Neuronal oscillations in the subthalamic nucleus and the motor symptoms of Parkinson’s disease

Abstract – Adam Zaidel

Midbrain dopaminergic neurons and their projections to the basal ganglia (BG) degenerate in Parkinson's disease (PD), leading to a cascade of physiological abnormalities in the BG. Primary studies on the primate and rodent models of PD have demonstrated changes in firing rates, increased synchrony and exaggerated oscillations in the Parkinsonian BG - particularly in the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi). Although a clear causal connection between STN beta-oscillations and the symptoms of PD still remains unclear, it has been shown that pathological oscillations are suppressed by volitional movement, dopamine replacement therapy (DRT) and STN deep brain stimulation (DBS). STN DBS is state-of-the-art surgical treatment for advanced PD in patients who have developed side effects to DRT. However, it currently works on a suboptimal ‘open-loop’ basis. Understanding the relationship between STN beta-oscillations and PD symptoms can offer directions for providing appropriate neuronal feedback, enabling more effective (optimized) ‘closed-loop’ STN DBS. My research has therefore focused on elucidating the relationship between pathological oscillations and PD symptoms.

During surgery for implanting an STN DBS macroelectrode in human patients with advanced PD, microelectrode recording (MER) is often utilized to verify localization of the STN physiologically. In this thesis I analyzed a total of 334 MER trajectories from 136 PD patients (8 with a prior pallidotomy) undergoing STN DBS surgery at Hadassah University Hospital. For 28 patients, goniometers (for joint angle measurement) were attached to the contralateral wrist and elbow, enabling quantification of STN responsiveness to passive arm movement and monitoring of limb movement (including tremor).

When comparing the MERs from patients with prior pallidotomy to those of regular patients, I found that prior pallidotomy reduced and modified neuronal activity in the
STN of PD patients\textsuperscript{19}. In particular, it reduced STN beta-oscillations and overall power. This finding added to the recent body of evidence that PD treatment reduces beta-oscillations in the STN. It also challenged the classical understanding of basal ganglia connectivity, which places the STN up-stream to the GPi (the target of pallidotomy). These results highlight the critical role of direct projections from the BG to brain-stem structures and suggest a possible GPi–STN reciprocal positive-feedback mechanism.

Through analyzing the spatial and spectral characteristics of the STN MERs, I discovered that pathological beta-oscillations comprised a continuous stretch within the STN, and were limited to a distinctly-bounded dorsolateral oscillatory region (DLOR). This is in contrast to the current notion that beta-oscillations form a gradient across the STN - a misconception that arose from pooling data across subjects (each with a distinct DLOR, but of different lengths). I then designed a method to delimit the DLOR automatically by means of power spectral density (PSD) analysis and the use if a Hidden Markov Model (HMM)\textsuperscript{20}. When comparing clinical scores to this finding, I revealed that the length of the DLOR recorded in the macroelectrode-implanted trajectory predicted a favorable outcome of STN DBS (R=0.67, P<0.0001). Additional evidence for the clinical importance of the DLOR came from my supplementary findings that the DLOR demonstrated increased somatosensory responses vs. the ventral STN region (62\% vs. 25\% of sites tested respectively, P<0.01), and that the active macroelectrode, independently selected by optimal clinical outcome, coincided with the centre of the DLOR. The manuscript describing the results of this study has been submitted to Brain (which has invited resubmission after revision).

However, the relationship between STN beta-oscillatory power and treatment of specific PD symptoms was still unclear. Through reviewing the literature and analyzing our patient’s MERs, I observed that beta-oscillations were present for both the tremor dominant and rigid-akinetic subtypes of PD\textsuperscript{21}. I therefore expanded my analysis to compare improvement of specific PD symptoms to different PD treatments (STN DBS vs. levodopa). In line with my results regarding DLOR length, I found that increased STN beta power was associated with postoperative clinical improvement. In contrast, the
preoperative response to medication (levodopa) did not correlate with DLOR length (P=0.33), however, it did tend to be associated with increased beta (and decreased low frequency, 3-7Hz) STN power. Further analysis associated different beta-frequency oscillations (~25Hz vs. ~15Hz) and different PD symptoms (axial vs. distal) with STN DBS vs. levodopa, respectively, highlighting possible differences between the mechanisms of these treatments. These results are detailed in the Brain submission mentioned above.

In a complementary study, I have demonstrated that the consensus, that in PD the extent of preoperative levodopa responsiveness predicts the efficacy of STN DBS, may be the result of problematic statistical methods. I was able to reproduce previously published results on our data (N=48 patients), but did not observe a correlation between STN DBS efficacy and preoperative levodopa responsiveness when using fractional scores of motor improvement. These results (in conjunction with the finding that different beta-frequencies and PD symptoms are associated with STN DBS vs. levodopa) imply different therapeutic mechanisms for levodopa and STN DBS, and therefore question the validity of using substantial preoperative levodopa responsiveness as a selection criterion for STN DBS. The manuscript describing this study has been conditionally accepted to Movement Disorders.

In conclusion, my PhD thesis has revealed that the spatial and frequency characteristics of beta-oscillations in the STN trajectory predict the response of PD motor symptoms to STN DBS. This finding can be used for outcome optimization of STN DBS surgery. In addition, this understanding has provided new directions for closed loop DBS, including the possibility of targeting specific symptoms. My unexpected finding that levodopa medication and STN DBS are not congruent challenges current opinion regarding the mechanisms of these treatments and calls for reappraisal of classical clinical practice in selecting patients for STN DBS.
List of research publications:

Peer Reviewed:
4. Zaidel A, Ritov Y, Bergman H & Israel Z. Levodopa and subthalamic deep brain stimulation responses are not congruent (Conditionally accepted for publication in *Mov Disord.*)

Under Review:
1. Adam Zaidel, Alexander Spivak, Benjamin Grieb, Hagai Bergman & Zvi Israel, Subthalamic span of particular β-frequencies predicts treatment efficacy for specific Parkinsonian symptoms (*resubmission invited to Brain*)
2. Raz A, Eimerl D, Zaidel A, Bergman H & Israel Z. Propofol decreases neuronal discharge rate and increases β-oscillatory activity in the Subthalamic Nucleus of Parkinsonian patients (submitted to *Anesthesiology*)

Book Chapters:

Abstract References


7. Weinberger, M, Hutchison, WD, and Dostrovsky, JO. Pathological subthalamic nucleus oscillations in PD: Can they be the cause of bradykinesia and akinesia? Exp Neurol. 20.09


