Interrogating basal ganglia circuit function in Parkinson's disease and dystonia

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Abstract

Background: The dichotomy between the hypo- versus hyperkinetic nature of Parkinson's disease (PD) and dystonia, respectively, is thought to be reflected in the underlying basal ganglia pathophysiology.

Objective: Investigate differences in globus pallidus internus (GPi) neuronal activity, and short- and long-term plasticity of direct pathway projections.

Results: GPi neurons were slower, burstier, and less regular in dystonia. In PD, symptom severity positively correlated with the power of low-beta frequency spiketrain oscillations. In dystonia, symptom severity negatively correlated with firing rate, and positively correlated with neuronal variability and the power of theta frequency spiketrain oscillations. Dystonia was moreover associated with less long-term plasticity and slower synaptic depression.

Conclusion: We substantiated claims of hyper- versus hypofunctional GPi output in PD versus dystonia, and provided cellular-level validation of the pathological nature of theta and low-beta oscillations in respective disorders. Such circuit changes may be underlain by disease-related differences in plasticity of striato-pallidal synapses.

Keywords: basal ganglia, globus pallidus, Parkinson's disease, dystonia, neurophysiology, synaptic plasticity

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by non-motor manifestations and motor symptoms including tremor, bradykinesia, rigidity, postural instability, and freezing of gait [1]. Dystonia is a movement disorder characterized by involuntary muscle contractions, repetitive movements, and abnormal fixed postures [2]. While PD is characterized as a collection of hypokinetic syndromes (apart from tremor and levodopa-induced dyskinesias), dystonia is considered a hyperkinetic movement disorder.

The dichotomy between the hypo- versus hyperkinetic nature of PD and dystonia, respectively, is thought to be reflected in the underlying basal ganglia pathophysiology. In particular, basal ganglia circuitry that involves “direct” (D1-mediated striatal projections to the internal globus pallidus; GPi) and “indirect” (D2-mediated striatal projections via the external globus pallidus and subthalamic nucleus to GPi) pathways has been implicated in these disorders [3]. In PD, activity in the indirect pathway is upregulated while the direct pathway is downregulated, both of which converge towards increased GPi-mediated inhibition of thalamocortical motor networks [4]. Conversely, dystonia has been hypothesized to occur as a result of hypofunctional indirect pathway activity [5,6] and/or hyperfunctional direct pathway activity [7], producing decreased GPi-mediated inhibition of thalamocortical motor networks. These circuit differences would thereby result in increased GPi firing rates in PD and decreased rates in dystonia; which has been substantiated by some [8,9] but not all [10] human single-neuron studies. In addition to potential differences in single-neuron firing properties, each of the disorders has been associated with aberrant synchronization at the neural aggregate level; namely, increased beta (13-30Hz) and theta (4-12Hz) local field potential (LFP) oscillations in PD [11] and dystonia [12], respectively.

Despite opposing neurocircuit pathologies, deep brain stimulation (DBS) of the GPi is a widely used treatment for the motor symptoms of both PD and dystonia. However, the timescales of symptomatic improvement after GPi-DBS and the reappearance of symptoms upon stimulation cessation are markedly longer in dystonia (minutes-hours-days) compared to PD (seconds-minutes) [13]. These differences in timescales may be the result of disease-specific dynamics of various forms of synaptic plasticity [14]. Intriguingly, high-frequency GPi stimulation has been shown to induce synaptic depression of inhibitory striato-pallidal (GPi) projections during stimulation (short-term plasticity effects), followed by an enduring potentiation of these

projections after stimulation cessation (long-term plasticity-like effects) in both patients with PD [15] and dystonia [16]. However, the dynamics of these plastic effects have not been directly compared between disorders.

In this work, we compared GPi single-neuron activities (rate and oscillation -based features) between PD and dystonia, and investigated the relationships between electrophysiological features and disease severity. Moreover, we investigated differences in the dynamics of short- and long-term plasticity of the direct pathway projections.

Methods

Patients and clinical scores

For the single-neuron feature analysis, data were collected from 19 patients with non-genetic dystonia (135 included segments; see Supplementary Materials for information on subtypes) and 44 patients with PD (222 segments) during awake microelectrode-guided GPi-DBS surgeries [17]; after overnight withdrawal of antiparkinsonian medications in patients with PD. Corresponding preoperative clinical scores for PD using the Unified Parkinson's Disease Rating Scale Part III (UPDRSIII) and dystonia using either the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) were also amalgamated for each patient. Given that UPDRSIII includes both hypokinetic and hyperkinetic symptoms of PD, we further sought to disaggregate the score by only considering items 23-26 in UPDRSIII, which assess hypokinetic symptoms of PD. To enable comparison across different dystonia scales, clinical scores were normalized (0-100%) with respect to the maximum severity per scale (108 for total UPDRSIII, 32 for hypokinetic only UPDRSIII, 85 for TWSTRS, and 120 for BFMDRS). For plasticity analyses, data were collected from a subset of 8 patients with dystonia (12 recording sites) and 10 patients with PD (13 recording sites). A data summary is available in Supplementary Table 1. Each patient provided informed consent and experiments were approved by the University Health Network Research Ethics Board and adhered to the guidelines set by the tri-council Policy on Ethical Conduct for Research Involving Humans.

Intraoperative data acquisition

Two independently driven microelectrodes (600μm spacing; 0.2–0.4MΩ impedances; ≥10kHz; sampling rate) were used for recordings; amplified using two Guideline System GS3000 amplifiers (Axon Instruments, Union City, USA) and digitized using a CED1401 data acquisition system (Cambridge Electronic Design, Cambridge, UK). For single-neuron data, units were sampled across the spatial extent of GPi as part of the standard of care neurophysiological mapping procedure; as previously described [17]. For plasticity data, microstimulation was delivered from one microelectrode using biphasic (cathodal followed by anodal) pulses (100μA, 150μs) from an isolated constant current stimulator (Neuro-Amp1A, Axon Instruments), while recording field evoked potentials (fEPs) using an adjacent microelectrode at the same depth; as

done previously [15,16,18]. Initially, ten low-frequency stimulation (LFS) pulses were delivered at 1Hz to obtain baseline measurements of fEP amplitudes (i.e., functional readouts striato-pallidal inhibitory efficacy). Then, a standard high-frequency stimulation (HFS) tetanizing protocol was delivered (four 2s blocks of 100Hz, each separated by 8s) [16], after which another set of LFS pulses was delivered to obtain measurements of post-HFS fEP amplitudes (plasticity protocol depicted in Fig. 2A). Long-term plasticity analysis involved quantifying fEP changes before versus after HFS. Short-term plasticity analysis involved quantification of successive fEP amplitudes during HFS.

Offline analyses and statistics

GPi high-frequency discharge (HFD) neurons [17] of >4 signal-to-noise ratio and <1% interspike interval violations were included in the single-neuron analyses. Segments were band-pass filtered (300-3000Hz) and template matched, after which neurophysiological features were extracted from each segment, including per patient median firing rate (FR), and the ninetieth percentile of the burst index (BI), coefficient of variation (CV), and oscillatory power across the theta (4-8Hz), alpha (8-12Hz), low-beta (12-21Hz), and high-beta (21-30Hz) frequency bands. Oscillatory power was extracted using Lomb's periodogram, performed on the autocorrelation function of single-neuron segments; as previously described [19]. The burst index was computed by taking the ratio of the means from a two-component Gaussian mixture model applied to the log interspike interval distribution, a modification of the previous mode-over-mean ISI method [20]. Neuronal features were compared between PD and dystonia using 2-tailed Mann-Whitney U (MWU) tests due to non-normality of features. Spearman correlations were employed to investigate relationships between extracted features and clinical scores. For comparing differences in single-neuron features between PD and dystonia, significant results were followed up with post hoc multiple comparisons with a Bonferroni correction. For clinical correlations, non-parametric Monte Carlo permutation tests were used, avoiding assumptions about data distribution. The tested values were randomly shuffled 5,000 times to form a probability distribution, with the p-value reflecting the original sample rank. All tests underwent adjustment for multiple comparisons, controlling the false discovery rate (FDR) at an α-level of 0.05.

All fEP measurements for plasticity analyses were normalized with respect to the root mean square amplitude of the rectified pre-stimulation LFP (low-pass filtered at 50Hz). For long-term

plasticity analyses, the median normalized fEP amplitudes pre- versus post-HFS at each recording site were analyzed using a linear mixed model (LMM) with patient ID as a random factor, normalized fEP amplitudes as the response variable, and epoch as a fixed effect, to establish whether plasticity was elicited in each disorder. The percentage change from pre- to post-HFS was also compared across disorders using a LMM with patient ID as a random factor. For short-term plasticity analysis, the dynamic change of the first five fEP amplitudes during the first train of HFS was assessed; normalized with respect to the first fEP amplitude for each train. Given the relatively rapid rate of attenuation of fEP amplitudes in GPi with HFS [16,18], the first five fEPs were fit with a double-exponential function, and the half-life of the faster decaying exponential component was used as a readout of the rate of attenuation. Half-life measurements were then compared across disorders using a using a LMM with patient ID as a random factor.

Data Sharing

The data that support the findings of this study are available in a public repository (see: https://osf.io/nqzd2/)

Results

Differences in single-neuron features

In dystonia, FR was lower (MWU test; p=.0252) and neurons were burstier (higher BI; MWU test; p=.0024) and less regular (higher CV; MWU test; p<.0001) compared to PD (Fig. 1A). However, there were no significant differences in spiketrain oscillations in the delta (MWU test; p=.6265), theta (MWU test; p=.3649), low beta (MWU test; p=.1176), or high beta (MWU test; p=.4585) frequency bands (Fig. 1B). The post hoc Bonferroni correction (adjusted significance threshold to $p < 0.0071$) indicated that firing rate difference between PD and dystonia did not survive multiple comparisons (Supplementary Table 3). A neuronal feature summary is available in Supplementary Table 2.

Clinical correlations

For rate-based spiketrain features, no clinical correlations were found for PD. In dystonia, symptom severity negatively correlated with FR (Spearman's rho=-0.49, p=.0370) and positively correlated with CV (Spearman's rho=0.48, p=.0364; Fig. 1C). For oscillatory spiketrain features, symptom severity positively correlated with low beta in PD (Spearman's rho=0.30, p=.0426), with a marginally stronger correlation for PD hypokinetic symptoms only (items 23-26 of UPDRSIII, Spearman's rho=0.32, p=.0330; Supplementary Fig. 3), and theta in dystonia (Spearman's rho=0.51, p=.0242; Fig. 1C). However, none of the clinical correlations survived Benjamini-Hochberg FDR-correction for multiple comparisons (Supplementary Table 4).

Long-term plasticity-like effects

In PD, fEP amplitudes were significantly greater after compared to before HFS (LMM; p = .0075, effect size = 5.42 ± 1.79; Fig. 2C), while in dystonia, the increase approached but did not reach statistical significance (LMM; p = .0708, effect size = 2.82 ± 1.45; Fig. 2C). The percent change in fEP amplitude was significantly greater in PD compared to dystonia (LMM; p = .0396, effect size = 12.40 ± 5.41; Fig. 2D).

Short-term plasticity

Half-life values extracted from double exponential fits on the first five fEPs during HFS were significantly greater in dystonia compared to PD (LMM; p = 0.0139, effect size = 1.04 ± 0.37; Fig. 2G).

Discussion

In this work, we leveraged the intraoperative environment to characterize GPi spiketrain features and to record and manipulate the efficacy of inhibitory direct pathway striato-pallidal projections, in order to derive insights about disease-related features of basal ganglia circuit function in PD and dystonia. In particular, we found that GPi neurons exhibited lower firing rates, but greater burstiness and variability in dystonia compared to PD (Fig. 1A). While no differences were found in the power of spiketrain oscillations across disorders (Fig. 1B), we found that PD symptom severity positively correlated with the power of low-beta frequency spiketrain oscillations, whereas dystonia symptom severity positively correlated with the power of theta frequency spiketrain oscillations (Fig. 1C). Dystonia symptom severity moreover correlated negatively with firing rate, and positively with neuronal variability. These results are discussed in greater detail with respect to previous literature in the subsequent Discussion section entitled "*Neuronal correlates of PD and dystonia*." In response to electrical stimulation (protocol depicted in Fig. 2A), we found significant increases in the amplitudes of positive-going stimulation-evoked field potential amplitudes (considered to reflect striato-pallidal synaptic strength; as exemplified in Fig. 2B) before versus after HFS in both PD and dystonia (Fig. 2C); with recording sites in PD exhibiting significantly greater increases (Fig. 2D). While changes to evoked potential amplitude before versus after stimulation can be considered to be reflective of long-term plasticity [15,18], the dynamics of evoked potentials during HFS (as depicted in Fig. 2E) can be considered as reflective of short-term synaptic plasticity [18,21]. To this end, our findings are suggestive of faster latency synaptic depression in PD compared to dystonia (Fig. 2F/G). Plasticity findings are discussed in greater detail in the Discussion section entitled "*Direct pathway plasticity*."

Neuronal correlates of PD and dystonia

The basal ganglia circuit models of PD and dystonia have been suggested to be driven by an imbalance between direct and indirect pathways [22,23]. While hyperfunctionality of the indirect pathway and hypofunctionality of the direct pathway are associated with PD [24], the direct pathway has been suggested to be hyperfunctional in dystonia [7]. To this end, our findings (Fig. 1A) of lower firing rates in dystonia compared to PD may further substantiate [8,9] such claims, whereby greater inhibition of GPi would produce decreased inhibitory output, and thus under-

inhibition of thalamocortical motor networks, giving rise to hyperkinetic motor symptoms; whereas the opposite would be true in PD [3]. These claims are further substantiated by findings of an inverse relationship between firing rate and disease severity in dystonia (Fig. 1C; rate-based features); although the opposite was not found in PD. Despite the lack of correlations with firing rate in PD, our findings seem to align with those of Muralidharan and colleagues [25], who showed that GPi neuronal firing rates may not directly correlate with motor severity but exhibit variability across the disease severity continuum in parkinsonian non-human primates (initially increasing, then decreasing, then increasing again at mild, moderate, and severe disease manifestations, respectively). Thus, while GPi discharge rates may change in PD, such changes may not be reflected by linear relationships with motor sign development and progression. Indeed, variability in spike firing rates in PD may be reflected in the considerable overlap in spiking activity between PD and dystonia (Fig. 1A), with many dystonia patients exhibiting higher discharge rates compared to PD patients. While differences in discharge rates were nevertheless observed between PD and dystonia, it may be that the combination of rate and pattern (reflected in the BI and CV) changes best differentiates the two disorders.

From a neural synchronization standpoint, we recently showed that pathological oscillations at the neural aggregate / LFP level are likely encoded by periodic oscillations in the firing rates of single neurons [26]. In the current work, we did not find significant differences in the power of spiketrain oscillations across disorders (Fig. 1B). Although previous research has reported differences in the LFP power between PD and dystonia [27,28], a study in non-human primates found no such differences in single-neuron oscillatory strength [8], as reflected in our findings. However, despite a lack of difference in overall power across disorders, we were able to derive disease/frequency-specific relationships with respect to clinical scores (Fig. 1C; oscillatory features). In particular, we provided evidence of relationships between the power of spiketrain oscillations in the theta and low beta frequency bands and the severity of motor symptoms in dystonia and PD, respectively; providing a cellular level validation of previous frequency-specific LFP clinical correlation studies in people with PD (beta oscillations) [11] and dystonia (theta oscillations) [12]. Indeed, Muralidharan and colleagues [25] also showed linear group-level relationships between low-beta frequency spiketrain oscillations and disease severity in parkinsonian non-human primates, despite the lack of linear relationships with spike discharge rates (as discussed above).

Direct pathway plasticity

We have previously shown that the amplitude of positive-going inhibitory fEPs is directly associated with the duration of neuronal inhibition [15,29], thus serving as a viable substrate of inhibitory synaptic transmission efficacy. These observations are supported by work in animals demonstrating the reversal of both positive-going extracellular fields and neuronal inhibition with the application of GABA antagonists [30,31]. Importantly, we previously [29] demonstrated that low latency inhibitory fields recorded in the subthalamic nucleus (GPe-mediated) are far smaller in amplitude and are resilient during HFS (i.e., minimal synaptic depression), whereas high latency inhibitory fields recorded in substantia nigra pars reticulata and GPi [16] (striatum-mediated) are far larger in amplitude and are subject to potent synaptic depression during HFS; thus, enabling electrophysiological discernment of these distinct inhibitory projections in humans.

To this effect, our findings may suggest disease-specific differences in mechanisms underlying both short- [32] and long-term [33,34] forms of synaptic plasticity of direct pathway projections (Fig. 2). Converging evidence from past animal and human studies suggests that dystonia is associated with impaired synaptic function and abnormal synaptic plasticity [35–37]. Compared to healthy controls, it has been shown that transcranial magnetic stimulation induced motor evoked potentials (MEPs) are hyperexcitable in dystonia [38,39], and somatosensory and motor cortical plasticity is greater [40]. Likewise, enhanced long-term potentiation at cortico-striatal synapses has been shown in rodent models of dystonia [41,42]. While our finding that long-term potentiation effects are greater in PD compared to dystonia (Fig. 2D) is difficult to corroborate with this literature, one potential explanation can be that all of our PD patients are long-term users of levodopa. We have previously shown that the intake of this antiparkinsonian dopaminergic medication leads to potent increases in the magnitude of direct pathway plasticity [15]. Although patients are 12hr withdrawn form antiparkinsonian medications for surgery, it could be that striato-pallidal synapses are nevertheless chronically over-sensitized from prolonged use of dopaminergic medication; which is a well-known hypothesis related to the manifestation of levodopa-induced dyskinesias (a hyperkinetic feature) in PD [43]. Indeed, a lack of depotentiation of striato-pallidal projections has previously been observed in patients with levodopa-induced dyskinesias [44]. As such, excessive plasticity of these projections may corroborate hyperkinetic features of dystonia and levodopa-induced dyskinesias in PD.

In addition, the variation in the modulation of these striato-pallidal projections to electrical stimulation may also be reflective of differences in the mechanism by which DBS operates across PD and dystonia, despite a common stimulation target. Clinical studies in dystonia have shown that DBS leads to a more rapid improvement in the transient, dynamic muscle contractions (phasic components) of the disorder when compared to the sustained, continuous muscle contractions (tonic or fixed components) [45]. The early improvement of the phasic component has been suggested to be associated with direct suppression of abnormal activity in the GPi [46], whereas the improvement of tonic components has been associated with long-term potentiation-like synaptic plasticity in TMS studies [14,47]. This contrast with PD, where the, the maximal clinical response to DBS occurs within a much faster time course [13,48]. The present study shows disease-specific differences in the dynamics associated with modulation of direct pathway projections; thus, potentially providing a local synaptic rationale for the differential time courses associated with the clinical effects of DBS in the same target. Specifically, we found faster rates of synaptic depression during HFS and greater post-HFS long-term plasticity-like effects in PD compared to dystonia, implying that striato-pallidal synapses in dystonia are perhaps more resistant to change compared to PD. Our findings may therefore explain the phenomenon that functional benefits of DBS require longer time courses in dystonia, if the effects of DBS rely upon network reorganization, which involves adjustments in neural connectivity or synaptic efficacy in response to stimulation [47]. Indeed, the benefits of GPi-DBS in dystonia have also been shown to persist for long periods of time even after the cessation of stimulation [14]. In PD, washout effects take longer with GPi-DBS compared to STN-DBS [49], and long-term dyskinesia reduction has also been observed with GPi-DBS even when DBS is off [50,51]. While further work is certainly required to better understand disease-related differences in plasticity, our findings may nevertheless motivate the development of periodic intermittent (ON/OFF) DBS strategies which periodically modulate synaptic plasticity for therapeutic benefits which outlast stimulation delivery, as have recently been employed in preclinical work [52,53].

Limitations and future directions

Important limitations of intraoperative/intracranial studies in humans include a lack of access to healthy control data (hence comparison across disorders), the inability to use pharmacological interventions to verify pathway specificity of elicited responses, and time constraints preventing

thorough scrutinization of time courses of long-term plasticity-like effects. Indeed, GPi receives the greatest abundance of inhibitory inputs from striatum (direct pathway), but also it also receives inhibitory inputs by way of GPe (indirect pathway). Although we can functionally disaggregate these pathway-specific responses based on differences in morphology and dynamics of GPe-mediated versus striatum-mediated inhibitory fEPs [21]; the possibility of compounded effects cannot be completely ruled out. While our neuronal investigations provide cellular level support for closed-loop targeting of disease-related neural oscillations [54,55], future applications of DBS may also benefit from closed loop tuning of basal-ganglia-thalamo-cortical circuit dynamics and plasticity through chronic monitoring of evoked potential responses [56]. Indeed, optogenetic studies in parkinsonian rodents have demonstrated the ability to achieve lasting therapeutic efficacy via periodic activations of striatal direct pathway projections [52,53], likely leveraging long-term plasticity-like mechanisms. An additional limitation of this study is that we did not stringently monitor personal medication intake or levels of intraoperative sedation; however, all patients with PD were asked to withdraw from medications the night before surgery, and the analyses only included patients operated on awake. It is important to consider that classifications of PD and dystonia as hypo- and hyperkinetic disorders can be considered oversimplifications, as there can be contradictory comorbidities and drug- and DBS-related effects [57,58]; though our results do not change substantially when only hypokinetic PD features are considered (Supplementary Fig. 3). Additionally, our analyses involved pooling of patients with various forms of dystonia. While we did not observe differences across dystonia subtypes (Supplementary Fig. 1), future studies in larger patient cohorts would are warranted. Finally, as many findings in Fig. 1 do not survive corrections for multiple comparisons, we suggest interpretation of results with caution. Despite this, many of our findings related to neuronal correlates are generally in line with previous literature, especially related to oscillatory correlates of PD and dystonia.

Conclusion

We substantiated claims of hypo- versus hyperfunctional GPi output in PD and dystonia, while furthermore providing cellular-level validation of the pathological nature of theta and low-beta oscillations in respective disorders. Such circuit changes may be underlain by disease-related differences in plasticity of striato-pallidal synapses, which are seemingly less plastic and/or respond slower to change in dystonia compared to PD.

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Author Roles

(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.

S.S: 1C, 2A, 2B, 3A; K.A.S: 1C, 2A, 2B, 3A; L.A.S: 1C, 2A, 2C, 3A; C.F: 1C, 3B; E.H: 1C, 3A; A.A.K: 1B, 3B; M.H: 1B, 3B; S.K.K: 1B, 3B; A.M.L: 1B, 3B; A.F: 1B, 3B; W.D.H: 1A, 1B, 1C, 2B, 3B; L.M: 1A, 1B, 1A, 1C, 2B, 3B.

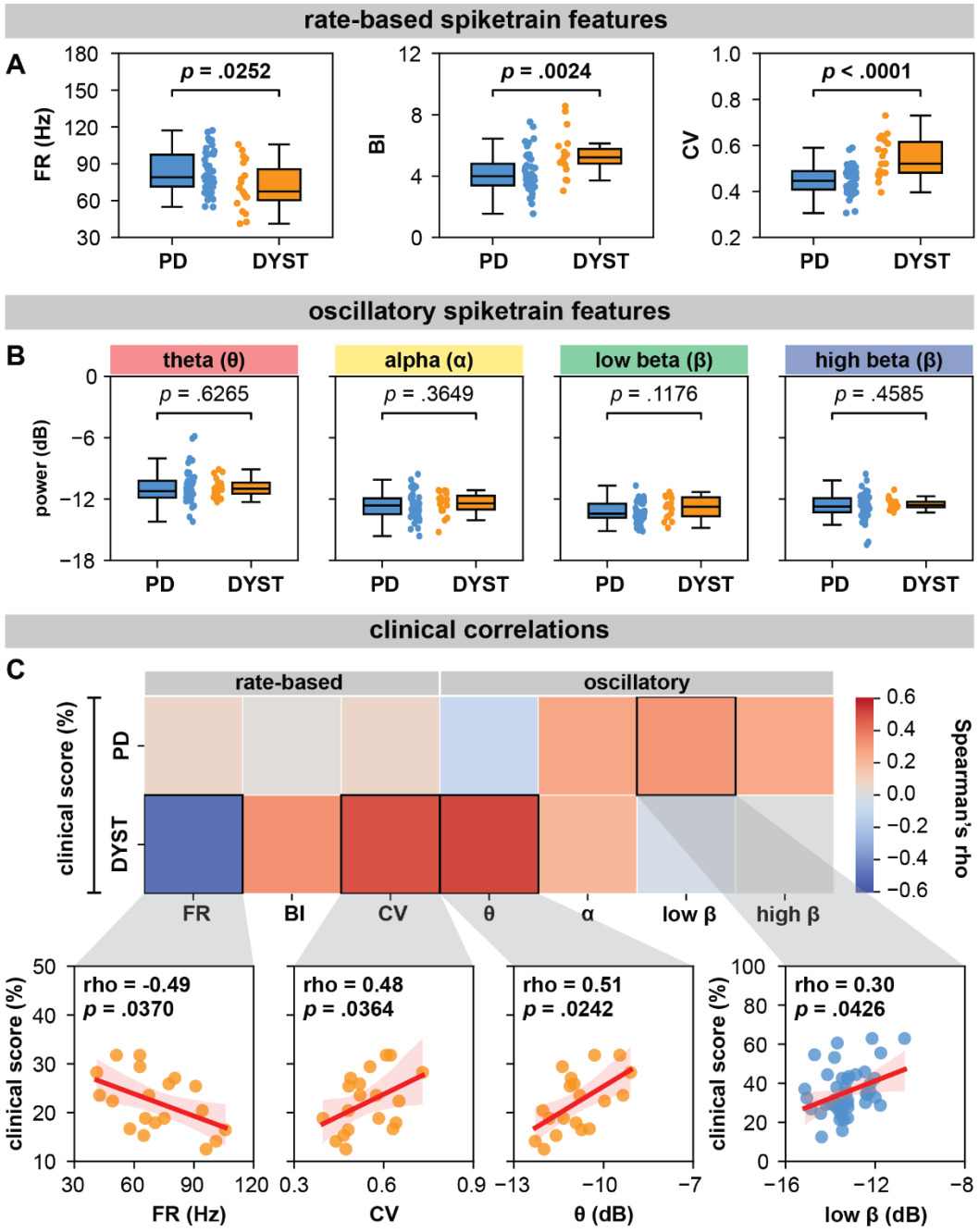

Fig 1 – GPi spiketrain feature analyses and clinical correlates of PD and dystonia. (A) With respect to (A) rate-based spiketrain features, firing rate was greater in PD while burst index (BI) and coefficient of variation (CV) were greater in dystonia; whereas no differences were found for (B) oscillatory spiketrain features for theta, alpha, low beta, high beta frequencies. MWU statistical results depicted are not corrected for multiple comparisons; after correction using the Bonferroni method, only CV and BI results remain significant (please see Supplementary Table 3). (C) In PD, the power of low beta spiketrain oscillations positively correlated (Spearman correlation) with symptom severity; in dystonia, neuronal firing rate negatively correlated with symptom severity, whereas CV and the power of theta spiketrain oscillations positively correlated with symptom severity. Depicted scatterplots are results that were significant before correction for multiple comparisons; however, none of the results persist after Benjamini-Hochberg correction for false discovery rate (please see Supplementary Table 4).

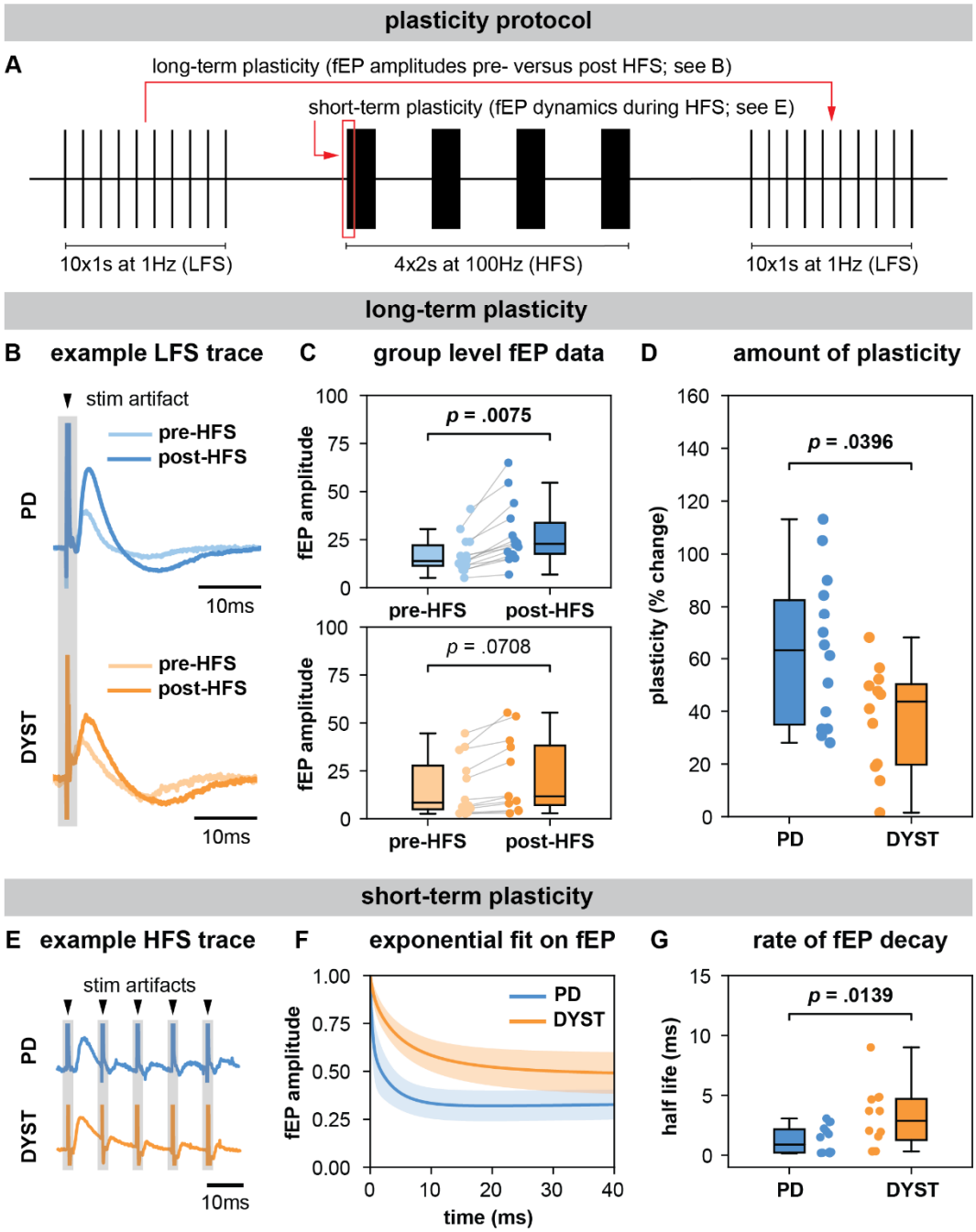

Fig 2 – Long-term and short-term effects of HFS on striato-pallidal plasticity in PD and dystonia. (A) Schematic of the plasticity protocol to assess long-term plasticity via fEP amplitude comparisons pre- versus post-HFS and short-term plasticity via fEP dynamics during HFS. (B) Highlights example fEP traces for measuring long-term plasticity pre- versus post-HFS, with (C) displaying group-level fEP amplitudes pre- versus post-HFS across diseases. (D) Illustrates the amount of plasticity (i.e., percentage change in fEP amplitudes pre- versus post-HFS) in both PD and dystonia, with PD showing higher levels of plasticity. (E) Provides an example of fEP traces during HFS for assessing short-term plasticity, with (F) depicting group-level decay rates of fEP amplitudes using an exponential fit on the fEP amplitudes over the first 5 stimulus pulses across diseases. (G) Shows the half-life of the fitted exponential (i.e., rate of attenuation of fEP amplitudes) between PD and dystonia, with PD demonstrating faster fEP attenuation.

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