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Short pauses in thalamic deep brain stimulation promote tremor and neuronal bursting

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HIGHLIGHTS

- Pauses in thalamic DBS decreased tremor suppression relative to regular DBS in human subjects.
- Firing rate and entropy of model neurons in a thalamic network model correlated well with tremor power.
- Pauses reduce thalamic DBS efficacy by preventing masking of pathological burst activity.

ABSTRACT

Objective: We conducted intraoperative measurements of tremor during DBS containing short pauses (⩽50 ms) to determine if there is a minimum pause duration that preserves tremor suppression.
Methods: Nine subjects with ET and thalamic DBS participated during IPG replacement surgery. Patterns of DBS included regular 130 Hz stimulation interrupted by 0, 15, 25 or 50 ms pauses. The same patterns were applied to a model of the thalamic network to quantify effects of pauses on activity of model neurons.
Results: All patterns of DBS decreased tremor relative to 'off'. Patterns with pauses generated less tremor reduction than regular high frequency DBS. The model revealed that rhythmic burst-driver inputs to thalamus were masked during DBS, but pauses in stimulation allowed propagation of bursting activity. The mean firing rate of bursting-type model neurons as well as the firing pattern entropy of model neurons were both strongly correlated with tremor power across stimulation conditions.
Conclusions: The temporal pattern of stimulation influences the efficacy of thalamic DBS. Pauses in stimulation resulted in decreased tremor suppression indicating that masking of pathological bursting is a mechanism of thalamic DBS for tremor.
Significance: Pauses in stimulation decreased the efficacy of open-loop DBS for suppression of tremor.

1. Introduction

Thalamic deep brain stimulation (DBS) is an effective therapy for treatment of essential tremor, but the neural mechanisms of action underpinning its efficacy are not well understood. The effects of DBS are strongly dependent on stimulation frequency; high frequency (>100 Hz) DBS alleviates postural tremor (Kuncel

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et al., 2006; Sydow et al., 2003), whereas low frequency DBS is clinically ineffective and may exacerbate tremor (Cagnan et al., 2013; Pedrosa et al., 2013). Therapeutic efficacy is also sensitive to the temporal pattern of stimulation (Birdno et al., 2007, 2008; Brocker et al., 2013; Dorval et al., 2010; Montgomery, 2005) and increasing evidence suggests that long pauses during stimulation ($\geqslant$50 ms) reduce tremor suppression during Vim thalamic DBS (Birdno et al., 2012; Kuncel et al., 2012). Pauses during stimulation can lead to rebound burst firing in thalamic neurons following a release from inhibition, mediated by a T-Type Ca^{2+} current (Jahnsen and Llinás, 1984; Person and Perkel, 2005), and this phenomenon is hypothesized to exacerbate tremor.

In this study we measured responses to patterns of thalamic DBS with short pauses ($\leqslant$50 ms) in human subjects with essential tremor (ET) and in a validated biophysical network model of ventral thalamus (Birdno et al., 2012) to determine if there is a critical pause duration for tremor suppression. Results from clinical and computational studies indicate that short pauses in stimulation trains decrease DBS effectiveness and enable propagation of pathological bursting activity in the cerebello-thalamocortical pathway. In the absence of pauses, stimulation masked burst activity and regularized firing patterns in the thalamic network model. These results suggest that activation of cerebellar afferent inputs to the thalamus mediates the therapeutic effects of DBS, and provide the groundwork for development of improved temporally-patterned stimulation to treat postural tremor in persons with ET.

2. Methods

We measured postural tremor during temporal patterns of high frequency stimulation with short pauses (15–50 ms) in human subjects with ET and DBS in the ventral intermediate nucleus (Vim) of the thalamus. The effects of the same patterns on neuronal firing patterns were quantified in a computational model of the Vim thalamic network.

2.1. Human subjects enrollment

We recruited patients with Vim thalamic DBS for ET undergoing elective implantable pulse generator (IPG) replacement surgery at Duke University Medical Center, Emory University Hospital, and Wake Forest Baptist Medical Center. The study protocol was reviewed and approved by the respective Institutional Review Boards prior to study initiation. Candidate subjects were screened for inclusion at least three months following DBS electrode implant or revision. All participants were capable of performing a postural tremor assessment task, neurologically stable, and capable of understanding the study and consent form. Subjects participated on a volunteer basis and provided written informed consent prior to enrollment. Nine subjects completed at least two of the three randomized blocks of the study protocol and were included in data analysis.

2.2. Intraoperative setup

Intraoperative studies were conducted using methods previously described (Swan et al., 2014) and briefly summarized below.

Subjects withheld anti-tremor medications for at least 12 h prior to surgery. Preoperative and intraoperative sedatives were not administered until the research measurements were complete. Subjects were positioned comfortably supine, prepared and draped with one arm fully exposed and mobile to facilitate interaction with the experimenters. A triaxial accelerometer (CXL04LP3, Crossbow; San Jose, CA) was fixed to the dorsum of the hand to measure tremor responses during the experiment. The depleted IPG was then explanted under local and monitored anesthesia care. The exposed DBS extension cable was connected to an external stimulator outside the sterile field via a sterile adapter (1 × 4 Pocket Adaptor for Deep Brain Stimulation, #64001; Medtronic Inc., Minneapolis, MN), an extension cable (Multi-lead Trailing Cable, #355531; Medtronic Inc.), and a custom extension cable.

An optical stimulus isolator (bp Isolator; FHC Inc., Bowdoinham, ME) connected to a laptop-controlled, isolated multifunction data acquisition device (USB-6216 BNC; National Instruments, Austin, TX) delivered unilateral stimulation to the electrode implanted contralateral to the arm used for tremor measurement. Charge-balanced, biphasic, regulated voltage pulses similar to those produced by the clinical IPG were used to deliver temporal patterns of stimulation generated by custom software (LabVIEW; National Instruments, Austin, TX). Clinically programmed values for all other stimulation parameters were replicated when possible (Table 1). Subjects with monopolar stimulation contact configurations were switched to bipolar configurations by changing stimulation return to a clinically unused contact (2/9 subjects). Some subjects experienced discomfort in response to intraoperative stimulation at the clinically programmed stimulation amplitude, and the voltage was decreased to the maximum tolerable level for these individuals (3/9 subjects). IPGs near end-of-life often require an increased stimulation amplitude to compensate for lower current output due to decreased battery supply voltage (Montuno et al., 2013). Therefore, intraoperative stimulation at the clinically programmed voltage may have caused discomfort due to delivery of more current than the depleted IPG produced. Some subjects experienced paresthesias in response to stimulation, but these were not reported as uncomfortable. Stimulation amplitude was increased above the clinical level for one subject to improve tremor control. There were no adverse events during this study.

2.3. Stimulation pattern design

We measured tremor during temporal patterns of high frequency DBS with short pauses, high frequency DBS without pauses, and the DBS off condition (Fig. 1a). Stimulation patterns with pauses were comprised of constant-frequency pulse trains periodically interrupted by periods of no stimulation. Pauses of 15, 25, or 50 ms occurred at a rate of 4.4 Hz in three of these patterns, consistent with the primary tremor frequency in ET patients (Deuschl et al., 1998), and 50 ms pauses occurred at 2.2 Hz in another pattern. The interpulse intervals of pulse trains between pauses were constant within each pattern, but varied between stimulation patterns such that the geometric mean frequency for all patterns was 130 Hz. Pauses decreased the total percentage of time that pulses were delivered by 6.6%, 11.0%, or 22.0% relative to constant 130 Hz stimulation.

2.4. Experiment protocol

Stimulation patterns were presented in a randomized block design and subjects were blinded to the stimulation pattern

Table 1
Subject demographics and clinical stimulation parameters. Experimental settings, when different from clinical settings, are given in parentheses.

ID	Age/sex	Stimulus contacts	PW (μs)	Amplitude (V)
A	59/M	2+1−0−	150	3.0 (2.5)
B	67/F	1+0−	60	3.6 (3.0)
C	78/M	2−1−C+ (3+)	90	4.2 (6.0)
D	85/F	2+0−	120	4.3
E	69/M	3−2−1+	90	4.4
F	68/M	1−C+ (3+)	90	4.3
G	49/F	2+1−0−	120	5.6
H	69/F	2+1−0−	90	4.6
I	86/M	1+0−	90	3.4 (3.2)