Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation

N.J. Ray a,⁎, N. Jenkinson b, S. Wang b, P. Holland b, J.S. Brittain a, C. Joint b, J.F. Stein a, T. Aziz b

⁎ Corresponding author.
E-mail address: nicola.ray@DPAG.ox.ac.uk (N.J. Ray).

Introduction

Parkinson’s disease (PD) is characterised by a poverty and slowness of voluntary movements (akinesia and bradykinesia), muscle rigidity and tremor at rest. Deep recordings in the basal ganglia of patients with PD undergoing functional brain surgery have revealed an excessive synchrony between neuronal populations in specific frequency bands. Pathological activity arises after degeneration of dopaminergic projections from the substantia nigra pars compacta to the striatum, but the exact mechanisms are unclear, as is how such activity contributes to Parkinsonian symptoms. Recently however, research has revealed some important relationships between such activity and the symptoms of PD and its’ treatment (Kuhn et al., 2006). The relationship existed for reductions in scores that indexed the degree of beta power suppression after dopamine intake; however the effects are small and can only be seen in specific patients. Nonetheless, research tends to show that treatments for PD reduce beta synchrony in the basal ganglia. One such report demonstrated a positive correlation between improvements in motor symptoms and the degree of beta power suppression after dopamine intake; measured via local field potential (LFP) recordings in the subthalamic nucleus of patients after surgery to implant DBS electrodes (Kuhn et al., 2006). The relationship existed for reductions in scores that indexed the degree of bradykinesia and rigidity, but not tremor. Similar relationships have been reported for reductions in cortico-cortical beta coherence in the scalp electroencephalogram (EEG) (Silverstein et al., 2005).

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Abstract

Parkinson’s disease is treated pharmacologically with dopamine replacement medication and, more recently, by stimulating basal-ganglia nuclei such as the subthalamic nucleus (STN). Depth recordings after this procedure have revealed excessive activity at frequencies between 8 and 35 Hz (Brown et al., 2001; Kuhn et al., 2004; Priori et al., 2004) that are reduced by dopamine therapy in tandem with improvements in bradykinesia/rigidity, but not tremor (Kuhn et al., 2006). It has also been shown that improvements in motor symptoms after dopamine correlate with single unit activity in the beta range (Weinberger et al., 2006). We recorded local field potentials (LFPs) from the subthalamic nucleus of patients with Parkinson’s disease (PD) after surgery to implant deep brain stimulating electrodes while they were on and off dopaminergic medication. As well as replicating Kuhn et al., using the same patients we were able to extend Weinberger et al. to show that LFP beta oscillatory activity correlated with the degree of improvement in bradykinesia/rigidity, but not tremor, after dopamine medication. We also found that the power of beta oscillatory activity uniquely predicted improvements in bradykinesia/rigidity, but again not tremor, after stimulation of the STN in a regression analysis. However improvements after STN stimulation related inversely to beta power, possibly reflecting the accuracy of the electrode placement and/or the limits of STN stimulation in patients with the greatest levels of beta oscillatory activity.

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Using microelectrodes to record the activity of single units within the subthalamic nucleus during DBS surgery (Weinberger et al., 2006) found that the percentage of cells manifesting oscillatory activity in the beta range correlated with the degree by which PD motor symptoms improved after dopamine replacement therapy. Surprisingly however, the incidence of oscillatory units did not correlate with the severity of symptoms before treatment. This suggests that beta oscillatory activity does not fully characterise motor impairment in PD, perhaps especially in the advanced stages reached by patients undergoing deep brain stimulation (DBS). However it might instead relate to the magnitude of the response of the basal ganglia to dopaminergic agents.

It is not yet clear if DBS of the STN also reduces beta oscillatory activity. The artefact recorded during stimulation precludes accurate measurement of neuronal oscillatory activity. Also, studying the time period immediately after stimulation while the effects of treatment persist has yielded conflicting results (Wingeier et al., 2006; Foffani et al., 2006). Therefore, deciding whether the relationship reported by Kuhn et al. (2006) between beta oscillatory activity and benefits from dopamine also exists for STN stimulation is not possible with current data. It is possible however to test the relationship reported by Weinberger et al. (2006) showing that beta oscillatory activity correlates with the degree to which symptoms respond to dopaminergic medication, as this does not require measurements of beta oscillatory activity during or after DBS.

DBS of the subthalamic nucleus has been suggested to improve Parkinsonian symptoms by disrupting pathological beta oscillatory activity. Therefore given the relationships between beta oscillatory activity and the dopaminergic response, it is reasonable to expect that beta power will also relate to the response to STN stimulation. Determining what this relationship is could help us to predict which patients will benefit most from surgery. However the effectiveness of STN stimulation depends on many factors, including the degree of the pre-surgery dopaminergic response and the accuracy of the electrode placement. Any investigation into the relationship between beta oscillatory activity and the efficacy of surgery should therefore control for the influence of such variables on improvements in symptoms.

The related but different associations between activity in the beta band and dopaminergic medication found by Kuhn et al. (2006) with local field potentials, and Weinberger et al. (2006) with single unit activity is yet to be demonstrated in the same set of patients. Since the unit activity was also found to be coherent with the simultaneously recorded LFP in the Weinberger et al., study, we should also be able to detect the relationship they found between the incidence of oscillating units and dopaminergic response using LFP data. In the present study we were able to corroborate both these findings in a single sample of patients using LFP recordings.

We also report evidence to support a negative association between power in the beta range and the efficacy of STN stimulation.

Methods

Patients and surgical procedure

Patients (n = 7) were between ages 55 and 65 and had been diagnosed with PD a mean of 16 years previously. Their clinical details can be found in Table 1. One patient’s post-operative data was not available. In all but one unilateral implantation, DBS electrodes were implanted bilaterally in the STN. Our surgical procedure has been detailed elsewhere (Liu et al., 2001). DBS electrodes were considered accurately placed in the STN by the surgical and clinical team if there was effective intraoperative and post-operative stimulation, and post-operative MRI confirmation of at least one electrode contact in the STN region.

Local field recordings

Patients were studied over two separate days (off and on medication) in the days following surgery, before their DBS electrodes were implanted. Any investigation into the relationship between beta oscillatory activity and the accuracy of the electrode placement. Any investigation into the relationship between beta oscillatory activity and the efficacy of surgery should therefore control for the influence of such variables on improvements in symptoms.

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Clinical assessment

Assessment of Parkinsonian symptoms was by the motor subscale of the unified Parkinson’s disease rating scale (UPDRS). Only items that were separated by hemibody were included. The scores were then divided into two subscales, separating those pertaining to tremor or bradykinesia/rigidity. The UPDRS was administered on and off Parkinsonian medication by a specialist nurse 3 months (and not more than 12 months) both pre- and post-surgery. Improvements after medication (dopa-response) were calculated as follows: [(UPDRS off meds –UPDRS on meds)/ UPDRS off meds] × 100. Improvements due to STN stimulation (stim-response) were always measured off medication by the following: [(UPDRS pre-surgery –UPDRS post-surgery)/ UPDRS pre-surgery] × 100.
Analysis

Signals were downsampled to a common sampling frequency of 1000 Hz. Autospectra were estimated using the discrete Fourier transform. 60 s of data were extracted from each record and spectra were generated using Welch’s overlapping segments (Welch, 1967) with 1 s windows and 50% overlap. The contact pairs displaying the maximum 8–35 Hz activity off medication was selected for further analysis. The maximum peak within this band was determined using Matlab scripts which calculated the frequency bin with maximum power, and corroborated by visual inspection of the frequency spectra. Peak power was then calculated from the adjacent two bins on either side of the peak frequency. The same band was then used to calculate power in the on medication recordings. Significant peaks could not be determined in 2 sides, and these have not been included in the analysis. Percentage of power decreases were determined by the following calculation: [(power off medication−power on medication)/power off medication]×100.

We ensured that all variables were normally distributed using Kolmogorov–Smirnov tests. Spearman’s rho was used to compute correlations between improvements in the UPDRS scores and beta power, chosen because the UPDRS is a rating scale. N.B. none of the findings are altered if a Pearson’s correlation is used. Next we used a multiple regression analysis (with each variable entered simultaneously) to determine the predictive power of beta oscillatory activity and the response to dopamine on improvements in motor symptoms due to STN stimulation. Improvements in bradykinesia/rigidity after STN stimulation were regressed simultaneously on the improvements in pre-surgery bradykinesia/rigidity symptoms after dopamine and beta power off medication. Also, improvements in tremor after STN stimulation were regressed simultaneously on the improvements in pre-surgery tremor symptoms after dopamine and beta power off medication. All statistical analysis were performed in SPSS (SPSS for windows version 15, SPSS Inc., Chicago, Illinois).

Results

The clinical details of the patients are reported in Table 1, along with UPDRS scores on and off medication, pre- and post-surgery. 11 out of the 13 sides tested showed prominent peaks within the 8–35 Hz (beta) band. Individually defined peaks were reduced by an average of 54.3% after dopamine \((t=3.3, P<0.01, df=10)\). Consistent with previous reports (Kuhn et al., 2006), suppression of beta power correlated with changes in the bradykinesia/rigidity UPDRS scores for the contralateral limbs \((r=0.7, P<0.05, N=11)\) (Fig. 1) but not with changes in tremor sub-scores \((r=-0.3, P=0.15, N=9)\) (2 patients had pre-operative UPDRS scores of 0 and were therefore excluded from this analysis) (Fig. 2).

We found no correlation between beta power and baseline motor symptoms \((r=-0.35, P=0.15, N=11)\) (data not shown), but a significant positive relationship between baseline beta power (off medication) and improvements in motor symptoms after dopamine intake \((r=0.68, P=0.01, N=11)\), as previously reported by Weinberger et al. (2006). Further, we found that this relationship exists only for the bradykinesia/rigidity scores \((r=0.61, P<0.05, N=11)\) (Fig. 3), and not tremor scores \((r=0.28, P=0.23, N=9)\) (Fig. 4).

We obtained post-operative UPDRS scores in 6 of the patients, one of whom received a unilateral implant. In another only one side was included due to the absence of a beta peak in the other. In two sides pre-operative UPDRS tremor scores were 0, therefore they are not included in the analysis regarding tremor. After STN DBS, the off drugs motor UPDRS scores were reduced by a mean of 41% \((t=3.7, P<0.01, df=10)\). The mean reduction in bradykinesia/rigidity UPDRS scores
was 37% ($t=3.2$, $P<0.01$, $df=10$), while the mean reduction in tremor UPDRS scores was 59% ($t=2.2$, $P=0.052$, $df=8$).

Improvements in motor symptoms after STN stimulation, analysed as a whole or separately for bradykinesia/rigidity and tremor, did not correlate directly with beta peak power measured off medication (Motor: $r=0$, $P=0.5$, $N=10$, bradykinesia/rigidity: $r=0.1$, $P=0.4$, $df=10$, tremor: $r=-0.2$, $P=0.3$, $N=8$). However the response to STN stimulation is likely to be influenced by other factors such as the pre-surgery response to dopamine. Improvements in motor symptoms after dopamine and off medication beta power were therefore entered into a multiple regression to determine how well they could predict improvements in motor symptoms after STN stimulation.

We found that after removing one outlier with a standardised residual greater than 2SD (filled dot in Fig. 5), bradykinesia/rigidity improvements after dopamine and off medication beta power did significantly predict improvements in bradykinesia/rigidity after STN stimulation ($R^2=0.64$, $F=8.2$, $P<0.05$). Both variables alone contributed significant predictive power to the change in bradykinesia/rigidity scores after STN stimulation (change in bradykinesia/rigidity after dopamine: $t=3.9$, $P<0.001$, off medication beta: $t=-3$, $P<0.05$) (Fig. 5).

To ensure that the significant correlation between the two independent variables, reported above, did not contaminate the results of the regression we computed collinearity statistics. These revealed that the tolerance between beta power off medication and the change in bradykinesia/rigidity after dopamine was 0.73, indicating that each had enough independent variance to use them together in the regression analysis.

In a similar multiple regression, the improvements in tremor scores after STN stimulation could not be predicted by the improvements in tremor scores after dopamine and off medication beta power ($R^2=0.04$, $F=1.1$, $P=0.4$). Each independent variable alone did not contribute significant predictive power (change in tremor scores after dopamine: $t=1.4$, $P=0.21$, off medication beta power: $t=-0.7$, $P=0.52$) (Fig. 6).

**Discussion**

Using LFP recordings, we are able to corroborate the findings reported by Weinberger et al. (2006) and Kuhn et al. (2006) in a single sample of patients. Weinberger et al. made microelectrode recordings during surgery to implant DBS electrodes in the STN. They found that while the incidence of neurons oscillating within the beta range did not correspond with the severity of motor symptoms, it did correlate with the responsiveness of motor symptoms to dopamine replacement therapy. Kuhn et al. found that beta oscillatory activity measured by local field potentials in the days immediately following STN surgery is reduced after dopamine in accord with the concurrent reduction in bradykinesia and rigidity, but not tremor. As well as confirming both findings, we were also able to show that the association between beta oscillatory activity and the responsiveness of motor symptoms to dopamine reported by Weinberger et al. follows the same pattern as that described by Kuhn et al. i.e. existing only for the bradykinesia/ rigidity symptoms, and not tremor.

The lack of a correlation between baseline motor symptoms and beta oscillatory activity suggests that beta in the STN does not fully characterise the Parkinsonian state (but might also reflect the fact that, unlike the percentage change in beta with medication, baseline beta oscillatory activity measurements are not normalised and are therefore contaminated by variance due to factors such as the accuracy of the electrode placement, thus weakening potential relationships). This may be especially true for patients with advanced PD, like those opting for DBS surgery, whose symptoms may reflect...
pathologies in wider brain areas. However the relationships between beta oscillatory activity and improvements after dopamine intake support suggestions that dopamine depletion can lead to a greater impact of cortical activity on the STN (Magill et al., 2001; Sharott et al., 2005). Thus, beta oscillatory activity measured via local fields or microelectrodes might relate to the degree of loss of nigrostriatal dopamine inputs, and therefore the degree to which the basal ganglia responds to dopaminergic agents.

It remains to be explained why none of the relationships reported above exist for tremulous symptoms, even though tremor is improved by dopamine medication (but see Levy et al., 2000). These findings suggest a model of PD in which loss of dopamine causes excessive beta oscillatory activity in basal-ganglia nuclei which results in bradykinesia and rigidity. The loss of striatal dopamine also causes tremor, but this relates to alterations in the network activity of the internal globus pallidus (GPI) (Filion and Tremblay, 1991), which then induces activity in tremor cells of the ventral lateral thalamus (Pare et al., 1990). Moreover, tremor could be related to pathology in circuits other than those involving the basal ganglia (Stein and Aziz, 1999). However, some studies have reported finding tremor related activity in the STN (Levy et al., 2002; Rodriguez-Oroz et al., 2001). It remains to be seen if this activity is specifically related to changes in tremor symptoms after dopamine.

Activity in STN single units was previously shown to be statistically coherent with, and time locked to activity in the LFP (Levy et al., 2002; Kuhn et al., 2005 respectively). Further, in the Weinberger et al. study there was synchrony between the beta activity recorded in the single units and the simultaneously recorded LFP, and the incidence of oscillating units correlated with percentage of beta power in the LFP. It is reasonable then to expect that the relationship between patients’ benefit from dopamine and beta oscillatory activity can be found with both LFP and microelectrode recordings. However given that beta oscillatory activity in the LFP was observed even in patients with small numbers of oscillating units, it would be of interest to determine the relative contribution of each to the relationship with motor improvements after dopamine.

Given the findings reported by Kuhn et al. and Weinberger et al., and replicated here, it is reasonable to assume that a relationship also exists between beta LFP activity and improvements in motor symptoms after DBS of the STN. Initially we found no such direct correlation. However symptoms that are not responsive to dopamine tend to also not be responsive to STN stimulation (Benabid et al., 2000; Lang and Widner, 2002) possibly due to the non-basal-ganglia origin of some symptoms. This relationship, and that just described between beta power and the dopaminergic response could be obscuring the association between STN stimulation efficacy and beta oscillatory activity. Indeed, in a multiple regression analysis which holds variance due to an independent variable (pre-surgery dopaminergic response) constant while assessing the strength of the relationship between the independent variable of interest (response to STN stimulation) and the dependent variable (beta power off medication), we found that beta power off medication could significantly predict improvements in bradykinesia/rigidity scores. A similar regression using UPDRS scores relating to tremor revealed that beta oscillatory activity off medication did not significantly predict improvements in tremor after STN stimulation. In contrast to the relationship between beta power and the dopaminergic response, beta oscillatory activity was negatively associated with improvements in bradykinesia/rigidity after STN stimulation. This suggests that while improvements after STN stimulation require symptoms to be responsive to dopamine they also depend inversely on the level of beta oscillatory activity within the STN. Patients with least beta oscillatory activity in the LFP, after removing variance due to the dopaminergic response, will respond most to STN stimulation.

The association between beta oscillatory activity in the LFP and improvements after STN stimulation can be interpreted in two ways. Firstly, low levels of beta oscillatory activity might be easier to disrupt. In patients with greater levels stimulation of the STN might only partially disrupt beta oscillatory activity, therefore allowing residual beta oscillatory activity to be transmitted through the basal-ganglia cortical loops and resulting in the incomplete treatment of symptoms. Note however that this explanation depends on the assumption that beta oscillatory activity causes PD symptoms, rather than just correlates with them. Alternatively the results may be explained by a post-operative “stun effect” in which patients’ symptoms are improved even without stimulation. During surgery acute increases in LFP beta power indicate that DBS electrodes are positioned within the STN (Brown and Williams, 2005). However due to perioperative oedema it is possible that beta oscillatory activity is temporarily disrupted when LFPs are recorded a few days post-operatively. A negative correlation between the benefits from STN stimulation and beta power would ensue if this effect was greatest in patients with better localised electrodes. Unfortunately it is difficult to disentangle these effects using the present data.

Regardless of which of these effects contributes most to the relationship, these data suggest that it may be possible to use beta power measurements in the LFP post-surgery to predict which patients will benefit most from STN stimulation, thus aiding clinicians during the post-operative stages. It is also possible to measure beta oscillatory activity before surgery using magnetoencephalography (MEG), which can localise sources of activity even in deep brain structures, or by inferring basal-ganglia activity from cortical EEG recordings. This data would enable us to dissociate the stun effect described above from the relationship between beta oscillatory activity and the efficacy of STN stimulation. Should the relationship survive, it may be used to provide an important pre-surgery measure of the expected benefit for each patient.

In summary we can confirm Kuhn et al. (2006), that beta oscillatory activity is reduced after dopamine therapy, and that this reduction correlates with improvements in bradykinesia/rigidity, but not tremor. In the same set of patients we also found significant correlations between LFP beta power measured off medication and the benefit from dopamine therapy, previously reported by Weinberger et al. (2006) with microelectrode recordings. Further, we found that the relationship reported by Weinberger et al. was only true for bradykinesia/rigidity, and not tremor symptoms. Taken together these findings suggest that beta oscillatory activity may reflect the loss of dopaminergic input to the striatum, and therefore the degree to which the basal ganglia respond to dopaminergic agents. We also found that benefits from STN stimulation were negatively associated with beta LFP activity after the variance due to the dopaminergic response was controlled for. This suggests that the efficacy of STN stimulation is dependant in opposite ways on the dopaminergic response and the level of baseline beta oscillatory activity, which may in future be used to more accurately predict each patients response to DBS of the STN.

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