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The left ventrolateral prefrontal cortex as a more optimal target for accelerated rTMS treatment protocols for depression?

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Dear Editor-in-chief of Brain Stimulation

The international brain stimulation community is following new developments with accelerated rTMS treatment protocols for depression with great interest [1]. In particular the Stanford Neuromodulation Therapy (SNT) protocol, which yields response and remission rates unchallenged by any other (accelerated) rTMS stimulation protocol for treatment resistant depression (TRD), and shows response and remission rates up to 80–90% [2,3], is rightly attracting much attention. The SNT protocol, which includes high-dose accelerated intermittent theta-burst stimulation (aiTBS), was recently approved by the FDA for TRD, encouraging the widespread use of such promising treatment protocols. Importantly, the exact individual cortical target location is determined *a priori* by taking into account the (negative) functional connectivity (FC) between the subgenual anterior cingulate cortex (sgACC) and specific areas within the left dorsolateral prefrontal cortex (DLPFC). While this follows the literature on precision targeting, it is important to point out that in the SNT trials, these individual (negatively) functionally connected stimulation targets with the sgACC all appear to be closely grouped, specifically more anteriorly and laterally and appear to be located within the left ventrolateral prefrontal cortex (VLPFC) (see also Fig. 1A). This suggest that this part of the prefrontal cortex may be a potentially more optimal stimulation target for accelerated rTMS paradigms. Since one of the limitations to the diffusion of such successful accelerated rTMS protocols could be the availability of (f)MRI scans [4], further research is of great importance to find out whether an optimal stimulation target for such accelerated rTMS protocols can be localized without expensive and limited available scanning procedures.

To further investigate the hypothesis, we reanalyzed our previous left DLPFC accelerated high-frequency (HF)-rTMS treatment protocol in nineteen antidepressant-free TRD patients (for details see Ref. [5]), which included (F-18) fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET) measurements. Although we used a whole brain analytical approach, consistent with the aiTBS sgACC FC findings in Cole et al. [2,3], we hypothesized that the sgACC-to-brain metabolic connections in relation to best clinical outcome would also lie within these left VLPFC areas. For more detailed information on demographics, aiTBS treatment protocol, and analytical approaches see supplemental material.

Consistent with our hypotheses, we found that clinical improvement (BDI-II percentage change) was significantly correlated with weaker baseline sgACC metabolic connectivity to the left inferior frontal gyrus (k = 45, MNI = −51, 18, 12; peak T-value = 5.46; cluster-level FDR-corrected), part of the left VLPFC. See also Fig. 1A. These correlations with the BDI-II percentage changes were not caused by potential outliers in sgACC metabolic connectivity patterns. We also evaluated sgACC metabolic connectivity with percent changes on the HDRS, but no significant correlations were observed here.

Cole and colleagues [3] suggested that these sgACC anti-correlated stimulated ventrolateral 'DLPFC' targets are part of an affective circuit that results in the reduction of both melancholic symptoms and depression severity. In support of this contention, Siddiqi et al. [6] also found that stimulating the left DLPFC more anteriorly and laterally (with conventional daily rTMS) reduced sadness and melancholic symptoms, whereas stimulating the DLPFC more dorsally was more likely to affect 'anxiosomatic' symptoms. We have recently found evidence supporting the latter assumption with our aiTBS treatment protocol [7]. To some extent, this may also explain why correlations with clinical improvement were observed with the BDI-II and not the HDRS, since the BDI-II focuses more on the 'cognitive symptoms' of the depressed state [8]. Importantly, Cole et al. [2,3] included different types of depression (excluding bipolarity and psychosis), so one might speculate that stimulation of the left VLPFC may be independent of the type of depression and also regardless of which accelerated rTMS protocol was applied. One explanation could be that stimulating the VLPFC with accelerated (high dose) rTMS may affect sgACC neuronal activity more directly via the VLPFC functional connections towards the orbitofrontal cortex, another important region in reward processing in mood disorders and strongly connected to the sgACC [9]. Our electrical field modeling (see Fig. 1B) seems to be in line with this assumption. Although the sgACC electrical field strength appears to be quite low for every coil localization, and independently of the left/right/entire sgACC, the highest electrical field strength is observed with our sgACC-left VLPFC metabolic connectivity spot (centroid, MNI: −48, 24, 9). Also, lower sgACC electrical field strengths are found at our actual structural (dorsal) left DLPFC stimulated target (MNI: −45, 30, 31). Given the assumption that functional and structural connections from the more dorsally located DLPFC subregions towards the sgACC

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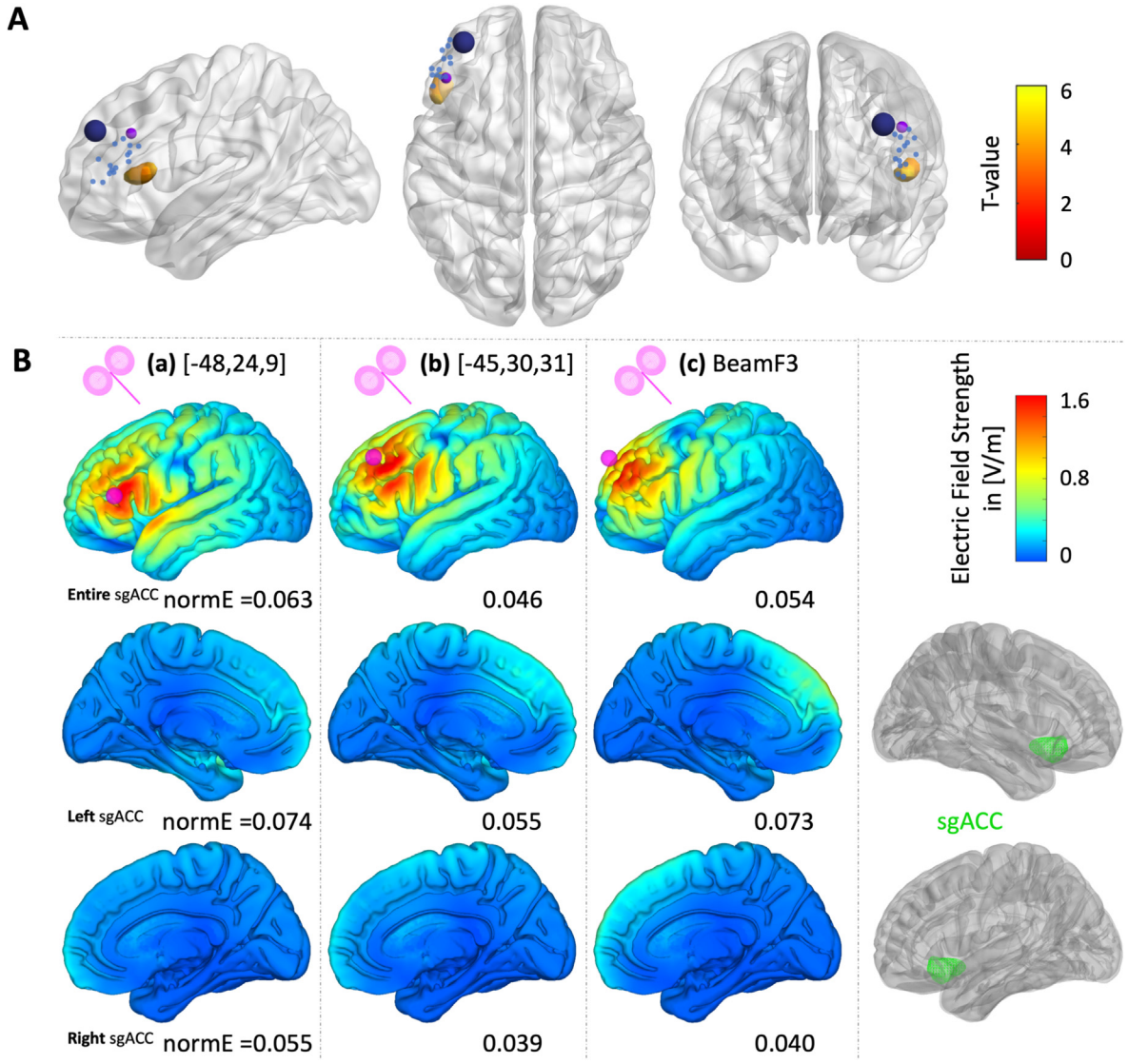

Fig. 1. A) Glass brain images of the significant (left) sgACC seed-based covariance connection with the left inferior frontal gyrus depicted in orange. The purple dot represents the left DLPFC stimulated area (MNI = −45, 30, 31). The smaller blue dots represent the individual stimulated cortical targets from the Cole et al. [4] paper. The large blue dot represents the BeamF3 spot (MNI = −35.5, 49.4, 32.4). B) Distribution of the electric field norm. Electric field modeling was performed on MNI152 mesh using SimNIBS (version 3.2.6). The stimulation intensity, coil orientation (calculated for a Magstim 70-mm figure-of-eight coil) and coil-to-scalp distance was set to dI/dt = 1 A/ms, 45° to midline and 4 mm, respectively. The coil center (purple dot) was positioned directly above the left prefrontal stimulation site (a) VLPFC: MNI = −48, 24, 9; (b) DLPFC: MNI = −45, 30, 31; (c) BeamF3. SgACC: subgenual Anterior Cingulate Cortex (depicted in green); NormE: Norm of the Electric field.

may be more indirect [10], this may also explain why in our stage III TRD sample, response rates were markedly lower (response/remission 35%, see also [5]) after left (dorsal) DLPFC stimulation.

Of course, we are fully aware that a clear comparison with the articles of Cole et al. [2,3] and our current ^{18}FDG-PET study is greatly complicated by methodological differences in stimulation target, rTMS frequency, clinical assessment, and brain imaging measurements, but nonetheless, our interregional metabolic covariance analysis confirmed the predictive value of sgACC functional metabolic left VLPFC connections to indicate a potentially more optimized stimulus target for TRD patients, regardless of depression type. Obviously, larger prospective RCT's will be needed to confirm this assumption. Moreover, if a more individualized sgACC functional connectivity approach proves mandatory [11], other imaging methods instead of (f)MRI, such as EEG [12], could be used in a broader perspective.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.03.009.

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