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Dear Dr Greenamyre,

We wish to submit our manuscript entitled "Comparison of oscillatory activity in subthalamic nucleus in Parkinson's disease and dystonia" for consideration of publishing by the Neurobiology of Disease.

In this manuscript, we studied the spectral and temporal patterns of oscillatory activity of the local field potentials (LFPs) recorded from subthalamic nucleus (STN) in patients with dystonia and Parkinson's disease (PD). It has been widely evidenced that a prominent beta frequency band activity in the STN of PD patients but still unclear whether such activity occurs in dystonic STN or not, and whether dystonia has another distinctive activity. While in a previously study published in the Neurobiology of Disease early this year (Wang et al, 2016. doi: 10.1016/j.nbd.2016.02.015.), no significant differences in both beta power and the coupling of beta phase to high frequency oscillation amplitude of subthalamic LFPs in dystonia and PD were reported. In comparison, our study shows contrary results that distinctive oscillatory patterns are found over both low frequency (5-10 Hz) and beta frequency (11-32 Hz) bands. To evaluate the oscillatory activities of LFPs, we used power spectra to specify oscillations in frequency domain and Lempel-Ziv complexity, which is unaffected to the amplitude of signal, to illustrate the dynamic temporal patterns in the time series. Moreover, a dystonic case with medication treatment in our data shows similar patterns of LFPs as in untreated PD rather than dystonia. This gives a hint that such patterns may be more tightly locked to pharmacological states than disease pathology *per se*.

Because of the differences in medication and recording states of these studies, our results are likely to be of great interest to the researchers, clinicians and scientists who read your journal and consider future studies in this field.

We confirm that this work is original and not currently under consideration for publication elsewhere. It has been approved by all authors to submit to the journal. We would like to recommend Dr Manuel Alegre, Dr Christian Moll, Dr Kai Bötzel, Prof Peter Silburn and Prof Alireza Gharabaghi as reviewers. If you may consider, please find their contact information following the letter.

Thank you for receiving and considering of this manuscript. We appreciate your time and look forward to your response.

Sincerely,

Xinyi Geng

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Dear Professor Greenamyre,

Thank you for affording us the opportunity to revise our manuscript. We have addressed the reviewers point below and highlighted changes in the main manuscript.

Reviewer #2: *The revised manuscript "Comparison of oscillatory activity in subthalamic nucleus in Parkinson's disease and dystonia" by Geng and colleagues addresses some of my concerns regarding the original version, however, some of my major comments were not addressed sufficiently.*

1. LZC - The relation of this measure to oscillations is non-straightforward (see for example Aboy et al., IEEE, 2006) and does not merely describe the beta oscillation in an "amplitude independent" manner. Thus, it should be dropped (my recommendation) or explained very explicitly and the interpretation of its results clearly stated, especially as this manuscript is not intended for engineers or physicists.

We would rather keep some mention of the LZC results as they help limit the confound due to signal amplitude variance between subjects and sides due to any slight differences in the targeting of electrodes.

We have now revised and included the description of the use of LZC as follows:

Methods: "Power spectra characterise average distributions of signal variance over frequency, but do not fully capture temporal patterns in the time series. Lempel-Ziv complexity (LZC) measures the random level of a time series by evaluating the regularity/randomness and numbers of repeats in the binary sequence. For a totally random time series, the patterns of the sequence are theoretically unpredictable and there are a higher number of different subsequences. The number of subsequences is limited for regular oscillations and the LZC value is lower compared to more random signals, like white noise. The LZC is generally independent of the amplitude scaling as the signal is converted to binary sequences (Ziv and Lempel. 1977; Zhang et al. 2001; Gomez et al. 2011). Hence, it is relatively immune to LFP signal variations due to minor differences in surgical targeting, and has previously been shown to be negatively correlated with the strength of beta band synchronisation (Chen et al. 2010).

The pre-processed signals were band-pass filtered over low frequency, low beta and high beta (band-pass centred on the peak in each band ± 3Hz wide) and a high gamma band over 60-140 Hz (band-pass centred on the peak ± 10Hz wide). In the absence of a peak the frequency in the low frequency and beta bands was taken to be that of the peak in the respective band in the group average. The individual neural oscillations of STN LFPs were converted into a binary sequence by thresholding using the median value of the amplitude of the neural oscillations as the threshold and the LZC applied on every 1 second epoch and averaged (Ziv and Lempel.1977; Chen et al. 2010).

The principle of LZC is to measure the number of distinct patterns in a 0-1 sequence by scanning the sequence from left to right and counting the number of patterns every time a new one occurs. The LZC was computed with the following steps:

(1) Initialise the sequences S and Q as two subsequences of the digitalized time series,

$s_1, s_2, \ldots, s_N$. SQ is the concatenation of S and Q and SQπ is defined as SQ with the last symbol being deleted. At the beginning, SQπ = s_1 and the counting number of distinct pattern C_N =1.

(2) Scan the unprocessed sequence, $s_3, s_4, \ldots, s_N$, by removing the first symbol and adding it in Q. If Q belongs to SQπ, then Q is not a new pattern, then append the next unprocessed symbol in Q and repeat the judgement until the renewed Q does not belong to SQπ, then the Q is a new pattern.

(3) Increase the counting number C_N by one. The Q is appended to S and then reset to empty. Update the unprocessed sequence and repeat from step (2) until Q is the last character.

(4) The LZC is then derived by the formula:

$$\mathrm{LZC} = \frac{\mathrm{C_N}}{\mathrm{N}/\log_2(\mathrm{N})}$$

where N is the length of the sequence.

Discussion:

"*Dynamics of activity*

The LZC characterizes the complexity of a given signal by measuring the repeatable patterns in the signal, and is derived by counting the number of the new subsequences (Ziv and Lempel. 1977; Zhang et al. 2001; Aboy et al. 2006). The LZC reflects the rate of new patterns in the sequence, which is related to the randomness and predictability of the signal, and is also influenced by the level and distribution of the noise in the signal (Aboy et al. 2006). The LZC is low when the signal is regular and predictable, and it is high when the signal is random and less predictable. For example, the LZC decreases when the EEG signal becomes synchronised with high-amplitude slow waves (Andrillon et al. 2016), and is a robust measure reflecting the decrease of neural complexity of spontaneous EEG during general anesthesia (Schartner et al. 2015). This is able to accurately track the level of consciousness in patients and health subjects under anesthesia and during sleep (Zhang et al. 2001; Andrillon et al. 2016). In PD patients, resting state MEG signals show less complexity than in control subjects (Gomez et al. 2011). STN local field potentials in PD patients also have reduced complexity, and there is significant negative correlation between the complexity of these signals, assessed using LZC, and akinesia-rigidity (Chen et al. 2010). The LZC may therefore be considered a useful tool for capturing neural dynamics."

The following references have also been added.

Aboy M, Hornero R, Abásolo D, et al. Interpretation of the Lempel-Ziv complexity measure in the context of biomedical signal analysis. IEEE Trans Biomed Eng 2006;53: 2282-2288.

Andrillon T, Poulsen AT, Hansen LK, et al. Neural Markers of Responsiveness to the Environment in Human Sleep. J Neurosc 2016;36: 6583-6596.

Gómez C, Olde Dubbelink KT, Stam CJ, et al. Complexity Analysis of Resting-State MEG Activity in Early-Stage Parkinson's Disease Patients. Ann Biomed Eng 2011;39: 2935-2944.

Schartner M, Seth A, Noirhomme Q, et al. Complexity of Multi-Dimensional Spontaneous EEG Decreases during Propofol Induced General Anaesthesia. PloS One 2015;10.

Zhang XS, Roy RJ, Jensen EW. EEG complexity as a measure of depth of anesthesia for patients.

IEEE Trans Biomed Eng 2001;48: 1424-1433.

Ziv J and Lempel A. Universal algorithm for sequential data compression. IEEE Trans Inform Theory 1977;23: 337-343.

2. Single case report - The authors have made some changes to the manuscript but have left the conclusion based on a speculation regarding this single case report as a very significant result and specifically left it as the main conclusion in the abstract. It should be dropped from the abstract and preferably also from the discussion.

Conclusions related to this single case have now been removed from the abstract and from the 'conclusion' section at the end of the Discussion.

Reviewer #3: *It is indeed unfortunate that the issue of stereotactic reconstruction of the recording sites could not be addressed, as the referee considers this important for the correct interpretation of the data. To the credit of the authors, this caveat is now acknowledged in the manuscript. The other issues have been adequately addressed. I have no further concerns.*

We share the reviewer's disappointment with respect to the available imaging, but are pleased that the reviewer feels that the revised discussion on this topic reproduced below helps highlight this study limitation.

"Recordings from the patient groups were derived from different centres which raises the possibility that there were subtle differences in the targeting. We were unable to explore this issue further due to the generally thick acquisition slices made during post-operative imaging in the patients with dystonia and the unavailability of some of the imaging in some of the archival patients. Targeting variance may increase the variance between subjects as LFP amplitude is dependent on the distance from the generator. Our spectral normalization and use of the LZC help address this issue. In Supplementary Methods we also include the spectral results when we average across all electrode contacts so as to further limit the effects of any potential small systematic variation in the targeting between the centres, although such averaging has the drawback that spatial resolution is limited and we can only ascribe those spectral findings to the STN area. Nevertheless, the differences between conditions in data from the broader STN area were similar to those presented in the main results."

Highlights

- Spectral power and temporal patterns of the oscillation in subthalamic nucleus in dystonia and Parkinson's disease are distinctive.
- Dystonic case on aripiprazole shows association with a similar spectral pattern in the subthalamic nucleus as in untreated patients with Parkinson's disease.
- The same region can be involved in different patterns of circuit dysfunction that may explain the paradox whereby functional surgical approaches to the same target can improve different conditions.

Comparison of oscillatory activity in subthalamic nucleus in Parkinson's disease and dystonia

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Abstract

Objectives. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has been successfully used to treat both Parkinson's disease (PD) and dystonia. Local field potentials (LFPs) recorded from the STN of PD patients demonstrate prominent beta frequency band activity. It is unclear whether such activity occurs in the STN in dystonia, and, if not, whether dystonia has another distinctive neural population activity in the STN. **Methods**. Twelve patients with PD, and eight patients with dystonia underwent DBS electrode implantation targeting the STN. Seven dystonia patients were off medication and one was on aripiprazole and clonazepam. LFPs were recorded from the DBS electrodes in PD in the on/off medication states and in dystonia. Power spectra and temporal dynamics measured by the with Lempel-Ziv complexity of the LFPs were compared among these states. **Results**. Normalised power spectra and Lempel-Ziv complexity of subthalamic LFPs differed between dystonia off and PD on/off, and between PD off and on over the low frequency, beta and high gamma bands. Patients with dystonia and off medication had lower beta power but higher low frequency and high gamma power than PD. Spectral power in the low beta frequency (11-20 Hz) range was attenuated in medicated PD. **Conclusion**. The results suggest that dystonia and PD are characterized by different patterns of oscillatory activities even within the same nucleus, and exaggerated beta activity may relate to hypo-dopaminergic status.

Keywords: Subthalamic nucleus; oscillation; dystonia; Parkinson's disease.

Abbreviations: STN: subthalamic nucleus; PD: Parkinson's disease; LFPs: local field potentials; DBS: deep brain stimulation; GPi: globus pallidus internus; LZC: Lempel-Ziv complexity; BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale; CDQ-24: Craniocervical Dystonia Questionnaire; UPDRS: Unified Parkinson's disease rating scale.

Acknowledgements: Thanks to Dr. Huiling Tan, Nuffield Department of Clinical Neurosciences, University of Oxford, UK and Dr. Yongzhi Huang, Suzhou Institute of Biomedical Engineering and Technology, Chinese Academy of Sciences, China in providing valuable comments on signal analysis.

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Relevant conflicts of interests/financial disclosure: Nothing to report.

Authors' Roles:

Xinyi Geng designed experiments, analyzed and interpreted the data and drafted manuscript. Jianguo Zhang collected local field potentials data, managed the clinical evaluation of dystonia patients, conducted experiments and revised manuscript. Yi Jiang helped collect local field potentials data and managed the clinical evaluation of dystonia patients. Keyoumars Ashkan, Thomas Foltynie, Patricia Limousin, Ludvic Zrinzo, Alexander L Green and Tipu Aziz helped collect local field potentials data,

managed the clinical evaluation of Parkinson's patients and commented on the manuscript. Peter Brown helped supervise the data analysis and preparation of the manuscript. Shouyan Wang helped supervise the data analysis and review manuscript.

Introduction

Evidence is accruing that there is synchronised oscillatory activity in some of the basal ganglia nuclei that typically occurs in the beta frequency band in Parkinson's disease (PD) and in the theta frequency band in dystonia (López-Azcárate et al. 2010). It has been widely reported that the local field potentials (LFPs) from the subthalamic nucleus (STN) exhibit excessive beta activity in patients with PD (Brittain and Brown. 2014). Such activity is suppressed by treatment with levodopa and by deep brain stimulation (DBS) of the STN (Eusebio et al. 2011; Kühn et al. 2005; Whitmer et al. 2012). Moreover, therapy induced suppression of beta levels correlates with the degree of induced clinical improvement, particularly with changes in bradykinesia and rigidity (Kühn et al. 2005; Kühn et al. 2008a; Kühn et al. 2009; Özkurt et al. 2011; Ray et al. 2008; van Wijk et al. 2016; Weinberger et al. 2006; Zaidel et al. 2010).

In contrast, in patients with dystonia, oscillatory activity over a low frequency band (4-10Hz) has been frequently reported from the globus pallidus internus (GPi) (Foncke et al. 2007; Lee et al. 2013; Moll et al. 2014; Silberstein et al. 2003; Weinberger et al. 2011). This low frequency activity in GPi is coherent with the EMG of dystonic muscles (Chen et al. 2006a; Liu et al. 2006; Sharott et al. 2008). Moreover, it is suppressed during effective DBS of the same nucleus (Barow et al. 2014). Dystonia patients do not generally show elevated beta activity in the GPi (Silberstein et al. 2003; Weinberger et al. 2011), unless treated with the monoamine vesicle depletor tetrabenazine (Kühn et al. 2008b) or in some patients with secondary dystonia (Whitmer et al. 2013).

However, as most of the data in patients with PD and dystonia come from recordings in different sites doubt remains as to whether spectral changes are site, phenotype or disease specific. GPi can be a DBS target for both dystonia and PD, and case series contrasting recordings from the GPi in these two diseases are concordant and support the existence of discrete spectral patterns along the lines of those described above (Silberstein et al. 2003; Weinberger et al. 2011). More recently, STN, a classical DBS target in PD, has been used as a stimulating target to treat dystonia (Chou et al. 2005; Kleiner-Fisman et al. 2007; Ostrem et al. 2011 and 2013). However, where the subthalamic nucleus is concerned there is only one case series contrasting the LFP patterns in patients with dystonia and PD, and this suggested no difference in the spectral pattern of local field potentials between the two diseases (Wang et al. 2016). This would imply that any disease difference present at the level of the globus pallidus is local and not a feature of the wider interconnected circuits of the basal ganglia. Yet a microelectrode study and a case report describing findings in the STN point to a difference between these in dystonia and PD also within this nucleus (Schrock et al. 2009; Neumann et al. 2012). Given these contrasting results at the level of STN we felt it important to further investigate the spectral patterns of the STN LFP in dystonia and PD. (Neumann et al. 2012). We hypothesised that low frequency and beta band activities will differentially characterize the two disorders, even when recordings are made from the same site. In addition, we tested whether high gamma activity in the STN, previously postulated to be prokinetic, might be elevated in dystonia (Brown. 2003).

Material and methods

Subjects and surgery

All patients gave written informed consent to take part in this study, which was agreed by the local ethics committees. Eight patients with dystonia which had treatment failures with botulinum toxin (Table 1), underwent DBS electrode implantation in Tian-Tan Hospital, Capital Medical University, Beijing, China. Seven patients with dystonia underwent bilateral STN implantation and one with bilateral STN and GPi implantation, although only STN recordings are included in this study. Archival data from twelve subjects with PD were also analysed (Table 1); seven who underwent surgery at the John Radcliffe Hospital, Oxford University, Oxford, UK and five who underwent surgery at the National Hospital for Neurology and Neurosurgery or Kings College Hospital, London. Six of these patients with PD have previously been reported (Anzak et al. 2016). 10/12 patients with PD underwent bilateral STN implantation, one underwent unilateral STN and thalamus implantation, and one unilateral STN implantation only. The two groups did not differ in age (unpaired t-test, p=0.159). All patients underwent evaluation for motor impairments using respective clinical scales, the Unified Parkinson's Disease Rating Scale part III – motor exam under on/off medication state for PD patients, and Burke-Fahn-Marsden Dystonia Rating Scale or Craniocervical Dystonia Questionnaire for dystonia patients (Muller et al. 2004; Susatia et al. 2010). The L-dopa equivalent dose in PD groups was calculated based on conversion factors in a previous report (Tomlinson et al. 2010).

The procedures for STN targeting and DBS electrode implantation have been previously reported (Chou et al. 2005; Foltynie and Hariz, 2010). The STN was localized on the fused pre-operative frameless magnetic resonance (MR) and framed computed tomography (CT) images. The electrodes were targeted at the dorsolateral area of the STN in both groups. The targets were calculated and determined using the Frame link planning station (Medtronic, Minneapolis, MN, USA). The DBS electrodes were Medtronic 3389 (Medtronic, Minneapolis, MN, USA) with four platinum-iridium cylindrical surface contacts. Each contact was 1.27mm in diameter and 1.5mm in length, and separated by 0.5mm. The most caudal contact was contact 0 and the most rostral contact 3. Subjects had local anesthesia and were awake during the operation to allow for the intraoperative evaluation of stimulation effects. The final positioning of the electrode was selected to maximize clinical improvements and, in particular, minimize side-effects during intra-operative stimulation (Starr. 2002). The placement of DBS electrodes was confirmed with fused post-operative images and pre-operative MR images on the same software as for pre-operative planning.

Recording

Patients of both groups were recorded from externalized electrode leads while sitting at rest post-operatively 1-3 (mean 2) days following surgery in dystonia and 2-5 (mean 3) days in PD. Patients were not instructed to suppress any involuntary movement but were asked to avoid voluntary movement during recording. In the dystonia patients, case d8 was treated with clonazepam and aripiprazole during recording from the externalised electrode. Case d4 had a history of treatment with haloperidol and tiapride but ceased these two months before surgery. All datasets in dystonia were acquired at the Department of Neurosurgery, Beijing Tian-Tan Hospital, Capital Medical University, Beijing, China. In figure 1 the dystonia off group refers to the seven cases d1 to d7, and dystonia on refers to case d8, the

only dystonia patient on medication at the time of recording. In the PD group, all patients were recorded in both on and off medication conditions, using medication as prescribed preoperatively.

In dystonia patients, bipolar LFPs were recorded from the adjacent four contacts (contact pairs: 01, 12, 23) of each DBS electrode. The signals were amplified, notch filtered to remove 50Hz line noise, band-pass filtered over 1-500Hz using a Digitimer Amplifier (Model D360, Digitimer Ltd., Hertfordshire, UK) and recorded with a sampling frequency of 2 kHz using a CED 1401 (Cambridge Electronic Design, Cambridge, UK).

In PD patients LFPs were recorded monopolarly with respect to a linked earlobe reference using a TMSiporti amplifier (TMS international) and its respective software. Recordings were band-pass filtered between 0.5 and 500 Hz and sampled at 2048 Hz. Monopolar recordings of LFPs were subsequently converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per side) to limit the effects of volume conduction from distant sources. Line noise artefacts at 50 Hz and 100 Hz were removed using notch filters.

Signal processing

Signals were down-sampled to 1 kHz and pre-processed with bandpass filtering over 3-45 Hz and 60-140 Hz respectively. Signal processing, data analysis and statistical analysis were performed offline with scripts developed in MATLAB (MathWorks Inc., Natick, MA, USA). A continuous 50 seconds sample, free of artefacts signals, was selected from one bipolar channel on each side for analysis in each subject (details of channel selected in Table 1). The channel was selected for further processing on the basis of intra-operative testing and post-operative clinical programming, and if recording quality and artefact free data were insufficient at that channel an adjacent one was chosen.

Spectra analysis

Signals were bandpass filtered between 3-45 Hz and 60-140 Hz and then z-transformed to reduce the variance between subjects due to surgical targeting and recording. Power spectral density was calculated using the Welch's method (Shimanmoto et al. 2013; Welch. 1967) with 1 second sliding-window, 0.5 seconds overlap and 2048 points. T-tests were introduced for statistical comparison between groups. The normalised power spectra from the dystonia and PD groups were compared every 0.5 Hz over 3-45 Hz and 60-140 Hz. To allow for multiple comparisons across frequencies we opted for conservative criteria for significance; three or more consecutive bins with $p<0.001$. Moreover, to eliminate the effects of frequency variance, spectra were realigned to the frequency of peak power over 5-10 Hz, 11-32 Hz and 60-140 Hz respectively for statistical analysis. Note that dystonia case d6 was excluded in assessments of the high gamma band (60-140 Hz) due to broadband noise contaminating the observed frequencies. Note also that dystonia case d8 on aripiprazole was only included in group comparison in figure 1 as a single case, and excluded in the realigned spectra comparison between dystonia off medication and PD on/off medication groups in figure 2.

Dynamic analysis

Power spectra characterise average distributions of signal variance over frequency, but do not fully capture temporal patterns in the time series. Lempel-Ziv complexity (LZC) measures the random level of a time series by evaluating the regularity/randomness and numbers of repeats in the binary sequence. For a totally random time series, the patterns of the sequence are theoretically unpredictable and there

are a higher number of different subsequences. The number of subsequences is limited for regular oscillations and the LZC value is lower compared to more random signals, like white noise. The LZC is generally independent of the amplitude scaling as the signal is converted to binary sequences (Ziv and Lempel. 1977; Zhang et al. 2001; Gomez et al. 2011). Hence, it is relatively immune to LFP signal variations due to minor differences in surgical targeting, and has previously been shown to be negatively correlated with the strength of beta band synchronisation (Chen et al. 2010).

The pre-processed signals were band-pass filtered over low frequency, low beta and high beta (band-pass centred on the peak in each band ± 3Hz wide) and a high gamma band over 60-140 Hz (band-pass centred on the peak ± 10Hz wide). In the absence of a peak the frequency in the low frequency and beta bands was taken to be that of the peak in the respective band in the group average The individual neural oscillations of STN LFPs were converted into a binary sequence by thresholding using the median value of the amplitude of the neural oscillations as the threshold and the LZC applied on every 1 second epoch and averaged (Ziv and Lempel.1977; Chen et al. 2010).

The principle of LZC is to measure the number of distinct patterns in a 0-1 sequence by scanning the sequence from left to right and counting the number of patterns every time a new one occurs. The LZC was computed with the following steps:

(1) Initialising the sequences S and Q as two subsequences of the digitalized time series, $s_1, s_2, \ldots, s_N$. SQ is the concatenation of S and Q and SQπ is defined as SQ with the last symbol being deleted. At the beginning, SQπ = s_1 and the counting number of distinct pattern C_N =1.
(2) Scanning the unprocessed sequence, $s_3, s_4, \ldots, s_N$, by removing the first symbol and adding in Q. If Q belongs to SQπ, then Q is not a new pattern, then append the next symbol in Q and repeat the judgement until the renewed Q does not belong to SQπ, then the Q is a new pattern.
(3) Increasing the counting number C_N by one. Q is appended to S and then reset to empty. Update the unprocessed sequence and repeat step (2) until Q is the last character.
(4) The LZC is then derived by the formula:

$$\mathrm{LZC} = \frac{\mathrm{C_N}}{\mathrm{N}/\log_2(\mathrm{N})}$$

where N is the length of the sequence.

Results

Different spectral characteristics in dystonia and PD

Examples of time-frequency spectra of LFPs recorded from electrodes targeting the STN are shown for a dystonic patient off medication, and for case d8 with dystonia but on clonazepam and aripiprazole, and for an exemplar PD patient recorded on and off medication (Supplementary figure 1). The normalised power spectra densities of 14 sides from 7 dystonia off medication patients and 2 sides from 1 on medication patient, together with 22 sides from 12 PD on/off medication patients are shown individually and averaged within groups in figure 1. Distinct spectral power peak was found in the beta band only in PD off and on groups and in the dystonia case d8 on clonazepam and aripiprazole, while elevated low frequency power and high gamma oscillation were found in the dystonia off group. Contiguously significant differences were found over 5-7 Hz between power spectra in dystonia off and PD on/off

groups (two-sample unpaired t-tests, $p<0.001$ in each of 3 and 5 contiguous bins respectively); over 16.5-18 Hz between dystonia off and PD off group ($p<0.001$ in each of 3 contiguous bins) and over 96.5-99.5 Hz between dystonia off and PD on/off groups ($p<0.001$ in each of 6 contiguous bins). Paired t-tests suggested a low beta power decrease in PD on compared to off state ($p<0.001$) but this did not reach our criteria for significance as it involved only one isolated bin. Moreover, the averaged spectral power over 24-30 Hz was significantly higher in dystonia case d8 on medication compared to dystonia off group (two-sample unpaired t-tests, $p<0.001$ in each of 9 bins) while the low frequency power decreased over 5-10 Hz (not significant). The significant differences between power spectra reported above were also present when all recording channels were separately averaged in dystonia (n=16 sides, 48 channels) and PD on/off medication (n=22 sides, 66 channels) and compared between the three groups (supplementary figure 2). This underscores that differences were not due to a bias in channel selection.

Comparison of realigned peak power in dystonia and PD

The frequency of spectral peaks varied among subjects. Peaks over the 5-10 Hz range had a mean frequency of 7.3 ± 1.5 Hz (mean ± SD) and 92 ± 8.6 Hz over the 60-140 Hz range in the dystonia off group, while those over the 11-32 Hz ranges had mean frequencies of 17.3 ± 6 Hz in the PD off group. Although spectral peaks in the PD off group were commonest in the low beta band and centred around 17 Hz, two sides of one PD patient off medication demonstrated peaks only in the upper beta band. This variability might lead to an under-estimate of the difference between patient groups so power spectra were therefore separately re-aligned to the maximum value in absolute power spectra from a given electrode within the low frequency and whole beta band ranges (figure 2). This procedure exaggerated the differences between the patient groups over the 5-10 Hz, 11-32 Hz and 60-140 Hz ranges, particularly within the beta band in which peak frequency variation was greatest (figure 2). Unpaired t-tests showed a significant difference between dystonia off and PD on/off states over the central frequencies ($p<0.001$ in each of at least 5 contiguous bins). The findings were similar if only peaks in the low beta band were selected for re-alignment before averaging (data not shown).

Dynamic analysis in dystonia and PD

LZC is a nonlinear dynamic analysis that provides a complexity measure of the temporal pattern of neural oscillations, and is not directly influenced by the amplitude scaling of the signal. Significant differences (figure 3) were found in LZC between dystonia off and PD on/off medication groups over low frequency ($F(2, 55) = 21.4$, $p < 0.0001$, one-way ANOVA), the low beta band ($F(2, 55) = 104.4$, $p < 0.0001$, one-way ANOVA) and the high gamma band $F(2, 53)=316.3$, $p<0.0001$, ANOVA). The LZC over the 5-10 Hz and 60-140 Hz bands in dystonia off condition was significantly lower than in the PD on/off groups (t-tests, $p<0.001$ in both conditions). The LZC in the low beta band was significantly higher in dystonia than in PD on/off groups (t-tests, $p<0.001$ in both conditions). Medicated PD also had a higher LZC in the low beta band compared to PD off state (t-test $p<0.005$).

Discussion

By comparing LFPs recorded postoperatively from electrodes targeting STN in patients with dystonia and PD, we have demonstrated significant differences in both spectral power amplitude and dynamic

oscillatory patterns between these conditions over low frequency and beta bands. This suggests that different oscillatory activities are associated with different phenotypes even in the same nucleus. Distinct circuit abnormalities might lend themselves to more targeted forms of DBS, including adaptive stimulation (Little et al. 2013).

Low frequency activity

Our results in patients with dystonia help address two questions: is prominent low frequency activity of the LFPs local to GPi or a basal ganglia circuit phenomenon, and is it specific to dystonia? Prominent low frequency activity of LFPs has been reported in dystonia in GPi (Liu et al. 2008; Moll et al. 2014; Sharott et al. 2008; Silberstein et al. 2003), and in STN (Neumann et al. 2012; Wang et al. 2016). Our data add to the evidence that low frequency activity is a basal ganglia circuit phenomenon rather than focal and this observation may help explain why DBS of both the STN and GPi can improve dystonia (Weinberger et al. 2011). However, is such low frequency activity specific to dystonia? In GPi low frequency activity is elevated in dystonic patients but not in patients with PD who are off their medication (Silberstein et al. 2003). A case report came to similar conclusions for STN (Neumann et al. 2012), but a large case series concluded that there was no difference in low frequency activity in STN between patients with PD and dystonia (Wang et al. 2016). That said, this case series demonstrated a trend towards higher relative theta activity in the STN in dystonia than in PD ($p = 0.0651$; their supplementary figure 2).

Our data point to a clear difference between the dystonic and untreated PD patients, both with spectral measures and LZC. However, this need not equate to a disease specific pattern of low frequency synchronisation in dystonia, as this activity in both the STN and GPi increases in those patients with PD who are treated and develop on-drug dyskinesia (Alonso-Frech et al. 2006; Chen et al. 2006b; Foffani et al. 2005; Rodriguez-Oroz et al. 2011; Silberstein et al. 2003; Silberstein et al. 2005; Weinberger et al. 2011), and so it may not be disease pathology specific. Others have linked elevated theta-alpha activity to mobile elements of dystonia (Barow et al. 2014), and as such it could be argued that exaggerated theta-alpha activity reflects a phenotype of mobile dystonia or dyskinesia, rather than being disease specific (Weinberger et al. 2011).

Beta activity

Prominent beta frequency band power has been consistently reported in the GPi and STN of PD patients withdrawn from their medication (Hammond et al. 2007). This was confirmed in the present PD cohort, but patients with dystonia, with the exception of one case, had no discrete or elevated beta power in STN. This is in line with some reports (Neumann et al. 2012; Weinberger et al. 2011), and was further borne out by the diminished LZC in the low beta band in PD patients, particularly when these were withdrawn from dopaminergic medications. Previously, the LZC of subthalamic 13-35 Hz oscillatory activity has been reported as correlating with clinical impairments in patients with PD (Chen et al. 2010).

However, Wang et al. (2016) found no difference in beta activity in STN between patients with dystonia and PD. Nevertheless, ten out of the twelve patients reported by the latter group were receiving treatment with benzodiazepines, which can cause widespread increases of beta power and decreases of theta band power (Jensen et al. 2005; Yamadera et al. 1993). The Wang et al. (2016) study also differed in other respects, including its intra-operative nature so spectral differences might have conceivably been attenuated by the use of a general anesthetic an hour or two before the recordings, or by a

difference in the stun effect experienced immediately after microelectrode recordings and macroelectrode implantation.

Our findings in case d8 highlight the particular importance of considering medication effects. This patient was taking clonazepam and aripiprazole. The latter is a partial agonist at D2 and 5-HT1A receptors and antagonist at 5-HT2A receptors (Jordan et al. 2002; Mailman et al. 2010; Shapiro et al. 2003), which in some individuals can induce parkinsonism (Raj et al. 2004; Oommen et al. 2006) and in this individual was associated with a spectral pattern of LFPs in the STN that was similar to that seen in untreated patients with PD. Similar changes have been reported in the GPi in patients with dystonia treated with tetrabenazine (Kühn et al. 2008b), and in combination these data raise the possibility that excessive beta activity may be a hall mark of hypodopaminergic activity in the basal ganglia rather than of any specific disease pathology. This remains to be clarified.

Gamma activity

Patients with dystonia had greater subthalamic LFP power around 92 ± 8.6 Hz (mean ± SD) than patients with PD, whether the latter were on medication or withdrawn from medication. Gamma activity has previously been considered prokinetic (Brown. 2003), and the finding of elevated activity in the subthalamic LFP in dystonia would be in line with this. Peaks in the gamma range, albeit at slightly lower frequencies (60-95 Hz), have also been reported in the subthalamic LFP in some of patients with PD when on medication, and have been associated with the presence of dyskinesias (Fogelson et al. 2005; Swann et al. 2016). Discrete peaks of local field potential activity at similar frequencies have been reported in motor cortex in a dyskinetic rodent model of PD (Halje et al. 2012) and in dyskinetic PD patients (Swann et al. 2016). Similar peaks have been reported in the human thalamus and globus pallidus in patients with dystonia, myoclonus and tremor, and so their mere presence may not be pathological (Kempf et al. 2009; Jenkinson et al. 2013). However, whether exaggeration of this rhythm relates to dyskinesias and dystonia remains a possibility, and the significance of the slight shift to higher frequencies in dystonia remains to be established.

Dynamics of activity

The LZC characterizes the complexity of a given signal by measuring the repeatable patterns in the signal, and is derived by counting the number of the new subsequences (Ziv and Lempel. 1977; Zhang et al. 2001; Aboy et al. 2006). The LZC reflects the rate of new patterns in the sequence, which is related to the randomness and predictability of the signal, and is also influenced by the level and distribution of the noise in the signal (Aboy et al. 2006). The LZC is low when the signal is regular and predictable, and it is high when the signal is random and less predictable. For example, the LZC decreases when the EEG signal becomes synchronised with high-amplitude slow waves (Andrillon et al. 2016), and is a robust measure reflecting the decrease of neural complexity of spontaneous EEG during general anesthesia (Schartner et al. 2015). This is able to accurately track the level of consciousness in patients and health subjects under anesthesia and during sleep (Zhang et al. 2001; Andrillon et al. 2016). In PD patients, resting state MEG signals show less complexity than in control subjects (Gomez et al. 2011). STN local field potentials in PD patients also have reduced complexity, and there is significant negative correlation between the complexity of these signals, assessed using LZC, and akinesia-rigidity (Chen et al. 2010). The LZC may therefore be considered a useful tool for capturing neural dynamics.

Limitations and strengths of the present study

Recordings from the patient groups were derived from different centres which raises the possibility that there were subtle differences in the targeting. We were unable to explore this issue further due to the generally thick acquisition slices made during post-operative imaging in the patients with dystonia and the unavailability of some of the imaging in some of the archival patients. Targeting variance may increase the variance between subjects as LFP amplitude is dependent on the distance from the generator. Our spectral normalization and use of the LZC help address this issue. In Supplementary Methods we also include the spectral results when we average across all electrode contacts so as to further limit the effects of any potential small systematic variation in the targeting between the centres, although such averaging has the drawback that spatial resolution is limited and we can only ascribe those spectral findings to the STN area. Nevertheless, the differences between conditions in data from the broader STN area were similar to those presented in the main results.

Interpretational ambiguity can be introduced when spectra are normalised by total spectral power in order to limit signal variance due to small differences in surgical targeting (Chen et al. 2010). Here, the results of analysis of z transformed spectral data were corroborated by the estimation of the LZC. This measure is not influenced by the amplitude scaling of the signal, but nevertheless is affected by the degree of beta activity, and negatively correlates with the latter (Chen et al. 2010).

Conclusions

In sum, the present data suggest that distinctive spectral patterns exist as basal ganglia circuit phenomena in PD and dystonia. It is the possibility that the same region can be involved in different patterns of circuit dysfunction that may explain the paradox whereby functional surgical approaches to the same target can improve different conditions (Brown and Eusebio. 2008).

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TABLE 1. Clinical summary

Case	Age /Sex	Diagnosis/main symptoms before operation	Medication	Pre-operative scales (dystonia: BFMDRS(MS,DS) /CDQ-24, off med; PD: UPDRS part-III, off/on med)	Channel selection
d1	21/M	dystonia, primary generalised	None	53 (43, 10)	L12, R12
d2	24/M	dystonia, primary generalised	None	50 (38, 12)	L12, R01
d3	44/F	dystonia, primary generalised	None	58 (46, 12)	L12, R12
d4	74/F	dystonia, neuroleptic induced cranial	None	24 (18, 6)	L01, R12
d5	25/M	dystonia, cranial with blepharospasm	None	28.5 (21.5, 7); CDQ-24: 90	L01, R01
d6	65/M	dystonia, cranial with blepharospasm	None	5.5 (5.5, 0); CDQ-24: 46	L23, R23
d7	52/F	dystonia, cranial with blepharospasm	None	4.5 (4.5, 0); CDQ-24: 44	L01, R12
d8	67/F	dystonia, cranial with blepharospasm	Clonazepam and Aripiprazole	12 (7, 5); CDQ-24: 62	L01, R12
p1	56/F	PD, bradykinesia	900mg LDED	26/7	L12, R12
p2	70/M	PD, freezing, gait	1100mg LDED	62/29	L12, R12
p3	59/M	PD, tremor	700mg LDED	28/5	L12, R23
p4	60/M	PD, freezing, bradykinesia	200mg LDED	25/13	L12, R12
p5	60/F	PD, bradykinesia, tremor, gait	1725mg LDED	63/7	L23, R12
p6	32/M	PD, left sided tremor	875mg LDED	52/13	R01
p7	68/M	PD, right sided tremor	475mg LDED	38/20	L23
p8	58/M	PD, bradykinesia, dyskinesia	270mg LDED	45/14	L23, R12
p9	60/M	PD, bradykinesia	600mg LDED	41/21	L12, R01
p10	60/F	PD, bradykinesia, gait	2000mg LDED	40/12	L01, R23
p11	65/M	PD, bradykinesia, rigidity, postural instability	1670mg LDED	23/7	L12, R01
p12	38/M	PD, tremor, mobility	370mg LDED	23/10	L12, R23

d1-d8: dystonia cases. p1-p12: PD cases. LDED = L-DOPA daily equivalent dose. BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale. MS = Movement Score. DS = Disability Score. CDQ-24 = Craniocervical Dystonia Questionnaire. UPDRS = Unified Parkinson's disease rating scale. Part – III: Motor Exam.

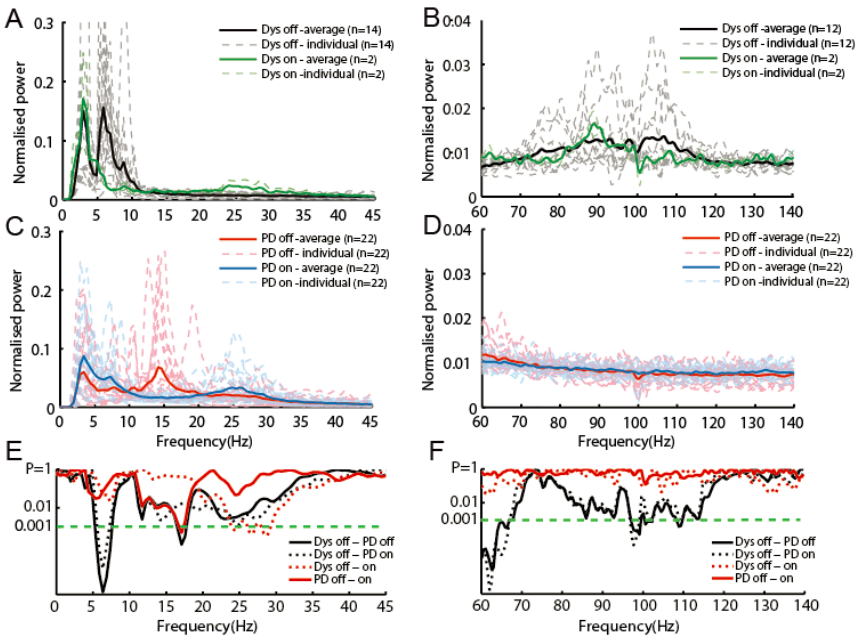


Figure 1. Group power spectra over 0-45 Hz (left) and 60-140 Hz (right) averaged across subjects with dystonia off medication (A and B, black line) and separately for case d8 on clonazepam and aripiprazole (A and B, green line); PD off levodopa (C and D, red line) and on levodopa (C and D, blue line). Dashed lines show individual spectra of all subjects in the respective conditions. Results of serial two-sample, unpaired t-tests between dystonia off medication and PD groups, one-sample t-tests between dystonia off medication and averaged case d8 on medication and paired t-tests between PD off and on (E and F). LFPs were z-transformed before spectral analysis. Spectral resolution is 0.5 Hz. Note ln (P) y axis scales in E and F.

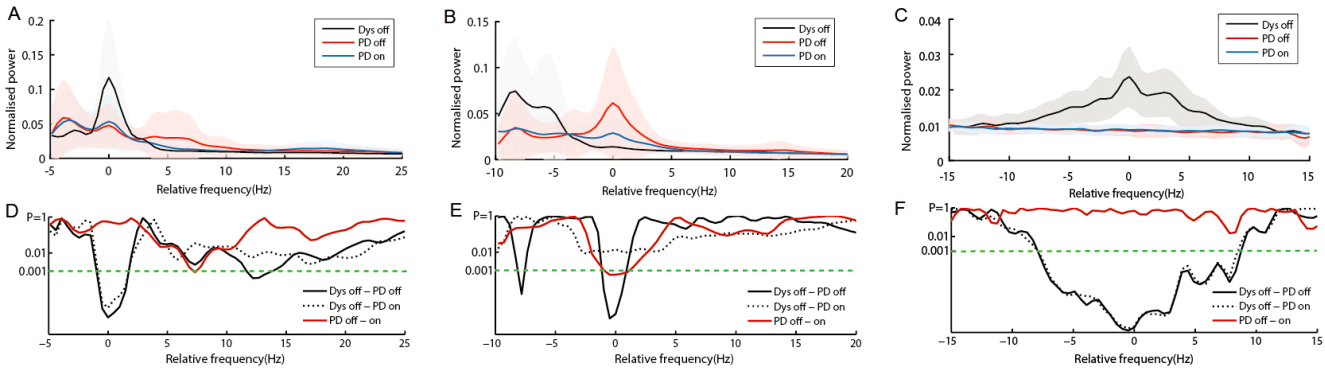


Figure 2. Group average normalised power spectra realigned to the peak frequency over 5-10 Hz in panel A, 11-32 Hz in panel B and 60-140 Hz in panel C. Results of serial two-sample, unpaired t-tests between the dystonia off medication (n=14 except n=12 for gamma band analysis) and PD group off (n=22) and on (n=22) medication and paired t-tests between PD on/off (both n=22) states are shown in D-F. LFPs were z-transformed before spectral analysis. The shadows in the respective colours denote ±1 standard deviations of the groups. As there were no clear gamma peaks in the selected channels of PD cases, 80Hz was taken as the centre frequency for realignment based on previous literature where fine-tuned gamma oscillations were usually found in 60-95 Hz (Kempf et al. 2009; Jenkinson et al. 2013).

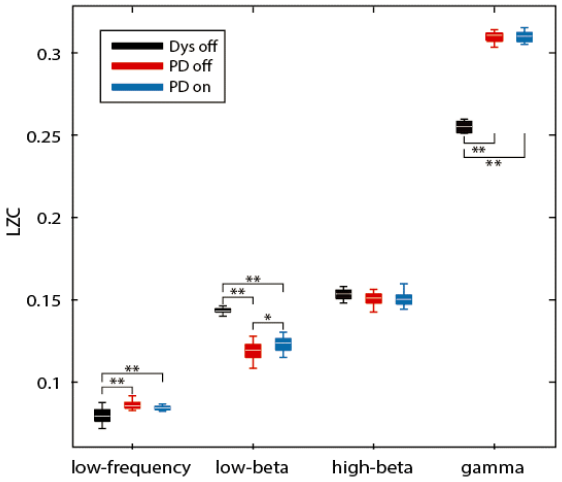
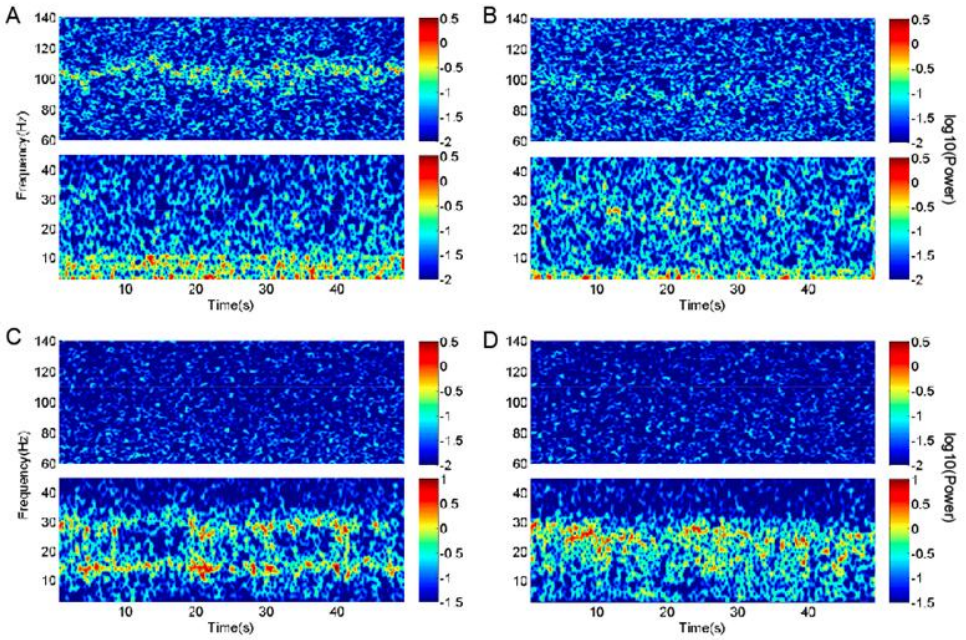
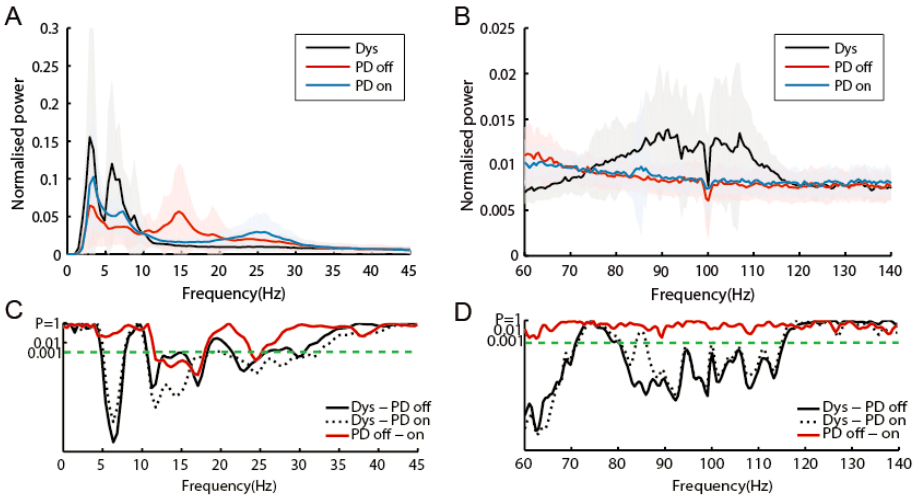


Figure 3. Complexity analysis of bandpass filtered LFPs centred on the peak frequency in low frequency band (5-10 Hz), low beta band (11-20 Hz), high beta band (20-32 Hz) and gamma band (60-140Hz). Significant differences were found in LZC among dystonia off, PD on and off conditions over low frequency ($F(2, 55) = 21.4$, $p < 0.0001$, ANOVA) , the low beta band ($F(2, 55) = 104.4$, $p < 0.0001$, ANOVA) and the gamma band $F(2, 53)=316.3$, $p<0.0001$, ANOVA). Note that two sides from one dystonic case (d6) were excluded for analysis in the gamma band due to artifacts. *$p \leq 0.005$, **$p \leq 0.001$, post-hoc t-tests.



Supplementary figure 1. Example time-frequency spectra of 50 seconds of LFPs over 3-45 Hz and 60-140Hz in dystonic case d4 off medication (A), dystonic case d8 on clonazepam and aripiprazole (B), PD case p5 off levodopa (C) and PD case p5 on levodopa (D). The window length for short-time Fourier transform was 2 seconds with 1.98 seconds overlap. Power amplitude shown in log value over the frequency of 3-45 Hz and 60-140 Hz respectively.



Supplementary figure 2. Group power spectra averaged across all bipolar channels in dystonia (A, black line, n=16 sides, 48 channels; B, black line, n=14 sides, 42 channels), PD off medication (A and B, red line, n=22 sides, 66 channels) and PD on medication (A and B, blue line, n=22 sides, 66 channels). Results of t-tests between dystonia and PD on/off medication (C and D, black solid/dash lines) and paired t-tests between PD off and on medication states (C and D, red line). LFPs were z-transformed before spectral analysis. The shadows in the respective colours denote ± 1 standard deviations of the groups. Spectral resolution was 0.5 Hz. Note ln (P) axis scale in C and D.

Figure 1

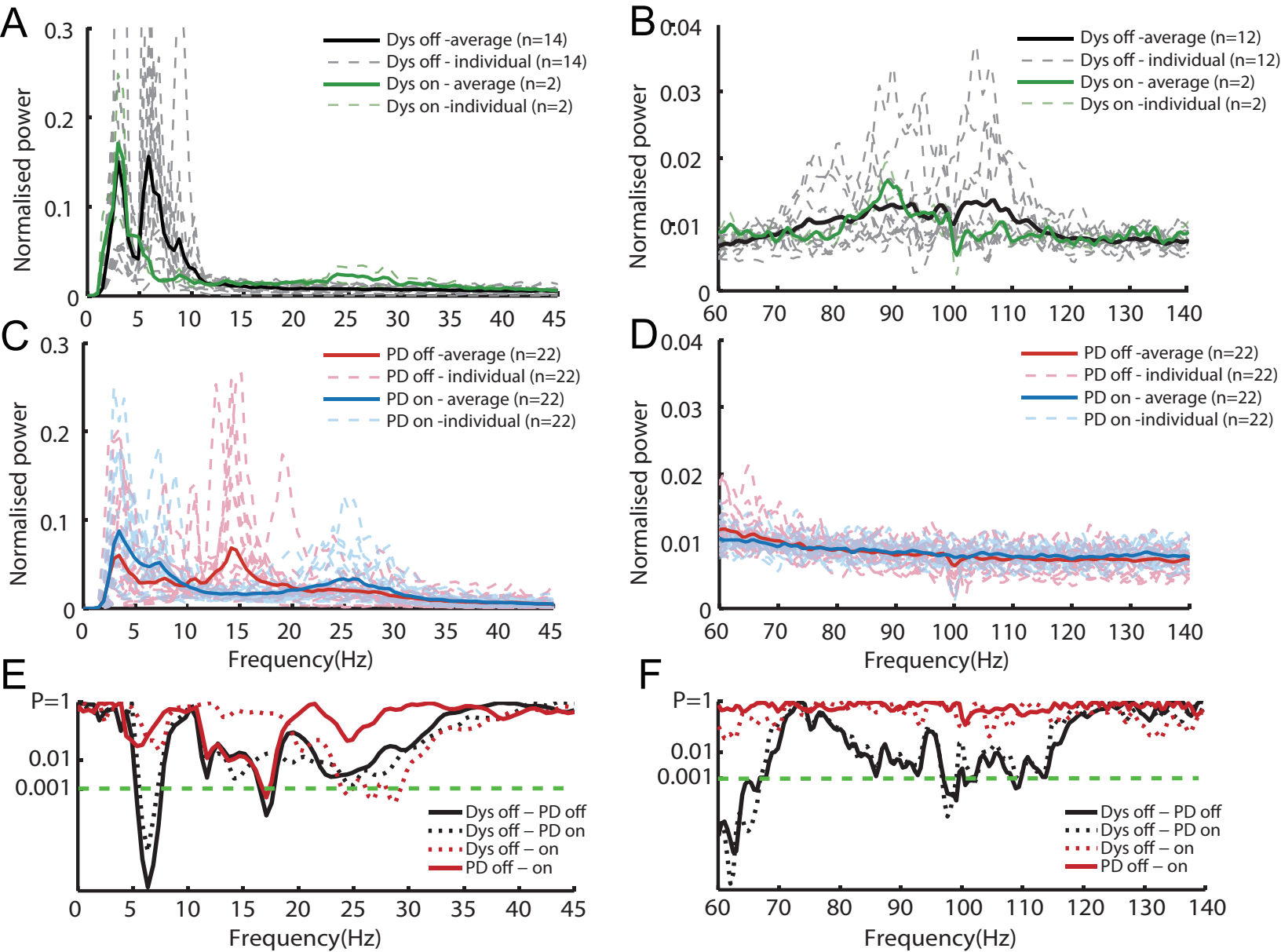

A
Normalised power
Dys off -average (n=14)
Dys off - individual (n=14)
Dys on - average (n=2)
Dys on -individual (n=2)
B
Normalised power
Dys off -average (n=12)
Dys off - individual (n=12)
Dys on - average (n=2)
Dys on -individual (n=2)
C
Normalised power
PD off -average (n=22)
PD off - individual (n=22)
PD on - average (n=22)
PD on -individual (n=22)
Frequency(Hz)
D
Normalised power
PD off -average (n=22)
PD off - individual (n=22)
PD on - average (n=22)
PD on -individual (n=22)
Frequency(Hz)
E
P=1
0.01
0.001
Dys off – PD off
Dys off – PD on
Dys off – on
PD off – on
Frequency(Hz)
F
P=1
0.01
0.001
Dys off – PD off
Dys off – PD on
Dys off – on
PD off – on
Frequency(Hz)

Figure 2

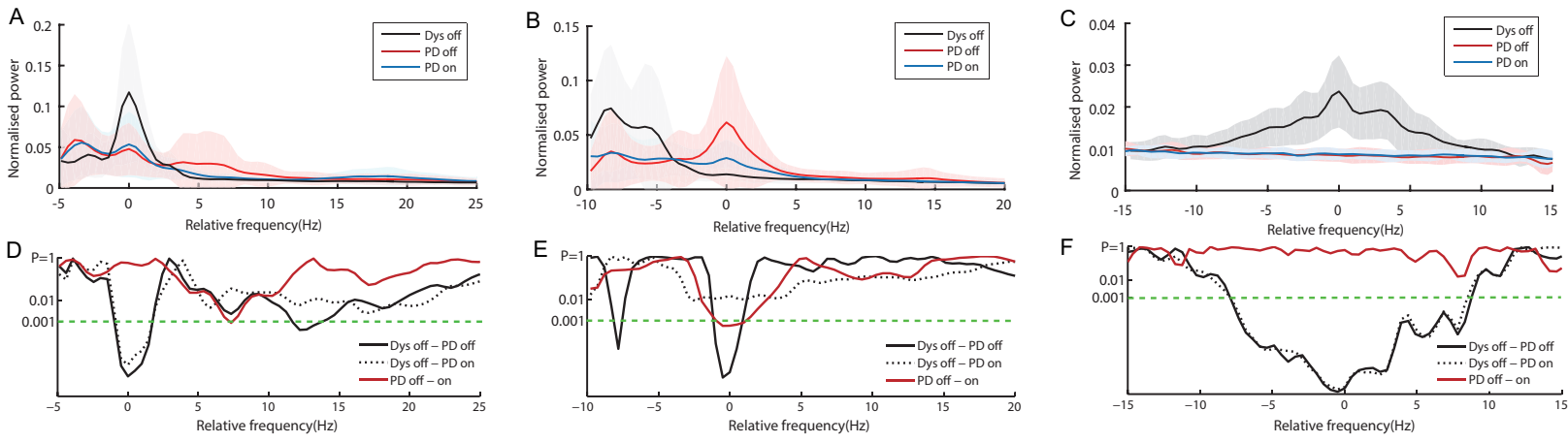

A
B
C
Dys off
PD off
PD on
Normalised power
Relative frequency(Hz)
D
E
F
P=1
0.01
0.001
Dys off – PD off
Dys off – PD on
PD off – on

Figure 3

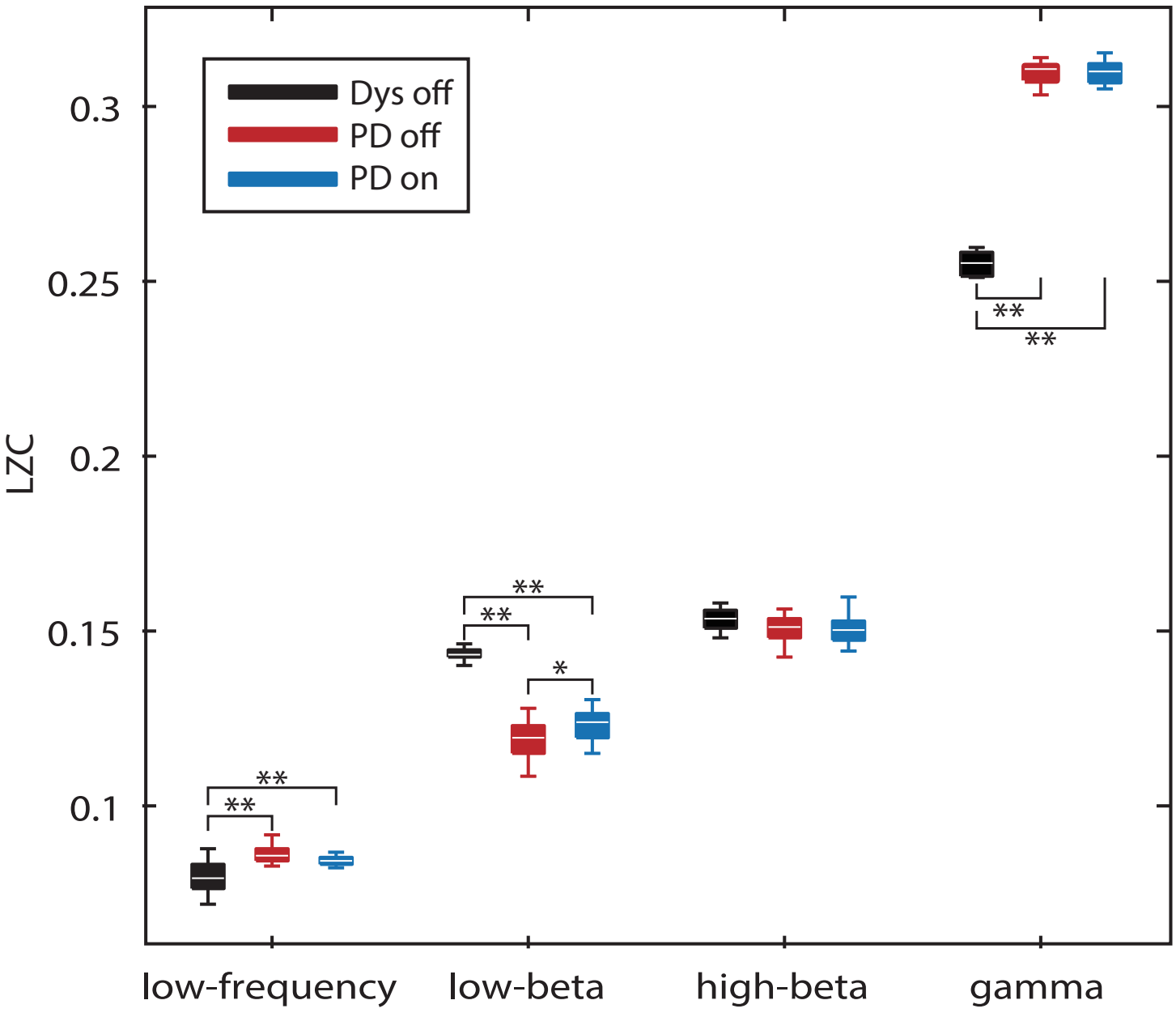

Dys off
PD off
PD on
LZC
0.3
0.25
0.2
0.15
0.1
**
**
**
**
**
*
low-frequency
low-beta
high-beta
gamma

Table-1

TABLE 1. Clinical summary

Case	Age /Sex	Diagnosis/main symptoms before operation	Medication	Pre-operative scales (dystonia: BFMDRS(MS,DS) /CDQ-24, off med; PD: UPDRS part-III, off/on med)	Channel selection
d1	21/M	dystonia, primary generalised	None	53 (43, 10)	L12, R12
d2	24/M	dystonia, primary generalised	None	50 (38, 12)	L12, R01
d3	44/F	dystonia, primary generalised	None	58 (46, 12)	L12, R12
d4	74/F	dystonia, neuroleptic induced cranial	None	24 (18, 6)	L01, R12
d5	25/M	dystonia, cranial with blepharospasm	None	28.5 (21.5, 7); CDQ-24: 90	L01, R01
d6	65/M	dystonia, cranial with blepharospasm	None	5.5 (5.5, 0); CDQ-24: 46	L23, R23
d7	52/F	dystonia, cranial with blepharospasm	None	4.5 (4.5, 0); CDQ-24: 44	L01, R12
d8	67/F	dystonia, cranial with blepharospasm	Clonazepam and Aripiprazole	12 (7, 5); CDQ-24: 62	L01, R12
p1	56/F	PD, bradykinesia	900mg LDED	26/7	L12, R12
p2	70/M	PD, freezing, gait	1100mg LDED	62/29	L12, R12
p3	59/M	PD, tremor	700mg LDED	28/5	L12, R23
p4	60/M	PD, freezing, bradykinesia	200mg LDED	25/13	L12, R12
p5	60/F	PD, bradykinesia, tremor, gait	1725mg LDED	63/7	L23, R12
p6	32/M	PD, left sided tremor	875mg LDED	52/13	R01
p7	68/M	PD, right sided tremor	475mg LDED	38/20	L23
p8	58/M	PD, bradykinesia, dyskinesia	270mg LDED	45/14	L23, R12
p9	60/M	PD, bradykinesia	600mg LDED	41/21	L12, R01
p10	60/F	PD, bradykinesia, gait	2000mg LDED	40/12	L01, R23
p11	65/M	PD, bradykinesia, rigidity, postural instability	1670mg LDED	23/7	L12, R01
p12	38/M	PD, tremor, mobility	370mg LDED	23/10	L12, R23

d1-d8: dystonia cases. p1-p12: PD cases. LDED = L-DOPA daily equivalent dose. BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale. MS = Movement Score. DS = Disability Score. CDQ-24 = Craniocervical Dystonia Questionnaire. UPDRS = Unified Parkinson's disease rating scale. Part – III: Motor Exam.

Supplementary figure 1

Click here to download Supplementary Material: Supplementary figure 1 - stft of four cases comparison.eps

Supplementary figure 2

Click here to download Supplementary Material: Supplementary figure 2- psd zscored with ttest- achn -shadow.eps