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Measurement of Evoked Potentials During Thalamic Deep Brain Stimulation

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ABSTRACT

Background: Deep brain stimulation (DBS) treats the symptoms of several movement disorders, but optimal selection of stimulation parameters remains a challenge. The evoked compound action potential (ECAP) reflects synchronized neural activation near the DBS lead, and may be useful for feedback control and automatic adjustment of stimulation parameters in closed-loop DBS systems.
Objectives: Determine the feasibility of recording ECAPs in the clinical setting, understand the neural origin of the ECAP and sources of any stimulus artifact, and correlate ECAP characteristics with motor symptoms.
Methods: The ECAP and tremor response were measured simultaneously during intraoperative studies of thalamic DBS, conducted in patients who were either undergoing surgery for initial lead implantation or replacement of their internal pulse generator.
Results: There was large subject-to-subject variation in stimulus artifact amplitude, which model-based analysis suggested may have been caused by glial encapsulation of the lead, resulting in imbalances in the tissue impedance between the contacts. ECAP recordings obtained from both acute and chronically implanted electrodes revealed that specific phase characteristics of the signal varied systematically with stimulation parameters. Further, a trend was observed in some patients between the energy of the initial negative and positive ECAP phases, as well as secondary phases, and changes in tremor from baseline. A computational model of thalamic DBS indicated that direct cerebellothalamic fiber activation dominated the clinically measured ECAP, suggesting that excitation of these fibers is critical in DBS therapy.
Conclusions: This work demonstrated that ECAPs can be recorded in the clinical setting and may provide a surrogate feedback control signal for automatic adjustment of stimulation parameters to reduce tremor amplitude.

Introduction

Deep brain stimulation (DBS) is an effective therapy for movement disorders, including essential tremor (ET) [1,2]. To treat ET and some patients with tremor-dominant Parkinson's disease (PD), the DBS lead is typically implanted in the ventral intermediate (Vim) nucleus of the thalamus, and is connected to an internal pulse generator (IPG) via a subcutaneous wire. The subsequent selection of stimulation parameters is an *ad hoc*, empirical process. Parameter adjustment sessions are inconvenient, time-consuming, and costly

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[3], and due to a lack of standardized programming approaches, parameters can often be improved [4]. Moreover, inappropriate parameter settings can lead to side effects [5] and deplete the battery more quickly than optimized settings [6]. An automated selection of DBS parameters could reduce follow-up visits and improve patient outcomes, using either external tremor measurements or internal neurological activity as a rapid feedback signal.

Implementing closed-loop DBS systems may provide an approach to automated selection and optimization of stimulation parameters. Neural activity measured during DBS may provide information related to symptoms, and both single-unit recordings and local field potentials (LFPs) have been proposed as potential feedback signals. Closed-loop DBS of the globus pallidus interna (GPi), triggered from single-unit activity measured from the primary motor cortex (M1), generated greater motor symptom reduction in MPTP-treated monkeys than continuous, open loop stimulation [7]. However, this approach required implantation of additional hardware, and the long-term stability of microelectrode recordings may not be sufficient for clinical use [8]. Alternatively, LFPs can be recorded from the DBS lead, and reflect synchronized oscillatory neural activity across wide networks [9]. Theta oscillations recorded from the thalamus may be related to tremor in ET and PD [10,11]. Proposed LFP-based closed-loop systems would titrate stimulation in response to changes in ongoing LFP activity [12], or select the most effective stimulation contacts and inform DBS voltage settings, as demonstrated for DBS treatment of PD [13–15]. However, further work is required to demonstrate that LFPs are sufficiently correlated with clinical symptoms to provide a surrogate closed-loop measure.

In the present work we investigated the evoked compound action potential (ECAP) as a potential feedback control signal for thalamic DBS. The ECAP is generated by synchronous activation of an ensemble of neural elements near the lead, and can be recorded from two non-stimulating contacts on the DBS lead implanted for therapy [16]. An ECAP-based closed-loop DBS system could potentially adjust stimulation settings automatically to generate activation of the appropriate neural elements. An analogous ECAP-based approach has successfully guided stimulation levels in cochlear implants [17,18] and spinal cord stimulation systems [19]. We showed previously the feasibility of recording ECAPs using a novel stimulus artifact suppression system in acute, preclinical experiments [16], and demonstrated the insight provided by ECAPs into the extent and types of neural elements activated during thalamic DBS [20]. The objectives of the present work were to determine: 1) whether ECAPs could be recorded during clinical DBS, 2) the source of the ECAP and any artifact, 3) changes in ECAP characteristics across DBS parameters, and 4) correlation of ECAP characteristics with changes in tremor across DBS parameters.

Methods and materials

We conducted intraoperative recordings of ECAPs under acute and chronic lead implantation conditions and investigated correlations between ECAP characteristics and tremor across stimulation parameters. Computational modeling was used to investigate the origin of the ECAP signal and stimulus artifact.

Human subjects

The protocol was reviewed and approved by the Institutional Review Boards at Duke University and Emory University, and subjects participated on a volunteer basis after providing written informed consent. The study enrolled 19 participants, 15 with ET, 3 with tremor-dominant PD, and 1 with Fragile X-associated tremor/ataxia syndrome (FXTAS) [21]. Two of the enrolled subjects did not complete the study. We recruited patients who were either undergoing surgical implantation of the Medtronic 3389 DBS lead in Vim (acute setting, $n = 8$) or replacement of their battery-depleted IPG and were at least three-months post-implant of a Medtronic 3387 or 3389 DBS lead in Vim (chronic setting, $n = 11$), as detailed in Table 1. Additional subject inclusion criteria included neurologically stable patients who could understand the study and consent form; exclusion criteria were an inability to execute motor tasks during the study, and clinically ineffective DBS for those persons receiving a replacement IPG. Subjects undergoing IPG replacement surgery were given monitored anesthesia care together with local anesthetic (1% lidocaine), such that they were responsive during the study, and were asked to decline sedation, which can otherwise reduce motor symptoms. Subjects undergoing initial DBS implantation are normally given local anesthesia, and sedation was provided only as necessary so as to minimize the effect on motor symptoms. If sedation was given, it was discontinued prior to data

Table 1
Subject demographic characteristics, lead information, and relevant medications taken or anesthesia delivered on the morning of the study.

Subject	Age/Gender	Diagnosis	Medtronic electrode	Mo. after implant	Medications taken morning of study (Approx. delay from delivery to study start time)
EP12A	65/M	ET	3389	34	None
EP12B	73/M	ET	3387	44	None
EP12C	68/M	PD	3387	58	None
EP12D	73/F	ET	3387	77	None
EP12E	76/M	PD	3387	40	None
EP13A	72/M	ET	3387	74	Gabapentin, divalproex before surgery; fentanyl before/during surgery (>15 min)
EP13B*	74/F	ET	3389	0	Primidone before surgery; fentanyl (80 min), midazolam (>50 min), dexmedetomidine (70 min) during surgery
EP13C*	73/F	ET with mild Parkinsonism	3389	0	Primidone before surgery
EP13E*	64/M	FXTAS	3389	0	Fentanyl during surgery (>15 min)
EP13F	74/M	PD	3387	90	Isoflurane, dexmedetomidine during surgery (30 min)
EP13G*	62/M	ET	3389	0	Propofol during surgery (45 min)
EP13H*	66/M	ET	3389	0	Propofol during surgery (>40 min)
EP13I*	70/F	ET	3389	0	Propofol (>30 min), fentanyl (>105 min) during surgery
EP13J*	61/F	ET	3389	0	Fentanyl before surgery; midazolam (65 min), propofol (70 min) during surgery
EP13K	71/M	ET	3387	176	Gabapentin before surgery
EP13L	69/M	ET	3389	74	None
EP13N*	69/F	ET	3389	0	Propofol during surgery (>50 min)

The time between delivery of medications or anesthesia and the start of the study are provided in parentheses. Asterisk (*) indicates that the subject underwent DBS lead implantation surgery.