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Frequency specific activity in subthalamic nucleus correlates with hand bradykinesia in Parkinson's disease

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ABSTRACT

Local field potential recordings made from the basal ganglia of patients undergoing deep brain stimulation have suggested that frequency specific activity is involved in determining the rate of force development and the peak force at the outset of a movement. However, the extent to which the basal ganglia might be involved in motor performance later on in a sustained contraction is less clear. We therefore recorded from the subthalamic nucleus region (STNr) in patients with Parkinson's disease (PD) as they made maximal voluntary grips. Relative to age-matched controls they had more rapid force decrement when contraction was meant to be sustained and prolonged release reaction time and slower rate of force offset when they were supposed to release the grip. These impairments were independent from medication status. Increased STNr power over 5–12 Hz (in the theta/alpha band) independently predicted better performance—reduced force decrement, shortened release reaction time and faster rate of force offset. In contrast, lower mean levels and progressive reduction of STNr power over 55–375 Hz (high gamma/high frequency) over the period when contraction was meant to be sustained were both strongly associated with greater force decrement over time. Higher power over 13–23 Hz (low beta) was associated with more rapid force decrement during the period when grip should have been sustained, and with a paradoxical shortening of the release reaction time. These observations suggest that STNr activities at 5–12 Hz and 55–375 Hz are necessary for optimal grip performance and that deficiencies of such activities lead to motor impairments. In contrast, increased levels of 13–25 Hz activity both promote force decrement and shorten the release reaction time, consistent with a role in antagonising (and terminating) voluntary movement. Frequency specific oscillatory activities in the STNr impact on motor performance from the beginning to the end of a voluntary grip.

Introduction

Maximal voluntary contractions demonstrate many of the motor impairments of PD. The development of force may be slow, peak force may be attenuated, force may wane more rapidly than normally and contraction offset may be delayed (Corcos et al., 1996; Gordon, 1998; Jordan et al., 1992; Kunesch et al., 1995; Ziv et al., 1998). Local field potential (LFP) recordings made from the basal ganglia of patients undergoing deep brain stimulation have suggested that the basal ganglia are involved in determining the rate of force development and the peak force developed early in the contraction (Anzak et al., 2012). Specifically, the level of theta/alpha and gamma band activity around the time of movement onset correlates with these aspects of initial performance. This is in line with growing evidence that the basal ganglia determine the force or vigour of a motor response (Turner and Desmurget, 2010).

However, the extent to which the basal ganglia might be involved in those motor impairments evident later in a maximal contraction, such as during a manual grip, is less clear. Here we relate LFP activities to difficulties in maintaining maximal force and in relaxing contraction on task termination in patients with PD. The rate of force decrement may be considered an aspect of bradykinesia, similar to the decrement in finger tapping that forms a hallmark of the condition (Ling et al., 2012). The difficulty in relaxing contraction has also been found to closely correlate with global measures of motor impairment (Corcos et al., 1996; Jordan et al., 1992; Kunesch et al., 1995). Our working hypothesis in the present study is that basal ganglia activities contribute to these aspects of performance and that this will be manifest in correlations between LFP activities and measures of force decrement and delayed offset. We also hypothesise that the same basal ganglia features might correlate with more than one aspect of motor performance

Abbreviations: LFP, local field potential; UPDRS, Unified Parkinson's Disease Rating Scale.

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and that such patterns of association might therefore allow inferences about the underlying function served by activities reflected in the basal ganglia LFP.

Methods

We extended the analysis made in a previously published cohort of PD patients (Anzak et al., 2012) and age-matched healthy controls (Anzak et al., 2011b) to include behavioural measures of performance made later in a maximal voluntary grip and analysis of the corresponding LFP recorded in PD patients.

Subjects

Ten patients with PD (mean disease duration 10 years, mean age 58 years, range 42–65 years; seven males) and ten age-matched healthy controls (mean age 60 years, range 41–73 years; seven males; with one new healthy control subject apart from those published in Anzak et al., 2011b) provided informed consent to take part in this study, which was approved by the local ethics committees. There was no significant difference between the ages of the two groups ($t_{18} = 0.570$, $p = 0.576$). The patients showed $59.9 \pm 5.7\%$ ($p < 0.0001$) improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa (L-DOPA), indicating good responsiveness to L-DOPA. Patients 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 dyskinesia. Other details about these patients have been previously reported (Anzak et al., 2012).

Experimental paradigm

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). A series of imperative visual (V) cues (illumination of a red light-emitting-diode—LED) were presented to the subjects, and the subjects were instructed to squeeze a force dynamometer "as fast and hard as you possibly can when the light comes on, maintain this for the duration of the light and release the grip when the light turns off." For each trial, the red LED was illuminated for 5 s and each trial was separated by 6–8 s rest. In half of these trials, randomly selected, a loud auditory stimulus (0.3 s duration, 1 kHz, 96 dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue (AV; auditory-visual cue). However, subjects were asked to just focus on responding to the V cues. The rationale for the number of trials executed and the inter-trial interval, as well as stimulus intensity has previously been described (Anzak et al., 2011a,b).

In patients, 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 L-DOPA dose administered, $155 \pm$ (SEM) 25 mg, two patients also received subcutaneous apomorphine). This sequence of recordings may have introduced a confound, since on medication performance may have been affected by fatigue. Healthy controls were also asked to undertake two experimental runs, with a 45- to 60-min break in between, in order to match any practice, habituation or fatigue effects in the patients.

Recordings

Grip force was measured one hand at a time in each subject using an isometric dynamometer (G200, Biometrics Ltd., UK). Bipolar LFPs were recorded from adjacent contacts of each DBS electrode (0–1, 1–2, 2–3) and pass band filtered between 0.5 and 500 Hz using either a D360 amplifier (Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) in combination with a 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK) and sampled onto a computer using Spike2 software (Cambridge Electronic Design), or TMSi porti (TMS international, Netherlands) and its respective software. All recordings were originally sampled at 2048 Hz. Analogue correlates of the visual and auditory stimuli and dynamometer output were recorded and digitised in a similar way.

Analysis

Analyses of both behavioural and LFP data were performed in Matlab (version 2010b). The grip force trajectory of each individual trial of each subject was first normalised against the maximal force each subject achieved in the V condition. The waning of force over the period during which maximal contraction was meant to be sustained was measured as the gradient (k) of the regression line fitting force over the period from peak force to the time of offset of the LED cue. Two parameters were derived to describe the force release on termination of grip: the release reaction time (R-RT) and the rate of force release (R-Rate). Release reaction time (R-RT) was operationally defined as the time interval between offset of the LED cue and onset of release of the contraction, with the latter defined as the time when grip force reduced to 90% of the average force over the one second before the offset of the cue. Releasing rate (R-Rate) was defined as the inverse of the time between the onset of the release of force and the point at which force reduced to 10% of the average force over the one second before the offset of the LED cue (see Supplementary Figure for schematic showing the definition of these measurements).

Notch filters (5th order zero-phase Butterworth filters) were used to remove the line noise artefacts at 50 Hz and 100 Hz. The average LFP across trials was subtracted from the original local field potential in each trial so that further analysis would estimate induced power. A time–frequency decomposition based on the continuous wavelet transform was then applied to each (average-subtracted) trial to analyse changes in induced LFP activity in the time–frequency domain. Event related LFP power was subsequently normalised by calculating the z-score of the power at each time point relative to the power between two seconds and one second before the cue, so that a value higher than zero indicated power higher than before cue and *vice versa*. The normalised induced power was aligned to cue presentation, and averaged across trials of a given type and subsequently across the three bipolar contacts for each STNr lead contralateral to the gripping hand. We averaged across all the contact pairs in a given electrode so as to avoid selection bias, although not all contacts will have been in the STN *per se*.

Statistics

Grand averages of behavioural and LFP data for different experimental conditions were calculated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, and then averaging across study participants. For LFP measurements, significant differences from baseline for each condition were first evaluated using one-sample t-tests. Differences between conditions were assessed with analyses of variance (ANOVA). Means $\pm$ standard error of means (SEM) are presented throughout the text, unless otherwise specified.

Generalised linear models were used to identify which, if any, frequency specific LFP activities were significant independent predictors for motor parameters during maximal grip and its release. Modelling included experimental condition (Drug status and Stimulus type) as factor predictor, average normalised induced power in