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Complementary roles of different oscillatory activities in the subthalamic nucleus in coding motor effort in Parkinsonism ☆

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ABSTRACT

The basal ganglia may play an important role in the control of motor scaling or effort. Recently local field potential (LFP) recordings from patients with deep brain stimulation electrodes in the basal ganglia have suggested that local increases in the synchronisation of neurons in the gamma frequency band may correlate with force or effort. Whether this feature uniquely codes for effort and whether such a coding mechanism holds true over a range of efforts is unclear. Here we investigated the relationship between frequency-specific oscillatory activities in the subthalamic nucleus (STN) and manual grips made with different efforts. The latter were self-rated using the 10 level Borg scale ranging from 0 (no effort) to 10 (maximal effort). STN LFP activities were recorded in patients with Parkinson's Disease (PD) who had undergone functional surgery. Patients were studied while motor performance was improved by dopaminergic medication. In line with previous studies we observed power increase in the theta/alpha band (4–12 Hz), power suppression in the beta band (13–30 Hz) and power increase in the gamma band (55–90 Hz) and high frequency band (101–375 Hz) during voluntary grips. Beta suppression deepened, and then reached a floor level as effort increased. Conversely, gamma and high frequency power increases were enhanced during grips made with greater effort. Multiple regression models incorporating the four different spectral changes confirmed that the modulation of power in the beta band was the only independent predictor of effort during grips made with efforts rated <5. In contrast, increases in gamma band activity were the only independent predictor of effort during grips made with efforts ≥ 5. Accordingly, the difference between power changes in the gamma and beta bands correlated with effort across all effort levels. These findings suggest complementary roles for changes in beta and gamma band activities in the STN in motor effort coding. The latter function is thought to be impaired in untreated PD where task-related reactivity in these two bands is deficient.

Introduction

Neuronal recordings in monkeys and imaging studies in healthy humans have suggested that the basal ganglia play an important role in the control of the scaling of motor responses, as often measured in terms of the amplitude, velocity or force of an action (Delong et al., 1984; Spraker et al., 2007; Turner and Anderson, 1997; Vaillancourt et al., 2007). However, it is not necessarily that the basal ganglia are themselves directly involved in the parameterisation of these measures through the control of muscular contraction; rather, along with other functions, they determine the effort or vigour to be attributed to a response that is then organised elsewhere (Schmidt et al., 2008; Shadmehr and Krakauer, 2008; Turner and Desmurget, 2010). Indeed, a distinction between effort and action dynamics would seem functionally relevant, as effort may increase while force and other measures stay constant or even fall, as might be the case when muscles begin to fatigue. Derangement of the effort ascribing function of the basal ganglia has formed the basis for recent theoretical accounts of motor impairment in Parkinson's disease (Mazzoni et al., 2007). Direct recordings from basal ganglia targets in patients suggest that local synchronisation in the gamma band may contribute to the selection of effort or force levels for voluntary movements. Thus the power over 60–80 Hz in the local field potential (LFP) in the globus pallidus correlates with the movement amplitude and velocity of the contralateral hand of patients with cranial dystonia, a condition that ostensibly spares hand function (Brücke et al., 2012). Similar correlations have been noted in patients with Parkinson's disease between power in the LFP of the subthalamic

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nucleus over 70–90 Hz and movement speed (Joundi et al., 2012), and between the LFP power in the subthalamic nucleus over 55–375 Hz and force (Anzak et al., 2012). Conversely, lower levels of 55–375 Hz power and their further reduction while contraction is meant to be sustained are both associated with greater force decrement over time in Parkinsonian patients (Tan et al., 2013).

Whether these correlations with effort measures are limited to the gamma band is, however, less clear. It is well established that beta band power in basal ganglia LFPs is suppressed prior to and during voluntary movements, but whether this might help dictate force measures is uncertain. Several studies have reported that the depth of beta desynchronization is relatively fixed regardless of force or movement speed (Anzak et al., 2012; Brücke et al., 2012; Joundi et al., 2012), consistent with the hypothesis that suppression of population synchrony in the beta frequency range serves a permissive role, allowing task-related rate coding and more focal neuronal assemblies to engage in task-specific processing related to voluntary movement (Brown and Williams, 2005). At odds with this though, other studies have reported that the level of suppression of beta power does vary with the details of task performance, including the force generated (Androulidakis et al., 2008; Kempf et al., 2007; Tan et al., 2013).

Some of these conflicting results may relate to the interdependency of spectral features and may be clarified by multivariate approaches to statistical dependencies (Anzak et al., 2012). However, task details may also be important. Here we test the hypothesis that both beta desynchronisation and gamma synchronisation in the basal ganglia relate to motor effort, but that their relative contributions depend on the level of effort exerted.

Methods

Subjects

Nine patients with idiopathic Parkinson's Disease (mean disease duration 13 years, mean age 62 years, range 49–69 years; 7 males) provided informed consent to take part in this study, which was approved by the local ethics committees. Patients underwent bilateral implantation DBS electrodes into the STN, as a prelude to therapeutic high frequency stimulation for advanced idiopathic PD with motor fluctuations and/or dyskinesia. Techniques to target and implant electrodes in the STN have previously been described (Foltynie and Hariz, 2010). Microelectrode recordings were not made during surgery. The permanent quadripolar macroelectrode used was model 3389 (Medtronic Neurologic Division, Minneapolis, MN, USA) featuring four platinum–iridium cylindrical surfaces. Its contacts are numbered 0, 1, 2, and 3, with 0 being the most caudal and contact 3 being the most cranial. Localisation was supported intra-operatively by the effects of direct stimulation (cases 1–4) and by immediate post-operative stereotactic imaging. Nonetheless, in acknowledgement 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 electrode contact 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. One out of the nine patients (case 1) had only one electrode externalized for testing, thus we could record from 17 STN regions (STNr). Clinical details of the patients are given in Table 1. The patients showed 53.4 ± 6.2% ($p < 0.001$) improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa, indicating good responsiveness to this drug.

Experimental paradigm

Subjects were seated in a comfortable chair with their shoulders adducted and their elbows flexed at about 90°. They were presented with a series of imperative visual cues (red light-emitting diode illuminated for 3 s), separated by 11–13 s, and instructed to 'choose an effort level from the scale provided and then to squeeze the force dynamometer at this chosen effort level when the light comes on and maintain this squeeze for the duration of the light'. The subjects were asked to report the effort level verbally right after each grip. They were also asked to try and randomise their selection of effort levels, so that all levels were represented. Subjects were provided with the Rated Perceived Exertion Scale with 10 levels ranging from zero to 10 (Borg, 1998; Supplementary material). Patients were asked to grip following illumination of the LED, but were not requested to respond as quickly as possible.

Recordings

Recordings were made when the patients were ON their usual dopaminergic medication, 3–6 days postoperatively, while electrodes were externalized and before implantation of the pulse generator. Grip force was measured one hand at a time using an isometric dynamometer with standard Jamar design, and it's handle set in the second of the five discrete grip diameter adjustments possible (G200; Biometrics Ltd, Cwmfelinfach, Gwent, UK; Sancho-Bru et al., 2008). The order in which left and right hands were tested was counterbalanced across subjects. Monopolar LFPs were recorded with a TMSi porti (TMS International, Netherlands) and its respective software. They were low and high pass filtered at 0.5 and 500 Hz, respectively. Force was only low pass filtered at 200 Hz. LFP and force were originally at 2048 Hz. The effort level the subject reported verbally after each grip was logged manually and then used to label each individual trial.

Analysis

The mean number (±SEM) of remaining trials per hand was 31 ± 2 grips. 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 normalized against the average maximal force that the subject achieved in their maximal effort trials. Normalized peak force, normalized peak yank (differentiation of force) and response time were calculated for each individual trial and averaged across trials with the same self-rated effort (SRE), before averaging across subjects. Response time was operationally defined as the time interval between cue onset and the point at which force exceeded 5% of peak force (taken as response onset).

LFP data were converted off-line to give three bipolar contact pairs (01, 12 and 23) per electrode. A time-frequency decomposition based on the continuous wavelet transform was then applied to LFP recordings from each trial to analyse changes in LFP activity in the time–frequency domain. Event related LFP power was subsequently normalized relative to the average power during the one second before the cue, so that a value higher than zero indicated power higher than before the cue and vice versa. The normalized (event related synchronisation, ERS, and event related desynchronisation, ERD) power was aligned to movement onset and subsequently averaged 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. Grand averages of behavioural and LFP data for a given SRE were calculated after deriving each of these variables from the individual grips made by a subject, averaging across trials for a given SRE in that subject, and then averaging across study participants.

Statistics

Statistical analyses were performed in SPSS Statistics 19 (SPSS Inc., Chicago, IL, USA). Visual inspection of Q–Q plots and Kolmogorov–Smirnov tests were used to confirm that behavioural measures and LFP data were normally distributed. Where necessary, raw data were transformed using a monotonic Box–Cox transformation prior to further parametric testing. Multiple regressions were used to identify which, if any, frequency specific LFP activities were significant