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The DLPFC-SGC functional connection predicts the plasticity response of SGC to rTMS

Dear Editor,

Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has been proven to be an effective method for treating depression. Although the efficacy is significant, there remains a potential for enhancement in both response and remission rates. One critical challenge resides in the identification of the optimal DLPFC target. Numerous studies have found that major depressive disorder (MDD) patients exhibit hyperactivity in subgenual cingulate cortex (SGC), which decreases after effective rTMS and other antidepressant treatments [1,2]. Additionally, SGC was an effective target for treating treatment-resistant depression with deep brain stimulation. Inspired by these observations, Fox et al. retrospectively discovered that the stronger the negative functional connectivity between the DLPFC target and SGC, the better the treatment outcome [3], and this finding has been repeatedly validated [4,5]. Further, Fox et al. suggested choosing the DLPFC point exhibiting the most negative connectivity with SGC as the target, and the efficacy of this target has been confirmed through subsequent clinical trials [6]. Taking these phenomena into consideration, some researchers postulated that TMS modulated SGC through the DLPFC-SGC pathway, ultimately producing antidepressant effects [3].

Concurrent TMS-fMRI studies have found that single-pulse TMS of the DLPFC induced transient effects in SGC in both healthy individuals and MDD [7,8], and the effect intensity was correlated with DLPFC-SGC connectivity. This evidence suggested that TMS may modulate the activity of SGC through the DLPFC-SGC pathway. However, the above-mentioned studies only focused on the transient effects of SGC induced by single-pulse TMS, and whether long-duration rTMS leads to structural and functional changes in SGC related to this pathway is currently unclear. This study aims to explore the relationship between the DLPFC-SGC functional connectivity and the plasticity of SGC.

This study recruited 13 patients with depression (9 females, age 29 ± 6 years) at the Shanghai Mental Health Center. The participants received 10Hz rTMS of the DLPFC for a total of 20 sessions. The stimulation target was the left DLPFC with the most negative group-average SGC connectivity (MNI coordinates = −42, 44, 30), and the coil was positioned based on the guidance provided by the Localite Neuronavigation System (NDI, Canada). The participants underwent Hamilton Depression Scale (HAMD) assessments, T1-weighted imaging, and resting-state fMRI (6.2 minutes) before and after the treatment. The preprocessing steps followed the procedure described by Fox et al. [3]. Individual connectivity between the DLPFC target and SGC was calculated, where the DLPFC target was defined as the gray matter voxel with simulated electric field values greater than 15 V/m, which is considered the minimum electric field value to evoke synaptic responses [9], and the time series of SGC was computed using the SGC-based seed map to improve the signal-to-noise ratio. The functional and structural plasticity of SGC were assessed by calculating the change rates of fractional amplitude of low-frequency fluctuations (fALFF) and gray matter volume (GMV), respectively. Functional plasticity was defined as $(fALFF_{t2} - fALFF_{t1})/fALFF_{t1}$, and structural plasticity was defined as $(GMV_{t2} - GMV_{t1})/GMV_{t1}$.

We correlated the clinical improvement to the change rates of fALFF and GMV with Spearman correlation coefficients. The results revealed significant correlations between the clinical change and the fALFF change ($r = -0.69$, $p = 0.004$, one-tailed), and between the clinical change and the GMV change ($r = 0.51$, $p = 0.039$, one-tailed), indicating that these plasticity measures well reflected the antidepressant response in SGC. Furthermore, we computed the Pearson correlation coefficients between the connectivity and the change rates of fALFF and GMV. The connectivity was significantly correlated with the fALFF change ($r = 0.57$, $p = 0.040$, $df = 12$), and with the GMV change ($r = -0.64$, $p = 0.018$, $df = 12$) in SGC (Fig. 1). We controlled for the effect of gender by regressing it out from the plasticity measures and clinical improvement.

We demonstrated that the DLPFC-SGC functional connectivity predicted the plasticity response in SGC. In conjunction with previous findings that the connectivity predicted the transient effects in SGC [8], our results collectively support the hypothesis that TMS modulates SGC via the DLPFC-SGC pathway depicted by functional connectivity. In order to bolster the reliability of our conclusion and to account for potential confounding variables, we have two considerations. Firstly, it was imperative to investigate whether the connectivity changes after the initiation of treatment. If such changes were observed, the mere discovery that baseline connectivity could predict SGC changes would be insufficient to support to the hypothesis regarding TMS modulating the SGC through the DLPFC-SGC pathway. To address this concern, we compared the pre- and post-treatment functional connectivity strength and found that there were no statistically significant changes (paired *t*-test: $p = 0.89$). Second, Fox et al. suggested that the DLPFC takes the initiative to inhibit the activity of SGC when SGC is overactive [3], which may lead to the correlation between connectivity and SGC plasticity in patients. To further investigate this, we included 12 new patients with depression as controls, who received 1Hz rTMS of the right orbitofrontal cortex (guided by AF8 in 10–20 system), and no correlation was found between SGC plasticity and DLPFC-SGC connectivity (fALFF: $r = 0.43$, $p = 0.162$; GMV: $r = -0.1$, $p = 0.7612$). This finding suggests that TMS intervention is a necessary condition for the relationship between connectivity and SGC plasticity. Furthermore, DLPFC target with more negative connectivity indicates a greater decrease in fALFF and an increase in GMV in SGC, aligning with the expectation of regulating the hyperactivity and volume reduction of SGC in MDD [10]. This finding contributes to the understanding of the TMS targeting approach based on SGC connectivity [3]. There are some limitations in this study, including the small sample size, which calls for replication in

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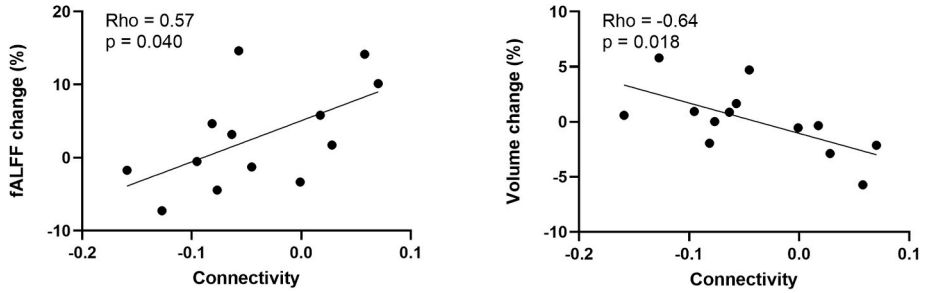

Fig. 1. The relationship between connectivity and SGC plasticity measured with A) fALFF and B) GMV.

larger samples. Future studies would benefit from incorporating diffusion tensor imaging to investigate the structural basis of the DLPFC-SGC pathway, which may have better correspondence with the response of SGC.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.09.016.

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