Is SGC-DLPFC Individualized Functional Targeting for rTMS in Treatment-Resistant Depression Associated With Better Outcomes?

Elizabeth C Gregory[1,2], Robin FH Cash[3,4], Andrew Zalesky[3,4], Daniel M Blumberger[5,6,7], Jonathan Downar[5,6,8], Zafiris J Daskalakis[9], Fidel Vila-Rodriguez[1,2]

[1]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada [2]Non-Invasive Neurostimulation Therapies (NINET) Laboratory, University of British Columbia, Vancouver, BC, Canada; [3]Melbourne Neuropsychiatry Centre, The University of Melbourne, Melbourne, Victoria, Australia; [4]Clinical Brain Networks Group, QIMR Berghofer, Brisbane, Queensland, Australia; [5]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [6]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [7]Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, Toronto, ON, Canada; [8]MRI-Guided rTMS Clinic and Krembil Research Institute, University Health Network, Toronto, Canada; [9]Department of Psychiatry, UC San Diego, San Diego, CA, USA

Background

- Repetitive Transcranial Magnetic Stimulation (rTMS) is an effective and well-tolerated intervention for treatment-resistant depression (Anderson et al., 2016).
- The **left dorsolateral prefrontal cortex** (DLPFC) is the standard treatment target, hypothesized to work through its connections with the **subgenual anterior cingulate cortex (sgACC)** (Cash et al., 2021). Anticorrelation of the BOLD fluctuation time series between the DLPFC and sgACC has shown a robust relationship to rTMS outcomes across several previous studies (*e.g.,* Fox et al., 2012; Fox et al., 2013; Weigand et al., 2018; Cash et al., 2019).
- Standard practice targets the DLPFC anatomically based on group-level DLPFC-sgACC anticorrelation. However, the distribution of anticorrelation within the DLPFC varies significantly from person-to-person (Fox et al., 2013).
- It is proposed that optimal treatment outcomes can be achieved by targeting rTMS using the site of maximal anticorrelation with the sgACC for each individual patient, thereby creating an individualized functional target (iFT) (Cash et al., 2021).

This retrospective study aimed to replicate previous findings, investigating the role of the following in treatment response:

1. **Proximity of the clinically applied target to the iFT for each patient**
2. **DLPFC-sgACC anticorrelation at the clinically applied target**

Methods

Participants and Intervention

- Baseline resting-state fMRI scans (10-minute duration) and T1 anatomical scans were collected for 389 patients with treatment-resistant depression as part of the **THREE-D clinical trial** (Blumberger et al., 2018).
  - Patients received 4-6 weeks daily treatment of either 10hz or theta-burst rTMS to left DLPFC. These treatment protocols were found to be non-inferior to one another in terms of clinical efficacy.
  - Treatment target was located using neuronavigation and identical across individuals (MNI coordinates [-38, 44, 26]).

Neuroimaging analysis

- Data was preprocessed using the fMRIPrep neuroimaging pipeline with AROMA-ICA (Esteban et al., 2019). White matter, cerebrospinal fluid, and global signal were regressed out as covariates (Fox et al., 2009).
- We assessed the relevance of the DLPFC-sgACC anticorrelation to treatment response in two ways:
  - iFT was derived by identifying the voxel within the DLPFC whose timeseries showed maximal anticorrelation with the sgACC ROI time series. The Euclidean distance was calculated between each patient's iFT and the clinically applied target.
  - sgACC-DLPFC connectivity at the clinically applied target was assessed by calculating correlating the timeseries at [-38, 44, 26] with the sgACC ROI timeseries.
  - Both measures were correlated with percent change in the Hamilton Rating Scale for Depression (HRDS) from baseline to end of treatment.

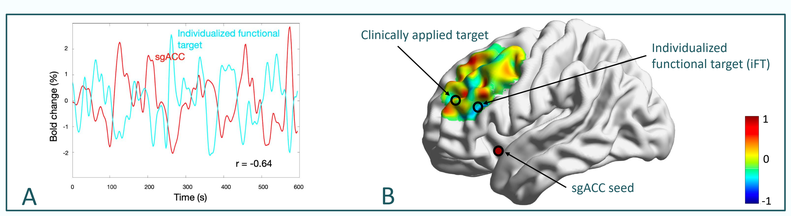

Figure 1. Example of iFT derivation and distance calculation in a single subject. A) shows the timeseries of the sgACC ROI and the DLPFC voxel which showed the largest anticorrelation to the sgACC (*ie* the iFT for this subject). B) Shows a functional connectivity map of the DLPFC with the sgACC seed (10 mm sphere at [6, 16, -10]) and demarks the locations of both the the clinically applied and individualized targets.

Results

- 340 subjects completed treatment and had acceptable baseline fMRI scans. Demographic variables are summarized in Table 1.
- iFTs are shown in Figure 2. Average distance to the clinically applied target was 29.19 mm (SD = 13.20). The average distance was no different between responders (defined as 50% or more reduction in HRSD score) and non-responders (T = 0.88, p = 0.34).
- There was no relationship between the distance to the iFT and clinical response (r = -0.07, p = 0.17), even after controlling for confounds including MRI scanner, treatment parameters, and clinical features (r = -0.10, p = 0.06). Findings are plotted in Figure 3A.
- Anticorrelation at the site of treatment was not associated with treatment response (r = -0.04, p = 0.50,), again even after controlling for confounds (r = -0.08, p = 0.17). Findings are plotted in Figure 3B.
- Distributions of distance to iFT and treatment site anticorrelation between responders and non-responders are shown in Figure 4.

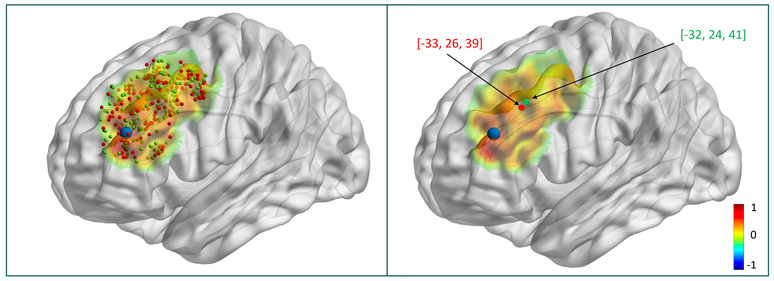

Figure 2. A) Map of individualized functional targets (iFTs) within the left DLPFC, the colourmap of which represents the average DLPFC-sgACC timeseries correlations of each voxel across all subjects. Red spheres represent iFTs for responders, green spheres represent iFTs for non-responders, and the blue sphere represents the actual target used for rTMS treatment [-38, 44, 26]. B) The average iFTs for responders (green sphere) and non-responders (red sphere) showed no difference in proximity to to the clinically applied target (blue sphere).

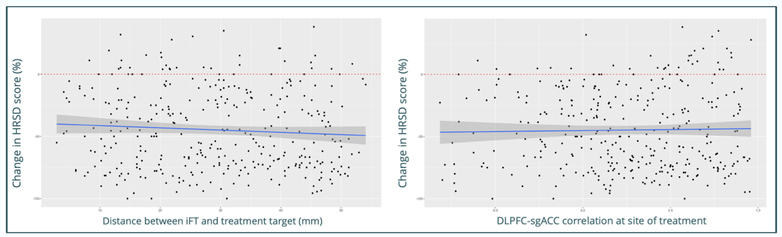

Figure 3. A) There was no relationship between proximity of the iFT to the optimal treatment site and improvement in depressive symptoms, measured by percent change in the HRSD score. B) There was no relationship between DLPFC-sgACC connectivity at the site of treatment and improvement in depressive symptoms, measured by percent change in the HRSD score.

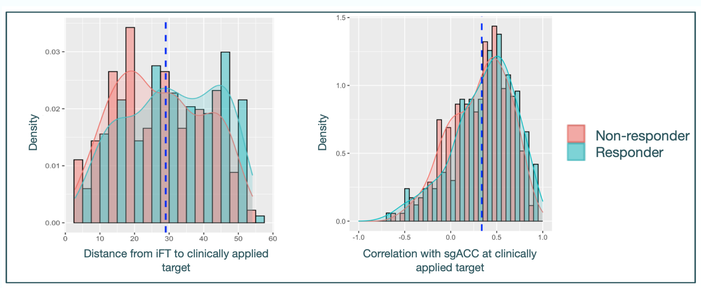

Figure 4. Distributions of variables of interest in responders and non-responders. Blue dashed lines represent the mean values of the x axis variable for each distribution. A) represents the distance from the iFT to the clinically applied target in each subject. The mean value was 29.07 (SD = 12.33) for responders and 27.94 (SD = 11.45) for non-responders. B) represents the correlation of the clinically applied target with the sgACC. The mean value was 0.27 (SD = 0.42) for responders and 0.24 (SD = 0.43) for non-responders.

Table 1. Demographic and clinical variables of patients in the study (n=340).

	Mean (SD) or Count (%)
Age	42.44 (11.43)
Number of years of education	16.40 (2.99)
Female	201 (59%)
Right handed	303 (89%)
Baseline HRSD score	23.29 (4.27)
End of rTMS HRSD score	13.00 (7.71)
% change in HRSD score	-44.79 (32.18)
Responder	171 (50.3%)
Remitter	111 (33%)
Age of onset	20.71 (10.77)
Length of current episode (months)	23.46 (28.93)
Anxiety comorbidity	176 (52%)
ATHF score	6.30 (3.34)
2 or more adequate trials	168 (49%)
Benzodiazepines	111 (33%)
Antidepressants	263 (77%)
Theta-burst stimulation	177 (52.1%)
rTMS stimulation intensity	49.65 (10.77)
Number of treatments	26.72 (4.68)

Discussion

This is the first study looking at iFT retrospectively in a large sample of patients undergoing rTMS for TRD.

- Proximity of rTMS stimulation to iFT did not associate with treatment response in our sample, in contrast to previous research using a sample of 20 patients (Cash et al., 2020).
- More surprisingly, we did not find that DLPFC-sgACC correlation at the clinically applied site was associated with treatment response, despite this being a widely-replicated finding (*e.g.,* Fox et al., 2012; Fox et al., 2013; Weigand et al., 2018; Cash et al., 2019, Cash et al., 2020). This may be due to the sgACC seed used in the current study which was contralateral to the DLPFC, whereas Ge et al. (2019) found only ipsilateral sgACC connectivity predicted treatment response.

The basis for this may relate to:

- Considerable variability across studies in treatment parameters, including targeting method, stimulation frequency and intensity, and number of treatments delivered.
- Differences in imaging analysis methods, including the definition of the sgACC and how the optimal site within the DLPFC is derived (Cash et al., 2021).
- fMRI data acquisition parameters and quality across studies.
- A lack of a true role of DLPFC-sgACC activity in response to rTMS treatment.

Future directions to understand our null results include:

- Employing seedmap methodology to increase signal-to-noise ratio (Cash et al., 2021).
- Deriving the optimal DLPFC site using methods such as cluster-based derivation and weighted seed cones (Cash et al., 2021).
- Exploring rTMS electrical field propagation in the brain and how this influences treatment response.

References

Anderson, R.J., Hoy, K.E., Daskalakis, Z.J., Fitzgerald, P.B., 2016. Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections 127, 3394–3405. https://doi.org/10.1016/j.clinph.2016.08.015

Blumberger, D.M., Vila-Rodriguez, F., Thorpe, K.E., Feffer, K., Noda, Y., Giacobbe, P., Knyahnytska, Y., Kennedy, S.H., Lam, R.W., Daskalakis, Z.J., Downar, J., 2018. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet (London, England) 391, 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2

Cash, R.F.H., Cocchi, L., Lv, J., Fitzgerald, P.B., Zalesky, A., 2020. Functional Magnetic Resonance Imaging–Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. JAMA Psychiatry 1–3. https://doi.org/10.1001/jamapsychiatry.2020.3794

Cash, R.F.H., Cocchi, L., Lv, J., Wu, Y., Fitzgerald, P.B., Zalesky, A., 2021. Personalized connectivity-guided DLPFC-TMS for depression: Advancing computational feasibility, precision and reproducibility. Hum. Brain Mapp. 42, 4155–4172. https://doi.org/10.1002/hbm.25330

Cash, R.F.H., Weigand, A., Zalesky, A., Siddiqi, S.H., Downar, J., Fitzgerald, P.B., Fox, M.D., 2021. Using Brain Imaging to Improve Spatial Targeting of Transcranial Magnetic Stimulation for Depression. Biol. Psychiatry 90, 689–700. https://doi.org/10.1016/j.biopsych.2020.05.033

Fox, M.D., Buckner, R.L., White, M.P., Greicius, M.D., Pascual-Leone, A., 2012. Efficacy of TMS targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. https://doi.org/10.1016/j.biopsych.2012.04.028

Fox, M.D., Liu, H., Pascual-Leone, A., 2013. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage 66, 151–160. https://doi.org/10.1016/j.neuroimage.2012.10.082

Ge, R., Downar, J., Blumberger, D.M., Daskalakis, Z.J., Vila-Rodriguez, F., 2020. Functional connectivity of the anterior cingulate cortex predicts treatment outcome for rTMS in treatment-resistant depression at 3-month follow-up. Brain Stimul. https://doi.org/10.1016/j.brs.2019.10.012

Weigand, A., Horn, A., Caballero, R., Cooke, D., Stern, A.P., Taylor, S.F., Press, D., Pascual-Leone, A., Fox, M.D., 2018. Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. Biol. Psychiatry 84, 28–37. https://doi.org/10.1016/j.biopsych.2017.10.028