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Connectivity derived thalamic segmentation in deep brain stimulation for tremor

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ABSTRACT

The ventral intermediate nucleus (VIM) of the thalamus is an established surgical target for stereotactic ablation and deep brain stimulation (DBS) in the treatment of tremor in Parkinson's disease (PD) and essential tremor (ET). It is centrally placed on a cerebello-thalamo-cortical network connecting the primary motor cortex, to the dentate nucleus of the contralateral cerebellum through the dentato-rubro-thalamic tract (DRT). The VIM is not readily visible on conventional MR imaging, so identifying the surgical target traditionally involved indirect targeting that relies on atlas-defined coordinates. Unfortunately, this approach does not fully account for individual variability and requires surgery to be performed with the patient awake to allow for intraoperative targeting confirmation. The aim of this study is to identify the VIM and the DRT using probabilistic tractography in patients that will undergo thalamic DBS for tremor. Four male patients with tremor dominant PD and five patients (three female) with ET underwent high angular resolution diffusion imaging (HARDI) (128 diffusion directions, 1.5 mm isotropic voxels and b value = 1500) preoperatively. Patients received VIM-DBS using an MR image guided and MR image verified approach with indirect targeting. Postoperatively, using parallel Graphical Processing Unit (GPU) processing, thalamic areas with the highest diffusion connectivity to the primary motor area (M1), supplementary motor area (SMA), primary sensory area (S1) and contralateral dentate nucleus were identified. Additionally, volume of tissue activation (VTA) corresponding to active DBS contacts were modelled. Response to treatment was defined as 40% reduction in the total Fahn-Tolosa-Martin Tremor Rating Score (FTMTRS) with DBS-ON, one year from surgery. Three out of nine patients had a suboptimal, long-term response to treatment. The segmented thalamic areas corresponded well to anatomically known counterparts in the ventrolateral (VL) and ventroposterior (VP) thalamus. The dentate-thalamic area, lay within the M1-thalamic area in a ventral and lateral location. Streamlines corresponding to the DRT connected M1 to the contralateral dentate nucleus via the dentate-thalamic area, clearly crossing the midline in the mesencephalon. Good response was seen when the active contact VTA was in the thalamic area with highest connectivity to the contralateral dentate nucleus. Non-responders had active contact VTAs outside the dentate-thalamic area. We conclude that

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; EV, explanatory variable; 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; HARDI, high angular resolution diffusion imaging; HFS, high frequency stimulation; 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; PMC, premotor cortex; S1, primary sensory 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; VL, ventral lateral; VP, ventral posterior; VTA, volume of tissue activated; cZI, caudal zona incerta

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probabilistic tractography techniques can be used to segment the VL and VP thalamus based on cortical and cerebellar connectivity. The thalamic area, best representing the VIM, is connected to the contralateral dentate cerebellar nucleus. Connectivity based segmentation of the VIM can be achieved in individual patients in a clinically feasible timescale, using HARDI and high performance computing with parallel GPU processing. This same technique can map out the DRT tract with clear mesencephalic crossing.

1. Introduction

The ventral intermediate nucleus (VIM) of the thalamus is an established surgical target, for stereotactic ablation and deep brain stimulation (DBS) in the treatment of tremor in Parkinson's disease (PD), essential tremor (ET) and multiple sclerosis (Benabid et al., 1989, 1991, 1993; Berk et al., 2004; Hariz et al., 2007; Pahwa et al., 2001; Pollak et al., 1993; Schuurman et al., 2008). A subjacent area, the caudal zona incerta (cZI), is another effective DBS target for the treatment of tremor (Blomstedt et al., 2007, 2009, 2010; Murata et al., 2003; Plaha et al., 2008).

The VIM is centrally placed on a cerebello-thalamo-cortical network in which pathological oscillations, possibly triggered by pallidal dysfunction in the case of PD, is thought to be culpable for tremor (Helmich et al., 2011). The cortical focus in this tremor network is in the primary motor cortex, connected to the dentate nucleus of the contralateral cerebellum through the dentato-rubro-thalamic tract (DRT) via the VIM (Baker et al., 2010; Dum and Strick, 2003; Gallay et al., 2008; Helmich et al., 2012; Jörntell and Ekerot, 1999; McIntyre and Hahn, 2010).

The VIM is not readily visible on conventional, stereotactic MR imaging sequences used in image guided and image verified surgery (Deistung et al., 2013; Lemaire et al., 2010; Traynor et al., 2011; Vassal et al., 2012). Identifying the nucleus traditionally involves indirect targeting relying on atlas-defined coordinates in relation to the anterior commissure (AC) – posterior commissure (PC) points as landmarks, along with other identifiable structures such as the lateral thalamic/internal capsule border (Schaltenbrand et al., 1977). Needless to say, this approach does not fully account for individual variability. Furthermore, surgery often needs to be performed with the patient awake to allow for intraoperative confirmation of targeting, thus increasing patient discomfort (Gross et al., 2006). Moreover, intraoperative confirmation is not always readily feasible e.g. when performing a thalamotomy using Gamma Knife (Witjas et al., 2015) or focused ultrasound (Elias et al., 2016).

To overcome this, various imaging techniques have been proposed to identify the VIM. Ultra-high field MRI provides high contrast-to-noise ratio in-between thalamic nuclei, better segmenting the nucleus, however, this modality is not readily available in a clinical setting (Spiegelmann et al., 2006). Another technique relies on contrast in coloured fractional anisotropy (FA) maps, a product of diffusion tensor imaging (DTI) (Lefranc et al., 2015; Sedrak et al., 2011). Simple visualisation of the first order tensor fields in DTI has also been used to generate deterministic tractography models of the DRT, which is then targeted by DBS (Coenen et al., 2011, 2014, 2016; Sammartino et al., 2016). This modality is commonly accessible in clinical settings and imaging is relatively swift to acquire and process; however, it carries limitations related to disentangling crossing fibres, tracking in areas of low anisotropy (e.g. the thalamus) (Ramnani et al., 2004) and overall accuracy (Petersen et al., 2016).

An emerging modality utilises high angular resolution diffusion imaging (HARDI) and probabilistic connectivity based segmentation of the thalamus (Behrens et al., 2003a; Calabrese et al., 2015; Lambert et al., 2016; Miller et al., 2011; Ramnani et al., 2004). This technique successfully models crossing fibres and grey matter (low anisotropy) connectivity and achieves high signal-to-noise ratio, but requires prolonged image acquisition and large computational resources which are impractical in clinical practice. Novel MRI acquisition techniques, such as Simultaneous Multi-Slice Imaging and Multi-Band Imaging (Feinberg and Setsompop, 2013) have reduced scanning time. Furthermore, advances in computer processing techniques and relying on graphical processing units to carry out diffusion analysis have facilitated the use of this modality in clinical practice (Hernandez et al., 2013; Hernandez-Fernandez et al., 2016).

The objectives of this study were to examine the feasibility of using probabilistic, connectivity based segmentation techniques to segment the thalamus in a group of PD and ET patients one year from VIM DBS; to generate probabilistic tractography models of the DRT tracts and to carry out a post-hoc analysis of the relation of the segmented VIM and

Table 1
Demographics, preoperative UPDRS-III (PD patients), FTMTRS (ET patients), postoperative FTMTRS ON/OFF DBS and stimulation parameters.

Patient		PD1	PD2	PD3	PD4	Mean	ET1	ET2	ET3	ET4	ET5	Mean
Age (yr.)*		67	63	64	67	65.3	56	49	66	78	70	63.8
Surgery		Left	Left	Bilat.	Left		Left	Left	Left	Left	Left	
Disease duration (yr.)*		5	6	10	10	7.8	10	10	6	12	11	9.8
Follow-up (month)		36	23	19	15	23.3	35	31	27	13	12	23.6
Preop. UPDRS-III tremor	OFF MED.	12	8	17	13	12.5	–	–	–	–	–	
subsection	ON MED.	12	8	11	8	9.8	–	–	–	–	–	
(PD patients)	IMP (%)	0 (0%)	0 (0%)	6 (35%)	5 (38.4%)	2.8 (18.4%)	–	–	–	–	–	
Preop. FTMTRS (ET patients)		–	–	–	–		55	66	93	97	97	81.6
Postop. FTMTRS	OFF DBS	32	33	129	55	62.3	44	71	93	89	63	72
	ON DBS	14	15	44	24	24.3	29	47	81	47	36	48
	IMP (%)	18 (56%)	18 (55%)	85 (66%)	31 (56%)	38 (58%)	15 (34%)	24 (34%)	24 (13%)	24 (47%)	24 (43%)	24 (34%)
ACTIVE CONTACTS	Left	1	2	2	0		1	0 plus 1	1	0 plus 3	3	
	Right	–	–	10	–		–	–	–	–	–	
	AMP (Volt)	2	2	2.6	1.8	2.1	2	2	2	2.5	2.5	2.2
	PW (μS)	60	60	60	60	60	60	60	60	60	60	60
	FREQ (HZ)	130	150	130	130	135	130	180	130	150	180	154

Yr.: year; IMP: improvement; AMP: amplitude; PW: pulse width; FREQ: frequency.