A Randomised, Double-Blind, Sham-Controlled Trial of Deep Brain Stimulation of the Bed Nucleus of the Stria Terminalis for Treatment-Resistant Obsessive-Compulsive Disorder

Philip E. Mosley FRANZCP PhD 1,2,3,4, François Windels PhD 3, John Morris PhD 3, Terry Coyne FRACS 3,5, Rodney Marsh FRANZCP 2,4, Andrea Giorni PhD 3, Adith Mohan MRCPsych FRANZCP 6,7, Perminder Sachdev FRANZCP PhD 6,7, Emily O’Leary PhD 8, Mark Boschen PhD 9, Pankaj Sah PhD 3,10 †, Peter A. Silburn FRACP PhD 2,3 †

1 Systems Neuroscience Group, QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia
2 Neurosciences Queensland, St Andrew’s War Memorial Hospital, Spring Hill, Queensland, Australia
3 Queensland Brain Institute, University of Queensland, St Lucia, Queensland, Australia
4 Faculty of Medicine, University of Queensland, Herston, Queensland, Australia
5 Brizbrain and Spine, the Wesley Hospital, Auchenflower, Queensland, Australia
6 Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney, Australia
7 Neuropsychiatric Institute, The Prince of Wales Hospital, Randwick, New South Wales, Australia.
8 The OCD Clinic, Bulimba, Queensland, Australia
9 School of Applied Psychology, Griffith University, Queensland, Australia
10 Joint Center for Neuroscience and Neural Engineering, and Department of Biology, Southern University of Science and Technology, Shenzhen, Guangdong Province, P. R. China

† = co-senior author

Correspondence to:
Dr Philip E Mosley, Systems Neuroscience Group, QIMR Berghofer Medical Research Institute, Herston, Queensland, 4029, Australia

E-mail: philip.mosley@qimrberghofer.edu.au
Telephone: +61 (7) 3839 3688

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1 ABSTRACT

Deep brain stimulation (DBS) is a promising treatment for severe, treatment-resistant obsessive-compulsive disorder (OCD). Here, nine participants (four females, mean age 47.9 ±10.7 years) were implanted with DBS electrodes bilaterally in the bed nucleus of the stria terminalis (BNST). Following a one-month postoperative recovery phase, participants entered a three-month randomised, double-blind, sham-controlled phase before a twelve-month period of open-label stimulation incorporating a course of cognitive behavioural therapy (CBT). The primary outcome measure was OCD symptoms as rated with the Yale-Brown Obsessive-Compulsive Scale (YBOCS). In the blinded phase, there was a significant benefit of active stimulation over sham (\(p = 0.025\), mean difference 4.9 points). After the open phase, the mean reduction in YBOCS was 16.6 ±1.9 points (\(\chi^2 (11) = 39.8, p = 3.8 \times 10^{-5}\)), with seven participants classified as responders. CBT resulted in an additive YBOCS reduction of 4.8 ±3.9 points (\(p = 0.011\)). There were two serious adverse events related to the DBS device, the most severe of which was an infection during the open phase necessitating device explantation. There were no psychiatric adverse events related to stimulation. An analysis of the structural connectivity of each participant’s individualised stimulation field isolated right-hemispheric fibres associated with YBOCS reduction. These included subcortical tracts incorporating the amygdala, hippocampus and stria terminalis, in addition to cortical regions in the ventrolateral and ventromedial prefrontal cortex, parahippocampal, parietal and extrastriate visual cortex. In conclusion, this study provides further evidence supporting the efficacy and tolerability of DBS for individuals with otherwise treatment-refractory OCD and identifies a connectivity fingerprint associated with clinical benefit.

Keywords: Deep brain stimulation; obsessive-compulsive disorder; amygdala; connectomic; prefrontal cortex
2 INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric condition with an estimated lifetime prevalence of between 1-2% (Kessler et al., 2005). It is characterised by the intrusion of ego-dystonic, anxiety-provoking thoughts (obsessions). These are accompanied by mental acts or behaviours (compulsions), which must be carried out to neutralise the obsessions, or to mitigate anxiety associated with them (American Psychiatric Association., 2013). Remission of symptoms with pharmacological treatment is rare (Erzegovesi et al., 2001) and persistent impairment is relatively common even with combination therapy (Bloch et al., 2006). Psychological treatment is often intolerable for those with a severe illness: deliberate exposure to obsessive thoughts during cognitive behavioural therapy (CBT) is aversive and distressing (Issakidis and Andrews, 2002). These factors mean that OCD is a chronic disorder with a detrimental effect on functioning across the lifespan, making it a leading neuropsychiatric cause of global disability (Mathers et al., 2008).

Deep brain stimulation (DBS) is a reversible and adjustable form of targeted neuromodulation that has been used successfully for the treatment of movement disorders such as Parkinson’s disease for over 25 years (Benabid et al., 1994; Schuepbach et al., 2013). DBS was first employed for the treatment of intractable OCD in the late 1990s (Nuttin et al., 1999), with initial surgical targeting in the anterior limb of the internal capsule (ALIC) informed by prior work using ablative neurosurgery (Nuttin et al., 2003). Further work reproduced these encouraging preliminary outcomes (Abelson et al., 2005; Farrand et al., 2018; Goodman et al., 2010; Greenberg et al., 2006), finding improved response with posterior migration of the target to the region of the caudal nucleus accumbens (NAcc) (Greenberg et al., 2010). The anteromedial segment of the subthalamic nucleus (STN) has also been a promising target for neuromodulation (Mallet et al., 2008). More recently, two randomised, placebo-controlled, crossover trials of DBS at the NAcc/ALIC interface (Denys et al., 2010) and the BNST/ALIC interface (Luyten et al., 2016) demonstrated a statistically-significant benefit of active stimulation over sham.

The clinical benefits (and side effects) of DBS for movement disorders arise not only from the effect of focal stimulation at the target nucleus, but also from the modulation of distributed brain networks structurally and functionally connected to the stimulation field.
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(Accolla et al., 2016; Akram et al., 2017; Chen et al., 2018; Horn et al., 2017; Mosley et al., 2020a; Vanegas-Arroyave et al., 2016). In a similar manner, brain networks associated with response to DBS for OCD can be delineated. In prior work, reduction in OCD symptoms 12-months after NAcc/ALIC DBS was associated with connectivity of the stimulation site with the right ventrolateral prefrontal cortex, with a fibre tract predictive of symptom reduction identified in the ventral ALIC bordering the BNST (Baldermann et al., 2019). A randomised trial directly comparing ALIC and anteromedial STN stimulation found both to be clinically effective targets but with distinct structural connectivity profiles and dissociable effects on mood and cognitive flexibility (Tyagi et al., 2019). However, a pooled analysis of four cohorts employing either STN or ALIC stimulation identified a universal tract associated with clinical response that could predict outcome in an out-of-sample cross-validation (Li et al., 2019). This tract traversed both the anteromedial STN and ventral ALIC, projecting to ventrolateral prefrontal cortex. Overall, these findings suggest that different surgical targets may act to reduce OCD symptoms through modulation of a shared network, whilst change amongst more fine-grained behavioural endophenotypes may result from modulation of networks that are not shared between targets (Dougherty, 2019).

In this study, using a randomised, double-blind, sham-controlled, staggered-onset design, we investigate the effects of DBS at the BNST/NAcc interface in a sample of Australian participants with severe, treatment-resistant OCD. We delineate the structural connectivity profile of effective stimulation and compare this with the aforementioned prior work. We also add CBT incorporating exposure and response prevention (ERP) to the open phase of the trial, in order to investigate whether this is now tolerable for our participants and leads to an additive clinical response, as has been identified in a previous cohort (Mantione et al., 2014). We report outcomes during the blinded phase and after one year of open stimulation following completion of CBT.
3 MATERIALS AND METHODS

3.1 Participants

All procedures were carried out in accordance with the experimental protocol approved by the Human Research Ethics Committees of the University of Queensland and UnitingCare Health. Participants aged 18-70 with severe, treatment-resistant OCD of at least five years duration were referred by their treating psychiatrists and evaluated independently by two psychiatrists in the research team (PEM and RM). The diagnosis of OCD was confirmed according to criteria defined by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) (American Psychiatric Association, 2013). Severity was denoted by a mean score of at least 24 on the Yale-Brown Obsessive-Compulsive Scale (YBOCS) (Goodman et al., 1989), measured twice at least two weeks apart by separate investigators. Treatment refractoriness was defined by insufficient response to at least: i) two trials of selective serotonin reuptake inhibitors at maximum tolerated dose for at least 12 weeks, ii) one trial of clomipramine at maximum tolerated dosage for at least 12 weeks, plus iii) one augmentation trial with an antipsychotic for at least eight weeks in combination with one of the aforementioned drugs, plus iv) one complete trial of ERP-based CBT confirmed by a psychotherapist. Exclusion criteria included pregnancy, a past history of a chronic psychotic or bipolar disorder, severe personality disorder, suicidality in the previous 12 months, substance use disorder (except tobacco), major neurological comorbidity or severe head injury, prior ablative neurosurgery and current implanted cardiac pacemaker, defibrillator or other neurostimulator. Suitable and consenting candidates were approved by an independent Mental Health Review Tribunal prior to neurosurgery. Prior to implantation of the first participant, the trial was registered on the Australian and New Zealand Clinical Trials Registry (Universal Trial Number: U1111-1146-0992).

3.2 Device Implantation

Bilateral implantation of Medtronic (Minneapolis, USA) 3389 quadripolar electrodes took place in a single-stage procedure using a Leksell stereotactic apparatus based on preoperative structural magnetic resonance neuroimaging (Supplementary Materials). The most ventral contact was sited posterior and inferior to the NAcc in the region of the lateral hypothalamus, with more dorsal contacts within the BNST approaching the posterior border of the NAcc.
Postoperative lead placement was confirmed with CT imaging. Electrodes were connected to an Activa PC+S implantable pulse generator (IPG) in either the pectoral or abdominal fascia. Analysis of long-term, ambulatory electrophysiological data will be reported in forthcoming work.

3.3 Timeline, Assessment and Intervention

Following device implantation, participants entered a one-month recovery phase during which all stimulators were off. Thereafter, participants began a three-month period during which their stimulators were either turned on or remained switched off whilst both participants and assessors were blinded to status. After this, participants continued in an open-label (unblinded) trial where all stimulators were on. Assessments took place at baseline one week before surgery, fortnightly in the recovery phase, monthly in the blinded phase and monthly for the first three months of the open phase, with the time between assessments subsequently extending to two and then three months. The primary outcome measure was OCD severity as assessed by the YBOCS score, derived from a ten-item semi-structured interview assessing obsessions and compulsions, with a maximum score of 40. Depressive symptoms were assessed as a secondary outcome with the Montgomery Åsberg Depression Rating Scale (MADRS) score, derived from a ten-item semi-structured interview with a maximum score of 60 (Montgomery and Asberg, 1979; Williams and Kobak, 2008). Participants were referred for a ten-session course of ERP-based CBT with a clinical psychologist (EOL or MB) during the open phase once DBS parameters had been optimised and YBOCS reduction had plateued.

Stimulation was commenced in an identical manner for participants regardless of whether they were turned on in either the blinded or open-label phase. Contact 1 (left hemisphere) and contact 9 (right hemisphere) were selected with an initial stimulation amplitude of 1 Volt, a pulse-width of 90 microseconds and a frequency of 130 Hertz. Stimulation was increased at weekly to fortnightly intervals in increments of 0.5-1 Volt to a target of 4.5 Volts. Stimulation settings were symmetric between hemispheres. If there was a relative lack of response as assessed with the YBOCS, additional stimulation changes were trialled: including further increases in amplitude in 0.1 Volt increments, a trial of a pulse-width of 120 microseconds or the activation of a second contact on each electrode. Psychotropic
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medications were unchanged throughout the trial unless requested for clinical reasons by the participant’s usual psychiatrist.

3.4 Randomisation and Blinding

Participants were randomly allocated in a 1:1 ratio to ‘on’ or ‘off’ groups in the blinded phase by an external statistician, using an online tool (https://www.sealedenvelope.com). Only the lead neurologist (PAS) and programming psychiatrist (PEM) were informed of the allocation. The psychiatrist assessing primary and secondary outcomes (RM) remained blinded to participant status. To reduce the likelihood of participants becoming unblinded by sensations associated with active stimulation, no contact testing was performed and the slow titration protocol was followed in all cases.

3.5 Statistical Analysis

Data analysis was performed in the R software environment (R Core Team, 2014). In the blinded phase of the trial, the mean change in YBOCS and MADRS score was compared between groups with a two-sample $t$-test. After one year of open stimulation and following a course of CBT, the reduction in YBOCS and MADRS score was assessed with the package lmerTest (Kuznetsova et al., 2017) using a random-intercept, random-slope, linear mixed-effects model incorporating demographic variables and baseline severity:

\[
YBOCS_{ij} \sim \text{TimeSinceDBS}_{ij} + \text{Age}_i + \text{Gender}_i + \text{YBOCS Baseline}_i + (1|I) + (1|\text{TimeSinceDBS}_i)
\]

with $i$ denoting participant and $j$ denoting timepoint and the term in bold (the accrued effect of DBS over time on obsessive and depressive symptoms) being the coefficient of interest. Hypothesis testing on a null model (omitting TimeSinceDBS) was performed with the anova function in the lavaan package.

Consistent with prior work, participants were defined as responders for OCD and depression if they attained a reduction of 35 % in YBOCS score and 50 % in MADRS score respectively.
3.6 Electrode Localisation & Volume of Tissue Activation

DBS electrodes were localized using the Lead-DBS toolbox version 2.2 (https://github.com/netstim/leaddbs/tree/develop) (Horn and Kuhn, 2015; Horn et al., 2019). Preoperative structural acquisitions were co-registered with postoperative CT imaging and then normalized into common ICBM 2009b nonlinear asymmetric space using the SyN approach implemented in advanced normalization tools (ANTs) (Avants et al., 2008). Electrode trajectories were reconstructed after correcting for brainshift in postoperative acquisitions by applying a refined affine transform in a subcortical area of interest calculated pre- and postoperatively. For each electrode, a volume of activated tissue (VAT) was estimated using a volume conductor model of the DBS electrode and surrounding tissue, based on each participant’s individualised stimulation settings and a finite element method to derive the gradient of the potential distribution (Horn et al., 2019). An electric field (E-field) distribution was also modelled (Vorwerk et al., 2018).

3.7 Structural Connectivity Estimation and YBOCS Reduction

Three methods were used to assess the relationship between the structural connectivity of the stimulation field and the primary outcome measure. Firstly, using the Lead-DBS toolbox, each participant’s VAT in each hemisphere was integrated with a normative whole-brain structural connectome incorporating six million fibres derived from 985 participants in the Human Connectome Project who had undertaken multi-shell diffusion-weighted imaging (Van Essen et al., 2013). Fibres traversing each participant’s VAT were selected from the group connectome based on the E-field gradient strength (i.e. fibres in peripheral VAT regions with a low E-field were down-weighted) and projected to the volumetric surface of the ICBM 2009b nonlinear asymmetric brain in 1 mm isotropic resolution. A connectivity profile for each participant was expressed as the weighted number of fibre tracts between the stimulation site and each brain voxel. Subsequently, each voxel on the corresponding connectivity profile was correlated with clinical improvement on the YBOCS score using a Spearman rank correlation coefficient, forming an ‘R-map’. Combined across all participants, these maps identify regions to which strong connectivity is associated with good clinical outcome, modelling ‘optimal’ connectivity from the stimulation field to the rest of the brain (Horn et al., 2017). To verify these findings, the data were cross-validated in a leave-one-out design. Each participant was sequentially excluded and the optimal connectivity profile was computed on the remaining participants. Subsequently, YBOCS
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reduction was predicted for the excluded participant based on comparison between individual and group connectivity estimates (using a Fisher z-transformed spatial correlation coefficient) and the empirical outcome was correlated with the predicted outcome derived from the remaining sample.

Secondly, individual fibres associated with YBOCS reduction were identified. Each whole-brain fibre was tested across the cohort between participants with a stimulation volume that encompassed the fibre (connected) and those where the fibre did not traverse the volume (unconnected). If there was a significant difference between YBOCS reduction in participants with connected and unconnected VATs (using a two-sided, two-sample $t$-test), then this fibre was identified as discriminative of outcome. This process yielded a ‘fibre $t$-score’, with high-values indicating that this fibre was strongly discriminative of clinical outcome (Baldermann et al., 2019). Only the top 5% of fibres positively correlated with the primary outcome variable were selected for analysis to mitigate the risk of false positive associations.

Finally, to explore whether connectivity to specific cortical regions was related to YBOCS reduction, a region of interest analysis was informed by findings from the aforementioned methods. Cortical parcellations were derived from the Desikan-Killiany-Tourville labelling protocol (Klein and Tourville, 2012; Klein et al., 2017), with connectivity estimates between each VAT and cortical region entered into the multivariate linear mixed-effects model to derive an estimate of effect size and statistical significance.

3.8 Data Availability

A de-identified data set containing demographic and outcome data can be provided by Dr Philip Mosley (Philip.Mosley@qimrberghofer.edu.au) on application, subject to institutional review board approval. Local ethics caveats and clinical privacy issues prohibit sharing of individual imaging data but a copy of the Lead-DBS group analysis database can be supplied.
4 RESULTS

4.1 Participants

Nine participants (four females, mean age 47.9 ±10.7 years, mean baseline YBOCS 32.7 ±2.6) were recruited, randomised and implanted (Figure 1 and Table 1). The first participant was implanted in late 2015 and the last in early 2019. Contacts selected for activation were located in the BNST posterior to the NAcc and inferomedial to the ventral pallidum (Figure 2). All participants completed the blinded phase and data was analysed according to originally-assigned group. During the open phase, one participant developed an IPG infection necessitating DBS device explantation and exit from the trial. Scores at trial exit were carried forward for the two remaining data points. The eight remaining participants completed a course of ERP-based CBT. One participant (06) switched antidepressants and antipsychotics during the trial due to non-response to DBS and persistence of clinically-significant symptoms.

4.2 Outcomes

In the blinded (on versus sham) phase, there was a statistically significant difference in YBOCS reduction in favour of active stimulation ($t = -2.9, p = 0.025$, mean difference 4.9 points, 95 % CI = 0.8-8.9) (Figure 3). There was no significant difference in MADRS reduction ($t = -1.1, p = 0.30$, mean difference 3.4 points, 95 % CI = -3.7-10.5).

After one year of open-label stimulation and a course of ERP-based CBT, the mean reduction in YBOCS was 17.4 ±2.0 points ($\chi^2 (11) = 39.9, p = 3.7 \times 10^{-5}$) with no statistically significant covariates (Figure 3). Seven participants were responders as defined by the 35 % YBOCS reduction criterion, with a mean percentage reduction across the cohort of 49.6 ±23.7. ERP-based CBT commenced an average of 10.1 ±2.6 months after DBS with a mean additive YBOCS reduction of 4.8 ±3.9 points ($t = -3.5, p = 0.011$, 95 % CI = 1.5-8.0). The mean reduction in MADRS was 10.8 ±2.5 points ($\chi^2 (11) = 26.7, p = 0.0051$) with age ($t = -2.7, p = 0.0084$) and baseline MADRS ($t = 13.4, p = 2.0 \times 10^{-16}$) being significant covariates. Six participants were responders as defined by the 50 % MADRS reduction criterion, with a mean percentage reduction across the cohort of 54.7 ±27.2.
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Figure 1 | Flow Diagram of Participant Recruitment, Randomisation & Treatment

Abbreviations:
- CBT = Cognitive Behavioural Therapy
- DBS = Deep Brain Stimulation
- IPG = Implantable Pulse Generator
- YBOCS = Yale Brown Obsessive-Compulsive Scale
DBS electrodes were localised with the Lead-DBS toolbox and represented in common ICBM 2009b nonlinear asymmetric space incorporating a 7-Tesla MRI at 100 micron resolution (Edlow et al., 2019), with subcortical parcellations derived from a recent high-resolution atlas (Pauli et al., 2018). A: 3-dimensional reconstruction in
the coronal plane showing electrode trajectories for the nine participants. B: 3-dimensional reconstruction in the axial plane showing the distribution of the aggregated stimulation field across the cohort (red), which can be seen to encompass the posterior segment of the nucleus accumbens (light green), the ventral pallidum (yellow) and the hypothalamus (blue). C: 2-dimensional reconstruction of active contacts in coronal plane. D: 2-dimensional reconstruction of active contacts in axial plane. E and F: 2-dimensional reconstruction of active contacts in sagittal plane. In the 2-dimensional representations coloured circles represent the second most inferior contact on each electrode (i.e. contact 9 on right electrode and contact 1 on left electrode).

Abbreviations: Ca = caudate, EXA = extended amygdala (BNST), GPe = globus pallidus external segment, HTH = hypothalamus, NAC = nucleus accumbens, PBP = parabrachial pigmented nucleus, Pu = putamen, SN = substantia nigra, STH = subthalamic nucleus, RN = red nucleus, VeP = ventral pallidum
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Figure 3 | Participant Outcomes
A and B: Time series of individual participant outcomes for primary (YBOCS) and secondary (MADRS) variables. Within each graph, group average trajectory is represented by a loess smoothed curve (white) ± 1 standard error (grey). Baseline measurement denoted by green outline, recovery phase by yellow outline and blinded phase by red outline. C and D: Boxplots of YBOCS and MADRS change by randomised group (on = green versus off = red) during the blinded phase. E and F: Raincloud plots of YBOCS and MADRS change across the full trial. Raincloud plots made with code provided by Allen et al. (2019) and van Langen. (2020).
4.3 Relationship of Structural Connectivity to YBOCS Reduction

The local dispersion of the stimulation field within neighbouring subcortical structures including the NAcc, ventral pallidum, hypothalamus and terminal fibres of the stria terminalis was not related to relief of OCD symptoms (Supplementary Material). Using a normative connectome to identify white matter fibres connected to the stimulation field in each hemisphere for each participant, those connections most highly associated with YBOCS reduction were found in the right hemisphere (Figure 4A). These included a tract passing through the midbrain, traversing the BNST and onwards to the right ventrolateral prefrontal cortex. A tract connecting the BNST with the right amygdala was also identified, with connecting fibres passing through the hippocampal white matter and traversing back into the BNST via the fornix.

An ‘optimal’ connectivity map derived from correlating each brain voxel (weighted by structural connectivity) to YBOCS reduction also identified the right ventrolateral and parahippocampal regions, as well as right extrastriate, parietal and dorsomedial prefrontal areas (Figure 4B and local maxima Supplementary Table 1). In a leave-one-out cross-validation, structural connectivity of the stimulation field was significantly associated with YBOCS reduction ($r = 0.76, p = 0.018$).

Based on these findings, corresponding cortical regions derived from the Desikan-Killiany-Tourville labelling protocol were entered into the multivariate, linear mixed-effects model. Structural connectivity of the right hemispheric stimulation field with right orbitofrontal ($t = -3.1, p = 0.013$), right parahippocampal ($t = -2.4, p = 0.042$), right pars triangularis ($t = -2.5, p = 0.036$), right pericalcarine ($t = -4.3, p = 0.0024$) and right supramarginal regions ($t = -2.5, p = 0.035$) was significantly associated with YBOCS reduction. Connectivity with the right paracentral ($t = -1.8, p = 0.11$) region was not statistically significant. Univariate correlations displayed in Supplementary Material.

4.4 Adverse Events

There were nine serious adverse events (SAEs) affecting four participants (Table 1). Five of these were attributable to one participant (06) who was a non-responder and was readmitted to hospital to manage persistent psychiatric symptoms. A further participant (04) was readmitted to hospital on two occasions to manage a recurrence of depressive symptoms.
Two SAEs were device-related. One participant (02) required re-siting of a DBS electrode that had migrated 3 mm from the target during implantation. This was accomplished without any further complication. One participant (05) developed an infection of the IPG that migrated to the extension leads necessitating removal of the DBS device. There were four adverse events affecting two participants (Table 1). These were transient in nature except for reduced libido (participant 02), which persisted throughout follow up. Notably, there were no psychiatric adverse effects considered to be device related. All participants (except 05 who withdrew) required IPG replacement due to battery depletion during the study.
Figure 4 | Structural Connectivity & YBOCS Reduction
A: White matter fibres connected to the stimulation field and discriminative of outcome were isolated in the right hemisphere. These included a fibre tract passing through the midbrain to the ventrolateral prefrontal cortex and a fibre tract connecting the site of stimulation with the amygdala. Fibres in this region also passed through the hippocampal white matter and returned to the BNST via the stria terminalis adjacent to the fornix. Subcortical parcellations of the amygdala, hippocampus and fornix were derived from recent automated segmentation methods (Amaral et al., 2018; Entis et al., 2012; Pipitone et al., 2014). B: An optimal connectivity profile was generated by identifying those brain voxels structurally connected with the stimulation field and most highly correlated with YBOCS reduction. Cortical regions implicated in this optimal right-hemispheric ‘R-map’ included ventromedial and ventrolateral prefrontal cortex, dorsomedial prefrontal cortex, medial temporal cortex, parietal cortex and extrastriate visual cortex. These findings were corroborated in a leave-one-out cross-validation, in which each participant’s percentage YBOCS reduction was predicted by comparing their structural connectivity profile with an optimal connectivity map derived from the remaining participants. C: In a region of interest analysis, cortical regions derived from the R-map were tested in a multivariate linear mixed-effects model for their association with YBOCS reduction.
### Table 1 | Details of Participants

| Participant | OCD Phenomenology & Age of Onset Previous Therapies † & Comorbidities YBOCS at Baseline | Psychotropic Medication Chronic Stimulation Parameters ‡ | Percentage YBOCS & MADRS Reduction at End of Open Phase | Serious Adverse Events | Adverse Events |
|-------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|------------------------|------------------|
| 1           | Contamination  
Onset age 10-15  
4 antidepressants / 3 antipsychotics  
Major depressive disorder  
YBOCS 32 | Clomipramine 150 mg  
Quetiapine 100 mg  
Olanzapine 5 mg  
DBS Right Hemisphere: C+ 8-9-4.5 V / 90 µs / 130 Hz  
DBS Left Hemisphere: C+ 0-1-4.5 V / 90 µs / 130 Hz | YBOCS = 53.1  
MADRS = 57.1 | Nil | Parasomnia (sleepwalking) |
| 2           | Harming others / Sexuality / Blasphemy  
Onset age 5-10  
16 antidepressants / 3 antipsychotics / ECT  
Major depressive disorder  
YBOCS 33 | Tranylcypromine 30 mg  
Nortriptyline 75 mg  
Diazepam 5mg  
DBS Right Hemisphere: C+ 9-3.5 V / 90 µs / 130 Hz  
DBS Left Hemisphere: C+ 1-3.5 V / 90 µs / 130 Hz | YBOCS = 69.7  
MADRS = 70.6 | Deviation of one DBS electrode during implantation requiring removal and re-implantation. | Pustule at IPG site  
Lead tightening behind ear  
Reduced libido |
| 3           | Sexuality  
Onset age 15-20  
12 antidepressants / 7 antipsychotics  
Nil  
YBOCS 29 | Clomipramine 50 mg  
DBS Right Hemisphere: C+ 9-4.5 V / 90 µs / 130 Hz  
DBS Left Hemisphere: C+ 1-4.5 V / 90 µs / 130 Hz | YBOCS = 51.7  
MADRS = 50.0 | Nil | Nil |
| 4           | Harming others  
Onset age 15-20  
9 antidepressants / 4 antipsychotics / ECT  
Major depressive disorder  
YBOCS 35 | Clomipramine 200 mg  
Quetiapine XR 400 mg  
Clonazepam 1.5 mg  
DBS Right Hemisphere: C+ 9-10-4.7 V / 90 µs / 130 Hz  
DBS Left Hemisphere: C+ 1-2.7 V / 90 µs / 130 Hz | YBOCS = 54.3  
MADRS = 35.3 | Two inpatient psychiatric admissions to manage recurrence of depressive symptoms | Nil |
| 5           | Sexuality / Symmetry  
Onset age 5-10  
9 antidepressants / 4 antipsychotics / ECT / rTMS  
Major depressive disorder / body dysmorphic disorder  
YBOCS 32 | Sertraline 100 mg  
Pregabalin 150 mg  
Clonazepam 0.25 mg  
DBS Right Hemisphere: C+ 9-4.5 V / 90 µs / 130 Hz  
DBS Left Hemisphere: C+ 1-4.5 V / 90 µs / 130 Hz | YBOCS = 28.1  
MADRS = 46.2 | Infection of IPG requiring DBS device explantation | Nil |
| 6           | Contamination  
Onset aged 5-10  
19 antidepressants / 5 antipsychotics / ECT / | Tranylcypromine 10 mg  
Imipramine 50 mg  
Clonazepam 0.5 mg | YBOCS = 0  
MADRS = -4.0 | Five inpatient psychiatric admissions to manage persistence of obsessive & | Nil |
|    | Age | Gender | History | Psychiatric symptoms | Onset | Current Medications | DBS Parameters | Outcome | Side Effects |
|----|-----|--------|---------|----------------------|-------|---------------------|----------------|---------|--------------|
| 7  | 50-55 | Male | Struggling to maintain a job, Obsessive-Compulsive Disorder, Depression | Doubt / Perfectionism | Onset aged 5-10 | Clomipramine 50 mg Sertraline 250 mg | DBS Right Hemisphere: C+ 9-10-4.5 V / 90 µs / 130 Hz DBS Left Hemisphere: C+ 1-2-4.5 V / 90 µs / 130 Hz | YBOCS = 48.6 MADRS = 80.0 | Nil |
| 8  | 45-50 | Female | Struggling to maintain a job, Obsessive-Compulsive Disorder, Depression | Checking / Magical thinking | Onset aged 5-10 | Clomipramine 125 mg Desvenlafaxine 200 mg Olanzapine 5mg | DBS Right Hemisphere: C+ 9-10-4.5 V / 90 µs / 130 Hz DBS Left Hemisphere: C+ 1-2-4.5 V / 90 µs / 130 Hz | YBOCS = 82.3 MADRS = 78.9 | Nil |
| 9  | 55-60 | Male | Struggling to maintain a job, Obsessive-Compulsive Disorder, Depression | Checking / Doubt | Onset aged 5-10 | Fluoxetine 80 mg Dexamphetamine 60 mg | DBS Right Hemisphere: C+ 9-10-5.0 V / 90 µs / 130 Hz DBS Left Hemisphere: C+ 1-2-5.0 V / 90 µs / 130 Hz | YBOCS = 58.3 MADRS = 77.8 | Nil |

‡ Consistent with MedRxiv stipulations, only 5-year age range is given to prevent participant identification

† For brevity, details of past psychotherapies not listed here

‡ On the quadripolar electrode, contacts are numbered 8-11 in the right hemisphere and 0-3 in the left hemisphere

Abbreviations: ECT = electroconvulsive therapy, IPG = implantable pulse generator, IR = immediate release, MADRS = Montgomery Åsberg Depression Rating Scale, rTMS = repetitive Transcranial Magnetic Stimulation, XR = extended release, YBOCS = Yale-Brown Obsessive-Compulsive Scale
5 DISCUSSION

In nine participants with severe, treatment-refractory OCD, we demonstrate that DBS of the BNST substantially alleviated symptoms, with a mean YBOCS reduction of 49.6% and seven participants meeting the threshold for clinically-significant response after 12-months of open-label stimulation. Moreover, we describe a statistically-significant benefit of active stimulation over sham during a 3-month, double-blind, delayed-onset phase. Our data adds to the emerging literature supporting the use of DBS as a therapy in otherwise treatment-resistant OCD and specifically reproduces prior work targeting the BNST. (Luyten et al., 2016) Open-label stimulation also significantly reduced co-morbid depressive symptoms, although this result should be viewed with more circumspection as depression was not a primary target of the intervention and two participants reported only mild symptoms at baseline.

Extending prior clinical findings, we also characterise a subcortical structural connectivity profile associated with optimal response to DBS at this target. Here, a right-hemispheric tract traversing the stimulation field and associated with YBOCS reduction connected the BNST to the amygdala. Connected fibres also involved the hippocampal formation and fornix, which form part of the circuit of Papez (Papez, 1995). From a physiological perspective, the BNST functions as a component of the ‘extended amygdala’ and drives a state of sustained apprehension (anxiety) (Lebow and Chen, 2016). Of note, recent work has also demonstrated a central role for the amygdala in mediating a rapid reduction in anxiety symptoms after ALIC DBS for OCD (Fridgeirsson et al., 2020), which heralds later improvement in obsessions and compulsions. Overall, this supports the role of DBS in facilitating fear extinction through reducing anxiety. Aberrant fear conditioning (enhanced acquisition and impaired extinction) is a central construct in the development and maintenance of OCD (Geller et al., 2017; Milad et al., 2013), and may explain why more severely affected individuals cannot tolerate or do not respond to exposure-oriented CBT (Geller et al., 2019). This may also explain why, after DBS, our participants were now able to tolerate, and accrue a statistically-significant additional benefit from CBT during open stimulation, consistent with previous work (Mantione et al., 2014).
Importantly, this improvement in fear extinction may be mediated via enhanced top-down input to the amygdala from the prefrontal cortex (Fridgeirsson et al., 2020). In our cohort, fibres associated with YBOCS reduction were also characterised passing to the prefrontal cortex and potentially representing a structural correlate of this effect. This connectivity profile was similar in distribution to that previously described by other centres employing different targets such as the NAcc / ALIC interface and the STN (Baldermann et al., 2019; Li et al., 2019). These findings support the existence of a common anatomical substrate that underpins response across discrete sites, as well as being consistent with prior work demonstrating that alterations in frontostriatal connectivity are implicated in the response to NAcc / ALIC DBS (Figee et al., 2011). Moreover, the distribution of connected fibres associated with YBOCS reduction was strikingly similar to prior research characterising the structural connectivity of the BNST in healthy participants (Kruger et al., 2015).

Connectivity of the stimulation field with right-hemispheric cortical regions of interest in the prefrontal, temporal, parietal and occipital lobes was also significantly associated with YBOCS reduction. Interestingly, these same regions have previously been implicated in morphometric analyses of structural connectivity, grey matter volume, cortical thickness, surface area and gyrification amongst individuals with OCD (Fan et al., 2013; Peng et al., 2014; Rotge et al., 2010; Yun et al., 2020), suggesting that there may be a neuroanatomic ‘fingerprint’ of susceptibility to OCD that is modulated by DBS. Importantly, using cross-validation, YBOCS reduction could be accurately predicted in a single participant by comparing their connectivity profile to a pooled analysis of the connectivity amongst the remainder of the cohort. This suggests that the recruitment of specific fibre pathways by the stimulation field is an important determinant of outcome. More generally, the right lateralisation of our findings is interesting given previous work that implicates right-hemispheric corticostriatal circuits in inhibition (Aron et al., 2004; Aron et al., 2007; Rae et al., 2015), impulsivity after subthalamic DBS for Parkinson’s disease (Mosley et al., 2018; Mosley et al., 2020b), and reduction of OCD symptoms after NAcc / ALIC DBS (Baldermann et al., 2019).

Serious adverse events were predominantly accounted for by persisting psychiatric symptoms in a non-responder with repeated readmissions to hospital. It is noteworthy that the connectivity profile of this individual was most distinct from the rest of the cohort with electrodes that were more anteromedial and a stimulation field that was less connected to the...
right-hemispheric regions of interest (Figures 2 and 4, Supplementary Figure 2), suggesting a potential explanation for this lack of response. IPG infection and device removal was the most significant device-related event, affecting one participant. No participants developed stimulation-related psychiatric side effects such as agitation, impulsivity and hypomania, as has previously been reported (Denys et al., 2010; Greenberg et al., 2010; Tyagi et al., 2019). This may have been attributable to our deliberately slow titration protocol and the use of lower stimulation amplitudes than have previously been described. However, despite the use of more modest amplitudes, IPG depletion occurred in all participants before the close of the trial, necessitating replacement.

The use of a staggered-onset rather than a crossover design in the double-blind phase could be considered a limitation. In previous trials using a crossover design (Denys et al., 2010; Luyten et al., 2016; Mallet et al., 2008), optimal stimulation settings were already determined after an open-phase, increasing the likelihood of a treatment effect in the active condition. However, based on prior work describing a significant rebound of aversive OCD symptoms after therapy interruption (Ooms et al., 2014), we considered it more ethically acceptable to delay treatment rather than cease a treatment that had previously been effective. Moreover, one significant benefit of our approach was that the likelihood of participants becoming unblinded by sensations associated with active stimulation was minimised.

The use of normative rather than participant-specific connectivity data is a further limitation and has been discussed elsewhere (Coenen et al., 2019; Li et al., 2019; Treu et al., 2020). Whilst participant-specific anatomical variability is lost, the quality of these group-average datasets is high and curated by teams with longstanding expertise. The reliability of analyses derived from these data may therefore be acceptable, and normative connectomic data has been employed to make out-of-sample predictions across disorders and treatment modalities (Al-Fatly et al., 2019; Baldermann et al., 2019; Horn et al., 2017; Joutsa et al., 2018; Weigand et al., 2018). Thus, whilst normative data should not be the basis for surgical decision-making in one individual, it may yield important insights into mechanisms of disease and treatment-response within and across cohorts.

In summary, in a cohort of participants with severe, treatment-refractory OCD, we demonstrate that active stimulation at the BNST is superior to placebo in a randomised, double-blind, sham-controlled, delayed-onset clinical trial, with a further significant benefit
accrued following a longer phase of open-label stimulation incorporating a course of ERP-based CBT. We also delineate a structural connectivity profile associated with clinical response, which comprised subcortical regions implicated in fear conditioning and emotional processing, as well as cortical regions implicated in prior morphometric analyses of persons with OCD. We anticipate that our findings will motivate more precise targeting of stimulation within these networks, using participant-specific connectivity data to optimise treatment at the individual level, as has been described in DBS for treatment-resistant major depression (Riva-Posse et al., 2014; Riva-Posse et al., 2018).
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8 FINANCIAL DISCLOSURES / CONFLICTS OF INTEREST

Dr Mosley has previously received an unrestricted educational grant from Medtronic for Parkinson’s disease research. He has received an honorarium from Boston Scientific for speaking at an educational meeting. The authors report no other conflict of interest.

9 ETHICS APPROVAL

Prior to the commencement of data collection, the full protocol was approved by the Human Research Ethics Committees of the University of Queensland and UnitingCare Health. All participants gave written, informed consent to participate in the study. All procedures were carried out in accordance with the approved protocol.
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