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Deep Brain Stimulation Evoked Potentials May Relate to Clinical Benefit in Childhood Dystonia

Nasir H. Bhanpuri [a,1], Matteo Bertucco [a,1], Diana Ferman [b], Scott J. Young [a], Mark A. Liker [b,c], Mark D. Krieger [b,c], Terence D. Sanger [a,b,d,*]

[a] Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA
[b] Department of Neurology, University of Southern California and Children's Hospital Los Angeles, Los Angeles, CA, USA
[c] Department of Neurosurgery, University of Southern California and Children's Hospital Los Angeles, Los Angeles, CA, USA
[d] Department of Biokinesiology and Physical Therapy, University of Southern California, Los Angeles, CA, USA

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ABSTRACT

Background: Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is a treatment for severe childhood-onset dystonia. A common challenge for clinicians is determining which contacts of the DBS electrode to stimulate in order to provide maximum future benefit to the patient.
Objective: To characterize how the cortical responses to DBS relate to stimulation parameters (i.e. electrode contacts, voltage, and pulse width) and clinical outcomes.
Methods: We examined 11 patients with dystonia undergoing DBS therapy (9–21 years old when implanted). We varied the active contacts, voltage, and pulse width of the stimulating electrode and analyzed the deep-brain stimulator evoked potentials (DBSEPs) measured with electroencephalogram, and assessed symptoms with the Barry-Albright dystonia scale. Statistical tests included: Repeated measures ANOVA, Mann–Whitney *U* test and paired *t*-test.
Results: DBSEPs near sensorimotor areas were larger ipsilaterally than contralaterally ($P = 0.007$). The rate of DBSEP amplitude increase with respect to stimulator voltage (voltage gain) and pulse width (pulse width gain) varied across subjects and stimulating contacts. Voltage gains were significantly higher among patients who showed larger improvements with DBS ($P = 0.038$). Additionally, a within-subject comparison of all patients showed that voltage gains were higher for contacts chosen for chronic stimulation as compared to those that were not ($P = 0.007$).
Conclusions: DBSEPs may be good predictors of therapeutic response to stimulation at different electrode contacts. Furthermore, effective DBS therapy appears to modulate sensorimotor cortex. These findings may help clinicians optimize stimulator programming and may eventually lead to improved targeting during implantation.

Introduction

Deep-brain stimulation (DBS) is now recognized as an important treatment for selected patients with severe movement disorders, including Parkinson's Disease, Essential Tremor, and Dystonia [1–3]. There is increasing interest in the use of DBS of the globus pallidus internus (GPi) for treatment of severe childhood-onset primary and secondary dystonia [4–8]. In order to achieve benefit from this therapy, devices must be programmed with the most effective settings [9]. Devices that are currently used permit selection of particular electrode contacts in order to specify stimulation location. In Parkinsonism and Tremor, patient response to stimulation is often immediate, and therefore, it is usually possible to select the most effective contacts by observing the response to therapy during single-day programming sessions [9]. Unfortunately, dystonic patients of all ages can take several months before showing a significant improvement in symptoms [1,5], and can take about 6 months to reach a steady state [5,8]. Furthermore, children are often poor reporters of side effects or intermediate levels of benefit.

Thus, there is a need for objective measures that can predict the response to stimulation that particular DBS contacts would provide

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* Corresponding author. Department of Biomedical Engineering, University of Southern California, 1042 Downey Way, DRB 140, Los Angeles, CA 90089-1111, USA. Tel.: +1 323 300 5970; fax: +1 323 297 2991.
E-mail address: tsanger@usc.edu (T.D. Sanger).

[1] These authors contributed equally to the manuscript.

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to individual children with dystonia. Current clinical practice for electrode selection often depends on a combination of: (1) post-operative image analysis to choose the contact(s) centrally located in the GPi, (2) inter-contact therapy impedance measurements which reflect the integrity of the electrical connection with neural tissue and (3) acute side effects during screening. However, these methods can be problematic with regard to: (1) because there may be more than one contact located in GPi; (2) because the most robust connection may be with tissue that does not affect motor symptoms; and (3) because side effects may be more informative regarding which location is ineffective (i.e. stimulating descending tracts), rather than which stimulation location is beneficial.

We propose that the effects of DBS on cerebral cortex should be used to inform electrode contact selection since all voluntary and most involuntary movements arise from activity that propagates through the cortical areas that project to brainstem and spinal cord. While it is thought that dystonia may arise from different sources (including basal ganglia [10,11], cerebellum [12–16], or sensory areas [17,18]), it eventually requires propagation of the abnormal signal through motor cortical areas [19]. Therefore, we hypothesize that GPi DBS is likely to be effective only when it modulates the activity of motor cortical regions through pallidothalamocortical pathways [19–21]. A method for measuring the effects of DBS on cortical activity is to record changes in scalp electroencephalogram (EEG) evoked by stimulation of the implanted electrode [21–24,40]. Such deep brain stimulation evoked potentials (DBSEPs) may help quantify the relative functional connectivity between (a) basal ganglia structures stimulated by DBS contacts and (b) cortical areas, and thus inform contact selection.

In addition, understanding the relationship between the cortical activity and the effectiveness of GPi DBS therapy may also have important consequences on neurosurgical targeting during DBS implant procedures. Typically, patients are under monitored anesthetic care (MAC) and woken during the final targeting stage of the implant procedure so that neural activity in the GPi can be recorded with microelectrodes. The neurosurgeon uses visual and/or auditory representations of the recorded voltage to precisely localize the eventual final position of the DBS electrode [25]. However, it can be difficult to waken children during the DBS implantation procedure, which can lead to decreased precision in targeting. Increasing knowledge about DBSEPs may lead to measuring them intraoperatively to enhance or perhaps supplant current targeting methods.

There is evidence to suggest that the mechanisms of the DBSEP are similar to the clinical mechanism of action of DBS in adult dystonia (where the stimulation electrodes used therapeutically consistently produced the largest DBSEPs [21]), but not in Parkinson's Disease (where the stimulation electrodes used therapeutically did not consistently produce the largest DBSEPs [22]). However, there are no reports of analyzing DBSEPs in children and little is known regarding if such analyzes can be used to inform electrode contact selection. We therefore examine two hypotheses: (1) DBS evoked potentials can be safely recorded from children and are similar to the evoked potentials seen in adults [21,22,24], (2) the characteristics of DBSEPs from an electrode contact pair can be related to the clinical efficacy of chronic stimulation at that contact pair.

Methods

Subjects

Eleven individuals who received DBS implants at 21 years of age or younger (at time of implant: 13.7 ± 4.5 SD, 9–21 years old; at

Table 1
Patient characteristics.

ID	Current age (years)	Age at implant (years)	Duration of implant (months)	Sex	Diagnosis	Pre-op BAD	Recording date BAD	Clinical settings - Left	Clinical settings - Right	Clinical contact pair (L)	Clinical contact pair (R)	Implanted device
01	10	9	17.5	F	Primary dystonia; DYT1 -	30	24	1–2+, 4.3 V, 270 μs, 180 Hz	1–2+, 3.5 V, 210 μs, 180 Hz	1–2+	1–2+	PCA × 1
02	10	7	43	F	Secondary dystonia; kernicterus	29	29	1,2,3-C+, 3.6 V, 210 μs, 130 Hz	1,2,3-C+, 3.8 V, 150 μs, 130 Hz	2–3+	2–3+	RCA × 1
03	11	11	9.25	M	Secondary dystonia; kernicterus	30	29	0–1+, 5.0 V, 300 μs, 185 Hz	1–2+, 5.0 V, 240 μs, 185 Hz	0–1+	1–2+	SCA × 2
04	12	11	12.5	M	Primary dystonia; DYT1 +	8	2	1–C+, 3.5 V, 120 μs, 185 Hz	1–C+, 3.5 V, 120 μs, 185 Hz	1–2+	1–2+	RCA × 1
05	12	8	50.5	F	Secondary dystonia; cerebral palsy	28	27	2–C+, 4.0 V, 270 μs, 120 Hz	2–C+, 4.0 V, 270 μs, 120 Hz	2–3+	2–3+	SCA × 2
06	15	14	12.5	F	Primary dystonia; DYT1 -	16	7	0–1+, 4.3 V, 210 μs, 180 Hz	0–1+, 4.5 V, 270 μs, 180 Hz	0–1+	0–1+	PCA × 1
07	17	17	5.75	M	Secondary dystonia; cerebral palsy	27	26	0–1+, 4.5 V, 210 μs, 185 Hz	0–1+, 4.5 V, 210 μs, 185 Hz	0–1+	0–1+	PCA × 1
08	17	16	20.25	M	Secondary dystonia; cerebral palsy	?	26	1,2-C+, 3.5 V, 120 μs, 160 Hz	1,2-C+, 3.5 V, 120 μs, 160 Hz	1–2+	1–2+	PCA × 1
09	19	19	5.5	F	Secondary dystonia; cerebral palsy	30	29	0–1+, 3.9 V, 210 μs, 185 Hz	2–3+, 3.8 V, 270 μs, 185 Hz	0–1+	2–3+	SCA × 2
10	21	14	89.75	M	Secondary dystonia; cerebral palsy	29	24	0–1+, 4.0 V, 210 μs, 120 Hz	1–2+, 5.0 V, 210 μs, 120 Hz	0–1+	0–1+	PCA × 2
11	22	21	22.75	F	Secondary dystonia; cerebral palsy	26	25	0–1+, 3.5 V, 210 μs, 240 Hz	0–1+, 3.5 V, 210 μs, 240 Hz	0–1+	0–1+	PCA × 1

BAD = Barry-Albright dystonia scale; DYT1+ = positive for genetic abnormality leading to dystonia; CP = cerebral palsy; stimulating contacts are designated as "C-A+", where C = cathode contact number and A = anode contact number; V = volts; μs = microseconds; Clinical contact pair = the experimental contact pair most similar to the stimulation settings by the patient's neurologist; PCA = PC Activa®; RCA = RC Activa®; SCA = SC Activa®.