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A brief demonstration of frontostriatal connectivity in OCD patients with intracranial electrodes

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ABSTRACT

Closed-loop neuromodulation is presumed to be the logical evolution for improving the effectiveness of deep brain stimulation (DBS) treatment protocols (Widge et al., 2018). Identifying symptom-relevant biomarkers that provide meaningful feedback to stimulator devices is an important initial step in this direction. This report demonstrates a technique for assaying neural circuitry hypothesized to contribute to OCD and DBS treatment outcomes. We computed phase-lag connectivity between LFPs and EEGs in thirteen treatment-refractory OCD patients. Simultaneous recordings from scalp EEG and externalized DBS electrodes in the ventral capsule/ventral striatum (VC/VS) were collected at rest during the perioperative treatment stage. Connectivity strength between midfrontal EEG sensors and VC/VS electrodes correlated with baseline OCD symptoms and 12-month post-treatment OCD symptoms. Results are qualified by a relatively small sample size, and limitations regarding the conclusiveness of VS and mPFC as neural generators given some concerns about volume conduction. Nonetheless, findings are consistent with treatment-relevant tractography findings and theories that link frontostriatal hyperconnectivity to the etiopathogenesis of OCD. Findings support the continued investigation of connectivity-based assays for aiding in determination of optimal stimulation location, and are an initial step towards the identification of biomarkers that can guide closed-loop neuromodulation systems.

Deep brain stimulation (DBS) holds promise as a novel treatment for severe and treatment-refractory neuropsychiatric disorders. DBS in the ventral capsule/ventral striatum (VC/VS) is especially helpful for some patients with Obsessive-Compulsive Disorder (OCD). Not all patients receive therapeutic benefit from DBS, and identifying OCD-relevant pathophysiology may improve therapy effectiveness and existing DBS protocols.

OCD is frequently linked to aberrant structure and function within a frontostriatal network that includes the medial prefrontal cortex (mPFC) and VS. OCD patients enrolled in DBS trials demonstrate hyperconnectivity between the mPFC and VS, which seems to be modulated by VC/VS-DBS treatment (Figee et al., 2013). Connectivity within frontostriatal networks—including the mPFC-VS circuit—is facilitated by delta (i.e., 1–4 Hz) oscillations (Wu et al., 2018), which are more pronounced at rest in OCD patients (Kamaradova et al., 2018; Perera et al., 2019; Koprivova et al., 2013). In general, successful treatment with VC/VS-DBS appears to depend on modification of this mPFC-VS delta-band networking. However, the precise mechanisms by which delta oscillations (re)code for symptom change are unclear. Delta amplitude (1–4 Hz) is suppressed by active VC/VS-DBS during

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symptom-provocation in treatment responders (Figee et al., 2013), but is similar across OFF/ON states in treatment responders at rest (Smith et al., 2020; Smolders et al., 2013). On the other hand, individual differences in modulation of resting delta from OFF to ON states predicts fewer post-treatment symptoms and more symptom improvement (Smith et al., 2020). Treatment-relevant neural changes are hypothesized to rely on DBS stimulation of fibers passing through the internal capsule dorsal-posterior to the VS and Nucleus accumbens (NAc). For example, treatment response may depend on the extent to which DBS perturbs fiber paths that support oscillatory coupling between the mPFC and VS.

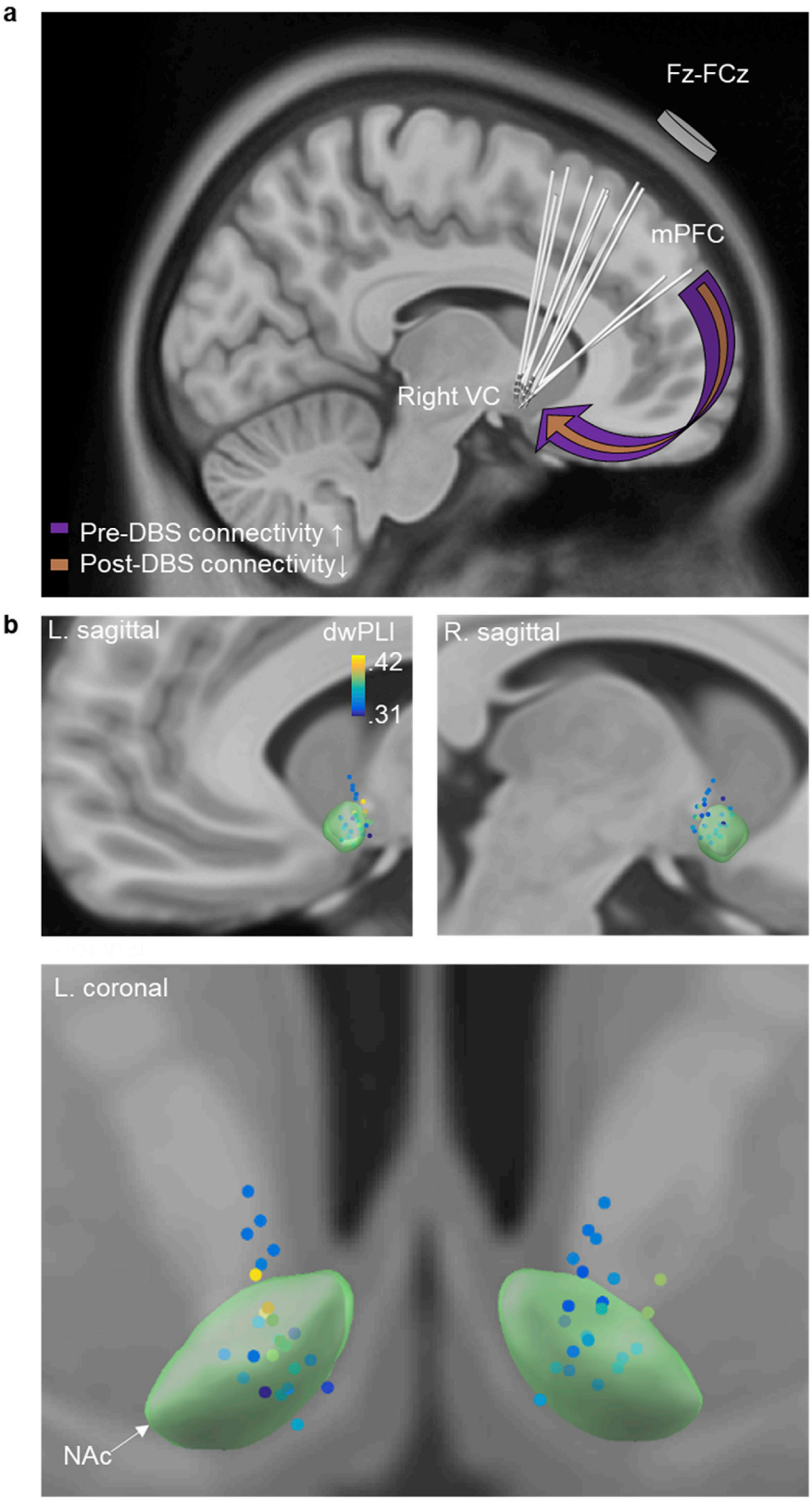

Fig. 1. Connectivity between the ventral capsule (VC) and medial prefrontal cortex (mPFC) is important to OCD symptomatology and may be normalized by VC/VS-DBS. Data in this figure reflect resting-state connectivity before stimulation. **(a)** Location of DBS electrodes for 12 of 13 participants (one participant was missing postoperative imaging), overview of study design, and study hypotheses. DBS is hypothesized to reduce mPFC-VC connectivity. A bipolar-referenced Fz-FCz electrode was used as an indicator of mPFC function. **(b)** Spatial distribution of connectivity strength for each DBS electrode. The shaded green area indicates the Nucleus accumbens (NAc), which was the stereotaxic target for electrode implantation. Dots indicate positions of DBS electrodes. Each dot is one DBS electrode for one participant. Dot color indicates intensity of connectivity strength with warmer colors (i.e., yellow) indicating stronger connectivity.

This may be especially the case for right-lateralized fibers (Figee et al., 2013; Baldermann et al., 2019; Valencia-Alfonso et al., 2012). Insofar as VC/VS-DBS works by disrupting mPFC-VS hyperconnectivity (Suetens et al., 2014; Mavridis, 2019; Gibson et al., 2017), it may be the case that electrodes in the VC showing stronger connectivity with mPFC at baseline are more likely to disrupt mPFC-VS hyperconnectivity and facilitate improvement of symptoms. In this way, measurement of perioperative mPFC-VS connectivity may facilitate postoperative selection of stimulation contacts with a high likelihood of desirable clinical effects. Before the realization of this possibility, it will be important to demonstrate the clinical significance of specific brain regions and oscillatory frequencies. Thus, we evaluated the correspondence between mPFC-VS perioperative connectivity, treatment outcomes, and DBS electrode location to 1) test hypotheses (Fig. 1a) regarding the importance of rightward mPFC-VS connectivity for treatment response to DBS, and 2) demonstrate a novel technique with possible clinical utility in guiding selection of DBS stimulation contacts postoperatively.

This study included thirteen patients (seven females) undergoing surgery for implantation of DBS leads (Model 3387 or 3389 DBS Lead; Medtronic; Minneapolis, MN, USA) bilaterally into the ventral internal capsule with at least one contact within the VS or NAc (Fig. 1b). Patient demographics and adverse events are shown in Supplementary Table 1. Additional details regarding study procedures and clinical outcomes are reported in Huys et al. (2019) The primary outcome variable was change in OCD symptoms (Yale-Brown Obsessive Compulsive Scale, YBOCS) from baseline to twelve month follow up; baseline YBOCS and twelve month YBOCS scores (e.g., not change scores) were secondary outcome variables (Huys et al., 2019). Most patients were responders at twelve month follow up (11/13; ≥35% reduction in YBOCS scores).

Simultaneous (5000 Hz sampling rate) scalp EEGs and intracranial LFPs (externalized DBS electrodes) were recorded 1–2 days after DBS surgery (i.e., perioperative, before stimulation was turned on). Resting-state recordings were approximately 8 min long with alternating eyes open or eyes closed blocks. There were six 1-min eyes-closed segments, and five eyes-open segments lasting 26-s each. A combination of zero-phase FIR filtering (1–40 Hz bandpass), thresholding (±150 μV), and ICA component subtraction was used to correct for nonneurogenic artifacts in line with recent recommendations (Lio et al., 2018). EEGs and LFPs were bipolar referenced (Fz-FCz scalp sensor; six bipolar DBS sensors, left: 0–1, 1–2, 2–3; right: 8–9, 9–10, 10–11 with 0–1 and 8–9 being the most ventral). Debiased Weighted Phase-Lag Index [dwPLI; Vinck et al., 2011] was used for estimating phase-synchronization between VC/VS and mPFC in the delta frequency band (1–4 Hz). This phase-synchronization index was our measure of functional connectivity.

DBS electrodes were localized using Lead-DBS software (http://www.lead-dbs.org) following the procedure described in (Horn and Kuhn, 2015) with some modifications. Briefly, postoperative computer tomography scans were linearly co-registered to preoperative MRI using Advanced Normalization Tools and the Lead-DBS brain shift correction module. Images were then normalized into International Consortium for Brain Mapping 2009b nonlinear asymmetric space using the SyN approach. Results were visually reviewed to confirm accuracy. Each bipolar sensor was mapped to the Euclidean midpoint between the coordinates representing the two electrode contacts from which the signal was recorded.

Connectivity was examined between VC/VS-DBS electrodes and the Fz-FCz scalp sensor. Several contacts were identified as therapeutic for each patient, nonetheless, the therapeutic contact (according to patient's subjective wellbeing) for the right-hemisphere at 12-month follow up was either 9–10 or 10–11 (dorsal and middle contacts) in 8/13 cases (Supplementary Table 2). Right-dorsal therapeutic contacts are consistent with previous work showing that this region is important for VC/VS-DBS treatment response (Baldermann et al., 2019; Li et al., 2020), and thus we focused our analyses on these right-dorsal electrodes. For each participant, the middle or dorsal DBS electrodes (9–10 or 10–11) with the strongest connectivity to Fz-FCz were used for correlation with outcome variables. One participant did not have useable data for either the 9–10 or 10–11 electrode, so the 8–9 electrode was used. Spearman rank order correlations are reported. To balance for type 1 and type 2 statistical errors, an uncorrected $p < .05$ was considered significant, but p-values corrected using the False-Discovery Rate method (FDR (Benjamini and Hochberg, 1995);) are also reported for comparison.

Connectivity coefficients between VC electrodes and FCz-Fz are displayed in Fig. 1b. Dorsal intracranial contacts (2–3, 10–11) demonstrated numerically stronger connectivity with FCz-Fz than ventral contacts (0–1, 8–9), but the difference in connectivity strength between dorsal and ventral contacts was not statistically significant (Wilcoxon signed rank test uncorrected $ps > .7$).

Fig. 2 shows the spatial distribution of connectivity-symptom correlations across six DBS contacts (left: 0–1, 1–2, 2–3; right: 8–9, 9–10, 10–11). The position of DBS contacts varied for each participant, and the same six correlation coefficients (at 0–1, 1–2, 2–3, 8–9, 9–10, 10–11) are depicted at each individual's DBS contact. In general, contacts that were in right-dorsal regions of VC were more strongly related to OCD symptoms.

Right lateralized frontostriatal connectivity was not significantly related to symptom change ($r = 0.239$, $p = .431$, FDR-$p = .431$) using the contact that was most strongly coupled with FCz-Fz. Instead, intracranial contacts that were most strongly coupled with FCz-FZ correlated with total OCD symptoms at baseline ($r = 0.646$, $p = .017$, FDR-$p = .052$; Fig. 2a) and after one year ($r = 0.583$, $p = .036$, FDR-$p = .054$; Fig. 2b), such that stronger connectivity predicted more OCD symptoms. There was a nonsignificant trend for stronger connectivity between FCz-Fz and 10–11 to predict greater reduction in symptoms at twelve month follow up ($r = 0.519$, $p = .102$, FDR-$p = .392$; Fig. 2c).

We hypothesized that perioperative mPFC-VS delta connectivity measured near the site of electrical stimulation would be related to symptom change and fewer posttreatment symptoms, especially for the right hemisphere. Connectivity strength was related to total symptoms at baseline and at follow-up, but the relationship between connectivity strength and symptom change was not statistically significant. Connectivity-symptom correlations were present for both right hemisphere and left hemisphere VC/VS electrodes, with somewhat different spatial distributions. Connectivity-symptom correlations were largest at right-dorsal VC regions (Fig. 2) consistent with previous tractrographic findings (Baldermann et al., 2019; Li et al., 2020).

Recent tractographic findings examining mechanisms of VC/VS-DBS treatment have pointed towards pathways near dorsal DBS contacts (Baldermann et al., 2019; Li et al., 2020; Liebrand et al., 2019). The present results are generally congruent with this previous work, and non-significant findings (e.g., Fig. 2c) could be the result of low statistical power, change-score reliability, and limitations of our LFP and EEG recording apparatus. For example, the recording volume of a bipolar-referenced electrode spaced apart 0.5 or 1.5 mm may have difficulty assessing pathways important for treatment outcome that lay dorsal to recording contacts. LFPs may also be diluted by activity in nearby grey matter (e.g., NAc; Fig. 1b). In this way, LFP recordings may be a crude representation of VC white matter function. Similarly, volume conduction in EEG recordings from frontal areas other than the mPFC (e.g., supplementary motor area) probably contributed to connectivity estimates and limits conclusions regarding the roles of the VC and mPFC specifically. Moreover, the VC and mPFC are two of many brain regions believed to play a role in the pathophysiology of OCD, and it is a relatively open question whether regions outside a VC-mPFC circuit are more/less informative with regard to prediction of change in self-reported symptoms (Baldermann et al., 2019; Li et al., 2020; Milad and Rauch, 2012; Fridgeirsson et al., 2020). The small sample used in this report precludes generalization of findings to the population, and replication of the present results will be important before drawing firm conclusions about translational potential or clinical utility. Notwithstanding these limitations, the results are consistent with the hypothesis that frontostriatal networking in the delta frequency is relevant to OCD

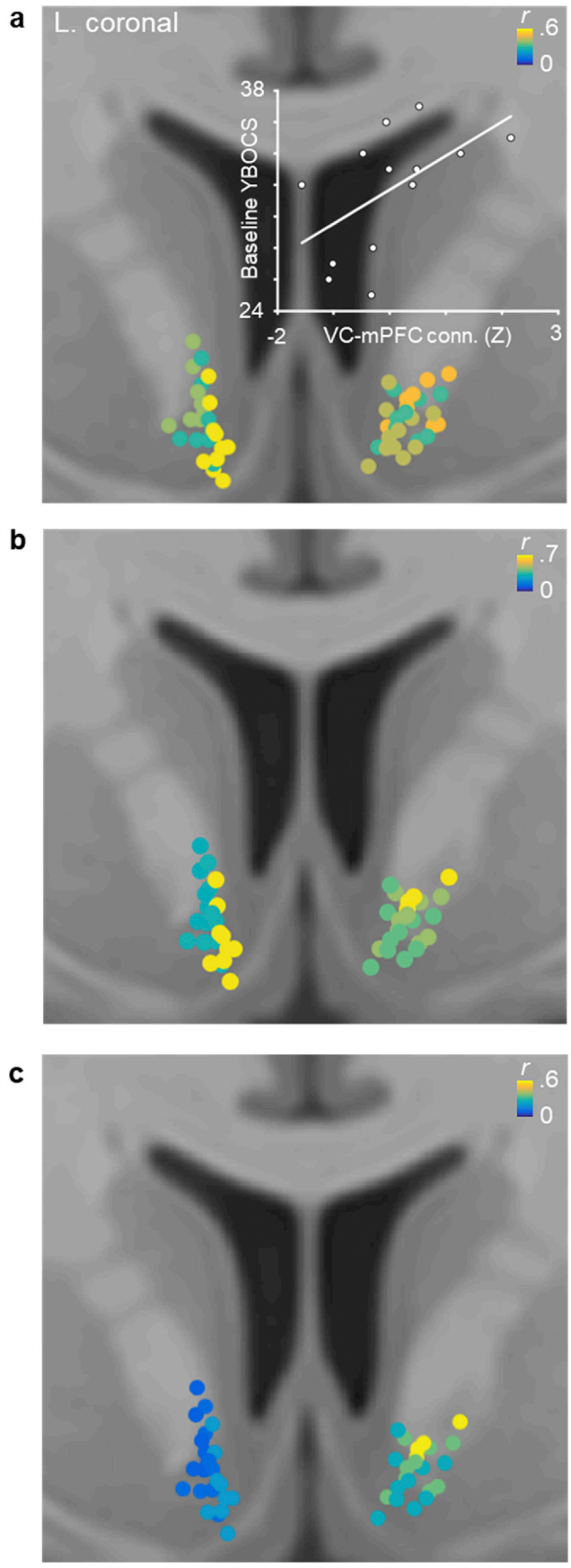

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Fig. 2. Between-subject correlations between VC-mPFC connectivity strength (dwPLI) and OCD symptoms (YBOCS scores) displayed on individual's DBS contacts. The position of DBS contacts varied for each participant, and the same six correlation coefficients (left: 0–1, 1–2, 2–3; right: 8–9, 9–10, 10–11) are depicted at each individual's DBS contact. **(a)** Depiction of correlations between perioperative connectivity strength and baseline OCD symptoms. Connectivity strength predicts more baseline OCD symptoms across VC regions. **(b)** Depiction of correlations between perioperative connectivity strength and OCD symptoms at twelve month follow up. Connectivity strength predicts more OCD symptoms at twelve months, especially in right-dorsal and left-ventral VC regions. **(c)** Depiction of correlations between perioperative connectivity strength and change in OCD symptoms from baseline to twelve month follow up. Connectivity strength was not significantly related to change in OCD symptoms, but there was a nonsignificant trend for contact 10–11 on the right side to predict symptom improvement ($r = 0.519$, $p = .102$, FDR-$p = .392$).

etiopathogenesis (Figee et al., 2011, 2013; Milad and Rauch, 2012) and support the notion that online monitoring of disease-relevant systems may be helpful for optimizing the efficacy of DBS treatments (Widge et al., 2018; Widge and Miller, 2019).

With regard to the study limitations noted above, future work will strive to collect recordings from mPFC and VS with high spatial resolution to clarify the importance of specific frontostriatal regions. In addition, simultaneous recordings collected from regions outside the mPFC and VS is another important goal, as multisite-multimodal recordings may be particularly informative for characterizing systemic changes resulting from DBS. For example, with some modification to surgical procedures, recordings during surgery from multiple loci across central (e.g., mPFC, VS, dlPFC, parietal cortex) and autonomic (e.g., vagal tone, skin conductance, pupillary response, cortisol) nervous systems could be used to fine tune placement of DBS electrodes (Bijanki et al., 2019; Ooms et al., 2014; Riva-Posse et al., 2019). Moreover, readouts from multisite implants (e.g., permanent intracranial electrodes in both the mPFC and VS) may be useful for adaptively optimizing DBS parameters (e.g., timing, frequency, stimulation location) in real-time (Zelmann et al., 2020). To this end, there are some promising initial findings suggesting that specific cognitive (Basu et al., 2020) and emotional (Bijanki et al., 2019; Riva-Posse et al., 2019) states can be induced with a combination of multisite recordings and adaptive/closed-loop DBS. With continued investigation and refinement of techniques, there is hope that these approaches will improve outcomes for patients with severe and treatment-refractory neuropsychiatric disorders.

CRediT authorship contribution statement

Ezra E. Smith: Conceptualization, Methodology, Formal analysis, Writing - original draft, Visualization, Software. **Thomas Schüller:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization, Investigation, Data curation, Software. **Daniel Huys:** Conceptualization, Supervision, Project administration, Funding acquisition, Resources, Writing - review & editing. **Juan Carlos Baldermann:** Investigation, Resources, Writing - review & editing. **Pablo Andrade:** Investigation, Resources, Writing - review & editing. **John JB. Allen:** Supervision, Resources, Writing - review & editing. **Veerle Visser-Vandewalle:** Investigation, Resources, Writing - review & editing. **Markus Ullsperger:** Project administration, Resources, Writing - review & editing. **Theo O.J. Gruendler:** Project administration, Supervision, Resources, Writing - review & editing. **Jens Kuhn:** Project administration, Supervision, Resources, Funding acquisition, Conceptualization, Writing - review & editing.

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et al., 2019, and Smith et al., 2020, but the present study was the first to report on perioperative electrophysiology for these patients. This project was funded by the German Research Foundation (KFO-219 ; KU 2665/1–2).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.117138.

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