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Dissociation of motor symptoms during deep brain stimulation of the subthalamic nucleus in the region of the internal capsule

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Abstract

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) can be an effective treatment for the motor symptoms of Parkinson's disease. The therapeutic benefits are voltage dependent and, in many cases, limited by the appearance of side effects, including muscle contractions. We have observed a number of clinical cases where improvements in rigidity were accompanied by a worsening of bradykinesia. Considering the anatomic position of STN and current approaches to implantation of the DBS lead, we hypothesized that this dissociation of motor symptoms arises from activation of pyramidal tract fibers in the adjacent internal capsule. The objective of this study was to assess the physiological basis for this dissociation and to test our hypothesis that the underlying etiology of this paradox is activation of fibers of the internal capsule. The effect of STN DBS at 80% of motor threshold for each of the four contacts was evaluated for its effect on rigidity, bradykinesia and akinesia in a single primate made parkinsonian with MPTP. Consistent with our observations in humans, this near-threshold stimulation was found to improve rigidity while bradykinesia and akinesia worsened. Worsening bradykinesia in the face of improvement of other motor signs in PD patients is suggestive of activation of pyramidal tract fibers during stimulation. This phenomenon may occur without overt muscle contraction and in the face of improved rigidity.

Keywords

Deep Brain Stimulation; Parkinson's disease; Subthalamic Nucleus; Internal Capsule

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment for the motor symptoms (e.g., tremor, bradykinesia and rigidity) associated with Parkinson's disease (PD) (Group, 2001). For most patients, bradykinesia and rigidity can be dramatically reduced, with average improvements at 6-months post-surgery of 42% and 58%, respectively, in the off-drug condition (Group, 2001). Successful outcomes depend however, on accurate targeting of the STN intra-operatively, including the need to position the lead away from neighboring structures to ensure that therapeutic levels of voltage can be achieved without unwanted side effects (e.g., muscle contraction, paresthesias, visual

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abnormalities and affective or behavior disturbances). Given that STN DBS targets the sensorimotor region, which is located along its dorsolateral aspect adjacent to the internal capsule, one of the most common side effects encountered during STN DBS programming is motor contractions. This effect is attributed to spread of current to the internal capsule, where stimulation of pyramidal tract (PT) fibers, including corticobulbar or corticospinal pathways, leads to activation of cranial or spinal motor neurons (Tommasi, et al., 2008). While the effect of supra-threshold activation of PT fibers is generally apparent, marked by focal, tetanic activation of skeletal musculature, the effects of sub-threshold currents on motor behavior are not well understood.

Evidence for sub-threshold activation of PT fibers has been revealed using electromyography, either alone (Ashby, et al., 1999, Ashby and Rothwell, 2000) or in combination with trans-cranial magnetic stimulation of the M1 cortical region (Cunic, et al., 2002, Hidding, et al., 2006). The impact of this sub-threshold stimulation on motor behavior is unclear. In our experience with programming patients with STN DBS implants we have observed that, while certain programming configurations yield reductions in rigidity, occasionally they can be associated with a simultaneous worsening of bradykinesia. We hypothesize that this dissociation of motor effects may result from spread of current to the PT fibers at levels that, while insufficient to cause overt activation (i.e., sub-threshold), may interfere with movement. To test the hypothesis that the underlying etiology of this paradox is activation of the PT, we studied the effect of STN DBS on motor behavior in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey at 80% of motor threshold (MT), defined as the lowest voltage required to induce muscle contraction in either the upper or lower limb or the orofacial region as determined through visual inspection.

The study was performed using a single, adult rhesus monkey (*Macaca mulatta*; female - 7.2 kg; ID # 04-m-001) that had been conditioned to allow for manipulation of its upper and lower extremities while seated in a primate chair. All surgical procedures and behavioral protocols were approved by the Institutional Animal Care and Use Committee of the Cleveland Clinic and complied with United States Public Health Service policy on the humane care and use of laboratory animals.

The monkey was treated with MPTP via unilateral injections through the right internal carotid artery during aseptic surgical procedures performed under isoflurane anesthesia. In order to induce a stable hemiparkinsonian syndrome, characterized by rigidity and bradykinesia on the left side of the body, a total of three separate, intracarotid injections were performed (dosages were 0.6, 0.5, and 0.6 mg/kg, with each delivered over a period of 15 minutes for a total overall dose of 12.8mg).

Detailed procedures for surgical placement of the recording chamber and DBS hardware have been described previously (Elder, et al., 2005, Miocinovic, et al., 2007). Briefly, prior to surgery, high-resolution MRI and CT scanning was performed. The resultant images were imported into the Cicerone software package, which enables interactive 3D visualization of co-registered MRI/CT images and provides a 3D brain atlas by which the optimal position of cephalic chamber can be determined. With the stereotaxic coordinate predetermined, the cephalic chamber was implanted in an aseptic surgical procedure under isoflurane anesthesia with the head held in a primate stereotaxic instrument. A craniotomy was trephined and a recording chamber stereotaxically placed over the craniotomy. Titanium screws were secured to the skull, and the implant system consisting of screws, recording chamber and a head stabilization receptacle were bonded together with dental acrylic.

After a period of recovery, the area of the STN was electrophysiologically mapped and a scaled version of the human DBS lead with four concentric, platinum-iridium contacts, 0.76

mm in diameter and 0.5 mm tall separated by 0.5 mm was implanted. The four contacts of the lead are numbered 0 through 3, with 0 representing the most distal contact. The distal end of the lead was implanted into the sensorimotor region of the STN, along its dorsolateral border with the internal capsule, with the proximal end attached to a modified extension wire at the level of the implanted chamber.

Testing was suspended for a period of 2 weeks to allow for the resolution of any implantation-related swelling around the tip of the lead. Thereafter, the location of the lead relative to the internal capsule was assessed by applying monopolar (i.e., contact negative, case positive) stimulation through each of the four contacts and determining the MT. Throughout the experiments, the frequency of stimulation was maintained at 135 pulses per second, with pulse duration set at 90 μ sec. Subsequently, the effect of stimulation at 80% of MT on motor behavior, including rigidity, akinesia and bradykinesia was evaluated intermittently over a period of two months. In contrast to the other motor signs, and consistent with previous experience in the macaque MPTP model (Bergman, et al., 1998, Burns, et al., 1983), tremor was minimal and inconsistent in this animal (See Table 1). As a result, those data were excluded from statistical analysis.

Motor function was evaluated by an experienced rater who was blinded to the experimental condition. A 0 – 4 rating scale, where zero represented normal motor function and 4 represents severe rigidity or marked slowness similar to that described in the Unified Parkinson's Disease Rating scale (UPDRS), was applied to each of the four motor categories. Bradykinesia was evaluated further using a reach and retrieval task, during which food rewards were presented to the animal using a modified Klüber board (a 1×3 matrix of food wells, 2 cm in diameter and 3 mm deep). The time from initial contact of the first piece of food until contact of the third piece of food to the mouth was recorded for analysis. The data for the reach and retrieval task are expressed as mean ($\pm$ SD) performance time (sec), while those for the motor function ratings of rigidity, bradykinesia and akinesia are expressed as the mean ($\pm$ SD) clinical score from the blinded examination. An analysis of variance (ANOVA) model for repeated measure designs was used to analyze differences, if any, between the monopolar configurations used to deliver stimulation and 1) the motor function ratings of rigidity, bradykinesia and akinesia and 2) reach and retrieval time. The individual metrics of motor function were set as the dependent variables while the electrode contact was used as the explanatory variable. In the case of significant multivariate findings, further exploration of the individual monopolar configurations was conducted to identify which electrode contacts were associated with motor function that differed significantly from the OFF condition. Significance level was initially set to 5% (i.e. $\alpha = .05$), with the Bonferroni correction for multiple comparisons applied to limit the probability of obtaining a significant result purely by chance. Based on the application of four planned comparisons, this resulted in a significance level of 1.2% (i.e., $p < 0.012$).

Figure 1A depicts the effect of stimulation through contact 1 of the DBS lead at voltage levels of 45%, 64% and 80% of MT on each clinical rating of motor function. A voltage-dependent improvement was observed in the rigidity of the animal, marked by a 30% reduction at 80% of MT. In contrast however, there was no improvement in either akinesia or bradykinesia at the lower of the two stimulus amplitudes and a tendency towards exacerbation of these two signs at 80% of MT. A similar disparity in motor function was observed at 80% of MT across three of the four contacts of the DBS lead. Table 1 presents the summary data for each of the monopolar configurations. As shown in Figure 1B, stimulation at 80% of MT was associated with improvements in rigidity regardless of the contact used to deliver the stimuli ($p < 0.01$). In contrast, the motor ratings for bradykinesia and akinesia, which initially showed slight improvements during stimulation through contact 0, worsened as the voltage source was shifted proximally along the electrode. For the

clinical rating scale data, the magnitude of this difference only achieved statistical significance for contact 3. Worsening of bradykinesia with more dorsal contacts however was more clearly demonstrated during the reach and retrieval task (Figure 1C), where performance times were found to be significantly reduced when stimulation was delivered through contacts 1, 2 or 3 ($p < 0.01$). While one would have expected a similar detrimental effect on bradykinesia, akinesia and the movement time task across all 4 contacts when stimulating at 80% MT, the difference in the net effect of stimulation through a particular contact on motor behavior may reflect a combination of the therapeutic effect at more optimally placed contacts, in this case contact 0, combined with a worsening effect secondary to activation of PT fibers. Although a postoperative CT was consistent with this hypothesis the animal died prior to completion of the study and histological confirmation of the location of individual contacts was not possible. Nonetheless the worsening of bradykinesia in the face of improved rigidity was consistent across multiple contacts and as one increased the voltage within an individual contact this dissociation was preserved providing compelling evidence in support of our hypothesis

We propose that the dissociation observed, specifically the aggravation of bradykinesia, arises as a side effect of current spread to the PT fibers in the adjacent internal capsule. In contrast to overt corticospinal or corticobulbar activation however, which would be associated with visible, focal activation of muscle fibers, the manifestation of bradykinesia may represent a subthreshold modulation of PT fiber activity. The exact mechanism of this effect is unclear, but may be consistent with the effect of depolarization pre-pulses on voltage-gate sodium channels described by Grill and Mortimer (Grill and Mortimer, 1995). Although in this case, the stimulation parameters, particularly the relatively narrow pulse width, may be insufficient to completely inactivate the sodium channel along the nodes of Ranvier, it may be sufficient to transiently disrupt transmission along the PT fibers. Moreover, the spatial variation of this effect, being greater closer to the current source, may disrupt the overall timing and pattern of the information transmitted along the corticospinal and corticobulbar pathways, which may be manifested clinically as bradykinesia.

Clinical studies of GPi DBS have reported similar paradoxical effects of stimulation on motor signs in patients with Parkinson's disease (Bejjani, et al., 1997, Krack, et al., 1998) and patients with dystonia (Berman, et al., 2009, Tisch, et al., 2007). In patients with PD, both Bejjani et al and Krack et al found that high amplitude DBS of the ventral portion of the GP resulted in a progressive worsening of akinesia, despite persistent improvements in rigidity. Both groups concluded that their results reflected the existence of at least two distinct functional zones (dorsal zone and posteroventral zone) within GP which mediate the paradoxical effect, arguing that the voltages applied were well below the motor threshold of patients in their subject cohort. In studying effects of GPi DBS on non-dystonic limbs in a group of patients with cervical dystonia, Berman et al (Berman, et al., 2009) found a worsening of motor function marked by slowing of movements and difficulties with handwriting and other activities of daily living. The stimulation-induced changes in movement speed ranged from moderate to severe and could not be completely dissociated from the beneficial effects of GPi DBS on dystonia, even with additional programming. Although the authors argue that the bradykinesia might arise from the same neural circuit mediating the antidystonic effect rather than from a neighboring structure, spread to the internal capsule could not be completely ruled out considering the location and the angle of the implanted DBS lead. Similarly, Tisch et al observed, in 2 out of 15 dystonia patients with GPi DBS, the development of delayed onset akinesia with gait slowing and difficulty arising from sitting and turning in bed (Tisch, et al., 2007). In both patients those features occurred with stimulation of ventral contacts and improved by changing to more dorsal contacts. Considering the anatomy, the angle and location of the DBS lead as well as the finding that the side effect was mitigated by using more dorsal contacts, we would propose

that the effect the author observed by stimulating the ventral contacts, which are closer to the internal capsule, might also be induced by the spread of current to the internal capsule. Although the published data from both STN DBS and GPi DBS suggest that the bradykinesia or other side effects produced during DBS might be related to the spread of DBS current to the internal capsule, some experiments have shown that the distance up to which neurons are effected by HFS depends on current intensities as well as electrode and tissue properties. Considering this interplay of current spread and its effect on neurons, different positioning of the electrodes within the region of STN also may effect both STN neurons and passing fibers inside and outside STN depending on the distance of the specific electrode to the PT fibers. (Holsheimer, et al., 2000, Ranck, 1975) Evidence for sub-threshold spread of current has been reported based upon EMG and TMS techniques in humans (Ashby, et al., 1999, Ashby and Rothwell, 2000, Cunic, et al., 2002, Hidding, et al., 2006), however our results provide the first indication of the potential link between this current spread and clinical outcome. These findings underscore the importance of deriving a complete physiological map of the STN region when performing stereotactic surgical procedures in order to optimize lead placement. In particular, a thorough mapping of the lateral border of the STN, using both MER and micro-stimulation techniques, should be completed in order to identify the course and distance of that margin relative to the implantation site. Poorly placed leads not only increase the amount of programming effort required to achieve maximal benefit increased, but likely limit the overall level of benefit that can be achieved due to the appearance of side-effects as voltage is increased. Unfortunately, the current group of DBS leads are only spatially selective along the z-axis, through the selection of one or another of the four contacts, and do not allow the user to selectively direct the current about the x- and y-axis. Hopefully future generations of electrodes will incorporate directional designs that will enable clinicians to better tailor the shape of the current field to affect the therapeutic target at the exclusion of those areas responsible for the induction of side effects.

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Figure 1.

Top Row: The effect of stimulus amplitude, as a percentage of MT, on clinical ratings for, from left to right, rigidity (blue), akinesia (green) and bradykinesia (red). MIDDLE ROW: The effect of stimulation at 80% of MT on the clinical ratings of rigidity, akinesia and bradykinesia for each of the four contacts of the DBS lead. BOTTOM ROW: Percentage change in motor performance on the reach and retrieval task is shown for each contact of the DBS lead when stimulation was delivered at 80% of MT; For all graphs, effects are expressed as percentage improvement in ratings relative to the off condition, with positive values representing improved behavior relative to baseline. (* $p < 0.012$)

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Table 1

Polarity		Voltage			Examination			R.R. Task	
' ₋ '	' ₊ '	Threshold (V)	80% MT (V)	Rigidity	Bradykinesia	Akinesia	Time (sec.)		
0	Case	1.1	0.9	1.44 ± 0.12	1.78 ± 0.27	1.58 ± 0.38	2.53 ± 0.38		
1	Case	1.1	0.9	1.59 ± 0.17	2.11 ± 0.20	2.01 ± 0.12	3.60 ± 0.56		
2	Case	1.3	1.0	1.53 ± 0.16	2.22 ± 0.23	2.23 ± 0.28	3.59 ± 0.53		
3	Case	1.6	1.3	1.74 ± 0.14	2.34 ± 0.17	2.34 ± 0.15	3.46 ± 0.29		
OFF	--	--	--	2.22 ± 0.23	1.95 ± 0.24	1.85 ± 0.24	2.71 ± 0.39		