a bivariate Pearson's correlation with HAMD score change. These brain measures were associated with HAMD score change to identify whether any measure is predictive of response at either one month or three-month follow-up. To understand this in a clinical context, we also compared responders and non-responders at baseline grouped according to response at one month and three month follow-up. All statistical analyses were performed in SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) and used an α level of $p<.05$. For the three resting-state networks, we tested for differences in baseline connectivity between responders and non-responders (at 1- and 3-months follow-up) using FSL's randomise permutation-testing tool (5000 permutations). Age, illness duration, age of onset, HAMD score, BDI score, and Thase and Rush scores were compared between the responder group and non-responder group at both time points, and no measure was significantly different.

3. Results

3.1. Therapeutic response to rTMS treatment

For therapeutic response, all available data is included (i.e. includes patients who were excluded for the fMRI analyses). Overall, at 1-month (i.e., at the end of the rTMS treatment) response rate was 63.64% (14/22 patients) and at three months, response rate was 66.67% (12/18 patients). HAMD scores were significantly reduced at both one month ($p<.001$) and three months ($p<.001$) compared to baseline.

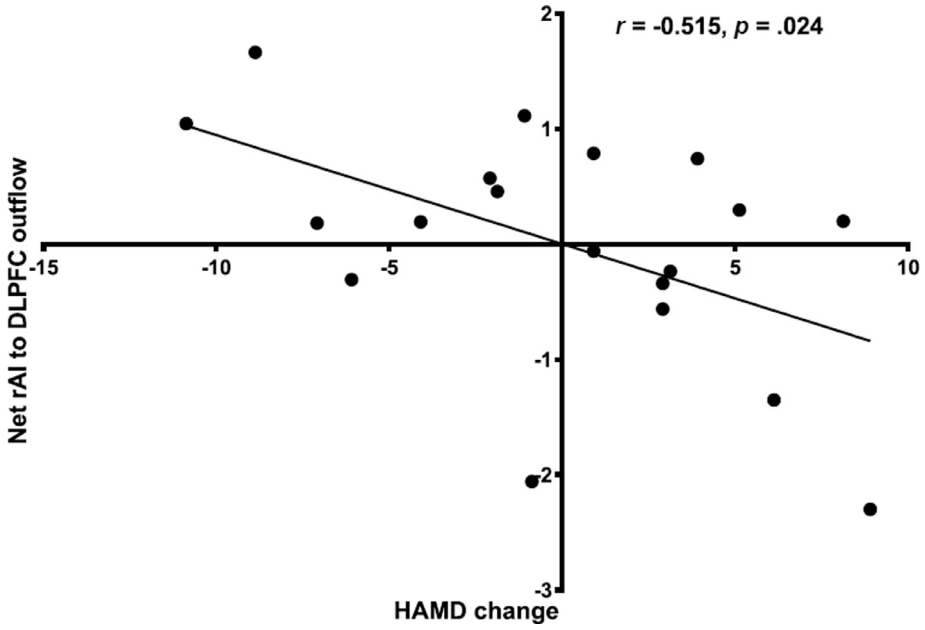

Figure 1 Correlation between the net rAI-to-DLPFC outflow at baseline and change in HAMD score at 1-month follow-up.

There was no statistically significant difference in response rates between the conventional rTMS and TBS protocols. The breakdown of response rates for each treatment are described in the supplementary materials.

3.2. Pre-post rTMS-induced changes

There were no significant changes in either functional or effective connectivity of the rAI and DLPFC target between baseline and follow-up. There were also no changes in CBF of the rAI between the two time points.

3.3. Baseline features associated with treatment response

We found a significant correlation between the net rAI outflow to DLPFC (rAI-DLPFC influence subtracted from the DLPFC-rAI influence) at baseline and degree of HAMD score change at one month follow-up ($r = -0.515$, $p = .024$) (Figure 1). This association was not observed at the three-month follow-up. Group comparisons between responders and non-responders concur with these findings showing DLPFC-rAI influence to be significantly different at baseline (t (17) = 2.27, $p = .036$). This was also consistent with the observation of a trend toward greater CBF in the rAI seed region in responders compared to non-responders at 1-month follow-up (t (16) = 2.04, $p = .058$). Moreover, the degree of CBF in the rAI at baseline was related to the degree of symptom improvement at 1-month ($r = 0.51$, $p = .03$). These results are illustrated in Figure 2.

3.4. Gross network connectivity

The dual regression between baseline and follow-up did not find significant pre-post treatment differences in the SN, DMN or CEN networks. However, responders and non-responders differed in the connectivity of SN, involving clusters that spanned the lingual and fusiform gyri and cerebellum ($p < .017$, corrected for multiple comparisons) suggesting that those who do not respond to rTMS by 1-month had increased connectivity (mean=2.43, SD=1.59) between SN and these posterior regions compared to those who respond (mean=−1.52, SD=1.14) (Figure 3). These findings were further corroborated through a significant correlation between HAMD score change at 1-month and the extracted cluster means of the SAL networks ($r = -0.725$, $p < 0.001$) (Figure 3). The classification based on the 3-month response data did not reveal any differences at baseline for any of the three networks.

4. Discussion

We demonstrated that response to rTMS treatment at the end of the four week regime (early response) can be predicted by the integrity of an extended salience-executive system, indexed by fronto-insular connectivity, salience network connectivity with visual processing regions as well as CBF of the rAI. However, this predictive power was diminished for sustained response (at the 3-month follow-up), suggesting the persistence of therapeutic response to rTMS is mediated by factors that are different from those that influence initial response. Despite the relationship between salience-executive system and early response, rTMS had no notable physiological effect on this system 3-months after the treatment.

Our data revealed that the net outflow of the rAI to the DLPFC target was predictive of early response. Specifically, response was superior in those who had more positive rAI-to-DLPFC influence (outflow) than DLPFC-to-rAI influence (inflow) before treatment began. A previous study using similar methods has shown patients with

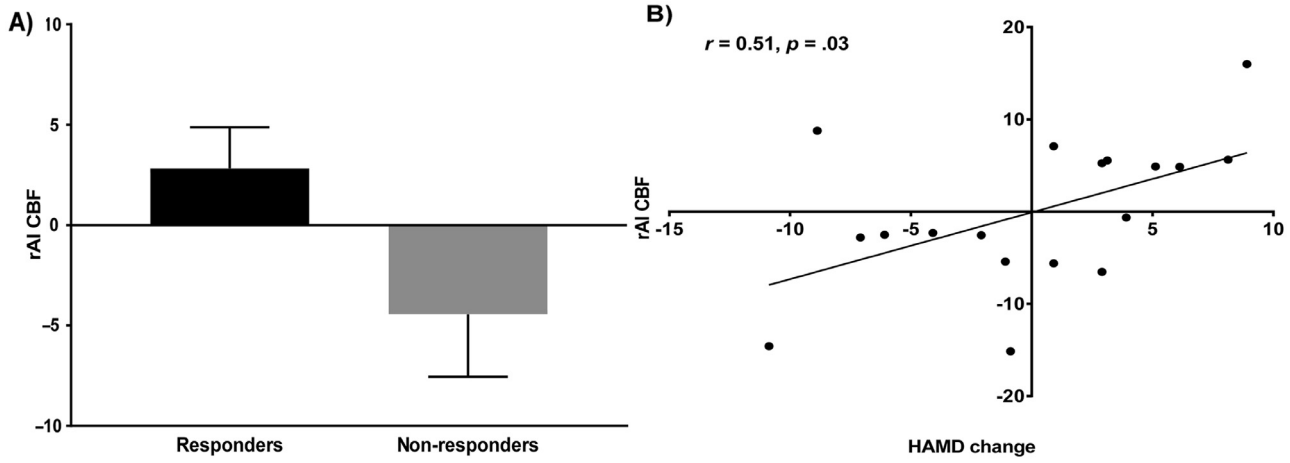

Figure 2 (A) Responders show trend toward greater CBF prior to treatment in the rAI compared to non-responders at 1-month and (B) the magnitude of response is related to the degree of CBF in the rAI.

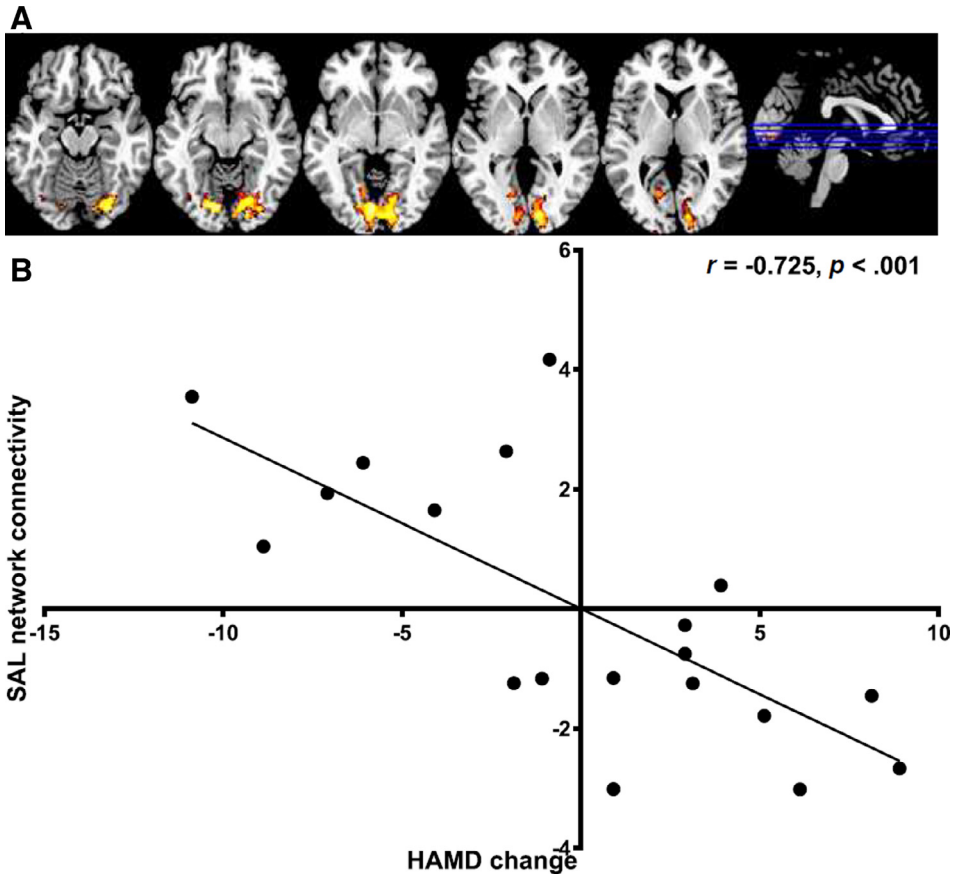

Figure 3 (A) Dual regression results showing difference in baseline salience network connectivity between responders and non-responders at 1-month follow-up, and (B) correlation between HAMD score change at 1-month and baseline salience network connectivity (means extracted from the significant clusters from the dual regression analysis of the salience network).

depression to have greater net outflow of the insula-to-frontal pathway (although this study looked specifically at medial prefrontal), while healthy controls showed the opposite pattern (Iwabuchi et al., 2014). Similar patterns have also been observed in schizophrenia compared to healthy controls (Palaniyappan et al., 2013). Therefore it appears that a more normal inflow/outflow balance between the rAI and DLPFC might enable the brain to better facilitate modulation of the fronto-insular system, which in turn allows alleviation of depressive symptoms. A direct comparison of

clinical responders with non-responders also showed greater (and positive) DLPFC-rAI influence in responders, and more negative influence in non-responders. In the aforementioned studies using GCA, healthy controls showed a negative influence of the frontal cortex on the rAI, again indicating that a more normal fronto-insular pattern of connectivity may be a marker for better response to rTMS treatment. We propose that the therapeutic effect induced by rTMS requires a degree of positive influence of the DLPFC on the rAI. In support of this, recent work has shown rAI functional connectivity with the DMN to predict response to rTMS treatment (Taylor et al., 2018). For further support, we found that the CBF of the rAI is greater in responders compared to non-responders, which is in harmony with McGrath et al. (2013) where hypo-/hypermetabolism of the rAI predicted response to cognitive behavioural therapy or antidepressant medication, respectively. This may seem an unexpected finding, given that the patients in the current study are largely unresponsive to antidepressant medication, and it appears that the rAI CBF may be a predictor for both antidepressant and rTMS treatment response. However, it is plausible that rTMS treatment response may be predicted differentially to antidepressant response by other unexplored regions and/or measures, which may include the connectivity measures observed here. While the exact pattern and network is not yet clear, it is evident that the functioning of the rAI is a key region that may inform responsiveness to rTMS treatment, and help to stratify patients into sub-populations within the depression syndrome that particularly respond to neuromodulation approaches.

This net rAI-to-DLPFC outflow did not predict longer-term response at three months. However, various factors are likely to contribute to longer-term clinical outcomes (e.g., dosage, external factors and/or life events). This difference in correlation between immediately post-treatment and several months post-treatment, puts forth the importance of further exploring predictors for longevity of response. Current neuroimaging studies of rTMS treatments commonly gather clinical outcome data at the end of the treatment period. However, more meaningful efficacy of rTMS should also encompass longer-lasting effects that considers both the greatest and most persisting symptom improvement.

Interestingly, we also found differences between responders and non-responders at 1-month in the salience network. Specifically, differences were seen in the connectivity of occipital regions with the core salience network. There appears to be a striking pattern where responders have a negative sensory-salience connectivity while non-responders have a positive connectivity. This is indicative of a specific biotype for response to rTMS that may be related to the processing of sensory information. In the recent study by Drysdale et al. (2017), increased connectivity of the visual cortex with limbic structures was observed in responders, and in addition, the most discriminating connectivity features between responders and non-responders included the visual region. Reports of aberrant functioning of visual regions are not uncommon in neuroimaging studies of depression (Iwabuchi et al., 2014; Sambataro et al., 2017; Veer et al., 2010; Zeng et al., 2012), though is not often considered core pathophysiology and therefore discussions on the implications are limited. Dysfunctions of the connectivity between visual regions and salience network likely contributes to an impaired processing and assessing of salient visual stimuli. Therefore, it would be valuable in future work to elucidate further the neural substrates of visual salience processing deficits in depression to understand whether a measure of such impairments could be a potential and simple marker for treatment response to rTMS.

Although recent works have demonstrated changes in functional connectivity following rTMS in depression (Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2013), we did not observe network changes, neither at the stimulated network, nor the major resting state networks. One notable difference is the timeframe of the post-treatment MRI: previous work acquired scans immediately following the end of the treatment period, while our patients were scanned two months following the end of treatment to explore longer-term modulation of networks and how this relates to response. Therefore, while we do not have the data, it is possible that our patients may have exhibited changes similar to these studies at one month. To date, there is no strong evidence that links the degree of treatment response with the degree of connectivity change, noting one recent study that reached only trend significance (Avissar et al., 2017). Nevertheless, while the low sample size does not allow a definitive conclusion, the potential for normalising this network through neuromodulation needs further exploration with emphasis on factors that relate to both the normalisation of connectivity and symptom improvement. Additional considerations include optimal number of sessions, which are likely to vary between patients. An adaptive design that allows treatment to continue until a predefined level of clinical response may be able to closer inspect the relationship between clinical response and connectivity change.

We note that overall, the response rate across all patients was quite high (55% for rTMS, 69% for iTBS). This is numerically higher than the meta-analytical reports indicating 45% response rates for 10-Hz rTMS and recent RCTs reporting 50% response rates for iTBS (Cao et al., 2018). We suspect that one of the reasons could be the acceptance of Thase and Rush's TRD stage 1 as an inclusion criteria, rather than more stringent definitions of TRD. It is also likely that there was an inflated response as a result of the novelty of the 2 interventions (no TMS clinics were operating in this region before this study was started). Our 3 months response rates were closer to those reported elsewhere (44% for rTMS) (Perera et al., 2016). Also, our sample size was limited; with a larger group size, the response rate may move closer to the rates reported in other studies (i.e., ~30%) (Berlim et al., 2014).

There are a number of limitations that we note may have an impact on our results. Firstly, the majority of patients were medicated which may either affect or be affected by rTMS treatment. However, it is both a challenge to seek unmedicated treatment-resistant individuals (as well as those who are willing to cease taking medication), and unrealistic to study unmedicated individuals, given that rTMS is usually offered to patients who have failed previous trials of antidepressants. For future work, it would be useful to investigate whether there are differential neurophysiological effects of rTMS depending on the type of medication/treatment – interactions between drug and neurostimulation will become

important as rTMS becomes increasingly common and routine in the treatment of depression. Secondly, we must note the limited sample size in our study, especially with respect to data available for both baseline-3-month, and responder-non-responder comparison. However, our results are in line with previous studies suggesting that resting-state connectivity metrics may be a practical and useful measure to assess suitability of rTMS treatment for depression, though larger datasets are necessary to assess the predictability of long-term response. We also note the lack of sham-rTMS arm and therefore cannot fully eliminate the placebo response, however future large-scale studies exploring the impact of the placebo effect are highly warranted.

5. Conclusion

Our study demonstrates that resting-state connectivity signatures can predict response to rTMS treatment in patients with resistant depression (irrespective of methodological variations in stimulus delivery). We provide evidence that the salience network may be key circuit that determines responsiveness to rTMS treatment at least in the short-term. We encourage future work to explore predictive biomarkers for long-term rTMS treatment outcomes.

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Contributors

SI was involved in the design, recruitment, data collection, data analysis, interpretation and wrote the first draft of the manuscript. DA managed the data collection, analysis and contributed to the interpretation and write up of the manuscript. SL was involved in the design, the recruitment and interpretation and write up of the manuscript. LP managed and contributed to the design, recruitment, data collection, analysis, interpretation and write up of the manuscript. All authors contributed to and approved the final version of the manuscript.

Conflict of interest

LP received travel support from Magstim Limited (makers of a TMS device) to speak at a meeting organized by them at Oxford, UK. LP owns stocks (value < USD 5000) in Shire plc. All other authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.02.012.

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