Correspondence

Subgenual Functional Connectivity Predicts Antidepressant Treatment Response to Transcranial Magnetic Stimulation: Independent Validation and Evaluation of Personalization

To the Editor:

Repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is an established therapy for refractory depression. However, treatment outcomes are variable and can depend on the precise stimulation loci targeted within the DLPFC. We therefore followed with interest the evidence presented in *Biological Psychiatry* by Fox *et al.* (1) and Weigand *et al.* (2) indicating that the extent of negatively (i.e., anti-) correlated functional connectivity (FC) with the subgenual cingulate cortex (SGC) at the precise DLPFC stimulation site predicts treatment outcome and can potentially facilitate FC-guided rTMS personalization. Thus, establishing the generalizability of these findings across different cohorts and magnetic resonance imaging (MRI) scanners is crucial, particularly given the increasing emphasis on reproducibility in neuroscience (3,4).

In this correspondence, we provide an independent validation corroborating these findings as well as new results concerning rTMS personalization. Both previous reports (1,2) sampled SGC FC at each individual's DLPFC stimulation site from group-level SGC FC maps derived from averaging individual FC maps from healthy or depressed individuals. Averaging across individuals yielded robust SGC FC maps, minimizing noise effects inherent to individual FC estimates. However, a potential disadvantage of determining stimulation loci based on a group-level FC map is that interindividual differences in FC are discarded. These differences may potentially improve rTMS personalization and aid prediction of individual treatment outcomes. Preserving interindividual variation may therefore facilitate, rather than hinder, treatment personalization. Therefore, as also noted by Fox *et al.* (1,5) and Weigand *et al.* (2), determining whether personalized SGC FC maps can improve the prediction of individual rTMS treatment outcomes remains of substantial interest. Based on their findings, both previous reports also proposed optimized left DLPFC stimulation loci that showed maximal anticorrelated SGC FC; however, it remained unclear how closely these coordinates might be approximated by other targeting methods. In the present study, rTMS was targeted to the left DLPFC using the recently developed F3 Beam approach (6), which was designed to better account for individual head shape.

We acquired data in 47 individuals with major depressive disorder (19 women, age 44 ± 13 years) who underwent T1, T2, and resting-state functional MRI (fMRI) (6 minutes). These individuals were part of a larger clinical study (Australian New Zealand Clinical Trials Registry: Investigating Predictors of Response to Transcranial Magnetic Stimulation for the Treatment of Depression; ACTRN12610001071011; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336262), in which 39 individuals subsequently completed 3 weeks of rTMS and 24 individuals completed 5–8 weeks of left-sided rTMS treatment (10 Hz, daily Monday through Friday) (7). Depression severity was assessed using the Montgomery–Åsberg Depression Rating Scale. Stimulation coordinates were reconstructed offline using combined T1 and T2 scans and converted from native to standard space using FSL Version 5.0.10 software (8) and customized MATLAB R2017a scripts (The MathWorks, Inc., Natick, MA). Briefly, preprocessing for FC analysis was performed according to the independent component analysis–based strategy for automatic removal of motion artifacts pipeline (9–12). In addition, global signal regression was implemented before bandpass temporal filtering (0.01–0.1 Hz) (11), as recommended (9) and implemented (1,2) elsewhere, for optimal evaluation of anticorrelated relationships (13). Data were nonlinearly aligned to Montreal Neurological Institute (MNI) 152 space. For each individual, FC was measured using the Pearson correlation coefficient computed between the SGC seed (10-mm sphere, centered at MNI 6, 16, −10 mm) (1) and 1) each individual's personalized stimulation site and 2) the spatial group-average stimulation site. Additionally, group-level SGC FC maps were determined for 1) the entire major depressive disorder cohort (n = 47) and 2) an independent dataset comprising healthy individuals (Human Connectome Project, n = 1020, 550 women, age 28.7 ± 3.7 years). Human Connectome Project data acquisition and processing are described elsewhere (14,15), and global signal regression was added post hoc. Using these group-level FC maps, FC was measured between the SGC seed and each individual's personalized stimulation site. For FC mapping, weighted cone seeds, designed to mimic the linear decay of the TMS pulse (5), were positioned at the individual cortical DLPFC treatment site (10-mm radius). Additional control seeds were placed as described below.

First, we replicated the finding by Fox *et al.* (1) and Weigand *et al*. (2) and found that the antidepressant efficacy of rTMS treatment is related to SGC FC at the DLPFC stimulation site, as measured using the group-level FC map ($\rho = -.53$; $p = .009$) (Figure 1A). This result was also replicated ($\rho = -.58$; $p = .003$) using the group-level SGC FC map generated from 1020 normative participants (Figure 1B). Interestingly, this relationship was preserved when individual resting-state scans were employed to determine SGC FC at the DLPFC treatment site ($\rho = -.613$, $p = .001$). Estimating treatment response based on each individual's stimulation site was significantly more accurate ($p < .05$; tested across 5000 permutations) than using the group-average stimulation site (MNI −43, 46, 32; $\rho = -.49$, $p = .015$). Improvement in Montgomery–Åsberg Depression Rating Scale scores was largest at anterolateral sites that had shown stronger anticorrelated signal with SGC (Figure 1C). To ensure that these results did not reflect a general characteristic of individual SGC connectivity across the cortex, we assessed SGC connectivity with control seeds placed within the visual network (MNI −30, −92, 6) (16), left temporoparietal junction (MNI −58, −52, 40), right DLPFC (MNI 43, 46, 32), and left occipital lobe (−43, −73, 33) (Figure 1A). FC with SGC at these sites did not bear a significant relationship to treatment

https://doi.org/10.1016/j.biopsych.2018.12.002
ISSN: 0006-3223

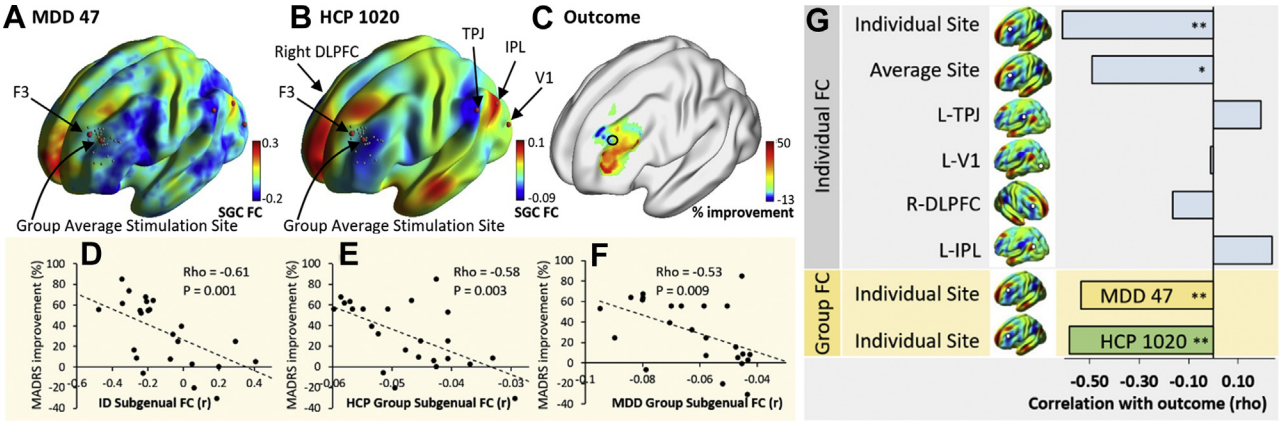

Figure 1. Subgenual cingulate cortex (SGC) seeded connectivity patterns are depicted based on **(A)** a cohort of 47 individuals with major depressive disorder (MDD) or **(B)** 1020 Human Connectome Project (HCP) participants. Anticorrelated functional connectivity (FC) (blue shading) is evident at the dorsolateral prefrontal cortex (DLPFC). FC with the SGC was determined at each individual's stimulation site (gray) as well as at the group average stimulation site and various control sites (right DLPFC, left temporoparietal junction [TPJ], inferior parietal lobule [IPL], and primary visual cortex [V1]), labeled in panel **(B)**. F3 Beam-based stimulation sites (gray) typically fell in a triangle between the F3 electrode and the stimulation sites proposed by Fox *et al.* (1) and Weigand *et al.* (2). **(C)** Heatmap showing treatment outcome in relation to stimulation site across the sample of 39 individuals with depression. **(D–F)** Greater treatment outcome (% change in Montgomery–Åsberg Depression Rating Scale [MADRS] score) was associated with more negative SGC FC at the individual DLPFC stimulation site. This result was consistent when determining connectivity using **(D)** individualized (ID) FC maps (n = 24), group connectivity based on **(E)** normative HCP data (1020 healthy participants), or **(F)** MDD data (47 participants). **(G)** Relationship between treatment outcome and FC at different cortical sites, determined either by individualized or group FC maps (*$p < .05$; **$p < .01$, two-tailed). Crucially, the relationship between SGC FC and treatment outcome was not significant at control sites. L, left; R, right.

outcome (visual cortex: $\rho = -.01$, $p = .97$; temporoparietal junction: $\rho = .19$, $p = .36$; right DLPFC: $\rho = -.17$, $p = .44$; left occipital lobe: $\rho = .24$, $p = .26$). Scatter plots are shown in Figure 1D–F, and correlation coefficients are compared in Figure 1G. Together, these results confirm that SGC-DLPFC connectivity is a specific marker of treatment outcome.

An additional point of interest is that Fox *et al.* (1) and Weigand *et al.* (2) proposed DLPFC coordinates showing peak anticorrelation with the SGC as potential future stimulation targets. Our data directly support this proposition. Furthermore, our results indicate that the F3 Beam approach resulted in the majority of participants' being stimulated in a triangle bounded by the F3 coordinate (17) and the sites outlined by Fox *et al.* (1) and Weigand *et al.* (2).

In sum, our data provide an independent validation indicating that rTMS clinical outcome is predicted by the degree of anticorrelation between fMRI signals in the DLPFC (target) and the SGC. Moreover, our findings demonstrate that treatment outcome may be estimated with similar accuracy by using either group-level or individual FC SGC maps, which may simplify clinical efforts to incorporate this approach together with neuronavigation. The advantages of personalized approaches for outcome prediction and target localization are likely to be realized in the near future, for example by lengthening MRI scan duration. Future research may focus on assessing whether a precision medicine approach targeting rTMS at the DLPFC based on SGC FC can enhance treatment outcomes.

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Acknowledgments and Disclosures

This work was supported by the Australian National Health and Medical Research Council Senior Research Fellowship B (Grant No. 1136649 [to AZ]) and Australian National Health and Medical Research Council grants (Grant Nos. APP1138711 and APP1099082 [to LC]). Human Connectome Project data were provided by the Human Connectome Project, Washington University–University of Minnesota Consortium (principal investigators, David Van Essen and Kamil Ugurbil; Grant No. 1U54MH091657) funded by the 16 National Institutes of Health Institutes and Centers that support the National Institutes of Health Blueprint for Neuroscience Research, and McDonnell Center for Systems Neuroscience at Washington University.

We thank all participants, nurses, and researchers involved in this study, in particular, David Elliot, Melanie Emonson, Caley Sullivan, Rodney J. Anderson, Kate Hoy, Susan McQueen, Bernadette Fitzgibbon, and Aaron Kucyi.

PBF has received equipment for research from Cervel Neurotech, Inc., Medtronic Ltd., MagVenture A/S, Neuronetics, Inc., and Brainsway Ltd.; has received funds for research from Cervel Neurotech, Inc., and Neuronetics, Inc.; is on scientific advisory boards for Bionomics Ltd. and LivaNova, PLC; and is a founder of TMS Clinics Australia. All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Nov 20, 2018; accepted Dec 4, 2018.

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