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Relationship of clinical efficacy to postmortem-determined anatomic subthalamic stimulation in Parkinson syndrome

S. McClelland[1], J.P. Vonsattel[2], R.E. Garcia[3], M.D. Amaya[2], L.M. Winfield[4], S.L. Pullman[4], Q. Yu[4], S. Fahn[4], B. Ford[4] and R.R. Goodman[3]

[1]Department of Neurosurgery, University of Minnesota Medical School, Minneapolis, MN, Departments of [2]Pathology, [3]Neurological Surgery and [4]Neurology, Columbia College of Physicians and Surgeons, New York, NY, USA

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Abstract. Objective/Background: Patients with medically refractory Parkinson's disease (PD) obtain significant clinical benefit from subthalamic nucleus (STN) stimulation. The degree to which a successful outcome relates to the anatomic location of the stimulating electrode has not yet been clearly established. Many studies have attempted to correlate the clinical result with the electrode location using postoperative magnetic resonance imaging (MRI) and there have been a few that used autopsy-determined locations. In this report, we describe long-term clinical follow-up in a patient with autopsy-determined electrode tip anatomic location. Methods: A 67-year-old patient with a 27-year history of idiopathic PD complicated by disabling motor fluctuations and dopaminergic dyskinesias underwent bilateral STN deep brain stimulation (DBS). He was prospectively followed in a long-term clinical protocol until his death 40 months after electrode placement. Postoperative magnetic resonance (MR) imaging and postmortem studies of this patient's brain were performed to localize DBS tip locations. Results: STN stimulation produced improvement of the patient's motor fluctuations, dyskinesias and clinical motor performance, especially appendicular tremors, rigidity and bradykinesia. MRI showed the electrode tips to be within 2 mm of the intended target. Postmortem brain analysis identified the right DBS tip location at the dorsomedial edge of the STN, with the left electrode in the vicinity (but not within) the STN. Chronic DBS elicited minor reactive changes were confined to the immediate vicinity of the electrode tracks. The pathological analysis demonstrated numerous cortical Lewy bodies and degenerative encephalopathy, establishing the diagnosis of transitional type diffuse Lewy body disease (DLBD) rather than simple PD. Conclusion: This patient obtained clinical benefit from STN stimulation typical of that seen for most PD patients. Both the MR analysis and the autopsy demonstrated electrode placement at or outside the boundaries of the STN, suggesting that that clinical efficacy may not depend on electrode location within the central region of the STN.

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Correspondence to
R.R. Goodman MD, PhD
Neurological Institute of New York, Department of Neurological Surgery,
■■■ Street name and No.?
New York, NY, USA
mccl0285@umn.edu

Introduction

Subthalamic nucleus (STN) stimulation is an effective treatment for advanced Parkinson's disease (PD) that is complicated by severe tremor, wearing off fluctuations and drug-induced dyskinesias [Benabid et al. 1994, Ford et al. 2004, Just and Ostergaard 2002, Limousin et al. 1995, Volkmann et al. 2001]. The surgical goal is to place the stimulating electrode in the central portion of the STN but the degree to which the outcome relates to the anatomic location of the electrode has not yet been clearly established. Previous retrospective reports have indicated that efficacy may not depend critically on electrode location if the electrode is within a 6 mm diameter cylinder centered at the STN center [McClelland et al. 2005a, 2005b]. Although many studies have attempted to determine the electrode location by postoperative magnetic resonance (MR) imaging [Hamid et al. 2005, Saint-Cyr et al. 2002, Starr et al. 2002], few reports have provided a correlation between clinical outcome and the electrode tip location as determined by autopsy [Counelis et al. 2003, Haberler et al. 2000, Henderson et al. 2002, Jarraya et al. 2003]. We describe the course and long-term outcome of bilateral STN stimulation in a patient with idiopathic PD, correlated with postmortem analysis.

Clinical materials and methods

Patient history/preoperative evaluation

This patient was a 67-year-old right-handed professor who first presented with micrographia and right hand resting tremor at age 40, followed shortly thereafter by tremor of his right foot and right-sided rigidity. He was formally diagnosed with Parkinson's disease the same year, and began treatment with amantadine, dopamine agonists and anticholinergics. His symptoms progressed, and became generalized. Carbidopa/levodopa was started after 9 years of illness, and provided excellent suppression of his symptoms. Over the next 5 – 10 years, he developed wearing off motor fluctuations as well as drug-induced dyskinesias. After 17 years of disease, his activities of daily living had become severely compromised by peak dose dyskinesias and episodes of severe offs, during which he experienced tachyphemic speech, poor mobility, gait freezing and falling (approximately once per month). He also developed episodes of forgetfulness, nocturnal confusion, hallucinations and paranoia, some of which was considered medication-induced. Despite his cognitive impairment, the patient underwent bilateral subthalamic nucleus (STN) stimulation after 27 years of Parkinson's disease due to his severe dyskinesias and wearing off motor fluctuations.

At the time of surgery, the patient showed levodopa responsiveness, peak dose dyskinesias, and a Mini-Mental status score of 27 out of 30. More extensive neuropsychological testing revealed impairments in immediate and delayed recall, visuospatial organization, attention, planning and sequencing. He was followed at regular intervals postoperatively as part of a study protocol, and returned to the Neurological Institute for detailed neurological examinations in the unmedicated state 1 year and 30 months after surgery. At these evaluations, his stimulators were assessed, and temporarily turned off so that the effect on the patient's symptoms could be measured.

Operation and postoperative course

Informed consent was obtained prior to implantation. The patient underwent MER-guided bilateral implantation of DBS electrodes directed to the STN as previously described [Goodman et al. 2006], utilizing a functional Cosman-Roberts-Wells stereotactic frame (CRW; Radionics Inc., Burlington, MA, USA) and the Stealth FrameLink 2.0 program (Medtronic Inc., Minneapolis, MN, USA) to yield the STN calculated coordinates relative to the inter commisural midpoint (ICM) (4 mm posterior, 4 mm inferior, and 12 mm lateral). The stimulators (Medtronic quadripolar electrode model 338940; Medtronic Inc., Minneapolis, MN, USA) consisted of platinum/iridium conductor wires and electrodes with a polyurethane/polytetrafluoroethylene insulation. The lead length was 40 cm and 1.27 mm in diameter, with four stimulation contacts spaced 0.5 mm apart at the tip of the electrode. The left STN electrode was implanted first to address his right hand tremor. Two MER passes were conducted prior to DBS electrode placement. Based on the MER results, the target was adjusted 1 mm anterior and 2.5 mm inferior to the initial stereotactic target and the DBS electrode was placed. His tremor was reproducibly suppressed with 3 volts of stimulation using 200 Hz and 60 pulse width, with no bothersome side effects. The right STN electrode was subsequently implanted following a single MER pass conducted along a mirror image to that for the DBS electrode on the left side, with similar confirmation of left hand tremor suppression (using 2 volts of stimulation), with placement adjusted 1 mm anterior and 2 mm inferior to the initial stereotactic target. Postoperative MR imaging (Figure 1) confirmed the location of each DBS electrode in close proximity to each calculated STN target. Bilateral cranial pulse generators and extension wires (Medtronic Soletra model 7426 pulse generators and model 749551 extension wires, Medtronic Inc., Minneapolis, MN, USA) were uneventfully implanted four weeks later as previously described [Goodman et al. 2006]. The parameters of stimulation were as follows: stimulation frequency on the right side was 185 Hz, voltage was 2.0 V, and the pulse width was 60 microseconds;

Table 1. Clinical characteristics and ratings.

	[1]Baseline "off"	[1]Baseline "on"	[1]1 year off meds off stim	[1]1 year off meds on stim	[1]1 year on meds on stim	30 months off meds off stim	30 months off meds on stim
UPDRS Part III (motor)	36.5	30.5	32	29.5	21.5	39	31
[2]UPDRS Part III: right items	7	4.5	7	7	2.5	6.5	8
[2]UPDRS Part III: left items	10	7	10.5	6.5	4	10.5	4
Hoehn and Yahr stage	3.0	2.5	4.0 ("off")		3.0 ("on")	4.0 ("off")	4.0 ("on")
Schwab and England ADL capacity	40%	65%	40% ("off")		65% ("on")	50% ("off")	50% ("on")
MMSE (out of 30)	27		25			21	
Weight (pounds)	154		153			158	

[1]Ratings were blinded using videotape [except for rigidity scores], as described in Reference [Ford et al. 2004]. [2]Includes these 9 items from UPDRS Part III: arm tremor at rest, leg tremor at rest, arm tremor with action, arm rigidity, leg rigidity, rapid fingertapping, rapid hand opening and closing, alternating hand movements, and repetitive toe tapping.

stimulator frequency on the left side was 185 Hz, voltage was 1.8 V, and pulse width was 60 microseconds. The patient did well postoperatively, with no complications.

Postoperative clinical course

After bilateral STN stimulation, the patient's dyskinesias and wearing off fluctuations improved. His medication intake was not significantly reduced. On blinded evaluations of his motor examination (UPDRS Part III) at one year, stimulation produced a 19% improvement in motor scores as compared to baseline [Ford et al. 2004]. The improvement was mainly accounted for by effects on tremor and appendicular bradykinesia and rigidity. The axial symptoms, including truncal flexion, gait, freezing and balance, did not improve. In addition, over time, he became progressively demented, with episodes of confusion, requiring nursing home placement. At the 30-month evaluation (unblinded), comparing the exam in the unmedicated and off stimulation state to the on-stimulation state, DBS continued to show a 20% improvement in motor function, especially involving the left hand. Of note, the left side score (right DBS) improved 60% with stimulation, while the right side score (left DBS) actually worsened slightly with stimulation/off medication. The clinical data are summarized in Table 1. Over the next year, his dementia and generalized decline progressed, and he died in the nursing home 41 months postoperatively, after 31 years of PD, at age 71.

Electrode targeting position

Subsequent merging of his preoperative and postoperative MRIs (utilizing the Stealth program) yielded the coordinates of his electrode positions relative to his ICM. His right electrode was 9.45 mm lateral, 5.70 mm posterior and 5.96 mm inferior to the ICM, while his left electrode was 10.90 mm lateral, 6.70 mm posterior and 2.36 mm inferior to the ICM. The Stealth program calculated the length of his anterior commissure/posterior commissure line to be 25.74 mm.

Pathological findings

The fresh brain was divided in the midsagittal plane. The left half brain was extensively dissected at the fresh state, and blocks were frozen at –180 °C (including the left STN, which was later thawed, formalin

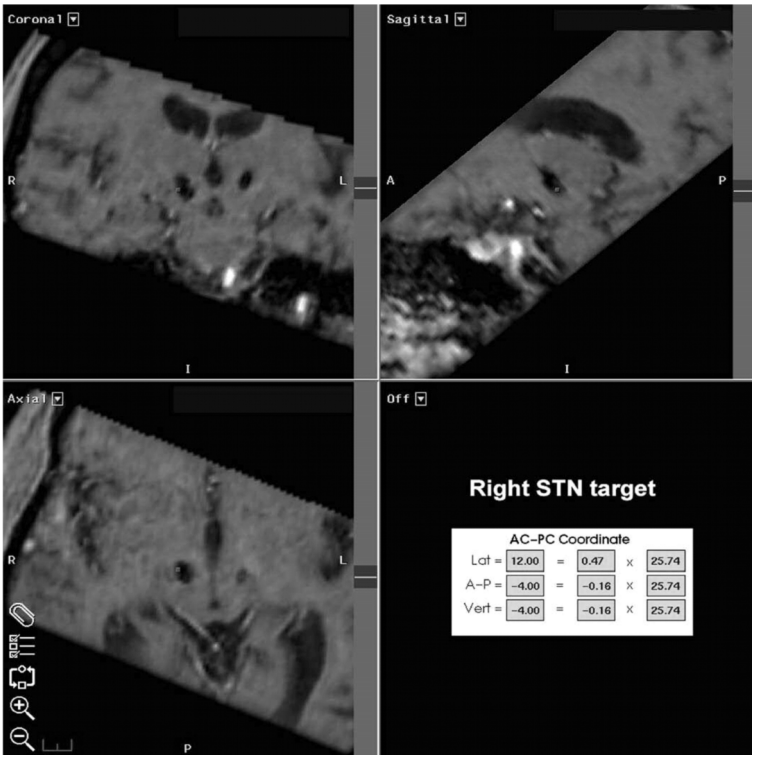

Figure 1A.

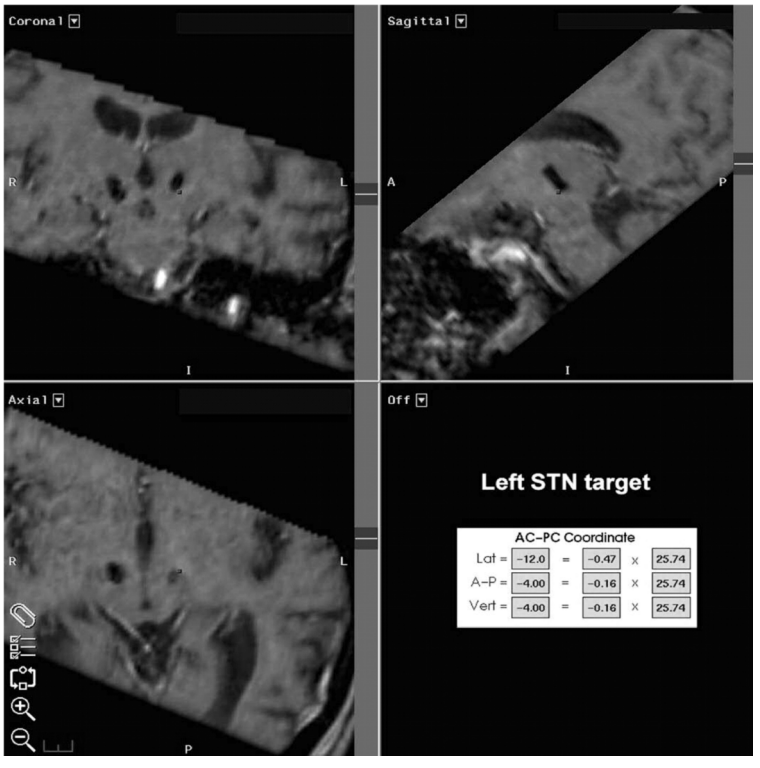

Figure 1B.

Figure 1. Postoperative volumetric axial T1-weighted magnetic resonance imaging (28 1-mm slices) reformatted using the Stealth FrameLink 4.0 workstation demonstrates placement of deep brain stimulation electrodes in the vicinity of the STN bilaterally with no evidence of hemorrhage. A) Right DBS electrode tip (low signal artifact) and the calculated right STN target (**red pixel ■■■**), B) Left DBS electrode tip (low signal artifact) and the calculated left STN target (**red pixel ■■■**).

■■■ Figures in color or the legend should be changed!

fixed, and processed for microscopical examination as described below). The right half-brain was immersion fixed in 10% formalin and neuropathologically evaluated as previously described, but with minor changes [Vonsattel et al. 1995]. Briefly, representative blocks of the cerebral cortex, amygdaloid nucleus, hippocampus, striatum and thalamus including the entire subthalamic nucleus, brainstem and cerebellum were embedded in paraffin. Then 7.0 m thick sections were obtained, and stained with Luxol fast blue counterstained with hematoxylin and eosin (LHE) for microscopic evaluation and assessment of the course of the DBS electrode track. In addition, selected sections were stained using Bielschowsky silver methods, or subjected to the following antibodies: AT8, -synuclein, ubiquitin, or -amyloid using the immunoperoxidase methods.

The outstanding changes included severe neuronal loss of the pars compacta of the substantia nigra, nucleus caeruleus and dorsal nucleus of vagus. Lewy body-containing neurons, and neurites were found in the dorsal nucleus of vagus, nucleus caeruleus, pars compacta of the substantia nigra, hypothalamus, substantia innominata, and throughout the neocortex. The extent of neocortical neuronal involvement with Lewy body met the diagnostic criteria of transitional type diffuse Lewy body disease [Kosaka et al. 1984]. With regard to the McKeith score [McKeith et al. 2005], sections of Lewy bodies subjected to -synuclein antibodies demonstrated the following number of neurons per 100 microscopic field containing a Lewy body: BA9 (up to 3 neurons) = 1; BA4 (up to 4 neurons) = 1; cingulate gyrus (up to 15 neurons) = 2; parahippocampal gyrus (up to 18 neurons) = 2; occipitotemporal gyrus (up to 7 neurons) = 2. Furthermore, occasional leptomeningeal and cortical vessels showed amyloid deposits within their media. Scant neurofibrillary tangles of Alzheimer were confined to the Sommer sector of the hippocampus, and were not found within the neo-

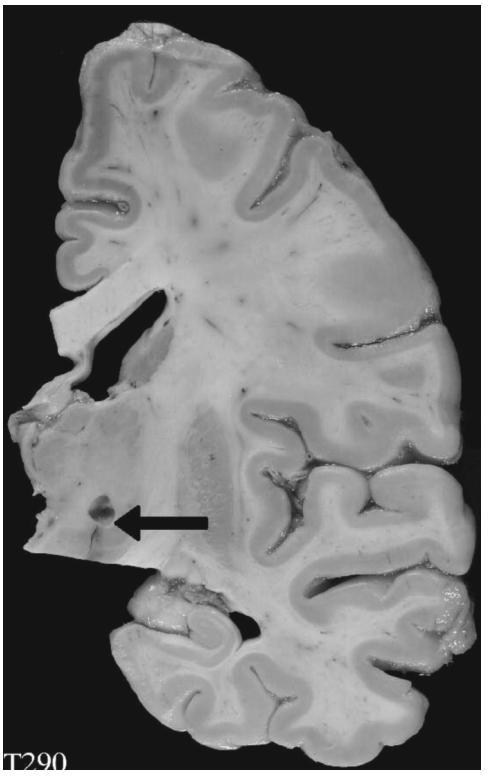

Figure 2A. Coronal section (posterior aspect) of the right cerebral hemisphere passing through the subthalamic nucleus and red nucleus. A well-outlined tissue defect (right DBS electrode track) with smooth borders involves the ventral lateral nucleus and the thalamic fasciculus with encroachment upon the dorsal edge of the subthalamic nucleus (arrow).

Figures 2B through 2E were stained with Luxol fast blue and counterstained with hematoxylin and eosin.

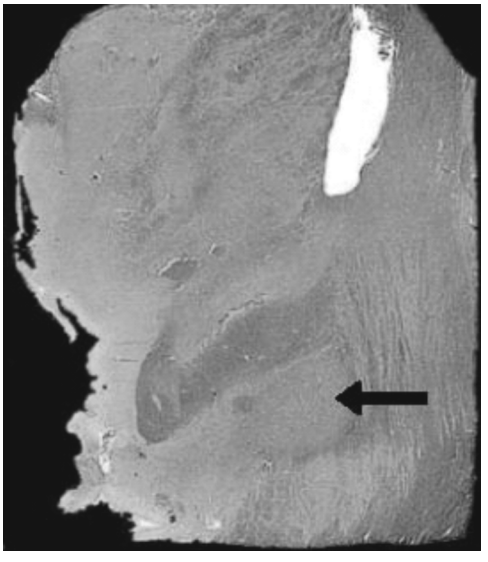

Figure 2B. Micrograph showing the right subthalamic nucleus (arrow) and the right DBS electrode track (optically empty space). The track involves the ventral anterior nucleus of the thalamus (original magnification 1).

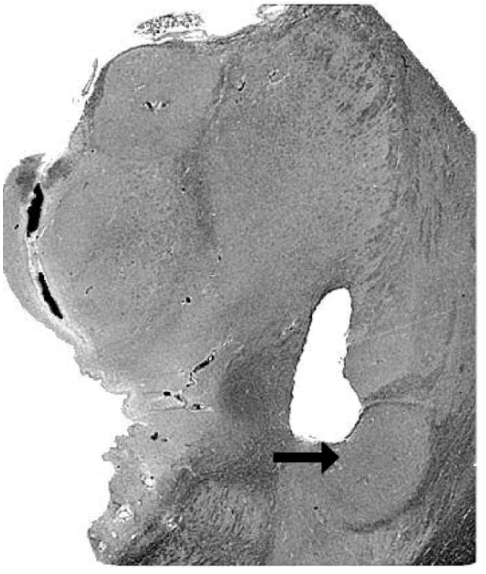

Figure 2C. Micrograph showing the right subthalamic nucleus about 3 mm caudal to the previous micrograph. The right DBS electrode track involves the ventral lateral nucleus and the thalamic fasciculus with encroachment upon the dorsal edge of the subthalamic nucleus (arrow; original magnification 100).

cortex. Rare neuritic plaques involved the prefrontal cortex (Brodmann area 9) only.

We correlated the postoperative location of our patient's STN electrodes with the clinical data and the postmortem examination. An important finding was that both electrodes were located in the vicinity of the STN, consistent with their location on postoperative imaging (Figure 1). By postoperative imaging, the position of the left electrode was 2.55 mm lateral, 1 mm posterior and 3.6 mm superior to that of the right electrode, which (on postmortem exam) clearly terminated in the dorsomedial portion of the STN (Figure 2C). Although both electrodes gave clinical effects on appendicular function, the right electrode provided superior effects on left-sided bradykinesia, rigidity and tremor items than the left electrode (Table 1).

Discussion

We describe a patient with a 27-year history of levodopa-responsive Parkinson's disease, complicated by severe wearing off motor fluctuations and dyskinesias, treated using bilateral STN stimulation. The patient derived

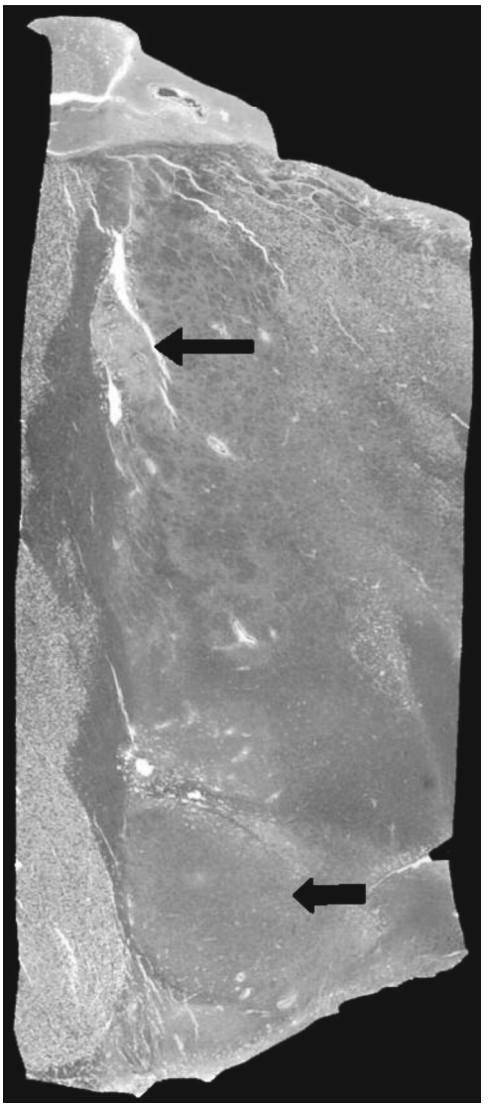

Figure 2D.

Figure 2D. Micrograph showing the left subthalamic nucleus cut at the same level as in Figure 2B. The left DBS electrode track involves the ventral anterior nucleus with encroachment upon the posterior limb of the internal capsule (original magnification 1).

Figure 2E. Microphotograph. The right DBS electrode track is shown at the lower left corner (optically empty space). The medial capsule of the subthalamic nucleus is between the track and the two intact neurons (center) of the STN. A macrophage is seen within the capsule (black arrow). (Original magnification 400).

Figures 2B through 2E were stained with Luxol fast blue and counterstained with hematoxylin and eosin.

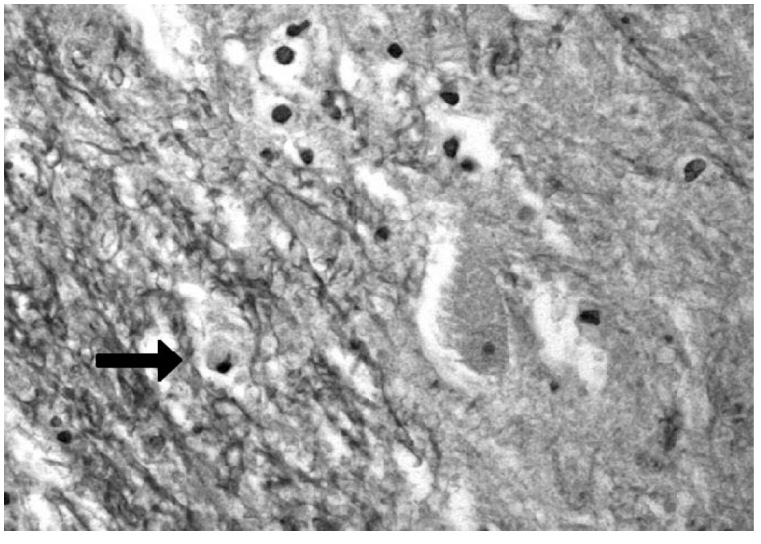

Figure 2E.

motoric benefit from his DBS, including reductions in dyskinesias and improvements in motor function. Thirty months after surgery, he had demonstrable improvements in hand and arm function, especially on the left side, although his course was marked by progressive dementia, tachyphemia, gait freezing and falling, and truncal flexion. He died 40 months after surgery, and 31 years of disease, at age 71.

Continuous electrical stimulation of the STN has been well-documented to produce sustained improvements in tremor, off severity/duration and dyskinesias, as well as reductions in medication requirement [Just and Ostergaard 2002, Limousin et al. 1998, Deep Brain Stimulation for Parkinson's Disease Study Group 2001, Kumar et al. 1998]. Although our patient showed postoperative motor improvement, his most debilitating symptoms – progressive dementia, postural instability, truncal flexion and dysarthria – are all symptoms that have not been reported to respond to medications or DBS therapy [Bloem et al. 1996, Vesper et al. 2002].

Many centers use microelectrode recording (MER) for electrophysiological mapping to optimize DBS electrode placement in the STN [Benabid et al. 1994, Saint-Cyr et al. 2002]. Postmortem studies provide a unique method of corroborating the accuracy of DBS placement with intraoperative electrophysiology and postoperative MR imaging. Autopsy studies following long-term DBS electrode implantation have been reported but the majority of these reports describe thalamic implan-

tation for essential tremor or deafferentation pain [Boockvar et al. 2000, Caparros-Lefebvre et al. 1994, Kuroda et al. 1991]. Of the four previously reported autopsy studies of STN electrode implantation [Counelis et al. 2003, Haberler et al. 2000, Henderson et al. 2002, Jarraya et al. 2003], only one provided clinical outcomes longer than three months [Jarraya et al. 2003].

As noted earlier, portions of the left half of the brain (including the STN region) were processed in a different fashion than the right. This prevented us from producing an equivalent demonstration of the electrode artifact at its termination. Some of the analysis of the left STN region was compromised by freezing artifact. However, given the position of the left electrode track relative to the right both proximal to termination (Figure 2D vs. 2B) and in their lateral/medial and anterior/posterior coordinates, it is reasonable to conclude that the left electrode terminated in the STN region, about 1 mm above the STN border. We do not have an explanation for the apparent termination of the left electrode above the STN border and the right in the rostral STN, since the MER results were used to target the ventral STN border. One seemingly likely explanation is that the DBS electrodes retracted slightly, immediately after insertion, and that the tissue that was only transiently affected by the electrode tip did not have any detectable permanent changes.

It is noteworthy that this patient's long-term clinical improvement postoperatively was achieved by a right-sided electrode apparently terminating in the periphery of the STN, or possibly just outside of the STN border, rather than well within the nucleus (Figure 2C). Although it is not known if greater clinical benefit may have been achieved with an electrode terminating in the center of the STN, the improvement of this patient's Parkinson/motor syndrome was comparable to our other STN DBS patients [Ford et al. 2004]. Using the appendicular scores (limb tremor, rigidity and bradykinesia items), even at 30 months postoperatively stimulation through the right electrode was associated with a 62% improvement. However, stimulation through the left electrode at 30 months postoperatively was associated with worsened UPDRS scores, suggesting that the tip location outside/above the STN was associated with a lack of clinical benefit. It is possible that the improvement in the global motor score may have been produced by the effective right-sided stimulation alone, with an unclear contribution of the left electrode.

It certainly is possible that the left electrode provided less benefit than the right because of its termination above the STN border. This could only have been determined in this patient if revision of the electrode, to terminate in the STN, had improved the clinical benefit. This suggests that revisions should be considered for STN DBS electrodes that are suspected to be providing suboptimal clinical benefit. The observations in this patient suggest that clinical benefit may not be strictly contingent on DBS tip location well within the STN, but at some distance from the center of the STN (possibly outside of its border), the clinical benefit is reduced. These findings are consistent with previous literature suggesting that electrodes within 3 mm of the STN center provide equivalent clinical efficacy, while those greater than 3 mm from the STN center may not [McClelland et al. 2005a].

It is important to note that the postoperative imaging correctly suggested that the right electrode tip was near or in the STN, while the left electrode tip appeared likely to terminate above the STN. Thus, combining the clinical response to each electrode with the position of postoperative imaging may be helpful in determining which electrodes should be considered for revision. Also, more pathological studies are warranted to evaluate the relationship between anatomic electrode tip location and clinical benefit.

The histopathological findings we report are similar to previous reports in humans and animals regarding deep brain stimulation, consisting of mild gliosis around the electrode path, with no neuronal loss close to the electrodes [Marsden and Parkes 1976, Vesper et al. 2002]. Our results demonstrate that placement of DBS electrodes causes minimal tissue reactivity, with no definite signs of late tissue damage caused by chronic electrical stimulation at different frequencies, consistent with previous findings [Haberler et al. 2000, Henderson et al. 2002, Jarraya et al. 2003, Stock et al. 1979].

Conclusion

We report an autopsy study of long-term DBS involving a patient with levodopa-responsive PD, who was found to have transitional type DLBD postmortem. Intraoperative, radiographic and clinical analysis demonstrated that motor symptom improvement was achieved by stimulating electrodes in the region of the STN, a finding confirmed by anatomical postmortem analysis. The electrodes in this patient were at the edge of the STN on the right side and likely outside the boundary of the STN on the left side. The right electrode provided the anticipated clinical motor benefit, while the left electrode did not provide clinical benefit. These observations suggest the possibility that placement of an electrode well within the STN may not be required for significant clinical benefit, but that an electrode placed too far from the boundary of the STN may not provide clinical efficacy. Our histopathological findings confirm that chronic DBS is safe and causes only mild tissue reaction. Future autopsy studies might aid in further elucidating the relationship between the neuroanatomical location of implanted electrodes and the clinical outcome.

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Conflict of interest

None of the authors received any financial support in conjunction with the generation of this article.

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