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Subcortical evoked activity and motor enhancement in Parkinson's disease

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ABSTRACT

Enhancements in motor performance have been demonstrated in response to intense stimuli both in healthy subjects and in the form of 'paradoxical kinesis' in patients with Parkinson's disease. Here we identify a mid-latency evoked potential in local field potential recordings from the region of the subthalamic nucleus, which scales in amplitude with both the intensity of the stimulus delivered and corresponding enhancements in biomechanical measures of maximal handgrips, independent of the dopaminergic state of our subjects with Parkinson's disease. Recordings of a similar evoked potential in the related pedunculopontine nucleus – a key component of the reticular activating system – provide support for this neural signature in the subthalmic nucleus being a novel correlate of ascending arousal, propagated from the reticular activating system to exert an 'energizing' influence on motor circuitry. Future manipulation of this system linking arousal and motor performance may provide a novel approach for the non-dopaminergic enhancement of motor performance in patients with hypokinetic disorders such as Parkinson's disease.

1. Introduction

A brief enhancement of motor performance in response to intense, alerting, or arousing stimuli, is a commonly experienced phenomenon. Under such circumstances, experimental evidence has shown that even *peak* motor responses can undergo augmentation, over and above the effects of maximal effort of will, both in healthy subjects (Woodworth, 1938; Angel, 1973; Anzak et al., 2011a) and in patients ordinarily hindered by the bradykinetic symptoms of Parkinson's disease (PD) (Valldeoriola et al., 1998; Ballanger et al., 2006; Anzak et al., 2011b, 2012). Anecdotal reports of a comparable effect – termed 'paradoxical kinesis' (Souques, 1921) – have described patients with advanced PD being able to jump up and run at the sound of a car accident (Daroff, 2008), the sensation of an earthquake (Bonanni et al., 2010), or sight of an approaching wall of flood-water (Schwab and Zieper, 1965). However, the neural pathways driving this remarkable phenomenon have remained enigmatic.

Accordingly, in the current study we investigate the possible mechanisms underlying the augmentation of peak motor performance by arousing stimuli. As a number of studies have now implicated a role of the basal ganglia in the scaling of voluntary movement (Turner et al., 2003; Thobois et al., 2007; Muthukumaraswamy, 2010; Grafton and Tunik, 2011; Brücke et al., 2012; Tan et al., 2015) including that at maximal effort (Anzak et al., 2012; Joundi et al., 2012), we test the hypothesis that activity in this network responsible for movement gain (Turner and Desmurget, 2010) also helps mediate additional enhancements in motor performance with arousing stimuli. To this end we capitalize on the unique opportunity afforded by therapeutic deep brain stimulation to record from key subcortical nuclei.

2. Materials and methods

2.1. Subjects

All subjects gave their informed consent to take part in the study, which was approved by the local ethics committees at our recording

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sites in Oxford, London and Bristol, United Kingdom. Eight patients with PD (mean disease duration 11.6 years, mean age 57.1 years, range 32–70 years, six males) underwent bilateral implantation of DBS electrodes into the STN, as a prelude to therapeutic high frequency stimulation for advanced idiopathic PD with motor fluctuations and/or dyskinesias. Techniques to target and implant electrodes in the STN have previously been described (Foltynie and Hariz, 2010). No microelectrode recordings were made, although the effects of direct stimulation were confirmed intra-operatively. In addition, the locations of the electrodes were confirmed with immediate post-operative stereotactic imaging. Nonetheless, in acknowledgment of the fact that not all electrode contacts could be expected to lie in the STN per se, we term the area sampled by the contact pairs the STN region, STNr. DBS electrode extension cables were externalized through the scalp to enable recordings prior to connection to a subcutaneous DBS pacemaker, implanted in a second operative procedure up to seven days later. Clinical details of the patients are available in Table 1. The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa (L-DOPA) was 70.0 ± 5.6% ($p = 0.018$, Wilcoxon signed-rank test between ON and OFF L-DOPA scores; data missing in one case) across subjects, indicating good responsiveness to L-DOPA in our study participants. A further PD patient was implanted in the pedunculopontine region (PPNr) and STNr/zona incerta, bilaterally, for freezing of gait (see last case in Table 1). The PPNr electrodes were placed using a transventricular trajectory so that all four electrode contacts were intended to lie within the PPN. The STNr electrodes were placed in the caudal zona incerta, with the central two electrode contacts lying adjacent to or clipping the STN. Details of the surgical procedure have been previously outlined (Khan et al., 2011).

2.2. Experimental paradigm

Subjects were presented with a series of imperative visual (V) cues, separated by 8.0 ± 0.5 s, and instructed to squeeze a hand-held force dynamometer "as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light" (red light-emitting-diode illuminated for 3 s). A loud auditory stimulus (40 ms duration, 1 kHz), at one of five different randomly selected sound pressure levels (82, 88, 94, 100, 105 dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue. However, subjects were asked to just focus on responding to the V cues. Fifteen cues of each sound pressure level (75 trials in total) were delivered in each experimental run. Trials were carried out in a blocked design, and left- and right-hand recordings were counterbalanced across subjects. Inter-trial intervals were shorter than in our previous studies (Anzak et al., 2011a, 2011b, 2012) to allow for a greater number of trials to be executed prior to correlative analysis, whilst avoiding an excessively lengthy paradigm in our patients with PD.

Grip force was measured one hand at a time in each subject using an isometric dynamometer (G100; Biometrics Ltd, Cwmfelinfach, Gwent, UK), with standard Jamar design and its handle set in the second of the five discrete grip diameter adjustments possible (Sancho-Bru et al., 2008). Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at about 90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992). Stimulus intensities were measured in a sound-proofed room with a Brüel and Kjaer 2260 Observer (Brüel and Kjaer, Nærum, Denmark) via an artificial ear and headphone adapter.

Table 1
Patient details. Surgical sites: (1) National Hospital for Neurology & Neurosurgery, London, (2) John Radcliffe Hospital, Oxford, (3) Kings College Hospital, London, (4) Frenchay Hospital, Bristol. UPDRS scores for Patient 8 were not available.

Site	Bilateral targets	Patient no.	Age/yrs	Disease duration/yrs	Daily L-DOPA equivalent dose/mg	Pre-op UPDRS OFF/ON Levodopa
1	STN	1	59	15	700	28/5
1	STN	2	60	17	1725	63/7
1	STN	3	32	10	875	52/13
1	STN	4	56	10	400	40/12
2	STN	5	70	12	1100	62/29
2	STN	6	60	7	200	25/13
3	STN	7	56	10	900	26/7
3	STN	8	64	12	300	n/a
4	STN& PPN	9	68	12	475	38/20

2.3. Recordings

In our nine patients with externalized DBS electrodes (8 bilateral STNr, 1 bilateral PPNr & STNr/ZI), LFP recordings were made 3–6 days after surgery. In order to complete the recordings in one morning, and limit intrusion on our easily fatigable post-operative patients, recordings were always made first after overnight withdrawal of anti-parkinsonian medication (OFF L-DOPA), and then again approximately 1 h after taking their usual morning dose (average morning L-DOPA dose administered = 186 ± 62 mg). Improvement with medication was confirmed through assessment of finger tapping, wrist rigidity and tremor (using the corresponding items of the motor UPDRS).

LFPs, and surface EEG from Fz and Cz were recorded monopolarly with respect to a linked earlobe reference using a TMSi porti amplifier (TMS international) and its respective software. EMG was recorded from orbicularis oculi to identify blinks. All recordings were band-pass filtered between 0.5 and 500 Hz and sampled at 2048 Hz. Analogue correlates of the visual and auditory stimuli and dynamometer output were recorded and digitized in a similar way. Monopolar LFP recordings were subsequently converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per side) to limit the effects of volume conduction from distant sources. Bipolar Fz–Cz was also created offline. The line noise artefacts at 50 Hz and 100 Hz were removed using notch filters (5th order zero-phase Butterworth filters).

2.4. Data analysis

Analyses of both behavioral and LFP data were performed in Matlab (version 7.10). Peak force (PF) and pre-motor reaction time (RT) were the chosen biomechanical variables of interest. Premotor reaction time was defined as the time interval between cue onset and the point at which force exceeded 5% of the PF (taken as response onset). We acknowledge that premotor reaction time is more usually considered to be the interval between cue presentation and EMG onset (Botwinick and Thompson, 1966). However, as in previous studies (Anzak et al., 2011a, 2011b, 2012) we found the use of EMG to be suboptimal in the context of maximal grips because of movement artefact and sampling error, due to activation of multiple muscles in this task. Peak yank (PY; where yank is defined as the rate of change of force, calculated by differentiation of the force signal) was also derived. Note too that the scalp EEG was contaminated by auditory blink reflexes to the intense stimuli and so was not analyzed further.

STNr LFP activity recorded from externalized DBS electrodes was decomposed into two components: evoked potentials, which are phase-locked to stimulus onset, and induced frequency-specific components, which are not (David et al., 2006). We sought to derive both these constituents in order to investigate whether STNr activity in either domain preceded and correlated with enhancements in motor performance. The techniques for derivation of evoked activity and event related induced power are outlined in Supplementary Material 1.

2.5. Statistics

Grand averages of PF, PY and RT, in response to each stimulus intensity, were calculated after deriving each of these variables from the