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TOPICAL REVIEW

Tissue response to deep brain stimulation electrodes: a review of animal and neurohistopathological studies

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Abstract

Objective. Deep brain stimulation (DBS) is a neuromodulation therapy widely used to treat various neurological and neuropsychiatric conditions, with thousands of patients undergoing the procedure every year. However, despite the immense improvement in quality of life that most patients experience after surgery, many questions still remain surrounding various elements of DBS, including how the brain tissue responds to DBS electrodes and how that interaction may affect the therapy. *Approach.* In this review, we build off a previous neurohistopathological review to encompass studies up to present date. *Main results.* We identified 33 cases with 63 electrodes from patients with various disease pathologies and DBS targets. We supplemented the findings with animal studies. *Significance.* These studies can provide evidence where neurohistopathological studies have not been performed. They can also offer predictions to guide future neurohistopathological studies. Better understanding of the tissue response to DBS electrodes can contribute to improved clinical outcomes.

1. Introduction

Deep brain stimulation (DBS) is an invasive neuromodulation therapy that utilizes implanted electrodes to deliver electrical stimulation to targeted structures to treat symptoms of various neurological and neuropsychiatric conditions. In particular, DBS has been a highly successful therapy for Parkinson's disease (PD) and other movement disorders, with over 12 000 new patients receiving the treatment each year [1]. FDA approval of levodopa medication for PDs in the 1970s proved to be extremely successful in treating many of the motor symptoms of PD [2], though it was subsequently revealed that long-term usage of levodopa is associated with a need for increasing doses as the cells in the Substantia Nigra die, leading to both reduced efficacy and increasing side-effects such as dyskinesias [3]. Tremor suppression using implantable DBS devices was demonstrated in the late 1970s [4], but the serendipitous discovery of suppression of Parkinsonian tremor with 100 Hz stimulation by Williams [5], coupled with the limitations associated with pharmacological treatments and parallel advancements in implantable devices for the brain, sparked a resurgence in the interest of DBS as a clinical therapy in the late 1980's [6]. An expanding number of clinical applications of DBS have since been approved by the FDA, namely essential tremor (1997), PD (2002), and epilepsy (2018) [7, 8] (figures 1(A) and (B)). Dystonia (2003) and obsessive-compulsive disorder (2009) have also been granted FDA approval under a Humanitarian Device Exemption [7].

Prior to the modern era of DBS, movement disorders were largely treated surgically using lesional techniques such as radiofrequency thalamotomy or chemical ablation [15]. The targets used for lesional therapies are the ones largely used now, including subthalamic nucleus (STN) and globus pallidus pars interna (GPi) in PD, GPi for dystonia, and motor thalamus (VIM) for Essential Tremor. Recent studies have demonstrated efficacy in PD patients with specific inclusion criteria, even when treated early in the disease [16, 17]. DBS has also been shown to be beneficial in Dystonia, both generalized and focal, although the results are less consistent than

in PD [18]. For non-FDA indications, whilst DBS was first used for psychiatric disorders in the 1970s and chronic pain thereafter, there has been a recent resurgence of interest in these applications [19–21]. Various brain structures, such as the subcallosal cingulate cortex, ventral capsule/ventral striatum, and nucleus accumbens, have been indicated as targets for treating psychiatric disorders [1]. Studies for targeting chronic pain currently focus on the periaqueductal/periventricular gray matter region and/or ventral posterior lateral/posterior medial thalamus [22]. However, many outcomes thus far are heterogeneous. Future optimization may be biomarker-based [23] or led by patient-specific targeting [24].

The 'classic' biomarker used in PD is the 'beta frequency' (13–30 Hz) that has been shown to correlate with the severity of the OFF-medication phase in many patients [25]. Other frequencies may also be important such as the correlation of gamma frequency (30–90 Hz) with dyskinesia [26]. 'Adaptive' stimulation using beta frequency has now been developed into routine treatment in DBS patients [27, 28]. Biomarkers for pain may include 'detecting' pain by recording local field potentials (LFPs) from the areas stimulated, first modeled in 2008, but more recently explored in the context of multi-targeting of nodes in the pain network in the brain and more intelligent programing based on LFP signatures [29]. Other biomarkers for DBS control may include external signals such as EMG for tremor [30, 31] or autonomic markers such as heart rate (HR) or HR variability [32, 33]. Other methods to perform 'precision targeting' take into account the patient's own white matter tracts (based on diffusion tractography), such as looking at connections from the GPi to thalamus and cortex in dystonia [34] or from sensory thalamus to cortex in pain [35].

As modern DBS emerged relatively recently, many key aspects of DBS remain under active inquiry. This includes the specific mechanisms involved with the therapeutic effects of electrical stimulation [36–38], reasons for neuropsychiatric side effects [39–41] (e.g. effects on impulsivity [42] and anhedonia [43]), optimization for non-PD/movement disorders [44, 45], and the brain-tissue response to the DBS electrodes [46]. With respect to the tissue response to DBS electrodes, available literature typically reports findings from post-mortem human brain samples, which are necessarily uncontrolled and limited in sample size. Here, we complement a review of available clinical studies with findings from controlled animal studies. We explore the evidence for neuroprotective and/or gliosis-suppressing effects of stimulation. A better understanding of the tissue response to electrodes may shed new light on the underlying mechanisms of therapy and side effects associated with DBS.

2. Animal studies

Animal studies provide a platform to enable controlled investigation of many aspects of DBS, including mechanisms of therapy, validation of potential targets of treatment for new applications, and optimization of device design and stimulation paradigms. Preclinical studies in the 1990s confirmed DBS targets for movement disorders, including the STN for PD [47–49]. Later studies dissected the mechanisms of DBS therapy using optogenetics in rodents [50, 51] and developed closed-loop strategies to optimize symptom management in non-human primate models of PD [52]. Exploration of alternative paradigms to the continuous high-frequency stimulation standard, e.g. variable and polyrthmic stimulation approaches, employ animal models to study therapeutic effects [53]. Expanding use of DBS in neuropsychiatric disorders likewise benefits from mechanistic studies that can be performed in animal subjects: optimization of stimulation paradigms and anatomical targeting, as well as exploration of underlying therapeutic mechanisms, have been performed in rodent studies for the use of DBS in obsessive-compulsive disorder and treatment-resistant depression [54–56]. Whereas clinical studies necessitate a more conservative approach, animal research can drive innovation in the development of new disease targets, stimulation paradigms, and device designs [57].

Histopathological analysis of the tissue response to DBS leads is used to assess the biocompatibility of the implanted electrodes, which can be performed in a controlled manner in animal subjects. However, many studies do not differentiate the impacts of stimulation relative to the tissue response to the electrode itself, which initiates insertional damage and a subsequent cellular response characterized by substantial neuronal loss, gliosis, inflammation, and changes to the structure and function of residual neurons [58–62]. An additional complication arises from the variation in electrode designs used in animal research, which are notably distinct from clinically used devices and employ vastly different form factors across studies and species [12–14] (figure 1(D)). Furthermore, animal studies in DBS often employ disease models, which likewise vary substantially, even for the same disease state (e.g. Parkinsonian disease models employ various neurotoxicant models and methods of initiating neuroinflammation and synucleinopathy) [63]. As such, assimilating findings across studies is challenging. Nonetheless, animal research has shed light on the glial and neuronal responses to DBS electrodes.

2.1. Glial response and relationship to stimulation

Gliosis is a hallmark of electrode implantation, particularly for devices with supracellular dimensions

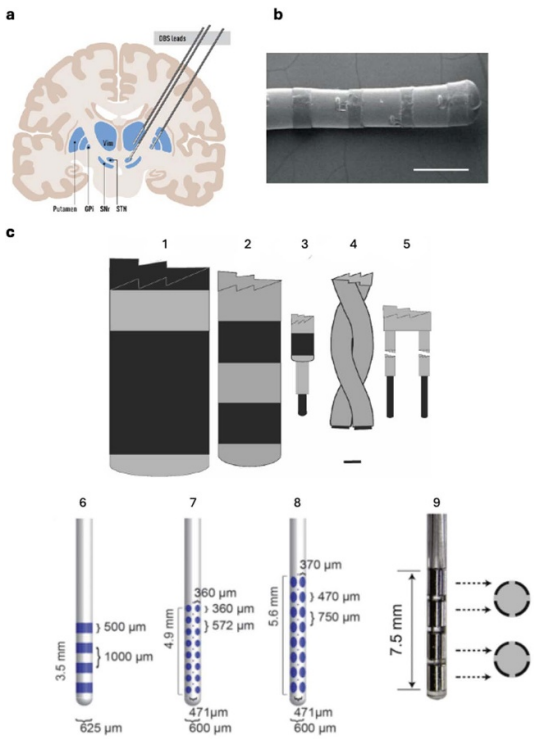

Figure 1. Deep brain stimulation (DBS) placement and lead configurations. (a) STN, GPi, and Vim are the most frequently targeted structures for DBS in movement disorders [9]. Reproduced with permission from [10]. © 2022 The Authors. Journal of Internal Medicine published by John Wiley & Sons Ltd on behalf of Association for Publication of The Journal of Internal Medicine. CC BY-NC-ND 4.0. (b) Scanning electron micrograph (SEM) of the Medtronic 3387 electrode, a 1–3–3–1 segmented lead. Reproduced with permission from [11]. © Guarantors of Brain 2004. (c) DBS leads vary vastly between (1, 6) human, (2, 7, 8) primates, (3–5) rodents, and (9) swine. Reproduced with permission from [12]. © 2009 Elsevier Ltd CC BY-NC-ND 4.0. © [2016] IEEE. Reprinted, with permission, from [13]. Reprinted from [14], Copyright (2021), with permission from Elsevier. Scale bars: (b) 2 mm; (c) 200 µm. *Open access sources, reprinted under a Creative Commons Attribution license.

constructed from rigid materials [64]. Microglia extend processes and display morphological characteristics of activation within the initial minutes and hours following device insertion [65]. An astrocytic response follows, with peak reactivity typically noted during the initial week following insertion and formation of an encapsulating sheath evident thereafter [66]. Understanding of the response of oligodendrocytes to brain implants is an emerging area of inquiry: Chen *et al* have observed damage to myelin and oligodendrocyte somata following electrode implantation [62], as well as a relationship with recording quality [67]. These results are aligned with recent work detailing transcriptomic changes indicative of glial reactivity, metabolic changes, and inflammation [68, 69].

Multiple groups have characterized gliosis surrounding implanted DBS electrodes in animal studies, most commonly using active devices. A study from Harnack *et al* [70] delivered three weeks of high-frequency stimulation through a microsimulation system in the STN of male Wistar rats. They identified reactive astrocytes, fibrillary gliosis, and an increase in small ellipsoid clusters which consisted of monocytes and histiocytes less than 20 μm away from the electrode tip. Griffith and Humphrey [71] implanted fine wire high-frequency stimulation electrodes in the motor cortex of the *Rhesus macaque* for 3 month and 3 year timepoints (figure 2). At both timepoints, they observed glial proliferation with an astrocytic scar near the electrode. However, the microglial reaction seen at the 3 month timepoint was no longer detectable at the 3 year timepoint. In 2017, Orlowski *et al* [72] conducted a longitudinal tissue study of DBS electrodes in the female Gottingen minipig. Microscopic observations found leukocytes, giant multinuclear cells, and a lead track that was surrounded by a capsule. They found a significant decrease in mean tissue reaction area at the 12 month timepoint ($n = 2 + 1$ control animal without DBS implantation) when compared to the 3 month ($n = 4$) and 6 month ($n = 5$) timepoints using Nissl and eosin staining. Glial fibrillary acidic protein (GFAP) staining showed a significant increase in astroglial tissue area at the 6 month timepoint when compared to the 3 month and 12 month timepoints, but no significant difference in the astroglial scar thickness across the three timepoints. Isolectin staining revealed a significant decrease in the microglial scar thickness at the 12 month timepoint when compared to the 3 month and 6 month timepoints. These observations are generally aligned with findings from non-stimulating electrodes, displaying glial activation as a component of the tissue response to implanted electrodes [68, 73].

Reported observations display conflicting results as to whether or not gliosis increases in stimulated tissue in comparison to non-stimulated controls [74]. In 2010, Rauch *et al* [75] employed a rat model of PD to study the pathophysiological mechanisms of DBS in the pedunculopontine nucleus (PPN). Eighty adult male Sprague–Dawley rats underwent unilateral lesioning in the substantia nigra; 43 rats were 6-ODHA-induced lesioned, and 37 rats were sham-lesioned. Three weeks later, bipolar electrodes were implanted into the pedunculopontine tegmental nucleus (PPTg) of all 80 rats, which is analogous to the human PPN. A recovery period of 1 week ensued before turning on continuous stimulation. Here, four groups were divided based on stimulation frequencies of 0 Hz (control) stimulation, 25 Hz stimulation, 25 Hz high stimulation (where the threshold for stimulation-induced behavioral side effects identified at 130 Hz was applied as the individual threshold for 25 Hz stimulation), and 130 Hz. Behavioral tests were carried out, and rats were perfused around 2 d after stimulation. Brain slices underwent Nissl and immunohistochemical staining. The authors noted that across all groups, continuous stimulation did not

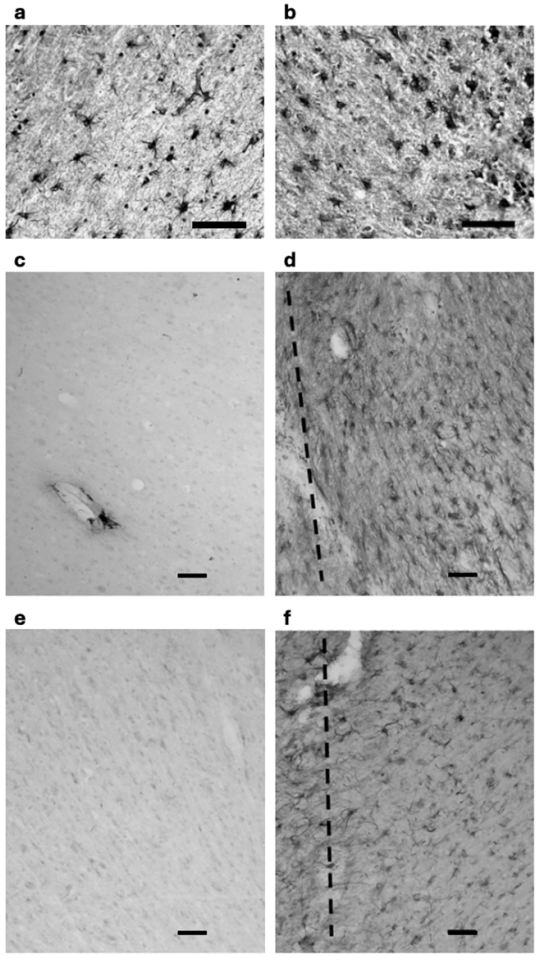

Figure 2. Reactive microglia (a)–(b) and astrocytes (c)–(f) along the electrode track following electrode implantation. (a) Microglia from control regions exhibit ramified microglia with multiple processes, typical of resting microglia. (b) Microglia immediately adjacent to the electrode track present with a highly rounded, amoeboid morphology and shorter, thicker processes, typical of reactive microglia. (c) & (e) Relatively low levels of GFAP staining for reactive astrocytes is present in unaffected areas of the cortex after 3 months (c) and 36 months (e) of electrode implantation. (d) & (f) GFAP staining reveals considerable hypertrophied reactive astrocytes in areas of the cortical tissue directly adjacent to the electrode after 3 months (d) and 36 months (f) of implantation. Reprinted from [71], Copyright (2006), with permission from Elsevier. Scale bars: 100 μm.

result in tissue damage beyond minor gliosis, though there was no quantification of the tissue response.

In contrast, a more recent report [76] from rats implanted with electrodes in the STN for a period of up to 8 weeks suggests that stimulation with clinically-relevant DBS parameters (130 Hz) for ∼6–7 h per day elicits an increase in GFAP expression in comparison to non-stimulated controls. Here, the data were assessed via quantitative immunohistochemistry, which revealed a statistically significant increase in astrogliosis in the interfacial tissue region (within ∼200 μms from the electrode surface). Microglia were relatively unaffected, with no statistically significant differences detected between stimulated, unstimulated (electrode-implanted), and control tissues. The histological findings were accompanied by observations of reduced impedance in stimulated animals, which was attributed to desorption of protein adhered to the electrode surface. Another recent study from Pinheiro Campos *et al* [77] compared striatal saline-injected rats (control), striatal 6-OHDA rats (PD model control), striatal 6-OHDA+sham STN DBS rats, and striatal 6-OHDA+STN DBS rats which were stimulated for 2 h for 5 d in a row. They identified that both rats with STN DBS and STN microlesions had a decrease in striatal cytokine expression and relative extracellular glutamate concentration. However, only rats in the STN DBS group had reduced inflammation, modulated astrocytes which were in an alternative and more neuroprotective state, and an increase in EAAT2 (a protein which helps to remove excess glutamate) in the striatum.

The tissue response also has been assessed in non-human primates. Cao *et al* [78] utilized a hemiparkinsonian model in the monkey model. Four adult male rhesus monkeys underwent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) infusion, which produced symptoms of rigidity and tremor. Following a 3 week stabilization period, the monkeys were implanted with clinical DBS devices. Two monkeys were implanted with the entire human DBS system consisting of a lead, extension wire, and implantable pulse generator, while the other two control monkeys were implanted with one lead in the right STN. Following 12 months of stimulation and behavioral assessments, the monkeys were anesthetized and brain tissue was collected. The authors identified cell necrosis and lymphocytic infiltration around the lead, and mild gliosis in the STN around the lead contact. They concluded that minor deviations in lead placement and continuous low-voltage stimulation did not result in observable changes in tissue damage. However, no direct comparison to non-stimulated tissue was made.

2.2. Neural response and relationship to stimulation

Similarly to the glial response, the neuronal response to DBS leads is dominated by the response to the electrode implantation and the nature of the foreign materials used. Non-DBS stimulation studies suggest a potential relationship between stimulation parameters and neuronal loss. McCreery *et al* [79] implanted activated iridium microelectrodes into the sensorimotor cortex of domestic cats and stimulated for 8 h per day for 30 d at 50 Hz. They found that continuous stimulation at 2 nC/phase and a geometric charge density of 100 μC cm^{-2} did not have an effect on the surrounding neuronal density. In contrast, continuous stimulation at 4 nC/phase and a geometric charge density of 200 μC cm^{-2} resulted in

cortical neuronal loss of over 150 μm in radius from the electrode tip. Similarly, 1 s on/1 s off stimulation at 4 nC/phase and a geometric charge density of 200 μC cm^{-2} also resulted in neuronal loss, but at a smaller diameter of around 60 μm from the electrode tip. Most of the neuronal loss observed with the 50% duty cycle stimulation was attributed to the mechanical injury of insertion and the long-term inhabitation of the device in the tissue.

For DBS, Harnack *et al* [80] studied the effects of stimulation duration and electrode material on the tissue response to high-frequency stimulation in the STN of male Wistar rats. They observed that stainless-steel (SS) electrodes at the 4 h timepoint caused significant tissue damage, neuronal cell death, and iron deposits when the charge density reached 3 μC cm^{-2}/phase. In comparison, platinum–iridium electrodes at the 4 h timepoint did not produce any significant neuronal damage beyond the damage of the electrode implantation, regardless of charge density within the tested range of 0–26 μC cm^{-2}/phase. Furthermore, platinum–iridium electrodes at the 3 d timepoint also did not produce any significant neuronal damage beyond the damage resulting from electrode implantation. Griffith and Humphrey's [71] study using rhesus macaques, which utilized platinum electrodes, also found no neuronal loss near the electrode. Supporting studies have recommended platinum–iridium due to its electrical, mechanical, and chemical properties, biocompatibility [81], performance in pulse tests, and better capacitive properties [82] over stainless steel, which has been shown to be more corrosive, leading to metal deposition in the brain [81]. Notably, most of the current commercial DBS electrodes designed for clinical use are made of platinum–iridium electrodes [83].

Interestingly, multiple studies suggest that DBS delivery can preserve neurons in animal models of degenerative disease states, implying a neuroprotective effect. A study from Wallace *et al* [84] studied how alteration (either kainic acid injections, a traditional method for STN ablation, or DBS) of the STN in MPTP-treated monkeys affected the survival of dopaminergic cells. They divided 28 adult male macaque monkeys into four groups: (1) no STN alteration ($n = 3$) where 1 monkey received no MPTP treatment and the other two did; (2) kainic acid injections ($n = 10$) where 5 monkeys underwent STN lesions prior to MPTP treatment, and the other 5 monkeys underwent MPTP treatment prior to STN lesions; (3) DBS ($n = 10$) where 5 monkeys underwent STN DBS prior to MPTP treatment, and the other 5 monkeys underwent MPTP treatment prior to STN DBS; and (4) 7 months of continuous DBS stimulation ($n = 5$) without MPTP treatment. They found a significantly higher number (20%–24%) of dopaminergic cells in the STN in the MPTP treated monkeys with both STN lesion and DBS, when compared to control monkeys. The authors suggest the possibility that DBS is neuroprotective to dopaminergic cells.

Similar effects have been observed in non-Parkinsonian disease models. A 2019 study conducted by Leplus *et al* [85] aimed to identify the effects of chronic DBS of the fornix in a transgenic rat model of Alzheimer's disease (TgF344-AD). The TgF344-AD rats were evaluated at the 18 month timepoint, and observations included elevated microglia and astrocytes, as well as neuronal loss. After 5 weeks, rats that received stimulation showed a significant decrease in cells positive for microglial (Iba1) and astrocytic (GFAP) markers in both the cortex and hippocampus, when compared to TgF344-AD rats without stimulation. Similarly, they observed a significant increase in neuronal count in the dentate gyrus and cortex in the TgF344-AD group, but no difference in neuronal count in the CA1 region between groups. These results seem to signify that DBS may offer a neuroprotective effect in Alzheimer's disease. They observed significant differences between wild-type and TgF344-AD rats in all conditions besides neuronal loss in the CA1 region but did not identify any significant difference between sham and DBS groups in the wild-type rats in any condition. Similarly, Chen *et al* [86] studied the effects of DBS of the anterior thalamic nuclei on the effects of neurogenesis in epileptic and healthy rats. Sprague Dawley rats were injected with normal saline or kainic acid to induce seizures 1 month before electrode implantation. They found a significant increase in NeuN (a marker for neuronal nuclei) expression in the epileptic rats that received DBS when compared to sham epilepsy rats. Again, this implies a potential neuroprotective effect of stimulation in a disease model (figures 3(A)–(D)).

Multiple studies have investigated the potential mechanisms underlying neuroprotective and gliosis-suppressant effects associated with DBS. For example, increases in striatal brain derived neurotrophic factor (BDNF) have been noted following STN DBS in Parkinsonian animal models [88, 89]. High frequency stimulation likely induces BDNF release in local neurons, which can initiate protection of dopaminergic neurons via canonical BDNF-tropomyosin receptor kinase B survival signaling [90]. Additionally, hypotheses related to stimulation-induced effects on neurogenesis have been explored. A study using male Sprague–Dawley rats [91] compared the neural progenitor cell and microglial response to DBS between four groups after two weeks: stimulation, sham, microlesion, and stimulation + bromodeoxyuridine (BrdU). They identified activated microglia in all groups; however, the density of activated microglia was significantly greater in the sham and microlesion groups when compared to the stimulation groups. They also observed an increase in progenitor proliferation, which was supported by increased BrdU-positive cells near the stimulation site. The authors

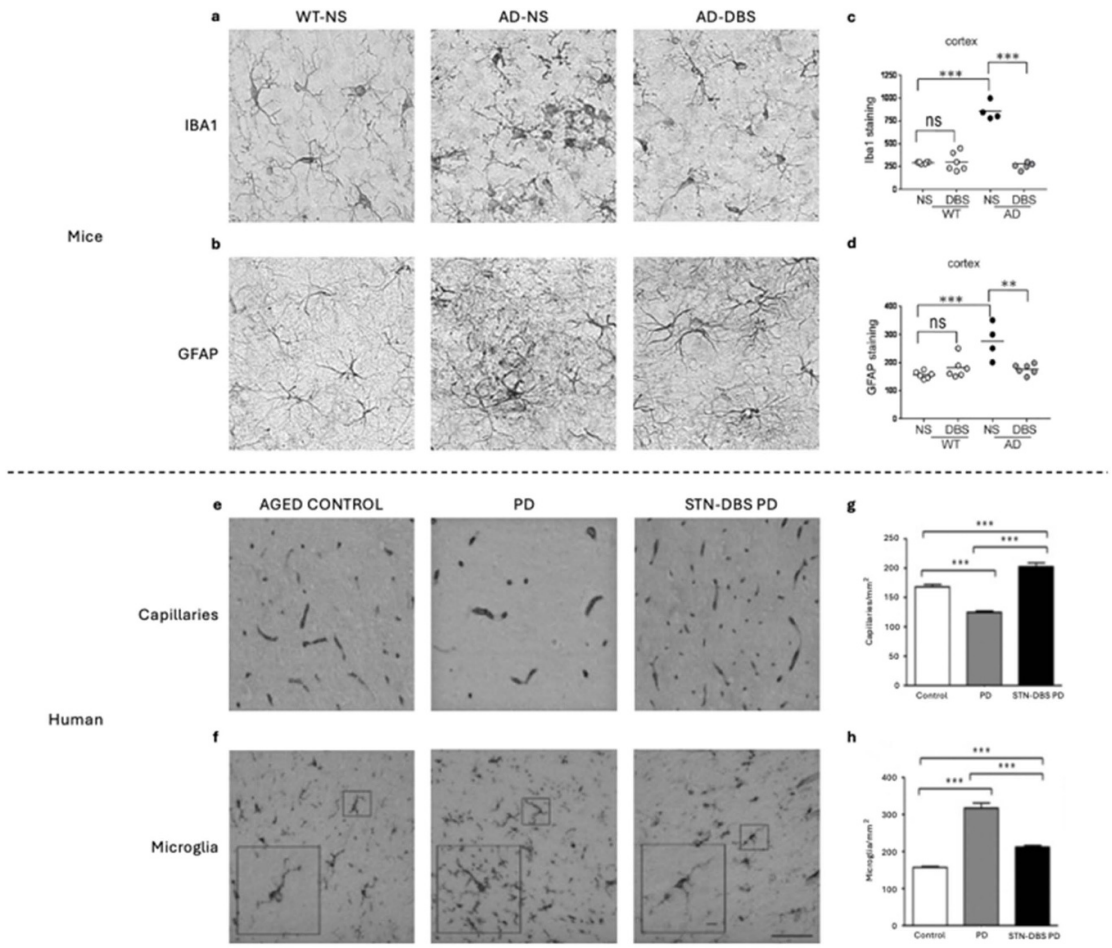

Figure 3. Stimulation may offer gliosis-suppressant abilities. (a)–(b) IBA1 (a) and GFAP (b) staining from wild-type non-stimulated (WT-NS), transgenic Alzheimer non-stimulated (AD-NS), and transgenic Alzheimer stimulated (AD-DBS) mice. (c)–(d) Quantification of IBA1 (c) and GFAP (d) staining in the cortex show a significant reduction in AD-DBS rats in comparison to AD-NS rats. Reproduced from [85], with permission from Springer Nature. (e)–(f) Capillaries (e) and microglia (f) images from aged control, Parkinson's disease (PD), and subthalamic nucleus stimulated Parkinson's disease (STN-DBS PD) patients. (g)–(h) Quantification of number of capillaries (g) and microglia (h) significant differences across all groups of subjects. Reprinted from [87], Copyright (2015), with permission from Elsevier. Scale bar: (e) 100 μm; (f) 50 μm, 10 μm for inset.

concluded that animals in the stimulation groups showed a significantly lower number of activated microglia when compared to animals in both the sham and microlesion groups.

3. Neurohistopathological studies

Neurohistopathological post-mortem studies have historically been restricted due to the limited number of participant samples. DiLorenzo *et al* [92] conducted a systematic review in 2014 that included 40 cases with 50 electrodes, and found that the most common tissue responses were fibrillary gliosis, presence of reactive astrocytes or mononuclear leukocytes, microglial activation, neuronal loss, and macrophages, in over 60% of the cases (figure 4). Here, we build on their prior review, and report on a series of case studies both before and since 2014.

We identified 33 cases with 63 electrodes (note that there is no patient specific neurohistopathological data for patients #8–17; electrodes #13–30), which we have detailed comprehensively in table 1 and supplementary table 1. Patients' age at DBS surgery ranged between 8 (one pediatrics case) to 80 years, and had an average of 71.03 months (range, 2–192 months) of stimulation (excluding patient #10 who died 1 d after surgery). 25 patients had a diagnosis of PD, 3 with tremor, 2 with multiple system atrophy (MSA) (clinical diagnosis of PD then revised to be MSA following post-mortem exam), 1 with Parkinsonism, 1 with dystonia, and 1 with Huntington's disease (HD). The most common target was the STN (24 cases, 48 electrodes), a basal ganglia structure widely targeted for DBS in PD patients [100] for the past four decades [101], as it is favorable for the fast reduction of PD dopamine medication usage [102]. This is followed by the ventral intermediate nucleus (Vim) (6 cases, 7 electrodes), a structure used to treat Essential Tremor and PD tremor [103], and the

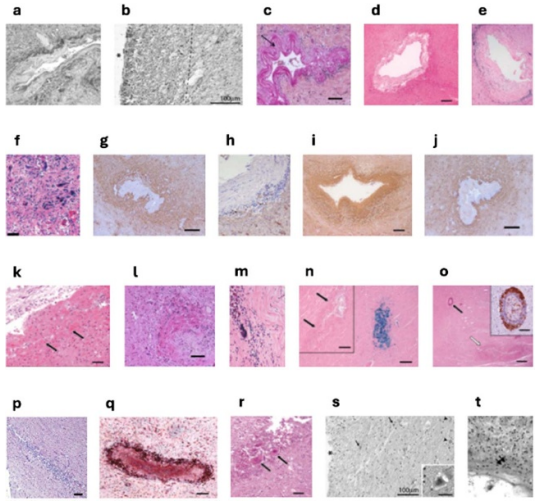

Figure 4. Examples of tissue response around DBS leads in patients. (a)–(b) Reactive astrocytosis. (c) Collagen lining. (d) Fibrohyaline sheath. (e) Fibrosis. (f) Giant cell reaction. (g)–(k) Gliosis. (l)–(m) Hemosiderin deposition. (n) Iron deposition. (o) Lymphocyte infiltration. (p) Meningothelial cells. (q) Microglial activation. (r) Multinucleated giant cells. (s) Change in neuronal morphology. (t) Rosenthal fibers. (a) Patient 5. Reproduced with permission from [93]. An Open Access or Creative Commons publishing model conveys no rights to use this material in any format without written permission from the JNS Publishing Group. (b) Patient 3. [94] John Wiley & Sons. Copyright © 2004 Movement Disorder Society. Scale bar: 100 μm. (c) Patient 7. Reproduced from [95], with permission from Springer Nature. Scale bar: 100 μm. (d) Patient 8. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 170 μm. (e) Patient 6. [97] John Wiley & Sons. Copyright © 2012 Movement Disorder Society. (f) Patient 1. Reproduced with permission from [98]. An Open Access or Creative Commons publishing model conveys no rights to use this material in any format without written permission from the JNS Publishing Group. Scale bar: 60 μm. (g) Patient 7 (Reproduced from [95], with permission from Springer Nature); Scale bar: 260 μm. (h) Patient 6. [97] John Wiley & Sons. Copyright © 2012 Movement Disorder Society. (i) Patient 11. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 170 μm. (j) Patient 7. Reproduced from [95], with permission from Springer Nature. Scale bar: 260 μm. (k) Patient 8. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 50 μm. (l) Patient 7. Reproduced from [95], with permission from Springer Nature. Scale bar: 100 μm. (m) Patient 6. [97] John Wiley & Sons. Copyright © 2012 Movement Disorder Society. (n) Patient 11. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 150 μm, 200 μm for inset. (o) Patient 8. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 340 μm, 60 μm for inset. (p) Patient 20 (Reproduced from [99], with permission from Springer Nature); Scale bar: 100 μm. (q) Patient 16. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 130 μm. (r) Patient 9. [96] John Wiley & Sons. © 2015 International Parkinson and Movement Disorder Society. Scale bar: 90 μm. (s) Patient 3. [94] John Wiley & Sons. Copyright © 2004 Movement Disorder Society. Scale bar: 100 μm. (t) Patient 5. Reproduced with permission from [93]. An Open Access or Creative Commons publishing model conveys no rights to use this material in any format without written permission from the JNS Publishing Group. *Open access sources, reprinted under a Creative Commons Attribution license.

GPi (4 cases, 8 electrodes), an alternative structure in the basal ganglia used for both PD and dystonia [104], and as an exploratory target for HD [105] (figures 1(A) and (B)). All reported electrodes were Medtronic 3387, 3389, 5535 which all have a surface material of platinum/iridium (figure 1(C)). DiLorenzo *et al* [92] noted that electrode material had an influence on the grade of focal tissue injury, with differences observed between platinum/iridium (Pt/Ir), platinum (Pt) only, and SS electrodes. They found Pt/Ir electrodes to be associated with lower grades of tissue damage when compared to Pt and SS electrodes; 73% of Pt/Ir, 28% of Pt, and 0% (out of one case) of SS electrodes showed no tissue damage [106].

3.1. Neuropathological findings

Gliosis was the most commonly reported neurohistopathological change, as identified in 38 of the 41 electrodes where reported. All seven electrodes that examined reactive astrocytes confirmed their presence. However, the limited sample size introduces uncertainties regarding the applicability of these findings to a larger population. Similarly, activated microglia were found in 17 of the 32 electrodes for which this finding was specifically reported. Interestingly, regarding neuronal loss at the DBS site, five electrodes reported no loss, while only three indicated a loss. Other less commonly reported histopathological changes reported include collagen-lining of electrode track, fibrosis, hemosiderin deposition, iron deposits, lymphocytes, macrophages, multinucleated giant cells, Rosenthal fibers, and spheroids. Examples of these findings can be found in figure 4. Each image corresponds to a patient number from table 1 and supplementary table 1.

3.2. Ongoing questions surrounding the tissue response to DBS electrodes

While most studies involving patients with bilateral electrodes either report no differences in neuropathological findings between the left and right sides (i.e. [108]) or do not specify any differences, a few studies do mention lateralization of the neuropathology. Vedam-Mai *et al* [97] found notable differences in the tissue response between the left and right lead, and Vedam-Mai *et al* [113] observed visible asymmetries in the gliotic response associated with the DBS lead defect in some of their cases. Additionally, while Gelpi *et al* [111] found that patients generally exhibited similar histopathological responses on both sides, they did note specific differences, such as the presence of a fibrotic capsule on one side and its absence on the other. Details of these differences are listed in table 1 and supplementary table 1. However, this effect may instead be attributed to

Table 1. Patient demographic and neurohistopathological data around DBS leads in patients. General: NR = not reported. Target: L = left; R = right; STN = subthalamic nucleus; Vim = ventralis intermediate nucleus; GPi = globus pallidus pars interna. Neurohistopathological findings: if reported with severity: 0 = none; 1 = minimal/few/mild/increased; 2 = moderate/some; 3 = substantial/many/numerous. If reported without severity: Y = yes; N = no.

Patient #	Target	Duration of stimulation (months)	Gliosis	Reactive astrocytes	Activated microglia	Neuronal loss	Other tissue response	Citation
1	L STN	3	3	NR	NR	NR	• Hemosiderin deposition associated with the track • Numerous multinucleated giant cells, neovascularization, and numerous glial cytoplasmic inclusions surrounding the track • Inflammatory infiltrate mainly composed of CD68-positive macrophages and B and T lymphocytes • Occasional spheroids in surrounding brain parenchyma	[98]
	R STN	3	3	NR	NR	NR	• Hemosiderin deposition associated with the track • Numerous multinucleated giant cells, neovascularization, and numerous glial cytoplasmic inclusions surrounding the track • Inflammatory infiltrate mainly composed of CD68-positive macrophages and B and T lymphocytes • Occasional spheroids in surrounding brain parenchyma	[98]
2	R Vim	12	0	NR	NR	NR	'Brownish-tan rim of tissue' surrounding the track	[107]
3	L Vim	88	NR	Y	0	3	• Hemosiderin deposition along the track • Myelin pallor within 0.5 mm of the tip	[94]

(Continued.)

Table 1. (Continued.)

4	L STN	29	3	3	NR	0	• Lumen of the track lined with thin layer of collagen • Capsule wall constituted of an area with few cells and axons • Lymphocytes, macrophages, neutrophilic granulocytes, and occasional neurons were found in the capsule • No iron deposits	[108]
	R STN	29	3	3	NR	0	• Lumen of the track lined with thin layer of collagen • Capsule wall constituted of an area with few cells and axons • Lymphocytes, macrophages, neutrophilic granulocytes, and occasional neurons were found in the capsule • No iron deposits	[108]
5	L STN	71	1	NR	Y	NR	• Focal foreign-body giant cell reaction, hemosiderin-laden macrophages, scattered lymphocytes, reactive changes of piloid gliosis, and Rosenthal fibers found within the capsule surrounding the lead	[93]
	R STN	71	1	NR	Y	NR	• Focal foreign-body giant cell reaction, hemosiderin-laden macrophages, scattered lymphocytes, reactive changes of piloid gliosis, and Rosenthal fibers found within the capsule surrounding the lead	[93]

(Continued.)

Table 1. (Continued.)

Patient #	Target	Duration of stimulation (months)	Gliosis	Reactive astrocytes	Activated microglia	Neuronal loss	Other tissue response	Citation
6	L STN	13	1	NR	NR	NR	• No acute necrosis, inflammation, hemorrhage, or fibrotic reaction associated with the track	[97]
	R STN	11	1	NR	NR	0	• No acute necrosis, inflammation, hemorrhage, or fibrotic reaction associated with the track • Marked fibrosis around the cavity formed by the lead tip • Fibrocollagenous 'capsule' surrounded by focal hemosiderin deposition and associated with onspecific inflammatory infiltrate composed of mature lymphocytes	[97]
7	L STN	72	Y	NR	Y	NR	• Lymphocytes and macrophages (including a few multinucleate giant cells) surrounding the track • Track fully lined by collagen with adjacent Perl's positive iron-containing pigment	[95]
	R STN	72	Y	NR	Y	NR	• Lymphocytes and macrophages (including a few multinucleate giant cells) surrounding the track • Track fully lined by collagen with adjacent Perl's positive iron-containing pigment	[95]
8	L STN	24	NR	NR	NR	NR	NR	[96]
	R STN	24	NR	NR	NR	NR	NR	[96]
9	L STN	8	NR	NR	NR	NR	NR	[96]
	R STN	8	NR	NR	NR	NR	NR	[96]
10	L STN	* patient died 1 d after surgery	NR	NR	NR	NR	NR	[96]
	R STN	* patient died 1 d after surgery	NR	NR	NR	NR	NR	[96]

(Continued.)

Table 1. (Continued.)

11	L STN	61	NR	NR	NR	NR	NR	[96]
	R STN	61	NR	NR	NR	NR	NR	[96]
12	L Vim	77	NR	NR	NR	NR	NR	[96]
13	L STN	43	NR	NR	NR	NR	NR	[96]
	R STN	43	NR	NR	NR	NR	NR	[96]
14	L GPi	7	NR	NR	NR	NR	NR	[96]
	R GPi	7	NR	NR	NR	NR	NR	[96]
15	L Vim	15	NR	NR	NR	NR	NR	[96]
	R Vim	15	NR	NR	NR	NR	NR	[96]
16	L STN	32	NR	NR	NR	NR	NR	[96]
	R STN	32	NR	NR	NR	NR	NR	[96]
17	R Vim	90	NR	NR	NR	NR	NR	[96]
18	L GPi	48	NR	NR	NR	NR	NR	[109]
	R GPi	48	Y	NR	NR	NR	• Focal hemosiderin deposition at distal tip • A 'rim' of meningothelial/arachnoidal cells surrounding the lead tip defect • Gliosis and hemosiderin deposition along the track	[109]

(Continued.)

Table 1. (Continued.)

Patient #	Target	Duration of stimulation (months)	Gliosis	Reactive astrocytes	Activated microglia	Neuronal loss	Other tissue response	Citation
19	L STN	144	Y	1	NR	0	• Thin (<25 μm) fibrous sheath bordering the track • No demyelination • A small number of activated macrophages • Limited perivascular lymphocytic infiltrate near the electrode (<2 mm)	[110]
	R STN	144	Y	1	NR	0	• Thin (<25 μm) fibrous sheath bordering the track • No demyelination • A small number of activated macrophages • Limited perivascular lymphocytic infiltrate near the electrode (<2 mm) • A single foreign body inclusion located 2.3 mm from the center of the track	[110]
20	L GPi	2	1	1	Y	1	• Lymphocytes and macrophages (including multinucleate giant cells) surrounding the track • Activated macrophages and increased T cell lymphocyte activity	[99]
	R GPi	2	1	1	Y	1	• Lymphocytes and macrophages (including multinucleate giant cells) surrounding the track • Activated macrophages and increased T cell lymphocyte activity	[99]
21	L STN	192	1	NR	Y	NR	• Fibrotic capsule, myelin pallor, axonal swellings, and old pigment associated with the track • Moderate fibrotic capsule, mild surrounding, and occasional perivascular pigment associated with the tip	[111]
	R STN	192	1	NR	Y	NR	• Fibrotic capsule and myelin pallor associated with the track • Small capsule of connective tissue and occasional hemosiderin pigment associated with the tip	[111]

(Continued.)

Table 1. (Continued.)

22	L STN	96	1	NR	Y	NR	• Fibrotic capsule and myelin pallor associated with the track • Small fragments of STN associated with the tip	[111]
	R STN	96	2	NR	2	NR	• Fibrotic capsule, myelin pallor, and Rosenthal fibers associated with the track • Elongated lesion and no fibrotic capsule associated with the tip	[111]
23	L STN	180	1	NR	Y	NR	• No capsule associated with the track • Changes associated with the lateral aspects of the tip	[111]
	R STN	180	1	NR	Y	NR	• Mild fibrotic capsule associated with the track • Prominent fibrotic capsule, Rosenthal fibers, and multinucleated giant cells associated with the tip	[111]
24	L STN	138	1	NR	Y	NR	• Myelin pallor in adjacent cortex glial scar and fibrotic capsule associated with the track • Fibrotic capsule, myelin pallor, and Rosenthal fibers associated with the tip	[111]
	R STN	138	1	NR	Y	NR	• No capsule associated with the track • Mild to moderate fibrotic capsule and some Rosenthal fibers associated with the tip	[111]
25	L STN	24	3	NR	N	NR	N	[112]
	R STN	24	3	NR	N	NR	N	[112]
26	L STN	140	1	NR	N	NR	N	[112]
	R STN	140	1	NR	N	NR	N	[112]

(Continued.)

Table 1. (Continued.)

Patient #	Target	Duration of stimulation (months)	Gliosis	Reactive astrocytes	Activated microglia	Neuronal loss	Other tissue response	Citation
27	L STN	126	1	NR	Y	NR	N	[112]
	R STN	126	1	NR	Y	NR	N	[112]
	L VIM	126	1	NR	Y	NR	N	[112]
28	L STN	65	2	NR	N	NR	N	[112]
	R STN	65	2	NR	N	NR	N	[112]
29	L STN	262	2	NR	N	NR	N	[112]
	R STN	262	2	NR	N	NR	N	[112]
30	L GPi	94	3	NR	N	NR	• Remote hemorrhage in the internal capsule	[112]
	R GPi	94	3	NR	N	NR	• Remote hemorrhage in the internal capsule	[112]
31	L STN	7	0	NR	N	NR	• Intraparenchymal hemorrhages in the basal ganglia, thalamus, corpus callosum, pons, and midbrain	[112]
	R STN	7	0	NR	N	NR	• Intraparenchymal hemorrhages in the basal ganglia, thalamus, corpus callosum, pons, and midbrain	[112]
32	L STN	13	NR	NR	N	NR	• Multifocal subacute infarcts in the middle frontal gyrus and cerebellum with foamy macrophages and gliosis	[112]
	R STN	13	NR	NR	N	NR	• Multifocal subacute infarcts in the middle frontal gyrus and cerebellum with foamy macrophages and gliosis	[112]
33	L STN	62	2	NR	N	NR	N	[112]
	R STN	62	2	NR	N	NR	N	[112]

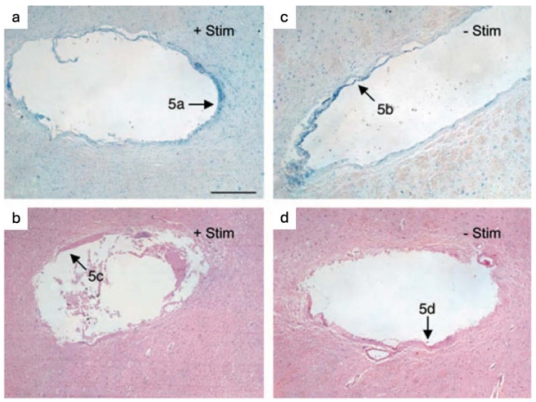

Figure 5. Evidence of a lack of neurohistopathological changes between areas that were and were not stimulated. (a)–(b) Toluidine blue (a) and hematoxylin and eosin (b) stained tissue from the subthalamic nucleus, the area that was electrically stimulated. (c)–(d) Toluidine blue (c) and hematoxylin and eosin (d) stained tissue from the thalamus, an area that was not electrically stimulated. [108] John Wiley & Sons. Scale bar: 0.5 mm.

the electrode insertion or complications with the lead itself, instead of inherent differences in the tissue on either side. Multiple studies have noted the effects of electrodes in areas with stimulation (active contact) versus non-stimulation (non-active contact) on the tissue response, and concluded no significant difference between stimulated and non-stimulated brain tissue adjacent to the electrode [93, 97, 108] (figure 5).

Due to the limited number of post-mortem DBS studies, numerous questions surround the safety of DBS for pediatric patients. In 2020, Giordano *et al* [99] presented the first post-mortem pediatric case of bilateral GPi DBS. They found no significant tissue changes following stimulation, suggesting that pediatric and adult histopathological findings following DBS stimulation may be comparable. Furthermore, they suggest that no substantial damage is caused by DBS electrode stimulation.

Similarly, the limited sample size and the difficulty in providing controls contribute to unanswered questions regarding the impact of stimulation duration on the severity of damage to the tissue around the DBS electrodes. Of the current studies that involve multiple cases with different simulation durations, some authors suggest that there is no difference between neurohistopathology based on duration (up to 70 months of simulation; [114]), and that differences are instead attributed to other case-by-case bases (average of 87 $\pm$ 76 months of stimulation; [113]). However, Gelpi *et al* [111] found that patients with chronic stimulation (between 96 and 192 months of stimulation), may experience moderate degeneration of the tissue adjacent to the electrode in comparison to shorter durations of DBS. They proposed several potential factors contributing to these findings, including chronic depolarization block, alterations in synaptic conduction, and long-term adjacency to a foreign body.

Additionally, as a result of the lack of controlled studies comparing multiple cases, there are uncertainties surrounding how disease diagnosis and the targeted structure affects the neurohistopathology. However, one study [96] reported that no difference was observed in the tissue adjacent to the DBS electrodes amongst eight PD and ET patients with targets in the STN, GPi, and Vim, despite the vast differences between the two diseases and amongst the three different targeted structures.

Although limited, neurohistopathological studies have also investigated how DBS may alter the long-term progression of disease, specifically the prospect that DBS could provide neuroprotective and gliosis-suppressing effects. Many studies highlight this potential, citing positive effects on synaptic function and neurogenesis [111]. Pienaar *et al* [87] quantified capillaries and microglia from PD, STN-DBS treated PD, and aged control patients. They found a significant difference between all groups, including between STN-DBS PD patients and PD patients that did not receive DBS (figures 3(E)–(H)). However, current conclusions are still varied, as Mazumder *et al*'s [115] results did not find that DBS offered any significant difference in dopaminergic cell loss, alpha-synuclein pathology, or astrogliosis in the substantia nigra or the STN. Future post-mortem case and cohort studies will provide more evidence to clarify these questions.

4. Conclusions and future directions

Animal and clinical studies provide different lenses on the topic of the tissue response to DBS electrodes. Previous animal studies revealed electrode material as a major determinant of the severity of the tissue response. Newer animal studies have alluded to the potential that stimulation may hold in offering a neuroprotective effect to the tissue. Interestingly, many reports suggest that there does not seem to be a difference in the tissue response to areas that received and did not receive stimulation around the electrode tract, nor were there reported differences in the tissue response based on disease duration or diagnosis in the clinical data. Furthermore, based on the one pediatric study available, pediatric and adult histopathological findings following DBS stimulation may be comparable. However, more data is needed. Questions remain about the nature of tissue encapsulation in the clinical setting, and how it influences the effects of stimulation. The variability and scarcity of human tissue samples following DBS is an impediment to direct assessment of impacts of the tissue response on stimulation efficacy in the clinical setting.

Computational modeling is one avenue to shed light on the practical implications of the tissue

response to DBS electrodes. Important work has been done to understand the influence of tissue encapsulation on the spatial extent of the neuromodulatory effect of stimulation, defined as the volume of tissue activated (VTA). Estimates of the VTA, coupled with neuroimaging techniques, may be used to inform presurgical planning of electrode placement to optimize clinical outcomes [116–118]. Understanding the spatial extent of stimulation can shed light on the potential mechanisms underlying both desired therapeutic effects as well as unwanted side effects. Recent evidence suggests that symptomatic management with DBS can be remarkably specific to the stimulated white matter tract (e.g. tremor alleviation is related to stimulation of tracts connected to primary motor cortex and cerebellum, bradykinesia is treated with stimulation of tracts connected to supplementary motor cortex, etc) [119, 120]. Newer modeling efforts focus on simulating the activation of specific axonal pathways in response to DBS [121–123], which can reveal insights into the relationship between variables associated with stimulation (e.g. electrode placement, parameter settings) and pathway recruitment [123]. While these topics are extensive enough to warrant a separate literature review, the use of computational modeling remains an important tool to predict the impact of the characteristics of the electrode–tissue interface on the efficacy and side effects of DBS.

Future experimental studies are needed in this area to expand on current limitations in available data to further understand how the brain-tissue response to DBS electrodes both can contribute to and hinder the efficacy of stimulation therapies. Particularly, longitudinal monitoring of the structural and functional consequences of both the impact of the device, as well as the potential effects of stimulation, on surrounding neural circuitry are needed. Additional controlled studies are needed to parse apart the effect of stimulation in comparison to insertional damage and the presence of the indwelling electrode array. These observations should be interpreted in the context of the limited, but growing, assessments of post-mortem brain tissue samples from patients. Computational modeling can be used to predict the potential effects of stimulation on surrounding tissue. Expanded study in each of these important areas is needed to fully understand the impact of the tissue response to electrodes on the outcomes of DBS therapy.

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