

This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



## Neuroanatomical Study

# Pre-operative DTI and probabilistic tractography in four patients with deep brain stimulation for chronic pain <sup>☆</sup>

S.L.F. Owen <sup>a,\*</sup>, J. Heath <sup>a</sup>, M. Kringelbach <sup>a</sup>, A.L. Green <sup>a,b</sup>, E.A.C. Pereira <sup>b</sup>,  
 N. Jenkinson <sup>a,b</sup>, T. Jegan <sup>b</sup>, J.F. Stein <sup>a</sup>, T.Z. Aziz <sup>b</sup>

<sup>a</sup> Oxford Functional Neurosurgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

<sup>b</sup> Department of Neurological Surgery, John Radcliffe Hospital, Oxford, UK

Received 8 May 2007; accepted 11 June 2007

---

**Abstract**

This study aimed to examine, using diffusion tensor imaging (DTI), differences in electrode placement in four patients undergoing deep brain stimulation for chronic neuropathic pain of varying aetiology. A pre-operative DTI was obtained for each patient, who was then implanted with deep brain stimulation electrodes in the periventricular/periaqueductal grey area with good pain relief. Using seeds from the postoperative MRI scan, probabilistic tractography was performed from the pre-operative DTI.

© 2008 Elsevier Ltd. All rights reserved.

**Keywords:** Deep brain stimulation; Pain; Periaqueductal grey; Periventricular grey; Probabilistic tractography; Diffusion tensor imaging

---

**1. Introduction**

The periventricular and periaqueductal grey area (PVG/PAG) is part of the central pain inhibitory system controlling nociceptive pain, and has been used as a target for deep brain stimulation (DBS) for the alleviation of chronic pain for nearly three decades.<sup>1–3</sup> However, one of the key elements to a successful outcome is correct electrode placement through accurate stereotactic targeting. Some research into the PVG/PAG area has suggested that this region is somatotopically organised.<sup>4–6</sup> This study aimed firstly to examine differences in the pathways present in four patients with chronic pain of varying aetiology who had been implanted with deep brain electrodes, and secondly to determine if pre-operative probabilistic tractography could aid surgical planning for DBS in the PVG/PAG.

Pre-operative diffusion tensor imaging (DTI) was performed on four patients with chronic pain of varying aetiology. All patients were subsequently implanted stereotactically with a Medtronic 3387<sup>®</sup> deep brain electrode (Medtronic Sofamor Danek, Memphis, TN, USA) in the PVG/PAG area and a postoperative MRI was performed to check electrode placement. Probabilistic tractography was then performed on four seed areas that covered the length of the electrode contacts.

**2. Methods and materials**

Each patient had a T1-weighted axial MRI scan (2 mm thick slices parallel to the AC-PC line) prior to surgery. For surgery, a stereotactic frame base ring was applied to the patient's head under local anaesthesia. A stereotactic CT scan was then performed and using the Radionics Image Fusion<sup>®</sup> and Stereoplan<sup>®</sup> programme (Integra Radionics Inc., Burlington, MA, USA) the MRI scan was volumetrically fused to the stereotactic CT scan. This technique has been used since 1995 to eliminate errors using MRI stereotaxy alone that arise from the spatial distortions intrinsic to magnetic fields. The co-ordinates for

---

<sup>☆</sup> Support: SLFO is supported by the Norman Collisson Foundation, and TZA, by the Medical Research Council, and MLK by The Wolfson Charitable Trust.

\* Corresponding author. Tel.: +44 1865 234745; fax: +44 1865 224786.

E-mail address: [sarah.owen@physiology.ox.ac.uk](mailto:sarah.owen@physiology.ox.ac.uk) (S.L.F. Owen).

the PVG/PAG were then calculated. A double oblique trajectory was used with an entry point just anterior to the coronal suture, and laterality of approach dictated by ventricular width. A 2.7 mm twist drill skull perforation was then made to pass the electrode. The PVG/PAG was proximally located 2–3 mm lateral to the wall of the third ventricle and 2 mm anterior to the level of the posterior commissure, and distally the deepest electrode lay in the superior colliculus.

After washing the scalp with alcoholic chlorhexidine, a parasagittal posterior frontal scalp incision 3.0 mm from the midline was made contralateral to the side of pain. The PVG/PAG area was then implanted with the deep brain electrode where stimulation induced relief of pain or a sensation of warmth in the area of pain. The deepest electrode was noted to be in a satisfactory position if eye bobbing was induced at an intensity of stimulation at least twice that required for sensory effects. The electrode was then fixed to the skull using a miniplate prior to externalisation. Immediately post operatively the patient had a T1-weighted axial MRI scan (2 mm thickness, zero spacing) to confirm correct electrode placement. Further details of our surgical technique have previously been described elsewhere.<sup>7</sup>

The electrode was externalised for a week of trial stimulation. Pain was assessed before surgery and during post-operative stimulation using a McGill pain questionnaire (MPQ) on both occasions, in the presence of a specialist nurse (Table 1). For analysis of data, the ranked pain-rating index (PRI(R)) was used. In this method of scoring, each word in a category is assigned a number, depending on its severity. Using this method, the overall PRI(R) (out of 78), sensory PRI(R) (out of 42), affective PRI(R) (out of 14), evaluative PRI(R) (out of 5) and miscellaneous PRI(R) (out of 17) was calculated. The extension lead and pulse generator were then fully implanted under general anaesthesia after the trial period.

Diffusion-weighted data was acquired following the attainment of informed written consent in accordance with the local Oxford Research Ethics committee approval.

Images were acquired on a 1.5 Tesla MRI scanner (echo planar imaging, fov = 256 × 208 mm, matrix = 128 × 104, slice thickness 2 mm, in-plane resolution = 2 × 2 mm, TR 15 s, TE 106.2 ms). The diffusion weighting was isotropically distributed along 60 directions using a b-value of 1000 smm<sup>-2</sup>. For each set of diffusion-weighted data, 5 volumes with no diffusion weighting were acquired at points throughout the acquisition. Three sets of diffusion-weighted data were acquired for subsequent averaging to improve signal to noise. The total scan time for the diffusion weighted imaging (DWI) protocol was approximately 30 minutes.

A high-resolution T1-weighted structural image was also obtained with a three-dimensional 'FLASH' sequence (TR = 12 ms, TE = 5.6 ms, flip angle = 19°, with elliptical sampling of k-space, giving a voxel size of 1 × 1 × 1 mm in 5.05 minutes).

Images were analysed using tools from The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library ([www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)). Non-brain tissue was extracted from the image using the Brain Extraction Tool (BET). Diffusion data was analysed using the FMRIB Diffusion Toolbox (FDT) as previously described.<sup>8</sup>

The post-operative MRI was registered to the DWI using the FMRIB Linear Registration Tool (FLIRT). This step was performed to produce a combined image in which the seed sites could accurately be plotted from the postoperative MRI scan to the DWI scan. The deep brain stimulating electrode has four contact points in line spread over 12.1 mm including the tip). To make sure that the resulting tracts covered all contacts masks were made of each seed. FDT tractography was run from two 4 × 4 × 4 mm voxel seeds, with 5000 streamlines per seed voxel. Seeds were chosen from two 2 mm adjacent slices for each contact. The results for each contact were then combined and divided by four to give an average of all streamlines passing through each voxel. These were then opened onto the combined postoperative/diffusion space and thresholded at a minimum of 10 streamlines and a maximum of 5000 streamlines through each voxel for analysis.

### 3. Results

All four patients received unilateral DBS implantation (Table 2), two on the right and two on the left. Both the arm and leg pain patients reported significant subjective postoperative pain relief, with a drop in their post-operative MPQ PRI(R) scores ( $p < 0.05$ ; Wilcoxon signed ranks test) scores from 55 to 43 in the patient with arm pain, and 29 to 0 in the patient with leg pain. One of the stroke pain patients with hemi body pain did not achieve long term benefit from deep brain stimulation, and therefore was explanted after the 1 week trial period. The second stroke patient initially had good results, but unfortunately had a broken wire some time later. The

Table 1  
Pre- and post-operative McGill pain questionnaire (MPQ) ranked pain rating index (PRI(R)) scores for each patient

Subject	Sensory/ 42	Affective/ 14	Evaluative/ 05	Miscellaneous/ 17	Total
<i>Pre-operative</i>					
1	31	9	4	11	55
2	16	1	4	4	28
3	6	2	0	3	11
4	13	5	5	6	29
<i>Post-operative</i>					
1	28	6	2	7	43
2	N/A electrode explanted after trial period due to poor efficacy				
3	0	0	0	0	0
4	0	0	0	0	0

Table 2  
Patient history, site of stimulation, contacts used and outcome

Patient	Pain history	Site, side of stimulation	Contacts used	Pain relief achieved
1	Right brachial plexus injury	Right PVG	0 – 1 – 2+	Yes
2	Stroke, left hemi body pain	Right PVG	Failed trial	No, Explanted
3	Stroke, right hemi body pain	Left PVG	0 + 3–	Yes, but explanted due to wire breakage
4	Traumatic amputation, left lower leg stump pain	Left PVG	0 + 1–	Yes

PVG = Periventricular grey area.

stimulator was subsequently switched off and explanted, and could not be replaced as by this time the patient was too demented to be able to cooperate in any further surgery.

The probabilistic tractography results across all four patients can be seen in Table 3. Connections were found in the following areas: 3/4 patients in the mediodorsal thalamus (MDT) in contact 0, 3/4 patients in the central sulcus in contact 1 and 3/4 patients in the pre central gyrus in contact 3 (Fig. 1). All other areas (also shown in Table 3) including all connections from contact 2 were found in only 2 patients (50%).

#### 4. Discussion

Deep brain stimulation of the PVG/PAG area has been found to be effective in alleviating neuropathic pain of varying aetiologies,<sup>9</sup> and although there are very few studies describing the pathways in the PVG/PAG for DBS, a number of studies have been performed to distinguish the roles, organisation and function of specific areas that have been suggested or are known to have an involvement in chronic neuropathic pain syndromes. These studies appear to correlate with the probabilistic tractography results in our patients. DTI studies seeded in the PVG/PAG by Sillery (2005),<sup>3</sup> and Hadjipavalou et al (2006)<sup>10</sup> show connections to the frontal lobes, and horse radish peroxidase (HRP) studies by Erickson et al (2004),<sup>11</sup> reveal labeled cells within the PAG area after injection into the MDT. The other area with many connections is the pre-central gyrus and central sulcus, that has been a target for motor cortex stimulation (MCS) for pain across surgical groups for varying aetiologies with mixed results.<sup>12–15</sup>

It is well documented that the pain neuromatrix has strong links to the affective components of pain. One theory states that pain other than physical sensation governs homeostatic behavioural drive, and thus pain cannot only be considered as a physical condition. The reason for an

Table 3  
Tract connections in each patient determined using probabilistic tractography seeded from each deep brain stimulation electrode contact points

Area	1	2	3	4	Total
<i>Contact 0</i>					
SFG	x	✓	✓	x	2
PCG	✓	✓	x	✓	2
Central sulcus	x	✓	✓	x	2
STG	x	x	✓	✓	2
CM	✓	✓	x	x	2
MDT	x	✓	✓	✓	3
AN	x	x	✓	✓	2
VPL	✓	x	x	✓	2
Superior colliculus	x	✓	x	✓	2
Caudate nucleus	x	x	✓	✓	2
Putamen	x	x	✓	✓	2
Internal capsule	✓	x	x	✓	2
Cerebellum	✓	✓	x	x	2
<i>Contact 1</i>					
SFG	✓	✓	x	x	2
Central sulcus	✓	✓	x	✓	3
STG	x	x	✓	✓	2
VL	✓	✓	x	x	2
MDT	✓	x	✓	✓	3
AN	x	x	✓	✓	2
Internal capsule	✓	x	x	✓	2
Putamen	x	x	✓	✓	2
<i>Contact 2</i>					
SFG	✓	✓	x	x	2
PCG	✓	✓	x	x	2
STG	x	x	✓	✓	2
AN	x	x	✓	✓	2
Putamen	x	x	✓	✓	2
<i>Contact 3</i>					
SFG	✓	✓	x	x	2
PCG	✓	✓	x	✓	3
STG	x	x	✓	✓	2
AN	x	x	✓	✓	2
Internal capsule	✓	x	x	✓	2
Putamen	x	x	✓	✓	2
Superior colliculus	✓	x	x	✓	2

Each column represents a single patient. See Table 2 for patient characteristics.

SFG = superior frontal gyrus, PCG = pre-central gyrus, STG = superior temporal gyrus, CM = centromedial nucleus, MDT = mediodorsal thalamus, AN = anterior nucleus, VPL = ventral posterolateral nucleus, VL = ventrolateral nucleus.

increased or changed set of behaviours associated with pain is new strong thalamocortical projections involving the affective components of pain that are created. These connections affect behaviour toward the chronic pain as much as the physical stimulus.<sup>16</sup> Therefore, treating chronic pain syndromes requires consideration of the affective, as well as the sensory component, of pain, and treating both with the same degree of success. At present this is not always possible. This is demonstrated by our results with an even distribution of affective and sensory connections in all patients. However, individually patients 1 and 2 are more heavily biased toward sensory connections, where as patients 3 and 4 have a more even balance

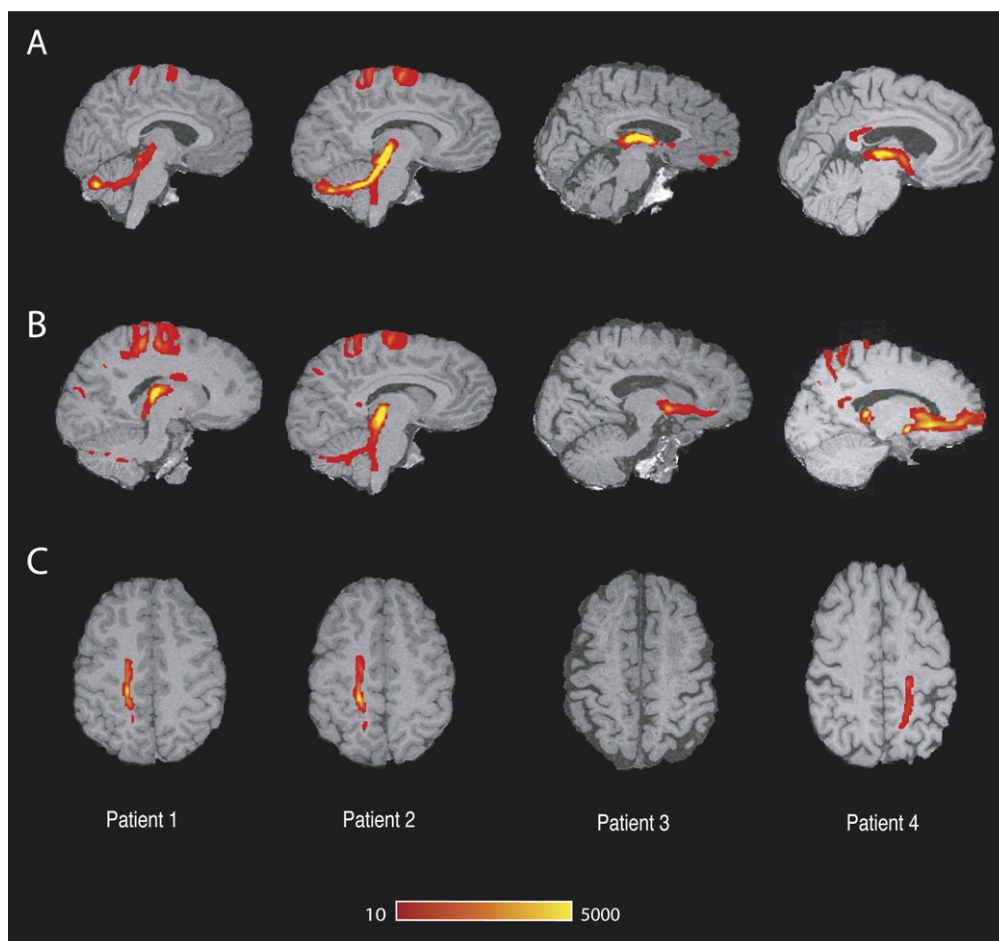


Fig. 1. Probabilistic tractography results showing the tracts found in 75% of patients (A) mediodorsal nucleus (B) central sulcus (C) pre-central gyrus. This figure is available in colour at [www.sciencedirect.com](http://www.sciencedirect.com).

between the two connections types, and include both the anterior and mediodorsal thalamic nuclei compared to patients 1 and 2 where connections are seen to the mediodorsal nucleus only. This could suggest that the trajectory of the stimulator is slightly different in patients 1 and 2 compared to patients 3 and 4, (Fig. 2) or that there may be some degree of somatotopy within the PVG/PAG where the site of stimulation is deeper for more superior structures such as the arm and the face and more superior for the lower limbs creating an ‘upside down’ somatotopy for the whole body, that is, the lower body areas are uppermost, and in addition the somatotopic map is tilted, being slightly higher anteriorly than posteriorly. Somatotopy of the PVG/PAG area has been suggested in previous studies where a movable electrode distinguished a difference in the ears, fore paws, hind paws and tail of rats,<sup>4</sup> and 5 separate clusters of neurons connecting the PVG/PAG with differing areas of the spinal cord.<sup>5</sup> Studies by Bittar et al. (2005)<sup>6</sup> also suggested using DBS that there was an ‘upside down’ somatotopy in the same area in man.

There are several methodological issues that should be considered when interpreting these tractography results. First, it is not possible to differentiate incoming from outgoing pathways in diffusion data. Second, tractography is sensitive primarily to large fibre pathways, therefore smaller pathways, or those through regions of fibre crossing or complexity may not be detected, as synapses cannot be detected with the methods used here. Therefore other areas that are well known to be part of the pain matrix do not appear to be connected to electrode sites in these patients.

## 5. Conclusion

Considering the restrictions of these methods, it is clear that further research is necessary to improve tractography software to produce more accurate fibre tracking. Additionally, development of DTI scanning techniques that would allow post-operative DTI scanning would be important. With these developments, our results suggest that probabilistic tractography as a surgical planning tool may be a possibility in the future.

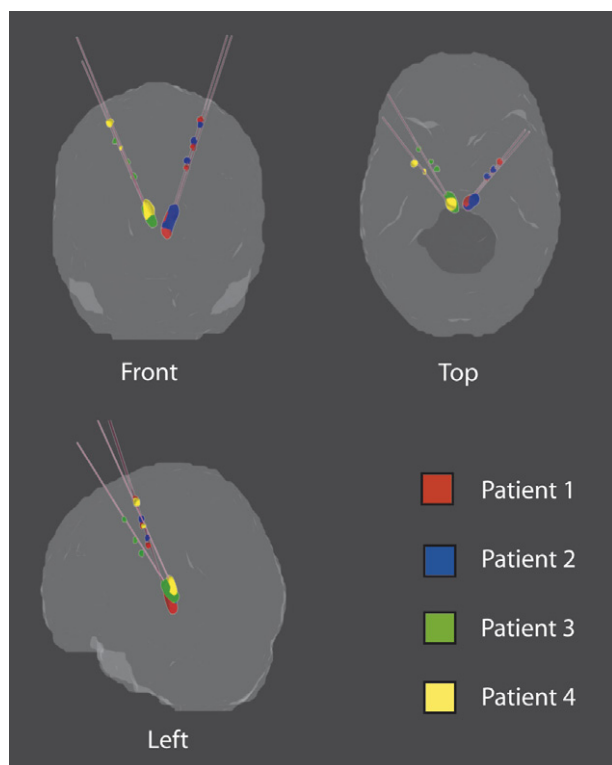


Fig. 2. 3D images of the trajectory of the electrode placement in each patient. Note stimulators for patients with arm pain (1 & 2) are deeper than patients with leg pain (3 & 4). This figure is available in colour at [www.sciencedirect.com](http://www.sciencedirect.com).

## References

- Richardson DEAH. Pain reduction by electrical brain stimulation in man. Part 1: Acute administration in periaqueductal and periventricular sites. *J Neurosurg* 1977(47):178–83.
- Richardson DEAH. Pain reduction by electrical stimulation in man. Part 2: Chronic self-administration in the periventricular grey matter. *J Neurosurg* 1977(47):184–94.
- Sillery E, Bittar RG, Robson MD, et al. Connectivity of the human periventricular-periaqueductal gray region. *J Neurosurg* 2005;103(6):1030–4.
- Soper WY, Melzack R. Stimulation-produced analgesia: evidence for somatotopic organization in the midbrain. *Brain Res* 1982;251(2):301–11.
- Klop EM, Mouton LJ, Holstege G. Segmental and laminar organization of the spinothalamic neurons in cat: evidence for at least five separate clusters. *J Comp Neurol* 2005;493(4):580–95.
- Bittar RG, Nandi D, Carter H, et al. Somatotopic organization of the human periventricular gray matter. *J Clin Neurosci* 2005;12(3):240–1.
- Owen SL, Green AL, Stein JF, et al. Deep brain stimulation for the alleviation of post-stroke neuropathic pain. *Pain* 2006;120(1–2):202–6.
- Behrens TE, Woolrich MW, Jenkinson M, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magn Reson Med* 2003;50(5):1077–88.
- Bittar RG, Kar-Purkayastha I, Owen SL, et al. Deep brain stimulation for pain relief: A meta-analysis. *J Clin Neurosci* 2005;12(5):515–9.
- Hadjipavlou G, Dunckley P, Behrens TE, et al. Determining anatomical connectivities between cortical and brainstem pain processing regions in humans: a diffusion tensor imaging study in healthy controls. *Pain* 2006;123(1–2):169–78.
- Erickson SL, Melchitzky DS, Lewis DA. Subcortical afferents to the lateral mediodorsal thalamus in cynomolgus monkeys. *Neuroscience* 2004;129(3):675–90.
- Tsubokawa T, Katayama Y, Yamamoto T, et al. Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)* 1991;52:137–9.
- Canavero S, Bonicalzi V, Paolotti R, et al. Therapeutic extradural cortical stimulation for movement disorders: a review. *Neurol Res* 2003;25(2):118–22.
- Canavero S, Bonicalzi V. *Central Pain Syndrome Pathophysiology, Diagnosis and Management*. New York: Cambridge University Press; 2007.
- Nandi D, Smith H, Owen S, et al. Peri-ventricular grey stimulation versus motor cortex stimulation for post stroke neuropathic pain. *J Clin Neurosci* 2002;9(5):557–61.
- Craig AD. A new view of pain as a homeostatic emotion. *Trends Neurosci* 2003;26(6):303–7.