

# Postmortem studies of deep brain stimulation for Parkinson's disease: a systematic review of the literature

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**Abstract** Deep brain stimulation (DBS), arguably the greatest therapeutic advancement in the treatment of Parkinson's disease since dopamine replacement therapy, is now routinely used. While the exact mechanisms by which DBS works still remain unknown, over the past three decades since it was first described, we have gained significant insight into several of the processes involved. Though often overlooked in this regard, increasing numbers of postmortem and autopsy studies are contributing significantly to our understanding. In this manuscript, we review the literature involving the pathological findings from autopsies in patients who have undergone deep brain stimulation surgeries for Parkinson's disease. The major results show that multiple stereotactic targeting methods can be accurate at placing leads in the desired nuclei that help with clinically effective results, that perioperative complications and inaccurate diagnosis as determined by autopsy can lead to suboptimal stimulation effect and that the normal long-term effects of chronic stimulation include fibrosis around the electrodes and a mild immune response. In addition, recent results suggest mechanisms by which DBS might be effective in Parkinson's disease i.e., through rescuing pathological changes in microvasculature and by promoting the proliferation of neural progenitor cells.

**Keywords** Deep-brain stimulation · Parkinson's disease · Autopsy · Postmortem · Histology

## Introduction

Deep brain stimulation (DBS) has been shown in multiple randomized clinical trials to significantly improve the motor symptoms of Parkinson's disease when compared to medication alone (Deuschl et al. 2006; Weaver et al. 2009). Given this benefit, it is a surgery that is being performed with increased frequency and current trials are investigating its use even earlier in the disease course (Charles et al. 2014). With the increasing number of patients undergoing DBS for Parkinson's disease, there has also been an associated increase in the number and scope of publications that have studied these patients postmortem. While initial publications were primarily case reports to verify accurate placement of the electrode in the target of interest, or to evaluate the etiology behind complications or poor effect, more recent studies have started to evaluate the effects of chronic deep brain stimulation on patients with Parkinson's disease and have shed light on the disease pathology itself as well as what effects deep brain stimulation might have on the natural course of the disease. In this article, we review the literature involving postmortem studies on Parkinson's disease patients with deep brain stimulators and discuss the primary questions that have been addressed with these studies.

## Material and Methods

We performed a Medline search of all articles from January 1, 1999 to February 1, 2017 using combinations of the phrases, "Deep Brain Stimulation" and "Postmortem" and "Parkinson". A similar search was performed using either "Post-mortem" or "Autopsy" in place of "Postmortem". In all, 36 results were found. Results were filtered to include only articles written in English and those addressing human subjects (see Table 1). After filtering, 13 articles, including case series and case reports,

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**Table 1** Systemic review process

	Criteria	Number of articles removed or added	Number of articles remaining
Medline search	“Postmortem” OR “Post-mortem” OR “Autopsy” AND “DBS” + “Parkinson” AND January 1999 to February 2017	-	36
Filters	Humans English	23 filtered	13
Secondary additions	Applicability to current review	10 added	23

were identified and included in the review. Further investigation into these articles revealed 10 other articles whose scope was consistent with the purposes of this review (Haberler et al. 2000; Henderson et al. 2002; Jarraya et al. 2003; Gross et al. 2004; Hariz et al. 2004; Lezcano et al. 2004; Nielsen et al. 2007; Ullman et al. 2011, 2012; Vedam-Mai et al. 2014). Of these final 23 articles, 8 primarily addressed the overall chronic effects from deep brain stimulation in Parkinson’s disease (Haberler et al. 2000; Nielsen et al. 2007; Sun et al. 2008; Vedam-Mai et al. 2011, 2014; Pienaar et al. 2015; Kronenbuerger et al. 2015; Pal et al. 2017), 4 identified the misdiagnosis of multiple systems atrophy (MSA) as the source of a poor response to deep brain stimulation (Chou et al. 2004; Lezcano et al. 2004; Ullman et al. 2012; Thavanesan et al. 2014), 4 verified either the accurate placement of the DBS electrode using different navigation modalities or the safety of MRI in confirming location (Counelis et al. 2003; Gross et al. 2004; Ullman et al. 2011; Al-Helli et al. 2015), 4 demonstrated that placement of lead close to, but not inside of, the ideal location in the subthalamic nucleus (STN) still resulted in a good clinical response (Henderson et al. 2002; Hariz et al. 2004; McClelland et al. 2007; Guehl et al. 2008) and 3 were used to identify complications from surgery (Henderson et al. 2001; Jarraya et al. 2003; Vedam-Mai et al. 2012). For conciseness and consistency in reviewing these topics, we subdivided these articles into the following sections (see Tables 2, 3, 4): “Verification”, “Complications”, “Alternative pathologies”, and “Long-term effects”.

## Results

### Verification

Since the borders of classic stimulation sites in stereotactic surgery, such as the STN, are difficult to discern on imaging studies, one of the most fundamental questions in the field is whether the desired target was actually reached. This question

is also one of the first and most commonly addressed by post-mortem case studies where neuropathological analysis is used to determine the location of the electrode tract relative to the desired targeted nucleus. While the results from these published reports are varied (see Table 2), the overarching conclusion is that, regardless of the technique used, including either with or without microelectrode recording (MER), accurate placement into the targeted nucleus can be achieved but is not necessarily guaranteed nor necessarily required for good clinical effect.

The use of MER in combination with MRI-based imaging is the gold standard for localization in the deep brain procedures and case reports in the literature have used postmortem analysis to verify accurate placement with this technique into both the STN (Counelis et al. 2003) and the ventral intermediate nucleus (VIM) of the thalamus (Gross et al. 2004). In both cases, there was no significant evidence of damage along the two to three additional tracts that were used for MER, arguing against what is one of the most common criticisms of this technique, i.e., that it increases risk and causes additional unnecessary damage. In addition, in the STN case report, the authors noted that the originally proposed tract missed the targeted nucleus entirely by a few millimeters, suggesting that the MER-based adjustments were crucial in this case for accurate targeting. It should also be noted, however, that other authors have contested this viewpoint and, by re-evaluating the neuropathological evidence provided in the original case report, have argued that the importance of MER in this case was overstated, as the postmortem analysis shows placement of the electrode lead in the medial aspect of the STN on the left, in contrast to the dorsolateral aspect which is what was targeted (Hariz et al. 2004).

On the other hand, a case report using imaging only-based localization techniques that forgo MER has also shown accurate bilateral STN electrode placement on post-partum analysis (Al-Helli et al. 2015). Post-operative verification in this approach relied on high-resolution MRI with the DBS implanted and the autopsy analysis showed no evidence that this caused

**Table 2** Verification studies on the postmortem analysis of DBS in Parkinson's disease

	Type ( <i>n</i> )	Disease pathology	Target	Duration of stimulation	Method of targeting	Accuracy as verified by pathology	Clinical effect	Findings
Henderson et al. 2002	Case report (1)	PD	BI STN	2 months	Imaging + intraoperative stimulation	Right electrode above target, left electrode within target	Improvement in tremor, bradykinesia, rigidity and movement	Good clinical effect despite inaccurate placement on one electrode.
Counelis et al. 2003	Case report (1)	PD	BI STN	None	MER + imaging + intraoperative stimulation	Both electrodes within target	-	Accurate placement with MER.
Gross et al. 2004	Case report (1)	PD	Right VIM	12 months	MER + imaging + intraoperative stimulation	Electrode within target	“Effective” tremor suppression	Accurate placement and good clinical effect with MER.
McClelland et al. 2007	Case report (1)	PD	BI STN	40 months	MER + imaging + intraoperative stimulation	Right electrode at the dorsal edge of target, left electrode 1mm above target	Improvement in UPDRS III motor score by 60% for the right electrode and a worsening by 25% for the left electrode	Good clinical effect despite suboptimal placement on right electrode. Inaccurate placement and diminished clinical effect on left electrode.
Guehl et al. 2008	Case report (1)	PD	BI STN	72 months	Imaging + intraoperative stimulation	Both electrodes above target	Improvement in UPDRS III motor score by 50% and decrease in L-Dopa requirement by 30%	Good clinical effect despite inaccurate placement in both electrodes.
Sun et al. 2008	Case report (1)	PD	BI STN	71 months	MER + imaging + intraoperative stimulation	Both electrodes above target	Reductions in motor fluctuations and decrease in L-Dopa requirement by 39%	Good clinical effect despite inaccurate placements in both electrodes.
Al-Helli et al. 2015	Case report (1)	PD	BI STN	72 months	Imaging + intraoperative stimulation	Both electrodes within target	-	Accurate placement with imaging only-based technique

Parkinson's disease (*PD*), bilateral (*BI*), subthalamic nucleus (*STN*), ventral intermediate thalamus (*VIM*), microelectrode recording (*MER*)

appreciable damage to the brain tissue surrounding the electrode, which is important in validating the safety of MRI in patients with implanted DBS electrodes. In this way, it agreed with work carried out by Ullman et al. who demonstrated, using postmortem brains from DBS patients, that even 3.0T imaging does not lead to histopathological evidence of thermal damage from the implanted electrodes (Ullman et al. 2011).

While these case reports show that accurate placement in the targeted nucleus is possible with or without MER, it is impossible to generalize a practice recommendation either for or against MER based on these studies. Indeed, even with the stronger evidence found in the literature using radiographic and clinical

results from deep brain stimulation procedures performed with or without MER (Zeiler et al. 2013; Mirzadeh et al. 2014, 2016), the results are still not definitive, with strong arguments on either side. One of the biggest questions in this debate is whether accurate placement of the DBS electrode within the STN per se is even a requisite to a good clinical response and there have been a few studies using neurohistological evidence that suggest it might not be necessary.

Indeed, over the past two decades, four case studies were published that analyzed the postmortem brains of patients who had good clinical responses to DBS of the bilateral STN at up to 6 years post-operatively and found that at least one electrode

was noted to be outside the targeted nucleus in each case, with both leads outside the STN in two of the cases. The technique used in each case was independent of the accuracy, as autopsies on patients with both MER-based and imaging only-based techniques demonstrated both one (Henderson et al. 2002; McClelland et al. 2007) and two electrodes out of the target (Guehl et al. 2008; Sun et al. 2008) in equal numbers. This agrees with data from a case series of 19 postmortem brains referred from various institutions, in which approximately 12% of the electrodes were found to not be placed in the targeted regions (Vedam-Mai et al. 2011). While it is unclear to what degree the stimulation was effective in all these patients, the assumption can be made that it was effective enough to not require revision surgery.

### Complications

Another area of deep brain stimulation where autopsy studies offer insight is in identifying the etiology behind suboptimal results. The postmortem literature suggests that, at least in some cases, a complication either directly or indirectly from the surgery can be the source. These include an abnormal reaction to the electrode, a migration of the electrode, or worsening secondary pathologies (see Table 3).

For example, a reported published in 2012 analyzed the brain of a 74-year-old man with Parkinson's disease who had undergone staged bilateral DBS of the STN prior to passing away from a cardiac event 11 months later (Vedam-Mai et al. 2012). Surgery for the left STN had been performed first and the patient experienced immediate and consistent motor benefit. Approximately 2 months after the left-sided surgery, another surgery was performed on the right; however, the results from this stimulation were never as good as from the left. The postmortem brain showed abnormal fibrosis, characterized by the presence of a thick fibro-collagenous capsule, around the tip of the right electrode. Further analysis revealed hemosiderin around the lead, which the authors speculate might have been the result of a hemorrhage during lead placement that healed through fibrosis.

Similar findings of suboptimal responses have been shown to be secondary to lead migration and inaccurate positioning. In a 2001 report, a 69-year-old male underwent DBS of the left ventral intermediate nucleus (VIM) of the thalamus with lead externalization for tremor dominant Parkinson's disease (Henderson et al. 2001). He had a notable postoperative course complicated by the pulling out of his extension leads prior to placement of the pulse generator, with anterior displacement of the intracranial lead on imaging. He subsequently underwent a second surgery for placement of a new lead (keeping the first lead in place) but, after implantation of the pulse generator, was noted to have a variable and unsustained response. In addition, he had a rapid progression of symptoms on the ipsilateral (left) side. Three years after surgery, the patient died of sepsis and a postmortem analysis of his brain showed that the first lead had

migrated into the anterior thalamus and there was associated damage in this area. However, it also showed that the second lead, which had been intended for the VIM, was actually placed in the centromedial/parafascicular nucleus and stimulation had resulted in drastic cell loss of over 90% in this nucleus as well, significantly more than the contralateral side. Both of these factors were felt to play a crucial role in his poor response and drastic decline after surgery.

Of course, even without abnormal physiological responses or technical complications, poor responses from DBS surgeries can also be the result of the surgery worsening an underlying secondary pathology. For example, in a 2003 report, a 67-year-old female underwent bilateral STN DBS for motor symptoms including levodopa-associated dyskinesias (Jarraya et al. 2003). Prior to surgery, however, she demonstrated mild cognitive declines. After surgery, her cognitive decline progressed and she subsequently passed away 18 months later from pulmonary embolism. Autopsy studies were consistent with the diagnosis of Parkinson's disease and accurate placement of the electrodes in the STN; however, as the authors argued, given the cognitive impairment, the patient in this case was not an appropriate candidate for surgery and the surgery likely precipitated her cognitive decline.

### Alternative pathologies

As described above, technical missteps, abnormal physiological responses or poor patient selection can all be the source of complications and poor responses to deep brain stimulation therapy. However, another etiology for a poor response is an inaccurate diagnosis. For example, in a 2004 case report, a 54-year-old male who underwent bilateral STN DBS after 9 years of levodopa, had responsive motor symptoms that was initially felt to be idiopathic Parkinson's disease (Chou et al. 2004). While he had a reduction in his motor symptoms intraoperatively, post-operatively he had a rapid decline in both motor and cognitive function and died 12 weeks after surgery from aspiration pneumonia. Postmortem analysis revealed numerous alpha-synuclein-positive cytoplasmic inclusions throughout multiple areas of the brain, including the cerebellum and brainstem, in addition to the subcortical nuclei, which confirmed the diagnosis of multiple systems atrophy (MSA). MSA is often misdiagnosed as Parkinson's disease by even experienced neurologists as they share many clinical features (Litvan et al. 1997). In addition, this was an unusual presentation of MSA, as roughly only 13% of patients have a response to dopamine replacement (Wenning et al. 1997) but the poor response of MSA to DBS is not unusual even in such cases. Indeed, similar cases have been published by multiple authors (Lezcano et al. 2004; Ullman et al. 2012; Thavanesan et al. 2014). In all these reports, patients with autopsy-confirmed MSA were initially diagnosed with parkinsonian symptoms responsive to dopamine replacement and underwent bilateral deep brain stimulation surgeries and, in all cases, a transient

**Table 3** Complication and alternative pathology studies on the postmortem analysis of DBS in Parkinson's disease

	Report type ( <i>n</i> )	Disease pathology	Target	Duration of stimulation	Pathology	Clinical course	Reason for suboptimal response
Henderson et al. 2001	Case report (1)	PD	Left VIM (×2)	36 months	Anterior displacement of one electrode and medial displacement of another into the centromedian thalamic nucleus	Suboptimal response with rapid ipsilateral progression	Post-operative lead migration
Jarraya et al. 2003	Case report (1)	PD	BI STN	18 months	Expected post-operative findings	Rapid cognitive decline after surgery	Worsening underlying cognitive deficits precipitated by surgery
Chou et al. 2004	Case report (1)	MSA	BI STN	3 months	Diffuse alpha-synuclein throughout multiple regions of the brain	Rapid cognitive and motor decline postoperatively	Poor response of MSA to stimulation
Lezcano et al. 2004	Case report (1)	MSA	BI STN	18 months	Diffuse alpha-synuclein throughout multiple regions of the brain	Rapid cognitive and motor decline postoperatively	Poor response of MSA to stimulation
Ullman et al. 2012	Case series (2)	MSA	BI Gpi, BI STN	48 months, 40 months	Diffuse alpha-synuclein throughout multiple regions of the brain	Rapid cognitive and motor decline postoperatively	Poor response of MSA to stimulation
Vedam-Mai et al. 2012	Case report (1)	PD	BI STN	11 months	Abnormal fibrosis around right electrode	Good response to left electrode, suboptimal response to right electrode.	Likely hemorrhage during placement of right electrode led to abnormal scarring
Thavanesan et al. 2014	Case report (1)	MSA	BI STN	48 months	Diffuse alpha-synuclein throughout multiple regions of the brain	Rapid cognitive and motor decline postoperatively	Poor response of MSA to stimulation

Parkinson's disease (*PD*), multiple system atrophy (*MSA*), bilateral (*BI*), subthalamic nucleus (*STN*), ventral intermediate thalamus (*VIM*), globus pallidus internus (*GPI*)

improvement in motor outcomes quickly deteriorated, accompanied by worsened cognitive and overall outcome. This agrees with the general consensus that deep brain stimulation is not typically recommended for patients in whom MSA is suspected.

In summary, postmortem studies have offered insight into the underlying etiology behind poor responses and have shown that possible causes could be complications from surgery or alternative pathologies such as MSA. However, extrapolating an estimate for how often these situations occur is difficult, as they are only reported as case reports and likely highly underrepresented. However, it is important to keep these possible sources for suboptimal responses in mind as they can be often avoided by more stringent patient selection or operative technique.

### Long-term effects

One of the most straightforward things to note from the postmortem analysis of patients' brains who died from DBS is the neuropathological effects from chronic stimulation (see Table 4). One of the earliest reports in this regard was a case series published in 2000 that analyzed the brains of 8 patients with Parkinson's disease who underwent DBS brain stimulation of either the VIM (6 patients) or the STN (2 patients) for periods of time

ranging from 2 days to 70 months (Haberler et al. 2000). The results showed very similar responses irrespective of the duration of stimulation, excluding the one patient who died 2 days after stimulation. In all patients, there was a characteristic three-layer response around the electrode lead. First, there was a thin, less than 25  $\mu\text{m}$ , layer of fibrous tissue. Surrounding this was a thicker rim of fibrillary gliosis that was less than 500  $\mu\text{m}$ . Finally, surrounding this was an even thicker (approximately 1 mm) layer of loosely scattered glial fibrillary acidic-protein reactive astrocytes. There was also evidence of scarce mononuclear leukocytes and multinucleated giant cells in the tract and surrounding tissue. In 2007, a case report largely confirmed these findings in the postmortem analysis of a single patient with Parkinson's disease who died 29 months after high-frequency stimulation to the subthalamic nucleus (Nielsen et al. 2007) and they referred to the approximately 150- $\mu\text{m}$  layer of connective fibrous tissue and surrounding gliosis as a "capsule". Another case report in 2008 showed similar findings in the postmortem analysis of an 81-year-old man with Parkinson's disease who had undergone successful bilateral STN DBS for 71 months prior to dying from pneumonia. In this patient, however, they noted the presence of Rosenthal fibers in the gliotic tissue surrounding the lead. Interestingly, they were also able to find evidence of one of the test tracts that had initially been used during

**Table 4** Long-term effect studies on the postmortem analysis of DBS in Parkinson's disease

	Report type ( <i>n</i> )	Disease pathology	Target	Duration of stimulation	Pathology findings	Significance
Haberler et al. 2000	Case series (8)	PD	VIM(6, BI 3), STN(2, BI 1)	2d–70m	Characteristic 3 layer response to chronic stimulation 1: Thin (25 micron) layer of fibrosis 2: Fibrillary gliosis (500 microns) 3: Reactive astocytosis (1mm)	Describes a normal pathology change in response to chronic DBS
Nielsen et al. 2007	Case report (1)	PD	BI STN	29m	Characteristic response to chronic stimulation, similar to Haberler et al.	Confirms the normal response of DBS
Sun et al. 2008	Case report (1)	PD	BI STN	71m	Characteristic response to chronic stimulation similar to Harberler et al. with associated Rosenthal fibers	Includes the presence of Rosenthal fibers to the normal response of DBS
Vedam-Mai et al. 2011	Case series (19)	PD, ET (1), MSA (1), Unknwn (1)	STN(12), GPi (6), VIM (2) <sup>a</sup>	1m–102m	Characteristic response to chronic stimulation similar to Haberler et al. with notable exception of pathologic capsule formation	Documentation of one abnormal response to DBS and 18 normal responses.
Vedam-Mai et al. 2014	Case series (12)	PD	STN(8, 7BI), GPI(3, 2BI), VIM (1)	6m–156m	Increase neural progenitor cells in several regions of the brain in PD patients with DBS	Suggests a possible neuroprotective effect that DBS might have on PD patients
Pienaar et al. 2015	Case control (5 DBS, 5 control)	PD	STN	>12m	Microvasculature change including decrease in capillary number and endothelial cell thickness in PD patients that is rescued by DBS	Suggests a method by which DBS works through microvascular changes
Pal et al. 2017	Case control (11 DBS, 156 control)	PD	BI STN	52m (average)	Increase in alpha synuclein in the STN in PD patients with DBS	Suggests a possible toxic effect that DBS might have on PD patients

Parkinson's disease (*PD*), multiple system atrophy (*MSA*), essential tremor (*ET*), bilateral (*BI*), subthalamic nucleus (*STN*), ventral intermediate thalamus (*VIM*), globus pallidus internus (*GPI*), months (*m*), days (*d*)

<sup>a</sup> Two patients had more than one target utilized

the surgery on the left side. This tract also showed evidence of gliosis, although it lacked the thick capsule formation or Rosenthal fibers. A larger case series published in 2011 on over 19 postmortem brains also largely confirmed these findings with all but one of their brains showing the previously described layers

of fibrous and gliosis (Vedam-Mai et al. 2011). The abnormal brain had an unusually large fibrous capsule as described above (Vedam-Mai et al. 2012).

In 2015, a more detailed case series extended these results by evaluating the axonal changes with immunohistochemistry and

analyzing differences in the histopathological findings based on the etiology of death in 10 patients with either Parkinson's disease or essential tremor (Kronenbuerger et al. 2015). In addition to previously reported findings of gliosis around the electrode leads, they also reported on the presence of T-lymphocytes in over 90% of patients and multinucleated giant cells in approximately 70% of patients. In addition, they found an increase in axonal swellings that were immune-reactive to amyloid precursor protein at electrically active parts of the electrode. Finally, they showed that the cause of death was also a differentiating factor in the histopathological findings, with patients dying of septicemia showing more of a gliotic reaction around the electrodes than those dying from cardiac events.

More recent studies have increased our understanding of how the DBS might demonstrate its effects by comparing the postmortem brains of Parkinson's patients with DBS to those who did not receive DBS (see Table 4). For example, an investigative report in 2015 compared the brains of 5 patients with STN DBS for Parkinson's disease to an approximately equal number of Parkinson patients without DBS and non-Parkinson controls (Pienaar et al. 2015). In this interesting analysis, they found that, when compared to normal control, Parkinson patients had a decreased number of capillaries in the STN and decreased endothelial cell thickness. However, in the brains of patients who had DBS, there was an increase in the number of capillaries and the endothelial cell thickness when compared to controls. There was also an increase in the length of the capillaries when compared to both controls and non-stimulated Parkinson patients. This finding suggested that an etiology behind some of the symptoms of Parkinson's disease might be a disruption of the microvascular integrity and that a possible method for the effect of DBS is through improving this integrity. They further investigated this hypothesis with immunohistochemistry, which showed that the STN of Parkinson patients had a decrease in proteins associated with tight junctions and the integrity of the blood–brain barrier. However, in the brains of patients with DBS, these protein levels were rescued even higher than control levels. Further analysis showed an overexpression of VEGF in DBS patients, lending further credence to the hypothesis that DBS may improve damaged microvascular integrity in Parkinson's disease (Lee and Pienaar 2014; Pienaar et al. 2015).

Interestingly, this same group also found that, compared to controls, Parkinson patients had an increase in the number of microglia within the STN. However, in stimulated patients, there was a reduction in this upregulation of microglia. This correlates with recent animal studies that have shown that, in lesioned animal models, the upregulation of activated microglia by the lesioning process is mitigated by stimulation (Vedam-Mai et al. 2016). This reduction in the number of activated microglia is in turn associated with an increase in the number of neural progenitor cells in the animal model and builds on prior studies that were able to isolate neural progenitor cells from the postmortem brain of Parkinson's patients as well as from discarded

deep brain stimulating electrodes (Wang et al. 2012). It also agrees with previous work involving a postmortem analysis of 12 Parkinson patients with prior DBS, in which the investigators were able to use immunohistochemistry to compare the number of neural progenitor cells to matched non-stimulated Parkinson controls and non-Parkinson controls (Vedam-Mai et al. 2014). They found that stimulation was associated with an increase in the number of cells expressing neural progenitor markers in several regions of the brain, including the subventricular zones of the lateral ventricles and third ventricle as well as the tissue surrounding the DBS electrodes. The extent of this increase was up to 6-fold in some regions. Taken together, these results build on what is turning out to be a complex relationship between microglia and neural progenitor cells. With prior studies showing that the upregulation of microglia in response to inflammation is associated with decreased neurogenesis (Monje et al. 2003; Mosher et al. 2012), the overarching picture is one in which DBS may be able to decrease the detrimental influence of activated microglia and perhaps promote the proliferation of neural progenitor cells in Parkinson's disease. This might not only explain the improvement in motor symptoms seen with stimulation but also suggest the interesting possibility that stimulation might be neuroprotective or neurorestorative.

In 2017, however, another study compared the postmortem brains of stimulated versus non-stimulated Parkinson patients who donated their brains to the Arizona Study of Aging and Neurodegenerative Disorders and Brain and Body Program (Pal et al. 2017). In that analysis of 167 patients, 11 of whom had bilateral DBS STN, while the rest did not have any stimulation, they found no significant differences in the level of pigmented neuron loss in the substantia nigra. Interestingly, they also found a statistically significant increase in the amount of alpha synuclein, a key marker for Parkinson's disease, in the substantia nigra of the DBS patients. This increase was also found in several other regions of the brain, although, outside the substantia nigra, only the locus ceruleus and olfactory bulb were statistically significant. The increased alpha synuclein would suggest that DBS may have a possible toxic effect; however, as the authors stress, this conclusion cannot be obtained from this study alone given the limited sample size and cross-sectional nature of the study.

## Discussion

The recent increase in the number of DBS patients has led to an increase in the number and quality of publications analyzing the brains of these patients postmortem, thereby adding to an existing body of literature that attempts to give us a better understanding of the methods by which DBS is working (Dostrovsky and Lozano 2002; Johnson et al. 2008; Hess et al. 2013).

Thus far, the postmortem literature, which has been largely dominated by studies with low levels of evidence such as case

reports, has focused on questions that can be at least partially addressed with small sample sizes, such as validating accurate placement of the electrodes using particular techniques and/or demonstrating that good clinical effect can be achieved with electrodes located near but not necessarily in the targeted region. Indeed, while the published postmortem literature to date has shown neurohistologically that both MER- and imaging only-based targeting methods can be accurate in reaching the desired nucleus, it also demonstrates that neither method guarantees accuracy or that accuracy is even required for a beneficial clinical response. In this regard, it does not resolve the current debate in the literature regarding the efficacy of MER. Larger studies would be needed to further address this question.

Similarly, the small sample size studies in the postmortem literature has also proven useful in identifying etiologies that have led to poor clinical results, which include perioperative complications such as migrated electrodes, abnormal histological responses to the electrodes including excessive fibrosis and the presence of alternative pathologies, such as multiple system atrophy. However, once again, the limited size of the studies limits the degree to which we can estimate how often these complications and alternative pathologies are present in DBS patients. More recent studies are utilizing larger sample sizes to pursue an understanding of the global effects of DBS by evaluating the brains of DBS patients and comparing them to non-stimulated controls. So far, these studies have helped to describe what is likely a normal response to chronic stimulation, which includes the development of a thin fibrous layer, surrounded by two progressively larger gliotic layers. They have also begun to identify methods by which DBS could be effective, including through rescuing pathological changes in microvasculature and promoting neuroprogenitor proliferation. This goal is further advanced by the establishment of tissue banks where large numbers of postmortem brains can be analyzed to assess for overall trends (Vedam-Mai et al. 2011; Beach et al. 2015). The future of these much-needed endeavors will undoubtedly shed more light on the mechanism behind one of the most powerful tools in the treatment of Parkinson's disease.

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