



HAL
open science

Longer β oscillatory episodes reliably identify pathological subthalamic activity in Parkinsonism

Marc Deffains, Liliya Iskhakova, Shiran Katabi, Zvi Israel, Hagai Bergman

► To cite this version:

Marc Deffains, Liliya Iskhakova, Shiran Katabi, Zvi Israel, Hagai Bergman. Longer β oscillatory episodes reliably identify pathological subthalamic activity in Parkinsonism. *Movement Disorders*, 2018, 33 (10), pp.1609-1618. 10.1002/mds.27418 . hal-03838680

HAL Id: hal-03838680

<https://hal.science/hal-03838680>

Submitted on 9 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Title page

Title: Longer β oscillatory episodes reliably identify pathological subthalamic activity in parkinsonism

Author Affiliation: Marc Deffains, PhD, ^{1,2}, Liliya Iskhakova, PhD, ^{1,2}, Shiran Katabi, MSc, ¹, Zvi Israel, MD, ³ & Hagai Bergman, MD-PhD, ^{1,2,3}

1 Department of Medical Neurobiology, Institute of Medical Research Israel - Canada (IMRIC), The Hebrew University - Hadassah Medical School, Jerusalem 91120, Israel

2 The Edmond and Lily Safra Center for Brain Sciences, The Hebrew University, Jerusalem 91904, Israel

3 Department of Neurosurgery, Hadassah University Hospital, Jerusalem 91120, Israel

Corresponding Author: Marc Deffains

Department of Medical Neurobiology (Physiology), The Hebrew University - Hadassah Medical Center, P. O. Box 12272, Jerusalem, Israel 91120. Email: marcd@ekmd.huji.ac.il

Word count: 3700 words

Running title: Longer STN β episodes are a PD biomarker

Key words: Basal ganglia, Parkinson's disease, MPTP-treated monkey, β oscillations, Deep brain stimulation

Financial disclosures / Conflict of interest: This work was supported by grants from the Edmond and Lily Safra Center (ELSC) to M.D. and L.I.; the Israel Ministry of Absorption and the Teva National

Network of Excellence in Neuroscience (NNE) to L.I.; the Israel-US Binational Science Foundation (BSF) and the Adelis Foundation to Z.I. and H.B.; the European Research Council (ERC), the Israel Science Foundation (ISF), the German Israel Science Foundation (GIF), the Canadian Friends of the Hebrew University, the Rosetrees and Vorst Foundations and the Simone and Bernard Guttman Chair in Brain Research to H.B.

Abstract

Background

The efficacy of deep brain stimulation (DBS; primarily of the subthalamic nucleus, STN) for advanced Parkinson's disease is commonly attributed to the suppression of pathological synchronous β oscillations along the cortico-thalamo-basal ganglia (BG) network. Conventional continuous high-frequency DBS indiscriminately influences pathological and normal neural activity. The DBS protocol would therefore be more effective if stimulation was only applied when necessary (closed-loop adaptive DBS).

Objectives and Methods

Our study aimed to identify a reliable biomarker of the pathological neuronal activity in parkinsonism that could be used as a trigger for adaptive DBS. To this end, we examined the oscillatory features of paired spiking activities recorded in three distinct nodes of the BG network of two African green monkeys before and after induction of parkinsonism (via 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP, intoxication).

Results

Parkinsonism-related BG β oscillations consisted of synchronized time-limited episodes, rather than a continuous stretch, of β oscillatory activity. Episodic BG β oscillatory activity, although prolonged in parkinsonism, was not necessarily pathological since short β episodes could also be detected in the healthy state. Importantly, prolongation of the BG β episodes was more pronounced than their intensification in the parkinsonian state - especially in the STN. Hence, deletion of longer β episodes was more effective than deletion of stronger β episodes in reducing parkinsonian STN synchronized oscillatory activity.

Conclusions

Prolonged STN β episodes are pathological in parkinsonism and can be used as optimal trigger for future adaptive DBS applications.

Introduction

Parkinson's disease (PD) is the most common basal ganglia (BG) disorder and results from widespread degeneration of neurons including the midbrain dopaminergic neurons^{1,2}. The loss of the midbrain dopaminergic neurons leads to substantial dopamine depletion throughout the BG (especially in the striatum) which provokes abnormal BG neuronal activity. Abnormal synchronized β oscillatory activity has been found at multiple levels of the BG network, within and between BG nuclei, in both human PD patients and animal models of PD (e.g., 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP-treated monkeys and 6-hydroxydopamine lesioned rodents)^{3,4}. These pathological synchronous β oscillations are thought to disturb information flow through the BG network, thus resulting in the release of abnormal motor commands by BG output structures^{3,5,6}.

To date, deep brain stimulation (DBS) of the subthalamic nucleus (STN) is the most effective invasive treatment for advanced PD^{7,8}. Its efficacy is commonly attributed to the suppression of pathological BG β oscillations⁹⁻¹¹. However, conventional (i.e., continuous) STN-DBS, by influencing pathological but also physiological neural activity, can induce motor and non-motor side-effects^{12,13}. Importantly, the DBS protocol may be more effective when stimulation is applied only when necessary (closed-loop adaptive DBS)¹⁴⁻¹⁸. Therefore, identification of a reliable biomarker of the pathological neuronal activity in parkinsonism (that can be used as a trigger for adaptive DBS) is both fundamental and necessary.

Our study aimed to characterize the dynamics of BG β oscillatory activity and its importance in the materialization of pathological synchronous β oscillatory activity in parkinsonism. Synchronous β oscillations in the parkinsonian BG network have been detected in local field potential (LFP) and spiking activity^{3-5,19}. Here, we dissected the oscillatory features of the BG spiking (output) activity of two African green monkeys before and after induction of severe parkinsonism via MPTP systemic intoxication. To better appraise the temporal structure of the BG β oscillatory activity, we departed from classical average power spectral and coherence analyses to detect transient β episodes in the temporal domain²⁰. Finally, we deleted the β episodes as a function of their duration or magnitude, and re-examined the average power spectra and coherence histograms to uncover the optimal trigger for adaptive DBS applications.

Methods

Two female African vervet green monkeys (K and S, *Cercopithecus aethiops aethiops*), weighing \sim 4kg, were used in this study. All experimental protocols were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with the Hebrew University guidelines for the use and care of laboratory animals in research, supervised by the Institutional Animal Care and Use Committee of the Faculty of Medicine, the Hebrew University, Jerusalem, Israel.

Neuronal database

Data were collected from the two monkeys used in our previous study²¹. The earlier study dealt with single electrode recordings; whereas the current study was conducted on a dataset of simultaneously recorded pairs of neurons. Although, BG LFPs recorded by bipolar macro-electrodes reflects locally generated neuronal sub-threshold (e.g., synaptic input) activity, BG monopolar recorded LFPs are

considerably affected by EEG volume conductance ²². Since we used monopolar micro-electrodes to record BG neuronal activity, we limited our current database to paired spiking activities recorded simultaneously from two to eight electrodes inserted into the STN, the external segment of the globus pallidus (GPe) and the substantia nigra reticulata (SNr) before and after induction of parkinsonism (Figs. 1A and 1B). Parkinsonism induction and assessment methods are presented in the Supplementary Information.

To avoid biases caused by shadowing effects ²³, we limited this study to the spiking activity of neurons recorded by different electrodes (0.5-2mm distance). Neuronal database details are provided in Table S1. Data acquisition and database inclusion criteria are presented in the Supplementary Information. In order to boost the sensitivity of the correlation analysis ^{24,25} and overcome the confounding effects of different discharge rates in the three BG structures ²⁶, we used the surrounding (250-6000Hz digitally band-pass filtered) multi-unit activity (MUA) of the recorded cells (i.e., both the unsorted and the sorted single-unit activity), rather than the single-unit activity. Using MUA recorded around well-isolated and stable neurons (Table S1), we ensured the location of the recordings and ruled out shifts in electrode position during the recordings.

Power spectral and coherence analysis

The power spectral density (PSD) and coherence were calculated on the online 250-6000Hz band-pass filtered (hardware four-pole Butterworth filter) MUA of the neurons that met the database inclusion criteria. For each recording site, the Z-normalized MUA was calculated to obtain an unbiased estimate (by the electrode impedance and the amplitude of the recorded neuronal activity) of the oscillatory activity ²⁷ and then rectified (by the “absolute” operator) to detect oscillation frequencies below the range of the online band-pass filter ²⁷⁻²⁹. Thus, the resulting power spectral and coherence analyses

revealed the oscillatory features of the BG spiking activity and were not confounded by BG field potentials (< 250Hz). Additional details are presented in the Supplementary Information.

Detection and features of the β episodes

Fig. 2 provides a step-by-step depiction of the procedure for the detection of the significant β episodes. β episodes were characterized by their duration (e.g., 1, 1.5, 2, or 2.5s etc) and magnitude (i.e., mean RMS value or power of the 8-15Hz filtered signal over their duration). For each MUA, the frequency (number of episodes/minute) and mean duration (seconds) of the β episodes were calculated over their entire recording span. These two metrics were used to determine the episode prevalence for each MUA which was defined as: frequency * mean episode duration. Episode prevalence reflected the probability that MUA was oscillatory in the low β range. For each neuronal BG population and each state (healthy and parkinsonian), a linear regression analysis between duration and magnitude of the β episodes was performed to examine the relationship between these two features. Finally, in order to identify the best feature (duration vs. magnitude) to discriminate between healthy and parkinsonian β episodes, a Receiver Operating Characteristic (ROC) curve using different episode durations or magnitudes as decision thresholds was built for each BG neuronal population. Additional details are presented in the Supplementary Information.

Numerical episode deletion analysis

The numerical deletion of the β episodes consisted of deleting all the β episodes (detected in all the MUAs recorded in the parkinsonian state) that exceeded a certain duration or magnitude. Deleted β episodes were replaced by white Gaussian noise that has flat PSD - i.e., all frequencies have the same expected power and no coherence is expected between the replaced segments. Then, the β power and

coherence for each MUA and each MUA-MUA pair were calculated and averaged. We repeated the deletion procedure and calculated the β power and coherence as a function of the minimal duration and magnitude used for episode numerical deletion. Finally, we calculated the percentages of deleted healthy β episodes with the different minimal durations and magnitudes.

Statistics

Analyses were conducted identically on the different neuronal populations. The data for each neuronal population from the two monkeys were pooled since no significant differences were detected between them (Figs. S1, S5, S8 and S9). In the healthy state, the animals were engaged in a classical conditioning task²¹. To rule out the possibility that our main findings were due to the inclusion of the task periods in the healthy data, the frequency- and time-domain analyses were also conducted on inter-trial interval (ITI) data of the healthy state. Since the results were similar, if not otherwise specified, the healthy (control) results are derived from the continuous recordings (ITI + task data). All statistical analyses were performed using MATLAB 7.5 (Mathworks, Natick, MA, USA). Two-sample t-tests and Chi-square tests were used for statistical comparisons of two-group means and proportions, respectively. The criterion for statistical significance was set at $p < 0.05$.

Results

Materialization of parkinsonism-related β oscillations in the BG spiking activity of the MPTP primate model

As reported previously²¹, we found a significant (two-sample t-test, $p < 0.001$) increased low β (8-15Hz) power after MPTP intoxication in the surrounding MUAs of the STN, GPe and SNr neurons (Figs. 1C and S2, left). In addition, coherence analysis revealed that 8-15Hz oscillatory synchrony

emerged after MPTP intoxication in the STN, GPe and SNr - i.e., β coherence values increased significantly in the parkinsonian state (two-sample t-test, $p < 0.001$ for STN, $p < 0.01$ for GPe and $p < 0.05$ for SNr, Figs. 1C and S2, right). Importantly, healthy β power and coherence calculated during ITI + task periods and ITI only were not significantly different (Fig. S2, left and right respectively).

Finally, the same analyses conducted on the spike train (single-unit activity) of the well-isolated and stable neurons yielded similar results to those obtained from the surrounding MUA of the same BG cells (Fig. S3). Therefore, the MUA is a reliable representative of the oscillatory features of the local environment of the STN, GPe and SNr projection neurons.

Episodic β oscillatory activity within the BG network in parkinsonism

β oscillations could be episodic rather than persistent. We therefore searched for transient episodes of β oscillatory MUA in the temporal domain. Applying our episode detection algorithm to each MUA (Fig. 2), we calculated the frequency, the mean duration and the prevalence of β episodes within each MUA recorded for each BG neuronal population, before and after MPTP intoxication (Figs 3A, S4 and S6A). Our definition of episode prevalence (frequency * mean duration) reflects the probability that MUA is oscillatory in the 8-15Hz range and therefore differs from other definitions of episode probability^{30,31}; namely, the probability of observing β episodes during different task periods. We found that episode prevalence increased significantly (two-sample t-test, $p < 0.001$) in the parkinsonian state for the three BG neuronal populations (Figs. 3A and S6A). Nevertheless, although healthy β episodes were even less prevalent when detected during ITI only than when detected during ITI + task periods (Fig. S6A), the episode prevalence in the healthy state was above chance for the three BG neuronal populations. As depicted in Fig. 3B, these results remained the same when using different modes of calculation of the amplitude thresholds or different degrees of permissiveness of the amplitude thresholds.

Our decision to use relatively long 1-s bins to segment the data (thus enforcing the minimal β episode duration to 1s) was made to prevent excessive fragmentation of β oscillatory activity due to brief data fluctuations. Importantly, the significant (two-sample t-test, $p < 0.001$) parkinsonism-related increase in episode prevalence was also found using a smaller bin duration of 0.25s for β episode detection (Fig. S7), although episode frequency was higher and episode duration was shorter in comparison to the 1-s bin results (Fig. 3C).

In conclusion, we detected more β episodes than expected by chance in the BG network both before and after MPTP intoxication. However, the probability of observing such episodes significantly increased after MPTP intoxication. Thus, BG β episodes might not necessarily be pathological, but they appear to be more prevalent in parkinsonism.

Duration and magnitude of the BG β episodes - discriminating between “good” and “bad” β episodes in parkinsonism

Although the (linear) relationships between the duration and the magnitude (power) of the β episodes became stronger in the parkinsonian state for the three BG neuronal populations, their strength remained relatively weak (Pearson's $r \leq 0.39$, Fig. 4, first and second columns). More importantly, although we found significant (two-sample t-test, $p < 0.001$) parkinsonism-related increases both in episode duration and episode magnitude for the three neuronal BG populations, episode duration increased more strongly than episode magnitude in the parkinsonian state and notably in the STN (+120.58% vs. +19.14% for STN, +13.59% vs. +5.77% for GPe and +41.57% vs. +2.39% for SNr, Fig. 4, third column). This larger increase in episode duration was also maintained when the parkinsonian episode features were compared to the healthy episode features detected during ITI only (Fig. S6B). We therefore built ROC curves using the different episode durations and magnitudes as decision thresholds for classification of healthy

and parkinsonian episodes in each BG neuronal population (Fig. 4, fourth and fifth columns, respectively). Importantly, ROC curves of 5-fold cross validation yielded similar results. The best discrimination between healthy and parkinsonian episodes occurred in the STN (i.e., highest AUC values). However, although the AUC values were similar for duration- and amplitude-based discrimination, the shapes of the STN ROC curves were very different. Therefore, we focused on the region of the curve with low false positive rate (100-TNR), namely the region where the number of healthy episodes detected as pathological episodes was minimized. As expected, the partial AUC values³² (calculated for 100-TNR values of 20, 30, 40 and 50%) were higher for the duration- (partial AUC values = 0.08, 0.14, 0.21, 0.28, respectively) than the magnitude-based ROC analysis (partial AUC values = 0.04, 0.09, 0.16, 0.25, respectively). Finally, we identified the optimal cut-off value (i.e., optimal decision threshold) for episode duration- and magnitude-based discrimination that misclassified the least of healthy and parkinsonian episodes [i.e., maximal true negative rate (TNR) and true positive rate (TPR) or specificity and sensitivity, respectively]. In doing so, longer and stronger STN β episodes were defined as the STN β episodes with durations ≥ 2 s and RMS values ≥ 0.0532 , respectively.

Deletion of longer β episodes is more effective than deletion of stronger β episodes in restoring normal STN β power and coherence

To validate the results of the ROC analysis, we examined the effects of deletion of β episodes according to their duration or amplitude on the average STN β power and coherence. To do so, we calculated the β power and coherence for each MUA and each MUA-MUA pair recorded in the parkinsonian STN after numerical deletion of the β episodes exceeding a certain duration or magnitude (see Methods). We found that the deletion of longer parkinsonian STN β episode (≥ 2 s, Fig.5, left) dramatically and significantly reduced parkinsonian β power (-98.2%, two-sample t-test, $p = 0.0056$) and coherence (-92.5%, two-

sample t-test, $p < 0.001$) while deleting only 16.54% (444/2685) of healthy episodes. In contrast, although the deletion of the stronger parkinsonian episodes (RMS value ≥ 0.0532 , Fig. 5, right) also dramatically and significantly reduced parkinsonian β power (-102.7%, two-sample t-test, $p = 0.0036$) and coherence (-95.9%, two-sample t-test, $p < 0.001$), the proportion of deleted healthy episodes (50.09% or 1345/2685) significantly increased (chi-square test, $p < 0.001$). In line with these results, the proportion of deleted healthy episodes linearly increased with the minimal episode magnitude used for numerical episode deletion (Pearson's $r = 0.83$, Fig. 5, right). On the other hand, the proportion of deleted healthy episodes sharply increased as the minimal episode duration approached the episode duration threshold used to discriminate between short (“good”) and long (“bad”) episodes (strength of the linear relationship between the proportion of deleted healthy episodes and the minimal episode duration used for numerical episode deletion was considerably reduced compared to the amplitude-based deletion; Pearson's $r = 0.31$, Fig. 5, left).

Overall, the duration of BG β episodes was more widely distributed than their magnitude in parkinsonism and appeared to be a more reliable feature, especially in the STN, for discriminating between normal (“good”) and pathological (“bad”) episodes. Moreover, deletion of longer β episodes was more effective than deletion of stronger β episodes in reducing parkinsonian STN activity.

Discussion

BG β oscillations are episodic but not necessarily pathological

In this study, we found low β (8-15Hz) oscillations and synchrony in BG spiking activity after MPTP intoxication of African green monkeys (Figs. 1C, S1, S2 and S3) which coincides with the β oscillation frequency range reported for the MPTP-treated monkey³³⁻³⁷. Remarkably, recent human³⁸ and non-human primate³⁷ studies have shown that low frequency β oscillations ($< 20\text{Hz}$) are better correlated

with the clinical motor symptoms of PD and are also more sensitive to dopaminergic medication ³⁹. Moreover, an earlier study on human PD patients showed that STN neurons exhibited long, non-continuous, 8-20Hz oscillatory spiking activity that was coherent with their background MUA ²⁸. Similarly, examination of the dynamics of the β oscillatory spike-LFP synchrony in the STN of human PD patients revealed that synchronized β oscillatory activity in human parkinsonian STN is interrupted by irregular short de-synchronization events ⁴⁰. Recently, β bursts have also been detected in the LFPs recorded in the STN of human PD patients ^{41,42}. Here, the recordings over multiple BG nuclei revealed that parkinsonism-related episodic synchronized β oscillatory activity was not limited to LFP, but could also be detected at the spiking activity scale in the STN (BG input), as well as in the central (GPe) and output (SNr) structures of the BG network (Figs. 1C, S1, S2 and S3).

In research on human patients, healthy control groups are obviously not available for comparison. Here, we found that episodic β oscillatory spiking activity in the BG network was more prevalent in the parkinsonian state than in the healthy state (Figs. 3, S5, S6A and S7). Nevertheless, β episodes were also detected in the healthy state (Figs. 3, S5, S6A and S7). In normal behavior control, β oscillatory activity probably contributes to the maintenance of the current sensorimotor or cognitive state - the status quo hypothesis ^{43,44}. Consistent with this hypothesis, accentuation of brief β bursts has been observed in the cortical-BG network of healthy rodents during post-performance periods once the animals' behavior becomes habitual ⁴⁵ and/or a change in the animals' state is unlikely ^{30,46}. High levels of synchrony in LFP β oscillations have also been observed in the striatum of healthy non-human primates during hold periods ⁴⁷. Nevertheless, it has been shown that dopamine replacement therapy and STN-DBS abolish β oscillatory activity in the BG network in both human PD patients (e.g., see ^{39,48} for dopaminergic medication and ^{10,11} for STN-DBS) and animal models of PD (e.g., see ⁴⁹ for dopaminergic medication and ^{9,50} for STN-DBS), concomitantly with clinical improvement in hypokinetic symptoms. Moreover, a

recent study reported an elongation of episodic LFP β oscillations in the parkinsonian-like striatum (after inducible ablation of the striatal dopamine D2 receptors) of freely moving mice with a locomotion deficit⁵¹. Given the severity of the parkinsonian symptoms in our study, the animals' healthy behavioral state (engaged in the classical conditioning task²¹) differed from the parkinsonian (at rest) state. Nevertheless, frequency- and time-domain analyses conducted on ITI data and continuous recordings (ITI + task data) in the healthy state yielded similar results (Figs. S2 and S6). This excludes the possibility that the differences observed between the healthy and parkinsonian states were due to the inclusion of the task periods in the healthy data. Therefore, these previous and current findings indicate that episodic BG β oscillatory activity, even in parkinsonism, is not necessarily pathological. Nevertheless, extended β oscillatory activity observed along the BG network in parkinsonism may cause the hypokinetic symptoms of the disease (i.e., akinesia, bradykinesia and rigidity).

Optimization of deep brain stimulation therapy

Our results suggest that the dynamics of STN β oscillatory spiking activity might be used as a reliable biomarker of pathological neuronal activity in parkinsonism. In earlier studies, adaptive STN-DBS was delivered when the magnitude of STN β oscillatory LFP activity exceeded a certain threshold^{15,16,18}, thus suggesting that healthy and abnormal β oscillatory activity could be distinguished based on their magnitude. Recently, it has been shown that the magnitude of the β oscillatory LFP activity in the STN of human PD patients increases proportionally to the duration of the β oscillatory bursts⁴¹. We also found similar relationships between the magnitude (power) and the duration of the β episodes for the different BG neuronal populations (Figs. 4 and S8, first and second columns). However, unlike the latter study, here we report β episode durations of up to 40 s. Detection of such long β episodes might be explained by our choice to use the power in the frequency bands (6-8Hz and 15-20Hz) that flank the β

(8-15Hz) band for the calculation of the amplitude thresholds rather than the power in the β band ^{30,41,42}. When using the β power itself for the calculation of the amplitude threshold, very prolonged β episodes could lead to a very high amplitude threshold and might not be detected. Moreover, by enforcing the minimal β episode duration to 1s to prevent excessive fragmentation of β oscillatory activity, we naturally favored the detection of long β episodes (Figs. 3C, S4 and S7). Finally, this discrepancy in the pathological β episode duration between our and other recent human studies ^{41,42} might also be due to differences in experimental approaches, such as the species, the methods of parkinsonism induction (idiopathic disease vs. experimental induction), the time elapsed between the onset of parkinsonism and neuronal recordings, the severity of the parkinsonian symptoms and the dopamine replacement therapy history etc. In any case, we found that the increase in episode duration was more pronounced than the increase in episode magnitude at the spiking activity scale of the three distinct BG neuronal populations recorded in the parkinsonian state (Figs 4, and S8, third column and Fig. S6B), thus indicating that episode duration might be a better differentiating marker of the normal and pathological episodes in the parkinsonian state. We also showed that the best episode duration-based discrimination between healthy and parkinsonian episodes occurred in the STN (Figs. 4 and S8, fourth column). Therefore, at least in the parkinsonian STN, the prolonged β episodes might reliably be considered pathological.

In the current study, we did not attempt to correlate neural activity to the animals' behavior or clinical states on a short (seconds to minutes) time scale. Nevertheless, the results from our numerical episode deletion analysis indicate that at least in the parkinsonian STN, deletion of longer β episodes was more effective than deletion of stronger β episodes in reducing parkinsonian activity (Figs. 5 and S9, left vs. right). This strengthens the claim that longer, rather than stronger, STN β episodes are a reliable biomarker for pathological episodes in parkinsonism and potentially the optimal trigger for future adaptive DBS applications ⁵². The success of early studies on human adaptive stimulation ^{15,16,18,41,42}

could thus be due to the soft-start (ramping) nature of the stimulation following detection of the subthalamic β episodes, leading exclusively to effective stimulation at the time of the prolonged (i.e., pathological) epochs.

Acknowledgments

We thank Dr. Yaron Dagan for assistance with animal care, Dr. Atira Bick and Dr. Nanette Freedman for assistance with the coordination and execution of the MRI and PET scans, and Esther Singer and Dr. Sharon Freeman for English editing. We also thank Anatoly Shapochnikov for help in preparing the experimental setup and Dr. Hila Gabbay and Dr. Uri Werner-Reiss for general assistance.

Authors' role: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

M.D.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

L.I.: 1C, 2B, 3B

S.K.: 1C, 2B, 3B

Z.I.: 1C, 3B

H.B.: 1A, 1B, 2C, 3B

Financial disclosures of all the authors

This work was supported by grants from the Edmond and Lily Safra Center (ELSC) to M.D. and L.I.; the Israel Ministry of Absorption and the Teva National Network of Excellence in Neuroscience (NNE) to L.I.; the Israel-US Binational Science Foundation (BSF) and the Adelis Foundation to Z.I. and H.B.;

the European Research Council (ERC), the Israel Science Foundation (ISF), the German Israel Science Foundation (GIF), the Canadian Friends of the Hebrew University, the Rosetrees and Vorst Foundations and the Simone and Bernard Guttman Chair in Brain Research to H.B.

References

1. Jellinger KA. Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. *Mol.Chem.Neuropathol.* 1991;14(3):153-97.
2. Braak H, Del TK, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol.Aging* 2003;24(2):197-211.
3. Brown P. Bad oscillations in Parkinson's disease. *J.Neural Transm Suppl* 2006(70):27-30.
4. Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. *Trends Neurosci.* 2007;30(7):357-64.
5. Bergman H, Feingold A, Nini A, et al. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. *Trends Neurosci.* 1998;21(1):32-38.
6. Weinberger M, Hutchison WD, Dostrovsky JO. Pathological subthalamic nucleus oscillations in PD: can they be the cause of bradykinesia and akinesia? *Exp.Neurol.* 2009;219(1):58-61.
7. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N.Engl.J.Med.* 1998;339(16):1105-11.
8. Odekerken VJ, Boel JA, Schmand BA, et al. GPi vs STN deep brain stimulation for Parkinson disease: Three-year follow-up. *Neurology* 2016;86(8):755-61.
9. Meissner W, Leblois A, Hansel D, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain* 2005;128(Pt 10):2372-82.
10. Wingeier B, Tcheng T, Koop MM, et al. Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. *Exp.Neurol.* 2006;197(1):244-51.
11. Kuhn AA, Kempf F, Brucke C, et al. High-frequency stimulation of the subthalamic nucleus suppresses oscillatory beta activity in patients with Parkinson's disease in parallel with improvement in motor performance. *J.Neurosci.* 2008;28(24):6165-73.
12. Chen CC, Brucke C, Kempf F, et al. Deep brain stimulation of the subthalamic nucleus: a two-edged sword. *Curr.Biol.* 2006;16(22):R952-R53.
13. Ray NJ, Jenkinson N, Brittain J, et al. The role of the subthalamic nucleus in response inhibition: evidence from deep brain stimulation for Parkinson's disease. *Neuropsychologia* 2009;47(13):2828-34.

14. Rosin B, Slovik M, Mitelman R, et al. Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 2011;72(2):370-84.
15. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann.Neurol.* 2013;74(3):449-57.
16. Little S, Beudel M, Zrinzo L, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J.Neurol.Neurosurg.Psychiatry* 2016;87(7):717-21.
17. Kuhn AA, Volkmann J. Innovations in deep brain stimulation methodology. *Mov Disord.* 2017;32(1):11-19.
18. Arlotti M, Rosa M, Marceglia S, et al. The adaptive deep brain stimulation challenge. *Parkinsonism.Relat Disord.* 2016;28:12-17.
19. Rosa M, Giannicola G, Servello D, et al. Subthalamic local field beta oscillations during ongoing deep brain stimulation in Parkinson's disease in hyperacute and chronic phases. *Neuro-Signals* 2011;19(3):151-62.
20. Buzsaki G. *Rhythms of Brain*. New York: Oxford University Press, Inc, 2006.
21. Deffains M, Iskhakova L, Katabi S, et al. Subthalamic, not striatal, activity correlates with basal ganglia downstream activity in normal and parkinsonian monkeys. *Elife.* 2016;5:e16443.
22. Marmor O, Valsky D, Joshua M, et al. Local vs. volume conductance activity of field potentials in the human subthalamic nucleus. *J.Neurophysiol.* 2017;117(6):2140-51.
23. Bar-Gad I, Ritov Y, Vaadia E, et al. Failure in identification of overlapping spikes from multiple neuron activity causes artificial correlations. *J.Neurosci.Methods* 2001;107(1-2):1-13.
24. Bedenbaugh P, Gerstein GL. Multiunit normalized cross correlation differs from the average single-unit normalized correlation. *Neural Comput.* 1997;9(6):1265-75.
25. Gerstein GL. Cross-correlation measures of unresolved multi-neuron recordings. *J.Neurosci.Methods* 2000;100(1-2):41-51.
26. Matzner A, Bar-Gad I. Quantifying spike train oscillations: biases, distortions and solutions. *PLoS.Comput.Biol.* 2015;11(4):e1004252.
27. Zaidel A, Spivak A, Grieb B, et al. Subthalamic span of beta oscillations predicts deep brain stimulation efficacy for patients with Parkinson's disease. *Brain* 2010;133(Pt 7):2007-21.
28. Moran A, Bergman H, Israel Z, et al. Subthalamic nucleus functional organization revealed by parkinsonian neuronal oscillations and synchrony. *Brain* 2008;131(Pt 12):3395-409.
29. Deffains M, Holland P, Moshel S, et al. Higher neuronal discharge rate in the motor area of the subthalamic nucleus of Parkinsonian patients. *J.Neurophysiol.* 2014;112(6):1409-20.

30. Feingold J, Gibson DJ, DePasquale B, et al. Bursts of beta oscillation differentiate postperformance activity in the striatum and motor cortex of monkeys performing movement tasks. *Proc.Natl.Acad.Sci.U.S.A* 2015;112(44):13687-92.
31. Sherman MA, Lee S, Law R, et al. Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. *Proc.Natl.Acad.Sci.U.S.A* 2016;113(33):E4885-E94.
32. McClish DK. Analyzing a portion of the ROC curve. *Medical decision making : an international journal of the Society for Medical Decision Making* 1989;9(3):190-5.
33. Raz A, Vaadia E, Bergman H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. *J.Neurosci.* 2000;20(22):8559-71.
34. Soares J, Kliem MA, Betarbet R, et al. Role of external pallidal segment in primate parkinsonism: comparison of the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism and lesions of the external pallidal segment. *J.Neurosci.* 2004;24(29):6417-26.
35. Leblois A, Meissner W, Bioulac B, et al. Late emergence of synchronized oscillatory activity in the pallidum during progressive Parkinsonism. *Eur.J Neurosci.* 2007;26(6):1701-13.
36. Stein E, Bar-Gad I. beta oscillations in the cortico-basal ganglia loop during parkinsonism. *Exp.Neurol.* 2013;245:52-59.
37. Connolly AT, Jensen AL, Bello EM, et al. Modulations in oscillatory frequency and coupling in globus pallidus with increasing parkinsonian severity. *J.Neurosci.* 2015;35(15):6231-40.
38. Neumann WJ, Degen K, Schneider GH, et al. Subthalamic synchronized oscillatory activity correlates with motor impairment in patients with Parkinson's disease. *Mov Disord.* 2016;31(11):1748-51.
39. Priori A, Foffani G, Pesenti A, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. *Exp.Neurol.* 2004;189(2):369-79.
40. Park C, Worth RM, Rubchinsky LL. Fine temporal structure of beta oscillations synchronization in subthalamic nucleus in Parkinson's disease. *J.Neurophysiol.* 2010;103(5):2707-16.
41. Tinkhauser G, Pogosyan A, Little S, et al. The modulatory effect of adaptive deep brain stimulation on beta bursts in Parkinson's disease. *Brain* 2017;140(4):1053-67.
42. Tinkhauser G, Pogosyan A, Tan H, et al. Beta burst dynamics in Parkinson's disease OFF and ON dopaminergic medication. *Brain* 2017;140(11):2968-81.
43. Engel AK, Fries P. Beta-band oscillations--signalling the status quo? *Curr.Opin.Neurobiol.* 2010;20(2):156-65.

44. Brittain JS, Brown P. Oscillations and the basal ganglia: motor control and beyond. *Neuroimage* 2014;85 Pt 2:637-47.
45. Howe MW, Atallah HE, McCool A, et al. Habit learning is associated with major shifts in frequencies of oscillatory activity and synchronized spike firing in striatum. *Proc.Natl.Acad.Sci.U.S.A* 2011;108(40):16801-06.
46. Leventhal DK, Gage GJ, Schmidt R, et al. Basal ganglia beta oscillations accompany cue utilization. *Neuron* 2012;73(3):523-36.
47. Courtemanche R, Fujii N, Graybiel AM. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. *J.Neurosci.* 2003;23(37):11741-52.
48. Kuhn AA, Kupsch A, Schneider GH, et al. Reduction in subthalamic 8-35 Hz oscillatory activity correlates with clinical improvement in Parkinson's disease. *Eur.J.Neurosci.* 2006;23(7):1956-60.
49. Heimer G, Rivlin-Etzion M, Bar-Gad I, et al. Dopamine replacement therapy does not restore the full spectrum of normal pallidal activity in the 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine primate model of Parkinsonism. *J.Neurosci.* 2006;26(31):8101-14.
50. Moran A, Stein E, Tischler H, et al. Decoupling neuronal oscillations during subthalamic nucleus stimulation in the parkinsonian primate. *Neurobiol.Dis.* 2012;45(1):583-90.
51. Bello EP, Casas-Cordero R, Galinanes GL, et al. Inducible ablation of dopamine D2 receptors in adult mice impairs locomotion, motor skill learning and leads to severe parkinsonism. *Mol.Psychiatry* 2017;22(4):595-604.
52. Beudel M, Brown P. Adaptive deep brain stimulation in Parkinson's disease. *Parkinsonism.Relat Disord.* 2016;22 Suppl 1:S123-S26.

Figure Legends

Fig. 1. BG β synchronous oscillations are enhanced in parkinsonism. (A) Representative depiction of the recording setup. Coronal section 6mm posterior from the anterior commissure (AC - 6) with two microelectrodes located in the STN, adapted from Martin and Bowden (2000). In the current study, 1-8 microelectrodes were inserted simultaneously into a single BG nucleus in each recording session. (B) Synchronized STN multi-unit β oscillatory spiking activities. Left, 1-s example of two MUAs (online 250-6000Hz band-pass filtered signals) recorded simultaneously in the surrounding area of two well-

isolated STN neurons in the parkinsonian state. Right, 100 randomly-chosen superimposed waveforms of the extracellular action potentials of a cell sorted from its MUA. IS indicates the isolation score of the sorted cell. (C) Mean PSDs (left) and coherence estimates (right) of the MUAs and MUA-MUA pairs recorded in the vicinity of STN, GPe, SNr neurons in the healthy and parkinsonian states. To obtain the mean coherence estimate, individual coherence histograms were Fisher Z-transformed, averaged and then reverse Fisher Z-transformed to provide an unbiased estimate of the average coherence (i.e., bounded between 0 and 1). Abscissas are in log scale. The shaded areas mark SEMs. N is the number of recording sites and N_p is the average number of multi-unit pairs.

Fig. 2. Detection of the significant β episodes. Each Z-normalized 250-6000Hz band-pass filtered MUA was rectified using the “absolute” operator. Then, the 8-15Hz band-pass filtered signal (blue) and the 6-8Hz and 15-20Hz (flanking frequency bands) filtered signal (red) were extracted from the Z-normalized and rectified MUA. Finally, the two signals were segmented into consecutive overlapped (50%) 1-s bins and the RMS value was calculated for each 1-s bin. A significant β (8-15Hz) episode consisted of 1 to n consecutive bins with RMS values of the 8-15Hz filtered signal that exceeded 3 SDs of the mean RMS value of the 6-8Hz and 15-20Hz filtered signal. The horizontal red line represents the mean + 3 SDs of the 6-8Hz and 15-20Hz filtered signal.

Fig. 3. Episodic BG β oscillatory activity is more prevalent in parkinsonism. (A) Distributions of the values of episode prevalence for the BG neuronal populations in the healthy and parkinsonian states. For each MUA, the episode prevalence represents the probability that MUA is oscillatory in the β (8-15Hz) range. Superimposed distributions are displayed with equal bin resolutions (but with different bin numbers). Mode of calculation of the amplitude thresholds for the detection of the β episodes: absolute;

number of SDs: 3. N is the number of recording sites. Gray - healthy state; light green - parkinsonian state; dark green - overlapping bins. **(B)** Mean values of (\pm SEM) episode prevalence for the BG neuronal populations in the healthy and parkinsonian states as a function of the mode (relative and absolute) and the number of SDs (2, 2.5, 3 and 3.5) for the calculation of the amplitude thresholds for β episode detection. **(C)** Mean (\pm SEM) of the features (frequency, mean duration and prevalence) of β episodes in the healthy and parkinsonian states using 1-s or 0.25-s bins for binning data. Parameters for β episode detection and color code are identical to **(A)**. * and *** indicate significant ($p < 0.05$ and $p < 0.001$, respectively) differences between the healthy and parkinsonian states.

Fig. 4. β episode duration is a reliable metric to discriminate between healthy and pathological episodes within the parkinsonian BG network. First and second columns, scatter plots of the magnitude and the duration of the β episodes for the BG neuronal populations in the healthy and parkinsonian states, respectively. Red line represents the linear regression line between the features (magnitude and duration) of these episodes. r is the Pearson's correlation coefficient and p indicates the probability that $r = 0$. Third column, percentage of change in the duration and the magnitude of the parkinsonian β episodes for the BG neuronal populations. 100% represents the duration and the magnitude of the healthy β episodes. Fourth and fifth columns, ROC curves using different episode durations (1, 1.5, 2, 2.5, 3, 3.5s etc) and different episode magnitudes as decision thresholds for the BG neuronal populations (duration- and magnitude-based ROC curves, respectively). Red curves are the ROC curves of 5-fold cross validation for each dataset. AUC is the area under the ROC curve. Triangles mark the optimal cut-off values that correspond to the points on the ROC curves with the maximal vertical distance from the diagonal chance line. The cut-off value ensures the maximal true negative rate and true positive rate or TNR (specificity) and TPR (sensitivity), respectively. For each BG neuronal

population, healthy β episodes were re-detected after random pruning and truncation of the healthy MUAs to adjust for the number of multi-unit sites and the average length of recording in the two states. In all subplots, mode of calculation of the amplitude thresholds for the detection of the β episodes: absolute; number of SDs: 3.

Fig. 5. Deletion of longer β episodes is more effective than deletion of stronger β episodes in reducing parkinsonian STN activity. Mean β power (top) and coherence (bottom) in the parkinsonian STN as a function of the minimal duration (left) and minimal magnitude (right) used for the numerical deletion of the β episodes. For each minimal duration and magnitude of the deleted episodes, raw data were replaced by white Gaussian noise and the mean β power and coherence (green bars) were calculated. Red curves indicate the (expected) percentages of deleted healthy STN β episodes as a function of the minimal duration and magnitude for episode deletion. Triangles mark the episode duration threshold (left) and episode magnitude threshold (right) that correspond to the optimal cut-off values identified from the ROC analysis. Black and green horizontal lines indicate the healthy and parkinsonian STN levels, respectively (i.e., mean β power and coherence in the healthy and parkinsonian STN with no episode deletion). In all subplots, mode of detection of the β episodes: absolute; number of SDs: 3.