Deep Brain Stimulation has state-dependent effects on motor connectivity in Parkinson's Disease

Abbreviated title: Motor connectivity during STN DBS

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Pages: 30

Figures: 6 (+ 1 Supplemental Figure)

Tables: 2 (+ 1 Supplemental Table)

Word count: Abstract = 328; Introduction = 582; Discussion = 1860.

Abstract

Subthalamic nucleus Deep Brain Stimulation (STN DBS) is an effective treatment for advanced Parkinson's disease (PD), however its therapeutic mechanism is unclear. Previous modelling of functional MRI (fMRI) data has suggested that DBS has modulatory effects on a number of basal ganglia pathways. This work uses an enhanced data collection protocol to collect rare functional MRI data in patients with STN DBS.

Eleven patients with PD and STN DBS underwent functional MRI at rest and during a movement task; once with active DBS, and once with DBS switched off. Dynamic causal modelling and Bayesian Model Selection were first used to compare a series of plausible biophysical models of the cortico-basal ganglia circuit that could explain the fMRI activity at rest in an attempt to reproduce and extend the findings from our previous work. General linear modelling of the movement task fMRI data revealed DBS-associated signal increases in the primary motor and cerebellar cortices. Given the significance of the cerebellum in voluntary movement, we then built a more complete model of the motor system by including cerebellar-basal ganglia interactions, and compared the modulatory effects DBS had on different circuit components during the movement task and again using the resting state data.

Consistent with previous results from our independent cohort, model comparison found that the rest data were best explained by DBS-induced increased (effective) connectivity of the cortico-striatal, thalamo-cortical and direct pathway and reduced coupling of STN afferent and efferent connections. No changes in cerebellar connectivity were identified at rest. In contrast, during the movement task, there was functional recruitment of subcortical-cerebellar pathways, which were additionally modulated by DBS, as well as modulation of local (intrinsic) cortical and cerebellar circuits.

This work provides *in vivo* evidence for the modulatory effects of STN DBS on effective connectivity within the cortico-basal ganglia loops at rest, as well as further modulations in the cortico-cerebellar motor system during voluntary movement. We propose that DBS has both behaviour-independent effects on basal ganglia connectivity, as well as behaviour-dependent modulatory effects.

Keywords: Parkinson's disease; Deep brain stimulation; functional MRI; connectivity; basal ganglia

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become an established treatment for those with Parkinson's Disease (PD) (Limousin *et al.*, 1995, 1998; Deuschl *et al.*, 2006). Trials of DBS to treat other neurological and psychiatric diseases are under investigation, leading many to question its mechanism of action so as to maximise its utility (Laxton *et al.*, 2010; Holtzheimer and Mayberg, 2011; Gratwicke *et al.*, 2013). Clinically, DBS can mimic the effect of an ablative lesion, leading many to suggest that DBS "inhibits activity" in the same way; a theory appealing to firing rate-based models of basal ganglia circuitry (Albin *et al.*, 1989; DeLong, 1990; Beurrier *et al.*, 2001; Meissner *et al.*, 2005). However, both animal and computational models suggest that stimulation has a myriad of effects on different neuronal elements (Perlmutter and Mink, 2006; Deniau *et al.*, 2010; McIntyre and Hahn, 2010; Vedam-Mai *et al.*, 2012), including frequency-dependent reductions in STN firing rates (Beurrier *et al.*, 2001; Welter *et al.*, 2004; Meissner *et al.*, 2005), normalisation of cortical phase-amplitude coupling (de Hemptinne *et al.*, 2013, 2015), and both inhibition and excitation of downstream targets (Maurice *et al.*, 2003). Human electrophysiology has similarly revealed reductions in STN beta power (Kühn *et al.*, 2008; Eusebio *et al.*, 2011), and both neuroimaging and electroencephalography have demonstrated altered activity at the level of the cortex (Limousin *et al.*, 1997; Ceballos-Baumann *et al.*, 1999; Boertien *et al.*, 2011; Li *et al.*, 2012), suggesting that neuromodulatory effects, whether direct or indirect, are not limited to the target nucleus.

We have previously identified DBS-related changes in cortico-basal ganglia *effective* connectivity; i.e. changes in the way regions within the cortico-basal ganglia network impact on one another. Specifically, modelling of the blood oxygen level dependent signal (BOLD) revealed stimulation-related decreases in STN afferent (both hyperdirect and indirect) and efferent coupling, as well as increases in cortico-striatal, thalamo-cortical and direct pathway coupling whilst patients lay at rest (Kahan *et al.*, 2014). In addition, there are reports of DBS-associated increased functional connectivity in the motor cortex and premotor area using eigenvector centrality

analysis (Mueller *et al.*, 2013, 2018; Holiga *et al.*, 2015), and positron emission tomography studies have demonstrated that DBS reduces the expression of pathological patterns of functional connectivity such as the Parkinson's disease covariance or tremor patterns (Asanuma *et al.*, 2006; Wang *et al.*, 2010; Ko *et al.*, 2013).

Functional MRI in DBS patients has been largely avoided due to concerns about the effects of magnetic fields on the implanted DBS circuit. Until now, fMRI data has been collected exclusively using a single channel head-transmit/receive coil (Jech *et al.*, 2001, 2012, Kahan *et al.*, 2012, 2014). We developed a MRI protocol employing body-transmit MRI and a 12-channel receive coil (Kahan *et al.*, 2015), theoretically yielding an improved signal-to-noise ratio, whilst minimising any MR-induced electrode heating to <1.0˚C, in line with international guidelines.

In the current study, we model data from a cohort of PD patients with chronically implanted STN DBS, collected under our improved scanning protocol. We first ask whether we can reproduce previously identified changes in basal ganglia coupling in the resting state. We then use the data collected during a movement task to enhance the construction of our motor system models and explore whether there is a difference between DBS-related modulatory effects on effective connectivity during the "resting" state, and during the movement task state.

Methods & materials

This study was approved by the National Hospital and UCL Institute of Neurology Joint Ethics committee (09/H0716/51). All participants provided written informed consent in accordance with the Declaration of Helsinki.

Experimental design

We used a cross-sectional, unblinded, randomised, cross-over design to explore the effects of STN DBS on "resting state" effective connectivity, and voluntary movement-related brain activity and connectivity in patients with PD.

Patients

Eleven patients (ten males, one female) who met Queen Square Brain Bank criteria for idiopathic PD were recruited (Table 1). Stimulation parameters had been

previously optimised to clinical responses. Medication was withdrawn for 10-12 hours (overnight) before scanning. Inclusion was limited to those patients who could tolerate lying flat with minimal head tremor, while being both off medication and off stimulation. Unified Parkinson's Disease Rating Scale part III (UPDRS-III) motor scores were recorded both ON and OFF stimulation before scanning. Stimulation settings and system impedances were noted. UPDRS-III sub-scores were calculated for each patient including hemi-body scores (the sum of all lateralised items in the scale, including rigidity, bradykinesia and tremor).

MRI data acquisition

Onsite tissue-equivalent test-object thermometry experiments confirmed that the specific hardware and MRI sequences used in this study were safe to be used in patients with implanted Medtronic ActivaPC^{TM} DBS systems. Additionally, we confirmed that the MRI environment did not interrupt implanted pulse generator (IPG) function (Kahan *et al.*, 2015). Scanning was performed in a Siemens Avanto 1.5T MRI scanner (Siemens, Erlangen, Germany) using the body-transmit coil and a 12-channel receive-only head coil. This differs from our previous studies using a transmit-receive head coil (Kahan *et al.*, 2012, 2014). The decision to modify our protocol was motivated by theoretical signal-to-noise benefits. The specific absorption ratio (SAR) in the head was limited to <0.4W/Kg.

Patients were scanned with their stimulation ON and OFF, the order of which was randomised using a random number generator. Patients received three scans in each stimulation condition in addition to standard localiser and field map scans; (1) anatomical T1, (2) resting state fMRI, (3) movement task fMRI (see Supplementary Materials for sequence parameters). Patients entered the scanner with their DBS ON, and were either switched OFF or maintained ON before scanning, resulting in a ~10 minute latency between DBS manipulation and undergoing fMRI. During resting state fMRI, patients were told to lie in the scanner with their eyes closed and not to fall asleep. The movement task fMRI was based on a paradigm used previously (Kahan *et al.*, 2012). In brief, patients heard an audio stimulus ("beep") at a random interval (between 1-3 s) throughout the session, in addition to audio commands alternating between "rest" and "go" every 30 seconds. During "go" blocks, patients were instructed to perform a joystick movement with their left hand as fast as possible each time they heard a beep. A movement entailed displacing the handle from the centre in

a direction of their choice, and then returning it to the centre. Additionally, patients were instructed to plan their next movement between each beep. During "rest" blocks, patients were instructed to rest their hand on the joystick and ignore the beeps. Patients were given practice runs before entering the scanner, and were monitored throughout to ensure they were performing the task correctly. There were 9 rest and 8 movement blocks in each session. The table was then withdrawn from the magnet, keeping the patient's head in the head coil, and their DBS was switched to the opposite condition. Both patient and experimenter were unblinded to the DBS condition due to the magnitude of the treatment effect.

Processing the fMRI data

All analyses were performed using Statistical Parametric Mapping (SPM12b; http://www.fil.ion.ucl.ac.uk/spm). The first five scans of each session (one rest and one movement session per stimulation condition per subject = four sessions per subject) were removed and data were corrected for field inhomogeneity using the field maps. Data were then realigned and unwarped to account for any head movements throughout the fMRI sessions. Imaging data were then coregistered with anatomical scans, segmented, normalised to MNI space, spatially smoothed using a Gaussian kernel (8mm full-width half maximum) and quality controlled by visual inspection.

Experiment I: Are previously documented effects of STN DBS on resting state connectivity reproducible?

Resting state fMRI data were initially treated identically to those described in (Kahan *et al.*, 2014), with the exception that only right hemisphere data were analysed.

The resting state data from each stimulation condition were concatenated and modelled using a General Linear Model (GLM), which was comprised of a discrete cosine basis set containing functions with frequencies characteristic of resting state fluctuations (0.0078–0.1 Hz), a regressor encoding the effect of DBS, six nuisance regressors from each session capturing head motion, and confound time-series from extra-cerebral compartments.

Preparing the volumes of interest (VOIs)

Analysis of motor task fMRI (see experiment II) yielded functionally defined M1 coordinates for each subject, which were used to guide extraction of functionally

relevant data from the resting state dataset. The resting state M1 BOLD signal was summarized with the principal eigenvariate (adjusted for confounds: head movements and extra-cerebral compartments) of a sphere (radius 4 mm) of voxels centred on the subject-specific M1 coordinate.

Basal ganglia masks were created using probabilistic white matter connectivity atlases (Behrens *et al.*, 2003; Tziortzi *et al.*, 2014), and were used to restrict selection of subcortical voxels to regions of the putamen and thalamus that exhibit strong structural connectivity with M1 at a population level. A psychophysiological interaction (PPI) (Friston *et al.*, 1997) between resting state M1 activity and DBS, using the putamen and thalamus masks, was employed to define the voxels in the putamen and thalamus to be included in our connectivity analysis. Use of the PPI effectively guided data extraction towards voxels with a DBS dependent relationship with M1 voxels. The BOLD data from the putamen and thalamus respectively were extracted as above, centred on the peak T-statistic within each mask, producing three VOIs per subject (M1, putamen, thalamus). BOLD data from the STN were not considered because of its small size and loss-of-signal artefact caused by the DBS electrode.

Dynamic Causal Modelling (DCM)

DCM aims to explain observed neuroimaging data in terms of coupling (i.e., effective connectivity) within and between a network of brain regions (Friston *et al.*, 2003). Coupling in DCM is directed, and summarises the causal effect one region exerts on either itself (intrinsic), or on another region (extrinsic) – known as effective connectivity. This contrasts with functional connectivity, which usually concerns the correlations between two regions. For an introductory overview of DCM, see (Kahan and Foltynie, 2013).

The VOIs were used to construct a series of 32 DCMs (per subject) representing different hypothetical architectures. Two-state (Marreiros *et al.*, 2008) stochastic DCM for functional MRI (Li *et al.*, 2011) was used, endowing each node with excitatory and inhibitory subpopulations in receipt of noisy fluctuating inputs. The STN was modelled as a hidden node, whose noise precision (given the electrode artefact) was effectively zero, forcing the inversion routine to ignore the recorded signal from the node when estimating model parameters. In other words, although a

node with the connectivity fingerprint of the STN was included, only BOLD data from the other nodes was used to fit the model. Pallidal nodes were not included; rather, their connections were collapsed to simplify the model. Thus, the direct pathway was summarised as an excitatory connection from the putamen to the thalamus, and indirect pathway as an excitatory putamen-STN connection, and an inhibitory STN-thalamus connection. Although there is evidence for polysynaptic connections from the STN to thalamus that could result in excitatory coupling, for simplicity these connections were not modelled. The hyperdirect pathway was defined as the M1-STN connection, and the thalamo-cortical pathway was represented by the connection from the thalamus to M1. The 32 DCMs differed with regards which subset of connections were modulated by active DBS, and are shown graphically in Supplemental Figure 1.

Models were inverted using generalized filtering (Friston *et al.*, 2010; Li *et al.*, 2011), providing an estimate of the coupling parameters and model evidence. The 32 models from each of the 11 patients entered a Bayesian model selection (BMS) procedure (fixed effects assumptions) that compares the free energy of each model, taking into account the model fit and complexity (Stephan *et al.*, 2009; Penny *et al.*, 2010; Rigoux *et al.*, 2013). The model with the highest model evidence was considered the group winner. Winning model coupling parameters from each patient were then compared using two-tailed paired T tests to test for the effects of DBS. Significance was set at $p<0.05$.

Experiment II: The effect of STN DBS on voluntary movement-related brain activity and connectivity within the cortico-basal ganglia and cortico-cerebellar circuits

The effects of voluntary movement and DBS on regional BOLD signal

The joystick position data were interrogated and peak velocity (V_{max}), reaction time (RT), and randomness of direction choice were calculated (See Supplementary Materials). Pre-processed task fMRI data were analysed using the standard GLM framework; each subject's task sessions (one per stimulation condition) were entered into a single GLM and blocked stimulus functions were specified in each session coding the effects of voluntary movement. Head position confounds were excluded from first level GLMs due to collinearity with voluntary movement stimulus

functions. Stimulus functions were convolved with a canonical haemodynamic response function in the normal way, and the GLMs were then fitted to the data.

Three contrasts were specified; (1) the *main effect of movement*, (2) *movement x DBS interaction ON>OFF*, (3) *movement x DBS interaction OFF>ON*. The resulting T-maps from each subject were used for second-level (i.e. group) random effects inference. Clusters surviving a threshold of $p<0.05$ (family wise error corrected for multiple comparisons) at the whole-brain level were considered significant with a voxel intensity threshold of $p<0.001$ uncorrected.

Dynamic Causal Modelling of movement-related BOLD responses

The GLM was rotated for DCM analysis as previously described (Kahan *et al.*, 2014), and VOIs were extracted using the *movement x DBS (ON>OFF)* contrast and adjusted for confounds, while retaining the effects of interest (i.e. the *main effects of movement* and *DBS*, and the *movement x DBS interaction*). The regional BOLD signal from each node was summarised with the principal eigenvariate of a sphere of voxels (radius 4 mm) centred on the voxel within each mask demonstrating the largest *movement x DBS interaction*. Each structure was masked separately as described in Experiment I. The cerebellar mask was a spherical mask centred on the group maxima taken from the second-level analysis of *movement x DBS* interaction. This produced four volumes of interest (VOIs) per subject (M1, putamen, thalamus, cerebellum – see Supplemental Table 1 coordinates). Data from the M1, putamen, and thalamus were all contralateral to the limb moved, whereas data from cerebellum was from the midline and ipsilateral to the movement.

The basal ganglia loop was as modelled in Experiment I with additional connections projecting to and from the cerebellar node. The model comparison space posed the following questions; (1) is cerebellar connectivity (DCM A-matrix) best modelled as purely cortico-cerebellar coupling, subcortical-cerebellar coupling, or both, and (2), is the interaction between movement and DBS best explained by modulatory effects (DCM B-matrix) on cortico-cerebellar coupling, subcortical-cerebellar coupling, intrinsic coupling, or a combination of all three. The main effect of voluntary movement entered all the models as a driving input (DCM C-matrix) into M1 - see Figure 1.

Models were subsequently compared across all subjects using BMS (fixed effects assumptions). As previously, the model with the highest model evidence was considered the group winner, from which coupling parameters from each patient were extracted and compared using two-tailed paired T tests.

Experiment III: The effect of STN DBS on resting state connectivity including cortico-basal ganglia and cortico-cerebellar circuits

In order to compare connectivity during the movement task state with the resting state, the resting state data underwent a repeat DCM analysis in an identical way to that described in Experiment II, to incorporate the potential role of cerebellar connectivity. VOI locations from Experiment II were used to guide resting state VOI specification, and the same model space, posing the same questions of the data. The only difference was the absence of any explicit driving inputs (DCM C-matrix). Models and coupling parameters were compared in the same way.

Results

Clinical effect of STN DBS

All patients showed significant clinical improvement. UPDRS-III scores reduced from an average (± standard deviation) of 50 (±15.1) OFF DBS, to 23.9 (±10.6) ON DBS, equivalent to a mean improvement of 52.2% (±12.2%) ($p<0.05$). Improvements were observed across all sub-domains, and across both hemi-bodies (Figure 2).

Experiment I: Are the effects of STN DBS on resting state connectivity in the basal ganglia motor loop reproducible?

As previously, BMS revealed model 32 to be the most likely generator of the BOLD data at the group level. This model included DBS-related modulatory effects on the cortico-striatal, direct, indirect, hyperdirect and thalamo-cortical pathways. Statistically significant changes in coupling associated with DBS were detected in all connections. The magnitudes of change were much smaller when the coupling involved the STN, as was initially reported in (Kahan *et al.*, 2014). DBS was associated with increased coupling of the cortico-striatal, direct and thalamo-cortical pathways, and reduced coupling of the STN afferents and efferents – see Figure 3.

Experiment IIa: The effect of STN DBS on peak velocity and reaction time

STN DBS significantly increased V_{max} ($p < 0.05$), but improvements in RT were only trend significant ($p = 0.06$) – Figure 4. To confirm the validity of our analyses, we tested for correlations between V_{max} and total UPDRS-III, and bradykinesia sub-scores ON and OFF DBS. Only correlations between V_{max} and bradykinesia OFF scores were statistically significant (ON: $r = -0.59$, $p = 0.056$; OFF: $r = -0.62$, $p = 0.042$) suggesting that V_{max} was better related to bradykinesia than total UPDRS-III scores. No significant effect on directional randomness was detected (mean ON RNG: 0.54, mean OFF RNG: 0.56, $p = 0.542$).

Experiment IIb: The effect of STN DBS on regional voluntary movement-related BOLD responses

Tests for the *main effects of movement* contrast at the group level revealed characteristic movement task activations, consistent with the PET and fMRI literature that have employed similar tasks. We did not detect any obvious stigmata of motion artefact (e.g. cortical 'rims' or spurious ventricular activations).

The group-level *movement x DBS ON>OFF* contrast revealed two large clusters that survived whole brain correction, precisely located in the precentral gyrus hand area, and midline cerebellum (see Table 2, and Figure 4). We did not detect any significant DBS-related reductions in movement-induced regional response using the OFF>ON contrast. The finding of the cerebellar cluster motivated the inclusion of cortico-cerebellar coupling into our previously reported basal ganglia DCM.

Experiment IIc: The effect of STN DBS on cortico-basal ganglia and cerebellar dynamics during voluntary movements

BMS revealed model 10 to be the most likely generator of the BOLD data at the group level (posterior probability >99%). This model included the cerebellum reciprocally connected to both M1 and the basal ganglia, suggesting that voluntary movements engage both pathways. DBS-related modulatory effects impacted on the cortico-striatal, direct, indirect, hyperdirect and thalamo-cortical pathways, as well as both M1 and cerebellar intrinsic coupling, and the reciprocal subcortical connections, but not the cortico-cerebellar projections. DBS was associated with statistically significant changes (corrected using the Bonferroni procedure) in coupling at the group level for the M1 and cerebellar intrinsic coupling, the cerebellar projection to

the putamen, the STN afferent projections, and the STN efferent to the thalamus. DBS decreased the self-inhibitory tone of both M1 and cerebellum, and increased coupling in all other connections except for STN projections to the thalamus – Figure 5.

Experiment III: The effect of STN DBS on cortico-basal ganglia and cerebellar dynamics during rest

In contrast to the movement task state, BMS revealed model 1 to be the most likely generator of the resting state BOLD data at the group level (posterior probability >99%). This model had the cerebellum reciprocally connected to M1, with no significant cerebellar-subcortical resting state coupling. DBS-related modulatory effects impacted on the cortico-striatal, direct, indirect, hyperdirect and thalamo-cortical pathways, with no effects on any of the cerebellar pathways or local circuitry. Statistically significant changes in coupling associated with DBS were detected in the STN afferent and efferent connections at the group level (corrected using the Bonferroni procedure). The directions of change in the basal ganglia circuit were identical to those found in Experiment I – Figure 5.

As an exploratory analysis, we then looked for correlations between coupling strengths of connections modulated by DBS during the movement task, and the V_{max}. We then repeated this for coupling strengths calculated during the resting state. Correlations were found between V_{max} and coupling in the M1 and cerebellar self-inhibition, the STN afferent projections, and the STN projection to the cerebellum. Of note, with regards the STN afferent connections, stronger coupling during movement were associated with a greater V_{max}. However, when the same correlations were explored during rest, stronger coupling at rest were associated with a slower V_{max} (during movement) – Figure 6.

Discussion

In this series of experiments, we use rare *in vivo* human data from patients with PD and chronically implanted therapeutic STN DBS, to expand on our previous modelling of the basal ganglia, allowing us to dissect the effects of DBS on functional integration within the motor system.

STN DBS is associated with reproducible changes in basal ganglia coupling at rest

Data from this independent patient cohort treated in the same centre, reveal that STN DBS is associated with strengthening of the direct, cortico-striatal and thalamo-cortical coupling, and a reduction in hyperdirect, striato-STN and STN-thalamic coupling whilst patients lie at rest. This appears to remain largely true, even when cerebellar dynamics are also modelled, although the changes in cortico-striatal, direct and thalamo-cortical pathways did not survive our conservative statistical thresholding for multiple comparisons. The reduction of both afferent and efferent effective connectivity of the STN appears consistent with neural field models of the basal ganglia and effects of DBS, which demonstrate DBS-related mean membrane potential perturbations and reduction in network loop gains (Müller and Robinson, 2018). Our previous study (Kahan *et al.*, 2014) recruited a cohort who were slightly older (mean age 57 vs. 53), and who had been undergoing chronic therapeutic stimulation for longer (mean time since surgery 38 months vs. 18 months). Data collection also differed; this cohort was scanned using the body-transmit coil and 12-channel head receive-only coil (Kahan *et al.*, 2015), whereas previous data employed a transmit-receive head coil. Analysis of this cohort was limited to the right hemisphere because only right hemisphere functional localisation data was available, which effectively constrained our *n* to 11 hemispheres. Despite these differences, the modelled effective connectivity parameters, and the modulatory effects related to DBS were consistent.

Therapeutic STN DBS improves motor performance and increases motor-evoked responses in M1 & cerebellum

This study found STN DBS significantly increased BOLD activity during voluntary movements in both M1 and the cerebellum, as has been previously demonstrated using $H_2{}^{15}O$ PET in unilateral DBS patients (Payoux *et al.*, 2004). STN DBS has been shown to produce both increased and decreased evoked responses in different parts of the lateral cerebellar cortex during movements (Grafton *et al.*, 2006), and changes in *resting* cerebellar metabolism have been widely reported, in both the Vermis (Sestini *et al.*, 2002; Asanuma *et al.*, 2006; Cilia *et al.*, 2009; Bradberry *et al.*, 2012), and lateral cerebellar cortex (Hershey *et al.*, 2003; Vafaee *et al.*, 2004; Nagaoka *et al.*, 2007; Tanei *et al.*, 2009; Wang *et al.*, 2010; Garraux *et al.*, 2011; Volonté *et al.*,

2012). The cluster detected in this cohort is relatively medial, however probabilistic cerebellar atlases (Diedrichsen *et al.*, 2009) suggest that the peak cluster is centred on the right cerebellar V (probability 83%). As is evident from Figure 2, a number of the patients saw significant improvements in tremor with active STN DBS. Tremor has previously been associated with increased activity in both M1 and cerebellum (Helmich *et al.*, 2011; Mure *et al.*, 2011), and improvement during active DBS may have led to an underestimation of movement-related activity in both these regions, which might have contributed to the significant *movement x DBS* interaction demonstrated.

State-dependent integration of basal ganglia and cerebellar dynamics

Comparing the BMS results of data collected during a movement task, and data collected at rest revealed a number of interesting and novel insights. Firstly, during the resting state, cerebellar integration appears to engage cortico-cerebellar projections predominantly; models including subcortical pathways were less likely to generate the data at rest. This is not to say that the anatomical pathways do not exist, rather that they are not engaged. It is important to note that the anatomical substrate of our modelled cerebellar-cortical pathways are likely polysynaptic projections via the Vim/VLp thalamus (which is absent from our model). Our thalamic node, which summarises the output of the basal ganglia, would more accurately represent the VLa, VApc and VM nuclei.

In contrast, when the patient switches their behavioural state to perform a movement task, the reciprocal connections between the basal ganglia and cerebellum are additionally recruited. Anatomical evidence from primates suggests that cerebellar fibres project polysynaptically, arriving at the striatum, and connectivity from the basal ganglia to cerebellum is mediated through the STN (Hoshi *et al.*, 2005; Bostan *et al.*, 2010), and thus those specific pathways were included in our model space.

State-dependent modulatory effects of STN DBS

We also demonstrate that the modulatory effects of STN DBS appear to be similarly dependent on the behavioural state. This is most striking when looking at the effect of DBS on STN afferent coupling. During rest, DBS reduced coupling along the hyperdirect pathway and indirect pathways. This was first identified in our previous work (Kahan *et al.*, 2014), where it was noted that although STN DBS reduced

hyperdirect coupling, patients with stronger hyperdirect coupling had fewer symptoms. Our exploratory correlation analysis (Figure 6), contradicts this finding at rest, showing that stronger hyperdirect coupling during rest is associated with a slower peak velocity in our objective movement task. During movement however, STN DBS increases both hyperdirect and striatal-STN afferents, and correlation analysis reveals stronger coupling of both of those pathways is associated with faster peak velocities.

In addition, models including modulatory effects on intrinsic coupling (i.e. local self-inhibitory tone) were more favourable than without, and intrinsic coupling in both the cortex and cerebellum was correlated (albeit weakly) with movement speed. Dirkx et al., have seen similar results when exploring the impact of levodopa on resting tremor and intrinsic Vim coupling (Dirkx *et al.*, 2016, 2017). Of additional interest would be to identify how these connectivity changes relate to changes in beta (13-30Hz) phase and cortical broadband gamma activity (50-200Hz), also implicated as relevant to the mechanism of action of STN DBS (de Hemptinne *et al.*, 2013, 2015).

Limitations

A prominent source of noise in fMRI is motion of the subject during scanning, producing both spin-history and susceptibility-by-movement artefacts (Friston *et al.*, 1996; Wu *et al.*, 1997; Andersson *et al.*, 2001). As a means of nullifying this, specialist padding was used to fixate the patients' heads in the MRI head coil. Furthermore, data were first realigned and unwarped. Despite our efforts, we observed a degree of collinearity between head position and the *main effect of movement* condition. As a result, head position confounds were explicitly excluded from first level GLMs in Experiments II and III to maximise the efficiency with which voluntary movement responses were estimated. This efficiency would have been compromised by the inclusion of correlated or collinear head motion confounds (Farrar and Glauber, 1967; Friston *et al.*, 1994). This said, the DCM analyses are in principle less susceptible to instantaneous signal fluctuations related to motion, because DCM can only model the delayed haemodynamic response (Friston *et al.*, 2003). Nevertheless it is important that the results of Experiment II are interpreted in the context of a potential head motion confound (this applies only to the main effects of movement, not the interaction with stimulation, or the corresponding modulatory effects of DBS on connectivity).

Our models make a number of simplifying assumptions, most notably the absence of pallidal dynamics, and the sparsity of connections amongst the nodes. DCM does not necessarily quantify monosynaptic coupling, thus not all intermediate nodes are required to estimate effective connectivity between any two nodes. We have modelled DBS as a modulatory effect on coupling, not as a driving input to individual nodes. Thus, changes in coupling parameters do not inform us of how DBS reaches modulated nodes, or why it modulates them, rather they represent the consequence of the active DBS.

Additionally, due to signal drop-out around the electrode, it was not possible to record BOLD data from the STN itself. Therefore, we modelled the STN as a hidden node, enabling inference on its afferents and efferents based on the influence they exert on nodes from which precise recordings were available (David *et al.*, 2011; Marreiros *et al.*, 2012; Kahan *et al.*, 2014). In principle, our hidden node could be any brain region with the connectivity fingerprint specified by the model (i.e. any brain region excited by both M1 and the putamen, and that exerts inhibition on the thalamus). Given the anatomical and electrophysiological literature on the functional anatomy of the basal ganglia, our hidden node was attributed to the STN.

We assumed that within our patient cohort, STN DBS consistently modulates the same subset of connections. In other words, the model underlying each patient's data is the same (i.e. fixed). The degree of modulation of each connection however, varies from patient to patient randomly. This is in contrast to assuming that different patients have different connections modulated by DBS, as well as varying degrees of modulation. As such, a fixed effects BMS analysis was chosen as the most appropriate means of identifying the most likely single generative model given the observed data. By performing a random effects BMS analysis, we would be implicitly supporting what we feel to be an untenable assumption (Friston *et al.*, 1999, 2015; Stephan *et al.*, 2009; Rigoux *et al.*, 2013; Litvak *et al.*, 2015). In line with this, we used paired T-tests to explore the effect of DBS in relation to *random effects* on the parameters over subjects.

Medication was withdrawn for 10-12 hours before scanning, with a view to looking specifically at the effects of DBS, and maximising the clinical contrast between the experimental conditions. In other words, had we performed the study in the context of medications, not only would the results be confounded by the pharmacodynamics of

the medications, but also the clinical impact of DBS would be more subtle, perhaps making the neurobiological substrate more difficult to detect. The length of medication withdrawal was not empirically determined based on medication pharmacodynamics, but was pragmatic, so we cannot rule out some medication confounding effects. The impact of dopaminergic medications on the basal ganglia network has been looked at in similar studies (Dirkx *et al.*, 2017), but the specific effects on our proposed model require further study, especially given the substantial variability in medication doses in our small cohort.

We were able to recruit a typical cohort of PD patients with STN DBS, however it should be noted that the patients were all able to travel a short distance to the hospital in the morning having not had their morning medications, lie relatively still, and tolerate being in the scanner for 1-2 hours. Thus our findings might not generalise to those unable to meet such criteria.

Conclusions

We demonstrate that active STN DBS is associated with reproducible changes in effective connectivity within the cortico-basal ganglia motor loop. We then show that during voluntary movement task fMRI, active STN DBS was associated with increased activity in the primary motor cortex and midline cerebellar cortex. Modelling of this data reveals that (1) PD patients demonstrate behaviour dependent recruitment of basal ganglia – cerebellar connections, that are preferentially engaged during movement and not rest, and (2) STN DBS has behaviour dependent modulatory effects on pathways within the motor system, particularly STN afferent projections, as well as behaviour independent changes on the STN outflow to the thalamus.

Acknowledgements

The authors acknowledge the use of the UCL Legion High Performance Computing Facility (Legion@UCL), and associated support services, in the completion of this work.

Funding

This study was funded by the Brain Research trust (www.brt.org.uk). J.K. received funding from The Astor Foundation, The Rosetrees Trust, and the MHMS General Charitable Trust. T.F., L.Z., M.H. and the Unit of Functional Neurosurgery are funded by the Parkinson's Appeal and the Monument trust. T.F. also receives funding from Cure Parkinson's Trust, Parkinson's UK, John Black Charitable Foundation and the Michael J Fox Foundation. K.J.F. is funded by a Wellcome Trust Principal Research Fellowship (Ref: 088130/Z/09/Z). The work was undertaken by UCL/UCLH, who receives a proportion of funding from the UK Department of Health's NIHR Biomedical Research Centres funding scheme. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We confirm that any author affiliations or competing interests had no impact on the data.

Competing Interests

T.F., L.Z., M.H., and P.L. report that they have received honoraria from industry for invited talks. J.K. has received funding from Medtronic for academic conference travel. There are no patents, products in development or marketed products to declare.

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Figure legends

Figure 1: Experiment II and III Model Space – 12 competing models of the functional architecture underlying both the voluntary movement and resting states. For the movement fMRI data, the main effect of voluntary movement drives M1; this driving input was not present when models were fit to the resting data. Black arrows represent the recruitment of directed effective connectivity during the behavioural state. Green arrows represent modulation of effective connectivity by active DBS during the behavioural state. All models share modulatory effects on basal ganglia pathways.

Figure 2: Clinical improvements following STN DBS. All scoring was performed off medication. Higher scores confer greater impairment. Total scores were broken down into hemibody scores (not including axial scores), and into sub-domains of impairment. Blue dashed line indicates the maximum number of points in the respective sub-scale. * $p<0.05$.

Figure 3: Experiment I Model Comparisons and Coupling parameters – BMS revealed that Model 32 was the most likely generator of the data. The direction of modulatory effects on the various basal ganglia pathways are summarised by the green arrows. Red arrows represent excitatory effective connectivity, whereas blue arrows represent inhibitory effective connectivity. T tests revealed significant differences in all coupling parameters associated with active DBS. Note the difference in scale for the indirect and hyperdirect pathways compared to the direct pathway. * $P<0.05$ corrected for multiple comparisons using the Bonferroni procedure.

Figure 4: The effect of DBS on V_{max} and RT and regional BOLD activity. (A) The mean velocity plot for a single movement trial – ON and OFF compared. Cue sounds at time = 0 with joystick in central position. Positive velocity occurs when subject moves joystick away from the central position towards their chosen direction, slows to 0 at maximal displacement, then velocity is negative as the handle is returned to the centre position. (B) Mean RT and V_{max} ON and OFF stimulation. Note that RT differences are only trend significant. (C & D) Scatter plots of total UPDRS score, and bradykinesia sub-score against V_{max}. Maroon plots represent OFF values, blue plots represent ON values. Two clusters were identified as significant following whole brain correction in (E) M1 hand area contralateral to movements, and (F) midline cerebellum encompassing left crus V, vermis and right crus V & VI. Second

level SPMs overlaid on the MNI brain. SPMs are thresholded at a voxel level of $p<0.001$ (uncorrected), cluster extent threshold = 0. Additional activations at this threshold can be seen in the SMA and midbrain (E), although these did not survive cluster-wise corrected significance.

Figure 5: Model Comparisons and Coupling parameters – BMS revealed that Model 10 was the most likely generator of the movement data. Green arrows represent the pathways modulated by DBS. Black arrows represent non-modulated pathways engaged during voluntary movement. Box and whisker plots represent the between subject variability in coupling strength ON (blue) and OFF (red) DBS. BMS revealed that Model 1 was the most likely generator of the resting state data. Green arrows represent the pathways modulated by DBS. Black arrows represent non-modulated pathways engaged during rest. *$P<0.05$ (Bonferroni corrected).

Figure 6: Exploratory correlation analysis looking for relationships between coupling strength and measured peak movement velocity (V_{max}). Blue data points and lines of best fit represent DBS ON, red data points and lines of best fit represent DBS OFF. Pearson's r and p values are reported in line.

Supplemental Figure 1: Experiment 1 Model Space – The original 32 competing models in which a different subset of connections is modulated by active STN DBS. Circles represent the 4 nodes studied. ‡ The STN was included in the model but was treated as a "hidden node"; i.e., a node that BOLD data could not be recorded from, but has known involvement in network dynamics. Black arrows represent the presence of directed effective connectivity during rest. Green arrows represent modulation of effective connectivity by active DBS during rest.

Table legends

Table 1: Patient information. Patients had received chronic bilateral STN DBS for at least 3 months. Electrode implantation was performed using stereotactic T2-weighted MRI – for both preoperative targeting and immediate postoperative verification (Foltynie *et al.*, 2011; Zrinzo *et al.*, 2011), ensuring electrode contacts were well-sited within the STN. All patients received bilateral electrodes (Model 3389, Medtronic, Minneapolis) and a dual channel pacemaker ("implanted pulse generator" – IPG – ActivaPC™, Medtronic, Minneapolis) implanted in the left pectoral region. Scanning

proceeded with no adverse effects; DBS system impedances were unaffected by scanning, and following administration of medication, patients returned to their pre-scan clinical baseline. LED = daily levodopa equivalent dose, L = left, R = right. All UPDRS-III scores were conducted off medication. SD = standard deviation. Post-op = months since DBS implantation. R + L hemibody scores do not equal total score because there are additional points for axial signs that are not detailed in this table.

Table 2: Results of a group (i.e. second level) whole brain search for *movement x DBS ON>OFF* interaction. Clusters surviving cluster-wise significance (corrected using the family wise error correction for multiple comparisons = P_{FWE}) of $p<0.05$ were considered significant. Two clusters were found to be significant, one 245 voxel cluster in the cerebellum, and one 369 voxel cluster in the precentral gyrus. The three peak voxels of each cluster are reported. P_{unc} = uncorrected P values. A cerebellar atlas normalised to MNI space using FLIRT (Diedrichsen *et al.*, 2009) revealed that the cerebellar cluster encompassed the left crus V, as well as the Vermis and right-sided crus V and VI.

Supplemental Table 1: The mean coordinates of the centre of the VOIs used in DCM analysis.

Tables

Sub	Age	Hand	Post-op	LED	L hemibody		R hemibody		Total	
					OFF	ON	OFF	ON	OFF	ON
1	60	R	24	598.75	11	5	12	10	38	21
2	64	R	22	632.00	22	7	18	10	61	29
3	34	R	24	1190.00	29	12	24	11	69	30
4	43	R	5	825.00	11	7	5	1	26	12
5	50	R	28	72.00	21	11	18	8	55	28
6	43	R	7	600.00	21	13	16	11	52	31
7	49	R	37	882.00	26	14	24	15	75	45
8	52	L	25	460.00	17	2	17	7	45	12
9	58	R	12	370.00	23	8	19	7	54	22
10	61	R	9	1731.75	17	12	14	7	43	25
11	65	R	3	948.00	10	3	10	2	32	8
Mean	53		18	755.41	19	9	16	8	50	24
SD	9.7		11.2	443.50	6.3	4.1	5.7	4.0	15.1	10.6

Table 1

Cluster-wise			Peak-wise			MNI coordinates (mm)		
P_{FWE}	Voxels	P_{unc}	T	Z	P_{unc}	x	y	z
0.00180	245	9.4E-05	8.27	4.44	4.4E-06	6	-60	-18
Cluster B in Figure 4			*6.46*	*3.97*	*3.6E-05*	*4*	*-70*	*-30*
			6.36	*3.94*	*4.1E-05*	*-2*	*-60*	*-22*
0.00010	369	5.1E-06	7.79	4.33	7.4E-06	34	-22	60
Cluster A in Figure 4			*6.06*	*3.84*	*6.1E-05*	*42*	*-14*	*52*
			5.73	*3.73*	*9.5E-05*	*30*	*-22*	*70*

Table 2

VOI	Mean MNI coordinates (x,y,z mm)
M1	34, -22, 60
Putamen	27, -7, 5
Thalamus	20, -20, 9
Cerebellum	5, -60, -19

Supplemental Table 1