Electron microscopy of tissue adherent to explanted electrodes in dystonia and Parkinson’s disease


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Summary

Deep brain stimulation (DBS) is used to treat a variety of severe medically intractable movement disorders, including Parkinson’s disease, tremor and dystonia. There have been few studies examining the effect of chronic DBS on the brains of Parkinson’s disease patients. Most of these post mortem studies concluded that chronic DBS caused mild gliosis around the lead track and did not damage brain tissue. There have been no similar histopathological studies on brains from dystonic patients who have undergone DBS. In this study, our objective was to discover whether tissue would be attached to DBS electrodes removed from patients for routine clinical reasons. We hoped that by examining explanted DBS electrodes using scanning (SEM) and/or transmission (TEM) electron microscopy we might visualize any attached tissue and thus understand the electrode–human brain tissue interaction more accurately. Initially, SEM was performed on one control DBS electrode that had not been implanted. Then 21 (one subthalamic nucleus and 20 globus pallidus internus) explanted DBS electrodes were prepared, after fixation in 3% glutaraldehyde, for SEM (n = 9) or TEM (n = 10), or both (n = 2), according to departmental protocol. The electrodes were sourced from two patients with Parkinson’s disease, one with myoclonic dystonia, two with cervical dystonia and five with primary generalized dystonia, and had been in situ for 11 and 31 months (Parkinson’s disease), 16 months (myoclonic dystonia), 14 and 24 months (cervical dystonia) and 3–24 months (primary generalized dystonia). Our results showed that a foreign body multinucleate giant cell-type reaction was present in all TEM samples and in SEM samples, prewashed to remove surface blood and fibrin, regardless of the diagnosis. Some of the giant cells were >100 μm in diameter and might have originated from either fusion of parenchymal microglia, resident perivascular macrophage precursors and/or monocytes/macrophages invading from the blood stream. The presence of mononuclear macrophages containing lysosomes and sometimes having conspicuous filopodia was detected by TEM. Both types of cells contained highly electron-dense inclusions, which probably represent phagocytosed material. Similar material, the exact nature of which is unknown, was also seen in the vicinity of these cells. This reaction was present irrespective of the duration of implantation and may be a response to the polyurethane component of the electrodes’ surface coat. These findings may be relevant to our understanding of the time course of the clinical response to DBS in Parkinson’s disease and various forms of dystonia, as well as contributing to the design characteristics of future DBS electrodes.

Keywords: deep brain stimulation; dystonia; electron microscopy; giant cell reaction; Parkinson’s disease

Abbreviations: DBS = deep brain stimulation; GPi = globus pallidus internus; SEM = scanning electron microscopy; STN = subthalamic nucleus; TEM = transmission electron microscopy; VIM = ventralis intermedius nucleus of thalamus

Introduction

Benabid et al. (1987) were the first to report the suppressant effect of chronic stimulation of the nucleus ventralis internus (VIM) of the thalamus on tremor in Parkinson’s disease. Subsequently, VIM stimulation has been shown to be an effective treatment for other forms of severe tremor, including the action tremors associated with multiple sclerosis and essential tremor (Schuurman et al., 2000). Over time, the globus pallidus internus (GPI) and subthalamic nucleus (STN) have become the preferred targets for the treatment of medically refractory Parkinson’s disease (The Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001). More recently the first 5-year follow-up data for chronic bilateral STN stimulation for Parkinson’s disease were published (Krack et al., 2003), demonstrating that at 5 years, bilateral STN stimulation continued to alleviate the motor symptoms of Parkinson’s disease in the off-medication state, with the exception of speech, and also to improve patients’ capacity to perform their activities of daily living. In addition, on-medication dystonias were significantly diminished (Krack et al., 2003).

The obvious success of pallidotomy and then chronic GPi stimulation in managing levodopa-induced dyskinesia and ‘off’ dystonia in advanced Parkinson’s disease led to the adoption of the latter technique for treatment of various forms of medically intractable dystonia (Krauss et al., 1999, 2002; Coubes et al., 2000; The Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001; Parkin et al., 2002; Yianni et al., 2003a, b).

However, in spite of the increasing confidence in and widespread use of deep brain stimulation (DBS) for movement disorders, there is a paucity of data concerning the neuropathological consequences of chronic DBS in man. In fact, there have only been four single case reports and only one study looking at post mortem changes associated with chronic DBS in a total of 11 parkinsonian brains (Caparros-Lefebvre et al., 1994; Haberler et al., 2000; Henderson et al., 2001, 2002; Jarrahy et al., 2003). In these post mortem studies, the brains were fixed in formaldehyde, the DBS electrodes removed and the brain tissue examined by light microscopy. The first case report concerned a patient who received thalamic VIM stimulation discontinuously for 43 months (Caparros-Lefebvre et al., 1994). Small areas of gliosis and spongiosis were observed in a 1 mm perimeter around the electrode track. Sections above the active tip of the electrode revealed an accumulation of ‘lymphoid’, macrophagic and giant cells 2 mm around the electrode. The lymphoid cells were positive for UCHL1 [ubiquitin carboxy-terminal esterase L1 (ubiquitin thiolesterase), clone UCHL1], which is now recognized as being expressed by T-lymphocytes, macrophages and Langerhans cells of normal tissue. The second study involved the post mortem examination of eight brains, six that had received thalamic VIM stimulation and two STN stimulation (maximum duration 70 months) prior to death (Haberler et al., 2000). The authors concluded that chronic DBS did not cause damage to adjacent brain tissue, as neuronal parenchyma was well preserved, but mild gliosis around the electrode track was detected. However, in two brains (cases 6 and 7), which had been stimulated for 3 and 15 months, respectively, gliosis was more pronounced. In case 6, slight microglial activation, leukocytes, siderophages and single multinucleated giant cells were present, while in case 7 a mild inflammatory reaction involving multinucleated giant cells that were engulfing tiny fragments of foreign material was observed.

Henderson et al. (2001) reported the neuropathological effects of misplacing a DBS electrode in the thalamic centromedian–parafascicular complex (CM-Pf) in a 69-year-old man with Parkinson’s disease. The patient had initially had a DBS electrode placed in the thalamic ventral anterior nucleus, which became displaced and was replaced 1 week later. However, the second electrode was sited in the CM-Pf. The patient died 3–4 years later from staphylococcus sepsis and multiple myeloma. Neuropathological studies demonstrated limited astrogliosis and tissue vacuolation along both electrode tracts. Mild cell loss and gliosis were detected in the ventral anterior nucleus. However, in the CM-Pf a microthalamotomy was present (volume ~3 × 2 × 3 mm³), which was surrounded by extensive astrocytosis and neuronal loss that was in excess of that on the non-operated side and that typically detected in Parkinson’s disease. Henderson et al. (2002) also described the post mortem findings in a brain obtained from a Parkinson’s disease patient who had undergone bilateral STN stimulation for 2 months prior to death. Mild neuronal cell loss, gliosis and some tissue vacuolation associated with the subthalamic electrode tracts were detected. TUNEL (terminal deoxyribonucleotidyl transferase-mediated dUTP-biotin nick-end labelling) staining and analysis of cellular morphology revealed no evidence of ‘apoptosis’ (DNA fragmentation), but there was a mild inflammatory response without significant neuronal cell loss in this area. The next case report (Jarrahy et al., 2003) involved a Parkinson’s disease patient who died 2 years after STN electrode implantation. CD68 immunolabelling revealed a large number of activated macrophages around and at a distance from the STN cavity created by the electrode, and GFAP (glial fibrillary acidic protein) immunohistochemistry showed an increased density of astrocytes around the lesion.

There is only one post mortem study involving a patient with essential tremor, who died after having first left then right VIM stimulation for 16 and 10 months, respectively (Brockvar et al., 2000). Mild gliosis was found in the vicinity of the electrode tracts with occasional Gomori-stained iron deposits within the tracts. However, there is no histological information concerning the effects of DBS on the cerebral tissue of patients with multiple sclerosis or dystonia, the latter being of particular concern as patients with dystonia who have undergone DBS are often young and include children (Yianni et al., 2003b).
purposes. We also speculated that histological studies of post mortem brains from which electrodes had been explanted might not give a complete picture of the brain–electrode interaction, as the true interface between the DBS electrode and brain tissue could be attached to the DBS electrode.

Our hypothesis was that explanted DBS electrodes might have tissue attached to them that could provide valuable information on the brain–electrode interaction, which in turn might facilitate our understanding of the effects of DBS on patients with dystonia and Parkinson’s disease.

Patients and methods

Surgical technique

Implantation

After detailed explanations of the risks and potential benefits of the procedure, informed written consent was obtained from each patient. Implantation of Medtronic quadripolar 3387 DBS electrodes (Medtronic Inc., Minneapolis, MN, USA) into bilateral posteroventral GPi was performed under general anaesthesia for all the dystonia patients. For the two Parkinson’s disease patients, electrode insertion was performed under local anaesthesia with impedance monitoring and macrostimulation to assist accuracy of placement. One Parkinson’s disease patient (case 10) received bilateral GPi electrodes and the other (case 2) a right STN electrode. In every case surgery was performed using Image Fusion™ and Stereoplan™ (Radionics, MA, USA) to localize the targets by fusing the MRIs to the stereotactic CT scan (Orth et al., 1999). A more detailed explanation of this operative method is given elsewhere (Papanastassiou et al., 1998). The DBS leads were then connected to a subcutaneous programmable pulse generator (Kineta; Medtronic Inc.) implanted in the subclavicular tissue. No significant perioperative complications occurred. However, one patient (case 3) with primary generalized dystonia developed brief (~5 s duration) absence-like seizures, with a normal EEG and sleep-deprived EEG, 7 months after first having GPi electrodes implanted.

Explantation

The electrodes described in this study were removed for various routine clinical reasons (Table 1). Informed written consent to perform electron microscopy studies on the explanted electrodes was obtained from each patient prior to surgery according to the Declaration of Helsinki. At the time of revisional surgery the dysfunctional electrodes were unplated from the skull and gently withdrawn. The intracranial portion was then cut off with a pair of heavy-duty scissors and either

<table>
<thead>
<tr>
<th>Table 1 Details of the explanted electrodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient No.</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>Dystonia patients</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>030816</td>
</tr>
<tr>
<td>030817</td>
</tr>
<tr>
<td>030500</td>
</tr>
<tr>
<td>030501</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>030688</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>030383</td>
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<td>6</td>
</tr>
<tr>
<td>030362</td>
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<tr>
<td>7</td>
</tr>
<tr>
<td>030503</td>
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<tr>
<td>8</td>
</tr>
<tr>
<td>030594</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>030623</td>
</tr>
<tr>
<td>Parkinson’s disease patients</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>040112</td>
</tr>
</tbody>
</table>

A suboptimal position indicates that some of the patients failed to respond adequately to DBS. The reasons for this include: (i) lead displacement caused by severe cervical muscle spasm produced by dystonia or dyskinesias pulling the electrode; and (ii) a change in our view of the optimal position within GPi for electrode placement in dystonia to a more anterior position than that initially targeted and used to treat Parkinson’s disease. *Duration in situ indicates the duration that the electrode was actually resident in the brain. †Washed in saline prior to fixation. ‡Electrode grossly displaced from GPi to frontal cortex. §Surface of electrode examined by SEM after tissue stripped for TEM. L = left; R = right.
placed directly in fixative, or in some cases washed in phosphate-buffered saline (PBS) prior to fixation (see below).

**Electrodes**

All the electrodes described in this study were Medtronic quadripolar model 3387 (Medtronic Inc.). The stimulating surface of the 3387 electrode is made from platinum-iridium and the insulation around the conductor wires is a fluoropolymer. The outer insulating tube is 80A urethane and a urethane adhesive is used to secure the tubing. The electrodes were prepared for either transmission (TEM) or scanning (SEM) electron microscopy, or both. A control model 3387 electrode was donated by Medtronic Europe Sarl for examination by SEM. This electrode had not been implanted.

**Patients**

A total of 21 electrodes were explanted from patients. Eighteen electrodes were sourced from eight patients with various forms of dystonia and three electrodes from two patients with Parkinson’s disease. The demographic details of the patients and their medications at the time the electrodes were removed are given in Tables 2 and 3. The intracerebral sites at which the deep brain electrodes were located, the reason for their removal and the duration that the electrodes were resident within the brain are shown in Table 1.

**Electron microscopy**

SEM was carried out to determine the relative size and distribution of the cells present and examine the extent to which they covered the surface of the electrodes. TEM was used to examine the ultrastructure of the cells removed from the electrodes and thus aid their identification.

**SEM**

A total of 10 explanted electrodes were studied by SEM (two of these were also studied by TEM). Seven electrodes were immediately fixed in 3% glutaraldehyde. The remainder (030817, 030362 and 040113) were washed briefly in PBS prior to fixation (see Table 1). The electrodes were then dehydrated through an ascending series of ethanol and critical point dried using CO₂. The electrodes were then sputter-coated with gold prior to examination in a Cambridge S360 Scanning Electron Microscope.

**TEM**

A total of 12 explanted electrodes were studied by TEM (two were also studied by SEM). The electrodes were immersed as soon as possible after removal into 3% glutaraldehyde fixative. The surface of each electrode was then gently scraped off into the fixative and centrifuged. The resultant pellet was post-fixed in 1% osmium tetroxide, dehydrated through ascending grades of ethanol and embedded in Spurr’s resin. Semi-thin sections were stained with Toluidine Blue and examined by light microscopy.

### Table 2 Demographic and medication details of Parkinson’s disease patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Patient gender, age (years)</th>
<th>Disease duration (years)</th>
<th>Medication (daily dose/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Male, 52</td>
<td>8</td>
<td>Madopar dispersible (250 mg), Sinemet (1000 mg), cabergoline (10 mg), amantadine (200 mg), domperidone (30 mg)</td>
</tr>
<tr>
<td>10</td>
<td>Female, 61</td>
<td>16</td>
<td>Madopar (1250 mg), pergolide (2.8 mg), selegeline (5 mg), dothiepin (50 mg), clonazepam (0.5 mg)</td>
</tr>
</tbody>
</table>

### Table 3 Demographic and medication details of the dystonia patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Patient gender, age (years)</th>
<th>Type of dystonia</th>
<th>Disease duration (years)</th>
<th>Medication (daily dose/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female, 36</td>
<td>Primary generalized dystonia (DYT1 negative)</td>
<td>7</td>
<td>Clonazepam (3 mg), amantadine (400 mg), amitriptyline (20 mg), benzhexol (12 mg), paracetamol (3 g), lansoprazole (15 mg)</td>
</tr>
<tr>
<td>3</td>
<td>Male, 34</td>
<td>Primary generalized dystonia (DYT1 negative)</td>
<td>27</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>Female, 49</td>
<td>Cervical dystonia</td>
<td>8</td>
<td>Diazepam (60 mg)</td>
</tr>
<tr>
<td>5</td>
<td>Female, 23</td>
<td>Myoclonic dystonia</td>
<td>21</td>
<td>Amitriptyline (25 mg)</td>
</tr>
<tr>
<td>6</td>
<td>Female, 44</td>
<td>Cervical dystonia</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Male, 41</td>
<td>Primary generalized dystonia (DYT1 negative)</td>
<td>4</td>
<td>Carbamazepine (800 mg), clonazepam (2 mg), mirtazapine (45 mg)</td>
</tr>
<tr>
<td>8</td>
<td>Male, 58</td>
<td>Primary generalized dystonia (DYT1 negative)</td>
<td>13</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Male, 54</td>
<td>Primary generalized dystonia</td>
<td>&gt;20</td>
<td>Clonazepam (0.5 mg)</td>
</tr>
</tbody>
</table>
microscopy prior to ultrathin sectioning. Ultrathin sections were stained with uranyl acetate and Reynold’s lead citrate.

Results
The surface of the non-implanted (control) 3387 electrode studied with SEM is shown in Fig. 1. The results of the TEM and SEM studies for the electrodes explanted from the dystonia and Parkinson’s disease patients are described below, and are summarized in Table 4.

Dystonia patients

SEM
One electrode (020928) could not be examined because of poor fixation. Adherent cellular material was seen on all the other electrodes examined (Fig. 2). The electrodes that had not been washed prior to fixation were largely coated with erythrocytes embedded in fibrin. Less frequently, elongate cells with extensive processes were detected. The electrodes that had been washed revealed a more diverse cellular appearance. Macrophages and giant cells were clearly visible, the latter sometimes >100 μm in diameter (Fig. 3).

TEM
The quality of ultrastructural preservation varied, which was thought to be due to a delay in fixation in two samples. Nevertheless, all samples contained numerous conspicuous multinucleated giant cells (Figs 4 and 5). Macrophages were also present, containing numerous lysosomes and sometimes having conspicuous filopodia projecting from the plasma membranes (Fig. 5). It is likely that a significant proportion of both cell forms are derived from microglia. Both the multinucleated giant cells and the macrophages were often seen to contain

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Table 4 Summary of the EM findings for each patient

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Electrode–EM number</th>
<th>EM technique</th>
<th>EM findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>020639</td>
<td>SEM</td>
<td>Poor fixation</td>
</tr>
<tr>
<td>Dystonia patients</td>
<td></td>
<td>020928</td>
<td>SEM</td>
</tr>
<tr>
<td></td>
<td>030816</td>
<td>TEM</td>
<td>Various cell types including giant cells</td>
</tr>
<tr>
<td></td>
<td>030817</td>
<td>SEM*</td>
<td>Various cell types including giant cells</td>
</tr>
<tr>
<td></td>
<td>030500</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
</tr>
<tr>
<td></td>
<td>030501</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
</tr>
<tr>
<td>3</td>
<td>030068L</td>
<td>SEM</td>
<td>Variety of cellular material</td>
</tr>
<tr>
<td></td>
<td>030068R</td>
<td>SEM</td>
<td>Variety of cellular material</td>
</tr>
<tr>
<td></td>
<td>030284</td>
<td>SEM</td>
<td>Variety of cellular material</td>
</tr>
<tr>
<td>5</td>
<td>030338/9</td>
<td>SEM and TEM</td>
<td>Surface after cells stripped for TEM</td>
</tr>
<tr>
<td></td>
<td>030338R</td>
<td>SEM</td>
<td>Surface after cells stripped for TEM</td>
</tr>
<tr>
<td></td>
<td>030361</td>
<td>SEM*</td>
<td>Variety of cellular material</td>
</tr>
<tr>
<td></td>
<td>030362</td>
<td>SEM and TEM</td>
<td>Surface after cells stripped for TEM</td>
</tr>
<tr>
<td>7</td>
<td>030502</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
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<tr>
<td></td>
<td>030503</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
</tr>
<tr>
<td>8</td>
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<td>TEM</td>
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<td></td>
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<tr>
<td></td>
<td>030623</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
</tr>
<tr>
<td>Parkinson’s disease patients</td>
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<td>021274</td>
<td>SEM</td>
</tr>
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<td>10</td>
<td>040113</td>
<td>SEM</td>
<td>Variety of cellular material including giant cells</td>
</tr>
<tr>
<td></td>
<td>040112</td>
<td>TEM</td>
<td>Macrophages and MNGC</td>
</tr>
</tbody>
</table>

*Washed in saline prior to fixation. †Surface of electrode examined by SEM after tissue stripped for TEM. MNGC = multinucleate giant cells.
highly electron-dense inclusions. These probably represented phagocytosed material, which was similar in appearance to that often seen adjacent to the cells (Fig. 6). Some samples contained flattened elongated cells that were often degenerate.

**Parkinson’s disease patients**

**SEM**

SEM performed on electrode 021274 removed from the STN of case 2 was not washed prior to fixation, and thus revealed mainly blood and fibrin. Examination of electrode 040113 that had been in the right GPi of case 10 for 31 months revealed a variety of cells including giant cells (Fig. 7).

**TEM**

TEM performed on electrode 040112 that had been in the left GPi of case 10 for 31 months showed macrophages and multinucleate giant cells that were similar in appearance to those seen in samples from patients with dystonia.

**Additional study**

A sample of the polyurethane coat of one of the electrodes was scraped off using a scalpel blade and prepared for TEM, in the same way as the other samples, in order to ascertain whether the electron-dense inclusions were polyurethane particles. The ultrastructural morphology of the polyurethane scraping did not resemble that of the inclusions.

**Discussion**

In this study we demonstrate that tissue is attached to DBS electrodes after they have been removed for various clinical
purposes, and that this tissue can be examined with electron microscopy. In this way we have detected a multinucleate giant cell reaction that was present in all TEM samples and in samples examined by SEM that had been washed in saline to remove the covering blood and fibrin clot prior to fixation. This giant cell reaction appears to be present irrespective of the duration of implantation, which varied from 3 to 24 months in eight patients with heterogeneous forms of dystonia. There have been no similar studies for patients with dystonia, nor studies involving electrodes implanted within the GPi, with which to compare our findings.

In case 10, with Parkinson’s disease, bilateral electrodes were removed 31 months after implantation in GPi; a variety of cellular material, including giant cells, was found on SEM and TEM and demonstrated a multinucleate giant cell reaction.

Haberler et al. (2000) described the pathological findings in the post mortem brains of eight Parkinson’s disease patients who had been treated with DBS for up to 70 months. In six patients, stimulation had been in the VIM and in two patients in the STN. Mild gliosis around the lead track with preservation of neural parenchyma was observed in seven of the brains. The thickness of the fibrous sheath ranged from 5 to 25 μm and a narrow rim of fibrillary gliosis (<500 μm) abutted on this sheath. Adjacent to this was a <1 mm zone of loosely scattered glial fibrillar acidic protein-positive reactive astrocytes. These findings were considered to be compatible with reactive changes to the surgical placement of the electrode. However, in two brains (6 and 7) gliosis was more prominent and around the lead track slight microglial activation was seen. In brain 6, scarce mononuclear leukocytes, siderophages and single multinucleate giant cells were detected in the track and adjacent tissue (<500 μm) and in brain 7 a mild inflammatory reaction with multinucleated giant cells engulfing tiny fragments were observed (Haberler et al., 2000). Giant cells were also found in the Parkinson’s disease case described by Caparros-Lefebvre et al. (1994).

The precise origin of the multinucleate giant cells observed in our material, brains 6 and 7 examined by Haberler et al. (2000) and the post mortem case reported by Caparros-Lefebvre et al. (1994) is uncertain. Multinucleate giant cells can be formed by the fusion of a variety of blood monocyte-derived macrophages (Stephenson, 2000). It has been suggested that multinucleated giant cells in the brains of patients with AIDS may be derived from endogenous microglia (Dickson, 1986), and it has been shown that rat (Lee et al., 1993) and pig (Peterson et al., 1996) microglial cells can be induced to fuse, forming multinucleated giant cells, in culture. Therefore, the most likely sources of multinucleate giant cells seen in our samples are intrinsic parenchymal as well as perivascular microglia, perivascular cells and related resident CNS macrophages (Graeber et al., 2002), and circulating monocytes. In this regard, it is noteworthy that a large number of activated macrophages were detected post mortem with CD68 immunolabelling around a STN cavity left by a DBS electrode resident in a Parkinson’s disease brain for 2 years (Jarraya et al., 2003). Early experimental studies have demonstrated the induction of an in vivo multinuclear giant cell response in rabbit brains by glass foreign body implantation (Oehmichen and Huber, 1976). More recently it has been shown that foreign body giant cell formation can be induced in mice and rats by the subcutaneous implantation of modified polyurethanes (Kao et al., 1994, 1995; Mathur et al., 1997; Kao, 1999). Thus it is possible that the polyurethane component of the implanted electrodes studied here could have induced the macrophage infiltrate and the formation of the multinucleated giant cells.

Our finding of electron-dense inclusions and extracellular material is intriguing, as this supports the finding in one brain [case 7 examined by Haberler et al. (2000)] of multinucleate

Fig. 6 Transmission electron micrograph (sample 030816) of a multinucleate giant cell containing electron-dense inclusions (white asterisk), in close proximity to extracellular electron-dense material. Bar = 2 μm.

Fig. 7 Scanning electron micrograph (sample 040113) showing a variety of cells on the surface of the electrode. Bar = 100 μm.
giant cells engulfing tiny fragments of foreign material. The nature and origin of this material is not known. It is unlikely to be polyurethane, since it does not resemble the ultrastructural appearance of the surface electrode material that we examined. The nature of this material will need to be determined in future studies.

It is our experience, and that of several other groups, that DBS parameters, particularly voltage (but also pulse width in dystonia patients), need to be increased over time regardless of diagnosis (Parkinson’s disease, essential tremor, dystonia and multiple sclerosis) or target site (VIM, GPi and STN) (Krack et al., 2003; Sydow et al., 2003; Wishart et al., 2003; Yianni et al., 2003a). This phenomenon may in part reflect disease progression, particularly in multiple sclerosis (Wishart et al., 2003). However, the finding by Krack et al. (2003) that STN stimulation parameters are stable after 1 year at 5-year follow-up of Parkinson’s disease patients argues against disease progression being the main cause for the parameter increases, at least for Parkinson’s disease. Thus the development of tolerance to stimulation could be an important factor in Parkinson’s disease, and possibly other movement disorders. Tolerance could occur through adaptive physiological mechanisms, but it is possible that the tissue reaction to the implanted electrode plays a role, as glialis and/or the giant cell reaction might alter tissue impedance or distort current distribution. In this regard it is interesting that we invariably found a giant cell reaction to be present from 3 months after electrode insertion, and it is our experience that the greatest stimulator parameter adjustments occur within 3 months of DBS stimulation. It is noteworthy that in one Parkinson’s disease patient who died 2 days after electrode implantation, only fresh haemorrhage, perifocal oedema and axonal spheroids were found at post mortem (Haberler et al., 2000). Conversely, after DBS implantation a beneficial ‘stun’ effect on the movement disorder is sometimes seen, which is usually transient and attributed to a microlesion and possibly oedema around the DBS electrode (Caparros-Lefebvre et al., 1994). However, in some cases this effect persists so that the stimulator is not turned on for several months or even years (T. Z. Aziz and P. G. Bain, unpublished). Although a microthalamotomy effect is the most likely mechanism for the ‘stun’ effect, it is conceivable that the giant cell reaction or gliosis caused by the electrode plays a small role in maintaining benefit in these cases. In future it may be possible to perform quantitative neuromorphological studies using SEM to examine the time course of the tissue response and its relationship to the clinical and stimulation parameters.

It may be feasible to study the development of the reaction around implanted DBS electrodes in patients using positron emission tomography (PET). As activated microglia express mitochondrial peripheral benzodiazepine binding sites (PBBS) and \( ^{11} \text{C} \)N-[1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isouquinoline carboxamide], which is a selective ligand for PBBS, can be used as a PET tracer when labelled with \( ^{11} \text{C} \) (Banati et al., 2000; Gerhard et al., 2003). Another potential way of assessing the electrode–brain interaction might be by serial monitoring of the DBS electrode’s impedance in vivo using the standard physician model 7432 programmer and 7459 software (Medtronic Inc.). The former has the potential advantage of being able to show changes throughout the length of the electrode, whilst the latter might reveal changes confined to the vicinity of the electrical contacts. In this respect, it is relevant that Caparros-Lefebvre et al. (1994) found that the accumulation of inflammatory tissue in their post mortem case occurred predominantly around the electrode sheath rather than tip.

The long-term consequences of having an active DBS electrode within the brain are not fully known. One of our dystonia patients (case 3) developed absence-like seizures 7 months after bilateral GPi stimulation. However, it is reassuring that chronic thalamic stimulation for Parkinson’s disease and various forms of tremor, including essential tremor, and STN and GPi stimulation for Parkinson’s disease have been practised safely for over 10 years and 5 years, respectively (Benabid et al., 1987; Schuurman et al., 2000; The Deep-Brain Stimulation for Parkinson’s Disease Study Group, 2001). However, there is less long-evity of experience of GPi stimulation for various types of dystonia, particularly in children (Krauss et al., 1999, 2002; Coubes et al., 2000; Yianni et al., 2003a, b). The neuro-pathological consequences of DBS are of particular relevance to younger patients, because it could become desirable to remove the electrodes in the future so that better treatments become available.

Conclusions

DBS electrodes cause a giant cell reaction around them when implanted in the brains of patients with various forms of dystonia and Parkinson’s disease. This reaction is present from 3 months to at least 31 months onwards after implantation, and may possibly represent a response to the polyurethane component of the electrodes’ surface coat. These findings may be relevant to understanding the mechanisms underlying the course of the clinical response to DBS of patients with Parkinson’s disease and various forms of dystonia, and also possibly for improving the surface properties and biocompatibility of future DBS electrodes.

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References
