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Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease

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ABSTRACT

Objectives: Firstly, to identify subthalamic region stimulation clusters that predict maximum improvement in rigidity, bradykinesia and tremor, or emergence of side-effects; and secondly, to map-out the cortical fingerprint, mediated by the hyperdirect pathways which predict maximum efficacy.

Methods: High angular resolution diffusion imaging in twenty patients with advanced Parkinson's disease was acquired prior to bilateral subthalamic nucleus deep brain stimulation. All contacts were screened one-year from surgery for efficacy and side-effects at different amplitudes. Voxel-based statistical analysis of volumes of tissue activated models was used to identify significant treatment clusters. Probabilistic tractography was employed to identify cortical connectivity patterns associated with treatment efficacy.

Results: All patients responded well to treatment (46% mean improvement off medication UPDRS-III [$p < 0.0001$]) without significant adverse events. Cluster corresponding to maximum improvement in tremor was in the posterior, superior and lateral portion of the nucleus. Clusters corresponding to improvement in bradykinesia and rigidity were nearer the superior border in a further medial and posterior location. The rigidity cluster extended beyond the superior border to the area of the zona incerta and Forel-H_2 field. When the clusters where averaged, the coordinates of the area with maximum overall efficacy was $X = -10(-9.5)$, $Y = -13(-1)$ and $Z = -7(-3)$ in MNI(AC-PC) space. Cortical connectivity to primary motor area was predictive of higher improvement in tremor; whilst that to supplementary motor area was predictive of improvement in bradykinesia and rigidity; and connectivity to prefrontal cortex was predictive of improvement in rigidity.

Interpretation: These findings support the presence of overlapping stimulation sites within the subthalamic nucleus and its superior border, with different cortical connectivity patterns, associated with maximum improvement in tremor, rigidity and bradykinesia.

1. Introduction

Subthalamic nucleus (STN) high frequency stimulation is an established treatment in selected patients with advanced Parkinson's disease (PD) (Krack et al., 2003; Limousin et al., 1995; A. Williams et al., 2010). The STN is thought to comprise functional subdivisions implicated in motor, associative and limbic functions with degrees of overlap (Garcia-Garcia et al., 2016; Haynes and Haber, 2013; Lambert et al., 2012; Nakano et al., 1990; Nambu et al., 1996, 1997). The motor subdivision occupies the so-called 'dorsolateral' aspect; nevertheless, the most

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Abbreviations

AC	Anterior commissure
BEDPOSTX	Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques X
BET	Brain extraction tool
CI	Confidence Interval
CON	Connectivity
DBS	Deep brain stimulation
DF	Degrees of freedom
DICOM	Digital Imaging and Communications in Medicine
DWI	Diffusion weighted imaging
EVs	Explanatory variables
FLIRT	FMRIB's linear image registration tool
FMRIB	Oxford Centre for Functional MRI of the Brain
FNIRT	FMRIB's non-linear image registration tool
FoV	Field of view
FSL	FMRIB's software library
GLM	General linear model
GPU	Graphics processing unit
HARDI	High angular resolution diffusion imaging
IPG	Implantable pulse generator
LC	Levodopa challenge
LEDD	L-DOPA equivalent daily dose
M1	Primary motor cortex
MMS	Mini-mental score
MNI	Montreal neurological institute
MPRAGE	Magnetization-prepared rapid gradient-echo
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NHNN	National Hospital for Neurology and Neurosurgery
NIfTI	Neuroimaging Informatics Technology Initiative
PC	Posterior Commissure
PFC	Prefrontal cortex
SAR	Specific absorption rate
SD	Standard deviation
SE	Standard error
SMA	Supplementary motor area
SNR	Signal-to-noise ratio
SSEPI	Single-shot Echo Planar Imaging
STN	Subthalamic nucleus
TFCE	Threshold-free cluster enhancement
TMS	Transcranial magnetic stimulation
UPDRS	Unified Parkinson's disease rating scale
VBM	Voxel based morphometry
VTA	Volume of tissue activated
ZI	Zona incerta

effective target location has been contended. Authors have argued that contacts within the 'dorsolateral-STN' give the biggest improvement in UPDRS-III(Johnsen et al., 2010; Weise et al., 2013; Wodarg et al., 2012); others have maintained that contacts 'dorsal' to the STN, in the zona incerta (ZI) area and Forel-H_2 field, have superior efficacy (Cintas et al., 2003; Godinho et al., 2006; Maks et al., 2009; Plaha, 2006; Vergani et al., 2007; Voges et al., 2002; Yelnik et al., 2003; Zheng et al., 2009). A third group found both locations, or border contacts to be equally effective (Garcia-Garcia et al., 2016; Hamel et al., 2003; Herzog et al., 2004; Lanotte et al., 2002; Yokoyama et al., 2001; Zonenshayn et al., 2004).

This discrepancy is attributed to several factors. One is reliance on surrogate markers such as microelectrode recording (Cintas et al., 2003; Godinho et al., 2006; Hamel et al., 2003; Lanotte et al., 2002; Maks et al., 2009; Vergani et al., 2007; Weise et al., 2013; Yokoyama et al., 2001; Zonenshayn et al., 2004) and non-specific atlas coordinates or deformable atlases (Garcia-Garcia et al., 2016; Godinho et al., 2006; Hamel et al., 2003; Lanotte et al., 2002; Maks et al., 2009; Vergani et al., 2007; Yelnik et al., 2003; Zonenshayn et al., 2004) to identify the STN borders, not readily discernible on low or intermediate field MRI (Cho et al., 2010). Another is using postoperative CT instead of stereotactic-MRI to confirm contact location within the target, overlooking errors introduced by brain shift or image co-registration (O'Gorman et al., 2009; Petersen et al., 2010). Complicating matters further, is the STN's peculiar contour, double-oblique orientation and position within a junctional area where anatomical terms of location change, rendering

Table 1
Patient demographics, preoperative L-DOPA challenge, postoperative change in UPDRS III and medication requirement.

	Mean	SD	SE	Minimum	Maximum	Range
Age[a]	56.3	10.2	2.3	41	71	30
Disease duration[a]	11.2	4.3	1.0	4	22	18
Duration of motor fluctuations[a]	3.1	2.0	0.4	0	9	9
UPDRS III OFF (LC)	43.8	13.0	3.0	20	73	53
UPDRS III ON (LC)	17.4	9.9	2.3	4	42	38
UPDRS III Improvement (LC)	26.5	10.1	2.3	7	47	40
95% CI:21.6-31.3, t:11.4, df:18, p < 0.0001[c]	(61%)	(15.8%)	(3.6%)	(33%)	(91%)	(58%)
UPDRS III (OFF Med. OFF DBS) [b]	50.5	17.2	3.9	24	96	72
UPDRS III (OFF Med. ON DBS) [b]	27.1	12.5	3.0	14	51	37
UPDRS III Improvement[b]	23.4	12.8	3.1	8	45	37
95% CI:16.8-29.4, t:7.5, df:16, p < 0.0001[c]	(46%)	(17.4%)	(4.2%)	(22%)	(73%)	(51%)
UPDRS III ON Med. OFF DBS[b]	27.6	14.1	3.2	10	62	52
UPDRS III ON Med. ON DBS[b]	13.3	9.1	2.2	3	34	31
UPDRS III Improvement[b]	14.3	8.0	1.9	41	28	24
95% CI:10.4-18.3, t:7.6, df:17, p < 0.0001[c]	(52%)	(17.4%)	(4.1%)	(9%)	(81%)	(62%)
LEDD (Preoperative)	1,365.6	509.8	114	540	2,550	2010
LEDD (Postoperative)	770.6	306.6	68.6	320	1,266	946
LEDD Reduction with DBS	595	203.2	45.4	220	1,284	1,064
95% CI: 386.3-803.8, t:6, df:19, p < 0.0001[c]	(44%)	(39.9%)	(39.8%)	(40.7%)	(50.4%)	(52.9%)

CI: Confidence Interval; Med: Medications; SD: Standard deviation; SE: Standard error; df: degrees of freedom; LC: L-DOPA Challenge (preoperative); LEDD: L-DOPA equivalent daily dose.
[a] At surgery.
[b] At 12 months.
[c] 2-tailed paired-t test.