Deep brain stimulation for severe obsessive compulsive disorder: Efficacy and mechanisms of ventral striatum and subthalamic nucleus targets

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1. Background

1.1. Obsessive compulsive disorder (OCD) has a lifetime prevalence of 1-2 % and is characterised by intrusive unwanted thoughts and compulsive behaviours that vary in intensity, frequency and character. The standard treatment is cognitive behaviour therapy (CBT) and/or serotonin re-uptake inhibitor (SRI) medication but these are ineffective in up to 40% of cases [1]. Symptoms in this treatment-refractory subgroup can be sufficiently severe that patients are unable to perform activities of daily living, sustain work or maintain relationships. The English NHS National Specialised Commissioning Group has commissioned services to provide assessment and intensive CBT and pharmacotherapy for such patients. Although these have good results [2, 3] there remains a truly refractory subgroup for whom ablation of the anterior cingulate cortex is an option [4]. Prospective longitudinal studies of cingulotomy suggest a sustained 2-year response rate of 32% with few adverse events and a concomitant improvement in quality of life [5, 6].

1.2. Deep brain stimulation (DBS) may improve upon this success rate as the response can be modified following surgery - stimulation can be adjusted to optimise benefits and minimise adverse effects. DBS also has the advantage of reversibility in that stimulation can be switched off if the response is unsatisfactory and electrodes can be removed. Studies which have used similar response criteria to those of tissue ablation implicate two DBS brain targets as being particularly effective - the ventral striatum/ventral anterior capsule (VS/VC) and the subthalamic nucleus (STN). Two studies have found that 56% or 62% of patients respond with VS/VC electrodes stimulating ventral striatal grey matter and adjacent white matter fibres en route to and from medial and orbital frontal cortex [7, 8]; a third study found 75% responded with STN electrodes stimulating the boundary between associative and limbic grey matter, although the criterion for success was less strict than that of the VS/VC studies [9]. All three studies additionally found concomitant improvements in everyday function, suggesting that DBS can be considered a promising treatment for severe OCD.

1.3. Before DBS for OCD can be introduced into routine clinical practice, further research is required to determine the optimum DBS brain target. It may also be possible to improve upon the degree of response to DBS by understanding more about the mechanisms of action at the two target sites - although two-thirds were considered responders in previous studies, the patients remained symptomatic, being reduced from the 'extreme/severe' to the 'moderate' category [7]. Furthermore, although CBT will not have previously been effective in these patients, DBS may reduce symptoms enough to enable them to use CBT more effectively and, indeed, the combination may result in a better outcome than DBS alone. To address these questions we have brought together a network of specialist OCD clinicians, leading OCD cognitive neuroscientists and expert DBS clinicians to undertake the first UK study of DBS for severe, medically intractable OCD.

2. Aims and Hypothesis

2.1. The overarching aim is to compare the effects of VC/VS and STN DBS in the same patients. We will test the hypothesis, grounded in cognitive neuroscience, that DBS at both sites is better than either site alone for treating the symptom dimensions of OCD. Specifically, we will employ novel cognitive paradigms and neurophysiological measures of cortical synaptic function to test the hypothesis that VS/VC and STN DBS have different mechanisms of action and that alleviation of OCD symptoms is mediated by improvement in mood/anxiety with VS/VC DBS and by directly interrupting obsessions and compulsions with STN DBS. We will additionally determine whether adjunctive CBT enhances the response to DBS by providing the cognitive and behavioural skills to optimise symptom management and daily function.

3. Scientific Rationale

3.1. The VS/VC and STN are both 'stations' in the neural circuitry thought to be dysfunctional in OCD. The pre-eminent neurobiological model of OCD implicates abnormalities of orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and ventral striatum [10]. These structures are integral to limbic cortico-striatal-thalamo-cortical circuitry whereby cortical outputs synapse successively in ventral striatum, ventral pallidum and mediodorsal nucleus of thalamus before projecting back to cortex; within this system, the pallidum projects to thalamus either directly or indirectly via the subthalamic nucleus. It is therefore possible that the observed clinical improvement in OCD with DBS is due to high frequency electrical stimulation disrupting abnormal activity in the limbic circuit and that this can be obtained at either of the two target sites. However, the ventral striatum and STN are thought to have separate functions, important in different ways for modulating information processing in the cortico-striatal-thalamo-cortical circuitry essential for the control of behaviour. Thus, although both VS/VC and STN DBS affect the same neural circuit, their mechanism of action may be quite different and stimulation at each of these locations may have unique effects on the symptom dimensions of OCD.

3.2. Evidence for different clinical effects comes from findings that VS/VC DBS produced early and sometimes dramatic mood elevation and anxiety reduction prior to improvement in obsessions and compulsions whereas STN DBS, while diminishing obsessions and compulsions, had no effect on emotion [7, 9, 8]. This observation is relevant because mood and anxiety are significant symptom dimensions in OCD and increases or decreases in the severity of anxiety or depression are generally accompanied by parallel changes in the severity of obsessions/compulsions [11]. The ventral striatum, as well as being the first target of OFC/ACC cortical outputs, receives inputs from amygdala and midbrain dopaminergic neurones, which together provide the emotional and motivational impetus for goal directed behaviour [12]. The ventral striatum is therefore in a unique position, via its involvement in limbic cortico-striato-thalamo-cortical circuitry, to influence the cognitive and motor processing in parallel circuits which is preparatory for action selection and ultimately

manifest in thoughts and actions [12]. Denys and colleagues [8] proposed that VS/VC DBS influences OCD symptoms via its effect on anxiety and mood. Taking this further, we hypothesize that stimulation of ventral striatal neurones influences reinforcement learning and emotion processing thereby improving mood and reducing anxiety and resulting in a decrease in the intensity of obsessions and compulsions.

3.3. STN DBS on the other hand may have a more direct effect on obsessions and compulsions. The limbic STN, like the ventral striatum, is in a unique position to influence behavioural outputs of cortico-striatal-thalamo-cortical circuitry. This is because the STN receives a direct projection from right inferior frontal cortex which acts as a 'hyperdirect pathway', activation of which overrides neural processing in the direct cortico-striato-pallido–thalamic pathway. This results in the inhibition of ongoing, planned acts and thoughts [13]. We therefore hypothesise that, via this inhibitory mechanism, stimulation of STN neurones enables OCD patients to interrupt their repetitive thoughts and actions resulting in a decrease in obsessions and compulsions.

3.4. Accordingly, DBS at both sites, because of different mechanisms of action, is predicted to be clinically more effective than stimulation of either site alone. It also follows that if there are two mechanisms mediating OCD improvement, this should be evident in different patterns of cognitive and neurophysiological effects following DBS. In the proposed study we will test these predictions clinically and experimentally by using paradigms designed to distinguish the two hypothetical mechanisms of action.

3.5. The main aim of CBT is to enable OCD patients to obtain greater control over behaviour so that they can inhibit their repetitive thoughts and acts and switch to more meaningful alternatives. One abnormal mechanism contributing to such cognitive inflexibility is thought to be blunting of the value of positive and negative reinforcement normally used to guide responses and dependent on intact OFC-striatal neural circuitry [14]. Dysfunction of this cognitive control system has been shown in first-degree clinically unaffected relatives of OCD patients thus confirming this mechanism as a neurobiological phenotype of OCD [15].It is therefore hypothesised that DBS of VS/VC will improve the processing of reinforcing stimuli and that this will result not only in elevation of mood and reduction in anxiety but also in increased cognitive flexibility. We will test this by measuring the effectiveness of VS/VC DBS on clinical measures of mood, anxiety, obsessions and compulsions and relate these to changes in reinforcement learning and emotional processing using cognitive tasks sensitive to OCD which measure the ability to respond appropriately to reinforcing contingencies.

3.6. Attentional processes are also thought to contribute to impaired behavioural control in OCD. Being able to stop or inhibit planned acts when environmental circumstances change depends on the function of the right inferior cortical-STN hyperdirect pathway and can be operationalised by measuring the stop signal reaction time (SSRT) [16]. The finding of specific prolongation of SSRT in OCD patients and their unaffected first-degree relatives suggests that this cognitive abnormality is also a phenotype of OCD [17]. Although the neural substrate of this mechanism does not involve the limbic cortico-striato-pallido–thalamic circuit,

recent evidence suggests that neural systems outside this circuitry, involving the right inferior frontal cortex, are impaired in OCD [10]. We therefore hypothesise that STN DBS allows inhibition of repetitive thoughts and acts in OCD by facilitating the action of the hyperdirect pathway from the right inferior frontal cortex to STN. We will test this by measuring the effectiveness of STN DBS on obsessions and compulsions and relate these to changes in SSRT and performance on other tasks sensitive to right inferior frontal cortex function which measure the ability to inhibit pre-potent tendencies.

3.7. OCD symptoms and cognitive impairment may be mediated by abnormal cortical excitability due to aberrant long term depression (LTD) synaptic plasticity [18] and/or reduced GABA-mediated intracortical inhibition [19]. Transcranial magnetic stimulation (TMS) can be used to measure these neurophysiological processes safely in patients undergoing DBS and both abnormalities have been shown to normalise following DBS in other disorders [20]. We will use TMS to assess these neural processes before and after DBS in OCD patients and test for whether there are differential changes from the two DBS sites and whether combined VS/VC and STN DBS produces more vigorous improvements compatible with our hypothesis concerning the superior clinical effects of this condition. We will measure intracortical inhibition not only at rest but also during the anticipation of reinforcement, previously shown to affect motor cortex excitability [21] and which we predict will be specifically affected by VS/VC DBS.

4. Research Programme

4.1. Subjects: Six patients will be recruited from the OCD National Specialist Commissioned Services of Dr Lynne Drummond, South West London and St George's Mental Health Trust (SWLSG MHT) and Professor Naomi Fineberg, Herts Partnership NHS Foundation Trust (HPFT).

4.2. Inclusion criteria: The inclusion criteria have been designed to be consistent with previous OCD DBS studies and to ensure that patients have not responded in a useful and sustained manner to either modifications of medication or any form of CBT [4].

Patients must have undergone intensive treatment and have demonstrable treatment resistance as defined by:

a. At least two SRIs for a minimum of 12 weeks at optimal British National Formulary (BNF) doses.
b. Augmentation of SRI treatment with antipsychotic drugs administered at maximally tolerated doses or by extending the SSRI dose beyond BNF limits.
c. Two trials of CBT of at least 10 hours.
d. Failed inpatient treatment for OCD.

Patients must also satisfy the following criteria:

e. Age > 20 years.

f. Confirmation of a primary diagnosis of obsessive compulsive disorder (ICD10 F42.0—F42.9).
g. Duration of illness of at least 10 years.
h. At least 2 years of unremitting symptoms despite intensive psychopharmacological and psychological treatment or failure to sustain, over a 3 month period, a response to inpatient psychological treatment by at least 33% with accompanying optimised pharmacological therapy.
i. A minimum score of 32 on Yale Brown Obsessive Compulsive Scale (YBOCS) 22 thus constituting profound illness and a maximum score of 50 on the DSM IV General Assessment of Function Scale (GAF).
j. Ability to provide sustained informed consent.

4.3. Exclusion criteria

Current diagnoses of:

a. Substance misuse (ICD10 F10—F19)
b. Organic brain syndrome (ICD10 F00—F09)
c. Adult personality disorder (ICD10 F60—F69)
d. Pervasive developmental disorder (ICD10 F84)
e. Schizophrenia (ICD10 F20-F29)
f. Bipolar disorder (ICD 10 F30-31)
g. Contraindications to neurosurgery
h. Pregnancy

5. Study Design

See Figure 1

5.1. The study design will allow assessment of DBS at each of the two sites counterbalancing for order. Stimulation at both sites will not be included in the randomisation of order and will always occur last because:

a. The optimal stimulation parameters for each target alone will have already been identified for each individual and thus the optimum parameters in combination will be determined more quickly; *and*

b. We are predicting that stimulation of both sites will be the most efficacious condition and that withdrawal of effective therapy would risk higher rates of patient drop-out from the blinded evaluation and could be regarded as unethical.

5.2. We have opted not to have a wash-out period between the three DBS phases because:

a. Patients may not wish to have the DBS switched off if they have experienced symptom reduction by the previous DBS settings and this will risk higher rates of

patient drop-out from the blinded evaluation; this has been experienced in one previous study8.

b. The purpose of the study is to compare DBS at two sites both individually and together to establish the best site(s) for UK practice in the future - it is not to establish absolute efficacy at each site (which would require both on and off DBS phases) as this has been adequately demonstrated previously.

5.3. A potential criticism is that there may be a carry-over effect from previous stimulation parameters when patients are switched from the first site to the second site which will affect the assessments *(see Figure 1)*. Evidence about how long stimulation effects continue to affect OCD behaviour following cessation comes from two studies of STN DBS in which sham and active stimulation were compared [8, 9]. During a 2 or 4 week wash-out periods the patients switching from active to sham stimulation had reverted to their baseline symptom severity by the end of these periods. This suggests that the effect of 12 weeks of active stimulation at the second site will not reflect carry-over affects. In addition because we are counterbalancing for order, the presence of any carry-over effect can be examined at the end of the study.

5.4. Stages

Stage 1a: Consistent with the existing nationally commissioned clinical pathway, all potential participants will be offered the choice of anterior cingulotomy or DBS. Although this study is designed to examine the effect of DBS and not to compare the two procedures, adopting the standard care pathway will ensure that existing robust governance and consent procedures will be applied for all participants. Potential patients will be identified from the clinical case loads of Dr Lynne Drummond and Professor Naomi Fineberg. Their clinical files will be reviewed by their OCD specialist consultant, Dr Drummond or Professor Fineberg, and Professor Keith Matthews to establish that they fulfil the inclusion/exclusion criteria. Professor Matthews directs the OCD national specialist commissioned service for ablative neurosurgery at Ninewells Hospital, Dundee, and will ensure that the patients meet the criteria for suitability for anterior cingulotomy [4]. The OCD clinicians will discuss both procedures (anterior cingulotomy and DBS) with each patient and establish that they are able to provide written informed consent.

Stage 1b: A separate group of up to 20 patients will be identified for the purpose of undergoing all neuropsychological, neurophysiological and clinical assessments as are proposed for the group of patients being offered DBS. This group of patients will be identified through the same pathways. Same inclusion and exclusion criteria set for this trial will be applied to identify these patients. This group of patients will differ from the DBS group in the following aspects:

a) They are still being offered standard treatment of their refractory OCD in a specialist OCD Service.
b) They are not being offered DBS or neurosurgery.

All assessments will be performed on this group of patients at exactly the same intervals as those proposed for the patients undergoing DBS. Assessment data obtained from this group of patients will help us to improve the accuracy of the results obtained from the main trial by facilitating the identification of neuropsychological, neurophysiological and/or clinical changes specific to DBS.

Stage 2: Patients who opt for DBS will be referred the NHNN. At this visit the research protocol will be explained in detail to them. They will be offered the opportunity to visit the ward prior to admission. They will be seen in the multidisciplinary DBS clinic at the NHNN where they will be assessed for suitability for the surgery. Ability to provide written informed consent will be re-assessed at this stage thereby establishing consistency. Written informed consent will be taken at this stage if the patient is ready to decide. If the patient would like more time, written informed consent will be obtained at subsequent clinic appointments with Prof Fineberg or Dr Drummond.

Stage 3: Prior to surgery any serotonin reuptake inhibitor (SRI) medication will be withdrawn and they will remain free of this medication for the 10 days before surgery (see below). A time period of 7-21 days will be allowed for the careful down-titration of medication during the withdrawal process. The actual duration of withdrawal will be informed by decided by taking clinical and historical factors into account on a case-by-case basis. The participant might require an inpatient admission during the process of withdrawal from medication and a provision will be made for the same. We wish to undertake all assessments when patients are taking their routine medication. If they are taking SRIs we will undertake initial assessments at a separate visit to the hospital prior to admission for surgery and before their medication is withdrawn.

Stage 4: Patients will be admitted for DBS neurosurgery to a dedicated neuropsychiatry ward (Hughlings Jackson) at the NHNN. It is anticipated that they will stay for up to 14 nights, depending on whether the initial assessments have already been completed or not, and to allow post-operative recovery and the removal of the stitches by the surgical team 10 days after surgery.

Stage 5: Following discharge, stimulation will remain off for a minimum of 4 weeks to allow the mechanical effect of post-surgical oedema to resolve. This period can be extended, if necessitated by clinical reasons.

Stage 6: Randomisation and initiation of STN or VS/VC DBS for 12 weeks. The stimulation parameters will be adjusted on a daily basis until judged optimal (see below for details). Optimisation process will also be guided by a modified Visual Analogue Scale (VAS) to measure urges to perform compulsions and fluctuations in the mood. Specific behavioural challenges will be designed for each patient in accordance with their previous clinically documented symptoms of OCD and will be administered by the research psychiatrist during the optimisation process to elicit obsessive and compulsive responses. The strength and

intensity of these responses will be measured with modified Visual Analogue Scales by both patient and the psychiatrist. This may take up to 2 weeks; patients will have the option of being admitted to Hughlings Jackson ward or attending as a day case. If the latter, they may stay overnight at a local hotel with a carer (according to standard NHHN day unit procedures) or stay overnight at home if practical. Stimulation optimisation period will not be included in the 12 weeks allocated to the stimulation stage.

Stage 7: The current stimulation will be switched off for 24 hours and the alternative site stimulated for 12 weeks. The same procedures and options for hospital attendance in Stage 6 will apply.

Stage 8: The current stimulation will be switched off for 24 hours and both sites will be stimulated for 12 weeks. The same procedures and options for attendance in Stage 6 and 7 will apply.

Stage 9: Patients will continue with DBS at their best DBS site(s) and settings. This may require a further admission for stimulus/site adjustment as above if the current stimulation is not judged to be optimal.

Stage 10: After 12 weeks stabilisation on the best DBS settings and site, patients will be offered inpatient cognitive behavioural therapy at SWLSG MHT for 12 weeks.

6. Study procedures and assessments

6.1. Medication: Patients are likely to be taking a combination of high dose SRIs and antipsychotic medication. This medication will be kept constant throughout the study expect for the preoperative period. Evidence suggests that patients taking SRIs are at increased risk of bleeding because of a non-dose dependent reduction in platelet serotonin [23]. To decrease this risk, patients will be withdrawn from SRIs and be free of this medication for 10 days prior to surgery to allow platelets to be replaced. Medication will be reinstated during the post-operative period.

6.2. DBS Neurosurgery: All patients will undergo implantation of bilateral electrodes at both the VS/VC and STN sites under general anaesthesia. On each side, the two electrodes (STN and VC/VS) will be implanted through a single burr hole. A high-resolution MRI scan will be used to calculate target coordinates for each patient. An MRI will also be performed to verify accurate electrode location [24] immediately following surgery. Both scans will be performed under general anaesthesia. Each STN electrode will have 4 electrical contacts at its distal tip (with a 0.5mm separation) to allow fine tuning of the exact site for stimulation delivery. Each VS/VC electrode will have 4 electrical contacts at its distal tip (with a 1.5mm separation) to allow fine tuning of the exact site for stimulation delivery. Two non-rechargeable batteries (Activa PC) will be connected to the electrodes and positioned under the skin of the right and left chest wall so that they correspond to the same set of

electrodes for each patient: one for the 2 STN electrodes and one for the 2 VC/VS electrodes.

6.3. Magnetic Resonance Imaging: Routine pre- and post-operative MR images will be obtained from a single 1.5T MRI scanner (Siemens, Erlangen, Germany) using a head transmit/receive coil that does not extend over the chest to avoid RF exposure to areas outside the head and hence to minimize the area of the DBS circuit exposed. The MRI acquisition protocol is specifically designed to prevent the scanner-predicted head-average specific absorption rate (SAR) exceeding 0.4 W/kg while still providing adequate visualization of the target anatomy. The gradient slew rate (dB/dt) will be less than 20 T/s for all acquisitions. These MRIs will be when the patients are under general anaesthesia. On the day before surgery, patients will be invited to undergo a 3T diffusion tensor MRI scan when awake. This is not routine and is part of the research study; it will enable us to perform white matter tractography and identify the white matter output tracts and distal projection sites for each electrode.

6.4. DBS stimulus adjustment and blinding: Two neurologists making the DBS adjustments (Dr Thomas Foltynie and Dr Patricia Limousin) will allocate 3 patients to receive STN DBS initially and 3 to VC/VS DBS. All other team members and the patient will be blind to the allocation. Each electrode has 4 electrical contacts at its distal tip (with a 0.5mm separation) to allow fine tuning of the exact site for stimulation delivery. The optimal DBS parameters will be derived in an iterative fashion over a period lasting up to 2 weeks at the start of each 12 week stimulation block. This will require the patient to visit the DBS unit on a daily basis. At the outset, each contact will be screened with voltages up to 4V (STN electrodes) or 8V (VC/VS electrodes) using monopolar stimulation and a pulse width of 60us, and frequency of 130Hz. Note will be made of the immediate clinical effects from stimulation delivered through each contact in turn, and the threshold associated with positive and negative effects. Expected acute adverse effects of stimulation include transient sadness, anxiety, euphoria, giddiness or hypomania [7, 9]. These will be monitored and documented with the use of visual analogue rating scales which rate subjective feelings [24]. Stimulation will be adjusted to avoid any sustained negative physical or psychiatric symptoms. In the absence of any acute clinical effects, the post-operative imaging will be used to select the contact closest to the planned target. The initial optimal stimulation parameters will be refined according to patient feedback as often as necessary over the first 2 weeks, including possible use of stimulation through multiple contacts per electrode or using a bipolar configuration. These parameters will then be kept constant through the remainder of each 12 week block with further adjustment performed only in the event of delayed physical or psychiatric adverse events, considered by the trial team to be directly attributable to the stimulation.

6.5. Clinical assessments: OCD and co-morbid disorders will be assessed using The Mini International Neuropsychiatric Inventory (MINI) [26] as part of the assessment of inclusion/exclusion criteria. In addition, Young Schema Questionnaire (YSQ) [49] will be used to identify comorbid Personality Traits. Regular clinical assessments of the strength and

intensity of obsessive and compulsive symptoms will be made on Visual Analogue Scale (VAS) by using appropriate behavioural challenges, which will be designed specifically for each patient. Urge to perform compulsions will be monitored and quantified using similar VAS at each assessment point. The effect of DBS on OCD, affective symptoms, social function and quality of life will be assessed with the following validated scales:

OCD symptoms:

a. Yale-Brown Obsessive Compulsive Scale Symptoms checklist (YBOCS-I) [22]
b. Yale-Brown Obsessive Compulsive Scale (Version-II) [47]

Affective symptoms:

c. Montgomery Asberg Depression Rating Scale (MADRS) [27]
d. Beck Depression Inventory – Version 2 (BDI-II) [28]
e. Young Mania Scale (YMS) [29]
f. Barrett Impulsiveness Scale (BIS) [30]

Comorbid Tics:

g. Yale Global Tic Severity Scale (YGTSS) [48]

Anxiety:

h. Hamilton Anxiety Scale (HAS) [31]
i. Beck Anxiety Inventory (BAI) [32]

Social Function:

j. DSM IV General Assessment of Function scale (GAF)
k. Sheehan Disability Scale (SDS) [33]
l. Cognitive Assessment Instrument of Obsessions and Compulsions (CAIOC-13) [34]

Subjective wellbeing:

m. SF-36 [35] (quality of life scale)

6.6. Cognitive assessments:

Years spent in education will be noted for all patients before they undergo the tests for general cognitive function.

General cognitive function:

a. The National Adult Reading Test [36]
b. CANTAB Paired Associate Learning Task (PAL) [37]
c. Verbal Fluency [38]

Reinforcement learning and emotional processing:

d. The probabilistic learning and reversal task [39]
e. CANTAB Affective Go/No Go [36]

f. **CANTAB Reward Sensitivity Test**

Executive control:

g. CANTAB Stop Signal Reaction Time Task [36]

h. CANTAB ID/ED Task [36]

The rationale for using these tests is that both stop-signal inhibition and extra-dimensional set-shifting have been shown to be sensitive to OCD (as well as in their first degree relatives) [17]. Performance in both tasks is mediated by circuits including the inferior frontal cortex and orbitofrontal cortex [10, 40]. Our hypothesis predicts that the SSRT and ID/ED will be more sensitive to changes induced by STN DBS. Preliminary work indicates that OCD patients with high YBOCS scores may be impaired in probabilistic reinforcement learning (70/30%); the Affective Go/No Go tests attentional biases in mood states. Our hypothesis predicts that these two tests will be more sensitive to changes induced by VC/VS DBS. Paired associate learning has also been shown to be deficient in OCD [41], although the precise neural substrates for this deficit are not known. Mild word finding difficulty and forgetfulness have been reported following DBS in several disorders and will be assessed with verbal fluency and PAL. This battery of tests will take approximately 1 hour to administer.

6.7. TMS assessments

During TMS electromyography recordings will be made from abductor pollicis brevis (APB) and first dorsal interosseus (FDI) muscle using surface electrodes. Signals will be amplified and band pass filtered at a sample rate of 5000 Hz. TMS will be applied using a 70 mm figure of eight coil and Magstim 200 generators.

a. **Cortical plasticity assessment:**
Paired associative stimulation (PAS) after localisation of the "hotspot" the resting (RMT) and active (AMT) motor thresholds will be determined. At 0.5, 15 and 30 min after PAS, we will obtain a stimulus response curve; MEPs will be recorded at each intensity from RMT-10% maximum stimulator output to RMT+30%. The inhibitory PAS10 paradigm (200 pairs, at 0.25 Hz) will be used. Median nerve stimulation (constant current generator) at 3x perceptual threshold intensity (duration 0.2 ms) will be delivered before TMS over the APB "hotspot" (intensity at 1 mV MEP prior to the start of the procedure).

b. **Intracortical inhibition (SICI) assessment:**
TMS will be delivered to the FDI "hotspot". The first, conditioning-stimulus, will be set at 80% AMT and the second, test stimulus at a 1 mV MEP level when given alone. Interstimulus intervals of [2, 3] will be explored (n=12 per interval, randomly intermixed). SICI will be calculated by pooling 2 and 3 ms data and expressed as the ratio between conditioned and unconditioned trials. SICI will also be combined with a reward paradigm [21].

6.8. Timing of assessments and procedures: *(Please also see Table 1)* All assessment will be performed prior to surgery. Cognitive and TMS assessments will be performed additionally at the end of each of the 3 DBS periods, at the end of the optimisation of DBS period and at the end of CBT. Where possible, alternative forms of the tests will be used to avoid practice effects. Clinician-based clinical assessments will additionally take place monthly or more often if judged necessary. Patient self-report assessments will additionally take place at the end of each of the 3 DBS periods, at the end of the optimisation of DBS period and at the end of CBT.

7. Data Analysis

7.1. Descriptive analysis will be used to quantify changes in clinician-related YBOCS scores by using visual plots and specifying means and 95% CIs or medians and IQRs. We will then compare these changes using Friedman's ANOVA to account for the lack of independence between observations.

7.2. The primary efficacy measure will be the clinician-rated YBOCS total scores. Friedman's ANOVA across all 4 conditions (pre-op baseline and after 3 months DBS in STN, VC/VS and STN+VC/VS) will be performed. A categorical efficacy measure, responder/non-responder status after each 3 month DBS block will be defined as >/= 35% decrease in YBOCS and will be analysed with the McNemar exact test for comparison of the VC/VS and STN DBS conditions. Descriptive analysis in addition to Friedman's ANOVA will also be used to analyse the mechanistic hypotheses on the following variables: MADRS, SSRT, ID/ED, probabilistic reversal learning, affective go/no go scores and TMS. The additional benefit of CBT will be analysed using Wilcoxon matched-pairs before and after CBT.

7.3. These data will also allow an estimate of mean effect and variance of the main effect to be made to allow a sample size calculation for a future fully powered trial.

8. Ethics and patient safety

8.1. Clinical care: All patients will be under the care of NHS OCD specialised services and their local community mental health team (CMHT). Consistent with the existing nationally commissioned clinical pathway, all potential participants will be offered the choice of anterior cingulotomy or DBS. Although this study is designed to examine the effect of DBS and not to compare the two procedures, adopting the standard care pathway will ensure that existing robust governance and consent procedures will be applied for all participants.

8.2. Monitoring for potential DBS adverse effects: The published risks of STN and VC/VS stimulation are mainly hypomania and anxiety, which are voltage dependent and 8, 9 and either self-limiting or resolved by modifying the stimulation settings. Clinical worsening, including lowering of mood has also been reported after stimulation is switched off. To

monitor and manage any adverse effects, the following procedures will be in place for each patient:

a. Prior to surgery, in conjunction with the responsible OCD clinician (LD or NF) the study research clinician will contact the CMHT, speak to the responsible consultant and key worker about the study and provide regular progress reports.
b. Patients will remain in hospital following changes in DBS for at least 24 hours following the final stimulation adjustment.
c. Following discharge and throughout the 12 month experimental period, when the optimal stimulation site(s) and parameters are being established, patients will be assessed for adverse effects and change in mental state by the study research clinician weekly.
d. The study research clinician or deputy will be directly contactable by telephone in between these assessments 24/7.
e. If adverse events arise or mental state worsens, they will be seen urgently by the study team and be readmitted to NHNN if necessary.
f. The local mental health crisis team will be aware of the study and act as an emergency safety net for contact and assessment.
g. Following the completion of the study all patients will be seen by the DBS team at least every 6 months for the rest of their lives unless DBS is permanently switched off.

8.3. Neurosurgery: In the last 9 years over 300 patients with movement disorders and chronic pain syndromes have undergone DBS in our unit at Queen Square, The senior surgeon (MH) has over 23 years' experience with stereotactic neurosurgery in Sweden and the NHNN, including anterior capsulotomy for OCD and STN DBS for Parkinson's disease. The other surgeon has experience with more than 150 DBS procedures in several brain targets for many conditions including Parkinson's disease, dystonia, deafferentation pain, cluster headache, Tourette's syndrome and essential tremor. There have been no fatalities or clinically relevant haemorrhages. The safety and efficacy data emerging from the Unit of Functional Neurosurgery have been described as "a new benchmark" in functional neurosurgery [42]. Implantation of 2 electrodes (one on each side) is standard. The technique used for electrode implantation is such that the added surgical risk by implanting 4 electrodes rather than two is negligible - some of the Unit's movement disorders patients have needed implantation of 4 electrodes, 2 in each hemisphere in different targets, without complications, for example in dystonia (pallidum and thalamus) and Parkinson's disease (pallidum and subthalamic nucleus). There are also many examples in the literature of patients undergoing double target electrode implantation and stimulation safely and with significant efficacy. Such double targets have included: pedunculopontine nucleus and STN; motor and limbic areas of internal pallidum; associative areas of both thalamus and internal pallidum [43, 44, 45, 46].

9. Research team and environment

9.1. The research team is composed of a network of clinicians and neuroscientists.

9.2. Academic psychiatrists working for the NHS National Specialised OCD Service: Dr Drummond directs an inpatient service for severe OCD focusing on CBT; Prof Fineberg provides a dedicated outpatient service for severe OCD focusing on psychopharmacology; Prof Matthews leads the Advanced Interventions Service, Dundee, which offers cingulotomy for severe OCD. All patients will be assessed and recruited from this service. The CBT component of the proposal will be provided by Dr Drummond's team.

9.3. Cognitive neuroscientists: Profs Sahakian and Robbins are world leaders in the neurobiology of OCD; in collaboration with Prof Fineberg, they have defined cognitive phenotypes of the OCD spectrum and identified their neural substrates. They will provide essential advice on cognitive testing, including the use of tasks specifically developed by them for OCD, and analysis and interpretation of the data.

9.4. The DBS team have an established record in deep brain stimulation surgery. Neurologists, Dr Foltynie & Dr Limousin, have led the development of the systematic evaluation of positive and negative symptomatic responses to DBS. Neurosurgeons, Mr Zrinzo & Prof Hariz, have developed techniques to ensure that consistent electrode targeting can be performed safely with millimetre precision. The clinical team have extensive experience in the management of DBS patients including the cognitive aspects (Prof Jahanshahi). Prof Joyce has extensive experience in managing severe and complex mental illness, including OCD, and runs a neuropsychiatry service at The National Hospital. Prof Joyce routinely assesses candidates for DBS as part of their multidisciplinary preoperative assessment. The Sobell Department of Motor Neuroscience and the National Hospital for Neurology & Neurosurgery provides the ideal environment for the conduct of this research, incorporating the facilities to perform the DBS surgery and clinical evaluations.

9.5. The UCL R+D department will be involved in all necessary communications with the regulatory authorities.

10. Service user involvement, public communication and scientific dissemination: The Patient Information Sheet has been checked against the protocol by a service user with severe OCD and suggested amendments made. Communication of information to the lay public will be undertaken via UCL Media Relations. Results will be presented at national and international meetings and published in peer-reviewed journals.

11. Confidentiality: Data will be collected in both written and electronic format. Written data will be stored in a locked filing cabinet controlled by Professor Joyce. Electronic data will be held anonymously using an ID code. No personal data will be stores electronically. The ID code key will be held in a locked draw controlled by Professor Joyce.

12. Complaints: In the event of complaint about the conduct of the study, the complaint should be reported immediately to the Joint Research Office research-incidents@ucl.ac.uk who will decide which complaints policy applies and who will be the lead organisation. The NHS complaints

policy can only apply where the research subject is recruited through an NHS Trust. In other circumstances the UCL complaints policy will apply.

13. **Insurance:** University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. Potential insurance claims will also be reported immediately to the Joint Research Office.

14. **Archiving:** Each participating site recognises that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at UCL for 20 years from the study end.

15. **Data transfer (handling, processing and storage):** In the study, data generated during the assessments described in section 6 of this protocol will be collected from participants in accordance with the patient consent form, patient information sheet and section 5 of this protocol. The written and electronic patient data will be appropriately sent to Professor Eileen Joyce, Institute of Neurology, Queen Square, London WC1N 3BG for statistical analysis, and Professor Joyce will act as the data controller of such data for the study. Professor Eileen Joyce, Institute of Neurology, Queen Square, London WC1N 3BG will process, store and dispose of written and electronic patient data in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. Written patient data will be stored centrally at The Institute of Neurology in a locked filing cabinet controlled by the Chief Investigator. Electronic patient data will stored in anonymised form. The written and electronic patient data will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent.

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