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Comparison of oscillatory activity in subthalamic nucleus in Parkinson's disease and dystonia☆

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ABSTRACT

Objectives: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been successfully used to treat both Parkinson's disease (PD) and dystonia. Local field potentials (LFPs) recorded from the STN of PD patients demonstrate prominent beta frequency band activity. It is unclear whether such activity occurs in the STN in dystonia, and, if not, whether dystonia has another distinctive neural population activity in the STN.
Methods: Twelve patients with PD, and eight patients with dystonia underwent DBS electrode implantation targeting the STN. Seven dystonia patients were off medication and one was on aripiprazole and clonazepam. LFPs were recorded from the DBS electrodes in PD in the on/off medication states and in dystonia. Power spectra and temporal dynamics measured by the with Lempel-Ziv complexity of the LFPs were compared among these states.
Results: Normalised power spectra and Lempel-Ziv complexity of subthalamic LFPs differed between dystonia off and PD on/off, and between PD off and on over the low frequency, beta and high gamma bands. Patients with dystonia and off medication had lower beta power but higher low frequency and high gamma power than PD. Spectral power in the low beta frequency (11–20 Hz) range was attenuated in medicated PD.
Conclusion: The results suggest that dystonia and PD are characterized by different patterns of oscillatory activities even within the same nucleus, and exaggerated beta activity may relate to hypo-dopaminergic status.

1. Introduction

Evidence is accruing that there is synchronised oscillatory activity in some of the basal ganglia nuclei that typically occurs in the beta frequency band in Parkinson's disease (PD) and in the theta frequency band in dystonia (López-Azcárate et al., 2010). It has been widely reported that the local field potentials (LFPs) from the subthalamic nucleus (STN) exhibit excessive beta activity in patients with PD (Brittain and Brown, 2014). Such activity is suppressed by treatment with levodopa and by deep brain stimulation (DBS) of the STN (Eusebio et al., 2011; Kühn et al., 2005; Whitmer et al., 2012). Moreover, therapy induced suppression of beta levels correlates with the degree of induced clinical improvement, particularly with changes in bradykinesia and rigidity (Kühn et al., 2005; Kühn et al., 2008a; Kühn et al., 2009; Özkurt et al., 2011; Ray et al., 2008; van Wijk et al., 2016; Weinberger et al., 2006; Zaidel et al., 2010).

Abbreviations: STN, subthalamic nucleus; PD, Parkinson's disease; LFPs, local field potentials; DBS, deep brain stimulation; GPi, globus pallidus internus; LZC, Lempel-Ziv complexity; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; CDQ-24, Craniocervical Dystonia Questionnaire; UPDRS, Unified Parkinson's disease rating scale.

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In contrast, in patients with dystonia, oscillatory activity over a low frequency band (4–10 Hz) has been frequently reported from the globus pallidus internus (GPi) (Foncke et al., 2007; Lee and Kiss, 2013; Moll et al., 2014; Silberstein et al., 2003; Weinberger et al., 2011). This low frequency activity in GPi is coherent with the EMG of dystonic muscles (Chen et al., 2006a; Liu et al., 2006; Sharott et al., 2008). Moreover, it is suppressed during effective DBS of the same nucleus (Barow et al., 2014). Dystonia patients do not generally show elevated beta activity in the GPi (Silberstein et al., 2003; Weinberger et al., 2011), unless treated with the monoamine vesicle depletor tetrabenazine (Kühn et al., 2008b) or in some patients with secondary dystonia (Whitmer et al., 2013).

However, as most of the data in patients with PD and dystonia come from recordings in different sites doubt remains as to whether spectral changes are site, phenotype or disease specific. GPi can be a DBS target for both dystonia and PD, and case series contrasting recordings from the GPi in these two diseases are concordant and support the existence of discrete spectral patterns along the lines of those described above (Silberstein et al., 2003; Weinberger et al., 2011). More recently, STN, a classical DBS target in PD, has been used as a stimulating target to treat dystonia (Chou et al., 2005; Kleiner-Fisman et al., 2007; Ostrem et al., 2011, 2014). However, where the subthalamic nucleus is concerned there is only one case series contrasting the LFP patterns in patients with dystonia and PD, and this suggested no difference in the spectral pattern of local field potentials between the two diseases (Wang et al., 2016). This would imply that any disease difference present at the level of the globus pallidus is local and not a feature of the wider interconnected circuits of the basal ganglia. Yet a microelectrode study and a case report describing findings in the STN point to a difference between these in dystonia and PD also within this nucleus (Schrock et al., 2009; Neumann et al., 2012). Given these contrasting results at the level of STN we felt it important to further investigate the spectral patterns of the STN LFP in dystonia and PD. (Neumann et al., 2012). We hypothesised that low frequency and beta band activities will differentially characterize the two disorders, even when recordings are made from the same site. In addition, we tested whether high gamma activity in the STN, previously postulated to be prokinetic, might be elevated in dystonia (Brown, 2003).

2. Material and methods

2.1. Subjects and surgery

All patients gave written informed consent to take part in this study, which was agreed by the local ethics committees. Eight patients with dystonia which had treatment failures with botulinum toxin (Table 1), underwent DBS electrode implantation in Tian-Tan Hospital, Capital Medical University, Beijing, China. Seven patients with dystonia underwent bilateral STN implantation and one with bilateral STN and GPi implantation, although only STN recordings are included in this study. Archival data from twelve subjects with PD were also analyzed (Table 1); seven who underwent surgery at the John Radcliffe Hospital, Oxford University, Oxford, UK and five who underwent surgery at the National Hospital for Neurology and Neurosurgery or Kings College Hospital, London. Six of these patients with PD have previously been reported (Anzak et al., 2016). 10/12 patients with PD underwent bilateral STN implantation, one underwent unilateral STN and thalamus implantation, and one unilateral STN implantation only. The two groups did not differ in age (unpaired *t*-test, $p = 0.159$). All patients underwent evaluation for motor impairments using respective clinical scales, the Unified Parkinson's disease rating scale part III – motor exam under on/off medication state for PD patients, and Burke-Fahn-Marsden Dystonia Rating Scale or Craniocervical Dystonia Questionnaire for dystonia patients (Muller et al., 2004; Susatia et al., 2010). The L-dopa equivalent dose in PD groups was calculated based on conversion factors in a previous report (Tomlinson et al., 2010).

The procedures for STN targeting and DBS electrode implantation have been previously reported (Chou et al., 2005; Foltynie and Hariz, 2010). The STN was localized on the fused pre-operative frameless magnetic resonance (MR) and framed computed tomography (CT) images. The electrodes were targeted at the dorsolateral area of the STN in both groups. The targets were calculated and determined using the Frame link planning station (Medtronic, Minneapolis, MN, USA). The DBS electrodes were Medtronic 3389 (Medtronic, Minneapolis, MN, USA) with four platinum-iridium cylindrical surface contacts. Each contact was 1.27 mm in diameter and 1.5 mm in length, and separated by 0.5 mm. The most caudal contact was contact 0 and the most rostral

Table 1
Clinical summary.

Case	Age/sex	Diagnosis/main symptoms before operation	Medication	Pre-operative scales (dystonia: BFMDRS(MS,DS)/CDQ-24, off med; PD: UPDRS part-III, off/on med)	Channel selection
d1	21/M	Dystonia, primary generalised	None	53 (43, 10)	L12, R12
d2	24/M	Dystonia, primary generalised	None	50 (38, 12)	L12, R01
d3	44/F	Dystonia, primary generalised	None	58 (46, 12)	L12, R12
d4	74/F	Dystonia, neuroleptic induced cranial	None	24 (18, 6)	L01, R12
d5	25/M	Dystonia, cranial with blepharospasm	None	28.5 (21.5, 7); CDQ-24: 90	L01, R01
d6	65/M	Dystonia, cranial with blepharospasm	None	5.5 (5.5, 0); CDQ-24: 46	L23, R23
d7	52/F	Dystonia, cranial with blepharospasm	None	4.5 (4.5, 0); CDQ-24: 44	L01, R12
d8	67/F	Dystonia, cranial with blepharospasm	Clonazepam and Aripiprazole	12 (7, 5); CDQ-24: 62	L01, R12
p1	56/F	PD, bradykinesia	900 mg LDED	26/7	L12, R12
p2	70/M	PD, freezing, gait	1100 mg LDED	62/29	L12, R12
p3	59/M	PD, tremor	700 mg LDED	28/5	L12, R23
p4	60/M	PD, freezing, bradykinesia	200 mg LDED	25/13	L12, R12
p5	60/F	PD, bradykinesia, tremor, gait	1725 mg LDED	63/7	L23, R12
p6	32/M	PD, left sided tremor	875 mg LDED	52/13	R01
p7	68/M	PD, right sided tremor	475 mg LDED	38/20	L23
p8	58/M	PD, bradykinesia, dyskinesia	270 mg LDED	45/14	L23, R12
p9	60/M	PD, bradykinesia	600 mg LDED	41/21	L12, R01
p10	60/F	PD, bradykinesia, gait	2000 mg LDED	40/12	L01, R23
p11	65/M	PD, bradykinesia, rigidity, postural instability	1670 mg LDED	23/7	L12, R01
p12	38/M	PD, tremor, mobility	370 mg LDED	23/10	L12, R23

d1–d8: dystonia cases. p1–p12: PD cases. LDED = L-DOPA daily equivalent dose. BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale. MS = Movement score. DS = Disability score. CDQ-24 = Craniocervical Dystonia Questionnaire. UPDRS = Unified Parkinson's disease rating scale. Part – III: Motor Exam.