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Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease

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ABSTRACT

High frequency deep brain stimulation is an effective therapy for motor symptoms in Parkinson's disease. However, the relative clinical efficacy of regular versus non-regular temporal patterns of stimulation in Parkinson's disease remains unclear. To determine the temporal characteristics of non-regular temporal patterns of stimulation important for the treatment of Parkinson's disease, we compared the efficacy of temporally regular stimulation with four non-regular patterns of stimulation in subjects with Parkinson's disease using an alternating finger tapping task. The patterns of stimulation were also evaluated in a biophysical model of the parkinsonian basal ganglia that exhibited prominent oscillatory activity in the beta frequency range. The temporal patterns of stimulation differentially improved motor task performance. Three of the non-regular patterns of stimulation improved performance of the finger tapping task more than temporally regular stimulation. In the computational model all patterns of deep brain stimulation suppressed beta band oscillatory activity, and the degree of suppression was strongly correlated with the clinical efficacy across stimulation patterns. The three non-regular patterns of stimulation that improved motor performance over regular stimulation also suppressed beta band oscillatory activity in the computational model more effectively than regular stimulation. These data demonstrate that the temporal pattern of stimulation is an important consideration for the clinical efficacy of deep brain stimulation in Parkinson's disease. Furthermore, non-regular patterns of stimulation may ameliorate motor symptoms and suppress pathological rhythmic activity in the basal ganglia more effectively than regular stimulation. Therefore, non-regular patterns of deep brain stimulation may have useful clinical and experimental applications.

Introduction

High frequency deep brain stimulation (DBS) in the internal segment of the globus pallidus (GPi) or subthalamic nucleus (STN) is an effective and adjustable surgical treatment for motor symptoms of advanced Parkinson's disease (PD) (Benabid et al., 2009; Moro et al., 2010). Developed as a treatment for patients with advanced PD (Benabid et al., 1994; Limousin et al., 1995; Siegfried and Lippitz, 1994), DBS reduces tremor, rigidity, akinesia, and postural instability, and allows levodopa doses to be decreased (Follett et al., 2010; Limousin et al., 1998). Patients clinically diagnosed with idiopathic PD suffering from the cardinal motor symptoms are likely to receive benefit from DBS, with levodopa responsiveness predictive of its efficacy (Benabid et al., 2009).

The efficacy of DBS for PD is sensitive to the stimulation parameters, and high frequency (>100 Hz) DBS is more effective than low frequency (<100 Hz) stimulation (Kuncel et al., 2006; Moro et al., 2002; Rizzone et al., 2001). The frequency-dependent efficacy of DBS is a key element for the proposed mechanisms of DBS, including stimulation-induced regularization of pathological neuronal activity (Birdno and Grill, 2008) and silencing of the stimulated neurons

Abbreviations: PD, Parkinson's disease; DBS, deep brain stimulation; GPi, internal segment of globus pallidus; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale; IPG, implantable pulse generator.

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(Filali et al., 2004). The efficacy of DBS is also dependent on the amplitude, polarity, pulse width, and pattern of stimulation (Birdno et al., 2012; Dorval et al., 2010; Kuncel and Grill, 2004; Kuncel et al., 2006, 2007). However, the temporal pattern of stimulation stands out as a potentially important parameter space that has not been fully explored.

Non-regular temporal patterns of stimulation provide a means to probe the mechanisms of DBS (Birdno and Grill, 2008), and could potentially be used to expand the therapeutic efficacy of DBS (Feng et al., 2007; Rosin et al., 2011). Random patterns of stimulation are less effective at suppressing motor symptoms than regular stimulation in patients with essential tremor (ET) and PD (Birdno et al., 2008, 2012; Dorval et al., 2010). In patients with ET, non-regular stimulation patterns are less effective at suppressing tremor than temporally regular stimulation because sufficiently long gaps in the stimulation train allow pathological activity to propagate through the stimulated nucleus (Birdno et al., 2012). However, the features of non-regular stimulation patterns that influence clinical efficacy in PD are unknown.

We applied different temporal patterns of stimulation to human subjects with PD to determine which features of non-regular stimulation cause it to be less effective than temporally regular stimulation. Surprisingly, we found that three non-regular patterns of stimulation significantly improved performance on a simple motor task compared to regular stimulation. Subsequently, using a computational model of DBS in the basal ganglia, we showed that the efficacy of various stimulation patterns was strongly correlated with their ability to suppress pathological oscillations in the beta frequency range. These results highlight the potential importance of the temporal pattern of stimulation as a means to enhance the efficacy of DBS.

Methods

The efficacy of five temporal patterns of high frequency DBS was quantified using an alternating finger tapping task in human participants with PD. As well, the effect of each pattern on beta band oscillations was quantified in a computational model of the basal ganglia.

Human subject information

Individuals with DBS for PD undergoing implantable pulse generator (IPG) replacement surgery were recruited to participate in this study at Duke University Medical Center, Wake Forest Baptist Medical Center, and Emory University Hospital. Subjects were at least three months post DBS electrode implant/revision, capable of performing a simple finger tapping task, neurologically stable, and capable of understanding the study and consent form. The Institutional Review Boards at Duke University, Emory University, and Wake Forest University approved the study protocol, and subjects participated on a volunteer basis following written informed consent. Twenty-four subjects were consented for the study. Five subjects withdrew from the study before the experimental protocol began; nine subjects did not complete the experimental protocol; and ten subjects completed the protocol and were analyzed. DBS electrode target nucleus was either STN (7/10) or GPi (3/10). Subjects were asked to withhold PD medications for 12 h prior to surgery, and most (7/10) complied. Demographic characteristics and stimulation settings for each subject are shown in Table 1.

Intraoperative stimulation protocol

Sedation and analgesia were withheld when possible (8/10) and local anesthetic (lidocaine) was used. Following removal and disconnection of the depleted IPG, a sterile connection was made between the extension cable and the signal generation equipment, allowing different temporal patterns of stimulation to be delivered through the implanted electrode.

Custom software (LabVIEW, National Instruments, Austin, TX, USA) on a battery-powered laptop computer generated the experimental patterns of stimulation. The analog voltage outputs (DAQCard™-6062E, National Instruments, Austin, TX, USA) were optically isolated (bp Optical Isolator with Probe, FHC Inc., Bowdoin, ME, USA) from the stimulation hardware. The subject's clinical stimulation parameters and contact settings were maintained when possible. Subjects with case (+) programming (4/10) were switched to a bipolar configuration and one of the clinically inactive electrode contacts was set as (+). Subjects (4/10)

Table 1
Subject information.

Subject	Age/sex	Hemisphere/target tested	Electrode contacts[a,b]	AMP (V)[b]	PW (μs)	FREQ (Hz)[b]	PD medications or sedation 12 h prior to surgery
1	54/F	Right/STN	$2^-/0^+$ [$2^-/C^+$]	3.5 [4.8]	90	185 [100]	none
2	59/M	Right/GPi	$0^-/1^-/3^+$	4.0	60	185 [160]	None
3	59/M	Left/STN	$2^-/3^-/0^+$ [$2^-/3^-/C^+$]	2.5 [3.2]	90	185	None
4	65/M	Left/STN	$0^-/1^-/2^+$	3.8	90	185	Midazolam (1 mg)
5	61/F	Left/STN	$2^-/3^+$	4.5	90	185	Fentanyl (25 mcg) Dexmedetomidine (12 mcg) Clonidine (25 mcg)
6	64/F	Left/GPi	$2^-/3^+$ [$2^-/C^+$]	2.5 [3.5]	120	185	Carbidopa (25 mg) Levodopa (100 mg) Amantadine (100 mg)
7	59/F	Right/GPi	$2^-/3^+$	3.5 [3.9]	120	185	None
8	66/M	Left/STN	$1^-/3^+$	3.6	90	185 [167]	Carbidopa (25 mg) Levodopa (250 mg)
9	52/M	Left/STN	$1^-/2^-/3^+$	4.5	90	185	Carbidopa (50 mg) Levodopa (200 mg) Ropinirole (3 mg)
10	57/M	Right/STN	$1^-/2^-/3^+$ [$1^-/2^-/C^+$]	3.0	90	185	None

Abbreviations: M = male; F = female; AMP = amplitude; PW = pulse width; FREQ = frequency; STN = subthalamic nucleus; GPi = internal globus pallidus.

[a] Quadripolar DBS electrode contacts are numbered 0 through 3, with 0 most distal and 3 most proximal. Contact polarity denoted by '+' (cathode) and '−' (anode). C^+ indicates that the IPG case was used as the anode/current return.

[b] Experimental stimulation parameters are shown. Clinical settings different from the experimental settings are shown in brackets.