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 (LTP) -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 (223 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 (UPDRSIII) and dystonia (BFMDRS or TWSTRS) were also amalgamated for each patient. To enable comparison across different dystonia scales, clinical scores were normalized (0-100%) with respect to the maximum severity per scale (108 for 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. 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 autocorrlation function of single-neuron segments; as previously described [19]. Neuronal features were compared between PD and dystonia using 2-tailed Mann-Whitney U tests due to non-normality of features. Spearman correlations were employed to investigate relationships between extracted features and clinical scores.

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 compared using 2-tailed Wilcoxon signed-rank tests to establish whether plasticity was elicited in each disorder. The percentage change from pre- to post-HFS was also compared across disorders using a 2-tailed Mann-Whitney U test. 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 2-tailed Mann-Whitney U test.

Data Sharing

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Results

Differences in single-neuron features

In dystonia, FR was significantly lower (p=.0252) and neurons were burstier (higher BI; p=.0024) and less regular (higher CV; p<.0001) compared to PD (Fig. 1A). However, there were no significant differences in spiketrain oscillations in the delta (p=.6265), theta (p=.3649), low beta (p=.1176), or high beta (p=.4585) frequency bands (Fig. 1B). A 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=.0328) and a positively correlated with CV (Spearman's rho=0.48, p=.0358; Fig. 1C).

For oscillatory spiketrain features, symptom severity positively correlated with low beta in PD (Spearman's rho=0.51, p=.0256) and theta in dystonia (Spearman's rho=0.30, p=.0442; Fig. 1C).

LTP-like effects

In both PD (p=.0001) and dystonia (p=.0005), fEP amplitudes were significantly greater after compared to before HFS (Fig. 2B). The percent change in fEP amplitude was significantly greater in PD compared to dystonia (p=.0422; Fig. 2C).

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 (p=.0146; Fig. 2F).

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.

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 [20,21]. While hyperfunctionality of the indirect pathway and hypofunctionality of the direct pathway are associated with PD [22], the direct pathway has been suggested to be hyperfunctional in dystonia [7]. To this end, our findings of lower firing rates in dystonia compared to PD may further substantiate [8,9] such claims, wherein 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; although the opposite was not found in PD.

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 [23]. In the current work, while we did not find significant differences in the power of spiketrain oscillations across disorders, we were able to derive disease/frequency-specific relationships with respect to clinical scores. 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 LFP findings [11,12].

Direct pathway plasticity as a potential readout of disease-specific circuitopathy

We have previously shown that the amplitude of positive-going inhibitory fEPs is directly associated with the duration of neuronal inhibition [15,24], 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 [25,26]. Importantly, we previously [24] demonstrated that 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 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- [27] and long-term [28,29] forms of synaptic plasticity direct pathway projections. The disease-specific alterations of the efficacy of these projections with electrical stimulation may also reflect differential DBS mechanisms of action across diseases, despite a common stimulation target. Clinical studies in dystonia have shown that DBS leads to a more rapid improvement in phasic components of the disorder compared to tonic or fixed components [30]. The early improvement of the phasic component has been suggested to be associated with direct suppression of abnormal activity in the GPi [31], whereas the improvement of tonic components has been associated with LTP-like synaptic plasticity in TMS studies [14,32]. Contrasting these delayed effects in dystonia, the maximal clinical response to DBS in PD occurs within a much faster time course [13,33]. 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 LTP-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 indeed the effects of DBS, at least in part, rely upon network reorganization [14,32].

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 LTP-like effects. Future studies, which may record evoked fields via macroelectrodes connected to stimulators with chronic sensing capabilities, could provide the opportunity to substantiate these effects in the chronic setting. Furthermore, chronic monitoring of evoked fields may allow for microcircuit interaction to selectively modulate the efficacy of target synapses. Indeed, optogenetic studies in parkinsonian rodents have demonstrated the ability to achieve lasting therapeutic efficacy via periodic activations of striatal direct pathway projections, likely leveraging LTP-like mechanisms [34]. Conversely, a long-term depression paradigm may instead be beneficial in dystonia. While our neuronal investigations provide cellular level support for closed-loop targeting of disease-related neural oscillations [35,36], future applications of DBS may also benefit from closed loop tuning of basal-ganglia-thalamo-cortical circuit dynamics through modulation of plasticity. 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. Finally, 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 [37,38]. Additionally, our analyses involved pooling of patients with various forms of dystonia; however, we did not observe differences across subtypes (Supplementary Fig. 1).

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.

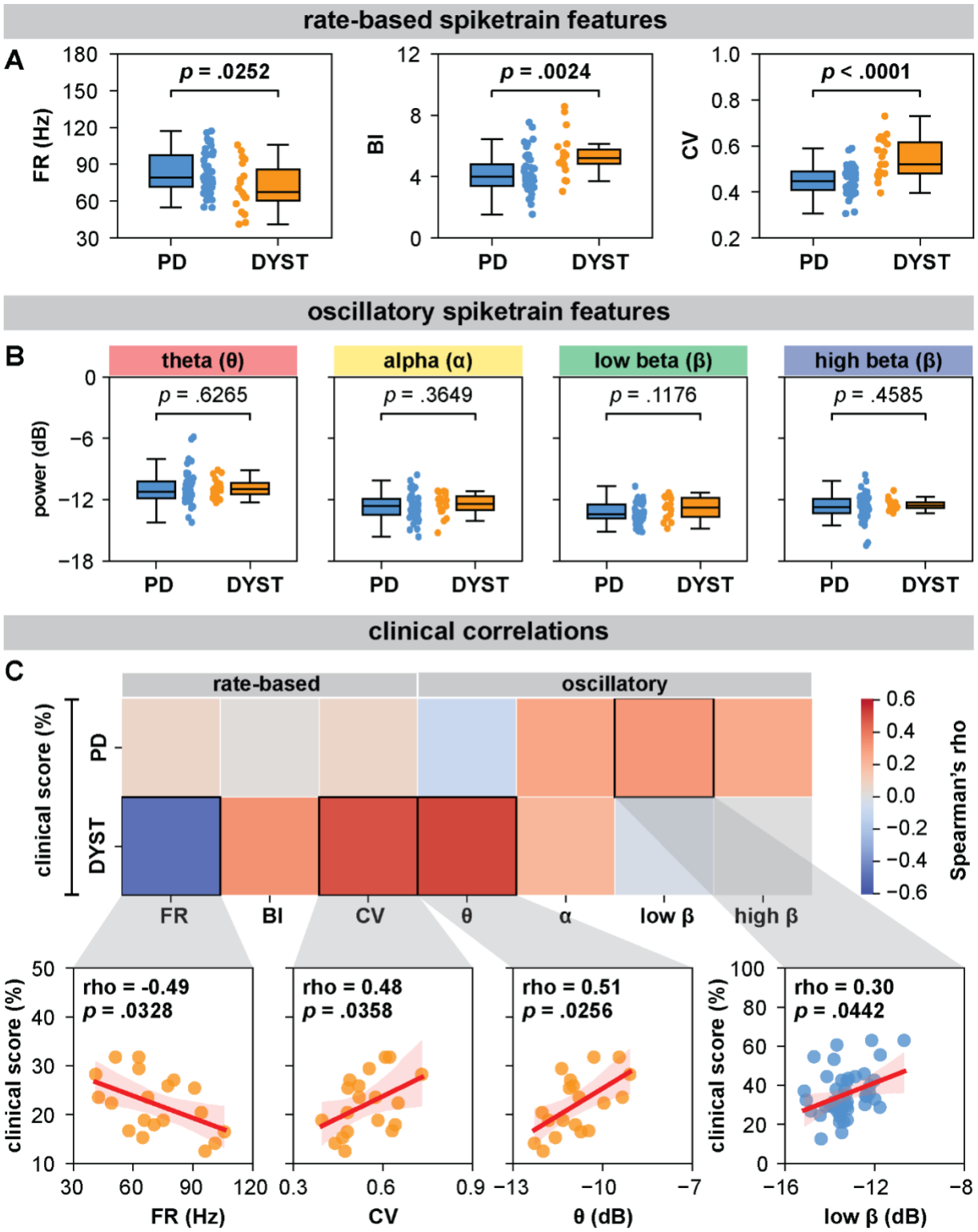

Fig 1 – GPi spiketrain feature analyses and clinical correlates of PD and dystonia. (A) In dystonia, GPi neuronal output was slower, burstier, and more irregular compared to PD; however, (B) there were no significant differences in spiketrain oscillations. (C) In PD, increased power of low beta spiketrain oscillations was associated with greater symptom severity. In dystonia, lower neuronal firing rates, higher neuronal irregularity, and increased power of theta spiketrain oscillations were associated with greater symptom severity.

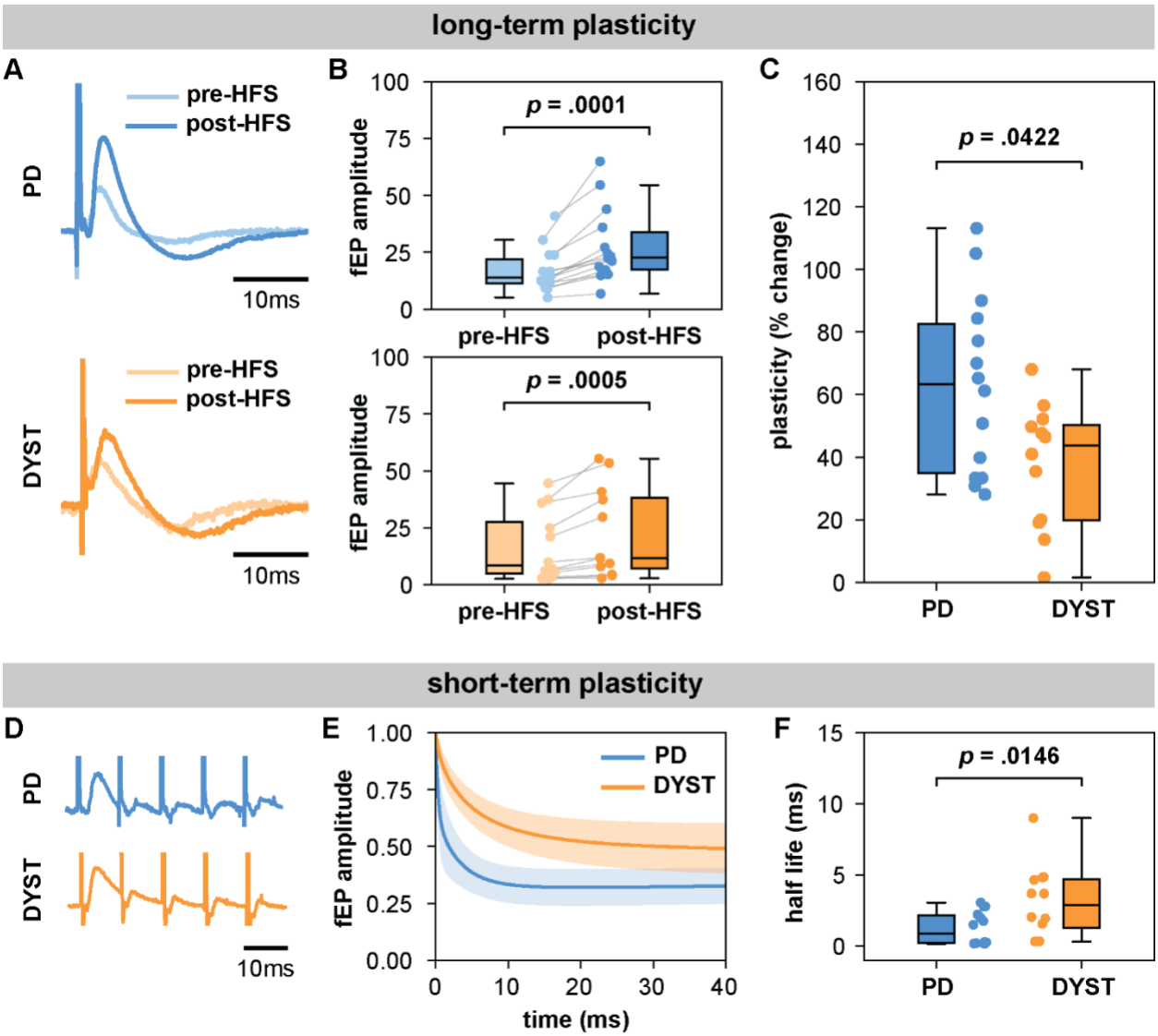

Fig 2 – Long-term and short-term effects of HFS on striato-pallidal plasticity in PD and dystonia. (A/B) While LTP-like effects were observed after HFS in both disorders, (C) fEP amplitude increases were greater in PD. (D/E) While synaptic depression was observed during HFS in both disorders, (F) the rate of attenuation of fEPs was faster in PD.

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