Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson’s disease

Moran Weinberger¹, Neil Mahant¹,⁴, William D. Hutchison¹,², Andres M. Lozano²,³, Elena Moro²,⁴, Mojgan Hodaie²,³, Anthony E. Lang²,⁴, Jonathan O. Dostrovsky¹,²

¹ Dept. of Physiology, University of Toronto, Toronto, ON, Canada; ²Toronto Western Research Inst., Toronto, ON, Canada ³Toronto Western Hospital, Division of Neurosurgery, University of Toronto, Toronto, ON, Canada ⁴Dept. of Medicine, Division of Neurology, University of Toronto, Toronto, ON, Canada

Running head: Subthalamic nucleus oscillatory activity

Corresponding Author:
Jonathan Dostrovsky
Dept of Physiology
Med Sci Bldg 3302
1 King’s College Circle
University of Toronto
Toronto, ON M5S 1A8
416 978 5289
416 978 4940
j.dostrovsky@utoronto.ca
Abstract

Recent studies suggest that beta (15-30 Hz) oscillatory activity in the subthalamic nucleus (STN) is greatly increased in Parkinson’s disease (PD) and may interfere with movement execution. Dopaminergic medications decrease beta activity and deep brain stimulation (DBS) in the STN may alleviate PD symptoms by disrupting this oscillatory activity. Depth recordings from PD patients have demonstrated beta oscillatory neuronal and local field potential (LFP) activity in STN, but its prevalence and relationship to neuronal activity is unclear. In this study, we recorded both LFP and neuronal spike activity from the STN in 14 PD patients during functional neurosurgery. 56 out of 200 single and multi unit recordings showed significant oscillatory activity at ~26 Hz and 89% of these were coherent with the simultaneously recorded LFP. The incidence of neuronal beta oscillatory activity was significantly higher in the dorsal STN (p = 0.01) and corresponds to the significantly increased LFP beta power recorded in the same region. Of particular interest was a significant positive correlation between the incidence of oscillatory neurons and the patient’s benefit from dopaminergic medications, but not with baseline motor deficits off medication. These findings suggest that the degree of neuronal beta oscillatory activity is related to the magnitude of the response of the BG to dopaminergic agents rather than directly to the motor symptoms of PD. The study also suggests that LFP beta oscillatory activity is generated largely within the dorsal portion of the STN and can produce synchronous oscillatory activity of the local neuronal population.
Introduction

Damage to the basal ganglia (BG) is well known to result in a variety of movement disorders highlighting the important although still poorly understood function of these nuclei in the motor system. The loss of nigral dopaminergic input to the striatum in Parkinson’s disease (PD) leads to a poverty and slowness of movements, rigidity and frequently also postural instability and tremor, but the mechanisms underlying these abnormalities remain unclear. Studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated monkeys and in PD patients suggest that one of the consequences of loss of dopaminergic inputs to the BG is increased synchronized oscillatory activity in the subthalamic nucleus (STN) and globus pallidus interna (GPi) (Bergman et al. 1994; Levy et al. 2000, 2002; Marceglia et al. 2006; Nini et al. 1995).

Depth recordings of local field potentials (LFPs) in STN of PD patients have demonstrated prominent oscillatory activity in the beta frequency band (15-30 Hz) (Brown et al. 2001; Cassidy et al. 2002; Kuhn et al. 2004; Levy et al. 2002), which is coherent with cortical EEG activity (Marsden et al. 2001b; Williams et al. 2002). The STN beta LFPs are decreased by dopaminergic medication and active movements (Alegre et al. 2005; Alonso-Frech et al. 2006; Cassidy et al. 2002; Doyle et al. 2005; Foffani et al. 2005; Kuhn et al. 2004; Levy et al. 2002; Priori et al. 2004; Williams et al. 2003). It has been suggested that the therapeutic effects of deep brain stimulation (DBS) are due to disrupting this pathologically increased synchronized beta activity (Brown et al. 2004; Filali et al. 2004; Jahanshahi et al. 2000; Lozano et al. 2002; Wingeier et al. 2006).
The origin of the beta LFP activity is still poorly understood. However, studies by Levy et al. (2000) demonstrated the existence of neurons in STN that fired rhythmically at frequencies within the beta band and many pairs of neurons were shown to fire synchronously in the beta range. Moreover, the STN oscillatory neurons fire in synchrony with the simultaneously recorded beta LFP and the beta LFP activity is maximal in the dorsal part of STN (Kuhn et al. 2005; Levy et al. 2002).

To further elucidate the relationship of the STN oscillatory neuronal activity and LFPs and their possible role in mediating the motor symptoms of PD, we simultaneously recorded neuronal and LFP activity from pairs of microelectrodes in the STN of PD patients at rest and off medication. Moreover, investigation of the changes in the neuronal and LFP beta activity with depth along the electrode trajectories, above and within the STN, allowed analysis of the distribution of these activities within the nucleus. Also of interest is whether there is a relationship between the incidence of beta oscillatory cells and the patient’s motor impairment and/or the effectiveness of dopaminergic medication in alleviating the patient’s parkinsonian symptoms. Thus we examined the relationship between the percentage of STN oscillatory cells and the degree of motor disability on and off dopaminergic medication. Clarification of the relationship between the recorded LFP, local neuronal discharge and clinical symptoms will provide further insight into the possible roles of these beta rhythms and their relationship to the therapeutic effectiveness of dopaminergic medication. The findings reported in this paper have been reported briefly in Weinberger et al. (2005).
Methods

Patients

We studied 14 patients with advanced PD who were undergoing stereotactic surgery for implantation of bilateral STN DBS electrodes. The group consisted of five women and nine men who, at the time of operation, had a mean age of 57 years (range 46-68) and a mean duration of PD of 14.1 ± 5.2 (mean ± SD) years. All patients were assessed preoperatively using the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al. 1987) before and after an acute levodopa challenge (Moro et al. 2002). During surgery the patients were awake and off dopaminergic medications for at least 12 hours from the last oral dose of antiparkinsonian medications. Demographic details of the patients are given in Table 1. The studies were preformed with approval of the University Health Network Ethical Review Board, University of Toronto. Patients gave written and informed consent prior to surgery.

Recordings

All recordings were performed in the resting state and under local anesthesia. Patients were not asked to perform any task, and epochs with movements were excluded. Neuronal activity and LFPs were recorded simultaneously from two independently driven, microelectrodes (~25 µm tip length, axes 600 µm apart, ~0.2 MΩ impedance at 1000 Hz) during the electrophysiological mapping procedure used to obtain physiological data for localizing the target for the DBS electrode placement. The localization procedure of the STN using microelectrode recording has been previously described in detail (Hutchison
et al. 1998). Briefly, the dorsal border of STN was noted by increase in background activity and high frequency neuronal discharge. As the electrodes were advanced past the ventral border of STN the background noise decreased until the electrode reached the substantia nigra pars reticulata, which was identified by higher frequency, lower amplitude discharges compared with STN. All recordings were amplified 5000-10000 times, filtered at 10 to 5000 Hz (analog Butterworth filters, high pass one-pole, low pass 2–pole) using two Guideline System GS3000 (Axon Instruments, Foster City, CA) amplifiers. The signals were digitized at 10 kHz with a CED 1401 (Cambridge Electronic Designs, Cambridge, UK). Pairs of simultaneous recordings of neurons and/or LFPs were generally at approximately the same depth. The mean linear distance between the pairs of recording sites was 0.83 ± 0.3 mm (mean ± SD, n=195).

Data analysis

Single and multiunit activity was discriminated using the wavemark template matching tool in Spike2 (Cambridge Electronic Design, Cambridge, UK). Only sites where good unit recordings were obtained were analyzed. At 24% of the sites the action potentials were well discriminated and deemed to be from a single unit. At the remainder of the sites we could not rule out the contribution from an additional one or more units and these were then termed multiunit recordings. However, the difference between the mean (± SD) firing rate of the single units and the multiunit sites was relatively small (39.1 ± 18.6 Hz vs 49.1 ± 24.5) suggesting that even in the multiunit cases, most of the discriminated spikes were probably from a single cell. In the remainder of the manuscript the use of the term cells refers to both single units and multi-unit recording sites. Spike
times and unfiltered LFP data were imported into MATLAB (version 6.5, The Math Works, Natick, MA) for further analysis. Recordings from 21 sides in 14 patients were analyzed. In 7 patients both right and left sides were analyzed, only left STN recordings were analyzed in 4 patients and right STN in 3 patients. Only data of ≥ 17 seconds duration during periods without movements (based on EMG recordings and observations) or artifacts were analyzed (range: 17-214 sec, mean ± SD: 36.5 ± 22.9 sec). Recording depths were realigned to the top of STN in each track, where 0 is the dorsal border of STN and negative values are ventral to this border.

The main statistical tool for data analysis used in this study was the discrete Fourier transform and its derivations calculated according to Halliday et al. (1995). After signals were down-sampled to 1 kHz, spectra of LFP power were estimated by dividing the waveform signal into a number of sections of equal duration of 1.024 s (1024 data points, 512 point overlap), each section was windowed (Hanning window) and the magnitudes of the 1024 discrete Fourier transform of each section were squared and averaged to form the power spectrum, yielding a frequency resolution of 0.97 Hz. The power was transformed to a logarithmic scale and shown in decibels (dB). Since the estimated power spectrum has a distribution which is analogous to a $\chi^2$ distribution, the 95% confidence intervals were given on the basis of the $\chi^2$ distribution (Jarvis and Mitra 2001) while the degrees of freedom is based on the number of windowed sections.

To estimate the relative beta power according to distance above or below the top of STN, we identified the frequency of the beta peak of each STN trajectory, and the mean power
across a 10 Hz window centered on the peak frequency was calculated at each recording site. LFP power at each recording site was then expressed as the percentage of the maximum power observed in the trajectory. Percentages of maximum power were averaged across subjects to give mean percentage of LFP beta power (Kuhn et al. 2005).

Spectral analysis of spike trains was performed using the Fourier transform (Halliday et al. 1995) and significant oscillations were detected using shuffling of spike trains (Rivlin-Etzion et al. 2006). Inter spike interval (ISI) shuffling generates a new spike train by using the time differences between adjacent spikes (first-order ISIs). Hence, the spectrum of the new spike train is determined solely by the first-order ISIs of the original spike train while higher-order effects (i.e., the time difference between spikes that are separated by 1 spike or more) are abolished by the shuffling process. Comparing the original spectrum to the new one enables one to detect patterns such as oscillations that are generated by higher-order ISIs. In order to obtain an accurate and less noisy estimate, we repeated the shuffling process 100 times and averaged the results. Subtraction of the new spectrum from the original spectrum resulted in a corrected spectrum, in which peaks were considered significant when they exceeded the upper 95% confidence limit. The confidence limit was estimated from the corrected spectrum based on the $\chi^2$ distribution as described above. Since the variance for the corrected spectrum is the same for all frequencies, the confidence interval depends solely on the degrees of freedom and the term is a constant that does not depend on the frequency (Rivlin-Etzion et al. 2006). Relative beta power according to depth for neuronal firing activity was estimated from
the original power spectrum in the same manner described above for estimating LFP power changes.

Coherence and cross-correlation analyses (Halliday et al. 1995; Rosenberg et al. 1989) were used to assess the relationship between simultaneously recorded data from separate electrodes and between LFP and spike data recorded from the same microelectrode. The coherence function provides a frequency domain bounded measure of association, taking on values between 0 and 1, with 0 in case of independence and 1 in case of a perfect linear relationship. Coherence can be estimated by direct substitution of the appropriate spectra as: $|f_{xy}|^2 / f_{xx} f_{yy}$ with 95% confidence level of $1-(0.05)^{1/(L-1)}$, where L is the number of disjoint sections. Cross-correlation provides a time domain measure of dependence between random processes and is defined by the inverse Fourier transform of the cross-spectrum $f_{xy}$. Cross-correlation can also be defined and estimated directly in the time domain; however the estimation via the frequency domain facilitates the construction of confidence limits (Halliday et al. 1995). In order to estimate the 95% confidence limits, the variance of the cross-correlation ($\text{var}_{\text{cross-corr}}$) was approximated based on the auto-spectra of the component processes ($f_{xx}$ and $f_{yy}$). Under the hypothesis that in the case of two independent processes the value of the cross-correlation function is zero, the upper and lower 95% confidence limits for the estimated cross-correlation are given by $0 \pm 1.96(\text{var}_{\text{cross-corr}})^{1/2}$. Correlation histograms of the 11-35Hz bandpass filtered LFP were plotted for delays of 500 ms (1 ms bin width). Peaks were considered significant if they exceeded the 95% confidence interval.
Changes in LFP power were evaluated by change-point analysis and control limits (Change-Point Analyzer 2.0 shareware program; Taylor Enterprises, Illinois). Change-point analysis iteratively uses a combination of cumulative sum (cusum) and bootstrapping to detect changes, and is more sensitive to change than control limits which is based on plots of serial deviations from the mean (Taylor 2000). Cusums were determined by plotting the sequentially summed deviation from the averaged power. Significant changes were determined by control limits that give the maximum range over which values are expected to vary (with 95% probability). The application of this technique to power changes in the basal ganglia has been used in previous studies (Cassidy et al. 2002; Kuhn et al. 2004; Williams et al. 2003). To examine the relationship between incidence of oscillatory cells and clinical motor symptoms and effectiveness of medications we used part III (motor) of the UPDRS “on” and “off” total scores as well as subscores as evaluated 8.1 ± 7.8 days (mean ± SD) before surgery. The effectiveness of the antiparkinsonian medications was calculated as the difference between the “on” and “off” scores, divided by the “off” score to give the percentage of benefit. Non-linear regression statistics in addition to linear regression were used to better describe the correlations using SigmaStat (version 3.1, Systat Software Inc., Richmond, CA).

Results

Coherence between neuronal and LFP beta oscillatory activity in the STN

Of 200 single and multiunit recordings in 14 patients, 56 (28%) displayed significant beta (15-30 Hz) oscillatory activity at 25.8 ± 3.7 Hz (mean ± SD). There was no significant
difference in the fraction of oscillatory cells between the single and the multiunit recordings (31.3% vs. 27% respectively, \( \chi^2 \) test). In 50 (89.3%) of the oscillatory cells, the oscillatory activity was coherent with the LFP recorded from one or both electrodes. Neuronal oscillatory activity at other frequencies was only rarely encountered. We observed significant coherence in the beta range between the LFPs at all the STN sites where LFP activity was recorded from both electrodes, even in cases where no peak in the beta band was observed in the LFP power spectrum. In contrast, the firing of only 17 of the 67 (25.4%) pairs of cells recorded from the two electrodes was significantly coherent in the beta range. Coherence was present in 9 of 10 cases where beta oscillations were detected in both cells and in 6 of 15 cases where beta oscillations were detected in just one cell; the firing activity in two pairs of cells was coherent even though no beta oscillations were detected in either cell. Figure 1 shows an example of coherence plots and correlograms from simultaneous recordings of neuronal and LFP activity where there was significant neuronal and LFP beta activity.

**Incidence of neuronal oscillatory beta activity is higher in dorsal STN**

The majority of the beta oscillatory cells was localized in the dorsal STN. The mean depths from the top of STN of the oscillatory (n = 56) and non-oscillatory (n = 144) cells (± SD) were -1.5 ± 1.1 mm and -2.1 ± 1.3 mm respectively (p = 0.001, t-test). Fig. 2A shows the distributions of the locations of the oscillatory and non-oscillatory cells at successive 0.3 mm intervals. The two distributions are illustrated by box-plots in Fig. 2B (median locations: -1.3 and -2.0 mm for oscillatory and non-oscillatory cells respectively). 75% of the oscillatory cells were found in the dorsal STN while 25% were in the ventral
STN ($p = 0.01$, $\chi^2$ test). On the other hand, there was no significant difference in the incidence of non-oscillatory cells in the dorsal and ventral STN (54% vs. 46% respectively). There was a significant relationship between the dorsal/ventral location and the presence/absence of neuronal beta activity ($p = 0.003$, $\chi^2$ test).

**LFP beta oscillations are greatest in dorsal STN**

The power of the beta activity recorded from the pair of microelectrodes in the 14 patients was calculated for 351 sites located from 5 mm dorsal to 5 mm ventral to the dorsal border of STN. Figure 3A plots the changes in the % maximum LFP power from each individual patient, and Figure 3B shows the average % maximum LFP power for all the 14 subjects as a function of depth in 0.5 mm intervals. Note that LFP power exceeds the upper 99% confidence limit (mean + 2.58 SD) for the intervals between -0.5 mm to -2.5 mm in STN. A similar distribution of the beta LFP power was also observed when recording depths were aligned to the bottom instead of the top of STN. Averaging the percentage of beta LFP power every 2.5 mm reveals significantly greater power in the dorsal part ($p < 0.001$, Mann-Whitney Rank Sum test) (Fig. 3C). The power in the ventral STN was significantly higher than the power above STN ($p = 0.002$). These results were confirmed by control charts and change-point analysis. Analyses were performed on the median LFP beta power in each site (Fig. 3D). Two significant changes were detected, the first change was an increase in power in the 0.5 mm interval between -0.5 to -1.0 mm and the second change was a decrease in power at the -2.5 to -3.0 mm interval. A similar analysis of the neuronal oscillatory power according to depth revealed
a gradual reduction in the mean beta power from the dorsal to the ventral border of STN (data not shown) resembling that found for LFP power.

The distributions of oscillatory cells and mean LFP beta power by depth within the STN reveal the same pattern of greater beta activity dorsally. Figure 4A shows the variations in mean % LFP beta power and % of oscillatory cells with depth within the STN in 0.5 mm intervals and the corresponding regression lines (Linear regression, $R^2 = 0.63$ and $R^2 = 0.71$ respectively). The relationship between depth within the STN and amount of beta activity is not significantly different for cells and LFPs (t-test for difference in slope, $p = 0.23$). Figure 4B shows the strong linear correlation between the percentage of oscillatory cells and the mean LFP beta power at different depths within the STN (Linear regression, $R^2 = 0.63$).

**Neuronal oscillations correlate with levodopa response**

The percentage of beta oscillatory cells in STN (including both sides) was found to vary greatly between patients (see Fig. 5), but interestingly was negatively correlated with the “on” drug UPDRS score (Fig. 5B) and positively correlated with the magnitude of the pre-operative levodopa response (Fig. 5C) (non-linear regression, $R^2 = 0.49$, $p < 0.05$ and $R^2 = 0.62$, $p < 0.005$ respectively; linear regression, $R^2 = 0.37$, $p = 0.02$ and $R^2 = 0.46$, $p < 0.01$ respectively). Similar significant correlations occurred between % beta oscillatory cells and medication response on tremor and on the other non-tremor sub-scores of the UPDRS (data not shown). However, no significant correlation was observed between the percentage of oscillatory cells and the “off” drug UPDRS score (Fig. 5A). Moreover, no
significant correlations were observed with the different “off drug” UPDRS sub-scores such as tremor, rigidity and postural instability. Figure 6 demonstrates the lack of association between the percentage of oscillatory cells and “off” total tremor scores.

**Discussion**

This study provides new data documenting the relationship of neuronal beta oscillatory activity to local field potential activity at the recording site and at a distance of about 1mm. In addition, we describe the distribution of neurons with oscillatory activity within STN. Most interestingly, our data show a significant positive correlation of neuronal oscillatory activity with the patient’s benefit from dopaminergic medication. The study also confirmed previous reports that oscillatory LFP activity in the beta range is consistently observed in all PD patients off dopaminergic medications (Alonso-Frech et al. 2006; Brown et al. 2001; Cassidy et al. 2002; Kuhn et al. 2004; Levy et al. 2002; Marceglia et al. 2006; Priori et al. 2004). However, unexpectedly the incidence of cells with oscillatory firing in the beta range varied greatly between patients.

Our results demonstrating coherence between neuronal discharge and LFPs in the beta range confirm and extend the findings of two previous reports (Kuhn et al. 2005; Levy et al. 2002). The Levy study only reported data from a single case showing statistically significant coherence between the LFP recorded from a macroelectrode and the discharge of a cell recorded about 1mm away, whereas the Kuhn study in 6 patients used spike triggered averaging of the LFP recorded from a different contact at the microelectrode tip less than 30um away to show that the activity of some of the neurons was timelocked to
the beta oscillations in the LFP. This is the first study to examine the coherence between unit activity and LFPs recorded both from the recording microelectrode and another microelectrode located about 1 mm away and showed that neuronal activity was frequently coherent with beta oscillatory activity recorded 1 or more mm away. Furthermore, the firing of 90% of the cells with beta oscillatory activity was coherent with the LFP in the beta range. Interestingly, the LFPs at all pairs of recording sites within STN showed significant coherence in the beta range even in cases where no peak in the beta band was observed in the LFP power spectrum. These observations suggest that the generators of the beta LFP oscillations are distributed and synchronized over a large region (at least several mm) of the STN.

The present study confirmed the observation in the Levy et al. (2000) study that pairs of cells in STN could be found which fired rhythmically and synchronously at beta frequencies. In total we found that 25% of the pairs fired coherently at beta frequencies which is comparable to the 30% in the Levy et al. study. However, the findings of the Levy et al. study suggested that beta oscillatory activity was present primarily in patients with tremor since all but one of the coherent pairs were from the patients with tremor where 47 % of the pairs were found to fire coherently. In contrast, the current study which included a larger and different population of patients failed to find such a relationship. The tremor patients in the Levy study were identified on the basis of their having tremor during the operation whereas in our study patients were defined as having tremor on the basis of the pre-op UPDRS tremor subscore. However this is unlikely to have had a major impact on the conclusions of the two studies and we ascribe the
difference to lower number of patients in the Levy study where only 3 patients were in the non-tremor group.

Unexpectedly, the percentage of cells with beta oscillatory activity varied greatly and ranged from a low of 0 cells to a high of 90% of STN cells per patient even though in all cases the local field potentials revealed the presence of beta oscillatory activity. It is possible that the variability in the number of oscillatory cells is a confound resulting from limited sampling. However, this would imply that only a relatively small part of the STN contains cells firing rhythmically at beta frequencies, which would seem unlikely and inconsistent with the data and conclusions discussed above. A more likely possibility is that STN neuron membrane potential oscillations which generate the beta LFPs are largely confined to the dendrites and do not necessarily strongly influence the probability of the neuron firing. Thus neurons with non-significant beta oscillatory firing may nonetheless contribute to the generation of beta oscillatory LFPs. With increased oscillatory synaptic inputs and/or somatodendritic coupling there would be increased probability and power of oscillatory spike activity. Even in the cases where there were only a small number of oscillatory neurons their activity could still produce a significant effect on STN target nuclei because a weak correlation among very many neurons could add up to become prominent at the population level (Schneidman et al. 2006).
Since only some of the cells in the dorsal STN fired in synchrony with LFP beta oscillations and in some patients with clear beta LFPs there were only very few oscillatory firing cells, it would appear that the oscillatory firing in STN is not the source of beta LFPs. However, we can not rule out the possibility that some of the ‘non-synchronous’ cells did have a weak synchronicity but that the coherence failed to reach significance. Nevertheless, we feel that a more likely source is oscillatory afferent inputs which are generated by oscillatory firing cells outside of the STN, possibly in cortex. For example, in vivo recordings from the rat STN demonstrate a close correspondence between synchronized neuronal and LFP activity following cortical stimulation (Magill et al. 2004). Phase estimates between the subthalamic area and cortical EEG suggest that cortical inputs drive STN LFP beta oscillatory activity (Fogelson et al. 2006; Marsden et al. 2001b; Williams et al. 2002) by two possible routes, either indirectly via the striatum/globus pallidus externus (GPe) or by a direct projection to the subthalamic nucleus (Parent and Hazrati 1995). Moreover, previous studies in a rodent model of parkinsonism have established that the cerebral cortex can induce pathological patterns of neuronal activity in the STN perhaps due to greater sensitivity of the STN to rhythmic cortical inputs (Magill et al. 2001; Paz et al. 2005). Recently, it has been suggested by Baufreton et al. (2005) that feedback GABAergic inhibition from the reciprocally connected GPe can prime STN neurons to respond more efficiently to excitatory input by increasing the availability of the postsynaptic voltage-dependent Na⁺ channels and is critical for the emergence of coherent beta oscillations between the cortex and STN in PD.
Our analysis of the distribution of local field potential beta oscillations revealed that they are maximal within the dorsal portion of the subthalamic nucleus and confirm similar recent findings by Kühn et al. (2005). That study however did not find a significant difference in power between the dorsolateral and the ventromedial STN, probably due to the limited number of recordings in the ventral part (Kuhn et al. 2005). This finding is supported also by our data showing that most of the beta oscillatory cells were observed within the dorsal part of the nucleus. Moreover, we were able to demonstrate a significant positive relationship between the percentage of oscillatory cells and the LFP beta power within the STN. This suggests that there is a close association between the power of the LFP beta oscillations and the neuronal beta oscillations. The LFP is likely to be generated by the postsynaptic potentials produced by rhythmic activity in STN afferents which terminate preferentially on neurons in the dorsal STN. The dorsal region is known to receive inputs from the primary motor cortex in the monkey (Monakow et al. 1978; Nambu et al. 1996) and to contain neurons responsive to passive and active movements (Abosch et al. 2002; DeLong et al. 1985; Rodriguez-Oroz et al. 2001). On the other hand, neurons in the more ventromedial STN are associated with the limbic and associative cortical regions and have no sensorimotor response (Maurice et al. 1998; Parent and Hazrati 1995). Thus, these results, showing the largest amount of oscillatory cells and the greatest LFP oscillations in the dorsal part, provide further evidence for the association of this region with motor functions and the target for DBS stimulation to alleviate PD motor symptoms (Marsden et al. 2001a).
The oscillatory activity is thought to interfere with initiation and regulation of movements, and if this were the case one might expect to find a positive correlation between the incidence of oscillatory neurons and the baseline UPDRS score off medication.

Interestingly, we did not observe a significant relationship between the "off" UPDRS scores and degree of oscillatory activity. The clinical features remaining after the L-dopa response are considered “nondopaminergic” (particularly those involving axial structures) and in part may be generated from pathology in other brain (particularly brainstem) regions that are affected in parallel to the nigrostriatal pathology (Schapira 2005). This may account for the correlation between the beta oscillatory activity and L-dopa response (i.e. dopaminergic features) and not with the off motor scores which combine both dopaminergic and non-dopaminergic features. A dissociation between beta oscillatory LFPs and the clinical symptoms was also observed by Priori et al. 2004 who showed that anticholinergic drug orphenadrine improved rigidity and tremor but also increased beta oscillatory activity.

Dopaminergic medication and active movements are known to decrease STN beta synchronization (Brown et al. 2001; Foffani et al.2005; Kuhn et al. 2004; Levy et al. 2002; Marsden et al. 2001b; Priori et al. 2002, 2004) and deep brain stimulation in the STN may alleviate PD symptoms by disrupting this oscillatory activity (Brown et al. 2004; Filali et al. 2004; Jahanshahi et al. 2000; Lozano et al. 2002). It has been hypothesized that dopamine action on the striatum acts as a filter for cortical input to the STN (Doyle et al. 2005; Magill et al. 2001, 2004; Sharott et al. 2005). Thus, the increase in number of STN cells with oscillatory beta activity might reflect the degree of
nigrostriatal dopamine deficiency. The positive correlation between the magnitude of the levodopa response and the oscillatory activity we observed may be related to the increase in the magnitude of the levodopa response with progression of PD (Zappia et al. 1997). This is consistent with the idea that abolishing the excessive beta activity by levodopa or DBS produces an improvement in parkinsonian symptoms. Our findings are also consistent with the recently reported findings that levodopa-induced reduction in subthalamic LFP power in the 8-35 Hz band as recorded post-operatively from DBS electrodes correlates with the simultaneously observed clinical improvement in PD patients (Kuhn et al. 2006).

However the fact that severity of the patients’ motor symptoms did not relate to the percentage of oscillatory cells suggests that beta oscillatory neuronal activity alone, may not reflect the clinical state of the patient and other mechanisms must also be involved in the pathophysiology and the contribution of each to the patient’s symptoms can vary. This is consistent with previous studies showing that administration of the drug orphenadrine, in contrast to levodopa, increases rather than decreases STN beta oscillations while decreasing tremor and rigidity (Priori et al. 2004), and that clinical improvement after DBS is not associated with a corresponding decrease in LFP beta activity in the STN of PD patients (Foffani et al. 2006).

It has been suggested by Bevan et al. (2002) that both the pattern of inhibitory input from the GPe and the polarization level of STN neurons are crucial in determining whether STN neurons fire in a single-spiking or oscillatory pattern. This implies that
neuromodulators, such as dopamine, that influence the membrane potential of STN neurons will have a profound effect on the activity in the GPe-STN network (Bevan et al. 2002). Based on this, we hypothesize that in the subgroup of patients who have a greater amount of neuronal oscillatory activity, the dopamine can act both by suppressing the overactivity of the indirect pathway at the level of the striatum and by changing the polarization level of STN neurons and blocking the oscillatory firing. In these patients, the STN might be more susceptible to rhythmic cortical inputs and therefore show a better response to levodopa in relation to those patients with smaller numbers of oscillating cells.
Acknowledgements: We wish to thank all the patients who participated in this study and Yu Yan Poon for her help with acquiring clinical data. The work was supported by the Canadian Institutes of Health Research grant to JOD (MOP-42505)
References


Marsden J, Limousin-Dowsey P, Fraix V, Pollak P, Odin P and Brown P.


recordings from deep brain stimulation electrodes in patients with Parkinson's disease.


Sterio D, Beric A, Dogali M, Fazzini E, Alfaro G and Devinsky O.


Williams D, Tijssen M, van BG, Bosch A, Insola A, Di L, V, Mazzone P, Oliviero A, Quartarone A, Speelman H and Brown P. Dopamine-dependent changes in the


Figure Legends:

**Figure 1.** Example of synchronized neuronal and LFP beta oscillatory activity (from one patient, right STN). [A] Raw data showing local field potential and multiunit neuronal discharge recorded simultaneously from the two microelectrodes. Both electrodes were -2.5 mm within the STN. Spikes and LFP activity derived by high and low pass filtering the raw signals at 125 and 100 Hz respectively. [B] LFP and multiunit neuronal discharge power spectra, obtained from the pair of recording sites, and their corresponding coherence and cross correlation functions. (a, b) LFP power spectra, dotted line indicates 95% confidence interval of the estimated spectrum. (c, d) Neuronal power spectra, solid and dotted lines indicate the corrected and the original spectra respectively (see methods), shaded area indicates 95% confidence interval for the absence of oscillatory activity. (e-j) coherence functions for each combination. Dotted line indicates 95% confidence limit for the absence of coherence. (k-p) Cross-correlograms and spike triggered averages (STA) of the 11-35 Hz band pass filtered LFPs. Dotted line indicates the 95% confidence interval.

**Figure 2.** Distribution of the total number of oscillatory and non-oscillatory cells located within the STN. [A] Reconstruction of an electrode track on the sagittal 12.0 mm lateral stereotactic STN map (Schaltenbrand and Wahren 1977) showing the total number of oscillatory (n = 56) and non-oscillatory (n = 144) cells located within the STN from top to bottom (0 to -5 mm respectively) in 0.3 mm intervals. Most of the oscillatory cells
were found in the more dorsal portion of the STN while the non-oscillatory cells were
equally distributed along the nucleus. [B] Box plots of oscillatory and non-oscillatory
cells’ distribution within the STN. Solid and dashed lines indicate the median and the
mean depths respectively (mean ± SEM: -1.5 ± 0.1 and -2.1 ± 0.1 mm for oscillatory and
non-oscillatory cells respectively, p = 0.001, t-test). Note the smaller number of
observations in the last mm of STN due to the fact that in many cases the extent of the
STN is less than five mm.

**Figure 3.** LFP beta power’s distribution from 5 mm above to the bottom of STN (-5 mm).
[A] Examples of the pattern of variations in the LFP beta power with depth as seen in
each patient. Each line represents one microelectrode recording track from one STN side
in one patient. Power was expressed as the percentage of the greatest beta LFP power
recorded during each track. [B] LFP power was averaged across subjects (n = 14, 21
sides x two electrodes) to give mean percentage maximum beta frequency (±SE) within
0.5 mm intervals. Dashed line indicates the upper 99% confidence limit. [C] Graphical
representation of the results of change-point and control chart analysis. Shifts in the
shaded background represent the two changes in the median % LFP beta power according
to change-point analysis. First change was increase in LFP power on entering the dorsal
STN (within -0.5 to -1 mm interval) and the second change was a decrease in power
within the ventral STN (within -2.5 to -3 mm interval). Dotted lines indicate 95% control
limits. Vertical dashed line represents the top of STN. [D] Bar graph represents the mean
percentage LFP power every 2.5 mm. Beta power was seen to increase significantly
within the dorsal part compared to above and ventral STN (** \( p < 0.001 \), Mann-Whitney Rank Sum test). Power was reduced in the ventral part but was still significantly greater than above STN (* \( p < 0.002 \)). No significant change was observed between the two segments above STN.

**Figure 4.** Relationship between mean % LFP beta power and percentage of beta oscillatory cells distribution within the STN. [A] Scatter plot showing the distributions of the mean % LFP beta power and the percentage of oscillatory cells every 0.5 mm with their corresponding regression lines. Solid and dashed lines represent linear regression of mean LFP power \( (R^2 = 0.63) \) and percent of oscillatory cells \( (R^2 = 0.71) \) distributions respectively. There is no significant difference between the two distributions (t-test for difference in slope, \( p = 0.23 \)). [B] Scatter plot shows strong correlation between the percentage of oscillatory cells and the % LFP beta power. Solid line indicates linear regression \( (R^2 = 0.63) \).

**Figure 5.** Correlation of the percentage of beta oscillatory cells, observed in each patient, with total motor UPDRS scores and clinical efficacy of levodopa medication, assessed pre-operatively (\( n = 14 \)). [A] Scatter plot showing no relationship between the amount of oscillatory cells and “off” motor UPDRS scores. [B] A negative relationship was observed with “on” motor UPDRS scores. Solid line indicates exponential decay regression curve \( (R^2 = 0.49, p < 0.05) \). [C] A positive relationship was observed with levodopa response which was expressed as the percentage of improvement in total
UPDRS score after levodopa intake. Solid line indicates logarithmic regression curve (R² = 0.62, p < 0.005).

Figure 6. The relationship between the percentage of beta oscillatory cells observed in each patient and “off” tremor UPDRS subscores assessed pre-operatively (n = 14). Scatter plot showing no relationship between the amount of oscillatory cells and “off” tremor UPDRS subscores.

Table 1. Demographic and clinical characteristics of the patients
Figure 1
Figure 2
Figure 3
Figure 4

A

B

Figure 4
Figure 5
<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years) and sex</th>
<th>Disease duration (years)</th>
<th>Motor UPDRS on/off drugs pre-op</th>
<th>Number of cells sampled</th>
<th>Power band used (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60 F</td>
<td>21</td>
<td>31/61.5</td>
<td>9</td>
<td>R STN 11-21Hz</td>
</tr>
<tr>
<td>2</td>
<td>51 M</td>
<td>10</td>
<td>13/50.5</td>
<td>6</td>
<td>L STN 22-32Hz</td>
</tr>
<tr>
<td>3</td>
<td>61 M</td>
<td>7</td>
<td>10.5/30.5</td>
<td>7</td>
<td>L STN 15-25Hz</td>
</tr>
<tr>
<td>4</td>
<td>52 F</td>
<td>19</td>
<td>15/68</td>
<td>10</td>
<td>L STN 22-32Hz</td>
</tr>
<tr>
<td>5</td>
<td>56 F</td>
<td>15</td>
<td>24/65</td>
<td>19</td>
<td>R STN 25-35Hz</td>
</tr>
<tr>
<td>6</td>
<td>68 M</td>
<td>9</td>
<td>33/46</td>
<td>10</td>
<td>R STN 20-30Hz</td>
</tr>
<tr>
<td>7</td>
<td>57 M</td>
<td>17</td>
<td>13/49</td>
<td>21</td>
<td>L STN 20-30Hz</td>
</tr>
<tr>
<td>8</td>
<td>65 M</td>
<td>21</td>
<td>22.5/41</td>
<td>8</td>
<td>R STN 25-35Hz</td>
</tr>
<tr>
<td>9</td>
<td>49 M</td>
<td>14</td>
<td>32.5/59</td>
<td>13</td>
<td>R STN 24-34Hz</td>
</tr>
<tr>
<td>10</td>
<td>46 M</td>
<td>9</td>
<td>15.5/58</td>
<td>7</td>
<td>L STN 20-30Hz</td>
</tr>
<tr>
<td>11</td>
<td>50 M</td>
<td>6</td>
<td>31/38.5</td>
<td>12</td>
<td>R STN 20-30Hz</td>
</tr>
<tr>
<td>12</td>
<td>57 F</td>
<td>15</td>
<td>9/31</td>
<td>31</td>
<td>R STN 20-30Hz</td>
</tr>
<tr>
<td>13</td>
<td>63 F</td>
<td>20</td>
<td>16/37.5</td>
<td>18</td>
<td>R STN 23-33Hz</td>
</tr>
<tr>
<td>14</td>
<td>54 M</td>
<td>14</td>
<td>8.5/32</td>
<td>29</td>
<td>R STN 20-30Hz</td>
</tr>
</tbody>
</table>