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Modulation of inhibitory plasticity in basal ganglia output nuclei of patients with Parkinson's disease

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Running title:

Inhibitory plasticity in Parkinson's disease

Abstract

Deep brain stimulation of certain target structures within the basal ganglia is an effective therapy for the management of the motor symptoms of Parkinson's disease. However, its mechanisms, as well as the pathophysiology of Parkinson's disease, are varied and complex. The classical model of Parkinson's disease states that symptoms may arise as a result of increased neuronal activity in the basal ganglia output nuclei due to downregulated GABAergic striato-nigral/-pallidal projections. We sought to investigate the stimulation and levodopa induced effects on inhibitory synaptic plasticity in these basal ganglia output nuclei, and to determine the clinical relevance of altered plasticity with respect to patients' symptoms. Two closely spaced microelectrodes were advanced into the substantia nigra pars reticulata (potential novel therapeutic target for axial motor symptoms) or globus pallidus internus (conventional therapeutic target) in each of 28 Parkinson's disease patients undergoing subthalamic or pallidal deep brain stimulation surgery. Sets of 1Hz test-pulses were delivered at different cathodal pulse widths (25, 50, 100, 150, 250us) in randomized order, before and after a train of continuous high frequency stimulation at 100Hz. Increasing the pulse width led to progressive increases in both the amplitudes of extracellular focally evoked inhibitory field potentials and durations of neuronal silent periods. Both of these effects were augmented after a train of continuous high frequency stimulation. Additionally, reductions in the baseline neuronal firing rate persisted beyond one minute after high frequency stimulation. We found greater enhancements of plasticity in the globus pallidus internus compared to the substantia nigra pars reticulata, and that intraoperative levodopa administration had a potent effect on the enhancement of nigral plasticity. We also found that lower levels of nigral plasticity were associated with higher severity motor symptoms. The findings of this study demonstrate that the efficacy of inhibitory synaptic transmission may be involved in the pathophysiology of Parkinson's disease, and furthermore may have implications for the development of novel stimulation protocols, and advancement of DBS technologies.

Keywords: basal ganglia; deep brain stimulation; GABA; globus pallidus; levodopa; Parkinson's disease; substantia nigra; synaptic plasticity

Introduction

Parkinson's disease is characterized by a loss of dopaminergic innervation from the substantia nigra pars compacta (SNc) to the striatum. This denervation is believed to cause increased neuronal activity within the inhibitory basal ganglia output nuclei, the substantia nigra pars reticulata (SNr) and globus pallidus internus (GPi) (Albin et al., 1989; Alexander and Crutcher, 1990; DeLong, 1990). This occurs as a result of a loss of inhibitory tone on the subthalamic nucleus (STN) due to excessive striatal inhibition of the inhibitory globus pallidus externus (GPe) via the D2-receptor-mediated indirect pathway, and a concurrent reduced striatal inhibitory tone on the SNr and GPi via the D1-receptor-mediated direct pathway (Surmeier et al., 2007). These changes, as well as changes in firing patterns (Levy et al., 2002; Brown, 2003), are believed to give rise to the symptoms of Parkinson's disease.

Currently, dopamine replacement by levodopa administration remains the most effective therapy for the management of Parkinson's disease symptoms. However, long-term therapy is complicated by motor fluctuations and levodopa-induced dyskinesias, which represent a substantial source of disability in some patients (Nutt, 1990; Obeso et al., 2000). Subsequently, deep brain stimulation (DBS) of the STN or GPi has been widely adapted as a conventional alternative management option (Benabid et al., 1994; Limousin et al., 1995; Kumar et al., 1998, 2000; Kleiner-Fisman et al., 2006; Perlmutter and Mink, 2006; Lozano et al., 2017); as well as recent promising studies demonstrating the efficacy of SNr-DBS, or combined STN/SNr-DBS for the treatment of axial motor symptoms in Parkinson's disease (Chastan et al., 2009; Weiss et al., 2011a, b, 2013). DBS mimics the effect of beneficial lesions (Bergman et al., 1990; Aziz et al., 1991; Heywood and Gill, 1997) or inactivation by injections of muscimol and lidocaine (Wichmann et al., 1994; Levy et al., 2001), suggesting that DBS may work by inhibition of neuronal activity.

The precise physiological mechanisms that give rise to Parkinson's disease symptoms, as well as the therapeutic mechanisms of action of DBS are complex and varied, and the effects of pulse width on neuronal activity have not been systematically studied; although several clinical studies have suggested that varying the pulse width can impact outcome (Rizzone et al., 2001; Moro et al., 2002; Reich et al., 2015). In this intraoperative study, we investigated the effects of single pulses of electrical stimulation at different pulse widths on the neuronal activity and synaptic events at recording sites of the basal ganglia output nuclei (SNr and GPi), before and after a train of continuous high frequency stimulation (HFS). We employed a unique methodology for eliciting and measuring focal evoked potentials (fEPs) in SNr and GPi using two closely-spaced microelectrodes. Using this methodology, we have recently demonstrated that a train of continuous high frequency stimulation (HFS) is capable of inducing a robust potentiation of

inhibitory synaptic plasticity within the SNr (Milosevic et al., 2017); here, we expand on this initial finding. The objectives of this study were to (i) investigate the pulse-width dependent effects of electrical stimulation on fEP amplitudes and neuronal firing at SNr and GPi recording sites, (ii) compare the changes in synaptic plasticity after a train of continuous HFS between the two output structures, (iii) investigate the effects of exogenous dopamine on synaptic plasticity in the SNr, and (iv) determine if a relationship exists between synaptic plasticity in the SNr and patients' axial motor symptoms. While it has been hypothesized that persistent changes to synaptic plasticity play a role in both adaptive and maladaptive responses to different forms of pathology and injury of the central nervous system (Kullmann et al., 2012), far less is known regarding the mechanisms of inhibitory (GABAergic) synaptic plasticity, compared to that evoked at excitatory synapses; especially within the human brain. The findings of this study demonstrate and implicate the involvement of inhibitory synaptic plasticity in Parkinson's disease, and furthermore may have implications for DBS programming, and advancement of DBS technologies.

Methods and materials

Patients

A total of 28 patients with Parkinson's disease undergoing microelectrode-guided placement of DBS electrodes into either the STN or GPi participated in this study, after overnight withdrawal from medication ("OFF"). In these patients, a total of 23 SNr recording sites (in 20 patients undergoing STN-DBS surgery) and 11 GPi recording sites (in 8 patients undergoing GPi-DBS surgery) were investigated. Seven of the (STN/) SNr patients were each given oral administration of 100mg of levodopa (Sinemet 100/25) after completion of the recordings on the first side, thus, the second side was considered "ON" (i.e. an additional 7 recording sites were investigated ON medication). There was an average of 40±3.5min (mean±SEM) between levodopa administration and recording from the SNr on the second side. For each patient we determined the Unified Parkinson's Disease Rating Scale (UPDRS) III total motor subscore and axial subscore (sum of speech, facial expression, arising from chair, posture, gait, postural stability, body bradykinesia, and neck rigidity) in OFF and ON conditions. All of the conducted experiments conformed to the guidelines set by the Tri-Council Policy on Ethical Conduct for Research Involving Humans and were approved by the University Health Network Research Ethics Board. Furthermore, all of the patients in this study provided written, informed consent prior to taking part in the study.

Data acquisition

Two independently driven microelectrodes (25μm tip lengths, 600μm apart, 0.2-0.4MΩ impedances, at 12.5kHz), which share a common ground on a stainless-steel intracranial guidetube were used for

recordings and microstimulation (Fig. 1A). Open filter recordings (5-3,000Hz) were amplified 5,000 times using two Guideline System GS3000 amplifiers (Axon Instruments, Union City, USA), digitized using a CED 1401 data acquisition system (Cambridge Electronic Design, Cambridge, UK), and monitored using Spike2 software (Cambridge Electronic Design). Microstimulation was delivered using an isolated constant-current stimulator (Neuro-Amp1A, Axon Instruments) with biphasic pulses (cathodal followed by anodal).

Microelectrode recording procedures

Techniques for electrophysiological identification of STN/SNr (Hutchison et al., 1998) and GPi (Hutchison et al., 1994) have been previously published. Briefly, stereotactic coordinates of the anterior commissure and posterior commissures were determined using a T1-T2 fusion MRI (Signa, 1.5T or 3T, General Electric, Milwaukee, USA) on a surgical neuronavigation workstation (StealthStation, Medtronic, Minneapolis, USA). Additionally, estimation of the location of the STN (x=12mm lateral, y=3mm posterior to MCP, z=3mm inferior to AC-PC) or GPi (x=20mm lateral, y=MCP, z=5mm inferior to AC-PC) was done based on the Schaltenbrand and Wahren (1977) standard atlas (Fig. 1B/C). Two microelectrodes were advanced in the dorsoventral direction beginning 10mm above the planned target. For STN/SNr trajectories, entry into the STN was confirmed based on an increase in background noise, and recording of single units with firing rates of approximately 20-40Hz, irregular firing patterns with periods of beta activity, and kinesthetic single units. After 4-6mm advancement, decreases in spike incidence signified exit from the ventral border of the STN and entry into the SNr was characterized by lower amplitude units with fast rates (80-100Hz) and regular firing patterns. For GPi trajectories, recording sites were confirmed based on presence of irregular, high frequency discharge (50-90Hz) neurons with responsiveness to movements, as well as border cells with highly regular 20-60Hz firing rates. After 10-12mm advancement, decreases in spike incidence signified exit from the ventral border, and the optic tract was confirmed based on visually evoked potentials elicited by brief flashes of light in the visual field as well as patients' reports of stimulation-induced phosphenes in the contralateral visual hemifield.

Stimulation protocol

At SNr or GPi recordings sites, stimulation trains were delivered from a single microelectrode to elicit fEPs, which were recorded by the adjacent microelectrode (600µm apart) at the same depth. Five sets of 1Hz "test pulses" (100µA for 10s; 10 pulses per set) were delivered at different cathodal pulse widths in randomized order (25, 50, 100, 150, 250µs), separated by 5-10s. This was followed by a "long-train" of HFS (100Hz, 100µA, 150µs pulse width, 10s), followed by another five sets of post-HFS "test pulses"

(see Fig. 1D). In the SNr OFF/ON levodopa patient subset, the first side was considered OFF, and the second side was considered ON. We have previously demonstrated that 1Hz pulses do not elicit changes (neither increases nor decreases) to fEP amplitudes in the SNr (Milosevic et al., 2018) or in the GPi (Liu et al., 2012), thus 1Hz serves as a suitable "test pulses" frequency.

Offline analyses and statistics

A post-stimulus plot of the average firing rate of all SNr neurons was constructed (10ms bins) to demonstrate the slow return to baseline firing with increasing pulse widths (only 50, 150, and 250μs depicted for clarity), before and after HFS (Fig. 1F). We also calculated the percentage-reduction in the neuronal firing rate after completion of the stimulation protocol with respect to the pre-HFS baseline firing of the neuron (paired sample t-test, one-tailed). Amplitudes of the fEP were measured from the pre-stimulus baseline to the peak voltage deflections after each stimulation pulse (Prescott et al., 2009; Liu et al., 2012; Milosevic et al., 2017; see Fig. 1E). Pre- and post-HFS fEP amplitudes were normalized with respect to the average fEP amplitude of the pre-HFS 150μs pulse width (i.e. all fEP measurements at a single recording site were divided by the average fEP amplitude of the pre-HFS 150μs pulse width train at the same recording site). The "silent period" was measured as the duration of neuronal inhibition after each stimulation pulse (i.e. between the stimulation pulse and the return of the first spike; see Fig. 1E). To measure the effects of pulse width and HFS on fEP amplitudes (Fig. 2A) as well as on silent periods (Fig. 2B) in the SNr, two-way repeated measures ANOVA (within subject factors) was used. Additionally, Pearson coefficients of correlation and p-values were obtained between normalized fEP amplitudes and silent periods pre- and post-HFS (Fig. 2C/D). To determine whether there was a difference in the amount of plasticity after HFS between SNr OFF and SNr ON (Fig. 3A), two-way split-plot ANOVA was used (within subject factor: pulse width; between subject factor: medication) to compare the post-HFS amplitudes across pulse widths. The same (within subject factor: pulse width; between subject factor: location) was done to compare post-HFS fEP amplitudes between SNr OFF and GPi (Fig. 3B). All ANOVAs were followed up with posthoc pairwise comparison t-tests with Bonferonni correction. The data were not normally distributed and were log transformed prior to ANOVAs. The 25μs pulse width often failed to elicit a measurable fEP (perhaps due to being below the threshold for activation, the recording not being "focal" enough, and/or this low-energy pulse not spreading to the recorded neuron), thus was not included in ANOVAs (further, a value of zero cannot be log transformed). Additionally, we obtained Pearson coefficients of correlation between SNr plasticity (i.e. increase in normalized fEP amplitude, calculated as the average of the pre-HFS normalized fEP amplitude subtracted from the average post-HFS normalized fEP amplitude at the 150μs pulse width), and both the UPDRSIII total motor subscore (Fig. 4A), and the axial symptom subscore (Fig 4B). Furthermore, we plotted (as vectors)

the changes that occur to the enhancements of fEP amplitudes after intraoperative administration of levodopa and the changes that occur to the clinical UPDRSIII total motor subscore (Fig. 4C) and axial motor subscrore (Fig. 4D) from the OFF to ON medication state.

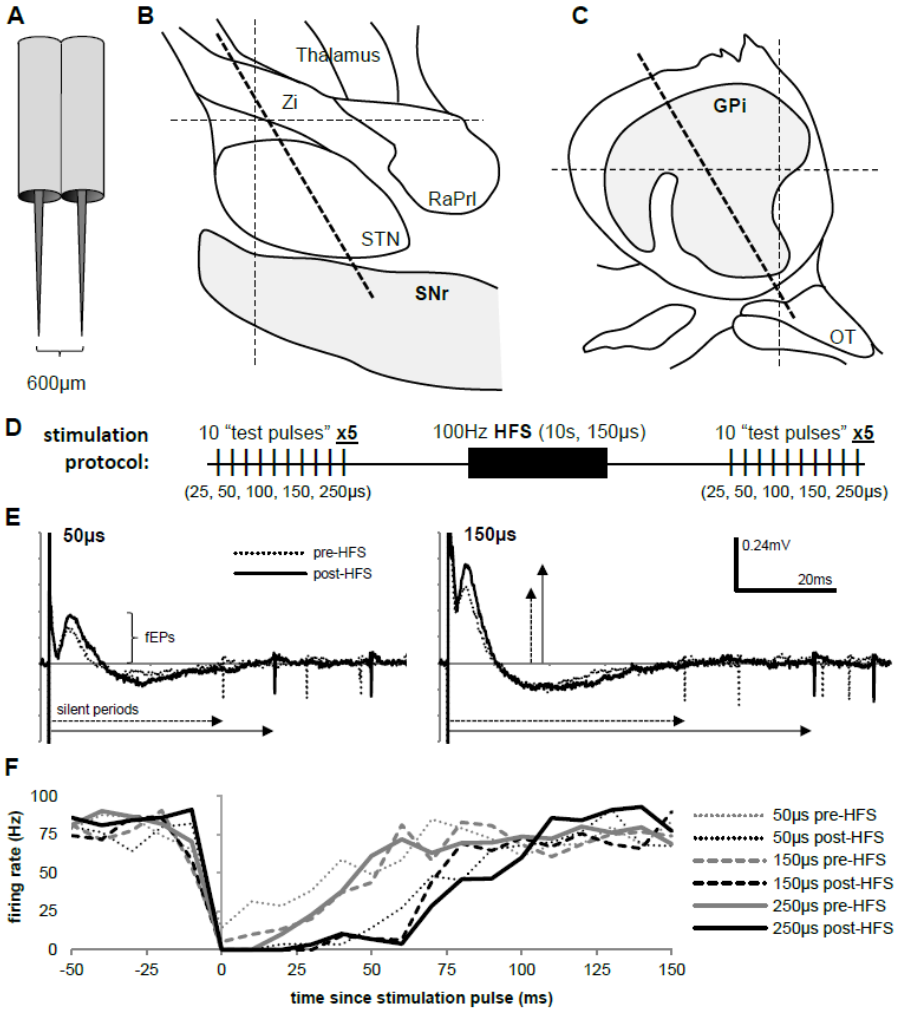


Figure 1 – Microelectrode configuration, experimental recording locations, stimulation protocol, and sample data. (A) Custom dual-microelectrode assembly with ~600µm mediolateral spacing. Representative (B) STN/SNr and (C) GPi microelectrode recording trajectories for electrophysiological mapping of the DBS target location. (D) Schematic of the stimulation protocol performed at SNr and GPi recording sites; five sets of 1Hz (100µA, 10s) "test-pulses" at different pulse widths (25, 50, 100, 150, 250µs in randomized order) were delivered before and after HFS (100Hz, 100µA, 10s, 150µs pulse width). (E) Sample data of a single pre- and post-HFS fEP and associated durations of neuronal inhibition (silent periods) elicited by a 50µs pulse (left) and a 150µs pulse (right) in the SNr. fEP amplitudes and silent periods were greater with larger pulse widths, and both variables were further enhanced after HFS. (F) Stimulation pulse width augmented the average latency of the return to baseline firing rate of neurons, before and after HFS. The graph depicts the poststimulus plot of firing rates at 10ms intervals after stimulus delivery (omitted from graph for clarity: 25µs and 100µs pulse widths).

Results

SNr plasticity OFF medication: fEP amplitudes and silent periods

We found that at SNr recording sites, both fEP amplitudes (Fig. 2A) and durations of neuronal inhibition (silent periods; Fig. 2B) progressively increased as the pulse width was increased, and that measurements of both variables were greater after HFS (HFS-induced synaptic plasticity). For fEP amplitudes ($n_{recording-sites}$=23) the main effects of pulse width [$F(3,66)=155.442$, $P<0.001$] and HFS [$F(1,22)=61.825$, $P<0.001$] were significant, with a significant interaction between the factors [$F(3,66)=4.954$, $P<0.01$]. Posthoc pairwise comparisons indicated significant ($P<0.001$) differences across all pulse widths and pre-/post-HFS. For silent periods ($n_{recording-sites}$=13), the main effects of pulse width [$F(3,36)=27.291$, $P<0.001$] and HFS [$F(1,12)=28.647$, $P<0.001$] were also significant, with no interaction between factors. Posthoc pairwise comparisons indicated significant differences pre-/post-HFS ($P<0.001$), and across all pulse widths ($P<0.01$); except between 100 and 150µs, and 150 and 250µs. We further demonstrated that the fEP amplitudes and silent periods were positively correlated (i.e. a larger fEP led to a longer silent period) both pre-HFS ($R^2=0.1275$, $P<0.001$; Fig. 2C) and post-HFS ($R^2=0.2810$, $P<0.001$; Fig. 2D), and in both cases the effects scaled linearly with the pulse width. In Fig. 1F we demonstrated an increasingly delayed rate of recovery of the neuronal firing after delivery of stimulation pulses. Furthermore, we found that after completion of the stimulation protocol, the neurons ($n_{recording-sites}$=13) fired at only 87.5% ($P<0.05$) of their pre-HFS baseline (measurements taken an average of 74±5.3sec after HFS). The firing rates were reduced from 107.2±10.0Hz to 93.8±12.3Hz. It must be considered that the increased silent periods after HFS may also be affected by this overall reduced neuronal firing that occurs after HFS. Accordingly, if the neurons fire at an average of ~94Hz after HFS, the interspike interval (ISI) would be ~10.6ms (time between two consecutive spikes). The reported silent period measurements are in the range of 37.8ms (at 50µs pre-HFS) to 81.5ms (at 250µs post-HFS). Thus, the comparatively small ISI only marginally factors into the prolonged silent periods.

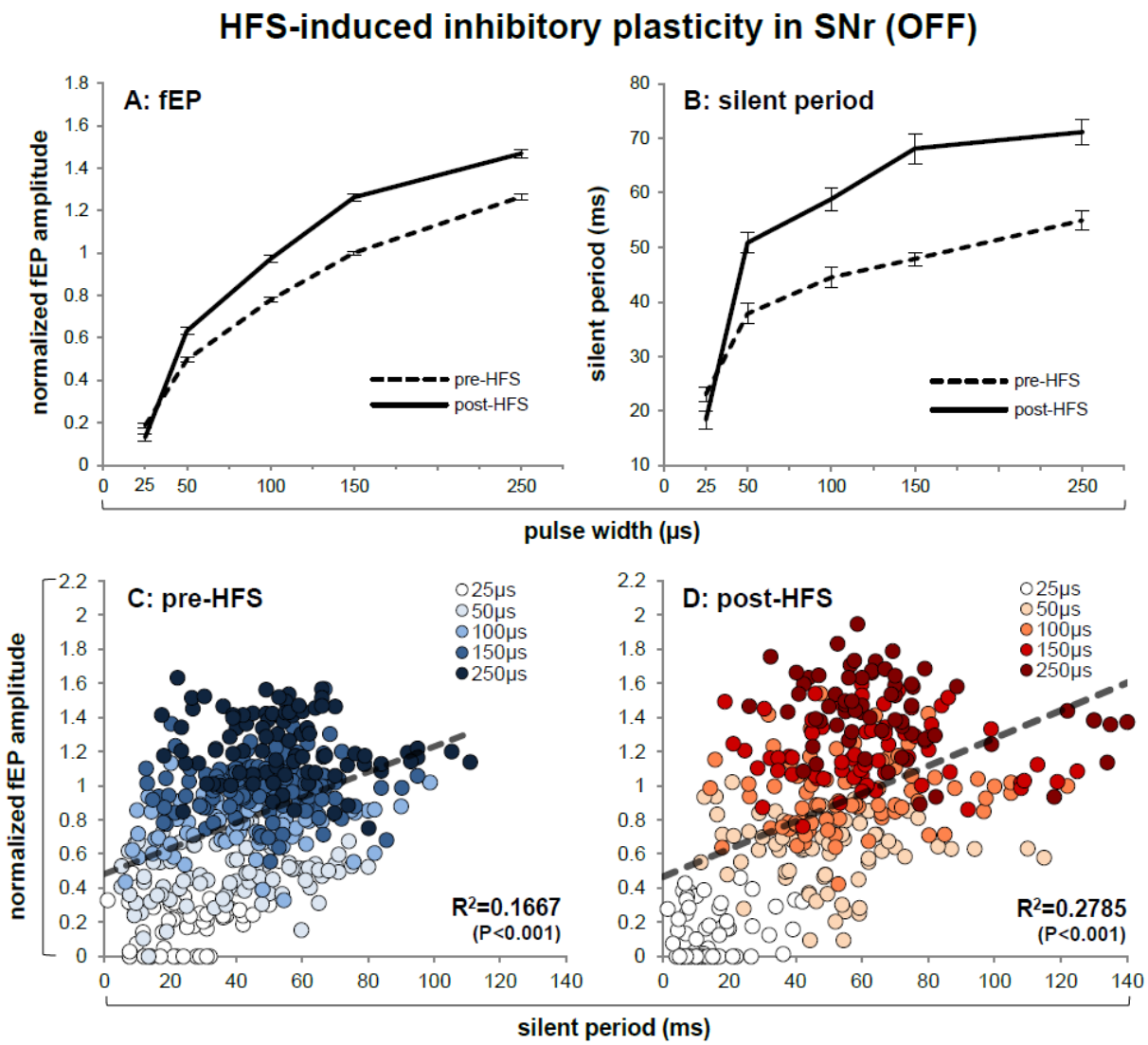


Figure 2 – HFS-induced inhibitory synaptic plasticity in SNr (OFF), and pulse-width dependent effects. Larger stimulation pulse widths elicited larger (A) fEP amplitudes ($n_{recording\text{-}sites}$=23), and longer (B) silent periods (durations of neuronal inhibition; $n_{recording\text{-}sites}$=13) (mean±SEM). Furthermore, after a continuous 10s train of HFS, both fEP amplitudes and durations of neuronal inhibition were greater. Taken together, these findings are indicative of HFS-induced enhancement of inhibitory synaptic plasticity, which scaled with pulse width. For fEP amplitudes, we found significant main effects of both pulse width [F(3,66)=155.442, P<0.001] and HFS [F(1,22)=61.825, P<0.001]. Likewise for silent periods, we found significant main effects of pulse width [F(3,36)=27.291, P<0.001] and HFS [F(1,12)=28.647, P<0.001]. Detailed statistics can be found in Results section (*SNr plasticity OFF medication: fEP amplitudes and silent periods*). Further, larger fEP amplitudes were associated with longer durations of neuronal inhibition (silent periods). The silent period was linearly correlated with fEP amplitude both (C) pre-HFS (P<0.001) and (D) post-HFS (P<0.001). Again, fEP amplitudes and silent period durations scaled with the stimulation pulse width.

Plasticity and levodopa (SNr OFF/ON): fEP amplitudes

Like SNr OFF medication, we demonstrated that at SNr recording sites ON medication ($n_{recording\text{-}sites}$=7) fEP amplitudes progressively increased as the pulse width was increased, and were larger after HFS (Fig. 3A). The main effects of pulse width [$F(3,18)=43.512$, $P<0.001$] and HFS [$F(1,6)=14.224$, $P<0.01$] were significant, with a significant interaction between factors [$F(3,18)=5.439$, $P<0.01$]. Posthoc pairwise comparisons indicated significant differences pre-/post-HFS ($P<0.001$), and across all pulse widths ($P<0.05$); except between 150μs and 250μs. Our results further imply that there was a greater synaptic potentiation at SNr recordings sites ON medication, compared to OFF medication. When comparing only post-HFS fEP amplitudes between SNr ON and SNr OFF, the main effect of medication [$F(1,28)=5.354$, $P<0.05$] was significant. The main effect of pulse width [$F(3,84)=108.538$, $P<0.001$] was also significant, with no interaction between factors. Posthoc pairwise comparisons indicated significant ($P<0.05$) differences across all pulse widths and ON/OFF medication.

Plasticity in different basal ganglia output nuclei (GPi/SNr OFF): fEP amplitudes

At GPi recording sites, fEP amplitudes also progressively increased as the pulse width was increased, and were larger after HFS ($n_{recording\text{-}sites}$=11; Fig. 3B). The main effects of pulse width [$F(3,30)=129.737$, $P<0.001$] and HFS [$F(1,10)=24.006$, $P=0.001$] were significant, with no interaction between factors. Posthoc pairwise comparisons indicated significant ($P<0.001$) differences across all pulse widths and pre-/post-HFS. Additionally, our results imply that there was a greater synaptic potentiation at GPi recordings sites, compared to SNr OFF medication. When comparing only post-HFS fEP amplitudes between GPi and SNr OFF, the main effect of location [$F(1,32)=5.677$, $P<0.05$] was significant, as was the main effect of pulse width [$F(3,96)=193.059$, $P<0.001$], with no interaction between factors. Posthoc pairwise comparisons indicated significant ($P<0.05$) differences across all pulse widths and between locations.

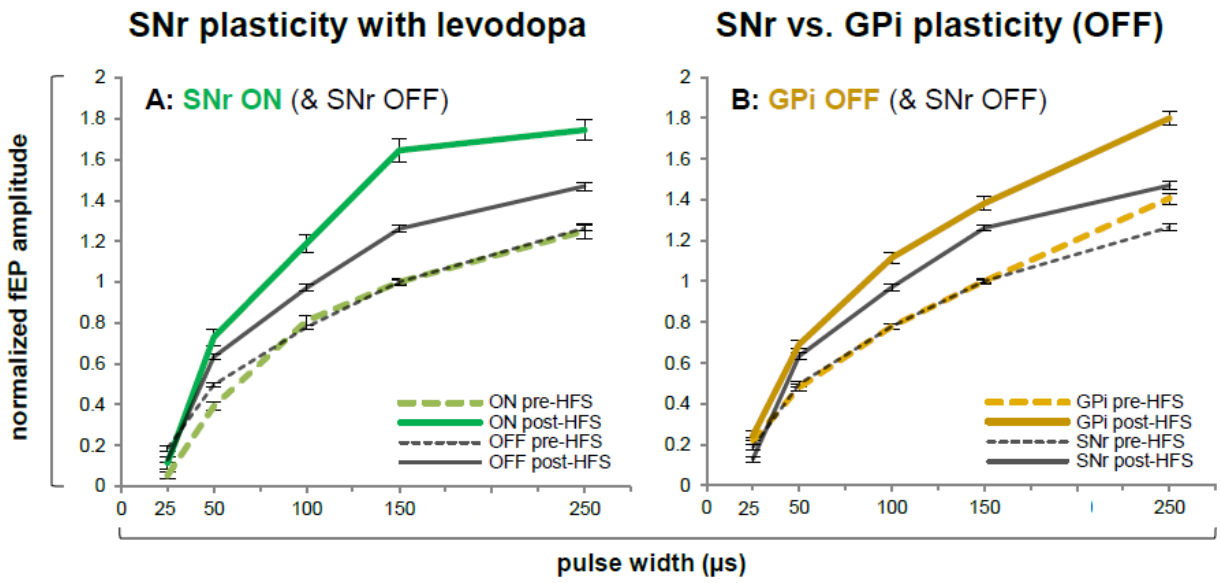


Figure 3 – (A) Effects of levodopa on SNr plasticity, and (B) differential modulation of plasticity between SNr and GPi OFF medication. Like SNr OFF medication, the fEP amplitudes in (A) SNr ON medication ($n_{recording\text{-}sites}$=7), and in (B) GPi OFF ($n_{recording\text{-}sites}$=11) increased as the pulse width was increased, and were further enhanced after HFS (mean±SEM). Our results also indicated that (A) levodopa further enhanced synaptic plasticity in the SNr, and that (B) synaptic plasticity in the GPi was greater than in SNr. 2-way split-plot ANOVAs comparing post-HFS fEP amplitudes between SNr OFF and (A) SNr ON, as well as comparing SNr OFF and (B) GPi OFF, reveled significant main effects of (A) medication [F(1,28)=5.354, P<0.05], and (B) location [F(1,32)=5.677, P<0.05]. Detailed statistics can be found in Results section (*Plasticity and levodopa (SNr OFF/ON): fEP amplitudes; Plasticity in different basal ganglia output nuclei (GPi/SNr OFF): fEP amplitudes*).

Clinical correlations

In Fig. 4A/B, we demonstrated that patients with higher severity UPDRSIII OFF medication scores had less plasticity (smaller increases in fEP amplitudes following HFS). Accordingly, we found significant inverse linear correlations between plasticity after HFS and both the UPDRSIII total motor subscore (R^2=0.4766, *P*=0.0015; Fig. 4A) and axial subscore (R^2=0.4303, *P*=0.0031; Fig. 4B). In Fig. 4C/D, we demonstrated the concurrent improvement of patients' clinical scores from OFF to ON medication and the increases in plasticity (in all but one patient) after oral administration of one tablet of Sinemet (100/25) in the ON/OFF patient subset. The average values of plasticity and symptom severity in OFF and ON conditions were calculated and displayed in each figure to demonstrate the mean improvement of both variables (bold arrow). The patient that did not have an increase in plasticity had the shortest time

between levodopa administration and performing of the stimulation protocol on the second side (26min), therefore there may not have been sufficient time to produce the ON condition (Lewitt et al., 2012; Hauser et al., 2018).

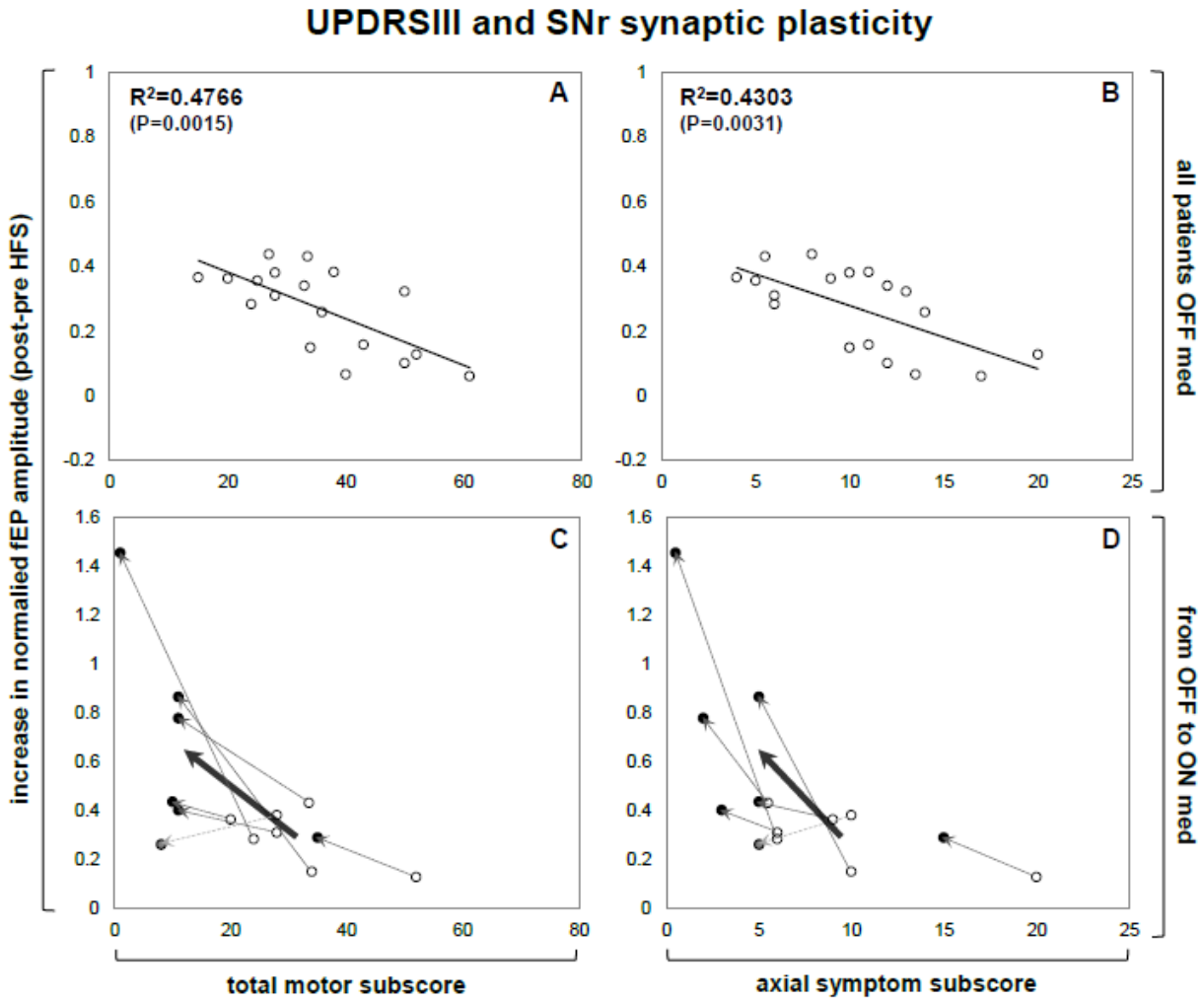


Figure 4 – SNr synaptic plasticity and clinical symptom correlations. The top figures demonstrate that patients with higher severity UPDRSIII OFF medication scores had less plasticity. There were significant inverse linear correlations between the amount of synaptic plasticity (the average pre-HFS fEP amplitude subtracted from the average post-HFS fEP amplitude) and UPDRSIII (A) total motor subscore, and (B) axial symptoms subscore. The bottom figures demonstrate concurrent improvements in clinical symptom severity when the patients were ON, with increases in synaptic plasticity after administration of one tablet of Sinemet (100/25). The bold arrows represent the average changes (from OFF to ON) in both the amount of synaptic plasticity, and UPDRSIII (C) total motor subscore, and (D) axial symptoms subscore.

Discussion

One main finding of this study is that increasing the stimulation pulse width progressively increased both the amplitude of extracellular inhibitory fEPs, and the durations of neuronal inhibition in the SNr and GPi. The concurrent increases of these responses are indicative of a pulse-width-dependent membrane hyperpolarization, likely due to activation of presynaptic terminals and a consequent inhibitory response via $GABA_A$-mediated Cl^- influx (Dostrovsky et al., 2000; Wu et al., 2001; Filali et al., 2004; Lafreniere-Roula et al., 2010; Milosevic et al., 2017). Since increases in pulse width lead to a larger volume of tissue activation (Butson and McIntyre, 2008), the amount of the hyperpolarization likely increased due to activation of more inhibitory presynaptic terminals. While the fEP amplitudes continued to rise with the pulse width, the silent period appeared to plateau at 150μs. The fEP is a continually increasing population response, while the silent period reflects the focal effects on a single neuron; and synaptically released neurotransmitters are known to saturate their receptors (Clements et al., 1996).

Our findings are consistent with the canonical findings of concurrent suppression of spontaneous neuronal activity with extracellularly recorded positive field potentials elicited by stimulation of caudato-nigral fibers in the substantia nigra of anesthetized cats (Yoshida and Precht, 1971). Precht and Yoshida (1971) also demonstrated the blockage of these responses by picrotoxin, implicating the involvement of GABA. Accordingly, histological findings have confirmed that the predominant afferent innervations of the SNr and GPi are the direct pathway GABAergic projections from the medium spiny neurons of the striatum (Ribak et al., 1979, 1981; Smith and Bolam, 1989; Rinvik and Otterson, 1993; Shink and Smith 1995; Parent and Hazrati, 1995a, b; Bolam et al., 2000; Smith et al. 2001). To a lesser extent, the afferents also include GABAergic projections from the GPe, and indirect pathway glutamatergic projections from the STN. Only ~10% of the total synapses on SNr somata are glutamatergic, while GABAergic projections account for the remaining ~90% (Rinvik and Otterson, 1993; Parent and Hazrati, 1995b). While the stimulation pulses delivered in this study likely led to a nonspecific (Milosevic et al., 2017, 2018) activation of presynaptic terminals, the results appear to reflect the predominant GABAergic afferent innervation.

The other major novel findings of this study are the elucidations of HFS- and medication-induced enhancements of inhibitory synaptic plasticity (that also increased with the stimulation pulse width) which occurred after a train of continuous HFS. Enhancements of plasticity were demonstrated by (i) increased fEP amplitudes after HFS, (ii) prolongation of neuronal silent periods after HFS, and (iii) a persistently reduced baseline neuronal firing rate after completion of the stimulation protocol. We found greater enhancements to the fEP amplitudes in the GPi compared to the SNr, and that levodopa

administration (Sinemet 100/25) had a potent effect on the enhancement SNr fEP amplitudes. Furthermore, individuals with lower enhancements of SNr plasticity had more severe axial, and global motor symptoms. Perhaps increased plasticity acts as a compensatory mechanism (Bezard and Gross, 1998) in order to the counteract the symptom-inducing loss of dopamine-mediated regulation of the direct and indirect pathways which project to the basal ganglia output structures (i.e., patients with greater plasticity are better able to regulate the strengths of the inputs to the SNr/GPi). While little is known about the mechanisms of inhibitory (GABAergic) synaptic plasticity, compared to excitatory (involving NMDA and AMPA receptors), there has been progress in this field of research in recent years (see reviews Castillo et al., 2011; Luscher et al., 2011; Kullmann et al., 2012). Potential mechanisms of inhibitory plasticity, the involvement of dopamine in plasticity, and the clinical/functional relevance of our findings are discussed below.

Mechanisms of inhibitory synaptic plasticity

While there are studies related to GABAergic long-term depression (LTD; ex. Lu et al., 2000; Wang et al., 2003), the focus of this discussion will be on the mechanisms pertaining to the enhancement of GABAergic plasticity. Experimental studies (Clements, 1996) have demonstrated that synaptically released neurotransmitters saturate their receptors; subsequently, the functional strength of GABAergic synapses is proportional to the number of $GABA_A$ receptors ($GABA_ARs$) on the postsynaptic membrane (Otis et al., 1994; Nusser et al., 1997). Recent research has demonstrated mechanisms of adjustment of GABAergic transmission, with a focus on $GABA_AR$-trafficking-mediated plasticity of inhibitory synapses (see Luscher et al., 2011). Indeed, Kittler et al. (2000) have demonstrated in hippocampal cell cultures that $GABA_A$ receptors cycle between the synaptic membrane and intracellular sites, as a means of modulating inhibitory synaptic currents. Studies have revealed that overexpression of the $GABA_AR$ associated protein (GABARAP; Wang et al., 1999; Chen and Olsen, 2007) facilitates the translocation of $GABA_ARs$ to the cell surface of hippocampal neurons (Leil et al., 2004). A study by Marsden et al. (2007) demonstrated in rat slices that activation of NMDA receptors, that induces excitatory LTD through AMPA endocytosis, simultaneously increases the expression of $GABA_ARs$ at the dendritic surface of hippocampal neurons; subsequently increasing amplitudes of miniature IPSPs. The study demonstrated that regulated trafficking of $GABA_ARs$ was dependent on GABARAP, as well as on the glutamate receptor interacting protein (GRIP), and Ca^{2+} calmodulin dependent kinase II (CaMKII). This data reveals that bidirectional trafficking of AMPA receptors and $GABA_ARs$ was driven by a single glutamatergic stimulation, which provided a potent postsynaptic mechanism for modulation of synaptic transmission (enhancement of inhibitory transmission).

It is possible then, that the stimulation-induced enhancements of inhibitory plasticity demonstrated in our study were also dependent on the presence and activation of glutamatergic subthalamic afferents of the indirect pathway. Although these glutamatergic afferents only account for ~10%, Marsden et al. (2010) demonstrated that only "moderate" chemical stimulation of NMDA receptors causes exocytosis of $GABA_A$Rs and potentiation of miniature IPSCs. Under such conditions, CaMKII translocates to inhibitory (but not excitatory) synapses that trigger $GABA_A$R insertion and enhance inhibitory transmission. Following "strong" glutamatergic stimuli, CaMKII translocates to excitatory synapses inducing NMDA-receptor-dependent long-term potentiation (LTP). The selective targeting of CaMKII to glutamatergic or GABAergic synapses provides neurons with a mechanism whereby synaptic activity can selectively potentiate excitation or inhibition. In the context of our findings, this may explain why patients with less plasticity had more severe symptoms. The canonical parkinsonian basal ganglia model suggests that symptoms arise from more degenerated GABAergic (direct pathway), and more pronounced glutamatergic (indirect pathway) innervation of the basal ganglia output nuclei (SNr and GPi; Albin et al., 1989; DeLong, 1990). Thus, less plasticity may be observed due to a "stronger" glutamatergic activation which may limit inhibitory potentiation, and would furthermore be associated with more severe symptoms.

Another form of inhibitory LTP has been described in the rat cerebellum at synapses between inhibitory stellate cells and Purkinje cells, termed rebound potentiation, which leads to a long-lasting (up to 75min) potentiation of $GABA_A$R-mediated IPSCs (Kano et al., 1992; Hirano 2016). Rebound potentiation is a heterosynaptic form of plasticity that is induced by depolarization of excitatory (glutamatergic) climbing fiber synapses. This activation causes an increase in extracellular Ca^{2+} concentration, and a subsequent activation of CaMKII, leading to an upregulation of postsynaptic $GABA_A$R function (Kawaguchi and Hirano, 2000, 2002, 2007; Kitagawa et al., 2009). While rebound potentiation has been found to be critically dependent on CaMKII-dependent alteration of GABARAP, and on GABARAP binding to $GABA_A$Rs, it occurs without measurable changes in cellular distribution or surface expression of $GABA_A$Rs (Kawaguchi and Hirano, 2007).

One of the first forms of short-term synaptic plasticity to be described may also be relevant; post-tetanic potentiation. However, studies in this domain of research are limited to non-GABAergic synapses (ex. motor end-plates and neuromuscular junctions, calyx of Held, pyramidal neurons, etc.). Nevertheless, post-tetanic potentiation is described as a presynaptic form of synaptic enhancement that occurs after sustained high-frequency synaptic activation (Schlapfer et al 1976; Baxter et al 1985, Wojtowicz & Atwood 1986; Zucker 1989; Zucker and Regehr, 2002; Balakrishnan et al., 2010). It can last several minutes, and becomes longer lasting when the stimulus frequency and duration are increased (Fioravante,

2011). Post-tetanic potentiation is believed to work by increasing the probability of neurotransmitter release either as a result of an increase in Ca^{2+} influx (Habets and Borst, 2006), and/or by a protein kinase C (PKC) -dependent increase in the Ca^{2+} sensitivity of vesicle fusion (Korogod et al., 2007). Of particular relevance to our findings is that post-tetanic potentiation is often only observed following recovery from prolonged stimulation that is accompanied by synaptic depression (Borst et al., 1995; Zucker and Regher, 2002). We have previously demonstrated (Milosevic, et al., 2017) that indeed there is a rapid attenuation of fEPs that occurs during HFS at 100Hz in the SNr (indicative of synaptic depression; also robustly observed in this study), after which synaptic potentiation occurs; while lower stimulation frequencies that failed to induce synaptic depression also failed to induce post-HFS potentiation.

In summary, while this intraoperative study performed in awake patients and is limited by the inability to discern the exact biological mechanisms involved in the measured enhancements of plasticity, the relevant basic research suggests that enhancements of inhibitory plasticity may be a result of (i) an increase in $GABA_AR$ expression at the postsynaptic cell surface, (ii) upregulated postsynaptic $GABA_AR$ function (without changes in surface expression, i.e., rebound potentiation), and/or increased presynaptic neurotransmitter release properties (i.e. post-tetanic potentiation).

Dopamine and plasticity

It has been well established that dopaminergic regulation (or lack thereof) of neuronal activity of the basal ganglia direct and indirect pathways plays an important role in Parkinson's disease. As such, Barone et al. (1987) have provided direct evidence of the presence of D1 dopamine receptors in the terminals of striatal projections to both the SNr and entopeduncular nucleus (homologous to the primate GPi), with GABA being the main neurotransmitter of these projections (Scheel-Krüger, 1986). Rat brain slice studies (6-hydroxy-dopamine; 6-OHDA lesion) have indeed demonstrated that D1 receptor activation by endogenous dopamine (Aceves et al., 1995), exogenous dopamine (Floran et al, 1990), and dopamine synthesized from levodopa (Aceves et al., 1991) enhances GABA release from both striatal projections to the SNr and entopeduncular nucleus.

Thus, the findings of greater enhancements of SNr plasticity after administration of levodopa reflects this ability of levodopa to enhance striato-nigral inhibitory transmission, while our finding of greater enhancements of plasticity in the GPi compared to SNr (in the OFF medication condition) may reflect higher levels of endogenous dopamine at GPi terminals. Indeed, immunohistochemical studies have provided evidence that the primate GPi receives "massive" dopaminergic innervation (Parent and Smith 1987; Lavoie et al., 1989).

Moreover, it has been demonstrated that D1 activation and the subsequent facilitated GABA release leads to enhancement of GABAergic IPSCs (Radnikow and Misgeld, 1998), as well as reductions in neuronal firing rates (Timmerman and Abercrombie, 1996) in SNr neurons. D1 receptor activity has been shown to be coupled with the formation of the secondary messenger cyclic adenosine monophosphate (cAMP) in the presynaptic terminals of SNr neurons (Jaber et al., 1996). Subsequently, Arias-Montaño et al. (2007) have demonstrated that cAMP formation leads to activation of protein kinase A (PKA), which enhances exocytosis of GABA vesicles by increased presynaptic Ca^{2+} influx through the involvement of P/Q-type voltage-activated Ca^{2+} channels.

Clinical and functional implications

The canonical parkinsonian "rate model" states that the output of the basal ganglia is increased due to a downregulation of the inhibitory striato-nigral/-pallidal projections of the direct pathway, and an upregulation of the excitatory subthalamo-nigal/-pallidal projections of the indirect pathway; due to a degenerated dopaminergic system. The net effect of this is greater downstream inhibition of the target motor areas which the basal ganglia output structures send their inhibitory projections to. Thus, our findings of lower levels of inhibitory plasticity being associated with more severe motor symptoms may be indicative of the overall levels of degeneration of the inhibitory direct pathway projections. Furthermore, these findings suggest that altered inhibitory plasticity within the basal ganglia may play a role in the pathophysiology of Parkinson's disease. Indeed, several studies have implicated altered plasticity in patients with Parkinson's disease (ex. Morgante et al., 2006; Ueki et al., 2006; Suppa et al., 2011; Prescott et al., 2014), and parkinsonian animal models (ex. Picconi et al., 2003, 2008). However, our findings demonstrate that HFS leads to a potentiation of the inhibitory direct pathway projections; and even more so after administration of levodopa. Enhancing the efficacy of the inhibitory projections would in turn adjust the synaptic weights of the inputs to the basal ganglia output structures (SNr and GPi), thus working to reduce their pathologically overactive output. While, current DBS delivery is continuous, we foresee that the enhancement of synaptic efficacy that occurs after HFS will become especially relevant in future applications of DBS with frequent OFF stimulation periods (i.e. closed-loop, intermittent, or cycling-DBS).

Although the SNr is not currently a conventional DBS target, studies (Chastan et al., 2009; Weiss et al., 2011a, 2013) have implicated it as an emerging complementary therapeutic target for the treatment of the axial motor symptoms of Parkinson's disease; including gait and balance disorders. Our clinical findings suggest that the SNr may indeed have a pathophysiological role in mediating axial motor symptoms. To that effect, Takakusaki et al. (2003) have demonstrated modulations of both postural muscle tone and locomotion induced by HFS (100Hz) of the SNr in unanesthetized acutely decerebrate cats. Additionally,

Burbaud et al. (1998) demonstrated that microinjections of GABA blockers into the SNr of healthy primates led to severe axial postural anomalies, and Henderson et al. (2005) demonstrated that SNr lesions could reverse postural abnormalities in hemiparkinsonian (6-OHDA lesioned) primates (however, without improvements in bradykinesia). Indeed, GABAergic SNr efferents descend to the brainstem ponto-mesencephalic area, including the pedunculopontine nucleus and mesencephalic locomotor region which are known to be involved in locomotion and postural control (Aziz et al., 1998; Pahapill and Lozano, 2000; Takakusaki et al., 2003, 2005).

The results of this study furthermore have implications for a novel control parameter for closed-loop DBS; fEP amplitudes. Since the fEP amplitude scales with medication state, it may be able to inform the DBS system about ON/OFF fluctuations. The system would thereby be able to reduce stimulation intensity when the patient is ON, and increase it when they are OFF or experiencing peak-dosage levodopa induced-dyskinesias. Furthermore, fEP amplitudes can inform the system about the efficacy of the inhibitory synapses and selectively re-potentiate synapses by delivering a train of HFS. Although this would require a permanent embedded system to measure fEP amplitudes, DBS technologies are evolving more rapidly than ever (Arlotti et al., 2016). Russo et al. (2018) have demonstrated an efficacious implementation of closed-loop spinal cord stimulation which controls stimulation dose by measuring the recruitment of fibers in the dorsal column and by using the amplitude of evoked compound action potentials (ECAPs) to treat individuals with chronic pain.

Finally, in Fig. 5 we propose a relationship between the stimulation pulse width and frequency for achieving neuronal inhibition by temporal summation of the silent period. If a stimulation pulse is delivered at an interstimulus interval which corresponds to the neuron's silent period, then that neuron will not fire (i.e., one can discern the minimal stimulation frequency required for complete neuronal inhibition by temporal summation of silent periods; see Fig. 5A). With shorter pulse widths, higher stimulation frequencies are required to achieve neuronal silencing, whereas longer pulse widths require lower frequencies to achieve the same effect. By this logic, the enhancement of inhibitory synaptic efficacy can be utilized to reduce electrical energy; for example, the same stimulation frequency can be used with a pre-HFS pulse width of 150μs, as can be used with a post-HFS pulse width of 50μs (see Fig. 5B). This may have implications for moderating DBS side effects, for example, to compensate for sub-optimal electrode placements in order to reduce stimulation of surrounding structures or fibers. Intermittently enhancing the efficacy of inhibitory synapses can allow for a reduction in the volume of tissue activation while maintaining neuronal inhibition, thereby having the potential to widen the therapeutic window (Reich et al., 2015). Currently, for optimal DBS efficacy, chronaxies have been estimated to be about 130 and 150μs for thalamic and pallidal stimulation, respectively (Holsheimer at al.,

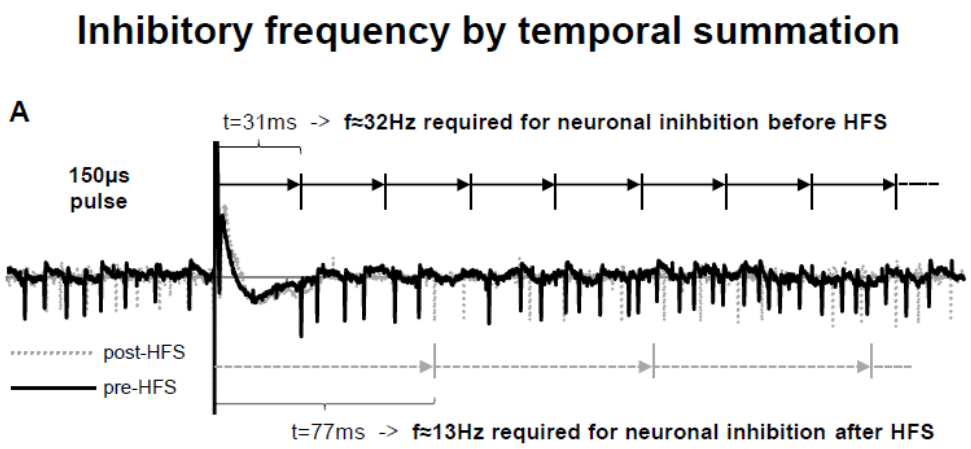
2000a, Holsheimer et al., 2000b). HFS-induced changes to pulse-width-dependent amplitudes/strengths of synaptic activation could allow for re-optimization of chronaxie values.

Limitations

A limitation of the present intraoperative study was the inability to use pharmacological interventions to help elucidate specific molecular mechanisms, or the exact pre-/postsynaptic nature of the enhancement of synaptic plasticity. On the contrary, human studies have advantages over animal studies in that it is not known how well animal models correspond to human pathology, or anatomy. Furthermore, stimulation via microelectrodes elicits a smaller volume of tissue activation than that produced by macroelectrode stimulation; thus, the effects we report arise from activation of only a subset of target neurons (Maggio et al., 2010). In lieu of a control population, our study compared different anatomical locations (SNr/GPi), as well as different medication states (ON/OFF). Additional pragmatic limitations include the inability to obtain measurements of synaptic plasticity at the same recording location under both medication states, as well as the inability to discern the exact time course (duration) of the enhanced plasticity. This would excessively prolong intraoperative time; however, obtaining such measurements would be an interesting prospective study in an appropriate animal model. An additional prospective study would be to investigate the effects of levodopa on plasticity in the GPi and preform clinical correlations in a larger GPi patient cohort. Finally, a pragmatic limitation of intraoperative studies in humans would be

Conclusions

We determined that increasing the pulse width led to concurrent increases in the amplitudes of inhibitory fEPs and the durations of neuronal silent periods in basal ganglia output nuclei. Both of these measured variables were enhanced after a train of continuous HFS, demonstrative of enhanced inhibitory synaptic transmission. We found greater enhancements in the GPi compared to the SNr, and that levodopa administration had a potent effect on the enhancement of SNr plasticity. Finally, we found that lower levels of SNr plasticity were associated with higher severity motor symptoms.



B

Frequency (Hz) for inhibition [=1/silent period]

pulse (µs)	25	50	100	150	250
pre-HFS	43.36	26.44	22.48	20.89	18.20
post-HFS	54.35	19.67	17.00	14.69	14.06
ON post-HFS	*<50*	*<19*	*<17*	*<14*	*<14*

Figure 5 – Proposed relationship between stimulation pulse width and frequency required for neuronal silencing. If a stimulation pulse is delivered just prior to the return of neuronal firing (i.e. at interstimulus intervals corresponding to the neuron's silent period), then complete neuronal inhibition would be achieved using the minimal possible stimulation frequency (i.e. complete neuronal inhibition by temporal summation of silent periods). (A) The figure demonstrates that after HFS, when inhibitory plasticity is enhanced, the duration of neuronal inhibition is prolonged, thus, the frequency required for complete neuronal inhibition (by temporal summation) can be reduced. This is representative data from one SNr recording site in a single patient. (B) The table displays the frequency required for complete inhibition of neuronal firing (by temporal summation) across all patients and all investigated pulse widths, before and after HFS. The values displayed are the inverses of the average silent period ($f_{inhib.}=1/T_{silent\text{-}period}$) at each pulse width (from Fig. 2B). A hypothesis that stems from this study is that when a patient is ON medication, the frequency required for neuronal silencing after HFS would be lower than when they are OFF (bottom of B). This is assumed since we have demonstrated that levodopa enhances fEP amplitudes and that fEP amplitudes were correlated with silent periods.

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