The active electrode in the living brain: The response of the brain parenchyma to chronically implanted deep brain stimulation electrodes

Keywords: Deep brain stimulation, glial scar, electrode-tissue interface

Running Title: Active Electrode in the living brain

Abstract

Background: Deep brain stimulation is an established symptomatic surgical therapy for Parkinson's Disease, essential tremor and a number of other movement and neuropsychiatric disorders. The well-established foreign body response around implanted electrodes is marked by gliosis, neuroinflammation and neurodegeneration. However, how this response changes with the application of chronic stimulation is less well-understood.

Objective: The aim of this review is to integrate the most recent evidence from basic science, patient and post-mortem studies on the effect of such an 'active' electrode on the parenchyma of the living brain.

Methods: A thorough and in-part systematic literature review identified 49 papers reporting on the effect of active stimulation using implanted electrodes on the brain parenchyma evidenced by changes in histology and impedance.

Results: Increased electrode-tissue impedance is consistently observed in the weeks following electrode implantation, stabilizing at approximately 3-6 months. Lower impedance values are observed around stimulated implanted electrodes when compared with un-stimulated electrodes. A temporary reduction in impedance has also been observed in response to stimulation in non-human primates. Post-mortem studies from patients confirm the presence of a fibrous sheath, astrocytosis, neuronal loss and neuroinflammation in the immediate vicinity of the electrode. When comparing stimulated and un-stimulated electrodes directly, there is some evidence across animal and patient studies of altered neurodegeneration and neuroinflammation around stimulated electrodes.

Conclusion: Establishing how stimulation influences the electrical and histological properties of the surrounding tissue is critical in understanding how these factors contribute to DBS efficacy, and in controlling symptoms and side effects. Understanding these complex issues will aid in the development of future neuromodulation systems that are optimised for the tissue environment and required stimulation protocols.

INTRODUCTION

Deep brain stimulation (DBS) is one the fastest growing areas of neurosurgery and has transformed the neurosurgical treatment of several movement and psychiatric disorders over the past 25 years. While its efficacy has been established, the exact mechanisms of action and possible adverse tissue responses, are not yet completely understood. Specifically, it is unclear exactly which structures are activated, whether neuronal damage occurs in the vicinity of the electrode and how the composition of the brain tissue changes due to long-term stimulation. Understanding the foreign body response of the tissue to the implanted electrode during chronic stimulation has important implications for identifying which structures can be directly excited or inhibited during DBS and in the design of more effective stimulation systems where the electrode properties are matched to the surrounding tissue.

In this paper we review the existing literature on the response of the brain to chronically implanted stimulation electrodes, with a focus on the effects of continuous stimulation on the brain parenchyma. The most recent evidence from basic science, patient and post-mortem studies is integrated to better understand the effect of such an active electrode on the living brain.

The review is divided into four parts. In the first part, basic science studies on impedance and histological changes in the living brain in response to active electrodes in the context of DBS are discussed. In the second part, insights gained from impedance data derived from DBS patients are presented and in the third part post-mortem studies providing evidence of structural changes within the brain parenchyma are summarised. In the last part, clinical relevance is discussed and current gaps in knowledge are also identified.

The review strategies adopted were inspired and informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines)[1] as outlined in the supplemental digital content 1.

PART 1: THE TISSUE REACTION TO THE ACTIVE ELECTRODE

Changes in Electrode-tissue Impedance and Histology – the Basic Science Perspective

Implantation of any electrode in the central nervous system (CNS) provokes a foreign body response. In the acute phase (up to 4 weeks), activation of microglia, oedema and bleeding, followed by breakdown of debris and reabsorption of fluid takes place[2-4]. During the chronic phase, low level neuroinflammation persists, activated astrocytes form a glial scar around the electrode and neuron density in the vicinity decreases[2,5,6], Figure 1. Activation of glial cells has been shown in response to a mismatch between mechanical properties of implanted electrodes and surrounding tissue, with stiff implants triggering enhanced levels of glial cell activation and inflammation than softer implants[7].

(FIGURE 1)

During stimulation, the electric current or voltage applied at the electrode changes the electric field in the region around the electrode, altering neural activity through inhibition or excitation of individual neurons and, thereby, influencing the behaviour of the associated neural circuits[8]. Together with presynaptic and postsynaptic compartments, astrocytes form part of the tripartite synapse and thus influence neuronal function. High frequency stimulation, similar to DBS, has been shown to cause calcium potentials in astrocytes and the release of gliatransmitters such as ATP, adenosine and glutamate[9,10]. There is increasing evidence that along with axonal activation, astrocyte activation, which is part of synapse establishment and maintenance, and neuroplasticity may also play a role in the beneficial effect of DBS[11].

The strength and distribution of the induced electric field depends on the applied current or voltage, the electrode-tissue interface and the electrical properties of the surrounding tissue. The transition of electron flow in the electrode to ion flow in the surrounding tissue is mediated by the electrode either through capacitive coupling, with charging and discharging of the electrode double-layer, or through faradaic reactions involving oxidation and reduction[12]. The electrode-electrolyte interface is commonly represented as a pseudocapacitive constant phase angle impedance in parallel with a charge transfer resistance[13], Figure 2.

(FIGURE 2)

The impedance measured at the electrode is determined by the double-layer at the electrode-tissue interface and the properties of the surrounding tissue. The impedance of the glial scar is relatively high compared with surrounding grey and white matter, thus increasing overall impedance and is has been suggested as a contributor to loss of efficacy of both stimulation and recording electrodes[14]. While changes in the impedance can influence the neuronal population stimulated by DBS for a constant stimulation voltage, it is not clear whether such changes are clinically relevant or whether they may be masked by adjustment of stimulation parameters in response to disease progression[15,16,17]. Monitoring changes in chronically implanted electrode impedance can help characterise changes in the electrical properties arising from the foreign body response. The impedance of most biological tissues, including brain tissue, varies as a function of both frequency and amplitude of the applied current. A full description of the electrode impedance across the frequency range of interest is provided through an impedance spectrum, though values are frequently reported at a single representative frequency, often 1 kHz[18].

While there is an abundance of published work on the CNS reaction to chronically implanted recording electrodes[5,19], relatively little information is available on corresponding changes in relation to active stimulation electrodes. Two studies have investigated changes in the impedance spectrum around active DBS electrodes. Kale *et al*. characterized early resistance changes in the nucleus accumbens during DBS (130 Hz, 100 µA, 90 µs) in one male Wistar rat for 3 days. Baseline resistance was 12 kΩ and increased daily to 13.5 kΩ at the end of 3 days[20]. Lempka *et al*. studied the impedance measured at DBS leads implanted into the STN and thalamus of one Rhesus macaque over 100 days. Deep brain stimulation was applied using clinically relevant parameters (130 Hz, 1 V, 90 µs) for 60 min and impedance spectra were recorded before and immediately after stimulation. Impedance increased from implantation (3 kΩ), peaked in the second week (16 kΩ) and stabilized at 8 kΩ. Application of 60 min DBS resulted in a significant temporary decrease in impedance, which began to recover once stimulation was stopped[21]. A similar reversible reduction in impedance following short-term stimulation using Utah arrays chronically implanted in the visual cortex of non-human primates has also been reported[22].

Histological studies have also shown changes in the properties of the glial scar with stimulation. Harnack *et al.*[23,24] studied neurodegeneration during short-, medium- and long term DBS in the

STN of male Wistar rats. Short-term DBS (4 h; 130 Hz, 0-300 µA, 60 µs) caused a wide ring of neural tissue damage, oedema, thermonecrosis, haemorrhage and iron deposits when stainless steel electrodes were used but no changes, beyond the damage caused by insertion, when platinum iridium (PtIr) electrodes were used. During medium-term DBS (72 h; 130 Hz, 100 µA, 60 µs), no differences in neurodegeneration between stimulation and control groups were visible[23]. In the longer-term (3 weeks, 131 Hz, 0-50 µA, 52 µs), when comparing stimulated to sham-stimulated groups, both groups showed neuronal loss and mild astrocytosis around the electrode tract. Stimulated electrodes had an additional accumulation of monocytes or histiocytes clustered around the electrode tip, suggestive of neuroinflammation with macrophage or monocyte displacement through injury of blood vessels or the blood-brain barrier[24].

Vedam-Mai *et al*. investigated DBS (130 Hz, 50 µA, 50 µs) in the rat STN delivered 1 hour/day for 2 weeks via stainless steel electrodes. The number of activated microglia and proliferating cells around the electrode tract were found to be lower in the stimulation group when compared with microlesioned or sham stimulation control groups[25].

Bilateral DBS in Goettingen minipigs resulted in a 60 µm ring of gliosis, activated microglia and macrophages out to 100 µm from platinum electrodes. Giant multinuclear cells and in some cases necrosis were also found. Histological changes were persistently present at 3, 6 and 12 months, however, no difference between the stimulated and unstimulated contacts on the electrode was observed[26].

Though investigating stimulation of the sensorimotor cortex rather than deep brain structures, the findings of McCreery *et al*., are relevant here as they are among the few studies to have compared histological data from unstimulated and stimulated chronically implanted electrodes following long term stimulation in the brain. Stronger astrocytosis and lower density of neurons in a <150 µm radius around stimulated iridium microelectrode arrays in the cat was observed for the stimulated electrodes when compared with unstimulated electrodes, Figure 3. Stimulation was applied for 30 days for an average of 8 hours/day (50 Hz, 200 µs, 10 or 20 µA)[27].

(FIGURE 3)

In summary, animal studies have clearly shown the advantage of PtIr electrodes which are standard in clinically implanted neuromodulation systems and also suggest some differences in

the brain's reaction to active versus passive electrodes. However, due to the wide variation in electrodes, targets and stimulation protocols examined, much uncertainty remains regarding the influence of chronic stimulation on the electrode-tissue interface and surrounding tissue. Characteristic glial scarring has been observed around both stimulated and unstimulated DBS electrodes in rats, though it is unclear whether there is a difference between the two conditions. Astrocytosis has been reported to be stronger around active electrodes implanted in the cat sensorimotor cortex[27] but slightly less following stimulation of the midbrain in cats[28]. Neurodegeneration in the immediate vicinity of active stimulation electrodes has been found to be slightly more prominent than around unstimulated electrodes[27]. However, the loss of neural density in close proximity of the electrode does not reflect a significant overall loss of neurons within the nucleus[29]. Finally, there appear to be differences in the characteristics of neuroinflammation in the vicinity of stimulation electrodes[24,25] and a temporary reduction in the electrode-tissue impedance following stimulation has been consistently reported[21,22].

PART 2: IMPEDANCE AT ACTIVE AND INACTIVE DBS ELECTRODES

Impedance changes in DBS Patients

Several studies have examined changes in electrode impedance in the months immediately following implantation of DBS electrodes using the ability of modern neurostimulators to check electrode impedance to monitor lead integrity, Table 1. In their seminal study on the first use of DBS of the ventral intermediate nucleus as a replacement for thalamotomy in patients with PD and essential tremor, Benabid *et al*. monitored impedance at 1 kHz in 11 patients. Impedance rose in the first months post implantation, from a mean of 794 Ω (range 499-1238 Ω) at 2 weeks, before plateauing and reaching a maximum of 1057 Ω (range 828-1483 Ω) at 3 months[30]. In a retrospective study of 20 patients, Lungu *et el*. reported a significant increase from week 1 to week 3 (1530 Ω vs. 2530 Ω), after which impedance remained stable until the maximum timepoint at 20 weeks[31]. Rosa *et al*. reported an initial drop in impedance (measured at 30 Hz) during the same time frame of 2 hours up to 30 days after implantation with the lowest values recorded 2 days after implantation. After 2 days an increase in impedance was noted but baseline levels were not reached at 30 days[32,33].

Long-term studies, including the studies of Wong *et al.*[34], Sillay *et al.*[35] and Knudsen *et al.*[36], reported fluctuations occurring primarily within the first 6 months. The retrospective study of Cheung *et al.* (2,863 measurements from 94 patients) found 1 kHz impedance to be stable after 6 months with only a slight upward trend to 12 months followed by a downward trend thereafter with a net decrease in impedance of 22 Ω per visit[37]. Time, electrical activity, implanted target, contact position and implantation side were found to be significant predictors of impedance. Another retrospective study examined the relationship between DBS contact activity and electrode impedance over several years, reporting a reduction in electrode impedance of 163 Ω/year at active electrodes[38]. Similarly, Abosch *et al.*[39] Hartmann *et al.*[40] and Satzer *et al.*[38,41] report a slight yearly decrease. The RNS NeuroPace system used for epilepsy is composed of depth electrodes which are similar to DBS electrodes and subdurally located cortical strip electrodes. Depth electrodes report similar increases in impedance during the first 3 weeks post-implantation and a slight decrease during the first year, before remaining stabile thereafter. Subdural strip electrodes in comparison had a reduced impedance in the first weeks after

implantation, with a higher variation in impedance than the depth electrodes, and remained stable after a few months[42,43].

When comparing impedance at stimulated and non-stimulated contacts, impedance has been consistently shown to be lower at stimulated contacts than at non-stimulated contacts on the electrode[37-39,44]. Stimulation has also been shown to induce a temporary and reversible reduction in measured impedance over a period of several hours[37,44]. A recent study by Eleopra *et al.* [45], reported on impedance values at segmented electrodes on directional leads. The directional contacts had a higher impedance (2035 Ω) compared to the ring contacts (942 Ω) due to their smaller surface area. The changes over time were similar to standard leads, and active directional contacts had a lower impedance values than inactive directional contacts.[45]

While overall trends are consistent, some variability is evident across individual studies possibly due to different recording schedules and baseline reference points. High inter-patient variability[35], and high variability within individual subjects and within electrode contacts in each subject[37] has been reported, posing a further challenge for comparison across conditions and studies.

PART 3: THE TISSUE REACTION IN PATIENTS

Pathohistological tissue changes affecting stimulation

While electrode impedance provides a proxy for changes occurring at the electrode-tissue interface, histological studies reveal structural changes and possible damage to the brain parenchyma. In patients post-mortem data provides information on the histological changes surrounding the DBS electrode in response to electrode implantation and chronic stimulation up to several years.

DiLorenzo *et al*.[46] conducted a comprehensive review of post-mortem studies including implanted systems in the brain from as early as 1977 discussing 40 unique cases. On histopathology, a fibrous sheath of 5–25 μm in diameter, astrocytosis, multinucleated giant cells[47], mononuclear leukocytes, macrophages, activated microglia and neuronal loss were observed in >50 % of cases. Damage to the parenchyma was mild to non-existent in most cases. Necrosis and spongiosis was only found in three cases from prior to 1997 (year of FDA approval of DBS), in which electrodes made of other materials (Pt and stainless steel) than PtIr were used. Persistent efficacy was correlated with the absence of tissue injury. Subsequent studies[48-52] have confirmed the histological changes summarized by DiLorenzo *et al*. For example, in a post-mortem study of gliosis surrounding chronically implanted DBS electrodes in 18 brains, Vedam-Mai *et al*., measured the thickness of the glial scar to be 122.5 μm or 162.5 μm, depending on the staining method used. The duration of stimulation (<5, 5-10 or >10 years) was not found to influence the thickness of the glial scar[50], Figure 4.

(FIGURE 4)

Contradictory evidence of both neuronal loss and no neuronal loss within 500 μm of the stimulating contacts on the electrode has been reported but studies are consistent in reporting preservation of neurons in the region beyond this. Post-mortem studies on DBS patients showed similar changes in the human brain to those observed in the animal studies.

Active and inactive contacts have been compared in relatively few studies (supplemental digital table 1). Haberler *et al*. performed a post-mortem investigation of 8 PD patients who had received DBS for up to 70 months. On histological examination there was 5-25 μm fibrous tissue sheet around the electrode and 500 μm of gliosis, with no correlation between the duration of

stimulation and thickness of the fibrous sheet. In 2 patients persistent activated microglia were present. No neuronal loss or axonal damage was detected. Tissue changes around active contacts and non-active contacts or insulated parts of the lead did not differ[53]. Similarly, De Vloo *et al.* did not find differences between active and inactive contacts in astrocytosis, neuronal loss, activated macrophages or microglia. On the other hand, Kronenbuerger *et al.* found enlarged axons or axonal spheroids to be elevated around active contacts while no difference in the extent of astrogliosis and neuroinflammation were seen[52]. Vedam-Mai *et al.* saw slightly increased astrocytosis around the active contact in comparison to the inactive contact in a study of 18 patients[50].

PART 4: SUMMARY AND CLINICAL RELEVANCE

Impedance at the DBS electrode-tissue interface increases gradually following surgery, stabilising at 3-6 months. The increase in impedance corresponds to the formation of the glial scar around the electrode in the region up to 500µm around PtIr electrodes, with most changes occurring within 50µm. A reversible reduction in impedance has been reported during temporary stimulation, potentially related to polarisation and dislodgement of adsorbed proteins from the electrode surface[21,54]. Similar mechanisms have been identified in the principles underpinning the rejuvenation of recording electrodes[54]. The safe charge density limit recommended by device manufacturers for chronically implanted stimulators is 30 µC cm^{-2} [55,56]. This is primarily based upon previous studies examining histological tissue damage during cortical stimulation in the cat [57,58,59], however, it is unclear how accurate these limits are for chronic high frequency stimulation of other brain structures[60].

During voltage-controlled stimulation changes in the electrode-tissue impedance directly affect the current delivered to the surrounding tissue, with current decreasing with increasing impedance. Fluctuations in impedance will result in variations in the current delivered to the target neurons and higher voltages will be required to maintain the same level of current and stimulation efficacy in the presence of increasing impedance. Stimulation devices which utilise constant current sources overcome this limitation as the current delivered to the tissue is specified and, therefore, does not vary with impedance at the electrode interface, Figure 2. Predicted voltage fluctuations arising from changes in electrode-tissue impedance during voltage-controlled stimulation were confirmed using DBS electrodes implanted in macaque monkeys[61]. The amplitude of voltage recordings within the brain were more variable during voltage-controlled DBS than current-controlled DBS which remained stable during stimulus-induced short-term changes in electrode impedance[61]. Consistent with this, in a retrospective study of 22 dystonia patients receiving GPi DBS, Lettieri *et al*. found that current-controlled stimulation produced better clinical outcomes 6-12 months post-surgery than voltage-controlled stimulation[62].

In conclusion, while histological and impedance changes in the tissue surrounding DBS electrodes show characteristics of the classic foreign body response to chronically implanted devices, a number of studies have shown additional changes around active electrodes when

compared with unstimulated electrodes. The additional mechanisms responsible for these differences have yet to be elucidated. Areas for future investigation include the response of astrocytes to electrical stimulation and subsequent influences on neural function, and the effects of stimulation on protein adsorption at the electrode and electrode-tissue impedance.

In terms of the electrochemistry at the electrode, the underlying relationship between charge-injection and tissue damage is not well understood[63]. Safety limits for charge and charge density that have been established have been conducted for electrodes and stimulation conditions that differ to those used for contemporary DBS therapies. These provide guidance for current applications, but it remains to be established whether they also apply to specific DBS protocols and electrodes which may differ across manufacturers. Safety limits for novel biomaterials need to be established. Corrosion of platinum multi-electrode arrays has been shown to appear in the long-term[64] and may also affect stimulation performance and the chronic tissue reaction, although corrosion after long-term implantation has not been observed in larger stimulation electrodes[65].

The ongoing development of high-density electrode arrays which allow for directional tuning of current for stimulation allow for more complex protocols where the active electrodes can vary dynamically over time. Similarly, closed-loop or adaptive DBS stimulation paradigms offer the potential for continuous adjustment of stimulation parameters and require stimulation and stimulation capability. Temporary effects of stimulation on electrode impedance should be considered as they may have a confounding effect for these types of stimulation protocols or during clinical parameter setting. Future studies need to be able to observe temporary peaks in current delivery.

Finally, the development of novel functional biomaterials for electrodes and electrode coating may help reduce the foreign body response, decrease impedance at the electrode-tissue interface and increase charge transfer density[66]. The use of nanomaterials, either conductive nanomaterials or in miniaturizing strategies, might improve sensitivity to the stimuli, stability in operating conditions, efficiency of charge transfer and minimize reaction of the surrounding tissue[67,68]. However, future studies are required to address the safety, performance and long-term efficacy of functionalised biomaterials for chronic neural stimulation *in vivo*, whose translation to *in vivo* application is not yet realised.

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Tables

Table 1: Overview of studies reporting DBS patient impedance at 1 kHz. Patient numbers, duration, lead and neurostimulator employed, baseline impedance and impedance changes in the short and long term are presented.

Study	Number of patients	Disorder	Study duration	Lead	Stimulator	Baseline impedance	Trend	
							Short-term	Long-term
Benabid *et al*. 1991[3]	32	PD, ET	3 months	Medtronic 1.2 mm Ø electrode	Itrel II	794 Ω	↑ at 3 months	↔
Hemm *et al*. 2004[45]	24	Dystonia	3 months	Medtronic 3389	Itrel II	1367 Ω	↑	
Rosa *et al.* 2010[34]	11	PD	1 month	Medtronic 3389	Kinetra	Not stated (at 30 Hz)	↓ at 2 hrs – 30 days	
Rosa *et al.* 2011[33]	7	PD	1 month	Medtronic 3389	Kinetra	1533 Ω at 30 Hz	↓ at 30 days	
Sillay *et al*. 2010[36]	63	PD, ET, Dystonia	9 months	Medtronic 3387	Soletra/ Kinetra	1048 Ω		↔
Abosch *et al.* 2012[40]	20	PD	3-7 years	Medtronic 3389	Kinetra	Not stated (at 30 Hz)	↑ for usntimulated contacts, ↓ for stimulated contacts	Slow ↓
Cheung *et al*. 2013[38]	94	PD, ET, Dystonia, other	6 months – 5 years	Medtronic 3387	Soletra	1200 Ω	↑ in 1year,	Slow ↓
Lungu *et al*. 2013[32]	20	PD	5 months	Medtronic 3389	Activa	1897 Ω	↑ to 4 weeks	
Sillay *et al*. 2013[36]	188	Epilepsy	Mean 27 months	RNS depth lead	Neuropace RNS	450 Ω	↑ to 3 weeks	↔ after 1 year
Wu *et al*. 2013[44]	7	Epilepsy	24-36 months	RNS depth lead	Neuropace RNS	557 Ω		↔
Satzer *et al.* 2014[39]	84	PD, ET, Dystonia	2 – 6 years	Medtronic 3387 or 3389	Soletra	Not stated		Slow ↓
Hartmann *et al.* 2015[41]	20	PD	1 – 13 years	Not stated	Not stated	Not stated		Slow ↓
Satzer *et al.* 2015[42]	62	PD	2 – 6 years	Medtronic 3389	Soletra/ Activa	Not stated		Slow ↓
Wong *et al.* 2018[35]	866	PD, ET, Dystonia, other	Mean 36 months	Medtronic 3387	Soletra/ Kinetra	Not stated		↔ after
Knudsen *et al.* 2019[37]	114		24 months	Medtronic 3389	Soletra/ Kinetra	1107 Ω	↑ at 5 to 12 months	↔ after

Eleopra *et al.* 2019[46]	11	PD	12 months	D-2202 directional lead	Vercise	ring 942 Ω, directional 2035 Ω	↓ at 5 days, ↑ until 6 months	↔ after

Figures

Figure 1: Acute and chronic response in the parenchyma surrounding the implanted stimulation electrode. Note the activation of microglia, influx of astrocytes and degeneration of neurons in the acute phase and marked astrocytosis with persistent inflammation in the chronic phase.

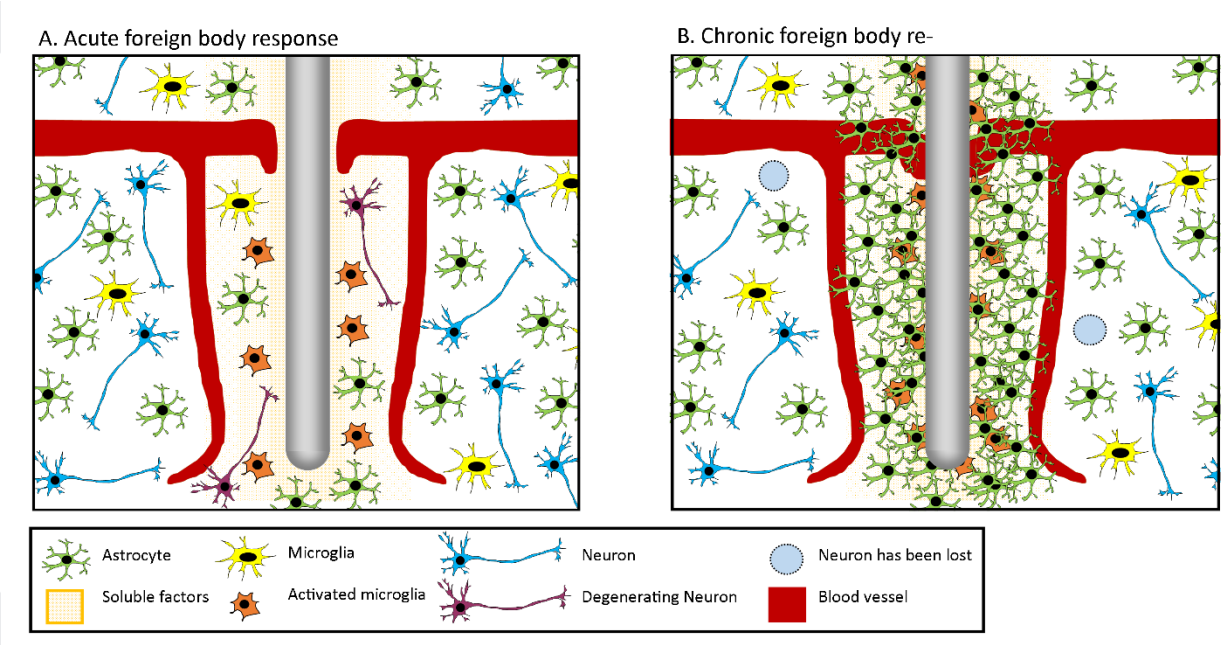


Figure 2: Electrical equivalent circuit model of the electrode double layer, glial scar and brain tissue for voltage-controlled (A) and current-controlled (B) stimulation, with the active electrode contact shown in yellow. The electrode-tissue interface is represented as the parallel combination of a pseudocapacitive constant phase element and charge transfer resistance (Z_{CPA} and R_{CT}) and the glial scar by C_{ET} and R_{ET}. The surrounding brain tissue is represented as a simple bulk resistance and capacitance (R_{Br} and C_{Br}). During voltage-controlled stimulation the impedance at the electrode influences the voltage distribution in the surrounding tissue. During current-controlled stimulation, the influence of the electrode-tissue interface (double layer and glial scar) on the voltage in the surrounding brain tissue is negligible, as all of the current, I, applied at the electrode passes into the surrounding tissue.

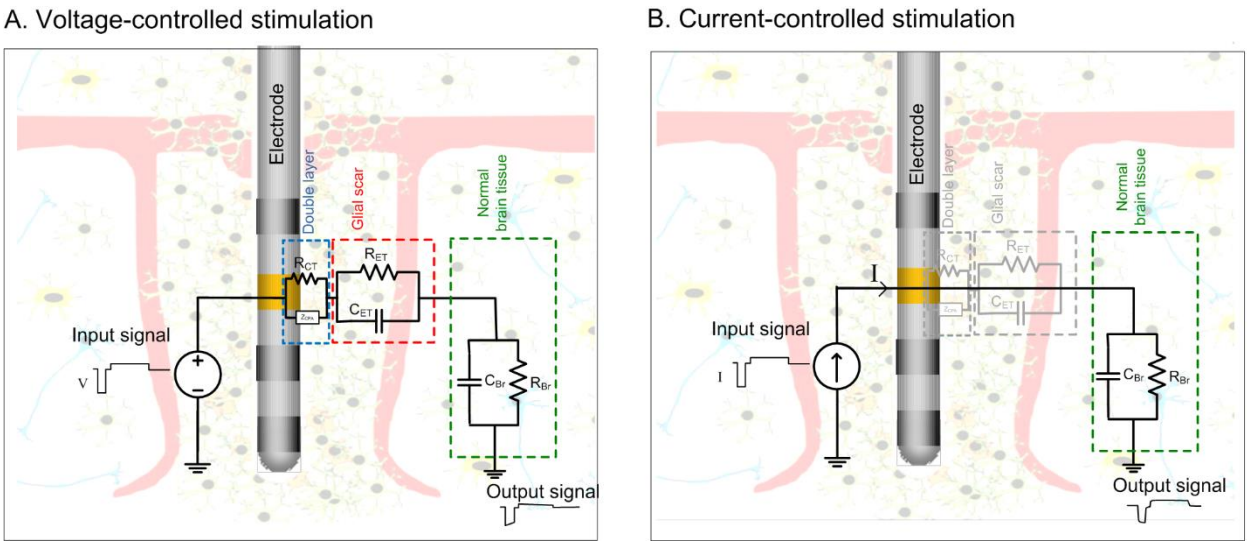


Figure 3: Histologic sections through the electrode tip sites (T) of an unstimulated (A) and stimulated (B, 2nC/phase) electrode in the cat cerebral cortex. Electrodes were implanted for 701 days. NeuN stain for neurons appears brown and GFAP stain for astrocytes appears black. Increased GFAP staining and less neuron density can be observed in close proximity to the electrode tract. Bar = 100 µm. © 2010 [BLINDED FOR REVIEW]. Used with permission.

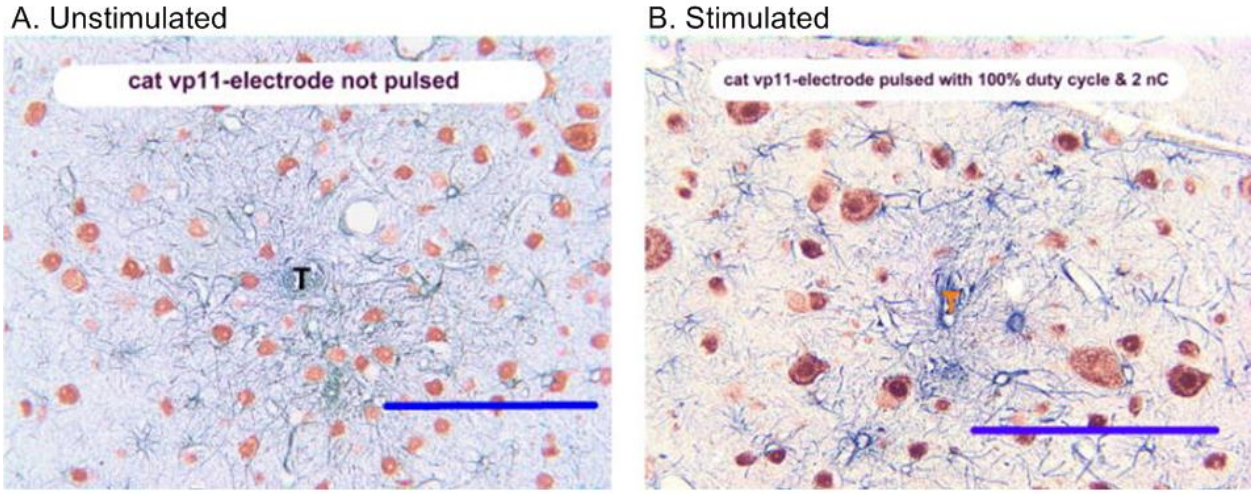
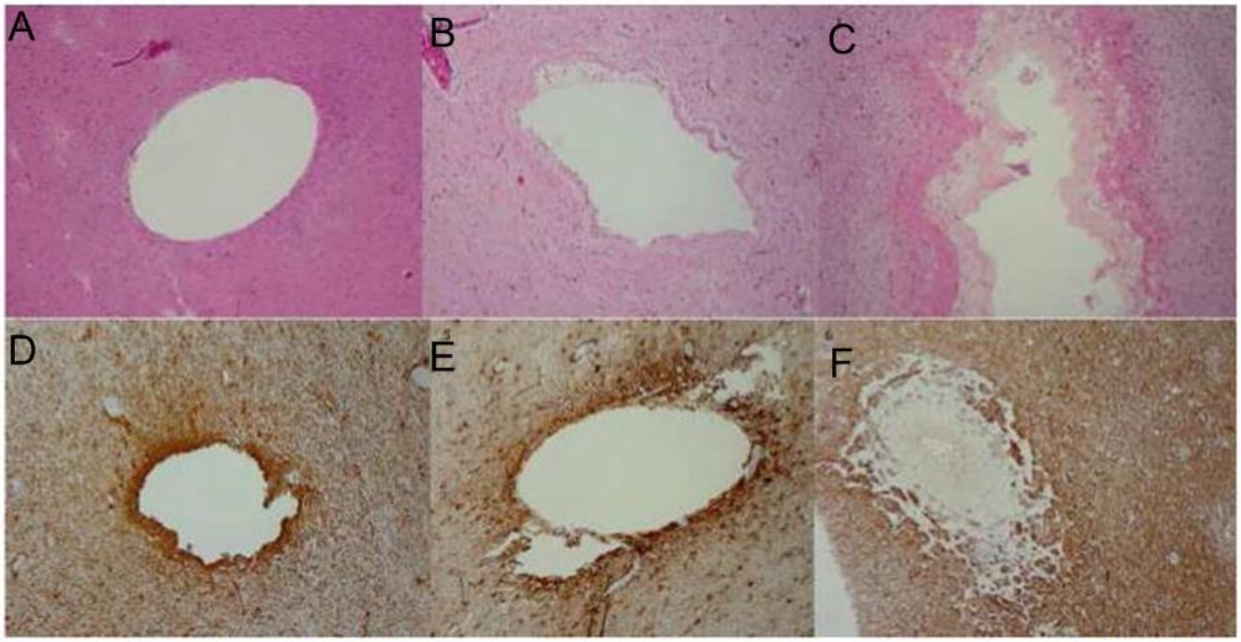


Figure 4: Histological (H&E, Panel A-C) and immunohistochemical (GFAP, panel D-F) section through electrode contact sites of DBS electrodes in the STN (A, B, D, E) and pedunculopontine nucleus (C, F) showing mild (A, D), moderate (B, E) and severe (C, F) gliosis. 10x magnification. © 2018 [BLINDED FOR REVIEW]. Used with permission.


A
B
C
D
E
F

Supplemental digital content

Supplemental digital content 1: review methods

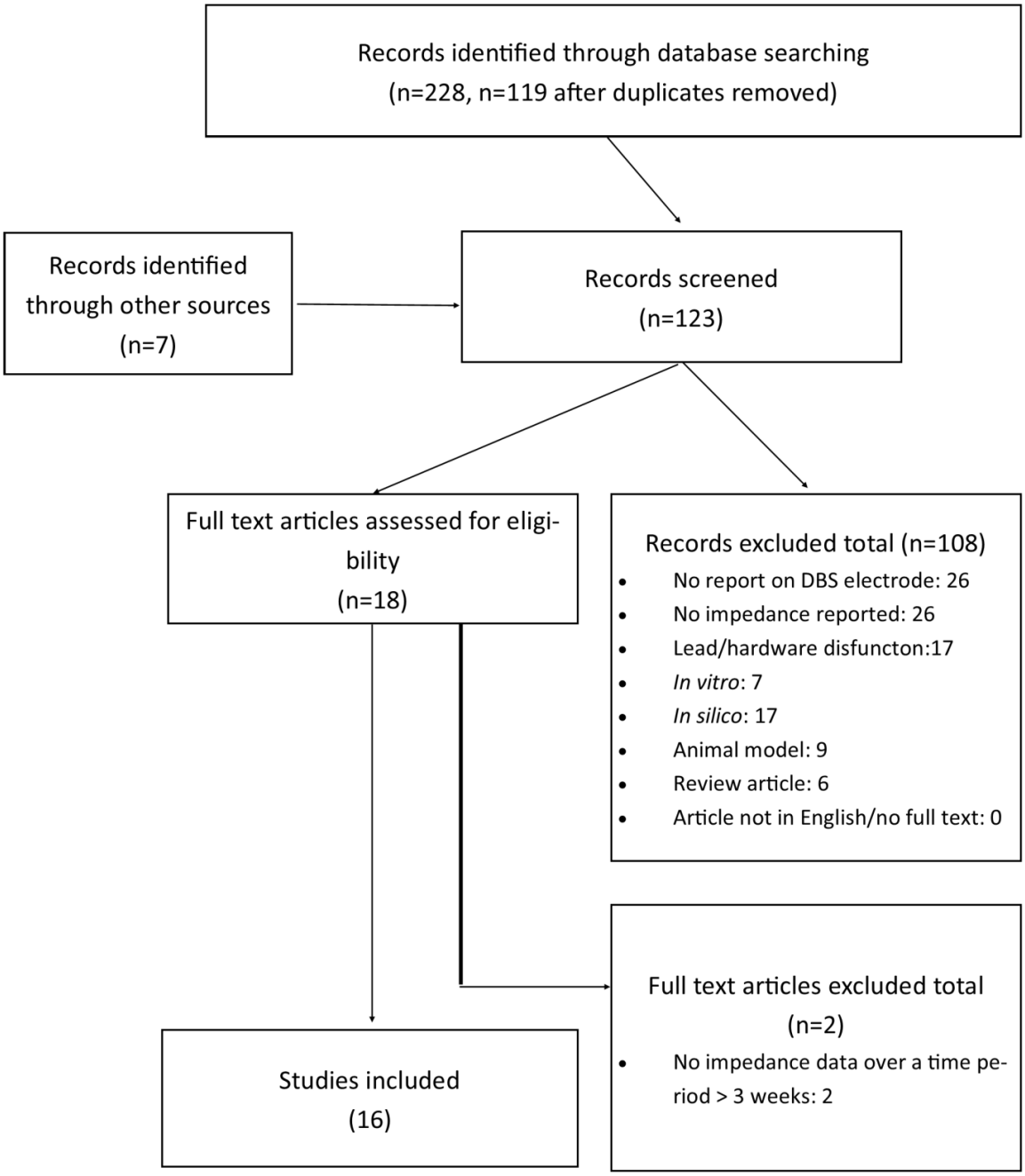
The conduct of this review was inspired by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA guidelines)[1]. These were followed where feasible. A systematic search of the MEDLINE and PubMedCentral databases was performed via Pubmed on several occasions with the last search in December 2019. For the basic science studies, combinations of the following search parameters were used: 'animal', 'rodent/rat', 'primate', '*in vivo*' 'impedance', 'DBS/deep brain stimulation', 'high-frequency stimulation', 'histopathology', 'charge density', 'implanted electrode', 'tissue response'. Studies reporting on changes in relation to the effect of active stimulation using implanted electrodes on the brain parenchyma were included. For impedance changes in patients, the following search parameters were used: 'DBS/deep brain stimulation' or 'high frequency stimulation' and 'impedance'. For pathohistological patient studies, the following search parameters were used: 'DBS/deep brain stimulation' or 'high frequency stimulation' and 'post-mortem', 'pathologic', 'clinicopathologic' or 'postmortem'. The reference lists of all included studies were then reviewed by the authors to identify additional papers within the inclusion criteria. The PRISMA flow diagrams for the impedance and pathohistological searches are presented in Figures 1 and 2. As the basic science studies of interest were distributed across a diverse range of areas, the presentation of this section of the review as a PRISMA flow diagram was not feasible. All of the included patient studies are listed in Table 1 and Supplemental digital table 1, respectively.

(SUPPPLEMANTAL DIGITAL FIGURE 1 and SUPPPLEMANTAL DIGITAL FIGURE 2, SUPPPLEMANTAL DIGITAL TABLE 1)

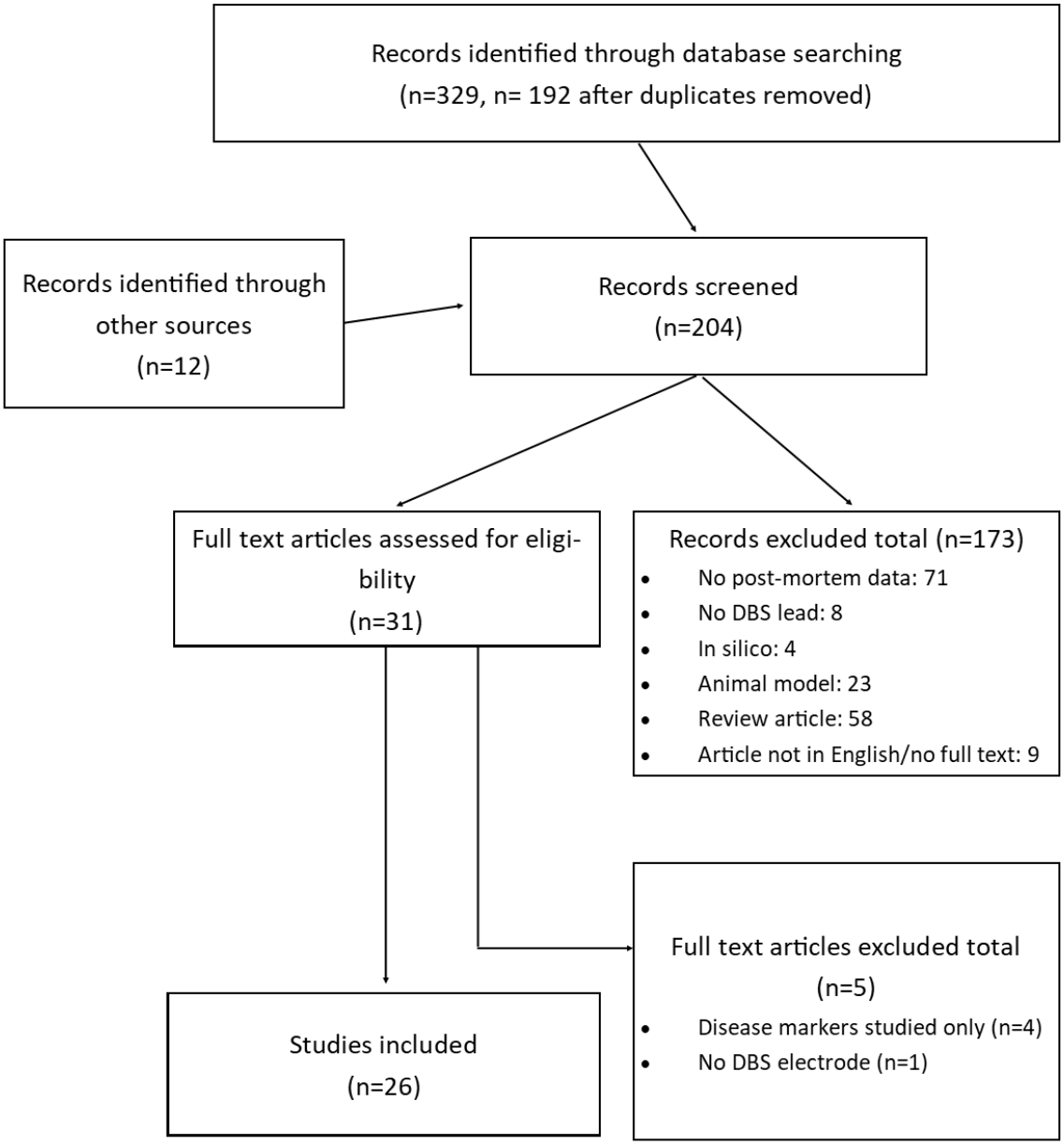
There were some methodological limitations. Basic science publications reviewed were too diverse to capture in one search, individual searches results yielded few papers of interest and the evidence was often not the main result of the paper. The approach used allowed the topic to be covered from a multidisciplinary perspective. Formal grading of the evidence was not conducted, however, study design and subject numbers are reported. For practical reasons the authors were not blinded to author or journal title during the review.

Study	Number of patients	Duration of DBS	Comparison of active vs. inactive electrode
Hosobuchi *et al.* 1977[69]	5	7 months	No
Gybels *et al.* 1980[70]	5	1 – 12 months	No
Boivie *et al.* 1982[71]	5	1 – 12 months	No
Baskin *et al.* 1986[72]	7	1 – 6 months	No
Kuroda *et al.* 1991[73]	1	20 months	No
Caparros-Lefebvre *et al.* 1994[74]	1	43 months	No
Haberler *et al.* 2000[53]	8	Up to 70 months	Yes
Boockvar *et al.* 2000[75]	1	16 months	No
Henderson *et al.* 2001[76]	1	24 months	No
Berciano *et al*. 2002[77]	1	3 weeks	No
Burbaud *et al.* 2002[78]	1	24 months	No
Henderson *et al.* 2002[79]	1	2 months	No
Counelis *et al.* 2003[80]	1	4 days	No
Jarraya *et al.* 2003[81]	1	24 months	No
Talmant *et al.* 2006[82]	1	24 months	No
Valldeoriola *et al.* 2006[83]	1	38 months	No
McClelland *et al.* 2007[84]	1	32 months	No
Guehl *et al.* 2008[85]	1	6 years	No
Pilitsis *et al.* 2008[86]	1	8 months	No
DiLorenzo *et al.* 2010[87]	1	12 years	No
Al-Helli *et al.* 2015[48]	1	6 years	No
Kronenburger *et al.* 2015[52]	10	Up to 7.5 years	Yes
Pienaar *et al.* 2015[88]	5	Not stated	Yes
Vadam-Mai *et al.* 2016[51]	1	32 months	No
DeVloo *et al.* 2018[49]	1	12 years	Yes
Vadam-Mai *et al.* 2018[50]	18	7 ± 6 years	Yes

Supplemental digital table 1: Reviewed pathohistological studies of DBS



Supplemental digital figure 1: PRISMA flow diagram, impedance data in patients.



Supplemental digital figure 2: PRISMA flow diagram, pathohistological data.

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