Brain Structures and Networks Underlying Treatment Response to Deep Brain Stimulation Targeting the Inferior Thalamic Peduncle in Obsessive-Compulsive Disorder

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Keywords
Obsessive-compulsive disorder · Deep brain stimulation · Inferior thalamic peduncle · Brain network · Treatment response

Abstract

\textbf{Background:} Obsessive-compulsive disorder (OCD) is a debilitating disease with a lifetime prevalence of 2–3%. Neuro-modulatory treatments have been successfully used in severe cases. Deep brain stimulation (DBS) targeting the inferior thalamic peduncle (ITP) has been shown to successfully alleviate symptoms in OCD patients; however, the brain circuits implicated remain unclear. Here, we investigate the efficacious neural substrates following ITP-DBS for OCD. \textbf{Methods:} High-quality normative structural and functional connectomics and voxel-wise probabilistic mapping techniques were applied to assess the neural substrates of OCD symptom alleviation in a cohort of 5 ITP-DBS patients. \textbf{Results:} The region of most efficacious stimulation was located in the regions of the ITP and bed nucleus of the stria terminalis. Both functional and structural connectomics analyses demonstrated that successful symptom alleviation involved a brain network encompassing the bilateral amygdala and prefrontal regions. \textbf{Limitations:} The main limitation is the small size of the ITP-DBS cohort. While the findings are highly consistent and significant, these should be validated in larger studies. \textbf{Conclusions:} These results identify a tripartite brain network – composed of the bilateral amygdala and prefrontal regions 24 and 46 – whose engagement is associated with greater symptom improvement. They also provide information for optimizing targeting and identifying network components critically involved in ITP-DBS treatment response. Amygdala engagement in particular seems to be a key component for clinical benefits and could constitute a biomarker for treatment optimization.

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Introduction

Obsessive-compulsive disorder (OCD) is a debilitating disorder characterized by persistent intrusive thoughts and compulsive, repetitive behaviours [1]. OCD has a lifetime prevalence of 2–3% and is associated with considerable morbidity and a high mortality risk [2, 3]. A fraction of patients, estimated to be as high at 25%, are considered treatment-refractory [4]. Neurosurgical and neuromodulatory treatments have been applied successfully in refractory patients [5–15]. Deep brain stimulation (DBS) employs precisely placed electrodes to deliver current to targeted brain structures to modulate brain functions [16]. DBS targeting the inferior thalamic peduncle (ITP) has been successfully used to alleviate OCD symptoms, with studies reporting an average symptom improvement of 50% at 1-year follow-up [6, 17]. OCD pathophysiology is thought to be caused by aberrant processing within fronto-striatal and fronto-limbic networks. However, controversy remains with regards to the roles of specific brain regions in terms of pathophysiology and symptom relief following treatment [5, 18–22].

The goal of the current study was to use connectomic mapping (using high-quality normative data) and voxel-wise probabilistic mapping techniques to elucidate the brain regions and networks involved in symptom alleviation following ITP-DBS in a previously reported five-patient cohort [6].

Methods

Subjects and Statistical Analysis

Five patients (3 females; age: 25–48 years) who had undergone ITP-DBS therapy were included in this study. All patients were considered responders, with clinical improvement at 12 months ranging from 39.4% to 72.7% (Yale-Brown Obsessive-Compulsive Scale [Y-BOCS]). Study details have been reported previously by Lee et al. [6] and Germann et al. [23]. All statistical analyses were performed using R (R 3.4.4, https://www.r-project.org) and RMINC (https://github.com/Mouse-Imaging-Centre/RMINC).

DBS Lead Localization and Volume of Tissue Activated Modelling

High-resolution pre- and post-operative structural MRI scans (General Electric SIGNA Excite 1.5T; 3-D spoiled gradient echo, axial T1-weighted, voxel size 1 × 1 × 1 mm, TR = 12.4 ms, TE = 5.3 ms, flip angle 20°) were used in conjunction with Lead-DBS software (https://www.lead-dbs.org/) to localize the DBS electrodes (Fig. 1a) and model the volume of tissue activated (VTA) as previously described [24–26]. Briefly, all images were non-linearly normalized to standard space [27], after which DBS electrodes were manually localized on the post-operative images and normalized to standard space using the above transform and correcting for post-operative brain shift when necessary [28]. Bilateral VTAs were modelled using the 12-months stimulation settings [29].

Probabilistic Voxel-Wise Efficacy Maps

Probabilistic stimulation mapping, which allows insights into the spatial patterns of efficacious stimulation [30–32], was performed using previously described methods [33]. Each pair of bilateral patient VTAs was weighted by the corresponding improvement at the 12 months post-operative follow-up, enabling the mean improvement across all patients to be computed at each voxel. The resulting average map was thresholded using a Wilcoxon signed-rank test ($p < 0.05$, at each voxel).

Normative Functional Mapping and Normative dMRI-Based Tractography

Using normative functional (resting state functional MRI-derived) and structural (diffusion MRI-derived) data, we performed connectomic analyses as previously described [26, 34–37]. Using the bilateral VTA pair as seeds, we calculated whole-brain correlation maps (r-maps) using a 1000-subject resting state functional MRI Brain Genomics Superstruct Project dataset (http://neuroinformatics.harvard.edu/gsp) (MATLAB script, The MathWorks, Inc., Version R2017b; Natick, MA, USA) [37, 38]. These maps quantify the functional connectivity between each seed and every other voxel in the brain. To identify key regions responsible for OCD symptom relief, whole-brain voxel-wise linear regression was performed to test the relationship between magnitude of functional correlation and symptom improvement.

As done previously [23, 39], we obtained structural connectivity maps by identifying all streamlines intersecting the seed out of a ~12-million fibre whole-brain tractography template assembled from a 985-subject diffusion-weighted MRI dataset (http://www. humanconnectomeproject.org) (in-house MATLAB script, The MathWorks, Inc., Version R2017b) [40]. To assess if impingement on any given streamline predicted improvement, a t test of Y-BOCS improvement comparing individuals whose lesion included this streamline and individuals who did not was performed. Streamlines with values of $p < 0.05$ were retained as “predictive” streamlines [39]. In addition, streamlines common to all VTAs were identified.

Amygdala Functional Connectivity Overlap Measure and Structural Connectivity

Having shown VTA-amygdala connectivity to be significantly related to improvement through whole-brain linear regression, we then computed additional functional connectivity maps (as described above) using the bilateral amygdala as a seed [41, 42]. This voxel-wise whole-brain correlation map was thresholded ($p_{Bonferroni} = 0.05$, whole brain) and binarized to identify all voxels that were significantly functionally connected to the bilateral amygdala. The volume overlap (in mm$^3$) between that binarized connectivity map and each bilateral VTA was then calculated. Then, this overlap volume was correlated with individual symptom improvement. Using dsi-studio (http://dsi-studio.labsolver.org/) and the HCP 1065 diffusion MRI template [43], the structural connectedness of each bilateral VTA (seed) to the left and right amygdala (target ROIs) was assessed by ascertaining the proportion of streamlines (out of 50,000) that project from the seed to the target ROIs.

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Results

Probabilistic Voxel-Wise Efficacy Maps

The corrected average map showed that voxels in proximity to the bed nucleus of the stria terminalis (BNST) and ITP were associated with highest symptom improvement (Fig. 1b).

Normative Functional Mapping

Functional connectivity with voxels in the bilateral amygdala region was significantly associated with individual symptom improvement at 12 months (\(p_{\text{uncorrected}} < 0.01\); following threshold-free cluster enhancement [44], these voxels passed \(p_{\text{Bonferroni}} < 0.001\) [whole brain]) (Fig. 2a).

Normative dMRI-Based Tractography

Both common streamlines and streamlines associated with better individual outcome were found in the central region of the anterior limb of the internal capsule (ALIC; Fig. 2b). These were in an almost identical location as streamlines previously identified to be associated with clinical benefits following MRI-guided focused ultrasound targeting the ALIC [23] and DBS of the subthalamic nucleus or ALIC [39] for the treatment of OCD (Fig. 2c). Previous studies have demonstrated that the streamlines project to the dorsal anterior cingulate and prefrontal area 46 [19, 23, 45], and individual functional engagement (as estimated by normative functional connectivity) of these two regions has been shown to predict individual Y-BOCS improvement (\(R = 0.83, R^2 = 0.69\), see Germann et al. [23]).

Amygdala Functional Connectivity Overlap Measure and Structural Connectivity

Volume of overlap with voxels significantly functionally connected to the amygdala was found to be highly correlated to individual outcome (\(R = 0.9; R^2 = 0.8; p = 0.039\)) (Fig. 3a). The individual outcome was found to be strongly related to the proportion of individual streamlines reaching the left (\(R = 0.7\)) and right (\(R = 0.6\)) amygdala. A linear model predicting improvement based on both of these streamline counts was able to predict the individual long-term outcome with high accuracy (\(R = 0.8; R^2 = 0.7; p = 0.07\)) (Fig. 3b).

Discussion

Studying a previously described patient cohort [6], we used voxel-wise probabilistic stimulation mapping and normative connectomics to investigate the local- and network-level neural substrates of OCD symptom improvement following ITP-DBS. The findings point to the bilat-
eral amygdala as playing a key role in treatment success. Previous studies have demonstrated that connectivity to the amygdala is important for the effectiveness of DBS for the treatment of OCD when targeting the ventral capsule/ventral striatum [46, 47], BNST [48], and anterior subthalamic nucleus [49].

The most efficacious DBS target region was found to be in the anterior hypothalamus in the vicinity of the ITP and BNST. The BNST is closely related to amygdalar function and has sometimes been referred to as the “extended amygdala” [50]. Indeed, DBS of the BNST has been shown to be superior to nucleus accumbens DBS for the alleviation of OCD symptoms [8]. A prominent role of the BNST and its connections in the pathogenesis of OCD has been suggested previously [51]. Detailed anatomical studies show that ITP – the target of the DBS group included in the current study – and its surrounding areas are highly connected to the amygdala [52, 53]. Increased activity and changes in functional connectivity of the amygdala are observed in OCD patients when viewing symptom-provoking stimuli [54, 55]. Also, increased molecular signalling from the amygdala has been shown to cause OCD-like behaviour in an animal model and this ceases once the hyperactivity is normalized [56]. DBS for the treatment of OCD appears to be effective, in part, by regulating amygdala hyperactivity [46, 47, 57].

ITP-DBS has been shown to be successful in treating OCD symptoms in the cohort described here and other

Fig. 2. Results of functional and structural normative connectivity analysis. a Voxel-wise linear model shows that individual functional connectivity with voxels in the bilateral amygdala is closely related with individual symptom improvement. No voxels outside the amygdala pass $p < 0.01$, and all amygdala voxels pass $p_{	ext{Bonferroni}} < 0.001$ following threshold-free cluster enhancement [44] (illustrated in MNI152 space using slices from a high-resolution template [65]). b Division of the ALIC according to the cortical areas the fibres are connected as determined by combined tracer and DTI investigation according to Safadi and colleagues [45]. c Streamlines overlaid on T1-weighted MRI slices in MNI152 space using slices from a high-resolution template [65]. Streamlines intercepted by the VTA of every ITP-DBS patient are shown in red, whereas streamlines significantly ($p < 0.05$) related to a better outcome are shown in green. Streamlines predictive of the treatment outcome of DBS targeting both the STN and ALIC identified by Li and colleagues are shown in blue [39]. Within the ALIC DBS targeting STN, ALIC or ITP seems to engage overlapping streamlines at the same dorsoventral location within the ALIC. This set of streamlines might constitute part of a common network associated with OCD improvement following DBS independent of the brain region targeted with the technique.
studies [6, 7]. We found streamlines in the central ALIC region to be predictive of improved outcome, replicating previous reports showing that tracts in this region of the ALIC, projecting to the dorsal anterior cingulate (area 24) and prefrontal area 46 [19, 23, 45], are important for treatment success [23, 39]. Both of these prefrontal areas have direct connections with the amygdala [58, 59]. The results of the present study suggest that a dysfunctional brain network encompassing the amygdala and prefrontal areas 24 and 46 is implicated in OCD symptom relief following ITP-DBS. Hyperactivity in these prefrontal areas has been described previously in OCD patients compared to control subjects when viewing OCD-provoking pictures [21]. Hyperactivity in the amygdala was also identified as the key contributor to OCD symptoms in a follow-up study of the same group [54]. Other studies report amygdala hyperactivity in OCD patients compared to controls [60] as well as increased amygdalar activity during symptom provocation [21, 54]. Taken together, these findings suggest that the amygdala plays a central role in the tripartite brain network underpinning OCD symptom relief following treatment.

**Limitations**

This study has a number of limitations. The main limitation is the small size of the ITP-DBS cohort. This case series only involved 5 patients and the findings should be validated in larger studies. Furthermore, while this retrospective analysis identifies modulation of amygdala activity as a key structure for clinical benefits, this should be confirmed in prospective trials.
Conclusion

This study is the first to identify the key role of amygdala for OCD symptom improvement after ITP-DBS. These findings highlight potential avenues for treatment optimization, including refined targeting and imaging-based biomarkers of treatment response. Such biomarkers would be particularly helpful for the selection of optimal stimulation settings in DBS patients (also known as “programming”), which is particularly challenging for psychiatric indications due to a lack of immediate clinical feedback [61]. Functional MRI-based biomarkers have shown potential for improved programming in Parkinson’s disease and could similarly be applied to OCD based on the activity of the amygdala [62].

Statement of Ethics

All subjects provided written informed consent and the study complies with all guidelines in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the institutional review boards (UHN, REB # 15-9777).

Conflict of Interest Statement

A.M.L. is a co-founder of Functional Neuromodulation and a consultant for Medtronic, Boston Scientific, Abbott, and Insighttech. All the other authors report no financial interests or potential conflicts of interest.

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Author Contributions

Conceptualization: J.G., A.B., G.J.B.E., F.V.G, A.L., W.K., and A.M.L.; data acquisitions: J.G., F.V.G., P.G., and V.B.; methodology and formal analysis: J.G., G.J.B.E., and A.B.; illustration: J.G. and F.V.G.; writing of original draft preparation, J.G.; review and editing: all the authors; all the authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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