

ORIGINAL ARTICLE

Preoperative DTI and probabilistic tractography in an amputee with deep brain stimulation for lower limb stump pain

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Abstract

This study aimed to find out whether preoperative diffusion tensor imaging (DTI) and probabilistic tractography could help with surgical planning for deep brain stimulation in the periaqueductal/periventricular grey area (PAG/PVG) in a patient with lower leg stump pain. A preoperative DTI was obtained from the patient, who then received DBS surgery in the PAG/PVG area with good pain relief. The postoperative MRI scan showing electrode placement was used to calculate four seed areas to represent the contacts on the Medtronic 3387[®] electrode. Probabilistic tractography was then performed from the preoperative DTI image. Tracts were seen to connect to many areas within the pain network from the four different contacts. These initial findings suggest that preoperative DTI scanning and probabilistic tractography may be able to assist surgical planning in the future.

Key words: Deep brain stimulation, diffusion tensor imaging, periaqueductal grey, periventricular grey, probabilistic tractography.

Introduction

The lower limb amputee population in England is thought to be approximately 52,000¹ and a recent study on pain in lower limb amputees with vascular disease in Liverpool revealed that just over half of the patients receiving lower limb amputation still suffered from stump pain 6 months after surgery.² Over the past few years various drug therapies have been tried such as oral gabapentin³ and amitriptyline,⁴ and via spinal injection, such as intrathecal fentanyl and lidocaine,⁵ and extradural bupivacaine and morphine⁶ without long-term success. Surgically spinal cord stimulation has been tried for this condition, however placebo-controlled studies on the effects of dorsal column stimulation report that most clinicians observed only moderate success rate with this technique.⁷ This conclusion has also been backed up by Canavaro & Bonicalzi.⁸ However, deep brain stimulation (DBS) in the periaqueductal/periventricular grey area (PAG/PVG) has produced more promising long-term results in patients suffering with neuropathic pain.^{9,10}

In recent years the development of DTI scanning techniques and probabilistic tractography have contributed to *in vivo* neuroanatomical studies on

humans, such as mapping out the human thalamus,¹¹ and distinguishing connections to three areas of the parietal cortices.¹² However, unlike HRP studies, synapses are not visible and no directionality can be deduced from connecting fibre tracts. However, preoperative DTI scanning and probabilistic tractography could possibly be useful to fine tune stereotactic target sites for deep brain stimulation by the identification of tract connections from the electrode and their correlation with clinical outcome.

First it is necessary to have a brief understanding of the pathways that make up the pain neuromatrix. Peripheral nerve fibres synapse at the level of the dorsal horn (A δ in layer I and V, and C fibres in layer II) that then decussate and travel up the contralateral side of the spinal cord forming the spinothalamic tract. These ascend to eventually terminate in the ventroposterolateral nucleus (VPL). From here fibres connect with the somatosensory cortex (S1). Another pathway involved in pain processing is the spino-reticular tract, nociceptive fibres along this pathway synapse in levels VII and VIII that then terminate at the level of the reticular formation in the pons and the medulla. This mainly involves the C fibres of 'slow pain', which then project to the hypothalamus, intra-laminae of the thalamus, the limbic system and

the cortical area of the cingulate gyrus. This pathway is concerned with relaying nociceptive information that contributes to the motivational and affective response to pain. Finally, the last tract is known as the spinomesencephalic tract. These fibres synapse in laminae I, IV, V and VI, and ascend to terminate in the areas of the PAG, nucleus cuneiformis and superior colliculus. This pathway is associated with the affective part of pain. The main thalamic nuclei involved in the ascending pathways for pain are the ventral medial posterior (VMpo) nucleus, which projects to the insular, the VPL, which projects to the primary sensory cortex (S1) and the medial dorsal nucleus, which projects to the anterior cingulate gyrus.

The descending pathways include the PAG/PVG a small area of grey matter that surrounds the cerebral aqueduct of sylvius. The importance of descending pathways is that they modulate a variety of PAG outputs including incoming pain stimulus.¹³ The PAG/PVG has direct connections (from the ventrolateral part) that are reciprocal with the amygdale.¹⁴ The descending projections via the nucleus raphe magnus modulate the responses caused by noxious stimuli of the spinal dorsal horn neurons. The ascending projections modulate the pain sensitive response in the thalamus.¹⁵ It has been suggested that the PAG has an inhibitory effect on the spinal nociceptive function through activating descending serotonergic and noradrenergic pathways arising from the rostral ventral medulla and pontine noradrenergic nuclei. Studies on rats have shown that some of the efferents from PAG terminate in the rostral ventral medulla and pontine noradrenergic nuclei, while a large proportion project to the intermediate subdivision of the pontobulbar reticular formation. It is suggested that the pathways (afferent and efferent) from these areas may mediate PAG evoked activities towards the spinal horn that inhibit spinal nociceptive function.¹⁶ Inhibitory pathways from the rostral ventral medulla, as well as the LC descend to the spinal cord and make inhibitory connections in laminae I, II and V of the dorsal horn.

This study aimed to trace the fibre tracts that had been seeded on the preoperative DTI scan using the four contact points of a Medtronic 3387[®] deep brain electrode that had been implanted into the PAG/PVG area as seed sites.

Case report

The patient was a 55-year-old male who underwent left lower leg amputation due to traumatic injury 25 years ago. Since the injury the patient has suffered from constant extreme stump hypersensitivity without any phantom limb pain to the extent that the lightest touch to the stump was excruciating.

Previous treatments have included drug therapy via epidural catheter, local anaesthesia injected

directly into the stump and three spinal stimulators. None of these treatments produced a successful outcome.

Materials and methods

Diffusion-weighted data was acquired following the attainment of informed written consent in accordance with local Oxford Research Ethics committee approval. Images were acquired preoperatively on a 1.5 T Siemens magnetic resonance imaging (MRI) scanner (echo planar imaging, f.o.v. = 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 s/mm². For each set of diffusion-weighted data, five 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 DWI protocol was approximately 45 min.

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 min).

The patient had a T1 weighted axial MRI scan (2 mm thick slices parallel to the AC-PC line) prior to surgery. For surgery, a CRW base ring was applied to the patients' head under local anaesthesia. A stereotactic CT scan was then performed and using the Radionics Image Fusion[®] and Stereoplan[®] programme the MRI scan was volumetrically fused to the stereotactic CT scan. This technique has been used since 1995 to eliminate the errors of using MRI stereotaxy alone that arise from the spatial distortions intrinsic to magnetic fields. The co-ordinates for the PAG/PVG are 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 PAG/PVG 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 PAG/PVG area was then implanted with a Medtronic 3387 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 externalization. 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.^{9,10}

The electrode was externalized 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, which preoperatively the patient scored at 10 for each category. For analysis of data, we used the ranked pain-rating index [PRI(R)].¹⁷ In this method of scoring, each word in a category is assigned a number, depending on its severity. Using this method, we calculated overall pain rating index—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). The extension lead and pulse generator was then fully implanted under general anaesthesia after the trial period.

The goal of probabilistic tractography is to obtain a connectivity index of the movement of water molecules along white matter pathways that reflect fibre organization. The application of probabilistic algorithms it is possible to develop a voxel-based connection maps from areas of interest into grey matter that are sensitive to normal pathways and structural changes. Therefore, it can be a useful tool to analyse the changes in white matter tracts caused by disease.¹⁸

Images were analysed using tools from FMRIB's software library (FSL^{www.fmrib.ox.ac.uk/fsl}).¹⁹ Non-brain tissue was extracted from the image using the Brain Extraction Tool (BET).²⁰ Diffusion data was analysed using 'FMRIB's Diffusion Toolbox' (FDT) as previously described.^{21,22}

The postoperative MRI image was registered to the diffusion image 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 diffusion weighted scan. The MedtronicTM 3387 deep brain-stimulating electrode is 1.3 mm in diameter and has four contact points measuring 1.5 mm each with a 1.5 mm gap separating each contact in line spread over 10.5 mm (12.1 including tip). To make sure that the resulting tracts covered all contacts masks were made of each seed. FDT tractography was run from two $4 \times 4 \times 4$ 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.

Results

After seeding the electrode contacts separately the highest amount of connections through all contacts were traced to medial orbital gyrus, superior temporal gyrus, putamen, mediodorsal thalamus, reticular nucleus and the anterior nucleus (Fig. 1). Connections in three of the contacts were found in the internal capsule, hypothalamus, corpus callosum, superior parietal gyrus and the central sulcus. Connections found in only two of the contacts include the amygdala, caudate nucleus, superior colliculus, pre- and postcentral gyrus. Finally, connections found in only one contact include the anterior orbital gyrus, hippocampus, globus pallidus, inferior temporal gyrus, lateral dorsal thalamus, ventro-posterior lateral thalamus (VPL), and the lateral posterior thalamus (Fig. 2). The results of all tracts present are shown in Table I.

The surgical outcome produced good pain relief from stimulation during and after surgery, to the point where the stump could be squeezed without discomfort. The patient also reported a dramatic drop in postoperative pain by scoring the MPQ in all categories to 0 when contact 0 was used for stimulation. However, the patient received no pain relief when stimulation was applied from the other contacts, the PRI scores for which are shown in Table II.

Discussion

In previous studies for deep brain stimulation for pain within the service at Oxford 75% of patients fully implanted found alleviation from stimulation within the PAG/PVG area, whereas less than 10% benefited from stimulation in the sensory thalamus only, and 20% benefited from stimulation in

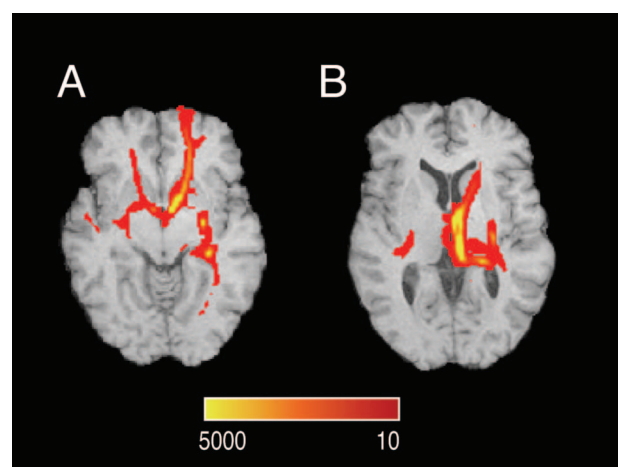


FIG. 1. (a) Axial slice showing the medial orbital gyrus, superior temporal gyrus and the reticular nucleus across all contacts. (b) Axial slice showing the mediodorsal nucleus, anterior nucleus and putamen across all contacts. Tracts have been thresholded from 5000 streamlines down to 10 streamlines. This figure is reproduced in colour in *British Journal of Neurosurgery* online.

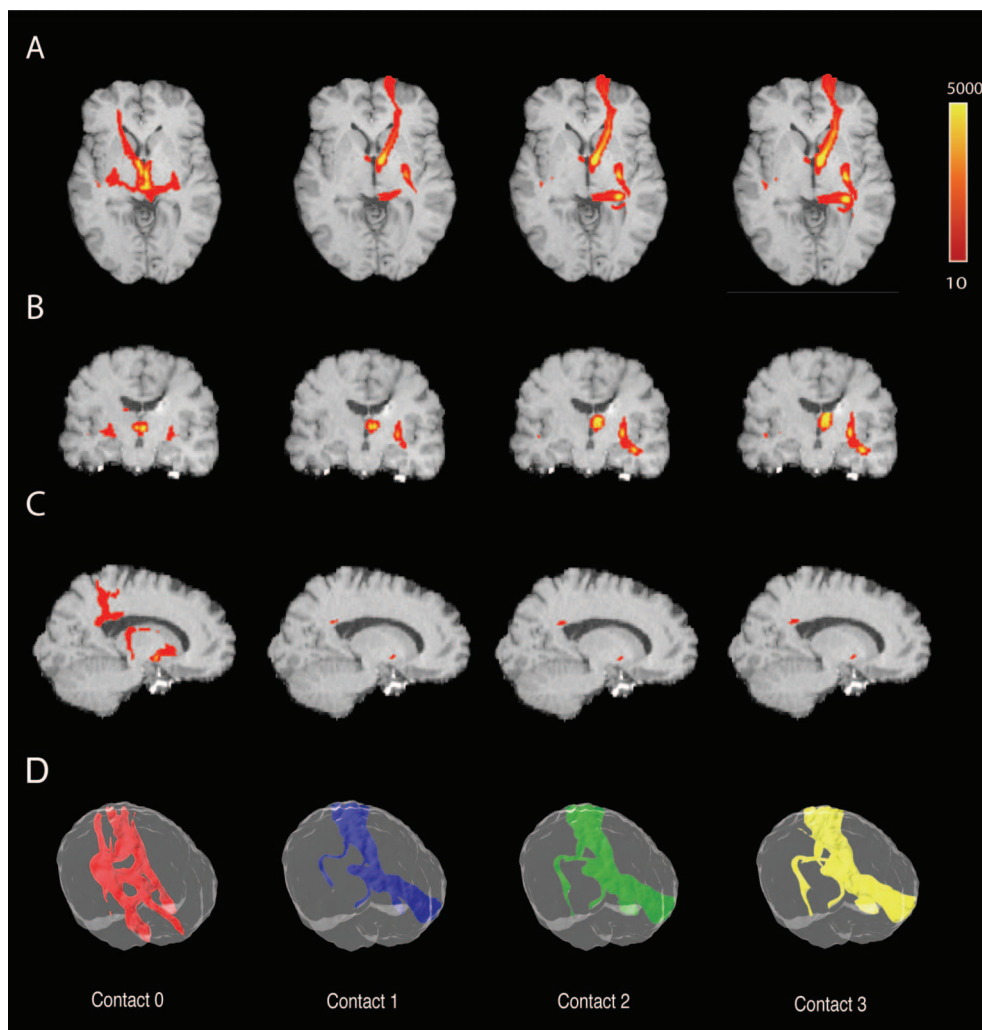


FIG. 2. (a) Axial, (b) coronal, (c) sagittal and (d) 3D rendering showing the variation of tract patterns between contacts at the same slice level. Note: contact 1, 2 and 3 have a similar pattern compared to that of contact 0 that produced the best pain relief on trial stimulation.

both areas.¹⁰ These results have now favoured implantation in the PVG/PAG as first choice over other areas for chronic neuropathic pain syndromes at Oxford.

In this study using probabilistic tractography we observed fibre pathways connecting the seeds from the electrode contact points to many areas within the brain that are known to be linked with the PVG/PAG and pain circuits. These results also correlate with other DTI studies in humans by Sillery *et al.*²³ However, the study also shows connections with some areas that are not relevant to the PVG/PAG, but are known to be responsible for other functions not connected with pain circuits. This may be that the seed areas on the tractography were too large and that could possibly be rectified with smaller seed sites or using smaller slices on the scan sequence; or that the upper two contacts are possibly placed above the PVG/PAG area, which would correlate with the clinical outcome where the best pain relief has been achieved with contact 0 (the deepest contact), and no pain relief was achieved from the trial stimulation of the other contacts. The probabilistic tractography results show connections to many of the cortical

regions associated with pain, and in particular contacts 0 and 1 show connections with important structures included in the affective dimension of the pain matrix such as the amygdala, VPL and mid-anterior orbitofrontal cortex. These connections do not appear to be present in contacts 2 and 3. It is thus likely that the positive outcome of this treatment is as much due to changing the activity in the regions modulating the affective responses in this patient, rather than only a change in the sensory dimension of pain.

There are several other 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. Secondly, tractography is sensitive primarily to large fibre pathways, therefore, smaller pathways or those through regions of fibre crossing or complexity may not be detected, the reason for this is that synapses cannot be detected with the methods used here. Therefore, areas such as the cingulate and insula that are well known to be part of the pain matrix do not appear to be connected to electrode sites as highly in these patients as might have been expected.

TABLE I. A table showing the results of tract connections from seeds taken in the PAG/PVG for each electrode contact, where 0 is the deepest contact and 3 is the upper most contact

Contact. no.	Anterior orbital Gyrus	Medial orbital gyrus	Superior temporal gyrus	Amygdala	Putamen	Hippocampus
3	x	√	√	x	√	√
2	x	√	√	x	√	x
1	x	√	√	√	√	x
0	√	√	√	√	√	x
Total	1	4	4	2	4	1
Contact no.	Internal capsule	Caudate nucleus	Hypothalamus	MD thalamic nucleus	Anterior thalamic nucleus	Reticular nucleus
3	√	√	x	√	√	√
2	x	x	√	√	√	√
1	√	x	√	√	√	√
0	√	√	√	√	√	√
Total	3	2	3	4	4	4
Contact no.	Superior colliculus	VPL thalamic nucleus	Corpus callosum	Pre-central gyrus	Superior parietal gyrus	
3	√	x	√	√	√	
2	x	x	x	x	√	
1	x	x	√	x	x	
0	√	√	√	√	√	
Total	2	1	3	2	3	
Contact no.	Central sulcus	Globus pallidus	Post central gyrus	Inferior temporal gyrus	Lateral dorsal nucleus	Lateral posterior nucleus
3	√	x	√	√	√	√
2	√	√	√	x	x	x
1	√	x	x	x	x	x
0	x	x	x	x	x	x
Total	3	1	2	1	1	1

Key: √ = tracts present; x = no tracts present.

TABLE II. Pre- and postoperative pain rating index (PRI) scores

	Sensory/42	Affective/14	Evaluative/05	Miscellaneous/17	Total
Preoperative	13	5	5	6	29
Postoperative	0	0	0	0	0

Conclusion

Overall, this study suggests that mapping the connections of individual contacts of a deep brain-stimulating electrode with probabilistic tractography produces different patterns of tracts between contacts, and therefore may be useful in the future to aid stereotactic targeting for deep brain stimulation.

Acknowledgements

SLFO is supported by the Norman Collisson Foundation and TZA by the Medical Research Council, and MLK by The Wolfson Charitable Trust.

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