Deep brain surgery for pain

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ii. Abstract

Deep brain stimulation (DBS) is a neurosurgical intervention now established for the treatment of movement disorders. For the treatment of chronic pain refractory to medical therapies, several prospective case series have been reported, but few centres worldwide have published findings from patients treated during the last decade using current standards of technology. This thesis seeks to survey the current clinical status of DBS for pain, investigate its mechanisms and their interactions with autonomic function, its clinical limitations and ablative alternatives.

Presented first is a review of the current status of analgesic DBS including contemporary clinical studies. The historical background, scientific rationale, patient selection and assessment methods, surgical techniques and results are described. The clinical outcomes of DBS of the sensory thalamus and periventricular / periaqueductal grey (PAVG) matter in two centres are presented including results from several pain and quality of life measures.

A series of translational investigations in human subjects receiving DBS for pain elucidating mechanisms of analgesic DBS and its effects upon autonomic function are then presented. Single photon emission tomography comparing PAVG, VP thalamus and dual target stimulation is described. Somatosensory and local field potential (LFP) recordings suggesting PAVG somatotopy are shown. ABPM results demonstrating changes with PAVG DBS are given and Portapres studies into heart rate variability changes with ventral PAVG DBS are detailed. Investigations using naloxone are then shown to hypothesise separate dorsal opioidergic and ventral parasympathetic analgesic streams in the PAVG. Finally, cingulotomy in lung cancer to relieve pain and dyspnoea results are discussed in the context of altering pain and autonomic function by functional neurosurgery. Pain and autonomic interactions and mechanisms in deep brain surgery for pain are then discussed alongside its limitations with proposals made for optimising treatment and improving outcomes.

iii. Acknowledgements

First and foremost I thank the patients who consented to outcome studies and in particular those who became subjects of translational investigations, willing to travel and often tireless despite chronic illness.

Alex Green advised me in science, surgery, use of autonomic equipment, DBS equipment and edited my early publications diligently. The method of mapping DBS electrode contacts to brain atlas positions using neuroimaging is his (appendix 2).

Tipu Aziz let me stand on giants' shoulders.(Pereira et al. 2008b)

Liz Moir tirelessly collated clinical outcomes at Oxford except one year when I collected them while she had a baby.

Rui Vaz, Paulo Linhares, Maria José Rosas and Clara Chamadoira undertook surgeries and assessments in Porto with Tipu Aziz and I advising.

Sandra Boccard performed statistical analysis for chapters 2 and 3.

Shouyan Wang taught me signals analysis and devised much of the software and methodology that enabled the invasive electrophysiological recordings.

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I dedicate this thesis to the memories of John Gillingham and Henry Schmidek, neurosurgical giants with feet of clay and iron. Both humoured my attempts to honour Voltaire's adage that the role of the physician is to entertain his patient while nature takes its course.(Pereira et al. 2008c; Pereira et al. 2009b)

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v. Abbreviations

ABPM	ambulatory blood pressure monitoring
AC	anterior commissure
ACC	anterior cingulate cortex
BP	blood pressure
BPA	brachial plexus avulsion
BPI	brief pain inventory
CRW	Cosman-Roberts-Wells
CT	computerised tomography
DBP	diastolic blood pressure
DBS	deep brain stimulation
EEG	electroencephalography
EMG	electromyography
ERP	event-related potential
HF	high frequency
HR	heart rate
HRV	heart rate variability
LF	low frequency
LFP	local field potential
MCS	motor cortex stimulation
MEG	magnetoencephalography
MPQ	McGill pain questionnaire
MRI	magnetic resonance imaging
UW-NPI	University of Washington neuropathic pain score
PC	posterior commissure
PET	positron emission tomography
PP	pulse pressure
PRI(R)	Pain rating index (ranked)
PAVG	periaqueductal and periventricular grey matter
rCBF	regional cerebral blood flow
SBP	systolic blood pressure
SCS	spinal cord stimulation
SEP	somatosensory evoked potential
SNR	signal to noise ratio
SPA	stimulation produced analgesia
SPET	single photon emission tomography
VAS	visual analogue scale
VP	ventral posterior thalamus
VPL	ventral posterior lateral thalamic nucleus
VPM	ventral posterior medial thalamic nucleus

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viii. Published chapters

Chapter 1 (in parts and variations)
1. Pereira EAC, Green AL, Nandi D, Aziz TZ (2007). *Deep brain stimulation: indications and evidence.* **Expert Review of Medical Devices.** Sep;4(5):591-603.

2. Kringelbach ML, Pereira EAC, Green AL, Owen SLF, Aziz TZ (2009). *Deep brain stimulation for chronic pain.* **Journal of Pain Management.** 2(3):301-314.

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Chapter 4
7. Pereira EAC, Wang S, Owen SL, Green AL, Aziz TZ (2013). *Human periventricular gray somatosensory evoked potentials suggest rostrocaudally inverted somatotopy.* **Stereotactic and Functional Neurosurgery.** Accepted

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Chapter 10 (in parts and variations)

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17. Pereira EAC, Paranathala M, Hyam JA, Green AL, Aziz TZ (2013). *Anterior cingulotomy improves malignant mesothelioma pain and dyspnoea.* **British Journal of Neurosurgery.** Submitted
16. Pereira EAC, Boccard SG, Chamadoira C, Linhares P, Rosas MJ, Rebelo V, Vaz R, Aziz TZ (2013). *Thalamic deep brain stimulation relieves neuropathic pain after amputation or brachial plexus avulsion.* **Neurosurgical Focus.** Submitted

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Awards

2007 **British Neurosurgical Research Group Best Presentation Prize**

2008 **Medtronic High Five Europe Oral Abstract Award**

2012 **American Association of Neurosurgeons William H. Sweet Young Investigator Award**

Section 1

The clinical status of deep brain stimulation for pain

Chapter 1: Introduction

1.1. Summary

Deep brain stimulation (DBS) is a neurosurgical intervention of demonstrated efficacy, safety and utility in the treatment of movement disorders. For the treatment of chronic pain refractory to medical therapies, many prospective case series have been reported, but few have published findings from patients treated during the last decade using current standards of neuroimaging and stimulator technology. Here the history, science, selection, assessment, surgery and personal clinical experience of DBS of the ventral posterior thalamus (VP), periventricular / periaqueductal grey matter (PAVG) and latterly rostral anterior cingulate cortex (ACC; Cg24) in patients treated now at two centres (John Radcliffe, Oxford and Hospital de São João, Porto) over 12 years is summarised.

Several experienced centres continue DBS for chronic pain with success in selected patients, in particular those with pain after amputation, brachial plexus avulsion (BPA), stroke and cephalalgias including anaesthesia dolorosa. Other successes include pain after multiple sclerosis and spine injury. Somatotopic coverage during awake surgery is important in the technique, with cingulate DBS considered for whole body pain or after unsuccessful DBS of other targets.

Findings discussed from neuroimaging modalities, invasive neurophysiological insights from local field potential (LFP) recording and autonomic assessments may translate into improved patient selection and enhanced efficacy, encouraging larger clinical trials.

This thesis seeks to survey the current clinical status and outcomes of DBS for pain, investigate its mechanisms and their interactions with autonomic function, its clinical limitations and ablative alternatives.

1.2. Historical background

The pioneer neurosurgeon Lauri Laitinen once commented that "when one sets out to make a historical survey of surgical attempts to relieve the tremor and rigor in Parkinson's disease, one cannot help feeling that it would have been a far easier task to list those nervous structures which have not been attacked" (Laitinen 1972; Pereira and Aziz 2006b). Neurosurgical attempts to relieve intractable pain mirror his wry observation, all structures from peripheral nerve, through dorsal root, spinal cord, midbrain and thalamus to cingulate cortex having been first lesioned and later electrically stimulated or perfused with analgesics or anaesthetics (figure 1.1). Yet chronic pain continues to present a considerable burden to society, transcending many debilitating medical diseases including cancer, stroke, trauma and failed surgery (Ashburn and Staats 1999). Its prevalence may be over 20% (Gureje et al. 1998). Neuropathic pain was recently redefined as pain caused by a lesion or disease of the somatosensory system (Jensen et al. 2011). Its symptom severity and duration are often greater than for other types of chronic pain (Torrance et al. 2006), with 5% of adults debilitated despite analgesic medication (Bouhassira et al. 2008). For such patients, neurosurgery offers several treatments.

The concept of ameliorating persistent pain by DBS originates from clinical studies six decades ago. On the basis of septal self-stimulation experiments in rodents (Olds and Milner 1954) and reports of analgesia in patients receiving septal DBS for psychiatric disorders (Heath 1954; Pool et al. 1956b), Heath and Mickle postulated that stimulating the same area that produced pleasure might relieve pain. They successfully reduced a patient's cancer pain over several weeks with intermittent stimulation (Heath and

Mickle 1960). The findings were replicated by a case series using improved equipment a decade later (Gol 1967).

Further impetus for DBS was provided in the mid-1960s by the theoretical paradigm shift initiated by Melzack and Wall's gate theory (Melzack and Wall 1965) and advances in stimulator technology. Gate theory was translated first into implantable peripheral nerve stimulators (Sweet and Wepsic 1968) and then into spinal cord stimulation (SCS) (Shealy et al. 1967), developed by Medtronic Inc. (Minneapolis, USA) into a commercially available permanently implantable device (Mullett 1978; 1987).

Identification of the PAVG regions as a target for DBS has its origins in animal research. Reynolds and others were able to perform major surgery in awake rodents using analgesia induced by periaqueductal grey (PAG) stimulation alone (Mayer et al. 1971; Reynolds 1969). Pain relief by PAVG DBS was first reported in patients by Richardson and Akil then Hosobuchi (Hosobuchi et al. 1977; Richardson and Akil 1977a; b; c). Evidence supporting ventral posterior lateral and medial (VPL/VPM) thalamic nuclei and adjacent structures as putative targets for DBS came from ablative surgery (Ervin et al. 1966; Mark and Ervin 1965; Mark et al. 1960; White and Sweet 1969) leading Hosobuchi to treat anaesthesia dolorosa with VPM thalamic DBS (Hosobuchi et al. 1973). Several others pioneered thalamic DBS including Mazars (Mazars et al. 1974; Mazars et al. 1973; Mazars et al. 1960; Mazars 1975) and Adams who, along with Hosobuchi, also targeted the internal capsule (Adams et al. 1974; Fields and Adams 1974; Hosobuchi et al. 1975). Observations from inadvertent localisation errors and investigations into current spread from the PAVG led others to target more medial thalamic nuclei including the centromedian-parafascicular complex

(Cm-Pf) (Andy 1980; Boivie and Meyerson 1982; Ray and Burton 1980; Thoden et al. 1979). The rostral ACC (Cg24) was recently targeted for DBS on the basis of functional neuroimaging demonstrating its activation and half a century of its lesioning by cingulotomy in cancer pain (Cosgrove and Rauch 2003; Foltz and White 1962a; Spooner et al. 2007), a topic revisited in chapter 9.

The rapid diffusion of electrical stimulation treatments for multifarious clinical indications by the mid-1970s led the United States (US) Food and Drug Administration (FDA) to sponsor a symposium to evaluate their merits (Gildenberg 1977b). Only pain treatments were documented to be both safe and effective (Gildenberg 1977a; 2006), albeit in an era when the long-term complications of the then recently discovered levodopa upon Parkinson's disease were yet to be revealed. Crucial primate investigations elucidating basal ganglia functions and presaging a renaissance in DBS for movement disorders had also not yet been undertaken (Pereira and Aziz 2006a; b).

Despite the consensus, the US Medical Device Amendments of 1976 compelled the FDA to request DBS manufacturers to conduct further studies to show the benefits of DBS for pain and an additional ruling in 1989 required clinical trials to demonstrate safety and efficacy. Two multi-centre trials were conducted, first in 1976 using the Medtronic Model 3380® electrode (196 patients) and second in 1990 with the Model 3387® (50 patients) that superceded it (Coffey 2001). The two studies were an amalgam of prospective case series from participating neurosurgical centres, neither randomised nor case controlled, and both suffered from poor enrolment and high attrition. Other shortcomings included heterogeneous case mixes with underspecified patient selection criteria, and subjective and unblinded assessment of patient outcomes. Confounds arose from inconsistencies in deep brain sites stimulated, numbers of electrodes used per

patient and stimulation parameters chosen. Improvements made to the later Model 3387 trial included limiting deep brain sites stimulated to two per patient and using visual analogue scores (VAS) to rate pain intensity for outcome assessment, but its included cases per centre were tiny, with a mean of five and median of three patients treated.

Neither trial satisfied study criteria for efficacy of at least half of patients reporting at least 50% pain relief one year after surgery. US FDA approval for analgesic DBS was therefore not sought by the device manufacturer. However, intriguingly, the large numbers of patients lost to follow-up resulted in a steady increase with time in the proportion of patients with at least 50% pain relief; two years after implantation they comprised 18 out of the 30 remaining patients (60%) followed-up in the Model 3380 trial and 5 out of the 10 in the Model 3387 trial (50%). Nonetheless, the trials resulted in the US FDA giving DBS for pain 'off label' status, thus precluding its approval by medical insurers (Coffey 2001; Long 1998; 2000). As a consequence, few clinical investigations into DBS for pain using current technology and techniques have been reported.

In the last decade only five centres, appear to have published case series of more than six patients (Green et al. 2006a; Hamani et al. 2006b; Levy 2003; Marchand et al. 2003; Owen et al. 2006a; Rasche et al. 2006; Yamamoto et al. 2006). Only about 20 groups worldwide reported long-term efficacy in up to 83% of patients with follow-up of up to six years (see table 1.1). In contrast, both other centrally implantable neurostimulation treatments for pain - SCS and motor cortex stimulation (MCS) - have continued to yield research publications, albeit mostly of uncontrolled case series (Nguyen et al. 2011; Taylor 2006), with small randomized, controlled, clinical trials in SCS emerging (Kemler et al. 2008; Kumar et al. 2008; Manca et al. 2008).

The Oxford experience is that DBS is superior to MCS for selected refractory pain syndromes (Nandi et al. 2002b). Similarly DBS appears more appropriate than SCS for certain pain aetiologies, although little published data exists controlling for surgeon and patient differences. Two retrospective studies from the same group have compared all three modalities of central neurostimulation, but the results are confounded first by different treatments trialled both between and sequentially within patients and second by limited outcome information (Katayama et al. 2001a; b). Recent reviews attempting to compare the three neurostimulatory therapies have been limited by variable outcome measures and hetereogeneous case mix (Coffey and Lozano 2006; Levy et al. 2011). Over the last twelve years, Oxford has treated many patients with analgesic DBS, regularly publishing results for many implanted and amenable to follow-up (Bittar et al. 2005d; Green et al. 2006a; Owen et al. 2007b; Owen et al. 2006a; Owen et al. 2006b). The Oxford and Porto experience is described and results detailed in chapters 2 and 3 alongside other current studies summarized here to clarify the current status of DBS for pain.

1.3. Patient selection

Historically, clinical approaches to DBS have sought to categorise patients first by cause of pain and second by dichotomising the pain into such categories as nociceptive or deafferentation, 'epicritic' or 'protopathic', peripheral or central. Such distinctions are largely unhelpful to patient selection here as a gathering body of human functional neuroimaging and electrophysiological evidence confirms that chronic pain arises concomitant with centrally mediated changes related to neuronal plasticity, regardless of aetiology (Anderson et al. 2006; Apkarian et al. 2005; Coderre et al. 1993; Melzack et

al. 2001; Schweinhardt et al. 2006; Stern et al. 2006). Thus, it can be assumed that chronic pain of organic origin following neural injury and refractory to medical treatment is largely central pain and thus neuropathic. The challenges to patient selection for DBS then become twofold. First the confirmation that the patient's pain is neuropathic and neither factitious nor psychogenic. Second the selection of those with neuropathic pain who are likely to derive benefit from DBS.

Essential to the patient selection process is assessment by a multi-disciplinary team consisting as a minimum of a pain specialist, neuropsychologist and neurosurgeon. Comprehensive neuropsychological evaluation forms best practice in patient selection for DBS to exclude psychoses, addiction and medically refractory psychiatric disorders and ensure minimal cognitive impairment (Lang et al. 2006; Saint-Cyr and Trepanier 2000; Shulman et al. 1982; Voon et al. 2006). Quantitative assessment of the pain and health related quality of life should be a requirement of the pre-operative patient selection process. The preference in Oxford is to use both VAS (scale 0–10) to rate pain intensity and the McGill pain questionnaire (MPQ) for pain evaluation (Carlsson 1983; Melzack 1975), the latter giving additional qualitative information and including a quality of life assessment. Alternatively the University of Washington Neuropathic Pain Score (UW-NPS) and Brief Pain Index (BPI) can be utilised, as is done in the Porto series (Cleeland and Ryan 1994; Galer and Jensen 1997). Quality of life can be assessed using the Short Form 36 (SF-36) and, in Oxford, the VAS part of the Euroqol five-dimensional assessment tool (EQ-5D), (Euroqol 1990; Medical Outcomes 1991; Ware et al. 1993). The patient records their VAS twice daily in a pain diary over a period of 12 days. The 24 VAS scores are reviewed to ensure consistency and clarified with the patient if inconsistent. The EQ-5D, SF-36 and MPQ are administered by the

pain specialist pre-operatively. The MPQ is repeated on a separate occasion independently by the neuropsychologist and scored using the ranked pain rating index. The Oxford experience is that certain items of the MPQ can predict a good response to DBS. In particular, over 80% of Oxford patients who describe 'burning' pain have found benefit from DBS, regardless of whether VP, PAVG or both are stimulated. Published patient data links resolution of burning pain with blood pressure (BP) reduction and long-term PAVG DBS analgesia implicating cardiovascular changes in this type of pain (Green et al. 2006c), but further multivariate analysis of other MPQ items, other brain targets and other measurable cardiovascular parameters are required to elucidate further the phenomenon.

The specific aetiology of the chronic pain appears less important to efficacy than its symptom history which may involve hyperalgesia, allodynia and hyperpathia. The pain must have a definable organic origin with the patient refractory to or poorly tolerant of pharmacological treatments. Surgical treatments may have been attempted, for example peripheral neuroablative or decompressive procedures for trigeminal neuralgia, however Failure of other neurostimulatory therapies should not be considered a prerequisite for DBS. Patients tend to have been refractory to medications for at least two years. One preference is to trial DBS rather than SCS or MCS in carefully selected patients wherever the aetiologies of chronic pain are consistent with neuronal reorganisation at multiple levels of the central neuromatrix.

Experience of DBS for pain after limb injury or BPA (Bittar et al. 2005d; Owen et al. 2006b) encourages its ongoing application. A paradigm shift towards central brain reorganisation as a mechanism underlying phantom limb pain (Ramachandran 2005; Ramachandran and Rogers-Ramachandran 2000) support its rationale. DBS for

amputation and BPA pain are focused upon by Porto in chapter 3. Other pain aetiologies for which good outcomes have been obtained using DBS are stroke (Owen et al. 2006a; Pereira et al. 2008d), cephalalgia including anaesthesia dolorosa (Green et al. 2003; Green et al. 2006a), multiple sclerosis (Hamani et al. 2006b), genital pain and malignancy (Owen et al. 2007b; Owen et al. 2006b). However, to select patients for DBS primarily by aetiology rather than by findings on history, examination and using assessment tools is to oversimplify their chronic pain and risk poor outcomes. Rather than using inflexible selection criteria, the preference in patient selection is expert opinion after multi-disciplinary assessment demonstrating quantitatively severe pain refractory to medication for at least one year with significantly impaired quality of life and qualitative pain suggestive of neuropathic changes without predominantly spinal involvement. There appears little merit in opiate or naloxone administration to determine suitability for DBS although a historical literature exists (Levy 2003). Medical contraindications to DBS include uncorrectable coagulopathy obviating neurosurgery and ventriculomegaly sufficient to preclude direct electrode passage to the surgical target unless guide tubes are used (Patel et al. 2007).

Considering cephalalgias, cluster headache has been successfully treated with DBS of the posterior hypothalamic nuclei and investigated using multiple translational methods as for chronic pain (Brittain et al. 2009; Owen et al. 2007a; Ray et al. 2007). As I review elsewhere (Grover et al. 2009), this debilitating condition has responded impressively to DBS in Oxford's initial experience and others' and is worthy of multi-centre, randomised, controlled clinical trials although recruitment of sufficient numbers of patients would be challenging. Further consideration of cluster headache is beyond the scope of this thesis.

1.4. Scientific rationale

1.4.1. Anatomy

Thalamic and midbrain DBS targets are contralateral to the painful side of the body, but the ACC is targeted bilaterally. Sites for DBS can be divided anatomically first into somaesthetic regions of the ventrobasal thalamus, second into more medial midbrain regions surrounding the third ventricle and aqueduct of Sylvius, including the grey matter (PAVG) and medial thalamic centromedian and parafascicular nuclei (Cm-Pf) and thirdly into rostral ACC area Cg 24, 20-25 mm posterior to the anterior horns of the lateral ventricles. The surgeon's ultimate adjustment of intracerebral electrode position is directed by awake patient reports of somaesthetic localisation during intra-operative stimulation. Such subjective information may alter the final electrode site by up to several mm from pre-operative target co-ordinates. A guiding principle is the established somatotopic organisation of the somaesthetic VP thalamic and PAVG regions. Human microelectrode studies reveal a mediolateral somatotopy in the contralateral ventroposterior thalamus, the head of the homunculus being medial and the feet lateral (Lenz et al. 1988). Subjective observation of a rostrocaudally inverted sensory homunculus in contralateral PAVG (Bittar et al. 2005c) is investigated in chapter 5. The PAVG target is found at a point 2-3 mm lateral to the third ventricle, 5-10 mm inferior to the posterior commissure (PC) and on average 10-15 mm posterior to the mid-commissural point. Its pertinent anatomical boundaries in the midbrain include the medial lemniscus laterally, superior colliculus inferoposteriorly and the red nucleus inferoanteriorly. Sensory thalamic targets are found 5-8 mm posterior to the mid-commissural point or in line with PC and from 5 mm below to 2 mm above it. The

VPM is targeted for facial pain only and found midway between the lateral wall of the third ventricle and the internal capsule, the arm area of VPL is 2-3 mm medial to the internal capsule and the leg area of VPL 1-2 mm medial to the internal capsule. The sensory thalamus is bordered by Cm-Pf medially, the internal capsule laterally, the thalamic fasciculus, zona incerta and subthalamic nucleus inferiorly, the thalamic nucleus ventralis intermedius anteriorly and the pulvinar thalamic nucleus posteriorly.

1.4.2. Physiology

A wealth of electrophysiological, anatomical and radiological evidence in humans and animals, reviewed elsewhere, establishes both PAVG and ventrobasal thalamus as structures important to pain perception and the pathophysiology of chronic pain syndromes (Behbehani 1995; Craig 2003; Gauriau and Bernard 2002; Kupers and Kehlet 2006; Peyron et al. 2000a; Romanelli and Esposito 2004; Sewards and Sewards 2002; Tracey 2005; Willis and Westlund 1997). The subtleties of hierarchical position and behavioural function of individual brain structures, whether sensory-discriminative, attentional, motivational-affective or hedonic, are much debated. However, the consensus is towards a pain neuromatrix also involving spinal cord, posterior hypothalamus, amygdala, and neocortical structures including somatosensory, insula, ACC and prefrontal cortex as depicted in figure 1.2 (Price 2000). Whether pain control is top-down or bottom-up in its hierarchy is unresolved and often depends upon the experimental paradigm used. Human electrophysiological studies of neuronal coherence have utilised somatosensory evoked potentials and Granger causality predictive modelling to suggest that PAVG exerts ascending modulation upon VP in a bottom-up model of pain processing, a finding that functional MRI would be unable to

confirm due to insufficient temporal resolution (Garcia-Larrea et al. 2000; Kupers and Kehlet 2006; Zambreanu et al. 2005).

Central to the rationale for DBS is the concept of aberrant neuronal firing at the target sites concomitant with the chronic pain. Human and animal electrophysiological experiments show increased thalamic neuronal firing in pain (Yamashiro et al. 2003). Comprehensive reviews of electrophysiological studies conclude that the mechanisms of analgesic stimulation are not clearly delineated (Duncan et al. 1991; Gybels and Sweet 1989; Levy 2003; Tronnier 2003; Weigel and Krauss 2004; Young and Rinaldi 1997). From insights revealed by basal ganglia microelectrode recordings and DBS for movement disorders reviewed elsewhere (Brown 2003; Engel et al. 2005; Hutchison et al. 2004), I postulate that altered rhythmic activity in VP and PAVG neurons is likely to play an important role in the pathophysiology of central pain. At either target, the Oxford clinical experience is that in general DBS at lower frequencies (≤50 Hz) is analgesic and higher frequencies (>70 Hz) hyperalgesic (Bittar et al. 2005a; Nandi and Aziz 2004; Pereira et al. 2008d), supporting a dynamic model whereby synchronous oscillations in discrete neuronal populations centrally modulate chronic pain perception. Analgesic DBS may therefore either disrupt pathological high frequency synchronous oscillations or, more likely, augment pathologically diminished low frequency synchronous oscillations in the thalamic and reticular components of a reticulo-thalamo-corticofugal pain neuromatrix. A positive correlation between analgesic efficacy at either DBS site and the amplitude of slow frequency (<1 Hz) VP LFPs has been shown (Nandi et al. 2003; Nandi et al. 2002a), allowing for physiologically modulated artefact (Xie et al. 2006). There is now also early evidence that patients off DBS have characteristically enhanced low frequency (8-14 Hz) power spectra of both PAVG and

VP LFPs when in pain (Green et al. 2009). Further research is required to elucidate if such neuronal signatures could aid patient selection, in particular if combined with technical advances in non-invasive functional neuroimaging and electrophysiological techniques like single photon emission computed tomography (SPET) and magnetoencephalography (MEG) to characterise functional neuronal connectivity (Kringelbach et al. 2007; Ray et al. 2009). SPET is utilised in chapter 5 to evaluate regional brain activation by analgesic DBS.

The PAVG is a structure optimally sited anatomically to integrate interoceptive function, both from adjacent mesencephalic cardiovascular centres and more distal pain processing areas. Its autonomic effects have been well studied in animals (Bandler et al. 1991; Bandler et al. 2000; Behbehani 1995; Carrive 1993; Rossi et al. 1994) and changes noted with DBS (Young and Rinaldi 1997). A positive correlation between degree of analgesia in patients receiving PAVG DBS and magnitude of BP reduction has been demonstrated (Green et al. 2006c), and shown that whereas dorsal PAVG stimulation can acutely elevate BP, ventral stimulation reduces it (Green et al. 2006b; Green et al. 2005a). Such findings advance investigations for objective markers of chronic pain and also potential selection of patients who may respond best to PAVG DBS. Indeed studies into ambulatory blood pressure monitoring (ABPM) as to whether such BP changes might be sustained in chapter 6 and investigations into heart rate variability changes in chapter 7 may provide objective somatic measures of efficacy that correlate to subjective rating scales. Detailed autonomic testing utilising such equipment as tilt-tables, Portapres and real-time VAS recording may also elucidate such possibilities.

Current thinking is that ventral PAVG DBS engages analgesia commensurate with passive coping behaviour whereas dorsal PAVG DBS may involve "fight or flight" analgesia with associated sympathetomimetic effects (Green et al. 2006c). However, evidence to substantiate the conjecture that PAVG DBS acts via augmenting endogenous opioid release is contentious. The hypothesis arose from animal experiments revealing stimulation produced analgesia reversed by naloxone (Akil and Liebeskind 1975; Akil et al. 1976) and human studies that also showed elevated levels of cerebrospinal fluid enkephalins and endorphins with DBS (Akil et al. 1978; Hosobuchi et al. 1977; Hosobuchi et al. 1979). However, the cerebrospinal fluid measures were artefactual (Dionne et al. 1984; Fessler et al. 1984) and double blinded investigation in humans has revealed no cross-tolerance between DBS and morphine and similar reversibility between naloxone and saline placebo (Young and Chambi 1987), confirming others' findings (Boivie and Meyerson 1982; Meyerson 1980). Chapter 8 seeks to clarify whether naloxone and placebo effects upon DBS are similar, arguing against an opioid dependent mechanism. Furthermore, naloxone and saline effects upon PAVG LFPs are assessed to evaluate if both opioids and contextual influences can modulate neuronal responses in the pain neuromatrix independent of DBS, in agreement with the dynamic rate model proposed above.

An obstacle yet to be surmounted in the quest to understand the mechanisms of analgesic stimulation is the lack of adequate animal models of chronic pain (Blackburn-Munro 2004; Oliveras and Besson 1988). In addition to their limited homology in chronic pain paradigms, the smaller brains of rodent and murine models increase targeting inaccuracies, in particular for small brainstem structures like PAVG. Such experience emphasises the important opportunities presented by patient based

translational research into DBS to study the mechanisms underlying its efficacious analgesia.

1.5. Surgical technique

Informed written patient consent is obtained after detailed explanations of the risks and potential benefits of the procedure and counselling for its duration of approximately two hours under moderate sedation and local anaesthesia with the head fixed and cranial stereotaxis applied. A week or more prior to surgery, patients have a T-1 weighted MRI scan. For surgery, a Cosman-Roberts-Wells (CRW) base ring is applied to the patient's head under local anaesthesia. A stereotactic CT scan is then performed and the MRI scan is volumetrically fused to it using computerised image fusion and stereotactic planning programs to eliminate spatial distortions that arise from magnetic field effects (Orth et al. 1999; Papanastassiou et al. 1998). The co-ordinates for the PAVG and VPL or VPM and entry trajectory are then calculated (figure 1.3). If ACC is being targeted, different calculations are made targeting 20-25 mm posterior to the frontal horns of the lateral ventricles (figure 1.4). A frontal trajectory avoiding the lateral ventricles is preferred. DBS targets are described in the previous anatomy section.

After a 3 cm parasagittal scalp incision and separate 2.7 mm twist drill craniostomy per electrode, both VP and PAVG have been implanted to date with Medtronic model 3387 or St Jude Medical model 6143 quadripolar electrodes. In the middle of the Oxford series, PAVG was favoured, but of late, VP implantation has commonly been chosen first. Excellent intra-operative analgesia obviates implantation of a second electrode in up to one third of patient, and VP is avoided in those with marked thalamic damage, for example following stroke. Many of the Oxford cohort have received PAVG or dual

target DBS. ACC is only implanted if the aforementioned targets do not give analgesia, in thalamic post-stroke pain or if the pain distribution is whole or hemibody. Final electrode position is determined by intra-operative clinical assessment reliant upon subjective reporting by the awake patient - microelectrode recording is not routinely used. Bipolar 5-50 Hz stimulation is performed initially, pulse width 100-450 μs, amplitude 0.1-3 V. VP stimulation aims to supplant painful sensation by pleasant paraesthesia and PAVG stimulation seeks to induce a sensation of warmth or analgesia in the painful area. Adjustment is primarily somatotopic so as to evoke appropriate topographic responses, but the assessor should be alert to pyramidal signs suggesting capsular involvement with VP DBS, and with PAVG DBS for oscillopia and reports of visual disturbances caused by superior collicular involvement or facial paraesthesia arising from medial lemniscus stimulation. Each electrode is fixed to the skull by a miniplate and its leads externalised parietally via temporary extensions. Immediately after surgery, a further stereotactic CT is performed and co-registered as before to confirm electrode position. MRI may be performed after surgery during the week prior to IPG insertion for further anatomical target corroboration.

After a week of post-operative clinical assessment, a decision is made whether to permanently implant the electrodes in a second operation under general anaesthesia. They are connected to an IPG implanted subcutaneously, usually infra-clavicularly or alternatively intra-abdominally in subcutaneous fascia. Both non-rechargeable and rechargeable IPGs have been used to date. The Oxford surgical technique is detailed further elsewhere (Bittar et al. 2005a; Joint et al. 2002; Pereira et al. 2007b).

1.6. Clinical assessment

All electrodes are externalised for a week of trial stimulation. During this period, the patient records VAS scores at least twice daily and is kept blinded to DBS settings. Targets are trialled individually for 1-2 days using the stimulator parameters described to determine which settings of quadripolar electrode contact polarities confer maximum analgesia to the optimal somatic region. Monopolar stimulation is also trialled if bipolar settings fail to give pain relief. After this period, both electrodes are trialled together for 1–2 days. If the patient is satisfied with the degree of pain relief obtained, full implantation of the efficacious electrode(s) is performed and DBS commenced at the optimised stimulation parameters. In general, surgeons do not decide between permanent implantation of PAVG, VP or dual site stimulation on any criteria other than demonstrable efficacy in each individual patient.

Another method favoured for evaluating analgesia in single cases and small groups of patients is the N-of-1 trial (McLeod et al. 1986; McQuay 1990; Pereira et al. 2007b). A randomised, placebo-controlled intra-patient trial is conducted whereby the patient receives pairs of treatment periods during which each intervention, be it DBS on or off or different stimulation targets or parameters, occurs once. The order of treatments is randomised and the effects of treatment or placebo can be compared between treatment periods. The validity of N-of-1 trials has been suggested using the VAS, and their concordance with overall MPQ has been demonstrated for VP, PAVG and dual target DBS (Green et al. 2004). Blinding and randomisation methodologies have also been adopted by others to investigate the efficacy of thalamic DBS (Marchand et al. 2003). However, the process is labour intensive for the clinician and thus not routinely practicable with limited clinical resources.

Patients ideally leave hospital the day after IPG implantation and their progress is followed by clinic appointments at one month, three months, six months and then six monthly thereafter. Initially, they are given a pain diary to record their VAS and stimulator settings weekly for review at follow-up. In addition to being able to switch the DBS on and off at will, they are usually only given control over its voltage up to 6V.

1.7. Evidence and literature review

There are no recent North American guidelines for DBS for pain due to its off-label indication in the USA. I have contributed to the European Federation of Neurological Socieies' guidelines on neurostimulation therapy for neuropathic pain which concludes that DBS should be limited to specialist centres willing to study and report their outcomes due to the few recent case series published (Cruccu et al. 2007). The UK National Institute for Health and Clinical Excellence approves it based on expert opinion and patient reported outcomes including Oxford patients (NICE 2011).

Several reviews of DBS for chronic pain have been published - many expert, some commentaries, several systematic (Adams and Hosobuchi 1977; Adams et al. 1977; Bendok et al. 2003; Bittar et al. 2005b; Burchiel 2001; Coffey 2001; Coffey and Lozano 2006; Cruccu et al. 2007; Duncan et al. 1991; Garonzik et al. 2001; Gildenberg 2006; Gybels 2001; Gybels et al. 1998; Gybels and Sweet 1989; Hosobuchi 1980; 1988; Kaplitt et al. 2004; Krauss et al. 2002; Levy et al. 2011; Levy 2003; Long 1998; Meyerson 1988; North and Levy 1994; Osenbach 2006; Rasche et al. 2006; Raslan 2006; Siegfried 1991; Simpson 1999; Simpson 2003; Stojanovic 2001; Tasker and Vilela Filho 1995; Wallace et al. 2004; Young and Rinaldi 1997).

A systematic search (for search methods see appendix 1) identifies a number of primary studies (Adams and Hosobuchi 1977; Akil et al. 1978; Baskin et al. 1986; Dieckmann

and Witzmann 1982; Green et al. 2006a; Gybels 1980; Gybels and Kupers 1990; Gybels et al. 1993; Hamani et al. 2006b; Hosobuchi 1978a; 1983; 1986; 1987; Hosobuchi et al. 1977; Hosobuchi et al. 1979; Katayama et al. 2003; Krauss et al. 2002; Kumar et al. 1997; Levy et al. 1987; Marchand et al. 2003; Mazars et al. 1974; 1979; Mazars 1975; Meyerson 1983; Nandi et al. 2003; Nandi et al. 2002b; Owen et al. 2007b; Owen et al. 2006b; Plotkin 1982; Rasche et al. 2006; Ray and Burton 1980; Richardson and Akil 1977a; b; c; Schvarcz 1980; Shulman et al. 1982; Siegfried 1987; Tasker and Vilela Filho 1995; Thoden et al. 1979; Tsubokawa et al. 1985; Tsubokawa et al. 1984; Tsubokawa et al. 1982; Turnbull et al. 1980; Young and Brechner 1986; Young and Chambi 1987; Young et al. 1985; Young and Rinaldi 1997). Published case series of at least six patients using current DBS targets are listed in table 1.1 and their efficacy summarised. Where the same authors reviewed their clinical data more than once, only their latest or largest patient series was considered. Pain relief scores showing 50% or more improvement or verbal ratings of 'good' or 'excellent' after surgery were considered successful outcomes and patients not permanently implanted included as failed outcomes. Not all authors reported such failures, however, leading to overestimation of efficacy in some reports. The literature is also obfuscated by varying and often simplistic or subjective outcome measures with a paucity of double-blind, placebo-controlled studies. Only four groups to my knowledge have published studies of at least six patients using current standards of target localisation and currently available models of deep brain stimulator in all patients with adequate follow-up and description of outcomes (Hamani et al. 2006b; Marchand et al. 2003; Owen et al. 2007b; Rasche et al. 2006). All other primary studies are based on cases first implanted

more than a decade ago, some using electrodes now no longer commercially available and some targeting the internal capsule.

VAS scores frequently did not mirror patients' subjective improvements in function and quality of life, suggesting its limitations as an assessment tool and consideration either of the emergence of a late tolerance phenomenon or unmasking of other types or regions of pain concomitant with increased patient activities of daily living. Specific DBS complications consented for are stroke (<1%), seizures (<1%), haemorrhage (0.3%), death (0.1%), the need for non-rechargeable (IPG revision surgery every 3-5 years due to limited battery life and infection (5%). Patients are also counselled for the possibility that they may derive no benefit from DBS or not tolerate it well, again necessitating its removal; no specific percentage is quoted as each case is best considered individually. Outcomes by aetiology from the Oxford cohort are described elsewhere (Bittar et al. 2005d; Green et al. 2006a; Green et al. 2004; Nandi and Aziz 2004; Owen et al. 2007b; Owen et al. 2006a; Owen et al. 2006b). However, detailed analysis of long-term outcomes of the complete Oxford cohort is analysed in chapter 2.

Table 1.1.1. Summary of case series of thalamic and periventricular deep brain stimulation for pain. PAVG, periventricular and periaqueductal grey and adjacent mid-line thalamic nuclei; VPL/VPM, ventroposterolateral and ventroposteromedial thalamic nuclei; VAS, visual analogue scale; MPQ, McGill Pain Quesionnaire; HRQoL, health related quality of life; NRS, numerical rating scale.

Study reference	Number of patients implanted	Deep brain target	% success: long-term (initially)	Follow-up time (months): range (mean)	Evaluation method used
(Mazars et al. 1974; 1979; Mazars et al. 1973; Mazars et al. 1960; Mazars 1975)	84 121	PAVG VPL/VPM	0 69	n/a	verbal report
(Akil et al. 1978; Richardson and Akil 1977a; b; c)	30	PAVG	70	1-46 (18)	self report; NRS
(Gybels 1980)	7	PAVG	16		nociceptive stimuli
(Schvarcz 1980)	6	PAVG	33	6-42	verbal report
(Ray and Burton 1980)	28	PAVG	76	1-33 (14)	n/a
(Shulman et al. 1982; Turnbull et al. 1980)	24	VPL/VPM	67	1-47 (10)	verbal report; HRQoL; analgesic use
(Dieckmann and Witzmann 1982; Thoden et al. 1979)	26 20	PAVG VPL/VPM	28	6-54	three category rating
(Plotkin 1982)	48 12	PAVG VPL/VPM	79	6-42 (36)	VAS
(Tsubokawa et al. 1985; Tsubokawa et al. 1984; Tsubokawa et al. 1982)	24	VPL/VPM	63	n/a	three category rating; activity; analgesic use
(Meyerson 1983)	41	PAVG VPL/VPM	41	n/a	VAS; HRQoL
(Adams and Hosobuchi 1977; Baskin et al. 1986; Hosobuchi 1978a; 1983; 1986; 1987; Hosobuchi et al. 1977; Hosobuchi et al. 1979)	65 77	PAVG VPL/VPM	77 (82) 58 (68)	14-168	verbal report; analgesic use
(Levy et al. 1987)	141	PAVG VPL/VPM	31 (59)	24-168 (80)	verbal report

Table 1.1.2.. Summary of case series of thalamic and periventricular deep brain stimulation for pain (continued). PAVG, periventricular and periaqueductal grey and adjacent mid-line thalamic nuclei; VPL/VPM, ventroposterolateral and ventroposteromedial thalamic nuclei; VAS, visual analogue scale; MPQ, McGill Pain Quesionnaire; HRQoL, health related quality of life; NRS, numerical rating scale.

Study reference	Number of patients implanted	Deep brain target	% success: long-term (initially)	Follow-up time (months): range (mean)	Evaluation method used
(Siegfried 1987)	89	VPL/VPM	67	n/a	VAS; verbal report; analgesic use
(Gybels and Kupers 1990; Gybels et al. 1993)	36	VPL/VPM	30 (61)	(48)	nociceptive stimuli
(Kaplitt et al. 2004; Tasker and Vilela Filho 1995)	25 43 12	VPL/VPM Both Other	14 (overall)	n/a	verbal report
(Young and Brechner 1986; Young and Chambi 1987; Young et al. 1985; Young and Rinaldi 1997)	178	PAVG VPL/VPM	50 (80)	12-180 (90)	VAS; analgesic use; HRQoL
(Kumar et al. 1997)	68	PAVG VPL/VPM	62 (78)	6-180 (78)	VAS, MPQ
(Krauss et al. 2002)	12	PAVG	n/a	n/a	n/a
(Tronnier 2003)	8 3 45	PAVG VPL/VPM Both	63 33 38	6-66	n/a
(Marchand et al. 2003)	6	VPL/VPM	83	(42)	NRS, nociceptive and placebo stimuli
(Hamani et al. 2006b)	21	PAVG VPL/VPM	24 (62)	2-108 (24)	VAS, use of DBS
(Green et al. 2006a; Nandi et al. 2003; Nandi et al. 2002b; Owen et al. 2007b; Owen et al. 2006b) not including latest results in chapter 2	38 34 24	PAVG VPL/VPM Both	49 (84)	6-60 (27)	VAS, MPQ, HRQoL

Figure 1.1. Structures in the pain neuromatrix targeted by ablative neurosurgery (in red) and electrical stimulation or neuromodulation (in green).

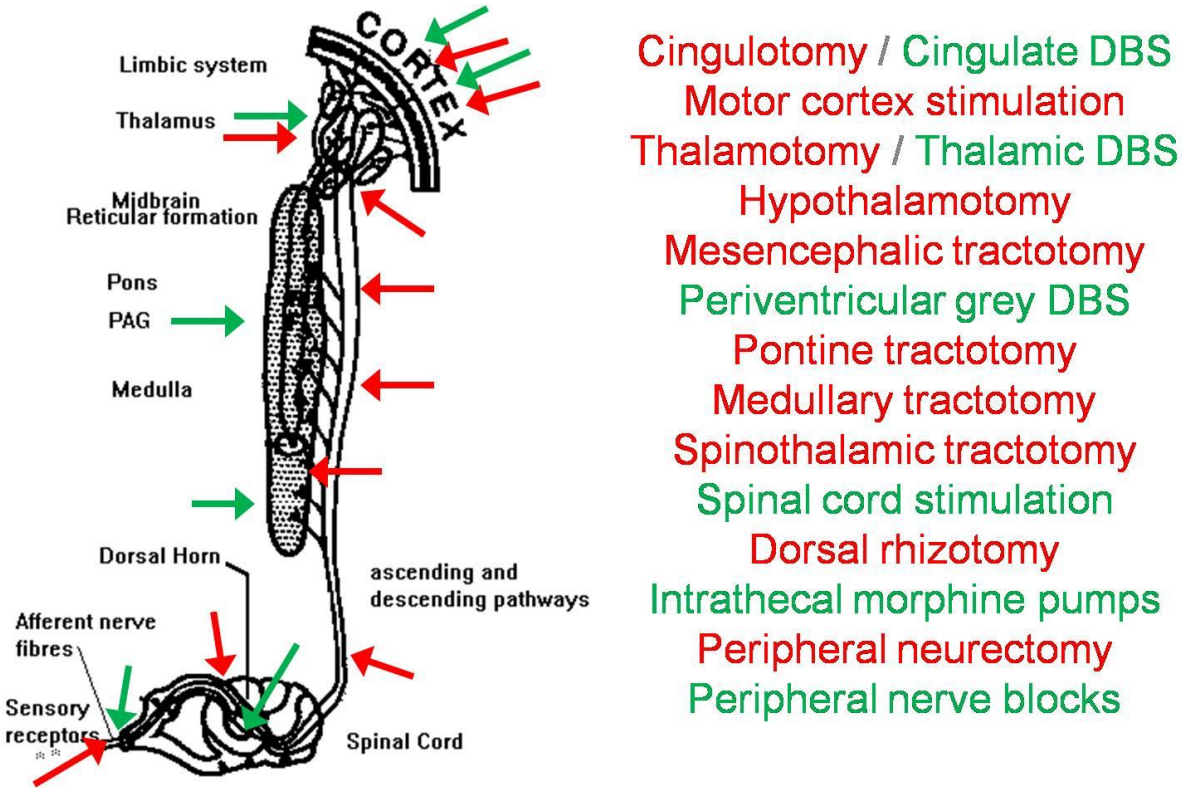


Figure 1.2. Schematic of brain structures in a contemporary pain neuromatrix including those targeted by deep brain stimulation*. PAG, periaqueductal grey*; PB, parabrachial nucleus of the dorsolateral pons; VMPo, ventromedial part of the posterior nuclear thalamic complex; MDvc, ventrocoaudal part of the medial thalamic dorsal nucleus*; ACC, anterior cingulate cortex*; PCC, posterior cingulate cortex; HT, hypothalamus*; S1 and S2, first and second somatosensory cortical areas; PPC, posterior parietal complex, SMA, supplementary motor area; AMYG, amygdala; PF, prefrontal cortex. After (Price 2000)

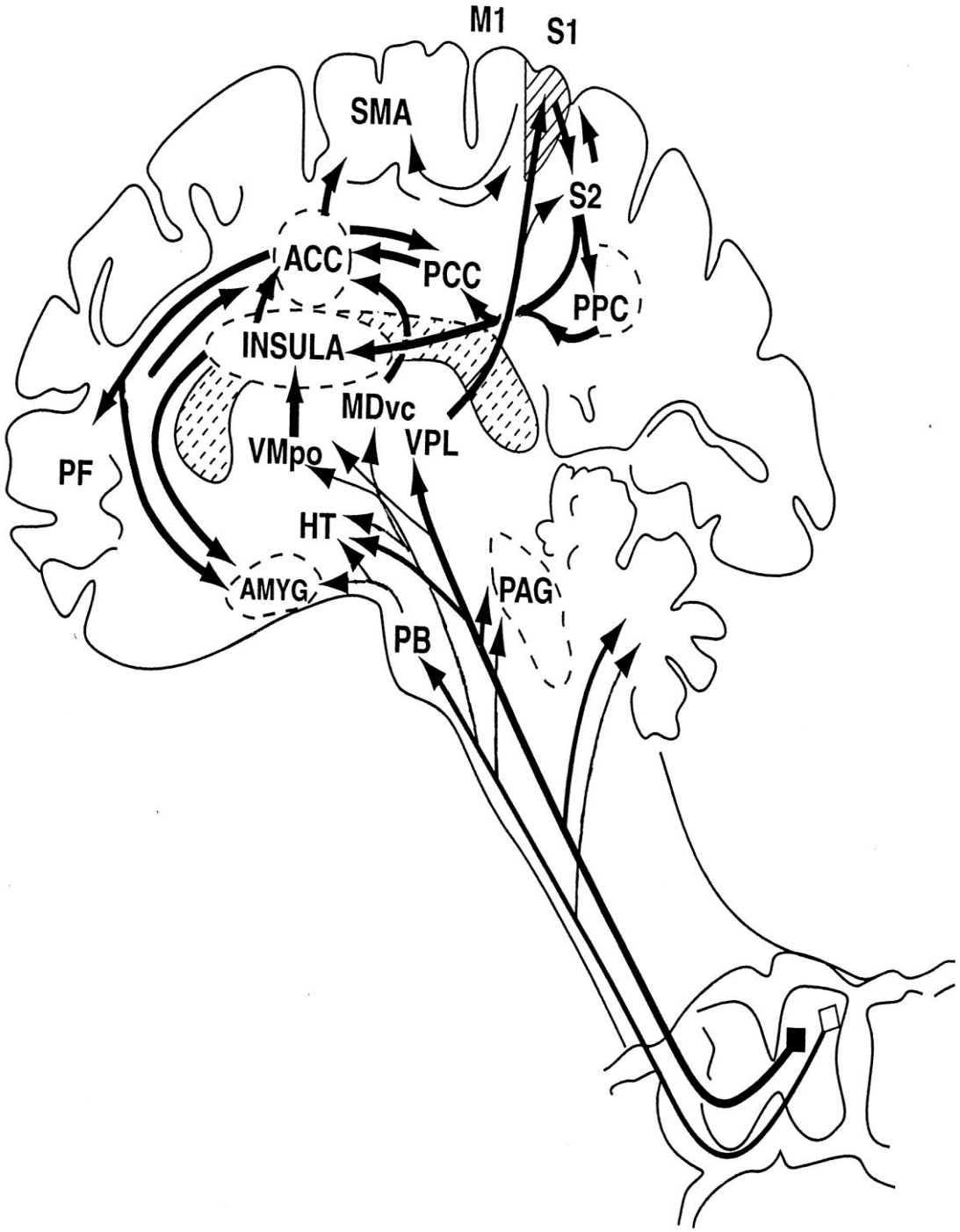


Figure 1.3. Fused MRI and CT images highlighted using heat mapping (axial, coronal and sagittal clockwise from bottom left) showing left PAVG electrode placement. Three-dimensional reconstruction of electrode trajectory is shown bottom right.

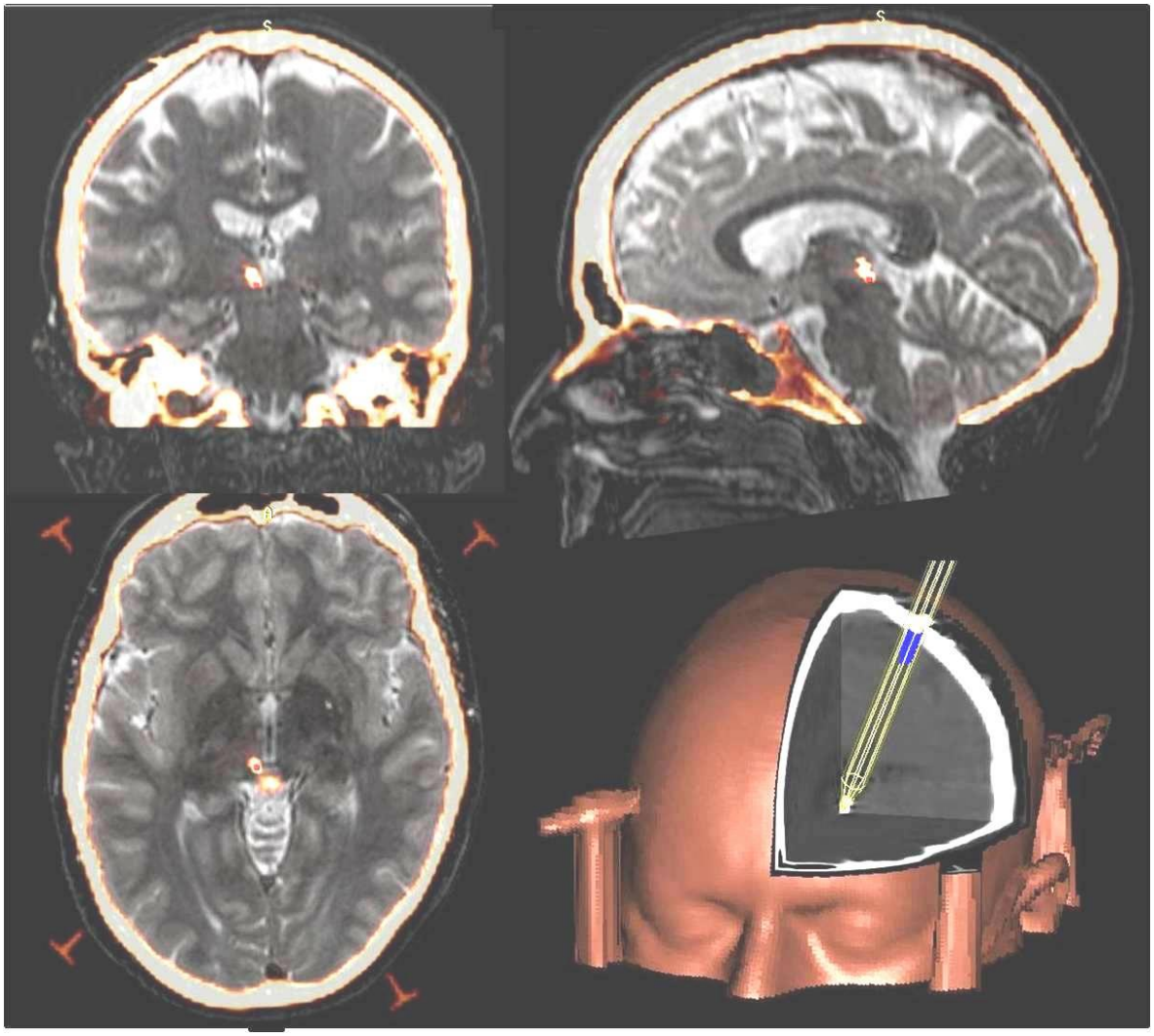
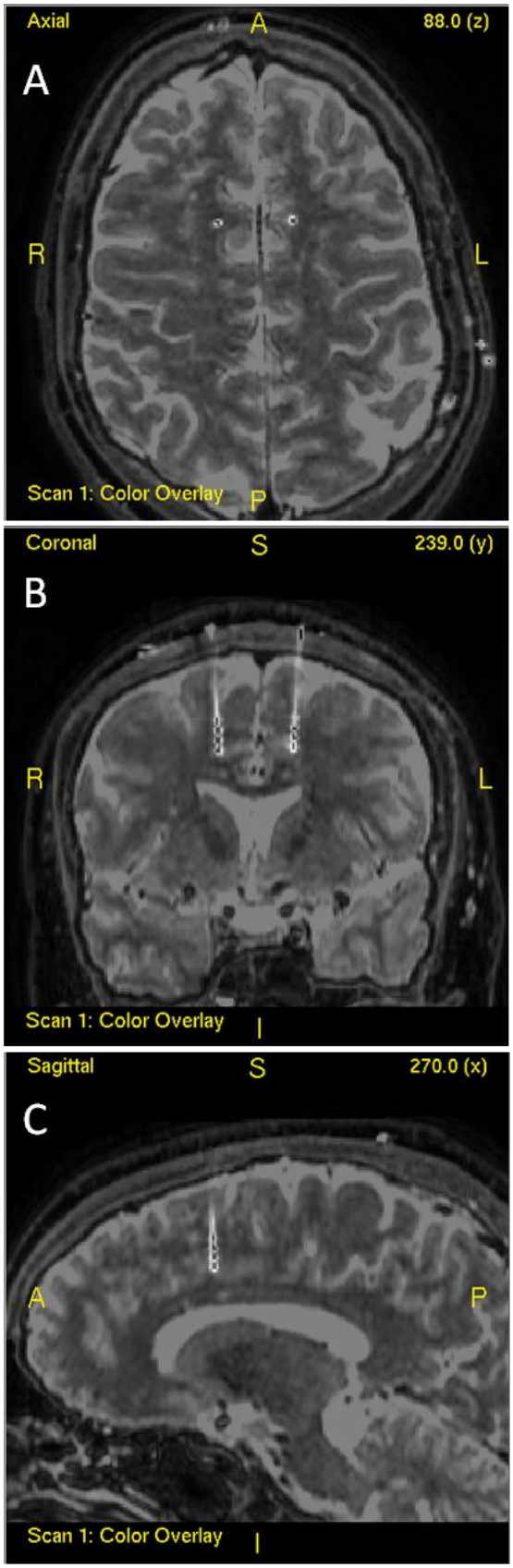


Figure 1.4. Fused MRI and CT highlighting Cg24 electrode placement (A. axial, B. coronal and C. sagittal).



Chapter 2: Long-term outcomes of deep brain stimulation for neuropathic pain at Oxford.

2.1. Summary

DBS to treat neuropathic pain refractory to pharmacotherapy has reported variable outcomes, and gained UK but not USA regulatory approval. This study prospectively assessed long-term efficacy of DBS for chronic neuropathic pain in a single center case series. Patient reported outcome measures were collated before and after surgery, using a visual analog score (VAS), Short Form 36 quality of life survey (SF-36), McGill pain questionnaire (MPQ) and EuroQol-5D questionnaires (EQ-5D; Health state). 197 patients were referred over twelve years, of whom 85 received DBS for various etiologies: 9 amputees, 7 BPA, 31 after stroke, 13 with spinal pathology, 15 with head and face pain and 10 miscellaneous. Mean age at surgery was 52 years and mean follow-up 19.6 months. Contralateral DBS targeted the PAVG (n=33), the VP thalamus (n=15) or both targets (n=37). Almost seventy percent (69.4%) of patients retained implants 6 months after surgery. 39 out of 59 (66%) of those implanted gained benefit and efficacy varied by etiology, improving outcomes in 89% after amputation and 70% after stroke. In this cohort, sustained >30% improvements in VAS, MPQ, SF-36 and EQ-5D were observed in 15 patients with >42 months follow-up, several outcome measures improving from those assessed at one year. DBS for pain has long-term efficacy for select etiologies. Clinical trials retaining patients in long-term follow-up are desirable to confirm findings from prospectively assessed case series.

2.2 Introduction

DBS is an invasive neurosurgical intervention established in movement disorders reported also to improve symptoms of epilepsy, Tourette's syndrome, obsessive-compulsive disorders, depression and cluster headache (Pereira et al. 2007b). The history of DBS for pain is reviewed in the previous chapter. Failed US multi-centre trials precluded US FDA approval (Coffey 2001). Pain was therefore decreed 'off label', precluding approval by medical insurers. Consequently few surgeons report DBS for pain using current technology and techniques and less regions approve it (Cruccu et al. 2007; NICE 2011; Pereira and Aziz 2011; Pereira et al. 2009a).

Described here is a prospective cohort study of twelve year duration evaluating outcomes of DBS for chronic neuropathic pain from a single center. Improvements in patient reported outcome measures of pain and quality of life are analyzed and challenges discussed, including patient selection, deep brain target choice, optimizing efficacy and overcoming tolerance.

2.3. Methods

Patients were referred by clinicians nationally to a single center multi-disciplinary team consisting of pain specialists, neuropsychologists and neurosurgeons. Neuropsychological evaluation excluded psychiatric disorders and ensured minimal cognitive impairment. A definable organic origin for pain was sought, with the patient refractory to or poorly tolerant of pharmacological treatments. Surgical treatments may have been attempted. Neuropathic pain refractory to medicines for at least two years permitted application for treatment funding. Informed consent was obtained from all

patients proceeding to surgery and the study was approved by the local ethics committee and Helsinki declaration adhered to.

DBS of either PAVG or VP or both targets was performed. Patients were counselled for the possibility that they may derive no benefit from DBS or not tolerate it well, necessitating its removal. The surgical technique is detailed elsewhere in chapter one. DBS targets were contralateral to the painful side (figure.2.1).

Targets were implanted with either Medtronic model 3387 (Medtronic Inc, Minneapolis, USA) quadripolar electrodes with 1.5mm contacts 1.5mm apart, or St Jude Medical 6143 (St Jude Medical, Minnesota, USA) with 1.5mm contacts 1.5mm apart. After a week of post-operative clinical assessment with continuous stimulation and titration of its parameters to optimize analgesia, a decision was made whether to permanently implant the electrodes under general anesthesia. They were connected to an implantable pulse generator (IPG; Medtronic Synergy®, Kinetra®, Activa PC® or Activa RC®, or St Jude Brio®) implanted in the chest or abdomen.

During post-operative assessment, each patient recorded VAS at least twice daily at set times while blinded to DBS settings. Targets were trialed individually then together for 1-2 days each using the analgesic stimulation parameters to determine which electrode contacts conferred maximum analgesia. VAS were averaged for the trial week and compared to pre-operative scores to assess for improvement. The decision to proceed to implantation of the IPG was made for each individual patient, guided by the Multi-Disciplinary Team.

Patients ideally left hospital a day after IPG implantation with progress followed by clinic appointments at approximately 5 weeks, three months, six months then yearly thereafter. Initially, they were given a pain diary to record their VAS and stimulator

settings weekly for review at follow-up. Continuous stimulation rather than on-demand was encouraged, but in addition to being able to switch the DBS on and off at will, they were usually only given control over its voltage which was typically limited by the clinician to a maximum amplitude of 4V.

Quantitative assessment of the pain and health-related quality of life were performed before surgery and as above. Both VAS (scale 0–10) to rate pain intensity and the MPQ were used (Melzack 1975), the former having anchors of `no pain' (0) and `the worst pain you can imagine' (10), and the latter giving additional qualitative information in domains of 'sensory', affective, 'evaluative' and 'miscellaneous' pain severity. Patients recorded VAS twice daily in a pain diary over 14 days. The 28 VAS scores were reviewed to ensure consistency and the mean was then calculated. McGill pain questionnaires (MPQ) were also completed before and after surgery and analyzed using the ranked pain rating index (PRI(R)).

Patients completed a short-form 36 question quality of life (SF-36®) health survey and Euroqol 5 domain (EQ5D) quality of life questionnaire alongside the pain questionnaires. SF-36® responses were regrouped into 8 domains of physical functioning (PF), role - physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role - emotional (RE), and mental health (MH). Results were scored by online tools (Kind et al. 1998; SF-36 2011). Norm-based scores allowed comparison between studies. SF-36® scores ranged from 0, an extreme dysfunction or symptom severity, to 100, an optimal function. Health state of patients was evaluated by EQ5D. Its two sections evaluate firstly the health state in five dimensions (mobility, self-care, usual activities, pain and anxiety) and secondly on a 'health' VAS, with '0'

being the worst state they can imagine and 100 the best. EQ-5D scores were calculated as detailed elsewhere (Euroqol 1990).

As pain assessments were repeated measures throughout the follow-up, pre- and post-operative scores were compared for each group of patients using a general linear mixed model, with a *P*-value of <0.05 taken as statistically significant and <0.01 taken as highly significant.

2.4. Results

2.4.1. Demographics

197 patients with chronic neuropathic pain were prospectively evaluated for suitability of DBS over 12 years from May 1999 to August 2011. 56 (28%) were unable to secure UK National Health Service funding for the treatment, 29 (15%) declined surgery, 15 (8%) had medical contraindications to surgery, 7 (4%) were deemed psychologically unsuitable and 3 (2%) were deemed not to be refractory to pharmacotherapy at time of assessment. 85 (43%) patients therefore proceeded to DBS.

60 males (71%) and 25 females (29%) had a mean age of 51.8 (SD 13.3) years. Nine patients were amputees suffering from phantom limb or stump pain (one arm and eight legs, one bilateral leg receiving bilateral DBS), 7 had complete BPA without cervical nerve root avulsion, 31 experienced post-stroke pain, 13 had pain after spinal damage of various causes (failed back surgery, arterio-venous malformation, syringomyelia, trauma, and transverse myelitis), 15 others had cephalgia (head and face pain of different causes including anesthesia dolorosa) and ten had miscellaneous etiologies such as genital pain and multiple sclerosis (‘Other’). Of the 85 patients operated upon,

74 (87%) felt sufficient analgesia for IPG implantation. The 11 (13%) unsuccessful etiologies were post-stroke (4/31; 13%), spinal (2/15; 13%) cephalgia (1/15; 7%) and miscellaneous (4/10; 40%). 15/74 implanted patients (20%) were excluded from analysis due to insufficient data. Reasons for loss of long-term data included subsequent dementia, emigration, refusal to attend appointments and death from other causes (usually cardiovascular or cancer). 59 patients' long-term outcomes were therefore analyzed (figure. 2.2). These comprised 9 after amputation (15%), 6 BPA (10%), 23 post-stroke (38%), 7 after spinal damage (12%), 11 cephalgia (18%), and 3 miscellaneous (5%) (table 2.1). There were no statistical differences found between baseline pain scores between etiologies.

2.4.2. Outcomes

Of the 59 patients with implanted DBS, 39 patients (66.1%) sustained a global improvement of their EQ5D health state at follow-up (table 2.2). The success of DBS varied by etiology, ranging from 50% after BPA to 89% after amputation (table 2.2). Considering this 39 patient group, demographics were similar to the overall 85 patient cohort operated upon: 28 (72%) were male with a mean age at surgery of 52.1 years (SD 13.3). Mean follow-up of outcomes was 27.9 months for this subgroup. 22/39 (56.4%) patients were followed up for 2 years or more and 14/39 (38.4%) for 4 years or more

Figure 2.3 and table 2.3 summarize pain and quality of life outcomes for the 39 patient-cohort. At 3 months after surgery, VAS was improved by 50.3% (SD 27.1, $P<0.001$), SF-36 improved by 38.7% (SD 66.8, $P<0.02$), MPQ improved by 38.1% (SD 54.7, $P<0.001$), EQ-5D improved by 27.2% (SD 20.4, $P<0.001$), Health state improved by 73.8% (SD 96.8, $P=0.001$). Throughout the first year, mean pain relief remained similar

(figure 2.3). VAS was improved by 45.8% (SD 25.1, *P*<0.001), SF-36 by 26.6% (SD 45.8, *P*<0.001), MPQ by 24.1% (SD 50.6, *P*<0.01), EQ-5D by 20.3% (SD 30.0, *P*<0.001) and Health state by 76.1% (SD 109.2, *P*<0.001) (table 2.3).

DBS efficacy varied by etiology for both pain outcomes and quality of life measures (table 2.4). For example, excellent pain relief at one year after surgery was seen for cephalgia in VAS (59.4%) and SF-36 (77.6%), while pain after spinal pathology improved best in VAS (63.0%) and MPQ (71.1%).

Comprehensive long-term outcome measures were available for almost all patients retained in follow-up (figure 2.4), and showed sustained analgesia with a moderate reduction in efficacy for some outcome measures, yet an improvement in quality of life as measured by SF-36. Four years after DBS, VAS was still improved by 36% (SD 39.2, P=0.002), SF-36 by 34% (SD 34.3, *P*<0.4), MPQ by 38.3% (SD 35.4, *P*<0.3), EQ-5D by 20.0% (SD 40.5, *P*<0.4) and Health state by 49.6% (SD 117.0, *P*=1) (table 2.5). 21 patients (53.8%) received PAVG stimulation only, 5 (12.8%) had stimulation of VP and 13 (33.3%) kept stimulation of both targets. Efficacy differences were not statistically significant. Mean stimulation parameters for PAVG were 22.8 Hz (s.d. 11.4), 193.8 µs (s.d. 104.5) and 2.3 v (s.d. 1.1) and for VP they were 32.7 Hz (s.d. 17.5), 202.1 µs (s.d. 103.3) and 3.0 v (s.d. 1.3). 25/60 patients (42%) required IPG changes. 11/60 (18%) had lead revisions, 4 after lead breakages following falls and 7 due to loss of analgesic effect despite stimulation cycling or breaks. Other complications included one lead erosion requiring removal and 7 infections, 2 successfully treated by antibiotics and 5/74 (7%) requiring device removal.

2.5. Discussion

Here described is the largest open label, prospective study of DBS for pain published in the last 5 years, only one other of similar size having been published in the last 15 years, albeit with less detailed outcomes (Rasche et al. 2006). The cohort presented here is significant, comprising approximately 5% of a largely historical global literature of less than 1500 reported cases (Levy 2003; Pereira and Aziz 2011; Pereira et al. 2009a). It also utilizes current DBS technologies and current standards of neuroimaging and stereotactic surgery.

Chapter 1 summarized all published peer-reviewed clinical outcomes data in DBS for pain case series comprising at least six patients. Since Mazars and co-workers', Richardson and Akil's, and Hosobuchi and Adams' pioneering studies and their long-term follow-up published in the 1970s and 1980s (Hosobuchi et al. 1977; Levy et al. 1987; Mazars et al. 1979; Richardson and Akil 1977a), only about 20 groups worldwide reported long-term efficacy in up to 83% of patients with follow-up of up to six years. Just five centers published results in the last decade (Hamani et al. 2006a; Levy 2003; Marchand et al. 2003; Rasche et al. 2006; Yamamoto et al. 2006). Not all authors reported their failed trials that obviated full device implantation, however, leading to overestimation of efficacy in some reports. The literature is obfuscated by varying and simplistic outcome measures that preclude meaningful meta-analysis, such as verbal self-reports comprising only three or five categories. The latest revision of the definition of neuropathic pain also encourages consideration of all patients in this study receiving DBS as having neuropathic pain (Jensen et al. 2011). Here different deep brain targets were not distinguished between based upon literature reviews suggesting their relative efficacy for neuropathic and nociceptive pain respectively, choosing

instead to frequently trial both targets during the same awake procedure if the first target tried did not have an effect (Bittar et al. 2005b; Levy 2003).

Outcomes by etiology from the Oxford patient cohort have been previously published elsewhere (Bittar et al. 2005d; Green et al. 2006a; Green et al. 2004; Nandi and Aziz 2004; Owen et al. 2006a; Owen et al. 2006b; Pereira and Aziz 2011; Pereira et al. 2009a), in particular by etiology to illustrate the different etiologies of chronic neuropathic pain amenable to DBS that include cranial and facial pain (Ervin et al. 1966; Green et al. 2006a), post-stroke pain (Owen et al. 2006a), BPA (Owen et al. 2007b), and amputation pain (Bittar et al. 2005d; Yamamoto et al. 2006). One criticism of this approach has been the occasional repetition of patient data serving multiple purposes in several clinical publications, making results difficult to follow (Coffey et al. 2011). However, presented here is a complete summary of a complete case series wherein certain previously reported trends persist, such as excellent initial efficacy in pain after amputation and stroke and sustained analgesia in cephalgia and spinal pathologies, and an overall efficacy (67%) emerges. The Oxford cephalalgia subgroup has previously been characterized by aetiology and stroke subgroup by anatomy elsewhere (Green et al. 2006a; Owen et al. 2006a). For head and face pain VPM is targeted first assessing for intra-operative paresthesia. Several limitations of the study that mirror those of the 1990s Medtronic trials are apparent (Coffey 2001): lack of randomization or case-controls; poor enrolment (selection excluding patients on clinical grounds together with refusal of funding for patients despite clinical selection); high attrition (loss to follow-up). Other shortcomings prevalent in the field of neuromodulation for chronic pain included heterogeneous case mixes with

underspecified patient selection criteria, and unblinded assessment of patient self-reported outcomes. Deep brain sites stimulated and stimulation parameters also varied. An alternative to DBS is MCS (Nguyen et al. 2011). It confers analgesia in two thirds of patients, comparable in efficacy to DBS. The published experience has been that DBS is superior to MCS for selected refractory pain syndromes (Nandi et al. 2002b), and more appropriate than SCS for certain refractory pain etiologies where the neuroplasticity may be predominantly cerebral rather than spinal. One group's retrospective studies have compared all three modalities of central neurostimulation, but the results are limited by different treatments trialed both between and sequentially within patients and by limited outcome information (Katayama et al. 2001a; b). Differences in efficacy between treatment modalities may reflect surgeon expertise and refinement of particular techniques.

While the analgesic mechanisms of DBS are unknown, aberrant rhythmic activity in VP and PAVG neurons is likely to play an important role in pain pathophysiology. Patients in pain have characteristically enhanced low frequency (8-15 Hz) power spectra of both PAVG and VP deep brain macroelectrode LFPs (Green et al. 2009). Further research is required to reveal if such neuronal signatures could aid patient selection or enable 'smart' demand-driven stimulation, in particular if combined with technical advances in non-invasive electrophysiological techniques to characterize functional neuronal connectivity (Mohseni et al. 2010; Pereira et al. 2007a; Ray et al. 2009). PAVG DBS also affects autonomic function (Green et al. 2006c; Pereira et al. 2010a; Pereira et al. 2010b; Young and Rinaldi 1997). These translational investigations advance the search for biomarkers to optimize the therapy. Some debate exists over whether PAVG DBS stimulates adjacent central thalamic and parafascicular nuclei alongside adjacent medial

structures such as reticular thalamus (Craig et al. 1994; Jeanmonod et al. 1993; Weigel and Krauss 2004). A more complete discussion is beyond the scope of this outcomes chapter, but it raises intriguing questions about whether PAVG DBS activates a more medial pain processing pathway incorporating emotional valence or acts via more lateral somatosensory thalamic nociceptive mechanisms. The picture is likely to be more complex with ventral and dorsal PAVG regions may contribute to distinct analgesic streams as suggested by later chapters (Pereira et al. 2010a; Pereira et al. 2013).

Both contemporary and older case series (Gybels and Sweet 1989), suggest that at least a quarter of patients successful during trial stimulation do not experience long term success beyond one year after surgery. One reason may be loss of patients at follow-up making reaching statistical significance more challenging. Challenges are to identify predictors of long-term efficacy and investigate tolerance. Progressive increases of stimulus amplitude have proven unhelpful (Kumar et al. 1997). The Oxford experience is that tolerance is often overcome by subtle alterations of either pulse width, frequency, or both or, failing that, breaks in stimulation. Importantly, the patients in the failed Medtronic trials and many other case series also received episodic cycling DBS whereas ours receive continuous stimulation. Nevertheless a subgroup remain either tolerant long-term or demonstrate progressive reductions in efficacy. Hypotheses include firstly, that patients genuinely become tolerant to the treatment, secondly that a particular pain characteristic is reduced but others unmasked become worse over time (Kamano 2003), and thirdly that chronic pain exhibits disease progression concomitant with increasing severity despite DBS as has been demonstrated in tremor (Favilla et al. 2012). Advances in stimulator technology such as the development of demand-driven

stimulators may not only reduce energy usage and IPG replacement, but also enable patient controlled analgesia and potentially overcome aspects of tolerance. Neuromodulation for neuropathic pain has positive experiences among physicians, high patient expectations and positive case series yet few randomized, controlled, clinical trials (Coffey and Lozano 2006; Levy et al. 2011). This prospective case-series experience encourages continued trials of the therapy.

Table 2.1. Demographics, aetiologies and baseline assessments of patients according to their outcome: 'Operated': patients who underwent DBS surgery; 'Stage 1&2': patients who retained DBS; 'Stage 1 only': patients who underwent DBS surgery but had no implanted IPG; 'No follow-up': patients with no pre- or post-surgery available pain assessment; 'Follow-up': patients with analyzable data; Abbreviations: 'n': Number, 'SD': Standard Deviation, 'M/F', Male/Female.

	Demographics						**Aetiologies**						**Baseline assessments**									
	n	Age at surgery (years)		Follow-up (months)		Sex Ratio	Phantom Limb	Brachial plexus	Post Stroke	Spine	Cephalgia	Other	VAS		MPQ		SF-Total		EQ-5D		Health State	
Outcome		**Mean**	SD	**Mean**	SD	**M/F**							**Mean**	SD	**Mean**	SD	**Mean**	SD	**Mean**	SD	**Mean**	SD
Operated:	**85**	**51.8**	13.3	**19.6**	23.9	**60/25**	**9**	**7**	**31**	**13**	**15**	**10**	**7.9**	1.4	**32.4**	14.9	**254.5**	56.7	**5.5**	1.584	**47.9**	23.8
Stage 1&2	**74**	**51.9**	13.1	**22.5**	24.3	**53/21**	**9**	**7**	**27**	**11**	**14**	**6**	**7.8**	1.4	**32.4**	15.0	**255.6**	56.6	**5.5**	1.6	**48.3**	23.8
Stage 1 only	11	**48.9**	16.1	**0.0**	0.0	**7/4**	**0**	**0**	**4**	**2**	**1**	**4**	**8.9**	0.8	**32.6**	16.3	**236.5**	68.2	**5.3**	0.6	**41.7**	27.5
Follow-up	**59**	**52.1**	13.3	**24.8**	22.8	**42/17**	**9**	**6**	**23**	**7**	**11**	**3**	**7.8**	1.4	**32.8**	15.1	**253.3**	57.0	**5.6**	1.7	**47.8**	23.5
No follow-up	15	**52.8**	11,0	**0.0**	0.0	**11/4**	0	1	4	4	3	3	**7.0**	2.8	**20.7**	15.9	**309.3**	87.6	**5.0**	1.4	**57.5**	46.0

Table 2.2. Outcomes of fully implanted DBS patients:demographics, early pain improvement, mean follow-up and deep brain targets of fully implanted patients with pain improvement (based on the different assessments). Abbreviations: 'n': number; 'SD': standard deviation; 'm/f': male/female; 'PAVG': periventricular grey area; 'VPL': ventroposterolateral thalamic nucleus.

Patients with implanted DBS

Aetiology	Total Number	Patients with Pain relief		Sex Ratio (m/f)	Age at surgery (years)		3 months Pain Relief on VAS Scores		Follow-up (months)		Implanted targets		
		n	%		Mean	(SD)	Mean	(SD, P-value)	Mean	(SD)	PAVG	VPL	Both
Phantom Limb	9	8	88.9%	7/1	**51.8**	(13.2)	**52.5%**	(30.3, 0.058)	**31.9**	(17.0)	5	2	1
Brachial plexus	6	3	50.0%	2/1	**33.7**	(06.4)	**44.4%**		**31.0**	(24.4)	3	0	0
Post-stroke	23	16	69.6%	14/2	**58.8**	(09.1)	**38.1%**	(28.2, 0.001)	**23.1**	(27.5)	10	0	6
Spine	7	4	57.1%	1/3	**53.8**	(13.6)	**68.7%**	(33.5, 0.097)	**27.8**	(18.6)	1	2	1
Cephalalgia	11	6	54.5%	2/4	**48.0**	(11.3)	**62.1%**	(11.3, 0.492)	**23.0**	(17.9)	2	0	4
Other	3	2	66.7%	1/1	**34.0**	(00.0)	**50.0%**		**60.0**	(17.0)	0	1	1
All	59	39/59	66.1%	28/12	**52.1**	(13.3)	**50.3%**	(27.1, <0.001)	**27.9**	(23.1)	21	5	13

Table 2.3. Pain score and pain relief for each assessment at consecutive follow-up times. Abbreviations: 'Pre', Pre-surgery; 'Post', Post-surgery; 'm', months; 'y', year; 'p-value': calculated on the difference between post-surgery and base-line scores.Abbreviations: 'Pre-op': pre-surgery; 'Post': post-surgery; 'm': months; 'y': year; p-value: significance of the difference with base-line score.

Patients with efficacious DBS

Assessments			Pain scoring				Pain Relief (%)		
			n	**Mean**	SD	P-value	n	**Mean**	SD
VAS Score	**Pre-op**		38	**7.9**	1.4				
	Post	**3m**	22	**4.0**	2.3	**< 0.001**	22	**50.3**	27.1
		6m	14	**5.3**	2.3	**< 0.001**	14	**36.5**	27.3
		12m	19	**4.9**	2.3	**< 0.001**	19	**38.7**	27.3
		< 1y	31	**4.3**	2.1	**< 0.001**	31	**45.8**	25.1
MPQ	**Pre-op**		38	**35.6**	13.5				
	Post	**3m**	19	**17.7**	13.8	**0.001**	19	**38.7**	54.7
		6m	15	**23.7**	18.1	0.124	15	**23.5**	65.2
		12m	19	**26.2**	17.6	0.599	19	**26.0**	35.0
		< 1y	31	**24.7**	16.6	**0.001**	31	**26.6**	45.8
SF-36	**Pre-op**		29	**247**	55.4				
	Post	**3m**	13	**318**	64	**0.001**	12	**38.1**	66.8
		6m	15	**282**	73	0.519	13	**14.3**	19.3
		12m	18	**288**	66	0.073	16	**7.7**	21.1
		< 1y	28	**291**	69	**0.006**	25	**24.1**	50.6
EQ-5D	**Pre-op**		31	**5.6**	1.7				
	Post	**3m**	12	**3.6**	1.2	**< 0.001**	12	**27.2**	20.4
		6m	13	**4.6**	2,0	0.146	13	**13.7**	35.9
		12m	18	**4.3**	1.6	0.112	16	**7.9**	32.6
		< 1y	29	**4.1**	1.6	**0.001**	27	**20.3**	30.0
Health State	**Pre-op**		28	**45.5**	22.4				
	Post	**3m**	12	**67.5**	15.7	0.002	11	**73.8**	96.8
		6m	13	**52.9**	20.1	0.648	13	**33.4**	52.7
		12m	17	**62.9**	20.3	**0.017**	14	**77.3**	115.2
		< 1y	28	**60.8**	18.1	**< 0.001**	24	**76.1**	109.2

Table 2.4. Pain relief according to aetiologies during the first year of follow-up. Pain assessment scores according to etiologies in the 39-patient group with DBS-induced pain relief. Abbreviations: 'n': number; 'SD': standard deviation.

		Pain relief (%)																			
		Phantom Limb				**Brachial Plexus**				**Post-stroke**				**Spine**				**Cephalgia**				**Others**			
	Pain assessment	n	**Mean**	SD	*P*-value	n	**Mean**	SD	*P*-value	n	**Mean**	SD	*P*-value	n	**Mean**	SD	*P*-value	n	**Mean**	SD	*P*-value	n	**Mean**	SD	*P*-value
1 year	VAS score	7	**38.7**	20.5	***0.004***	2	**25.8**	26.4	*0.401*	13	**44.2**	29.8	***<0.001***	3	**63,0**	24.8	***0.024***	4	**59.4**	8.1	***0.001***	2	**48.72**	26.8	*0.184*
	MPQ score	7	**31.8**	38.5	***0.043***	2	**25.9**	8.35	*0.18*	15	**15.6**	56.9	*0.191*	2	**71.1**	3.37	*0.18*	3	**20.5**	10.6	*0.109*	2	**55.76**	24.5	*0.18*
	SF-36 score	8	**17.6**	24.2	*0.093*	1	**28.3**			9	**9.91**	24.7	*0.374*	3	**27.2**	18.4	*0.109*	3	**77.6**	143.1	*0.593*	1	**28.4**		
	EQ-5D score	8	**31.7**	11.0	***0.011***	1	**0.0**			11	**6.74**	41,0	*0.514*	3	**34.7**	16.8	*0.109*	3	**36.5**	5.5	*0.102*	1	**6.7**		
	Health state	7	**81.5**	120.0	***0.005***	1	**116.7**			10	**38.87**	68.6	*0.291*	2	**56.3**	26.5	*0.205*	3	**197.2**	204.5	*0.086*	1	**46.7**		

Table 2.5. Comparison of short-term *vs.* long-term outcomes. Pain relief (%) at early stage (1y) and late stage (>4y). Abbreviations: 'n': number, 'Min': minimum score, 'Max': maximum score, 'SD': standard deviation, 'p-value': calculated on the difference between post-surgery and base-line scores. Abbreviations: 'n': number; 'SD': standard deviation.

		Patients with efficacious DBS							
Assessments		**Pain scoring**					**Pain Relief (%)**		
		n	**Mean**	SD	P-value		n	**Mean**	SD
VAS	**<1y**	31	**4,3**	2,1	0,000	**	31	**45,8**	25,1
	>4y	12	**4,9**	3,1	0,002	**	12	**36,0**	39,2
MPQ	**<1y**	31	**24,7**	16,6	0,001	**	31	**26,6**	45,8
	>4y	12	**22,7**	16,2	0,251		12	**38,3**	35,4
SF-36	**<1y**	28	**291**	69	0,006	**	25	**24,1**	50,6
	>4y	12	**314**	69	0,190		9	**34,0**	34,3
EQ-5D	**<1y**	29	**4,1**	1,6	0,001	**	27	**20,3**	30,0
	>4y	13	**3,9**	1,8	0,310		10	**20,0**	40,5
Health State	**<1y**	28	**60,8**	18,1	0,000	**	24	**76,1**	109,2
	>4y	13	**51,1**	19,6	1,000		8	**49,6**	117,0

Figure 2.1. Axial T1-weighted MRI showing (A) PAVG and (B) VPL laterally and PAVG medially DBS electrodes in situ.

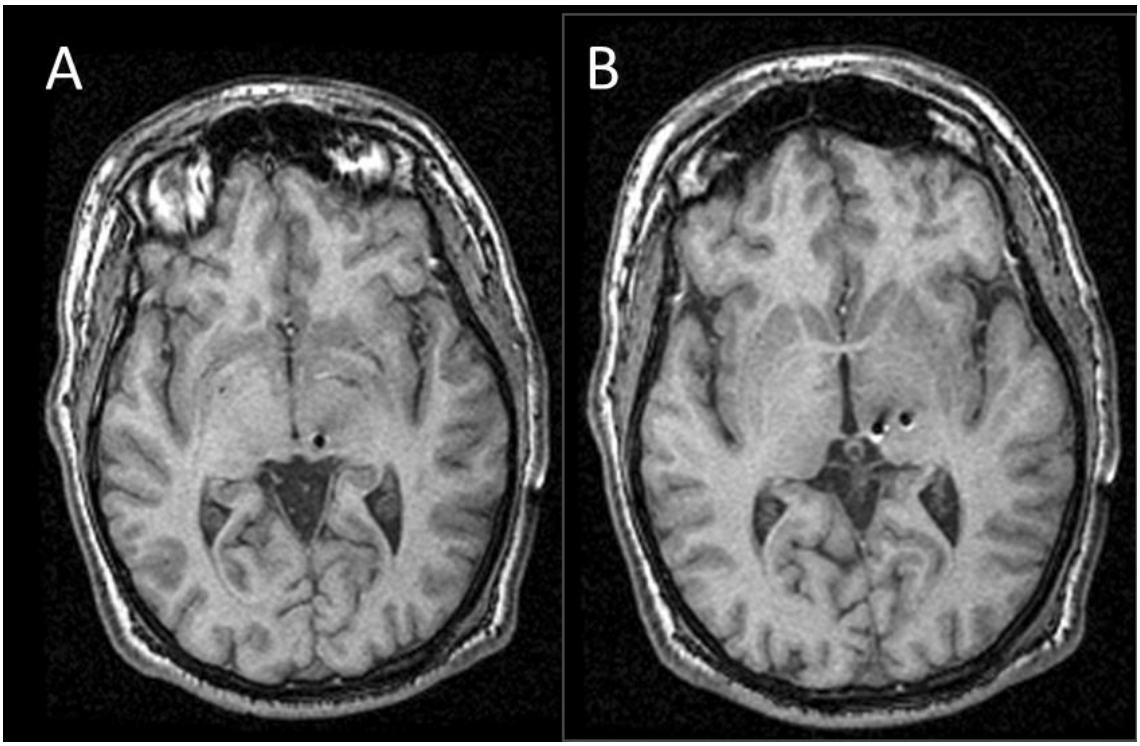


Figure 2.2. Flowchart illustrating numbers of patients at each stage of the study.

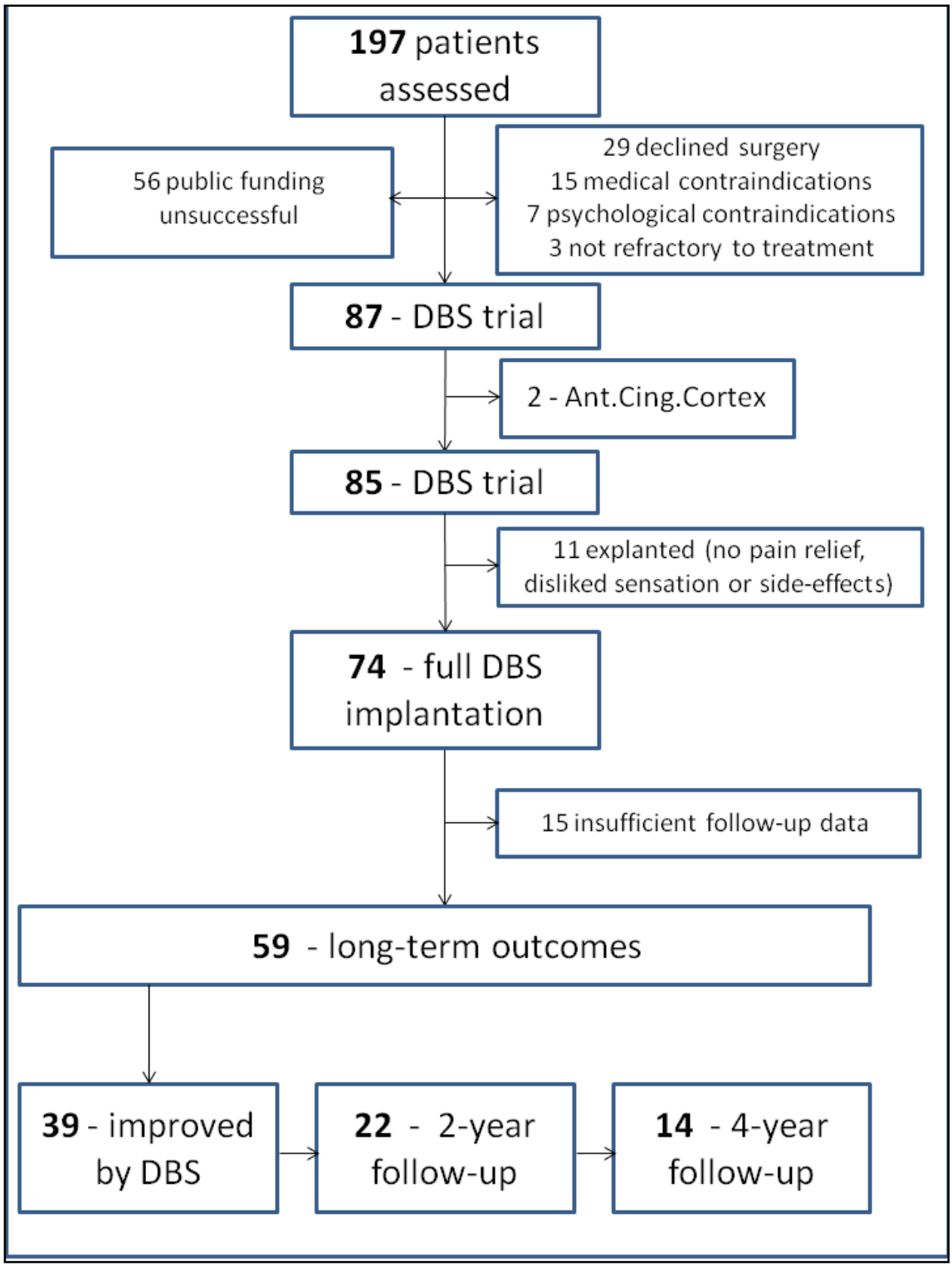


Figure 2.3. Short-term outcomes. Pain assessment scores (VAS, MPQ, SF-36, EQ-5D and Health State) before (Pre-op) and at follow-up after surgery. The median is indicated by the horizontal line inside the boxes. The boxes represent 2 quartiles, and the whiskers show minimum and maximum values. Stars upon bars indicate the statistically significance of the difference between scores before and after surgery. *: *P*-value<0.05 (statistically significant); **: *P*-value<0.01 (highly statistically significant).

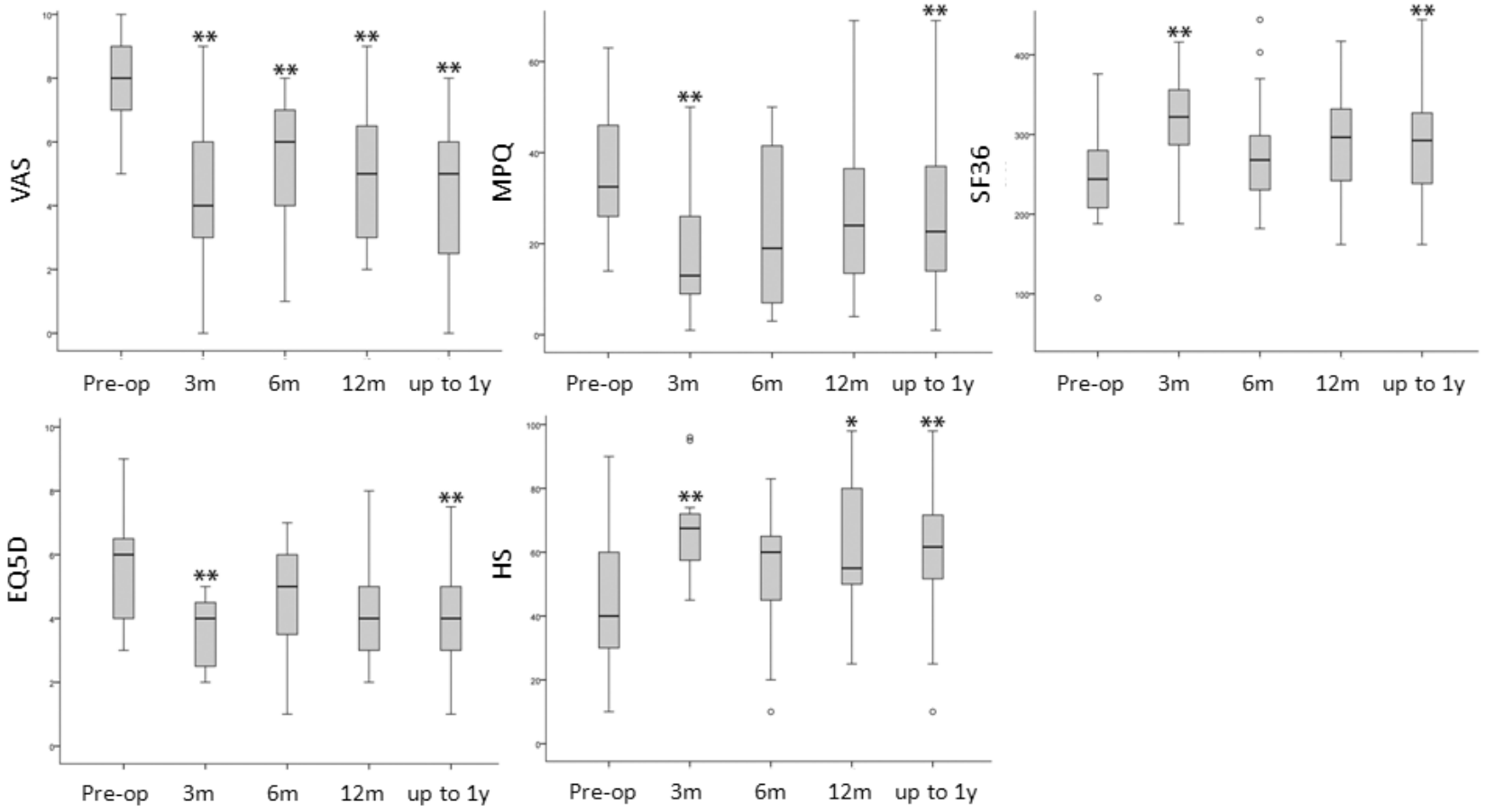
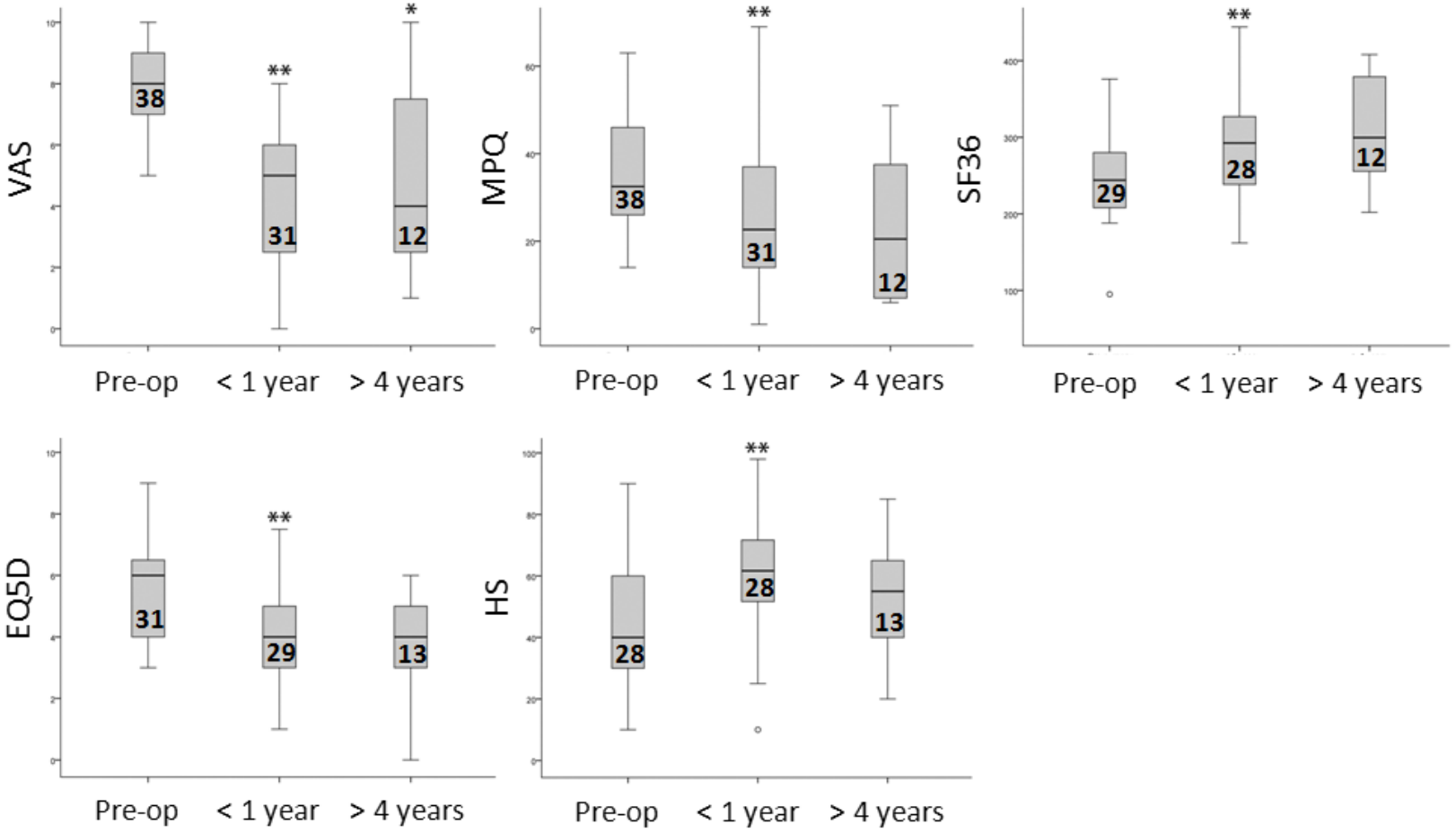


Figure 2.4. Comparison of short-term *vs.* long-term outcomes. Pain assessment scores before surgery (pre-op), at 1 year (<1y) and more than 4 years (>4y) after surgery. The median is indicated by the horizontal line inside the boxes. The boxes represent 2 quartiles, and whiskers show minimum and maximum values. Stars upon bars indicate the statistical significance of the difference between scores before and after surgery. *: *P*-value<0.05 (statistically significant); **: *P*-value<0.01 (highly statistically significant). The number of patients is indicated within the boxes.



Chapter 3: Thalamic deep brain stimulation in Porto relieves chronic pain after amputation and brachial plexus injury

3.1. Summary

This study prospectively evaluated efficacy at one year of DBS for phantom limb pain after amputation and deafferentation pain after BPA in a single center case series. Patient reported outcome measures were collated before and after surgery, using a visual analog score (VAS), Short Form 36 quality of life survey (SF-36), Brief Pain Index (BPI) and University of Washington Neuropathic Pain Score (UW-NPS). 12 patients were treated over 29 months, receiving contralateral ventroposterolateral (VPL) sensory thalamic DBS. 5 were amputees and 7 had BPA, all traumatic. One patient with BPA failed post-operative trial of externalised DBS. 11 patients proceeded to implantation and gained improvement in pain scores at 12 months. No surgical complications or stimulation side-effects were seen. After 12 months for amputation, mean VAS was improved by 90.0% (SD 10.0, $P<0.001$), SF-36 by 57.5% (SD 97.9, $P=0.127$), UW-NPS by 80.4% (SD 12.7, $P<0.001$) and BPI by 79.9% (SD 14.7, $P<0.001$). After 12 months for BPA, mean VAS was improved by 52.7% (SD 30.2, $P<0.001$), SF-36 by 15.6% (SD 30.5, $P=1.000$), UW-NPS by 26.2% (SD 40.8, $P<0.399$) and BPI by 38.4% (SD 41.7, $P<0.018$). Mean DBS parameters were 2.5 volts, 213 microseconds and 25 Hertz. DBS for pain has efficacy at one year for chronic, neuropathic pain after traumatic amputation and BPA. Clinical trials retaining patients in long-term follow-up are desirable to confirm findings from prospectively assessed case series.

3.2. Introduction

Phantom limb pain is uncommon with an incidence of 1-2 per 100,000, but presents a significant burden to the patient, affecting up to 85% of amputees.(Hall et al. 2006) Stump pain usually occurs at some time during the first month following amputation and resolves in many patients after two to three years without treatment except in the cases where phantom pain develops. The incidence of phantom pain is very variable but increases with more proximal amputations. The etiology and pathophysiological mechanisms of phantom pain are not clearly defined. However, both peripheral and central neural mechanisms have been described, along with superimposed psychological mechanisms. The management of phantom limb pain has little evidence base. While numerous treatments have been described, there is little clinical evidence supporting any particular therapy.

BPA commonly results in early deafferentation pain with a quarter of sufferers going on to experience severe neuropathic pain several years later that is usually refractory to pharmacotherapy.(Narakas 1978) BPA pains have been dichotomised into either continuous, often burning or throbbing and likely involving thalamic neuroplasticity, or shooting paroxysms associated with dorsal horn hyperactivity.(Parry 1980; 1984)

Both phantom limb pain after amputation and deafferentation pain after BPA fulfill a recently revised definition of neuropathic pain as pain caused by a lesion or disease of the somatosensory system.(Jensen et al. 2011) Neuropathic pain symptom severity and duration are often greater than other forms of chronic pain leading patients and clinicians to consider neurosurgery.(Torrance et al. 2006)

The indications of DBS and history of DBS for chronic pain are discussed in chapter one. A recent growing interest in its use for chronic pain refractory to medical

treatment has paralleled advances in DBS technology, neuroimaging and the publication of more rigorous case series regarding its long-term efficacy. Successful results have been shown in chapter two for multiple aetiologies, in particular for post-stroke, face pain, amputation and BPA.(Boccard et al. 2013)

Described here is a prospectively studied, open-label, consecutive case series of patients receiving VPL DBS for chronic neuropathic pain after amputation or BPA from a single Portuguese center establishing a DBS for pain service after a decade's experience of DBS for movement disorders in over 200 patients. Improvements in patient reported outcome measures of pain and quality of life are analyzed and challenges to DBS for pain discussed.

3.3. Methods

Patients were referred by clinicians nationally to a single center multi-disciplinary team consisting of pain specialists, neurologists, neuropsychologists and neurosurgeons at Hospital de São João, Porto, Portugal. Neuropsychological evaluation excluded psychiatric disorders and ensured minimal cognitive impairment. Neuropathic medications and other surgical treatments may have been attempted with limited success. Selection criteria included neuropathic pain refractory to medicines for at least two years together with absence of surgical contraindications such as coagulopathy or ventriculomegaly. Informed consent was obtained and the study received local ethical approval. Patients were counseled for the possibility that they may derive no benefit from VPL DBS or not tolerate it well, necessitating its removal.

For surgery, a Leksell stereotactic frame (Elekta Instruments, Stockholm) was applied to the patient's shaved head under local anesthesia. A stereotactic CT head scan of 2

mm slice thickness was performed with pre-operative T1 and T2 weighted MRI images of 2 mm slice thickness from a 1.5 T scanner volumetrically fused to it using FrameLink® *stereotactic* calculation *software* (*Medtronic*, Minneapolis). The Leksell stereotactic arc was then fixed to its frame on the awake, semi-sitting patient after chlorhexidine skin preparation and placement of a clear drape over the head. Intravenous vancomycin and cefotaxime antibiotic prophylaxis and dexamethasone were routinely administered before surgery commenced. A 14 mm burrhole was performed after 3 cm parasagittal U-shaped frontal scalp incision with minimal dural opening over a gyrus before Leksell radiofrequency electrode impedance check to 10 mm above target then DBS electrode insertion to target and intraoperative C-arm radiographic target confirmation.

Guiding principles for awake targeting of VPL are described in chapter two. The contralateral VPL was targeted for limb pain and found in the plane 10-13 mm posterior to the mid-commissural point and from 5 mm below to 2 mm above it. Its arm area is 2-3 mm medial and leg area 1-2 mm medial respectively to the internal capsule. Thus targeting was generally 12-14 mm lateral and 0-2 mm anterior to the PC. A transfrontal, extraventricular trajectory from an entry point on or near the coronal suture to ipsilateral VPL avoiding blood vessels and sulci was planned.

Targets were implanted with Medtronic Model 3387® quadripolar electrodes with 1.5mm contacts 1.5mm apart. Final electrode position was determined by intra-operative clinical assessment reliant upon subjective reporting by the awake patient rather than microelectrode recording. Tactile stimulation of the painful body part was performed intra-operatively to augment pain and assess response if necessary. At either target during surgery, DBS at lower frequencies (≤50 Hz) was analgesic and higher

frequencies (>70 Hz) hyperalgesic. Bipolar stimulation of 5-50 Hz was performed initially, pulse width 200-450 μs, amplitude 0.5-5 V. VPL stimulation aimed to supplant painful sensation by pleasant paresthesias. Adjustment was primarily somatotopic, with the assessor alert to pyramidal signs suggesting capsular involvement. Once satisfactory targeting had been achieved by microdrive adjustment, the patient's electrode was secured in place with a Stimloc® skull fixation device (*Medtronic*, Minneapolis). Electrode leads were externalized parietally via temporary extensions and electrode position confirmed by post-operative stereotactic CT again fused to pre-operative MRI. Typical surgery duration was 2-3 h including stereotactic planning.

After 48 h of post-operative clinical assessment with continuous stimulation and titration of its parameters to optimize analgesia, a decision was made whether to permanently implant the electrodes under general anesthesia. They were connected via new extension leads to a pulse generator (Medtronic Kinetra or Activa PC®) implanted in the chest. During post-operative assessment, each patient recorded visual analog scores (VAS) at least twice daily at set times while blinded to DBS settings. Targets were trialed using analgesic stimulation parameters to determine which electrode contacts conferred maximum analgesia. VAS were averaged for the trial period and compared to pre-operative scores to assess for improvement. The decision to proceed to implantation of the IPG was made for each individual patient, guided by the multi-disciplinary team.

Patients ideally left hospital a day after IPG implantation with progress followed by clinic appointments at one, three and six months then yearly thereafter. Continuous stimulation rather than on-demand was encouraged, but in addition to being able to

switch the DBS on and off at will, they were usually given control over its voltage only. This was typically limited by the clinician to a maximum amplitude of 4 V.

Quantitative assessment of pain and health-related quality of life were performed one month before surgery and after surgery at one, three and six months then annually by independent, blinded assessors. VAS to rate pain intensity, the University of Washington Neuropathic Pain Score (UW-NPS) and Brief Pain Index (BPI) were utilised.(Cleeland and Ryan 1994; Galer and Jensen 1997) Patients recorded VAS twice daily in a pain diary over 14 days. The 28 VAS scores were reviewed to ensure consistency and the mean was then calculated.

Patients also completed a short-form 36 question quality of life (SF-36®) health survey alongside the pain questionnaires. SF-36 responses were regrouped into 8 domains of physical functioning, role - physical, bodily pain, general health, vitality, social functioning, role - emotional, and mental health. Results were scored by online tools.(SF-36 2011) Norm-based scores allowed comparison between studies.

As pain assessments were repeated measures throughout the follow-up, pre- and post-operative scores were compared for each group of patients using a general linear mixed model, with a *P*-value of <0.05 taken as statistically significant and <0.01 taken as highly significant.

3.4. Results

Table 3.1 describes demographics of 12 consecutive patients treated over three years with surgeries from January 2009 to May 2011 including pain etiology and relevant pre-operative medications. Ten (83%) were male, two female (17%) and mean age was 53.6 years old (SD 9.3). All had traumatic injuries, only one not due to a motor vehicle

accident. All amputees had phantom pain and all BPA had preganglionic involvement. Mean duration of symptoms before surgery was 19.2 years (SD 12.9). One patient with BPA failed post-operative trial of externalized DBS, gaining due to lack of efficacy despite intra-operative paresthesia. 11 patients proceeded to full implantation after successful intra-operative and post-operative trialling and completed post-operative follow-up duration of one year. There were no significant surgical complications in this series and side-effects from stimulation were unremarkable. No patients required electrode or implantable pulse generator revisions to date.

Table 3.2 shows mean efficacious stimulation parameters for amputation and BPA cohorts respectively. All patients received continuous bipolar DBS with patient control of amplitude up to a clinician set maximum.

Table 3.3 summarises baseline patient reported outcome measure characteristics. There were no statistically significant differences between baseline characteristics between pain etiologies. Figure 3.1 illustrates baseline scores and improvements across the whole 11 patient cohort for all outcomes measures by box and whisker plots. At one month after surgery,

mean VAS was improved by 60.1% (SD 27.3, $P<0.001$), SF-36 improved by 30.1% (SD 75.5, $P=0.553$), UW-NPS improved by 47.1% (SD 37.1, $P<0.001$) and BPI improved by 51.4% (SD 33.3, $P<0.001$). Throughout the first year, mean pain relief was sustained and at 12 months VAS was improved from before surgery by 69.6% (SD 29.6, $P<0.001$), SF-36 improved by 34.6% (SD 69.1, $P=0.093$), UW-NPS improved by 50.8% (SD 41.2, $P<0.001$) and BPI improved by 57.3% (SD 37.8, $P<0.001$).

Although both amputation and BPA subgroups showed significant improvements initially with DBS sustained after one year (table 3.4, figure 3.2 and figure 3.3),

amputation pain improved most with benefits sustained across all pain outcome measures. BPA pain improvements in overall outcome scores were restricted to VAS. After 12 months for amputation, VAS was improved by 90.0% (SD 10.0, $P<0.001$), SF-36 improved by 57.5% (SD 97.9, $P=0.127$), UW-NPS improved by 80.4% (SD 12.7, $P<0.001$) and BPI improved by 79.9% (SD 14.7, $P<0.001$). After 12 months for BPA, VAS was improved by 52.7% (SD 30.2, $P<0.001$), SF-36 improved by 15.6% (SD 30.5, $P=1.000$), UW-NPS improved by 26.2% (SD 40.8, $P<0.399$) and BPI improved by 38.4% (SD 41.7, $P<0.018$).

Despite considerable improvements in pain scores, statistically significant overall improvements in SF-36 were not observed, with the exception of amputation pain one month after surgery which improved by 71.4% (SD 98.1%, P=0.013). However, analyses of SF-36 subscores across the whole cohort demonstrated significant and sustained improvements in

bodily pain ($P<0.001$ throughout) and physical functioning ($P=0.08$ at 6 m) with physical role and general health also approaching significance. In contrast with anecdotal patient reports (such as video 1), social functioning, vitality and emotional and mental health were not significantly improved. Highly significant ($P<0.001$) improvements were seen in most UW-NPS subscores including sharp, hot, intense, dull, deep and unpleasant pain but not cold, sensitive and itchy pain. Statistical analysis of these subscores by etiological subgroup was not performed to avoid type I errors, although considerable reductions in hot, sharp, deep and dull UW-NPS subscores in both amputation and BPA pain subgroups suggest DBS relieved both the continuous and paroxysmal components of neuropathic pain. BPI improvements were statistically significant ($P<0.001$) in both severity and interference domains.

3.5. Discussion

Described here is the second largest recent open label, prospective study of DBS for pain and the greatest contemporary single-center experience of DBS for limb injury pain. Although not a new therapy, DBS has advanced considerably over the last two decades, concomitant with advances in both stimulator technology and neuroimaging techniques, and by corollary improvements in efficacy and reductions in complications. The Porto results suggest that DBS can consistently deliver analgesia to patients with chronic neuropathic pain after amputation and BPA, with significant sustained improvements at one year. Its results exceed those predicted by the Oxford experience that it has drawn upon.(Boccard et al. 2013) The authors attribute such success to refined patient selection within specific etiologies suggested to have better outcomes within larger heterogeneous case series.(Levy 2003; Pereira and Aziz 2011; Pereira et al. 2009a) The study is also likely to have benefited from the Oxford neurosurgeons' 15 year learning curve with DBS for pain, thus supporting an argument for only undertaking DBS for pain in centers with access to appropriate expertise and experience willing to audit outcomes as per EFNS and NICE guidelines.(Cruccu et al. 2007; NICE 2011) Additional and alternative hypotheses include social and cultural factors such as the anecdotally observed stoicism of the Porto patients. Less state benefits for the disabled in Portugal than in the UK also encourage returns to work with successful analgesia. Interestingly, however, quality of life indices were not improved to the same extent as pain scores in either cohort, suggesting that improving analgesia does not necessarily improve quality of life in such patients.

Published peer-reviewed clinical outcomes data in DBS for pain case series comprising at least six patients are summarized in chapter one and elsewhere.(Pereira and Aziz

2011; Pereira et al. 2009a) Both phantom and stump pain after amputation and BPA deafferentation pain qualify as neuropathic pain under its latest definition.(Jensen et al. 2011) It was decided here to undertake VPL rather than PAVG DBS not because of the dogma that thalamic stimulation is more efficacious for nociceptive pain, (Bittar et al. 2005b; Levy 2003) but drawing upon the Oxford experience of VPL as a target with more clearly delineated intraoperative stimulation effects upon the awake or mildly sedated patient, less risk of side-effects or morbidity from inaccuracy and strong somatotopic localization for appendicular pain syndromes. The successs leads us to advocate VPL rather than PAVG as the first target of choice for a neurosurgeon commencing DBS for limb pain.

One limitation to this investigation that echoes the late twentieth century Medtronic trials of DBS for pain is lack of randomization or case-controls.(Coffey 2001) However, other shortcomings of those trials including heterogeneous case mixes, variable deep brain sites stimulated and stimulation parameter cycling, poor enrolment and loss to follow-up have not beset this study. Nor have problems prevalent in the field of neuromodulation for chronic pain including underspecified patient selection criteria, and unblinded assessment of patient self-reported outcomes.

Neurosurgical treatments offered for BPA include dorsal root entry zone (DREZ) lesioning with greatest improvements in paroxysmal pain and two thirds of patients improved long-term yet up to 10% having dysaesthesia and ipsilateral leg weakness.(Aichaoui et al. 2011; Friedman et al. 1988; Sindou et al. 2005) Motor cortex stimulation (MCS) has also been undertaken with equivocal results influencing paroxysms more than continuous pain, (Ali et al. 2012; Lefaucheur et al. 2009) and spinal cord stimulation (SCS) has been reported with limited success.(Garcia-March et

al. 1987; Zorub et al. 1974) No trials comparing neuromodulation treatments for BPA have been reported. A small comparative case series of 19 amputees has suggested DBS to be superior to SCS and MCS in ameliorating phantom limb pain in 60% of patients versus 32% with SCS and 20% with MCS, with two patients with both DBS and MCS implanted having better analgesia from DBS.(Katayama et al. 2001a) Mazars reported five patients with phantom limb pain whose pain disappeared after thalamic DBS.(Mazars et al. 1979) Other pioneers of DBS for pain, Hosobuchi, Kumar, Young and Levy, have all also reported improvements in phantom limb pain with DBS.(Hosobuchi 1986; Kumar et al. 1997; Levy et al. 1987; Young and Rinaldi 1997) The Oxford cohort had VAS improvements at one year of 38.7% in seven phantom limb pain and 25.8% in two BPA patients receiving a mixture of thalamic, periventricular grey and dual target DBS.(Bittar et al. 2005d; Boccard et al. 2013; Nandi et al. 2004) Porto's single center case series of 11 patients shows greater benefit at one year from VPL DBS, in particular for amputation pain, suggesting that the therapy retains a role in these difficult to treat conditions. Randomised, blinded controlled, clinical trials are desirable, both assessing the DBS on and off, and in revisiting comparison to other neuromodulatory therapies such as MCS and SCS alongside lesional treatments such as DREZ.

Aside from its established anatomical involvement in pain processing from spinothalamic tracts to insula, cingulate and primary somatosensory cortex, multifarious lines of evidence implicate the VP thalamus in central sensitization and descending facilitation of aberrant circuitry in the pain neuromatrix.(Lee et al. 2008; Woolf and Salter 2000) Specific mechanisms of central deafferentation and thalamocortical dysrhythmia that implicate sensory thalamic dysfunction in pain are suggested by non-

human primate lesional and human functional imaging studies and consequent thalamic reorganisation can be large.(Jain et al. 2008; Jones 2000; Llinas et al. 1999; Pereira et al. 2007a; Ralston 2005; Walton et al. 2010) Microelectrode recordings in chronic pain patients have shown enhanced bursting activity and increased stump representation in amputees.(Davis et al. 1998; Davis et al. 1996; Lenz et al. 1989) Patients in pain have characteristically enhanced low frequency (8-15 Hz) power spectra in VPL deep brain macroelectrode LFPs.(Green et al. 2009) MEG has also implicated disruption of thalamocortical dysrhythmia in the analgesic mechanism of DBS, perhaps by interrupting low frequency oscillations and bursting activity.(Ray et al. 2009) VPL DBS therefore appears a more pathophysiologically intuitive treatment than MCS and SCS for phantom limb and BPA deafferentation pain.

Both contemporary and older case series,(Boccard et al. 2013; Gybels and Sweet 1989) suggest that at least a quarter of patients successful during trial stimulation do not experience long term success beyond one year after surgery. One reason fortunately avoided here is loss of patients at follow-up making reaching statistical significance more challenging. Challenges are to identify predictors of long-term efficacy and investigate tolerance. Progressive increases of stimulus amplitude have proven unhelpful (Kumar et al. 1997). Tolerance may be overcome by subtle alterations of either pulse width, frequency, or both or, failing that, breaks in stimulation.(Boccard et al. 2013) Importantly, the patients in the failed Medtronic trials and many other case series also received episodic cycling DBS whereas ours receive continuous stimulation. Nevertheless a subgroup remains either tolerant long-term or demonstrates progressive reductions in efficacy. Hypotheses include firstly, that patients genuinely become tolerant to the treatment, secondly that a particular pain characteristic is reduced but

others unmasked become worse over time, (Kamano 2003) and thirdly that chronic pain exhibits disease progression concomitant with increasing severity despite DBS as has been demonstrated in tremor.(Favilla et al. 2012) Advances in stimulator technology such as the development of demand-driven stimulators may enable patient controlled analgesia and potentially overcome aspects of tolerance. Long-term follow-up of the patients in this cohort beyond one year will be important to adequately assess for tolerance phenomena.

Neuromodulation for neuropathic pain has positive experiences among physicians, high patient expectations and positive case series yet few randomized, controlled, clinical trials.(Coffey and Lozano 2006; Levy et al. 2011) Continued trials of the therapy for neuropathic pain after limb injury are encouraged from this promising prospective case-series experience.

Table 3.1. Patient demographics. F, female; M, male; AKA, above knee amputation; AEA, above elbow amputation; BKA, below knee amputation; BPA, brachial plexus avulsion; PG, pregabalin; GP, gabapentin; T, tramadol; DZ, diazepam; A, amitriptyline. * failed trial of deep brain stimulation.

Patient	Sex	Age at surgery (years)	Pathology	Symptom duration (years)	Pre-operative medications
1	F	71	R AKA	13	PG
2	M	45	L AEA	25	PG
3	F	57	L BKA	24	PG, GP
4	M	48	R AEA	16	PG
5	M	50	L AKA	20	GP, T
6	M	63	L BPA	4	PG
7	M	45	L BPA	18	PG
8	M	64	L BPA	50	PG
9	M	40	L BPA	14	PG, GP
10	M	56	R BPA	2	T, DZ
11	M	52	L BPA	32	PG, GP, T, A
12*	M	45	L BPA	12	PG, T, A

Table 3.2. Deep brain stimulation parameters. BPA, brachial plexus avulsion; N, number; A, amplitude; PW, pulse width; f, frequency; SD, standard deviation

		A (volts)		PW (μsec)		f (Hz)	
		mean	SD	mean	(SD)	Mean	(SD)
Amputation	5	2.7	1.1	204	74.7	18	8.4
BPA	6	2.4	1.1	220	41.0	30.8	13.6
Overall	11	2.5	1.1	212.7	56.1	25	12.8

Table 3.3. Baseline mean patient reported outcome measure characteristics. BPA, brachial plexus avulsion; N, number; Amp, amplitude; PW, pulse width; f, frequency; VAS, visual analog score; SF-36, short-form-36; UW-NPS, University of Washington Neuropathic Pain Scale; BPI, brief pain inventory. Standard deviations in brackets.

	Baseline pre-surgery							
	VAS		SF-36		UW-NPS		BPI	
Amputation	7	(2.8)	1048.6	(191.2)	72.2	(17.3)	13.6	(3.8)
BPA	9	(0.6)	1160.8	(203.0)	62.3	(14.3)	13.5	(1.9)
Overall	8.1	(2.1)	1109.9	(196.9)	66.8	(15.8)	13.6	(2.8)

Table 3.4. Baseline scores and percentage improvement for amputation and brachial plexus avulsion cohorts. N, number; m, months; Min, minimum patient outcome score or percentage improvement within subgroup; Max, maximum patient outcome score or percentage improvement within subgroup; SD, standard deviation; VAS, visual analog score; SF-36, short-form-36; UW-NPS, University of Washington Neuropathic Pain Scale; BPI, brief pain inventory. 'p-value' calculated on the difference between post-surgery and base-line scores. Statistically significant improvements of P<0.05 are in bold.

			Outcome Score					**Percentage improvement**					p value
			N	Min	Max	Mean	SD	N	Min	Max	Mean	SD	
Amputation	**VAS**	Pre-op	5	4	10	7.0	2.8						
		1m	5	0	7	2.8	2.6	5	30	100	**65.3**	25.0	**0.026**
		3m	5	0	8	3.2	3.0	5	20	100	**58.0**	28.6	0.054
		6m	5	0	6	2.4	2.6	5	-20	100	**64.0**	49.8	**0.013**
		12m	5	0	2	0.8	0.8	5	80	100	**90.0**	10.0	**0.001**
	SF-36	Pre-op	5	187	606	439	158						
		1m	5	602	708	634	44	5	-0.7	242.3	**71.4**	98.1	**0.013**
		3m	5	464	660	559	84	5	-0.3	148.1	**43.7**	60.9	0.288
		6m	5	512	632	563	55	5	-2.9	183.4	**49.2**	77.0	0.245
		12m	5	458	659	579	87	5	-1.52	230.0	**57.5**	97.9	0.127
	UW-NPS	Pre-op	5	53	99	72.2	17.3						
		1m	5	6	38	22.4	12.4	5	59	91	**69.6**	12.9	**< 0.001**
		3m	5	12	41	25.2	14.1	5	46	81	**66.2**	14.3	**< 0.001**
		6m	5	0	25	16.0	12.1	5	55	100	**77.6**	18.3	**< 0.001**
		12m	5	6	30	13.8	9.8	5	61	94	**80.4**	12.7	**< 0.001**
	BPI	Pre-op	5	9	19	13.6	3.8						
		1m	5	1	8	4.0	2.7	5	58	91	**72.8**	12.7	**0.001**
		3m	5	1	13	4.2	5.1	5	7	93	**69.6**	35.6	**0.001**
		6m	5	0	9	3.8	3.6	5	36	100	**70.0**	28.5	**0.001**
		12m	5	1	5	2.6	1.8	5	64	93	**79.9**	14.7	**< 0.001**
Brachial Plexus	**VAS**	Pre-op	6	8	10	9.0	0.6						
		1m	6	0	8	4.0	2.8	6	11	100	**55.7**	30.7	**< 0.001**
		3m	6	1	8	4.7	2.6	6	11	89	**48.8**	27.0	**0.001**
		6m	6	0	7	3.2	2.7	6	30	100	**66.1**	28.1	**< 0.001**
		12m	6	0	7	4.3	2.9	6	22	100	**52.7**	30.2	**< 0.001**
	SF-36	Pre-op	6	364	676	508	104						
		1m	6	360	598	475	96	6	-28.9	37.6	**-4.3**	24.4	1.000
		3m	6	290	684	553	149	6	-36.1	74.4	**11.7**	37.7	1.000
		6m	6	310	668	559	131	6	-31.7	73.6	**13.3**	36.0	1.000
		12m	6	415	625	569	87	6	-8.9	71.7	**15.6**	30.5	1.000
	UW-NPS	Pre-op	6	46	87	62.3	14.4						
		1m	6	8	84	44.5	28.1	6	-33	88	**28.3**	41.1	0.415
		3m	6	4	71	36.8	25.2	6	6	94	**41.8**	33.2	0.055
		6m	6	0	74	46.3	26.9	6	-17	100	**23.7**	41.2	0.648
		12m	6	0	73	44.3	25.2	6	-16	100	**26.2**	40.8	0.399
	BPI	Pre-op	6	12	17	13.5	1.9						
		1m	6	2	15	9.0	4.6	6	-25	83	**33.6**	35.4	**0.045**
		3m	6	1	12	6.8	4.2	6	8	92	**50.3**	29.4	**0.002**
		6m	6	0	12	6.5	4.0	6	0	100	**51.6**	32.7	**0.001**
		12m	6	0	15	8.3	5.2	6	-25	100	**38.4**	41.7	**0.018**

Figure 3.1. Overall outcomes. A. VAS (visual analog score), B. SF-36 (short-form-36), C. UW-NPS (University of Washington Neuropathic Pain Score), D. BPI (brief pain index), all before (pre-op) and at follow-up of 1, 3, 6 and 12 months after surgery. The median is indicated by the horizontal line inside the boxes. The boxes represent 2 quartiles, and the whiskers show minimum and maximum values. Stars above bars indicate the statistical significance of the difference between the post-surgery score and the pre-surgery score. *: *P*-value<0.01 (highly statistically significant).

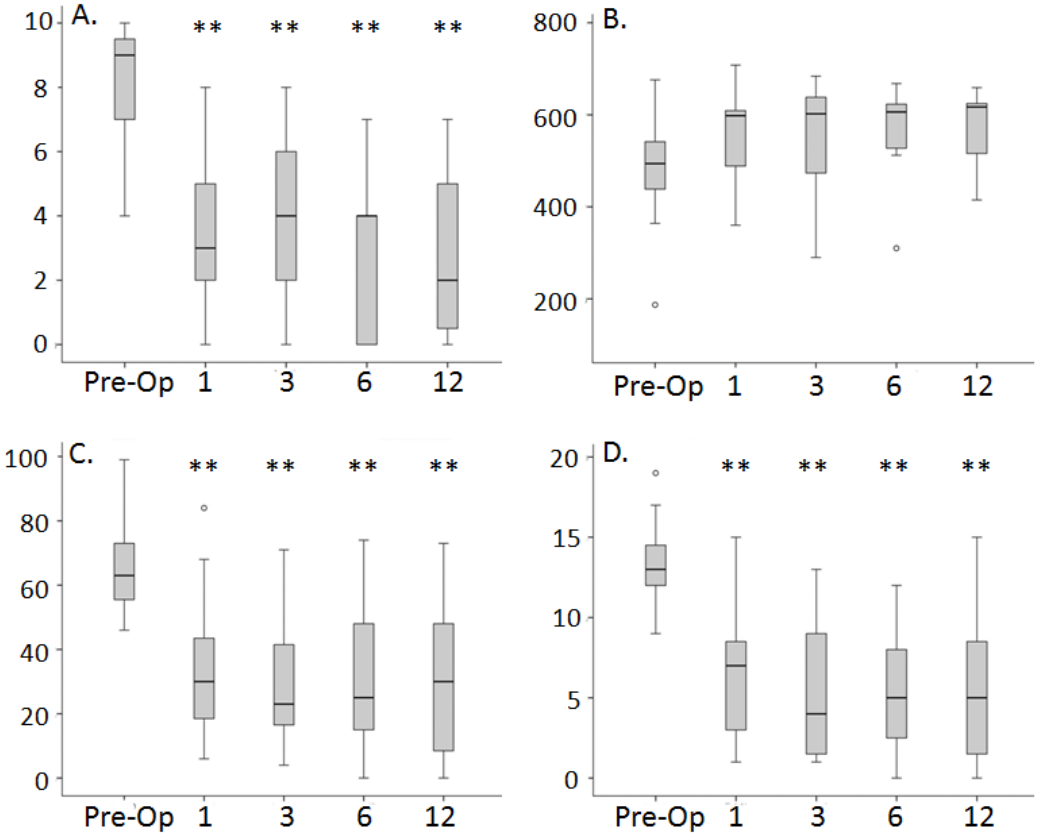


Figure 3.2. Amputation subgroup outcomes before (pre-op) and at follow-up of 1, 3, 6 and 12 months after surgery. A. VAS (visual analog score), B. SF-36 (short-form-36), C. UW-NPS (University of Washington Neuropathic Pain Score), D. BPI (brief pain index). The median is indicated by the horizontal line inside the boxes. The boxes represent 2 quartiles, and the whiskers show minimum and maximum values. Stars above bars indicate the statistical significance of the difference between the post-surgery score and the pre-surgery score. *: *P*-value<0.05 (statistically significant); **: *P*-value<0.01 (highly statistically significant).

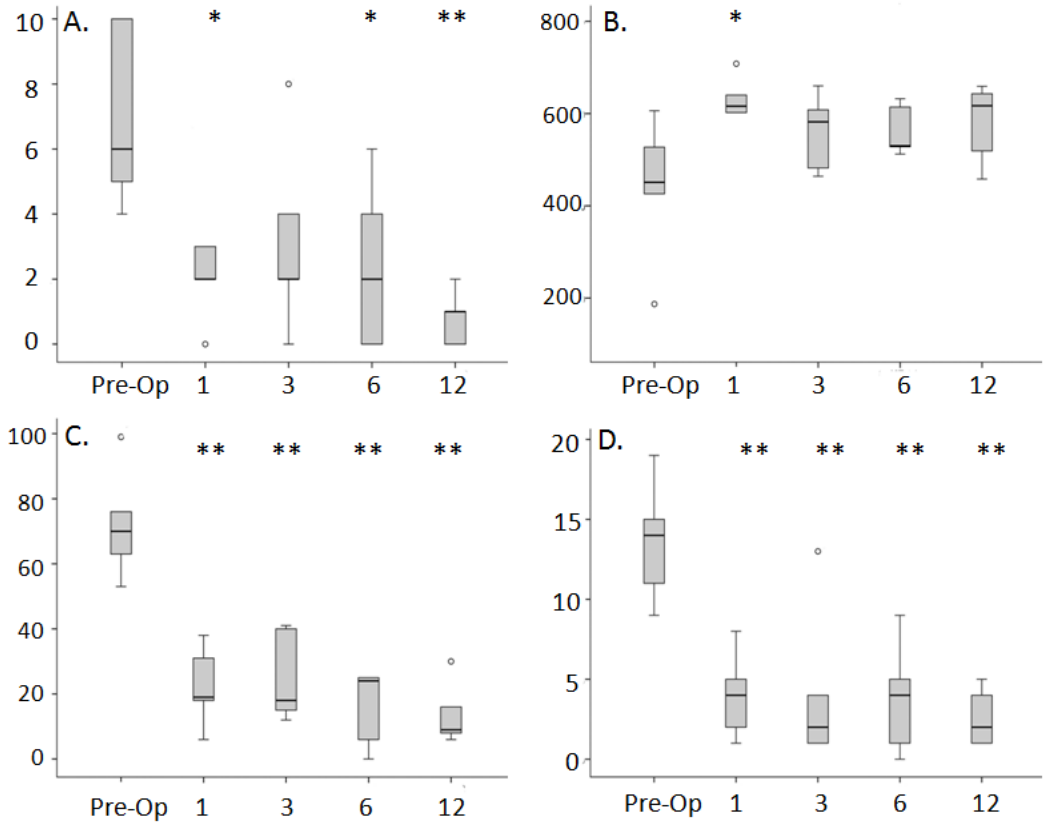
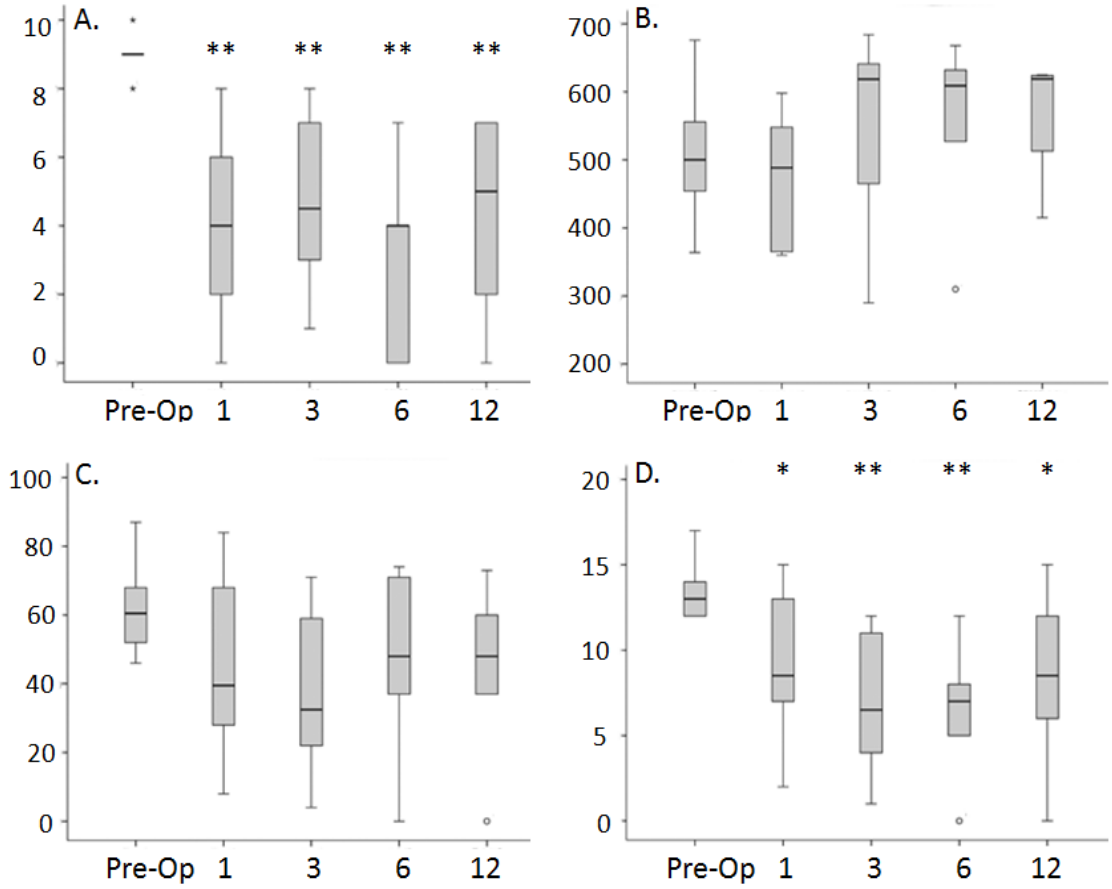


Figure 3.3. Brachial plexus avulsion subgroup outcomes before (pre-op) and at follow-up of 1, 3, 6 and 12 months after surgery. A. VAS (visual analog score), B. SF-36 (short-form-36), C. UW-NPS (University of Washington Neuropathic Pain Score), D. BPI (brief pain index). The median is indicated by the horizontal line inside the boxes. The boxes represent 2 quartiles, and the whiskers show minimum and maximum values. Stars above bars indicate the statistical significance of the difference between the post-surgery score and the pre-surgery score. *: *P*-value<0.05 (statistically significant); **: *P*-value<0.01 (highly statistically significant).



Section 2

Translational investigations into mechanisms of deep brain stimulation for pain

Chapter 4: Human periventricular grey somatosensory evoked potentials suggest rostrocaudally inverted somatotopy

4.1. Summary

Somatosensory homunculi have been demonstrated in primary somatosensory cortex and VP thalamus but not PAVG, a therapeutic target for DBS in chronic pain. Investigation of somatotopic representation in PAVG and assessment for a somatosensory homunculus. Five human subjects were investigated using electrical somatosensory stimulation and deep brain macroelectrode recording. DBS were implanted in the contralateral PAVG. Cutaneous arm, leg and face regions were stimulated while event-related potentials were recorded from deep brain electrodes. Electrode contact positions were mapped using MRI and brain atlas information. Monopolar P1 somatosensory evoked potential amplitudes were highest and onset latencies shortest in contralateral caudal PAVG with facial stimulation and rostrally with leg stimulation, in agreement with reported subjective sensation during intra-operative electrode advancement. A rostrocaudally inverted somatosensory homunculus exists in the human PAVG region. Objective human evidence of PAVG somatotopy increases understanding of a brainstem region important to pain and autonomic control that is a clinical target for both pharmacological and neurosurgical therapies. Such knowledge may assist DBS target localisation for neuropathic pain syndromes related to particular body regions like brachial plexopathies, anaesthesia dolorosa and phantom limb pain,.

4.2. Introduction

The midbrain PAVG regions are involved in pain processing and modulation.(Willis and Westlund 1997) Alongside the sensory thalamus, they have become the main anatomic targets for DBS for chronic neuropathic pain over four decades. (Hosobuchi et al. 1977; Hosobuchi et al. 1973; Kumar et al. 1997; Levy et al. 1987; Richardson and Akil 1977a). The procedure demonstrates good efficacy for an otherwise refractory group with approximately two thirds of patients gaining pain relief sustained for several years in aetiologies of amputation including phantom limb pain, BPA, face and head pain including anaesthesia dolorosa and post-stroke pain not affecting the whole body.(Boccard et al. 2013; Pereira and Aziz 2011; Pereira et al. 2009a)

DBS uniquely enables deep brain recording of LFPs in awake humans, thus obviating limitations of investigations in animals unable to report subjective sensations. It has been shown, by recording human LFPs, that a specific signature of neuronal activity in the PAVG correlates to reported pain intensity, (Green et al. 2009) and confirmed several lines of animal evidence that the PAVG has multiple integrative modulatory roles in the autonomic nervous system. (Bandler et al. 2000; Basnayake et al. 2011; Carter et al. 2012; Green and Paterson 2008; Hyam et al. 2012a; Pereira et al. 2010a)

Human electrophysiological stimulation and recording paradigms have contributed greatly to the somatotopic mapping of brain regions, notably with the pioneering studies of Penfield and Rasmussen during brain surgery in awake patients. (Penfield and Rasmussen 1950) Somatopic representation within basal ganglia structures, largely revealed by microelectrode investigations in humans and animals, has provided knowledge crucial to targeting DBS for movement disorders.(Romanelli et al. 2005) Such investigations have also detailed the somatotopic organisation of the VP thalamus.

This has been shown to exhibit a contralateral somatosensory homunculus, its most lateral nucleus corresponding to the foot and its most medial to the face. (Lenz et al. 1988) These findings guide anatomical targeting in DBS with face pain being treated by contralateral ventroposteromedial thalamic stimulation, arm pain by targeting the more medial aspect of the ventroposterolateral thalamus and leg pain by targeting its more lateral regions.(Pereira and Aziz 2011)

Evidence for sensory somatotopy in the PAVG is however sparse. Rodent stimulation-produced analgesia paradigms have suggested dorsal to ventral somatopic representation of head to tail. (Soper and Melzack 1982) Horse radish peroxidase studies in primates and cats have shown more rostral termination of lumbar spinothalamic afferents, a caudal preference for cervical afferent termination and a caudal distribution of trigeminal afferents.(Wiberg et al. 1986; 1987) The rostrocaudally aligned and inverted somatotopic representation suggested by such results echoes the well investigated sensorimotor homunculus of the anterior cerebellar lobe situated immediately posterior to the midbrain PAVG.(Manni and Petrosini 2004) Moreover, it was in agreement with Oxford's experience of awake patients during surgery who reported leg sensations with more rostral PAVG DBS and arm then face sensations with more caudal stimulation.(Bittar et al. 2005c) Nevertheless, objective human evidence of PAVG somatotopy has been not previously been reported.

PAVG LFPs were recorded here in five awake, human subjects during pulsed cutaneous electrical stimulation. The study aimed to investigate firstly whether LFPs from electrode contacts located at different anatomic locations rostrocaudally within the PAVG would vary in amplitude and onset latency dependent upon body part stimulated, and secondly whether such somatosensory evoked potential data could be correlated

with MRI and brain atlas information to confirm objectively a rostrocaudally inverted somatosensory homunculus in the PAVG.

4.3. Methods

4.3.1. Patients and deep brain stimulation surgery

Five patients with chronic neurophathic pain participated in the study. After comprehensive neuropsychological assessment, PAVG DBS was offered for treatment of chronic neuropathic pain. The study was performed in the first post-operative week after approval by local ethics committee and according to the Declaration of Helsinki, with informed written consent was obtained from all patients.

The surgical technique is decribed in chapter one and elsewhere and PAVG target shown in figure 1.3. (Bittar et al. 2005a; Joint et al. 2002; Pereira and Aziz 2011; Pereira et al. 2007b)

Each electrode was externalised for a week of trial stimulation, during which somatosensory stimulation was undertaken. Immediate post-operative CT fused with pre-operative MRI confirmed the electrode positions. The precise positions of the electrode contacts within the PAVG were determined by triangulation of the fused image electrode position relative to commissural, collicular and red nucleus anatomical landmarks using an imaging software program (MRIcro version 1.38, Chris Rorden). They were then mapped to a human brain atlas(Mai et al. 1998) as shown in figure 4.1. The method is detailed and further illustrated elsewhere,(Pereira et al. 2010a) and in appendix 2.

4.3.2. Somatosensory stimulation and deep brain electrode local field potential recording

Monopolar LFPs were simultaneously recorded from each of the four deep brain electrode contacts of each subject's externalised electrode during electrical stimulation with surface electrodes (Neotrode, Conmed Corporation). Skin surface electrodes were in turn placed over the contralateral common peroneal nerve posterior to the fibular head, median nerve on the volar wrist, and maxillary nerve on the cheek. Each anatomical site was stimulated for 220-360 s (mean 282 s) at frequency 2 Hz, pulse width 1 ms, and amplitude of 120% of each patient's sensory threshold established by brief initial surface stimulation. Both LFP and somatosensory stimulation signals were filtered between 0.5 Hz and 1 kHz, amplified with a gain of ×1000 and digitised at a sampling rate of 2.5 kHz (CED1902, Cambridge, UK), and displayed online with an adjustable time scale of seconds to minutes (SPIKE II v5.15, Cambridge electronics design, Cambridge, UK).

4.3.3. Event related potential acquisition and data analysis

Neurophysiological data segments of 200 s duration commencing at least 20 s after onset of the first electrical somatosensory stimulus were re-sampled at 4 kHz for analysis (MATLAB v7.2, MathWorks Inc.). Corresponding events were identified from a single channel recording containing the electrical stimulus. The selected data segments were first bandpass filtered (high pass 2 Hz; low pass 125 Hz) to cover the frequency range of therapeutic DBS, then Butterworth filtered at 50 and 100 Hz to remove alternating current mains artefacts and their harmonics. PAVG LFP segments of 1 s duration from 0.5 s pre-event to 0.5 s post-event were extracted, aligned with events and mean averaged to obtain the event-related potential (ERP) response to

somatosensory electrical stimulation, and hence the mean averaged somatosensory evoked potential (SEP) for each deep brain electrode contact. Normalised SEPs were compared between body parts stimulated and between electrode contacts by paired student's t-test using $p<0.05$ for statistical significance.

4.4. Results

4.4.1 Patient demographics

Patient demographics are summarised in table 4.1. All patients were male with a mean age of 49 years at surgery and mean pain duration of 12 years prior to surgery. Aetiologies varied between stroke, oral facial pain, head trauma, cerebral arteriovenous malformation and phantom limb pain. Mean stimulation parameters were amplitude 2.6 v, frequency 42 Hz and pulse width 240 μs. Four patients proceeded to internalisation of DBS, the other patient failing to receive relief from post-stroke pain during trial stimulation.

4.4.2. Stimulator placement

Medtronic 3387® DBS electrodes consist of four cylindrical contacts each measuring 1.5 mm in length with 1.5 mm of insulated electrode in between and at the tip. Electrode contact placement for each subject within the PAVG with adjacent structures labelled is shown in figure 4.1. Numbered from '3' to '0' by convention, from proximal to distal the electrode contact positions go largely from rostral to caudal and slightly lateral to medial. The accuracy of the plotting technique used is limited to the MRI and CT slice thickness of 2.0 mm.

4.4.3 Event related potentials

Figure 4.2 demonstrates ERPs from median nerve stimulation in all patients, showing a strong positive response of latency 80-100 μs (P1). Figure 4.3 compares P100 SEPs between body parts for each electrode contact moving from rostral (contact 3) to caudal (contact 0) in an example subject (DK), illustrating a shift in maximal amplitude for leg stimulation rostrally to face stimulation caudally. Figure 4.4 compares SEPs for each body part by electrode contact as a normalised percentage of the largest amplitude ERP for each particular body part in all five subjects from data summarised in table 4.2. Maximal mean normalised SEP amplitude was at contact 0 for the face (1.0+/-0), contact 1 for the arm (1.0+/-0) and contact 2 with leg stimulation (0.77+/-0.15) with statistically significant differences between maximal and other SEP amplitudes for each body part assessed ($p<0.05$). The results were consistent across patients, providing objective electrophysiological evidence of a somatosensory homunculus in the PAVG of the human midbrain.

4. 5. Discussion

Stereotactic targeting using anatomical landmarks, atlases, macroelectrode impedance assessment and microelectrode recording guide electrode placement in DBS. However, subjective reporting of somatotopic localisation during intra-operative stimulation of awake patients under local anaesthesia fine-tunes electrode position in PAVG DBS for chronic pain. Frequently one attempts to elicit a sensation of pleasurable warmth or analgesia by low frequency (<50 Hz) stimulation. Should this not be attained, high frequency (>70 Hz) stimulation is applied for a hyperalgesic effect to confirm response to stimulation. An intra-operative experience of subjects reporting increasingly superior

regional somatic sensation with progressively caudal advancement of the actively stimulating electrode within the PAVG has previously been described, (Bittar et al. 2005c) but objective measurement by LFP recording has not.

A small and inconsistent animal literature suggesting PAVG somatotopy mirrors the lack of human data to date. An upright rostrocaudal somatotopy has been described by microelectrode and lesioning experiments upon the reptilian torus semicircularis, whose laminar nucleus has been proposed to be homologous to mammalian PAVG due to species specific vocalisation behaviours elicited by electrical stimulation. (Foster and Hall 1978). Rodent stimulation-produced analgesia paradigms provide limited evidence for dorsal to ventral somatopic representation of head to tail. (Soper and Melzack 1982) However, horse radish peroxidase studies in primates and cats have shown more rostral termination of lumbar spinothalamic afferents, a caudal preference for cervical afferent termination and caudally distributed trigeminal afferents. (Wiberg et al. 1986; 1987) The rostrocaudally aligned and inverted somatotopic representation suggested by mammalian data mirrors the well investigated sensorimotor homunculus of the anterior cerebellar lobe situated immediately posterior to the midbrain PAVG. (Manni and Petrosini 2004) Moreover, it is consistent with an established body of evidence for columnar functional organisation of the PAVG. (Bandler et al. 1991) In contrast to the human midbrain corticospinal tracts which have recently been demonstrated by diffusion tensor imaging to have laterally oriented homunculi,(Verstynen et al. 2012) PAVG somatotopic organisation is likely to be oriented rostrocaudally in an orthogonal plane to its functional organisation in mediolateral and anteroposterior columns.

There are limitations to drawing conclusions in electrode targeting for DBS from demonstration of a rostrocaudally inverted homunculus from tactile somatotopy. While

awake patients report somatotopy intraoperatively with electrode advancement, analgesia from DBS may be independent of somatosensory pathways. PAVG DBS may or may not be opioid mediated,(Young and Chambi 1987) or indeed driven by altering autonomic function either by reducing sympathetic or augmenting parasympathetic tone, (Green et al. 2006c; Pereira et al. 2010a) as further chapters investigate. Such mechanisms would be consistent with the PAVG comprising part of a medial limbic pain neuromatrix modulating interoception in communication with medial frontal brain structures such as the ACC. (Kalisch et al. 2006; Pereira et al. 2007a) Extrapolation of the results to guiding DBS therapy in chronic neuropathic pain are also limited by the heterogeneous aetiologies and different body parts affected in a small group of patients. Current investigations are directed towards correlating PAVG DBS electrode location with clinical outcome by patients' affected body part to assess if somatotopic electrode placement influences efficacy. Further studies in high resolution diffusion tensor imaging may provide additional evidence for the proposed homunculus orientation. (Owen et al. 2008; Owen et al. 2007c) Nevertheless, by using invasive neurophysiology to demonstrate the first in vivo objective evidence of a rostrocaudally inverted homunculus in man, the data provide an important addition to our anatomical knowledge of the midbrain.

Table 4.1. Subject details. Summary of patient demographics, pain duration and aetiology and deep brain stimulation parameters.

Initials	Sex	Age at surgery (years)	Pain duration before surgery (years)	Pain aetiology	Amplitude (v)	Frequency (Hz)	Pulse width (μs)
DK	M	61	7	Stroke	2.2	10	180
PM	M	58	3	Oral pain (facial)	2.9	50	120
SP	M	34	24	Head trauma	2.8	20	450
SB	M	35	10	Brain arteriovenous malformation	2.0	80	150
TG	M	55	14	Amputation	3.0	50	300

Table 4.2. Mean normalised somatosensory evoked potentials (SEPs) compared between different body parts for each electrode contact in all subjects. Maximal average SEP amplitude was at contact 0 for the face (caudally), contact 1 for the arm and contact 2 with leg stimulation (rostrally).

Contact	Face		Arm		Leg	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
0 (caudal)	1.00	0	0.69	0.12	0.50	0.10
1	0.86	0.05	1.00	0	0.58	0.10
2	0.76	0.10	0.70	0.16	0.77	0.15
3 (rostral)	0.65	0.12	0.59	0.11	0.91	0.21

Figure 4.1. Sagittal positions of all PAVG electrode contacts relative to the mid-commissural point (MCP) and red nucleus (RN). Periaqueductal (PAG) and periventricular grey (PVG) is outlined in black. AC, Anterior Commissure; PC, Posterior Commissure; SC, Superior Colliculi. (background reprinted from Mai *et al*. Atlas of the human brain. San Diego: Academic Press, 1998, with permission from Elsevier).

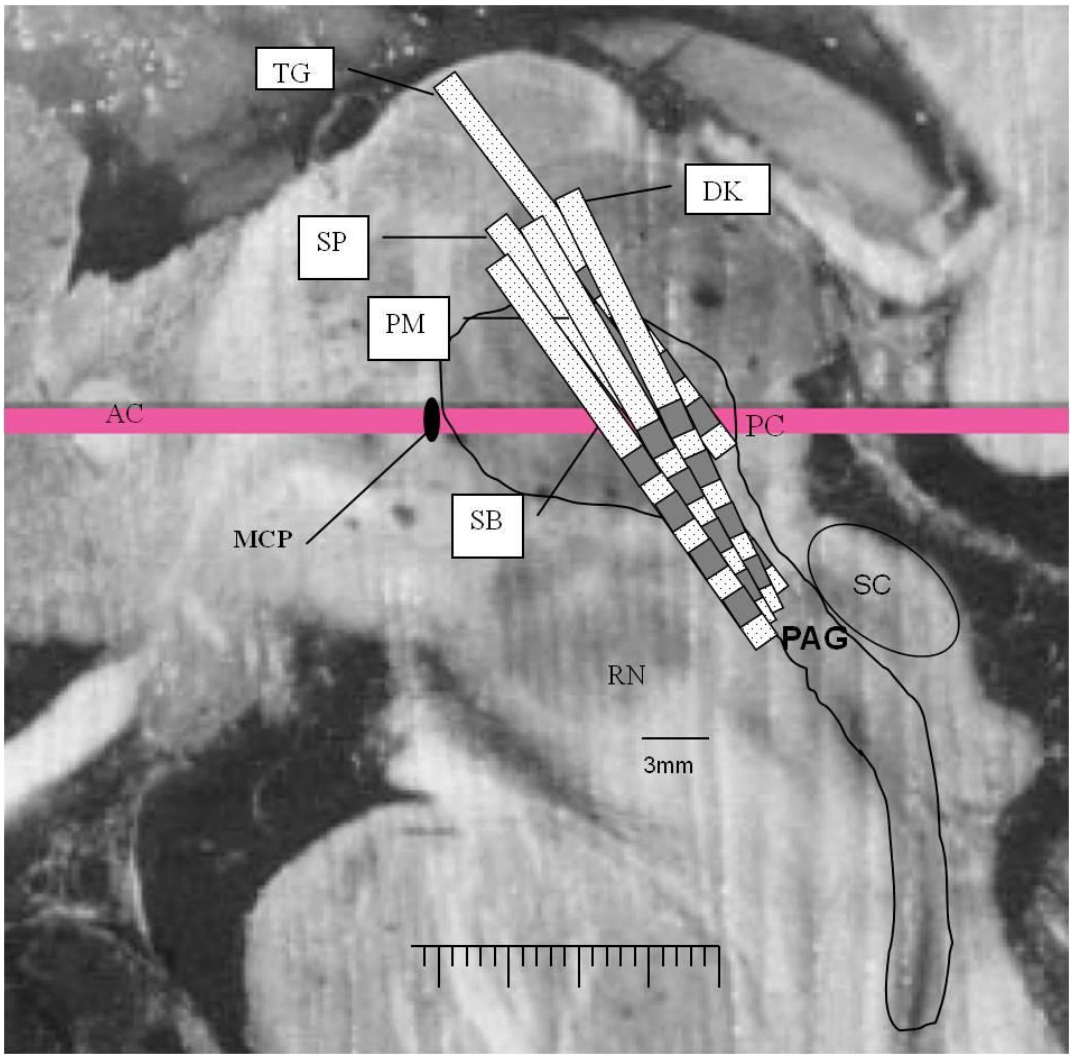


Figure 4.2. Median nerve stimulation ERPs across all subjects. A positive somatosensory evoked potential (SEP) with 80-100ms latency was found in all subjects.

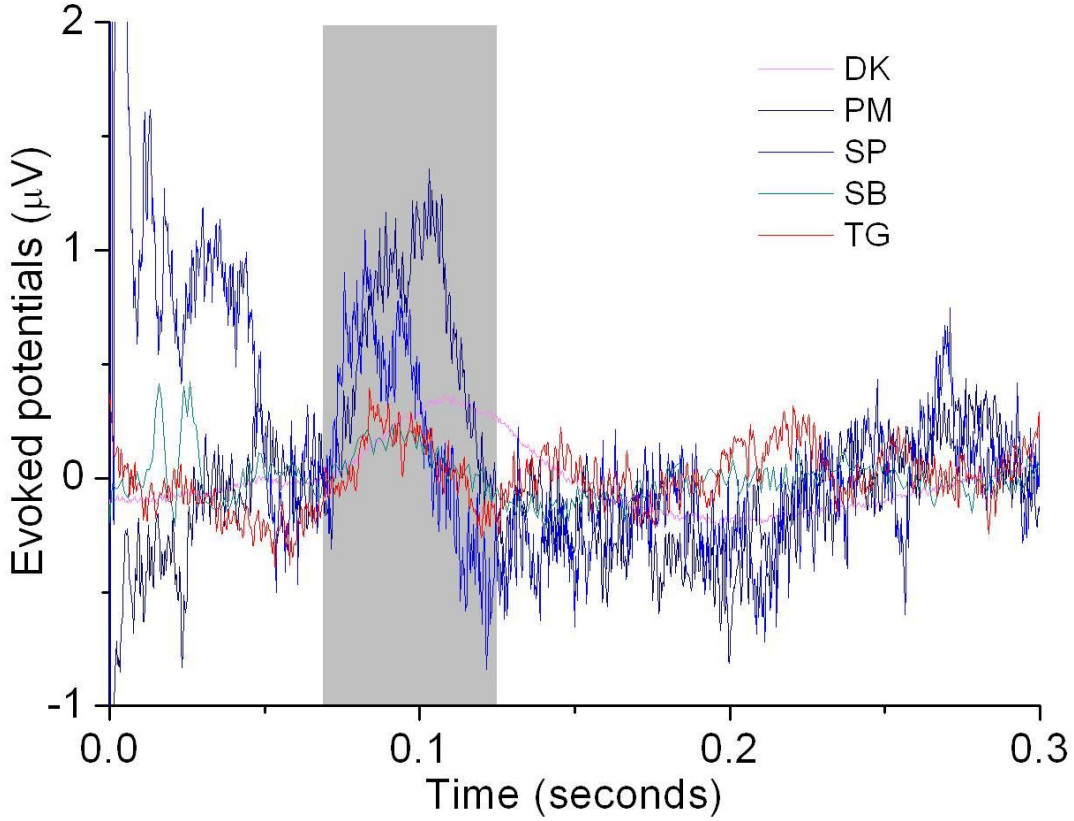


Figure 4.3. Somatosensory evoked potentials (SEPs) between different body parts for each electrode in an example patient. A. Rostral contact 3, B. Contact 2, C. Contact 1, D. Caudal contact 0. Facial SEPs (blue line) were largest in amplitude caudally, and conversely leg SEPs (red dots) rostrally.

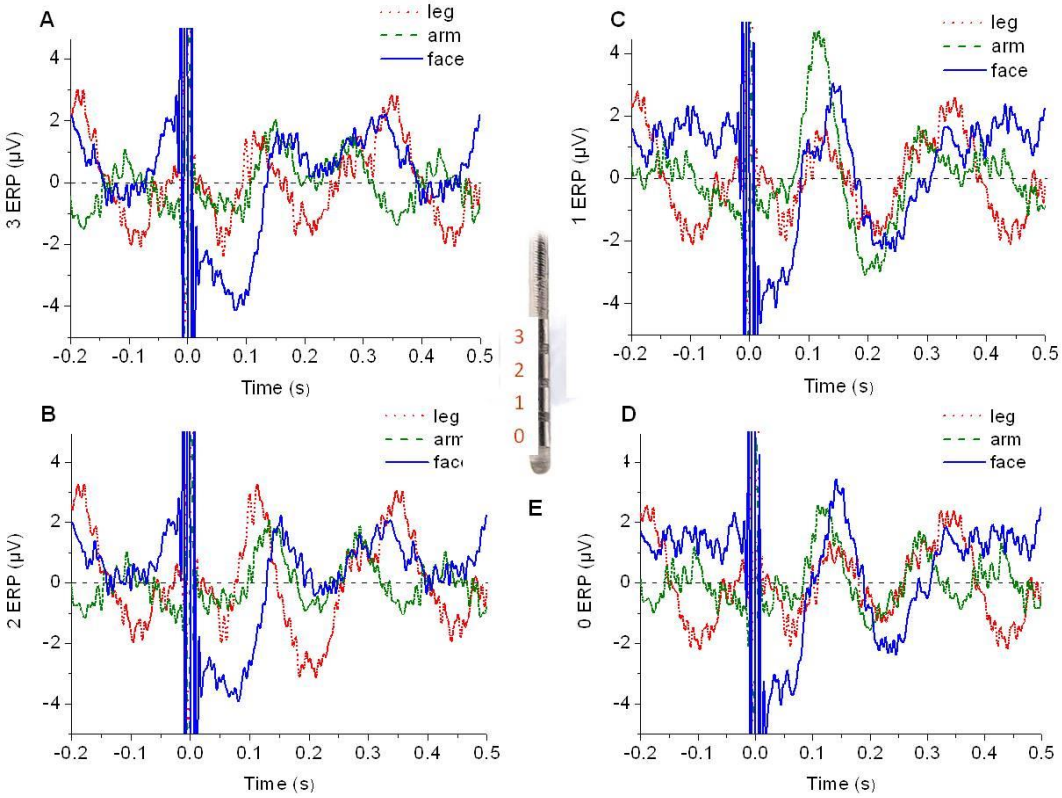
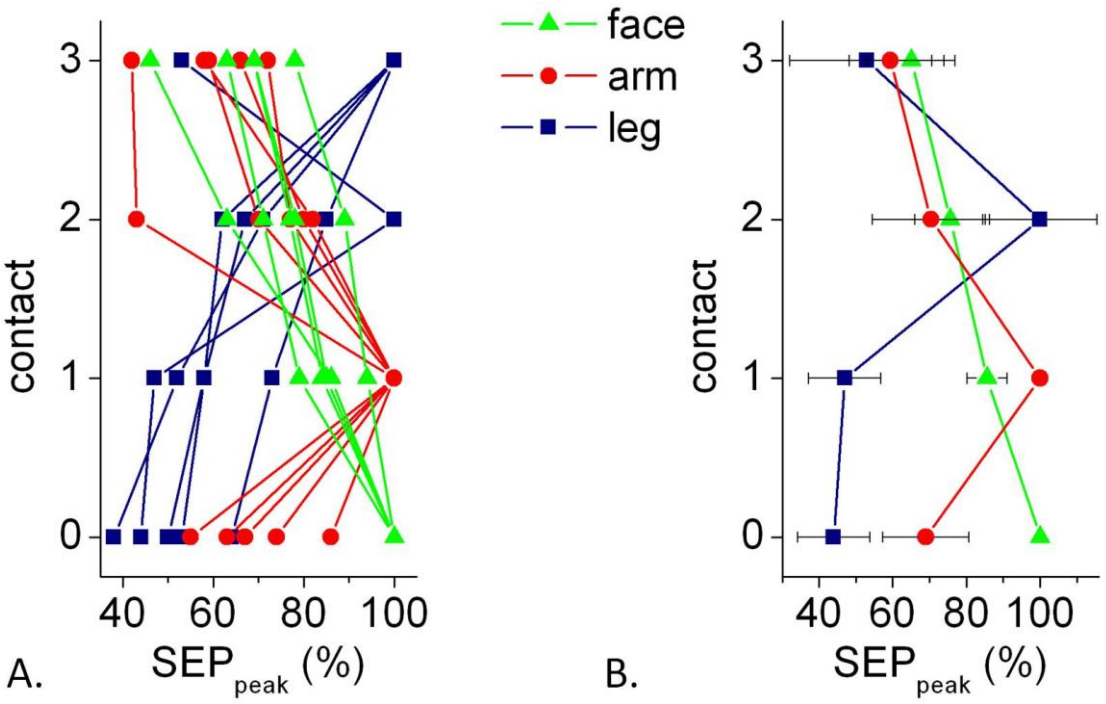


Figure 4.4. Normalised somatosensory evoked potentials (SEPs) compared between different body parts for each electrode contact in all subjects, A. with each subject's normalised SEP shown and B. as mean normalised SEPs with error bars. Maximal average SEP amplitude was at contact 0 for the face (caudally), contact 1 for the arm and contact 2 with leg stimulation (rostrally).



Chapter 5: Regional cerebral perfusion differences between periventricular grey, thalamic and dual target deep brain stimulation for chronic pain

5.1. Summary

Regional cerebral blood flow changes were evaluated in different subcortical brain targets following DBS for chronic pain. Three patients with intractable neuropathic pain were assessed; one had stimulating electrodes in VPL, one in PAVG, and one had electrodes in both targets. Pain relief was achieved in all patients. Cerebral perfusion was measured by single-photon emission computed tomography (SPET) to determine the effects of DBS. Comparison was made between individual scans using subtraction analysis. DBS consistently increased perfusion in the posterior subcortical region between VPL and PAVG, regardless of site of stimulation. Furthermore, thalamic and dual target DBS increased thalamic perfusion, yet PAVG DBS decreased perfusion in the PAVG-containing midbrain region and thalamus. Dual target stimulation decreased ACC and insular cortex perfusion. The study demonstrates regional differences in cerebral perfusion between three accepted and efficacious targets for analgesic DBS.

5.2. Introduction

DBS for chronic pain amelioration has been undertaken for over half a century, (Heath 1954; Pool et al. 1956a) its use preceding 'gate theory' by a decade. The VP thalamus has been targeted successfully for over three decades, (Hosobuchi et al. 1973) and PAVG similarly.(Richardson and Akil 1977a) A recent resurgence in its use for chronic pain refractory to medical treatment has paralleled advances in neuroimaging and DBS technology and the publication of cautiously interpreted prospective case series regarding its long-term safety and efficacy.(Hamani et al. 2006b; Owen et al. 2006b) Successful results have been shown for multiple aetiologies, in particular for post-stroke, limb and facial pain. (Bittar et al. 2005d; Boccard et al. 2013; Green et al. 2006a; Owen et al. 2006a) Nevertheless, several challenges preclude a move to large clinical trials of DBS for pain, in particular the lack of objective criteria to consistently select pre-operatively the patients likely to have satisfactory pain relief.

Lack of adequate animal models of chronic pain have frustrated progress, but deep brain neurophysiological recording in humans has revealed much mechanistically.(Green et al. 2006c; Nandi et al. 2003) Nevertheless, a great deal remains unknown about the mechanisms underlying analgesic DBS. DBS offers a novel and unique possibility for *in vivo* investigation of the functional role of the underlying neural circuitry in man by switching the stimulator on and off. The ensuing changes in whole-brain activity can then be mapped using neuroimaging methods.

Here presented are three cases of intractable neuropathic pain successfully treated with DBS and subsequently studied by SPET. SPET was chosen because the radioactive tracer can be administered during normal activity. The rapid uptake of the radioisotope used also enables the same patient to be scanned soon after the onset of pain or

alteration of DBS parameters. The risks of strong magnetic fields inducing heating or movement of the electrode or stimulator obviate routine use of functional MRI to map DBS-induced cortical activity.

PET, SPET and functional MRI have nonetheless been used in small numbers of patients to assess DBS for pain and chronic pain respectively, with mixed results. (Davis et al. 2000; Di Piero et al. 1991; Duncan et al. 1998; Garcia-Larrea et al. 2000; Iadarola et al. 1995; Kupers et al. 2000; Nandi et al. 2004; Peyron et al. 2000a; Rezai et al. 1999) Some studies reveal increased thalamic activation with thalamic DBS but none have compared VPL to PAVG or dual target stimulation to elucidate regional cerebral blood flow (rCBF) differences between different stimulation targets and target combinations.

5.2. Methods

5.2.1. Patients and deep brain stimulation

Three patients were studied (for demographics including pain aetiologies see table 1). Average duration of pain prior to surgery was 4.8 years.

After pre-operative assessment, DBS of PAVG and VPL were offered. The surgical technique is detailed in chapter 1 and elsewhere. (Bittar et al. 2005a; Joint et al. 2002; Owen et al. 2006a; Pereira and Aziz 2011; Pereira et al. 2009a)

Electrodes were externalised for a week of trial stimulation During which targets were tested individually (1–2 days each) for topographic coverage and optimal analgesia. Both electrodes were then tested together. With adequate analgesia, full implantation of the efficacious electrode(s) and of a subcutaneous programmable pulse generator

(Synergy®, Medtronic, Minneapolis, USA) was performed. Post-operative MRI scan confirmed the electrode positions (figure 2.1).

5.2.2. Pain Evaluation

Pre-operatively and one year after surgery, each patient recorded twice-daily visual analogue scores (VAS) of pain (scale 1–10) for 12 days. The 24 VAS scores were averaged to give single pre-operative and post-operative figures. Pre- and post-operative VAS were compared using paired *t*-tests with a two-tailed *P*-value of <0.05 taken as significant. McGill pain questionnaire (MPQ) were also completed on both occasions and anlalysed using the ranked pain rating index (PRI(R)). (Melzack 1975) Pre- and post-operative MPQ scores were compared using the Wilcoxon signed ranks test with a *P*-value of <0.05 taken as significant.

A third method favoured for evaluating analgesia in small groups and single cases is the N-of-1 trial.(McLeod et al. 1986; McQuay 1990) A randomised, placebo-controlled intra-patient trial is conducted whereby the patient receives paired sessions during which each intervention occurs once. Session order is randomised and effects of treatment or placebo compared between sessions. The validity of N-of-1 trials using the VAS, and their concordance with overall MPQ has been demonstrated for DBS. (Green et al. 2004) Here N-of-1 trials were conducted for two of the three patients one year after surgery, each trial using ten sessions with a cycling time between 'on' and 'off' DBS states that varied between patients as required (range 75 min to 120 min, average 91 min, SD 17 min).

5.2.3 Functional Imaging Acquisition and Analysis

SPET studies were acquired by triple-head Trionix TRIAD cerebral gamma camera with ultra-high resolution collimators. The subject was encouraged to relax in a dimly

lit room with their eyes closed. Intravenous technetium 99m-hexamethylpropyleneamineoxime (99mTc-HMPAO; 500 MBq; Nycomed Amersham International, Amersham, UK) was administered within 10 min of its constitution. Filtered back projection by Parzen filter and Sorensen attenuation correction were employed, providing 128 × 128 matrix images. The reconstructions were fitted individually onto a standard database template in Talairach coordinates (Hermes, Nuclear Diagnostics, Sweden). A fully automated, linear, nine-parameter (scale, translation and rotation for each *x*, *y* and *z*) fit was performed, initially by principal axis transformation later refined by a count difference minimisation algorithm (BRASS, Huddinge template, Nuclear Diagnostics, Sweden)(Van Laere et al. 2002), an analysis method of proven accuracy. (Slomka et al. 1997) Fit quality to template was inspected.. Prominent paranasal uptake can lead to initially suboptimal fitting, (Bradley et al. 2002), but all studies here fitted successfully by automated algorithm.

Once in standardised brain space, comparison was made between SPET images taken while DBS was either 'on' or 'off, for each individual patient. As the same Huddinge template was used for all scans, direct comparison of scans was possible. Hence, any rCBF differences demonstrated did not rely on prior assumptions, entire brains being compared rather than only regions of interest. Registration permits quantification of both severity and size of perfusion differences alongside inspection of the original and registered images. All processing was performed blinded as to whether DBS was 'on' or 'off'.

In each patient comparison, regions revealing ≥10%, ≥20% and ≥30% change in photon counts, relative to the corresponding scan were included. The 10% threshold was chosen to demonstrate statistically significant changes of clinical relevance. (Bradley et

al. 2002; Stapleton et al. 1994; Yianni et al. 2005) 20% and 30% thresholds were selected as regions of ≥20% and ≥30% perfusion reduction are highly significant changes that represent unequivocal regions of change equivalent to that seen in a significant stroke. (Berrouschot et al. 1998) Only regions of perfusion deficit in excess of 1 ml volume were included in the analysis. Each region was identified in accordance with named regions within the Huddinge atlas in Talairach space.

5.3. Results

5.3.1. Stimulator placement and pain relief

During a trial period of one week following surgery, all patients felt there was enough pain relief to warrant full implantation of the pacemaker (Synergy®, Medtronic Inc). Although dual channel, all patients were implanted with a Synergy® because of the longer battery life. If one channel was used, a plug was used to close off the inactive channel. The patients were then reviewed one month later to optimise the settings for maximum pain relief, and were reviewed six monthly thereafter. There were no significant surgical complications in this series and side-effects from stimulation were unremarkable.

Follow-up at one year was conducted and pain scores collated. One patient preferred chronic stimulation of the PAVG, one the VPL and one preferred both electrodes to be activated after trialling. The DBS targets used are summarised in table 5.1.

The efficacy of analgesia obtained for each patient is summarised in table 5.2, with individual components of the MPQ scores shown in table 5.3. The average reduction in VAS scores at one year was 37.0% (SD 5.2%, $P<0.01$). Analysis of the MPQ scores shows that the overall pain rating index (PRI(R)) reduced by 31.3% ($P<0.05$, Wilcoxon)

and that this reduction was mainly due to changes in the sensory category which showed an overall reduction of 25% ($P<0.05$, Wilcoxon). Of note, there is a large variation in improvements in the overall PRI(R) which ranged from a 5% to a 65% improvement. One patient was unavailable to partake in the N-of-1 trials; however both other patients' N-of 1 trials show a mean VAS reduction of 24.9% on average (SD 19.5%, $P<0.05$), demonstrating good concordance with overall PRI(R) and VAS scores. Of the three patients, one stopped all analgesics (all were on opiates, one on Gabapentin®) and one changed from regular opiate analgesia to 'as required' non-opiates. Degree of analgesia obtained, as evidenced by both postoperative pain scores and N-of-1 trials, does not appear to differ significantly between DBS targets (whether PAVG, VPL or both), although the significance of differences cannot be commented upon when comparing single cases alone. Similarly, the sites and types of pain are too varied to associate particular types of pain with DBS efficacy here.

5.3.2. Functional Imaging

All patients were investigated by SPET scanning both before stimulation ('off' DBS) and during it ('on' DBS) with scanning taking place between four and seven months after operation (average five months) and with two days between scans for each patient. A total of three pairs of SPET images were thus acquired (three 'on' DBS and three 'off' DBS). By employing BRASS analysis, the 'on' DBS were compared with the 'off' DBS images for each individual patient by subtracting one image from the other and vice versa. This allowed comparison to be made in both directions in order to look for perfusion defects in the presence or absence of DBS. Thus, areas that decreased their rCBF with stimulation switched on could be identified and, conversely, areas that increased their rCBF during DBS exhibited relative rCBF deficits in the 'off' DBS

images. Regions revealing ≥10%, ≥20% and ≥30% change in counts, relative to a common, absolute scale of counts, were included in the comparisons that follow. The individual patient results indicating regions, together with the percentage volumes of brain that those involved regions constitute, are displayed in table 5.4.

Figures 5.1-5.3 exemplify changes described below for each respective stimulation target. Consistent differences in rCBF were found, explicable by different anatomical targets of DBS, yet no obvious trends by gender differentiating the two men from the one woman in the study could be inferred.

Several regions of decreased rCBF were revealed in both sets of results for all patients, denoting areas either of relative hyper- or hypo-perfusion with chronic DBS compared with the absence of DBS. The percentage of total brain volume demonstrating decreased rCBF was also substantial for each respective patient. In the 'on' DBS group, percentage total brain volumes exhibiting rCBF reductions ranged from 5.7-18.3% amongst individuals at the 10% threshold, 0.3-8.3% at the 20% threshold and 0-4.0% at the 30% threshold. In the 'off' DBS analysis, percentage total brain volumes showing rCBF reductions ranged from 14.5-29.5% at the 10% threshold, 4.8-14.0% at the 20% threshold and 2.2-6.2% at the 30% threshold. Employing the Huddinge atlas to co-register regions of interest, the major areas of rCBF change could be identified. In the fitting of the SPETs to standard Talaraich space, the registration of the cerebrum was very good. However, Oxford's experience with SPET is that registration at the extreme peripheries of the cerebellum can be compromised leading to spurious artefactual rCBF changes. (Bradley et al. 2002) Thus minor peripheral cerebellar rCBF changes were excluded from the results.

Considering just the 30% threshold suggestive of very large rCBF differences, and considering PAVG stimulation alone, reduced ipsilateral lentiform nucleus and posterior subcortical rCBF (i.e. in the brain region between PAVG and thalamus) was found 'off' DBS. 'On' DBS, rCBF to the PAVG containing midbrain region, ipsilateral sensorimotor area and left prefrontal cortex were reduced. Similar results of posterior subcortical hypoperfusion 'off' DBS were seen at the more sensitive 20% threshold. In addition, at the less specific but still clinically significant 10% threshold reduced ipsilateral thalamic rCBF was found 'on' DBS.

With VPL stimulation at the 30% threshold, rCBF in posterior subcortical regions between thalamus and PAVG was reduced 'off' DBS. At the 20% threshold, contralateral thalamic hypoperfusion was seen 'off' DBS and reduced rCBF in limbic and frontal areas seen 'on' DBS. At the 10% threshold, contralateral posterior subcortical hypoperfusion was also seen 'off' DBS, and widespread reductions in rCBF to sensory and association areas 'on' DBS confirmed.

When stimulating both PAVG and VPL, hypoperfusion in contralateral subthalamic regions both between and adjacent to PAVG and VPL was revealed at the 30% threshold. 'Off' DBS, the subcortical hypoperfusion became posterior only, encompassing the region between PAVG and thalamus, but also bilateral. On increasing the detection sensitivity to detect 20% count differences, both posterior subcortical and ipsilateral (right) prefrontal hypoperfusion were found 'off' DBS, and generalised reductions in rCBF to several association areas including the ACC and insula found 'on' DBS. At the 10% threshold, these changes increased with additional contralateral thalamic hypoperfusion 'off' DBS.

5.4. Discussion

SPET enables cerebral function to be studied in humans in vivo. Reductions in rCBF may correlate to reductions in local neuronal metabolism and are thus likely correlates of reduced activity, be it excitatory or inhibitory. Shown here in three patients receiving pain relief by DBS firstly are distinct and consistent differences in PAVG versus sensory thalamic versus dual site stimulation and secondly similarities between all three stimulation paradigms. All three subjects had relatively increased rCBF of the 'posterior subcortical' region between PAVG and thalamus with DBS. In addition to the connections between the two structures, this brain region contains the centromedian-parafascicular complex that is heavily implicated in pain processing and has been targeted by DBS, (Weigel and Krauss 2004) with strong connections to the PAVG, as evidenced by histochemical staining and Oxford's diffusion tensor imaging (DTI) studies, (Owen et al. 2008) and a role in attentional orienting to behaviourally significant events. (Matsumoto et al. 2001; Minamimoto and Kimura 2002) Other structures present in the brain region include the zona incerta and substantia nigra which animal studies have implicated in nociception. (Li et al. 1992; Romo and Schultz 1989) PAVG DBS reduced rCBF to both ipsilateral midbrain and left prefrontal cortex, and to the ipsilateral thalamus to a lesser extent. Such findings suggest that PAVG DBS alone reduces perfusion in the PAVG itself and, by corollary, in thalamic and prefrontal regions to which it has direct connections. It also implicates the left dorsal prefrontal cortex in encoding emotional valency to pain in keeping with other studies giving laterality to prefrontal cortex emotional processing. (Drevets and Raichle 1998; van Honk et al. 2002)

The subject receiving thalamic stimulation also had increased rCBF to the contralateral thalamic region with DBS. SPET studies have shown increased thalamic perfusion in chronic pain, (Cesaro et al. 1991) yet increased thalamic metabolism with DBS is confirmed by PET studies and might reflect increased inhibitory neuronal processes. (Duncan et al. 1998; Kupers et al. 2000) VPL DBS reduced rCBF in both frontal and limbic cortical association areas, supporting evidence that thalamic DBS might act to 'gate' neocortical pain processing.

Dual site stimulation of VPL and PAVG together caused rCBF changes around both structures and increased contralateral thalamic rCBF yet reduced rCBF to neocortical association areas including the ACC. Such findings support a model whereby increased inhibitory activity in the thalamus gates and thus reduces neocortical pain processing. The evidence that either PAVG or thalamic stimulation directly reduce rCBF in neocortical pain association areas secondary to decreased PAVG rCBF or increased thalamic rCBF supports a "dual pathway" hypothesis for pain processing whereby the PAVG integrates attentional responses to pain and directly conveys such information to neocortical structures, but that the sensory thalamus may filter discriminative nociceptive information to neocortical sensory areas for more detailed processing. Such a model would be in keeping with the wealth of functional neuroimaging literature, (Peyron et al. 2000a; Zambreanu et al. 2005) and also with investigations using histochemical tract tracing and other modalities of neuroimaging like DTI. Such studies demonstrate, for example, direct connections between neocortical association areas and in particular the amygdala (a structure encoding rapid fear responses), the hypothalamus (a structure integrating interoceptive function) and the PAVG, and increased PAVG

activity when attending to emotional stimuli.(Bandler and Shipley 1994; Hadjipavlou et al. 2006; Keay and Bandler 2001)

Much electrophysiological, anatomical and radiological evidence in humans and animals establishes both PAVG and VPL as structures important to pain perception and the pathophysiology of chronic pain syndromes. (Behbehani 1995; Craig 2003; Gauriau and Bernard 2002; Peyron et al. 2000a; Romanelli and Esposito 2004; Sewards and Sewards 2002; Tracey 2005; Willis and Westlund 1997) The subtleties of hierarchical position and behavioural function of individual brain structures are much debated. However, the consensus is towards a pain neuromatrix also involving spinal cord, hypothalamus, amygdala, and somatosensory, insular, anterior cingulate and prefrontal cortex. Whether pain control is top-down or bottom-up in its hierarchy is unresolved and often depends upon the experimental paradigm used.

In conclusion, it has been shown here that DBS increases perfusion in the region between VPL and PAVG, comprising such structures as the centromedian-parafasicular complex, regardless of site of stimulation. These findings from perfusion changes further suggest that thalamic DBS is likely to increase inhibitory neuronal activity and PAVG DBS to decrease excitatory neuronal activity. The cerebellum is not implicated in nociception, thus the exclusion of artefactual cerebellar rCBF changes from these results is without consequence.

Caution should be exercised in interpreting rCBF changes related to small structures, since in the alignment of the individual SPETs there will be inevitable ‘blurring’ of the precise location of such small, centrally located structures. A further problem is that the spatial resolution of SPET does not allow precise anatomic localisation beyond that

presented here. As with PET, different midbrain structures, for example, are typically included in the same region of interest. (Peyron et al. 2000a)

Like PET, SPET measures neuronal activity only indirectly, but because individual structures vary as to whether their projections are predominantly excitatory or inhibitory, interpretation of changes in rCBF can be difficult. It is established that rCBF changes reflect neuronal activity changes downstream from cell bodies, mainly in terminal fields.(Schwartz et al. 1979) rCBF also increases with interneuronal activity either in that region or in more distant input pathways, such inputs being excitatory or inhibitory. (Ackermann et al. 1984; Gusnard and Raichle 2004) It is not clear how the effect of DBS synchronised oscillations upon aberrant neuronal firing relates to local perfusion changes. The cascade of potential responses to DBS is thus only loosely delineated mechanistically by currently available modalities of functional neuroimaging, and parallel research utilising neurophysiological methods like deep brain LFP recording in animal and human subjects is required. The increased spatial resolution provided by functional MRI has similar shortcomings. Moreover, although functional MRI with DBS has been performed, (Rezai et al. 1999) for resolution sufficient to delineate such structures the stimulating electrode could generate an artefact that would confound the data and the higher magnetic field risks potential electrode displacement and patient harm. SPET therefore provides a good functional imaging technique for investigating the patients included in this study if careful consideration is given to principles of blood flow interpretation in DBS. Further studies using other modalities like DTI, LFP recording in patients with pain of other aetiologies and minimal cerebral pathology receiving DBS, and functional MRI in patients with chronic pain provide complementary evidence to further elucidate pain mechanisms and

improve therapeutic prospects for these patients. Furthermore, the technique of MEG enables whole brain changes to be mapped with spatial resolution comparable to functional MRI, and temporal resolution of the order of milliseconds, with deep structure detection.(Hillebrand and Barnes 2002; Ioannides et al. 2004) The use of MEG to map changes with and without DBS has been described and holds much promise for increasing our understanding of central neural reorganisation leading to abnormal pain processing and the effects of DBS.(Kringelbach et al. 2007) Combining functional neuroimaging such as SPET, electrophysiology and technologies at their interface like MEG provides mechanistic insight that helps patient selection and guides clinical decisions.

Table 5.1. Summary of subject details and stimulator sites. PAVG, periventricular grey matter; VPL, ventroposterolateral nucleus of the thalamus.

Subject	Age/Sex	Diagnosis	Type of pain	Initial target	Best trial target	Final target used
1	62 F	Right cortical infarct (sub-arachnoid haemorrhage)	Left hemi-body pain Constant, severe	Right PAVG and right VPL	PAVG	PAVG
2	47 M	Right thalamic infarct	Left hemi-body pain Constant, severe	Right VPL	VPL	VPL
3	49 M	Post syrinx decompression	Right arm pain Constant, severe, burning	Left PAVG and left VPL	No difference	PAVG and VPL

Table 5.2. Pain relief obtained with DBS for each patient. VAS, visual analogue score; MPQ, McGill pain questionnaire.

Subject	Overall VAS				Overall MPQ				N-of-1 (at one year) number of correct answers (out of 10)	Mean VAS		
	Pre-op	One year post-op	p-value	% reduction (at one year)	Pre-op	One year post-op	p-value	% reduction (at one year)		On	Off	p-value
1	97	55	<0.01	43	51	18	<0.05	65	N/A	N/A	N/A	N/A
2	85	54	<0.01	34	22	15	<0.05	32	6	54	88	<0.05
3	89	59	<0.01	34	20	19	>0.05	5	10	80	90	<0.05

Table 5.3. McGill pain questionnaire pre-operative and post-operative ranked pain rating indices.

Subject	Sensory (/42)	Affective (/14)	Evaluative (/5)	Miscellaneous (/17)	Total (/78)
Pre-operative					
1	28	10	5	8	51
2	14	1	3	4	22
3	9	0	5	6	20
Post-operative (at one year)					
1	6	2	5	5	18
2	13	2	0	0	15
3	10	2	3	4	19

Table 5.4. Areas of perfusion deficit ≥10%, ≥20% and ≥30% noted on analysis of SPET subtraction data. For each individual patient, regions defined by Huddinge template are listed in descending order of count percentage difference. Both 'on' and 'off' DBS paradigms are included. Percentage of total brain volume exhibiting perfusion deficit is also displayed for each brain region in both the 'on' and 'off' state.

Threshold	Subject and target	Regions of relative hypoperfusion 'on' DBS compared to the 'off' state	'on' DBS total % deficits	Regions of relative hypoperfusion 'off' DBS compared to the 'on' state	'off' DBS total % deficits
10%	1. PAVG (right)	Right thalamus (17.8%), Left lateral temporal lobe (0.5%)	18.3%	Right posterior subcortical (10.7%), Left medial temporal lobe (0.4%), Left anterior subcortical (1.0%), Right sensorimotor (0.1%), Left parieto-temporal cortex (2.0%), Left superior parietal cortex (0.1%), Left occipital cortex (0.2%)	14.5%
	2. VPL (right)	Right lateral temporal lobe (0.5%), Left sensorimotor (0.5%), Right posterior orbital cortex (1.7%), Right lentiform nucleus (0.1%), Right superior parietal cortex (2.1%), Left lentiform nucleus (0.2%), Left parieto-temporal cortex (0.5%)	5.7%	Left posterior subcortical (29.5%)	29.5%
	3. both (left)	Right anterior subcortical (9.0%), Right parieto-temporal cortex (1.8%), Right posterior subcortical (1.4%), Left superior parietal cortex (0.3%), Left lateral temporal lobe (0.2%), Left posterior subcortical (3.1%), Right occipital cortex (0.5%)	16.3%	Right thalamus (20.0%), Left occipital cortex (1.2%), Left posterior orbital cortex (0.1%)	21.3%
20%	1. PAVG (right)	Right lentiform nucleus (5.8%), Left posterior subcortical (1.3%), Left anterior subcortical (0.2%), Left sensorimotor (0.9%), Left lateral temporal lobe (0.2%)	8.3%	Right posterior subcortical (3.3%), Right insular cortex (0.9%), Left lateral temporal lobe (0.1%), Left anterior subcortical (0.3%), Left posterior subcortical (0.2%),	4.7%
	2. VPL (right)	Right lateral temporal lobe (0.1%), Right anterior orbital frontal cortex (0.1%), Right parieto-temporal cortex (0.1%)	0.3%	Left thalamus (13.9%), Left occipital cortex (0.2%)	14.0%
	3. both (left)	Other subcortical (2.5%), Right parieto-temporal cortex (0.5%), Right posterior subcortical (0.6%), Right anterior cingulate gyrus (1.3%), Left superior parietal cortex (0.1%), Left insular cortex (0.1%)	5.1%	Right posterior subcortical (6.8%), Left posterior subcortical (0.2%), Left occipital cortex (0.3%), Right anterior dorsal frontal cortex (0.2%), Right lateral temporal lobe (0.1%)	7.5%
30%	1. PAVG (right)	Right sensorimotor (3.3%), Pons and midbrain (0.5%), Left anterior dorsal frontal cortex (0.2%)	4.0%	Right lentiform nucleus (0.6%), Right posterior subcortical (2.2%)	2.7%
	2. VPL (right)	None	0%	Left thalamus (5.1%), Right posterior subcortical (1.2%)	6.2%
	3. both (left)	Right anterior subcortical (1.5%), Right posterior subcortical (0.2%)	1.7%	Right posterior subcortical (1.9%), Left posterior subcortical (0.2%), Right occipital cortex (0.1%)	2.2%

Figure 5.1. Axial SPET showing hypoperfusion greater than 30% 'off' relative to 'on' PAVG DBS. Right posterior subcortical hypoperfusion is marked with crosshairs and the electrode contact site superposition with a white arrow. Note also the large area of hypoperfusion due to the right-sided cortical infarct.

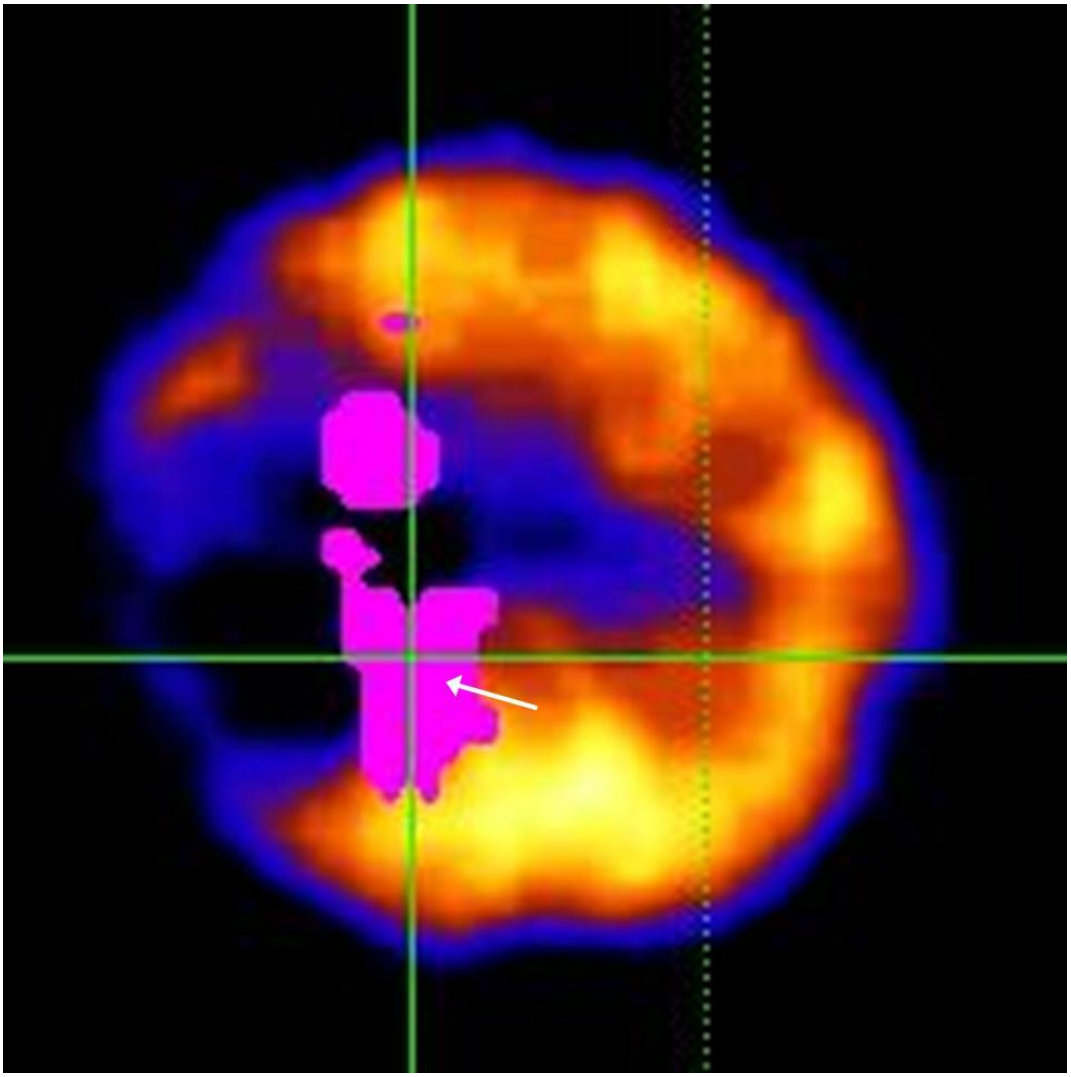


Figure 5.2. Coronal SPET showing hypoperfusion greater than 30% 'off' relative to 'on' VPL DBS. Left thalamic hypoperf\usion is marked with crosshairs and the electrode contact site superposition with a white arrow.

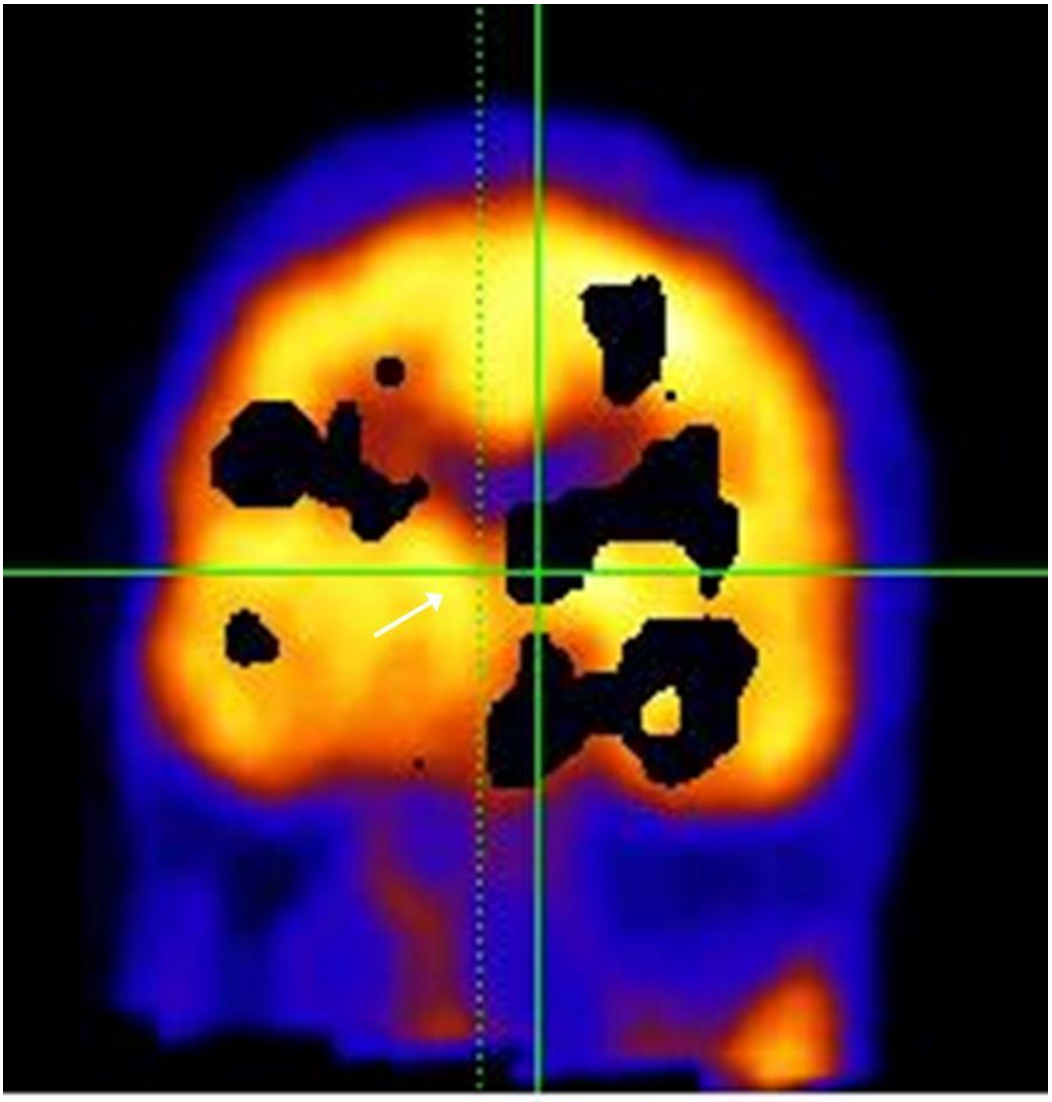
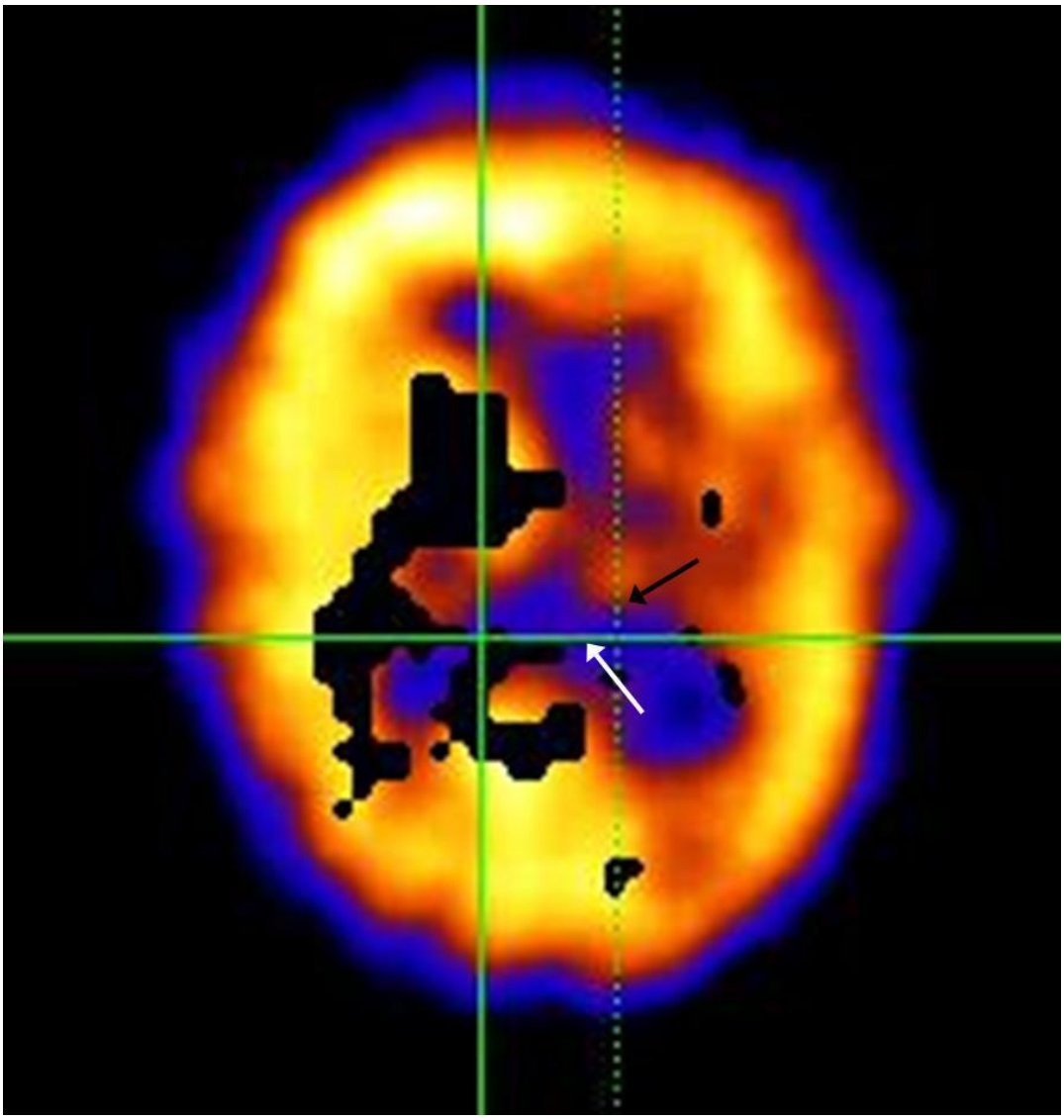


Figure 5.3. Axial SPET showing hypoperfusion greater than 30% 'off' relative to 'on' dualt target PAVG and VPL DBS. Right posterior subcortical hypoperfusion is marked with crosshairs, superposition of the VPL electrode contact site with a black arrow and PAVG with a white arrow.



Section 3

Autonomic interactions with deep brain stimulation for pain

Chapter 6: Sustained reduction in hypertension by deep brain stimulation

6.1. Summary

Deep brain stimulators were implanted in the left PAVG and sensory thalamus for right sided neuropathic facial pain refractory to other treatments in a man aged 58 years. PAG stimulation 8 months later acutely reduced systolic blood pressure (SBP) by 25 mmHg during revision surgery. One year post-procedure, ABPM demonstrated significant and sustained reduction in BP with PAG stimulation. Mean SBP decreased by 12.6 mm Hg and diastolic by 11.0 mm Hg, alongside reductions in variability of heart rate and pulse pressure. This neurosurgical treatment may prove beneficial for medically refractory hypertension.

6.2. Introduction

DBS of the PAVG area has been used for three decades to treat chronic neuropathic pain refractory to medical therapies.(Hosobuchi et al. 1977) Real time BP changes with PAG stimulation are commonly seen intra-operatively in humans. The PAG projects to medullary regions controlling BP, as well as having reciprocal connections with higher brain centres.(Behbehani 1995) Here it was assessed whether electrical stimulation of this area in an ambulatory patient caused a sustained reduction of hypertension.

6.3. Methods.

A 58 year old man was referred for DBS for facial pain refractory to both pharmacological analgesia and motor cortex stimulation. Three years earlier he had developed posterior lingual paraesthesia that progressed over several months into right-sided facial pain involving mainly the pharynx and maxillary trigeminal nerve branch territory. His medical history included hypertension and depression, daily medications comprising perindopril 8mg, felodipine 2.5mg, atenolol 50mg, nicorandil 10mg, atorvastatin 10mg, mirtazapine 45mg, carbamazepine 200mg, dothiepin 75mg, pregabalin 300mg., diazepam 5mg, and zopiclone 7.5mg.

Under local anaesthesia, intracerebral quadripolar electrodes (model 3387®, Medtronic Inc, Minneapolis, MN, USA) were implanted stereotactically into left PAG and ventroposteromedial thalamus (figure 6.1A). The Oxford surgical technique is detailed in chapter one and elsewhere.(Pereira and Aziz 2011; Pereira et al. 2009a)

Pain was reduced by PAG but not thalamic DBS intra-operatively, during the post-operative week and at six months' follow-up. Further surgery was performed at eight months follow-up after electrode fracture due to mild accidental head trauma. During revision surgery, PAG but not thalamic DBS reduced BP from 157.4/87.5 to 132.4/79.2

mm Hg (Medex Medical transducer, AS/3 anaesthetic machine, Datex-Ohmeda Inc., Tewksbury, MA, USA).

One year post-implantation, moderate hypertension despite medications above was recorded using manual sphygmomanometry (BP 150/110 mm Hg left arm; 155/115 mm Hg right arm). Having been 'off' DBS for 24 hours, the patient was not told whether his DBS was switched on or off, nor its settings; and before and during DBS his BP was recorded every 30 min for 16 h while awake and one hourly for 8 h while asleep using an oscillometric ambulatory BP monitor (model TM2430, A&D Instruments, Oxford, UK) fitted to his left arm. His pain visual analogue score (VAS) was recorded two hourly while awake. Real-time BP changes with DBS were assessed (Portapres, TNO, Amsterdam, The Netherlands). PAG DBS at 2.9 V, frequency 50 Hz and pulse width 120 μs elicited partial pain relief and objective BP reduction of 10-20 mmHg. A further 24 h period of ambulatory monitoring was performed with PAG DBS settings as above, the patient remaining blinded to all settings.

6.4. Results

Using the Student's *t* test for unpaired observations to determine differences, sustained significant decreases ($p<0.001$) in both systolic and diastolic BP were demonstrated with PAG DBS (figures 2A,B). Mean BP off DBS was 144.1/95.8 (s.e. 3.4/3.2) and on DBS 131.4/84.8 (s.e. 2.8/2.4), representing a mean diurnal systolic decrease of 12.6 mm Hg and diastolic reduction of 11.0 mm Hg. Reductions in heart rate variability (from range 50-68 bpm, s.d. 5.2 to range 53-63, s.d. 3.0) and pulse pressure (from range 27-79 mm Hg, s.d. 11.9 to range 33-65, s.d. 7.7) were also observed (figures 2C,D). Pain relief was significantly improved by DBS, mean VAS decreasing from 79% to 64% ($p<0.05$).

6.5. Discussion

PAG DBS can be an effective treatment for facial pain in patients refractory to other therapies. Degree of analgesia in such patients correlates positively with degree of acute BP reduction.(Green et al. 2006c) Whereas dorsal PAG stimulation can acutely elevate BP, ventral stimulation reduces it.(Green et al. 2005a)

This is the first report of sustained BP reduction with DBS. The distal electrode contact pair stimulated appears sited in ventral PAG both on MRI (figure 6.1B) and on electrode site reconstruction (figure 6.1C) using techniques detailed elsewhere.(Green et al. 2006c) The PAG is optimally situated anatomically to integrate interoceptive function, both from adjacent medullary cardiovascular centres and more distal pain processing areas.(Behbehani 1995) Figure 6.3 illustrates the columnar organisation of the PAG evidenced by animal experiments and its myriad connections to caudal structures affecting both analgesia, primarily through connections with thalamic, spinal, reticular and raphe nuclei, and cardiovascular changes, mainly through connections to medullary nuclei.

Analyses of ambulatory monitor use have shown reductions in diurnal mean BP from first to second days of usage in patients using such monitors for the first time.(Hermida et al. 2002) However, the patient studied here had received ambulatory monitoring on several occasions, the last only six weeks before. The novelty effects described elsewhere are without changes in heart rate in contrast to the reduction in heart rate variability with DBS shown here (figure 6.2C). Decreased variability of both heart rate and pulse pressure (figure 6.2D) together with diminished temporal oscillation in all measured cardiovascular parameters (figure 6.2) suggest that ventral PAG DBS exerts a sustained descending inhibition upon sympathetic vasomotor activity.

It is notable that the patient studied here had a significant reduction in pain with DBS alongside their sustained decrease in BP. It could therefore be argued that concomitant analgesia confounds studies of autonomic changes with PAG DBS. The profound interconnectivity between analgesic and autonomic pathways in this area of interoceptive integration is clear (figure 6.3).(Bajic and Proudfit 1999; Chen and Aston-Jones 1995; Craig 1995; Ennis et al. 1991; Farkas et al. 1997; Hudson and Lumb 1996; Lovick 1994; Marcinkiewicz et al. 1989; Mouton and Holstege 1994; 2000; Odeh and Antal 2001; Redgrave et al. 1988; Van der Horst and Holstege 1998; Wilson and Kapp 1991). It can therefore be argued that, in addition to possible opioid mediated analgesia, ventral PAG DBS may in part exert its analgesic effect either by ameliorating sympathetic or augmenting parasympathetic function. Current research into exercise and using measures such as heart rate variability and tilt table studies in patients receiving PAG DBS seek to delineate such factors.(Green and Paterson 2008) In addition, PAG DBS research using animal models of hypertension without chronic pain seek to eradicate the analgesic confound. Progress to clinical trials of PAG DBS for hypertension in patients without chronic pain requires robust evidence from both of these domains.

Approximately a quarter of hypertensives have poorly controlled BP. 3% are refractory to pharmacotherapy.(Alderman et al. 1988) Whereas DBS surgery entails a 1% stroke risk and some expense, sustained changes augur for potential benefits in treating them. Before then, long-term efficacy in further patients must be demonstrated, alongside complementary clinical and translational studies of autonomic DBS.

Figure 6.1. Electrode location. (A) Axial MRI showing lateral thalamic electrode tip and medial periaqueductal grey (PAG) lead. (B) Axial MRI showing electrode tip in ventral PAG (ventral PAG is above horizontal white line, dorsal is below). (C) Electrode contact positions superimposed on sagittal view. MCP = mid commissural point, RN = red nucleus, SC = superior colliculus, PAG = periaqueductal grey; PVG = periventricular grey (background reprinted from Mai *et al*. Atlas of the human brain. San Diego: Academic Press, 1998, with permission from Elsevier).

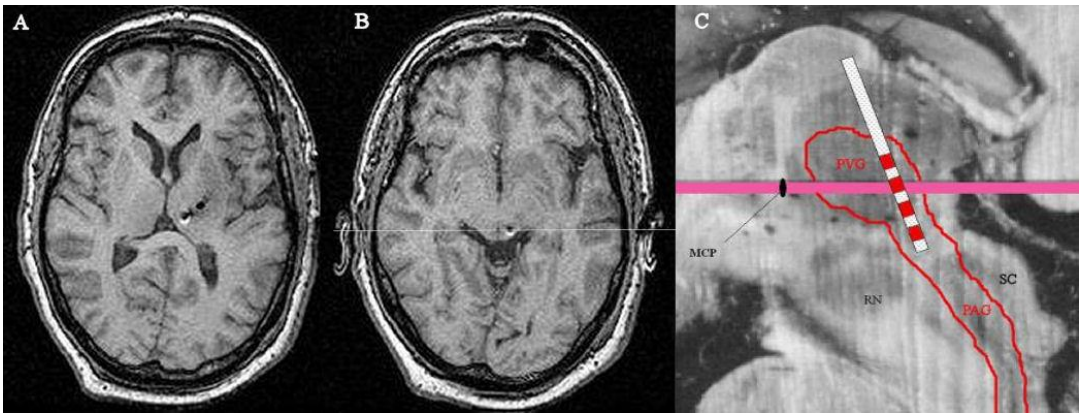


Figure 6.2. Changes with deep brain stimulation (DBS) showing readings from 24 hours prior to DBS (left of the blue vertical line) and from 24 hours with DBS (right of the blue vertical line). (A) Systolic blood pressure (SBP) changes (horizontal line at 140 mmHg delineates mild and moderate hypertension). (B) Diastolic blood pressure (DBP) changes (horizontal line at 90 mm Hg delineates mild and moderate hypertension). (C) Heart rate variation (beats per minute [bpm]). (D) Pulse pressure variation.

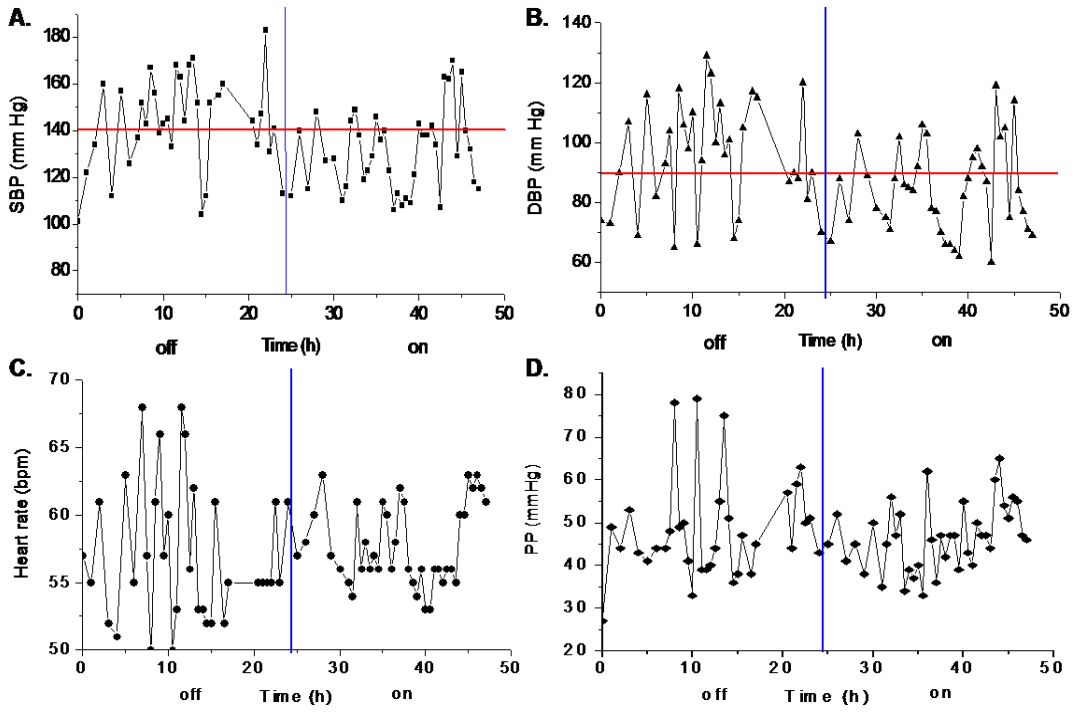
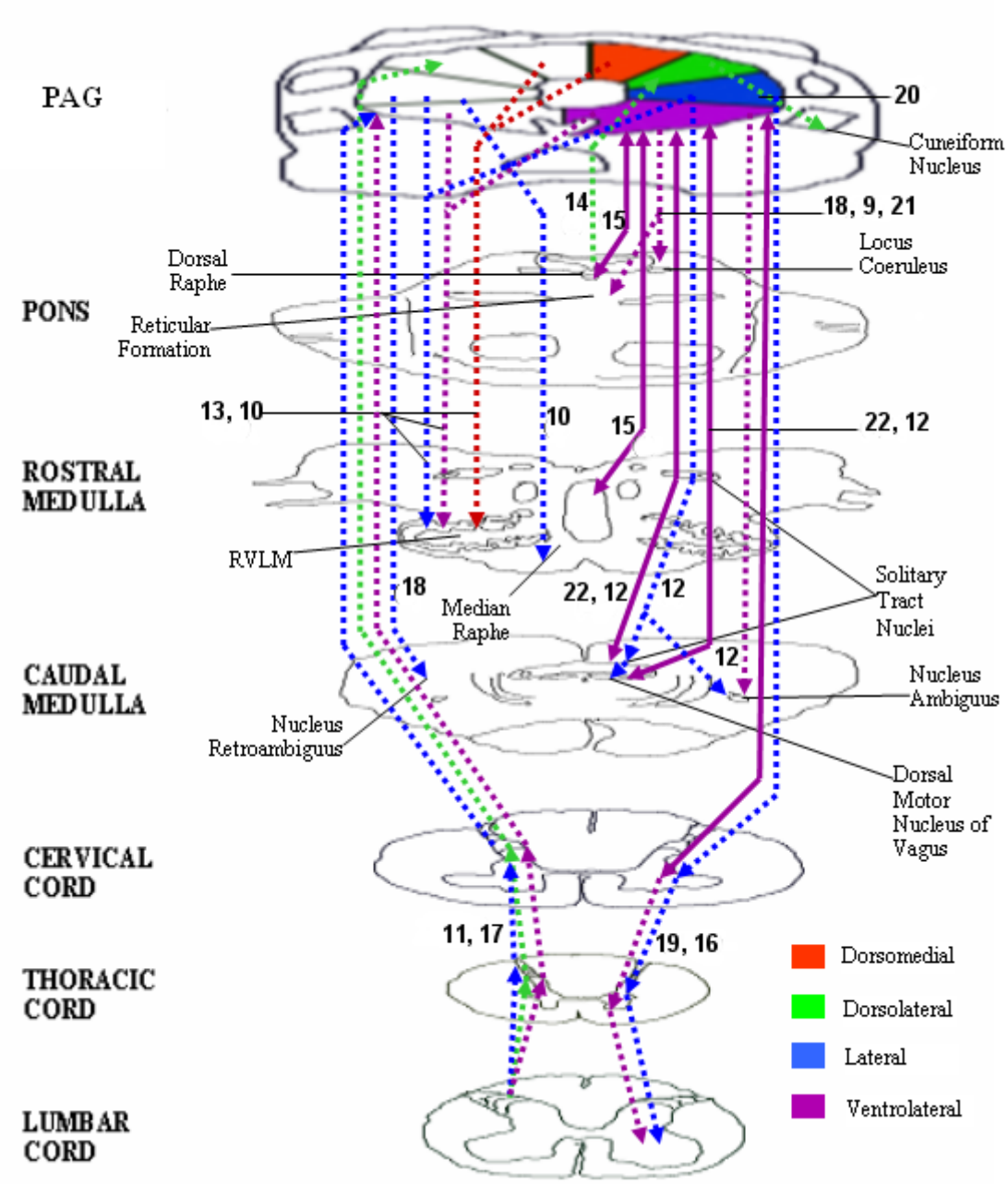


Figure 6.3. A schematic summary of the columnar organisation of the periaqueductal grey (PAG) and its connections to caudal areas controlling pain and blood pressure (based on animal studies). Solid lines show reciprocal connections and dashed lines show one-way projections. Numbers in brackets refer to specific references below. Some connections are shown on the left, and others on the right for clarity. RVLM = rostral ventrolateral medulla. (Bandler et al. 1991; Behbehani 1995; Carrive 1993; Rossi et al. 1994)



6.6. References in figure 6.3 labels.

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Chapter 7: Ventral periaqueductal grey stimulation alters heart rate variability in patients with chronic pain

7.1. Summary

The midbrain PAVG area is important both pain modulation and cardiovascular control via the autonomic nervous system (ANS). While changes in BP dependent upon dorsal or ventral electrode positioning have been described with PAVG DBS, little is known mechanistically about relationships between pain and cardiovascular regulation in humans. Heart rate variability (HRV) is an established measure of cardiovascular regulation, and an index of autonomic function. 16 patients undergoing DBS of the rostral PAVG for chronic neuropathic pain were investigated post-operatively to determine whether PAVG stimulation would alter HRV, and the subjects' perception of pain. Mean heart rate together with HRV, time and frequency domain measures, low frequency (LF) and high frequency (HF) power components of heart rate and the ratio of LF to HF were calculated before and during DBS. Ventral but not dorsal PAVG DBS significantly decreased the ratio of LF to HF power ($p<0.05$, $n=8$) with HF power significantly increased. Changes in LF/HF ratio correlated significantly with subjective reporting of analgesic efficacy using a Visual Analogue Score (VAS; $\gamma^2=0.36$, $p=0.01$, $n=16$). Diffusion tensor imaging and probabilistic tractography of 17 normal controls' seeding voxels from the mean ventral and dorsal PAVG stimulation sites of the 16 patient cohort revealed significant differences between rostral tract projections and separate, adjacent projections to ipsilateral dorsolateral medulla. Ventral PAVG DBS may increase parasympathetic activity to reduce pain via anatomical connections distinct from dorsal PAG DBS, which may act by sympathetic mechanisms.

7.2. Introduction

The PAVG is a structure optimally sited anatomically to integrate interoceptive function, both from adjacent mesencephalic cardiovascular centres and more distal pain processing areas. Its autonomic effects have been well studied in animals (Bandler et al. 1991; Behbehani 1995; Carrive 1993; Rossi et al. 1994) and changes noted with DBS (Young and Rinaldi 1997). Animal experiments have suggested that ventral PAG stimulation augments parasympathetic effects, concomitant with opioid mediated analgesia, whereas dorsal PAG stimulation is sympathomimetic and non-opioid mediated (Bandler and Carrive 1988; Depaulis et al. 1994), responses intimately related to affective changes such as fear and also described in humans (Fanselow 1991; Nashold et al. 1969). The 'freezing' and 'fight or flight' responses suggested to be mediated by ventral and dorsal PAG comprise the 'passive' and 'active' coping responses.

The history of PAVG DBS and its current indications have been reviewed in chapter one and elsewhere.(Pereira and Aziz 2011; Pereira et al. 2009a) It has been demonstrated that there is a positive correlation between degree of analgesia in patients receiving PAG DBS and magnitude of BP reduction and shown that whereas dorsal PAG stimulation can acutely elevate BP, ventral stimulation reduces it (Green et al. 2006b; Green et al. 2005b; Pereira et al. 2010b). Autonomic changes, such as tachycardia, hypertension, diaphoresis and lacrimation, although non-specific, are also established signs of pain or inadequate analgesia. Such findings advance investigations for objective markers of chronic pain and also potential selection of patients who may respond best to PAG DBS.

The rostral ventrolateral medulla (RVLM) contains nuclei that control the sympathetic system (Aicher et al. 1996; Hancock 1988), whereas the nucleus ambiguus and dorsal motor nucleus of the vagus drive the parasympathetic system (McAllen and Spyer 1976). Cardiovascular regulation depends on the balance of activity between these brain regions. Heart rate variability (HRV) is thought to provide a quantitative index of this balance and is easily measured.

In this study, therefore, adaptive effects on the autonomic regulation of the cardiovascular system were investigated during DBS for chronic pain to assess firstly whether objective changes in HRV correlate with degree of subjective analgesia and secondly whether such changes differ between dorsal and ventral PAG stimulation. Diffusion tensor imaging (DTI) was then used to assess whether dorsal and ventral PAG have different anatomical connections. DTI enables study of macroscopic axonal organization in the brain through fitting of a diffusion tensor to obtain the fractional anisotropy (FA) of neuronal tissue (Mori and Zhang 2006).

7.3. Methods

7.3.1 Patients and surgery

Sixteen patients with chronic neuropathic pain undergoing DBS of the PAG areas were recruited to the study. Patients were excluded if they 1) had an irregular heart rhythm; 2) had heart disease, including previous myocardial infarction or valvular disease; 3) were taking medication that might affect autonomic response, e.g., β-blockers or antidepressants; or 4) had any other disease, such as Parkinson's disease or alcoholism, that might affect the autonomic response. The study was performed according to the Declaration of Helsinki and approved by the Oxford local ethics committee, and

informed written consent was obtained from all patients. Subject demographics including age, sex and aetiology are summarized in table 7.1. 13 of the 16 subjects were male and three were female. Age ranged from 37 to 74 years old. Eight patients had post-stroke pain, three pain after amputation (including stump and phantom pain), one pain after BPA and the others pain after trauma or malignancy. All patients had contralateral PAG DBS, one had bilateral PAG DBS for bilateral amputation pain and four had additional thalamic DBS which was switched off during the study. The surgical technique and neuroprostheses used are detailed elsewhere.(Bittar et al. 2005a; Pereira et al. 2007b)

7.3.2. Protocol

ECG recordings were obtained during the first week after the initial implantation of the DBS electrode. All sessions were carried out on a single day at least 3 h after any meal at constant room temperature of 22 degrees Celsius. DBS was initially turned off for 30 minutes.

First, the awake subject sat for 10 minutes with the stimulator turned off, while recording ECG signals. Then, randomly selected, the stimulator was turned on or off for six 8-min periods. Between each of these ‘on’ or ‘off’ sessions, there was a 30-min rest period with stimulation off to allow the ECG to return to baseline. During the recordings, both the experimenter and the subject were blind as to whether the stimulator was on or off. The subject was asked to record his pain level on a visual analogue score (VAS; 0-10, 0 = no pain, 10 = worst pain ever experienced) to estimate pain severity during each session. DBS parameters were set so as to provide optimal analgesia for each individual and are detailed in table 7.1. Efficacious stimulation

frequencies ranged from 5 to 50 Hz, amplitudes from 1.0 to 5.0 v, and pulse widths from 60 to 450 μs.

7.3.3. Heart rate variability measurements

Lead II ECGs were recorded from left and right forearms using adhesive disposable Ag/AgCl surface electrodes (H27P; Kendall-LTP, Mansfield, MA), amplified 1000 times (CED 1902; Cambridge Electronic Design, Cambridge, UK). The recordings were digitized at 4000Hz with 16-bit resolution (CED 1401 Mark II, Cambridge Electronic Design, Cambridge, UK) using Spike II software (Version 5.0, Cambridge Electronic Design, Cambridge, UK). Each ECG data set was linearly down-sampled at 1000 Hz using Spike II software and fed into a custom-designed program to extract the HRV signal. The extraction method incorporated a peak detection algorithm that found the time of occurrence for every QRS complex in the ECG signal. The durations between successive peak locations were calculated to produce a time series of R-R intervals (RRI). All of the RRI time series were firstly edited automatically, after which careful manual editing was performed by visual inspection. The RRI time series were then cubically interpolated with a sampling interval of 0.5 s, and saved for further analysis.

7.3.4. Electrode location assessment

Post-operatively, each patient had either a CT or a T1 weighted MRI brain scan to determine the location of the stimulating electrode (figure 1.3). An imaging software program (MRIcro version 1.38, Chris Rorden) was used to determine the relative positions of the electrodes to each other and in relation to the mid-commissural point and midbrain red nucleus (table 7.1) using additional information from the pre-operative MRI if required. This technique is detailed in appendix 2. Patients were grouped into those with stimulating electrode contacts in eight more ventral locations in the PAG and

eight more dorsal locations, shown in figure 7.1, and comparison made between ventral and dorsal PAG DBS.

7.3.5. Signal processing

HRV was detrended using a method based on the 'Smoothness Priors' approach which operates like a time-varying finite-impulse response high-pass filter. This was performed to detrend the HRV before analyzing the power spectrum. Details of the method are described elsewhere (Tarvainen et al. 2002). In this study, the cutoff frequency was 0.02 Hz.

Spectral HRV power was calculated in accordance with previously published standards (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996), yielding the two frequency domain measures: LF power at 0.04–0.15 Hz and HF power at 0.15–0.4 Hz. Power frequency (Hz) was converted to ms^2 by auto-regressive power spectral analysis employing 1024 points and a model order of 16, using custom software. Normalized LF and HF power were computed as the integral of the power bands. The ratio of the logarithm of the LF to HF power was also calculated. Signal processing was performed in MATLAB$^{@}$ (v6.5; Math Works Inc., Natick,Ma.,USA).

7.3.6. Statistical analysis

To assess whether the HRV changed during the three 'stimulation off' compared with the three 'stimulation on' sessions, a one sample paired t-test was used. To assess whether the HRV was related to changes in VAS pain scores, linear regression analysis and Pearson correlation was performed. Before analyses, raw values of all variables were examined for deviations from normality by the Kolmogorov–Smirnov test. The level for significance was set at $p<0.05$. Statistical analyses were performed in SPSS

(v13, SPSS Inc., Chicago, IL, USA). Graphs were plotted using Origin (v7.5776, Northampton, MA, USA). All p values are two-tailed.

7.3.7. Diffusion Tensor Imaging

Diffusion weighted data was acquired for 17 healthy subjects on a Philips Achieva 1.5 Tesla Magnet using echo planar imaging, (70×2 mm thick slices, f.o.v. = 320×264x128; images reconstructed on a 176 matrix; TE 70 ms, TR 17497 ms; voxel size isotropic at 2x2x2 mm; 8 channel Head RF coil; 32 directions of diffusion weightings). 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/). Diffusion data was analysed using the FMRIB Diffusion Toolbox (FDT) detailed elsewhere. (Behrens et al. 2003) Probabilistic tractography was then implemented by FDT. The structural MRI was registered to the DTI using the FMRIB Linear Registration Tool to produce a co-registered image where seed voxels could be placed accurately.

Active DBS electrode contact positions were identified for each patient. For each DTI subject, two seed voxels were chosen, each representing the mean electrode positions of the ventral (13.1 mm posterior, 5.9 mm lateral and 7.1 mm inferior to the mid-commissural point; 7.6 mm distance from the centre of the red nucleus) and dorsal (19.3 mm posterior, 3.2 mm lateral and 5.6 mm inferior to the mid-commissural point; 12.5 mm from the centre of the red nucleus) PAG electrodes of the patients from data shown in table 7.1 and depicted in figure 7.1. Probabilistic tractography was performed in each normal subject for both seed voxels and results averaged and placed onto a Montreal Neurological Institute standard brain template, where tracts were thresholded at a minimum of 10 streamlines and a maximum of 1000 streamlines through each voxel for

analysis. The mean ventral and dorsal positions were loaded into a stereotactic planning computer (Radionics, MS, USA).

7.4. Results

7.4.1. Whole group HRV changes with PAG stimulation

Mean heart rate without stimulation of the PAG was 76.82 (SD 13.34) beats per minute (bpm) compared to 76.75 (SD 14.08) bpm with stimulation. This slight reduction was not statistically significant ($p=0.485$, $t=0.19$, $n=16$). Spectral analysis revealed the dominant frequency components of the heart rate between the on and off conditions. Figure 7.2 provides an example of frequency changes in two patients – one with a more ventral and the other with a more dorsal electrode location in the PAG. In the ventral example, stimulation reduced the LF component but increased the HF component. The normalized powers of both the LF and the HF components were compared between stimulation on and off conditions. Taking all patients, the mean LF component 'off' stimulation was 1.72 ms^2 (SD 0.18) versus 1.75 ms^2 (SD 0.15) 'on' stimulation. This change was not significant ($p = 0.19$, $t=1.37$, $n=16$). Similarly, HF showed no significant difference between the two conditions; 'off' = 1.52 ms^2 (SD 0.29) versus 'on' = 1.54 ms^2 (SD 0.28; $p=0.54$, $t=0.65$, $n=164$). However, LF/HF significantly reduced overall with stimulation, from 1.23 to 1.16 ($p<0.05$, $t=2.23$, $n=16$).

7.4.2. Ventral versus dorsal PAG stimulation

Differences were seen between the eight subjects with the most ventral and the eight with the most dorsal PAG electrodes (figure 7.3). Although their initial heart rates were similar ($p=0.21$, $n=8$) and did not change significantly on stimulation ($p=0.83$ in dorsal and $p=0.70$ in ventral groups, figure 7.3A), LF/HF reduced significantly in the ventral

PAG group during DBS (p=0.02, N=8; figure 7.3D) but not in the dorsal PAG group (p=0.93, n=8). This HRV ratio change associated with ventral PAG stimulation was caused mainly by increased HF power (p=0.01, n=8) which was not seen in the dorsal PAG group (p=0.67, n=8, figure 7.3C). In contrast, LF power showed no significant differences between dorsal and ventral PAG groups (p=0.31, n=8 for DBS 'off', p= 0.97, n=8 for DBS 'on'; figure 7.3B).

7.4.3. HRV and analgesic efficacy

Visual analogue scores (VAS) of pain were recorded before and during stimulation. Stimulation significantly reduced VAS overall with a mean 'off stimulation VAS' of 7.52/10 compared to a mean 'on stimulation VAS' of 4.34/10, an 84% reduction ($p<0.01$, n=16). These changes with stimulation were compared to the changes in LF and HF HRV within the same patients. Both HF power changes ($\gamma^2=0.27$, p=0.04, n=16, figure 5B) and the LF/HF power ratio ($\gamma^2=0.36$, p=0.01, n=16; figure 5C) correlated well with pain reduction and hence analgesic efficacy, whereas LF power changes did not (figure 7.4A).

7.4.4. Diffusion Tensor Imaging

Probabilistic tractography of 17 normal subjects with tracts thresholded from 10 to 1000 streamlines through each voxel demonstrated distinct cortical connections from ventral and dorsal PAG seed points and separate, adjacent connections to dorsolateral medulla (figure 7.5). Dominant ventral PAG connections included amygdala, nucleus accumbens, and ventromedial prefrontal cortex whereas prominent dorsal PAG connections included VP thalamus and primary somatosensory cortex.

7.5. Discussion

The new findings discussed below in this study are firstly that ventral but not dorsal PAG stimulation significantly increased the HF power and decreased the LF/HF ratio of HRV, suggesting that it may increase parasympathetic activity. Secondly, such changes in LF/HF ratio correlated significantly with reported analgesia. Thirdly, diffusion tensor imaging and probabilistic tractography revealed significant differences between cortical tract projections from the different PAG regions and separate, adjacent projections to ipsilateral dorsolateral medulla. The observations together suggest that ventral PAG DBS may increase parasympathetic activity to reduce pain via anatomical connections distinct from dorsal PAG DBS.

High frequency (0.15-0.4Hz) HRV power has been shown experimentally to be a marker of vagal parasympathetic control (Kamath and Fallen 1993; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Low frequency (0.04-0.15Hz) HRV power was initially thought to be related only to sympathetic cardiovascular activity, but recent evidence suggests that it is affected by both vagal and sympathetic tone (Pagani et al. 1997; Pumprla et al. 2002; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Under conditions of minimum postural or physiological stress, the parasympathetic influence on LF is thought to be greater than that of the sympathetic nervous system. Thus the LF component is abolished during pharmacological vagal blockade (Martinmaki et al. 2006). However, despite the dominance of parasympathetic activity on HRV, changes in the LF/HF ratio may still provide some indication of the balance between the sympathetic and parasympathetic effects upon the heart. Changes in LF/HF have been

found in various disease states including cardiac failure, diabetes mellitus and myocardial infarction (Kuch et al. 2004; Mestivier et al. 1997; Saul et al. 1988).

The relationship between the autonomic nervous system and pain is a complex one that has not been fully elucidated. It is known that sympathetic activity is increased in complex regional pain syndromes with alteration of the normal sympathetic vasoconstrictor reflex (Birklein et al. 1998). Similarly pain after amputation is frequently associated with complex regional pain syndromes and referred to as reflex sympathetic dystrophy. Furthermore the roles of higher brain centres in controlling HRV are poorly understood. There is evidence that HRV is linked to emotion (Appelhans and Luecken 2006). This is consistent with the notion that affective states are related to physiological arousal (Hagemann et al. 2003). Thus an affective state, such as pain, will promote arousal and this will be mediated by autonomic activation, which may manifest with changes in HRV. The polyvagal theory (Porges 1997) suggests that the rapid, myelinated, vagal system allows mammals to inhibit autonomic arousal, for example from pain, to produce a state of calmness. Theories of neurovisceral integration (Thayer and Brosschot 2005) characterise this vagal influence in a wider neural network subserving homeostatic responses. These theories predict, and it has been demonstrated (Appelhans and Luecken 2008), that a reduction in low frequency HRV is seen in subjects with less emotional pain valence and higher pain thresholds given similar nociceptive stimuli. Thus, descending vagal control may modulate analgesic efficacy.

Investigations into HRV changes and preliminary findings from ABPM that such BP changes are sustained (Pereira et al. 2008a; Pereira et al. 2010b) may provide objective somatic measures that correlate to subjective rating scales of efficacy as found in this

study. Detailed autonomic testing utilising such equipment as tilt-tables, Portapres (TNO, Amsterdam, The Netherlands) combined with real-time VAS recording would further elucidate both mechanisms and the validity and limitations of such correlative measures.

It seems that ventral PAG DBS may engage analgesia commensurate with increased vagal output and passive coping behaviour whereas dorsal PAG DBS may involve 'fight or flight' analgesia, perhaps with associated sympathomimetic effects (Green et al. 2006c). Either may act via an opioid mediated mechanism, suggested by animal experiments revealing stimulation produced analgesia reversed by naloxone (Akil et al. 1976) and human studies that also showed elevated levels of cerebrospinal fluid enkephalins and endorphins with DBS (Akil et al. 1978; Hosobuchi et al. 1977; Hosobuchi et al. 1979). However, the cerebrospinal fluid measures were artefactual (Dionne et al. 1984; Fessler et al. 1984) and double blinded investigation in humans has revealed no cross-tolerance between DBS and morphine and similar reversibility between naloxone and saline placebo (Young and Chambi 1987), confirming others' findings . Whether PAG DBS acts via endogenous opioid release therefore remains unclear and worthy of further investigation.

These results show that stimulation of ventral PAG caused a significant increase in the HF component of HRV and a significant reduction in the LF/HF ratio. The magnitude of these HRV changes correlated positively with the amount of analgesia reported.

These results fit with both polyvagal and neurovisceral integration theories of pain, suggesting that analgesia with DBS in chronic pain is associated with increased vagal parasympathetic activity. How much of this vagal activity is a direct result of PAG DBS, and whether this leads to or is a result of the analgesia, requires further study. It

is also worth noting that the ventral PAG group electrodes were on average 2.7 mm more lateral than the dorsal group electrodes, and therefore perhaps contributed more to 'autonomic inhibition', showing homology with ventrolateral versus dorsomedial columnar organisation well characterized in rodent PAG (Carrive 1993). It should also be noted that the dorsal ventral axis in figure 7.1 appears more in line with the brainstem overall rather than PAVG and alternative measurements to distance from MCP and RN could be performed to produce slightly different dorsal and ventral electrode groupings.

Also unknown, is whether higher brain regions are involved in the changes in HRV. SPET and MEG have been used to image changes in brain activity during PAG DBS. These showed that and insula are activated, which are medial components of the pain neuromatrix and are proposed to attribute emotional valence to pain (Kringelbach et al. 2007; Pereira et al. 2007a; Ray et al. 2009). Conducting such investigations alongside autonomic measures seem appropriate further studies. DTI and probabilistic tractography of normal control subjects have demonstrated strong connections to different cortical brain regions from ventral and dorsal PAG and separate, adjacent dorsolateral medullary connections. This suggests distinct ascending and descending functional neuroanatomic pathways from ventral and dorsal PAG likely to be involved in HRV and pain modulation.

PAG DBS for chronic pain is undertaken in specialist centres experienced in the technique in appropriately selected patients refractory to pharmacotherapy. Challenges to long-term efficacy and tolerance phenomena pervade DBS, spinal cord stimulation, motor cortex stimulation and other neurostimulatory treatments for this challenging patient group. At present, patient selection is guided by aetiology, clinical expertise and

qualitative aspects of the chronic pain as determined by the McGill pain questionnaire (Pereira et al. 2009a). HRV presents a promising, simply undertaken and swiftly analysed non-invasive tool that may help to identify patients most responsive to ventral PAG DBS, augmenting current patient selection methods and assisting post-operative DBS parameter titration with an objective somatic marker of analgesic efficacy. Larger studies and complementary autonomic experiments to evaluate its utility should be undertaken in this regard.

An obstacle yet to be surmounted in the quest to understand the mechanisms of analgesic stimulation is the lack of adequate animal models of chronic pain (Blackburn-Munro 2004; Oliveras and Besson 1988). In addition to their limited homology in chronic pain paradigms, the smaller brains of rodent models increase targeting inaccuracies, in particular for small brainstem structures like the PAG. This study emphasizes the important opportunities presented by translational research into DBS in human subjects for studying mechanisms underlying efficacious analgesia and advancing our understanding of central control of autonomic function.

Table 7.1. Subject details. Summary of patient demographics, pain duration and aetiology, deep brain stimulation parameters, distances of the stimulated periventricular grey electrode contact from deep brain anatomical landmarks (MCP, midcommissural point) and whether the contact studied is dorsal (D) or ventral (V).

Patient	Sex	Age at surgery (years)	Pain duration before surgery (years)	Pain aetiology	Amplitude (v)	Frequency (Hz)	Pulse width (μs)	Bipolar (B) or Monopolar (M)	Distance posterior to MC point (mm)	Distance from red nucleus (mm)	Dorsal (D) or Ventral (V)
1	M	38	13	Amputation (trauma)	1.0	5	210	B	13.5	7.3	V
2	M	37	4	Stroke (cortical)	3.5	5	390	B	12.0	7.1	V
3	M	74	20	Stroke (subcortical)	2.0	30	330	B	15.0	8.3	V
4	M	50	24	Stroke (subcortical)	1.6	40	450	B	13.0	8.5	V
5	M	61	5	Stroke (brainstem)	2.0	20	450	B	12.0	7.6	V
6	M	61	5	Stroke (brainstem)	4.9	30	450	B	12.0	7.6	V
7	M	60	19	Stroke (brainstem)	2.0	15	210	M	13.0	8.5	V
8	F	34	3	Scalp (schwannoma resection)	5.0	20	160	B	11.5	4.9	V
9	M	53	8	Amputation (trauma)	5.8	35	450	B	17.0	10.2	D
10	F	56	6	Amputation (ischaemia)	4.9	40	450	B	14.5 (left) 17.5 (right)	8.5 (left) 10.9 (right)	D
11	M	67	4	Stroke (cortical)	1.6	50	450	M	30.5	23.7	D
12	M	69	9	Stroke (thalamic)	3.0	20	150	B	17.5	24.6	D
13	M	29	6	Brachial plexus avulsion	5.0	30	450	B	16.0	9.8	D
14	M	34	14	Scalp (trauma)	2.8	20	450	B	19.0	12.0	D
15	M	56	2	Malignancy	1.1	20	60	M	17.0	8.9	D
16	F	37	9	Spinal Cord Injury	2.8	30	210	B	21.0 (left) 18.0 (right)	14.1 (left) 12.5 (right)	D

Figure 7.1. Sagittal positions of all dorsal (blue) and ventral (red) PAG electrode active contacts relative to the mid-commissural point (MCP) and red nucleus (RN). (background reprinted from Mai *et al*. Atlas of the human brain. San Diego: Academic Press, 1998, with permission from Elsevier).

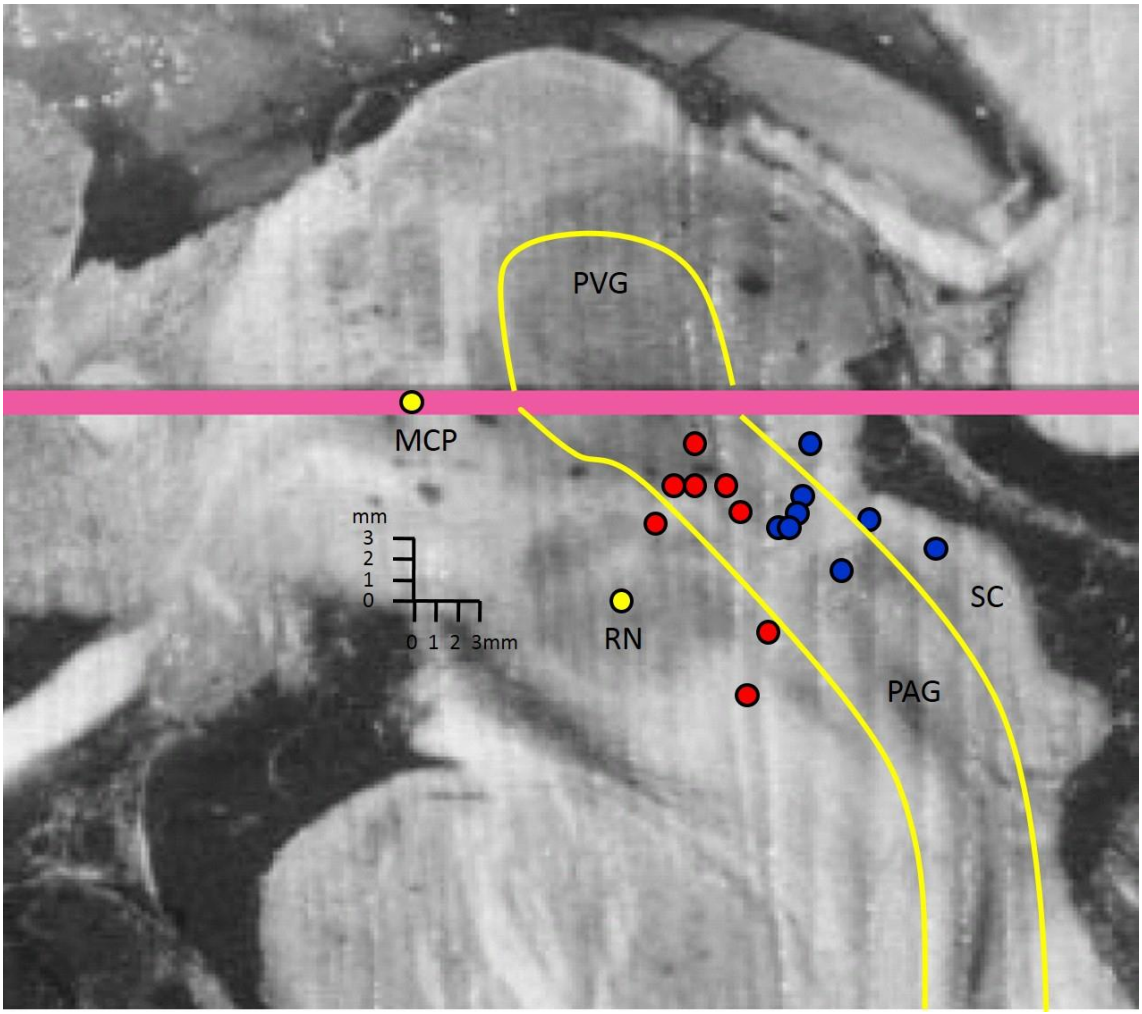


Figure 7.2. RR interval time series (A, B, D, E) and their power spectra (C, F) in two patients. Left: ventral PAG DBS; Right: dorsal PAG DBS. Black line: off DBS; grey line: during DBS. These example frequency changes show increased high frequency (HF) and decreased low frequency (LF) components with ventral stimulation.

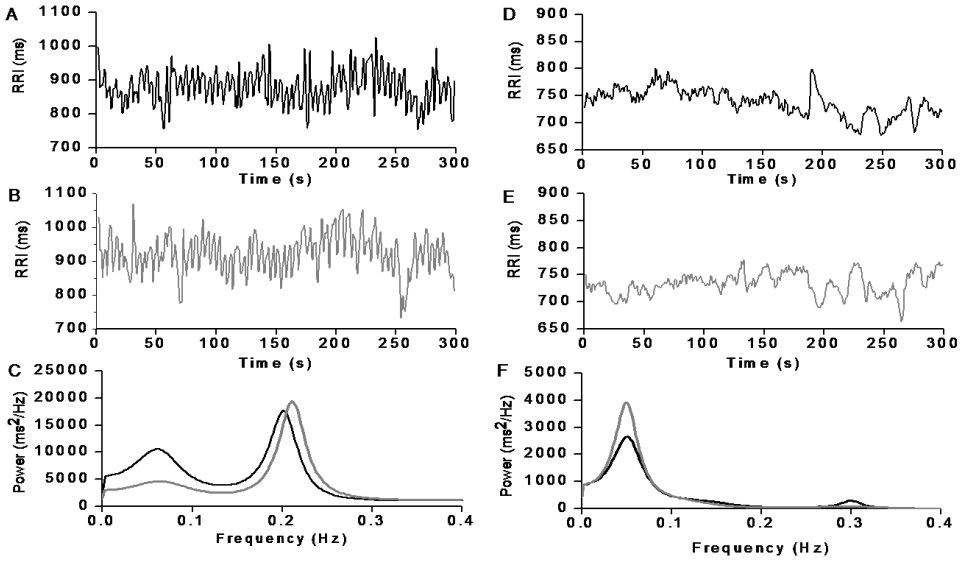


Figure 7.3. Dorsal and ventral group heart rate and heart rate variability (HRV) changes before and during stimulation. (A) Mean heart rate (+/- 1 s.e.), (B) HRV low frequency component (0.04-0.15Hz); (C) HRV high frequency component (0.15-0.4Hz); (D) LF/HF ratio. Heart rates were similar (p=0.21) and changed little on stimulation (dorsal p=0.83; ventral p=0.70). LF/HF ratio reduced significantly with ventral (p=0.02) but not dorsal stimulation (p=0.93), with significantly increased HF power in the ventral group (p=0.01).

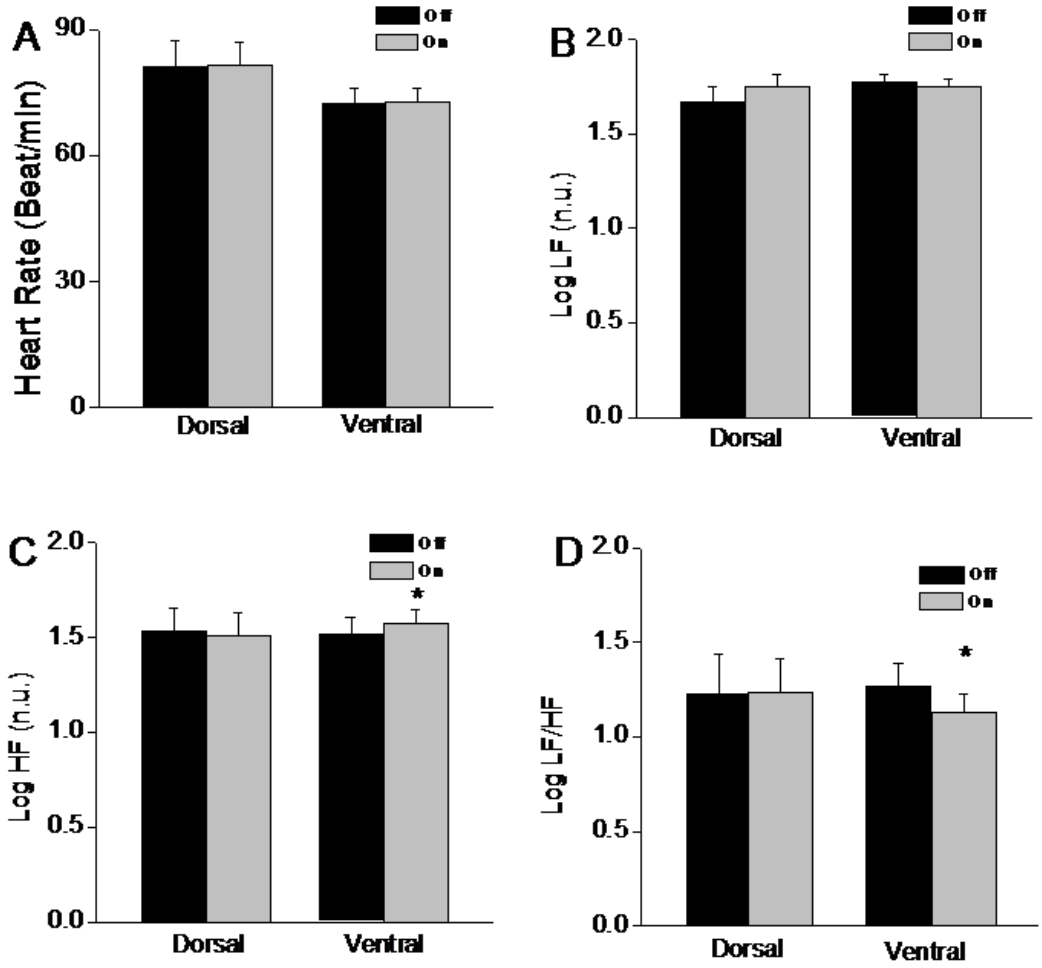


Figure 7.4. Pearson correlation between changes in heart rate variability (HRV) and Visual Analogue Scores of Pain (VAS). (A) low frequency power (γ^2=0.02); (B) high frequency power (γ^2=0.27); (C) LF/HF ratio (γ^2=0.36). Solid line: linear regression; outer dashed line: 95% confidence intervals.

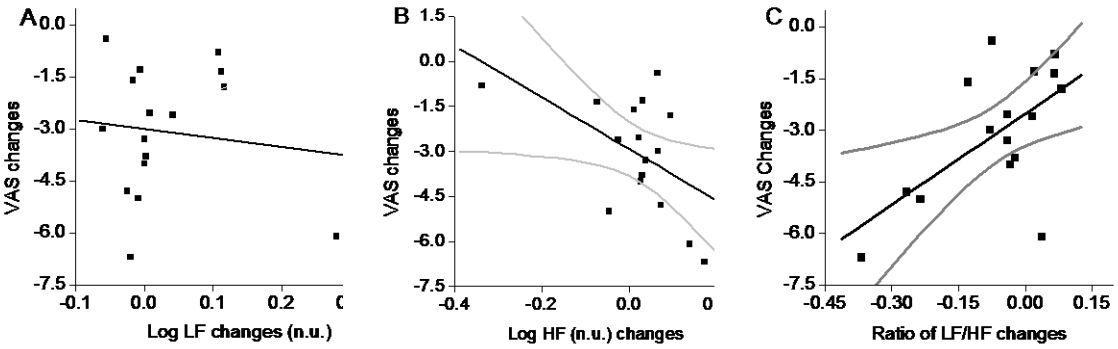
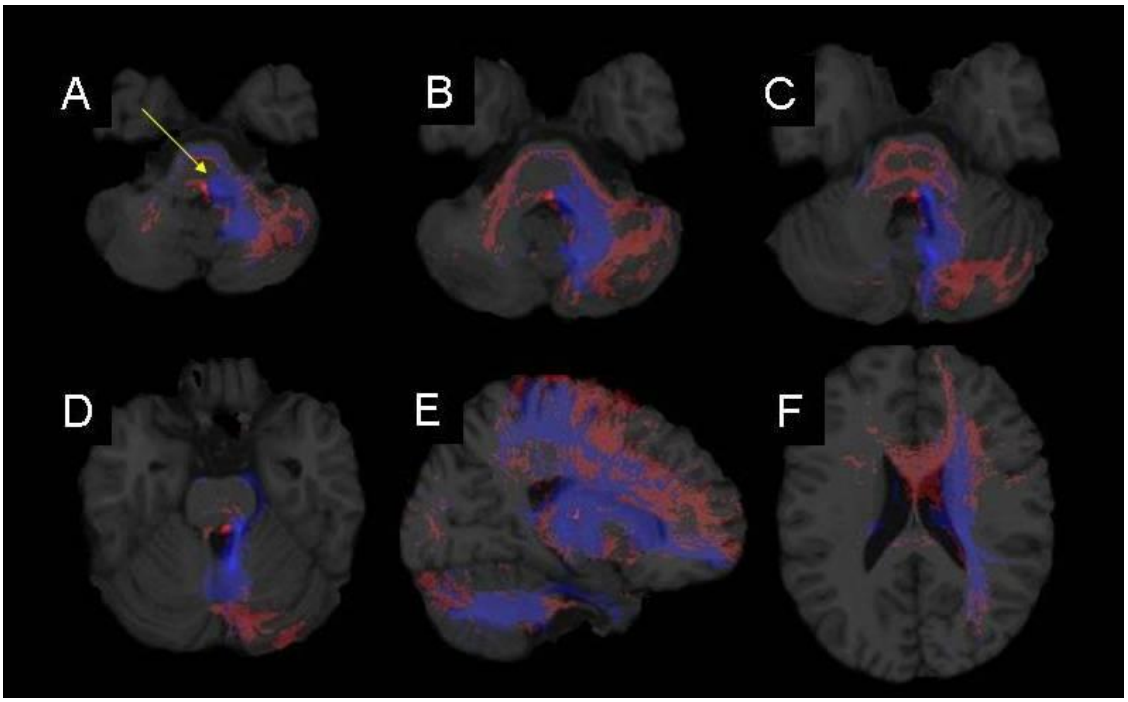


Figure 7.5. Probabilistic Tractography displayed in standard space showing tracts from the dorsal PAG (blue) and ventral PAG (red). (A-D) Axial sections through the medulla, lower pons, upper pons, and midbrain showing separate projections through the brainstem and cerebellum. Notable are separate but adjacent projections of both seeds along the ipsilateral dorsolateral medulla (arrow). (E & F**)** Sagittal and axial sections showing separate tracts, whole brain and cortical connectivity.



Section 4

Analgesic mechanisms of and ablative alternatives to deep brain stimulation for pain

Chapter 8: Elevated gamma band power in humans receiving naloxone suggests dorsal periventricular grey deep brain stimulation produced analgesia is opioid mediated

8.1. Summary

Changes in BP dependent upon dorsal or ventral electrode positioning with PAVG DBS have previously been described, yet controversy exists about whether DBS acts via endogenous opioid release. Here, LFP recording from PAVG DBS electrodes in humans was combined with naloxone and saline infusions to determine whether dorsal and ventral PAVG DBS act through opioidergic or other mechanisms. Four awake human subjects were investigated. DBS were implanted contralateral to the painful body part. Electrode contact positions were mapped using MRI and brain atlas information. Naloxone then saline were randomly administered to the blinded subjects and pain rated using a numeric pain rating scale at 30s intervals for 3 min. Two subjects received dorsal DBS electrodes and two had ventral placements. Significantly elevated gamma frequency band (30-90 Hz) power concomitant with pain exacerbation was found with naloxone versus both saline and rest in dorsal not ventral PAVG LFPs ($p<0.005$). Significantly elevated delta frequency band (0-4 Hz) power ($p=0.001$) was seen in one ventral PAVG subject with both naloxone and saline infusions. Dorsal PAVG DBS may reduce pain by augmenting endogenous opioid release. Elevated gamma oscillations enhance awareness of worsening pain with opioid blockade. Ventral PAVG DBS may act by separate possibly autonomic mechanisms. Increased delta oscillations indicate a survival rhythm involved in the initiation of passive coping responses to homeostatic changes.

8.2. Introduction

The midbrain PAVG regions are involved in pain processing, exerting descending modulation upon the spinal dorsal horn and substantia gelatinosa via raphe neurons, locus ceruleus and adjacent brainstem structures and giving ascending input to sensory thalamus and cortical components of the pain neuromatrix (Willis and Westlund 1997). Over four decades alongside the sensory thalamus, the PAVG has become the main anatomic target for DBS for chronic neuropathic pain, (Hosobuchi et al. 1977; Hosobuchi et al. 1973; Kumar et al. 1997; Levy et al. 1987; Richardson and Akil 1977a) as reviewed in chapter one. The procedure demonstrates good efficacy for an otherwise refractory group as described in chapter two and elsewhere (Boccard et al. 2013; Pereira and Aziz 2011; Pereira et al. 2009a).

DBS uniquely enables deep brain recording of LFPs in awake humans, thus obviating limitations of investigations in animals unable to report subjective sensations. It has recently been shown, by recording human LFPs, that a specific signature of neuronal activity in the PAVG correlates to reported pain intensity (Green et al. 2009). Yet identification of PAVG regions as a target for DBS has its origins in animal research. Surgery in awake rodents has been performed using analgesia induced by PAVG stimulation alone (Mayer et al. 1971; Reynolds 1969). Pain relief by PAVG DBS was first reported in patients by Richardson, Akil and Hosobuchi (Hosobuchi et al. 1977; Richardson and Akil 1977a; b; c). Comprehensive reviews of electrophysiological studies have concluded that the mechanisms of stimulation produced analgesia (SPA) are not clearly delineated (Duncan et al. 1991; Gybels and Sweet 1989; Levy 2003; Tronnier 2003; Weigel and Krauss 2004; Young and Rinaldi 1997).

The PAVG is a structure optimally sited anatomically to integrate interoceptive function, both from adjacent mesencephalic cardiovascular centres and more distal pain processing areas. Its autonomic effects have been well studied in animals (Bandler et al. 1991; Bandler et al. 2000; Behbehani 1995; Carrive 1993; Rossi et al. 1994) and changes noted with DBS (Young and Rinaldi 1997). A positive correlation has been demonstrated between degree of analgesia in patients receiving PAVG DBS and magnitude of BP reduction (Green et al. 2006c) and shown that whereas dorsal PAVG stimulation could elevate BP, ventral stimulation reduced it both acutely (Green et al. 2006b; Green et al. 2005a), and in a sustained fashion (Pereira et al. 2010b). Several lines of animal evidence that the PAVG has multiple integrative modulatory roles in the autonomic nervous system have also been confirmed.(Bandler et al. 2000; Basnayake et al. 2011; Carter et al. 2012; Green and Paterson 2008; Hyam et al. 2012a; Hyam et al. 2012b; Pereira et al. 2010a). Such findings advance investigations for objective markers of chronic pain and also potential selection of patients who may respond best to PAVG DBS.

Current thinking is that ventral PAVG DBS engages analgesia commensurate with passive coping behaviour whereas dorsal PAVG DBS may involve “fight or flight” analgesia with associated sympathetomimetic effects (Green et al. 2006c). It has been shown by heart rate variability analysis that ventral PAVG augments parasympathetic vagal tone concomitant with analgesia (Pereira et al. 2010a).

In contrast to a growing and largely consistent literature elucidating the role of PAVG in autonomic function, evidence to substantiate the conjecture that PAVG DBS analgesia acts via augmenting endogenous opioid release is contentious. The human PAVG is opioid receptor rich (Kuhar et al. 1973), and rodent experiments suggest that

analgesia after morphine is less effective after midbrain lesioning (Samanin et al. 1970). Further evidence can be stratified into studies focused upon tolerance, cross-tolerance, naloxone administration and assessment of endogenous opioid levels. Each is considered in the discussion, with conflicting results leading to disparate conclusions (Kumar et al. 1997; Young and Chambi 1987).

Whether PAVG DBS acts by opioidergic mechanisms to induce SPA is unproven from studies to date. One reason may be a failure historically to distinguish between dorsal and ventral PAVG DBS which may act by different mechanisms. Here the aim was to assess the effects of both naloxone and saline placebo upon both PAVG DBS SPA and LFPs to investigate if naloxone reversed SPA in either dorsal or ventral PAVG and whether increased awareness of pain correlated with enhanced γ oscillations.

8.3. Methods

8.3.1. Patients and deep brain stimulation surgery

Four patients with chronic neurophathic pain participated in the study. After comprehensive neuropsychological assessment, PAVG DBS was offered for treatment of chronic neuropathic pain. The study was performed in the first post-operative week after approval by local ethics committee and according to the Declaration of Helsinki, with informed written consent obtained from all patients.

The neurosurgical procedure and target localisation techniques are described in chapter one and published elsewhere.(Bittar et al. 2005a; Joint et al. 2002; Pereira and Aziz 2011; Pereira et al. 2007b)

Each electrode was externalised for a week of trial stimulation, during which somatosensory stimulation was undertaken. Immediate post-operative CT fused with

pre-operative MRI confirmed the electrode positions. The precise positions of the electrode contacts within the PAVG were determined by triangulation of the fused image electrode position relative to commissural, collicular and red nucleus anatomical landmarks using an imaging software program (MRIcro version 1.38, Chris Rorden). They were then mapped to a human brain atlas (Mai et al. 1998) as shown in figure 8.1A-D. The method is detailed and further illustrated in appendix 2 and elsewhere (Green et al. 2006c; Pereira et al. 2010a).

8.3.2. Deep brain electrode local field potential recording

Bipolar LFPs were simultaneously recorded from the three adjacent pairs of deep brain electrode contacts of each subject's externalised electrode during the week after surgery in a laboratory setting. LFPs were filtered between 0.5 Hz and 500 Hz, amplified with a gain of ×10,000 and digitised at a sampling rate of 2.5 kHz (CED1902 and CED1401 Mark II, Cambridge, UK), and displayed online with an adjustable time scale of seconds to minutes (SPIKE II v5.15, Cambridge Electronic Design, Cambridge, UK).

8.3.3. Naloxone and placebo administration and pain scoring

Each seated subject received venous cannulation into an arm. Baseline PAVG LFP activity was recorded for at least three minutes, after which 5 ml of first 0.9% saline was administered and post-injection LFP activity recorded for three minutes, then 400 μg naloxone was injected and LFP activity recorded for a further three minutes. Subjects and injection administrators were blinded to the injection type. Subjects were asked to rate their pain every 30 seconds throughout the recordings using a 0-10 numerical pain scale (NPS) where 0 was no pain and 10 was the worst pain imaginable, with their responses noted in real-time.

SPA was confirmed by use of a visual analog scale (VAS) pain diary twice daily for the 12 days preceding surgery and 12 days immediately after surgery to give mean VAS scores.

8.3.4. Data analysis

Contiguous LFP data segments of 30 s duration were visually analysed and those containing minimal artefact in each condition for each patient were re-sampled at 4 kHz for analysis (MATLAB v7.2, MathWorks Inc.). The selected data segments were first bandpass filtered (high pass 2 Hz; low pass 250 Hz) to cover the frequency range of therapeutic DBS, then Butterworth filtered at 50 and 100 Hz to remove resonant stimulus artefacts and their harmonics. Power spectral density analysis for each segment of bipolar recording was performed using neural signal processing lab software.

Power spectral density integrals were calculated to show power (μV^2) at six frequency bands δ (0-4 Hz), θ (4-8 Hz), α (8-12 Hz), β (12-30 Hz), γ_{low} (30-60 Hz) and γ_{high} (60-90 Hz). Each condition (naloxone and saline placebo) at each 30 s time segment sampled in each subject therefore generated eighteen frequency band power values (six for each of the three bipolar channels sampled per electrode). These were individually normalised against the corresponding mean power in the resting baseline condition at each frequency band for each channel in each subject.

The normalised data was analysed using a series of statistical tests. Before analyses, raw values of all variables were examined for deviations from normality by the Kolmogorov–Smirnov test. A repeated measures one way analysis of variance (ANOVA) was used to test whether there was significantly different activity between the three conditions (rest, naloxone, saline) at each frequency band (δ, θ, α, β, γ_{low}, γ_{high})

within the same subject. A two-way repeated measures ANOVA investigated the interaction of time, condition and power. Levene's test was used to assess whether variances between subjects were equal within each frequency band. Post-hoc analysis was performed using the Tukey test when variances were equal and the student's t-test based pair-wise comparisons (Tamhane's T2 test) if variances were not equal. The level for significance was set at $p<0.05$. Statistical analyses were performed in SPSS (v13, SPSS Inc., Chicago, IL, USA).

8.4. Results

8.4.1 Patient demographics

Subject demographics are summarised in table 8.1. All patients were male with a mean age of 58 years at surgery and mean pain duration of 10 years prior to surgery. Aetiologies varied between stroke, oral facial pain, failed back surgery and traumatic amputation. Mean stimulation parameters were amplitude 2.6 v, frequency 41 Hz and pulse width 313 µs. All patients proceeded to internalisation of DBS after successful trialling of externalised electrodes. While all patients had in the past tried opioid analgesia, none had histories of opioid dependency nor were any taking opioids at the time of testing.

8.4.2. Stimulator placement

Medtronic 3387® DBS electrodes consist of four cylindrical contacts each measuring 1.5 mm in length with 1.5 mm of insulated electrode in between and at the tip. Electrode contact placement for each subject within the PAVG with adjacent structures labelled are shown in figures 8.1.1 (sagittal) and 8.1.2 (coronal) with axial electrode paths shown in figures 8.1.3 and 8.1.4. Numbered from '3' to '0' by convention, from

proximal to distal the electrode contact positions go from rostral to caudal and slightly lateral to medial. The accuracy of the plotting technique used is limited to the MRI and CT slice thickness of 2.0 mm. All electrodes appeared situated in more rostral periaqueductal grey and adjacent periventricular grey. An anatomical distinction can be drawn between the more ventral electrode placements of patients A and B and more dorsal electrode placements of patients C and D.

8.4.3. Naloxone and placebo administration

Table 8.2 summarises statistically significant changes in frequency band power with naloxone or saline administration versus each other or rest, alongside alterations in pain both after DBS surgery and with naloxone. Subject A had an improvement in VAS from 9.3 to 7.1 with ventral PAVG DBS but no significant pain NPS or LFP changes with naloxone or saline. Subject B had a VAS improvement from 8 to 0 with ventral PAVG DBS, with NPS unchanged by naloxone or saline. δ (0-4 Hz) band power was significantly different between conditions (ANOVA, $p<0.001$) and elevated between both naloxone and rest (Tamhane, $p<0.001$) and saline and rest (Tamhane, $p=0.002$), with no significant difference between naloxone and saline. Subject C gained a reduction in VAS from 10 to 4 with dorsal PAVG DBS and an increase in NPS severity back to 10 immediately after naloxone administration, concomitant with a subjective sensation of impending doom. Significant power differences were found in both low (30-60 Hz) and high (60-90 Hz) γ bands (ANOVA, γ_{low} $p<0.005$, γ_{high} $p=0.007$). γ_{low} power was elevated with naloxone compared to both saline (Tamhane, $p=0.02$) and rest (Tamhane, $p=0.007$) only. γ_{high} power was increased by naloxone compared to both saline (Tamhane, $p=0.035$) and rest (Tamhane, $p=0.015$). There were no significant differences between saline and rest.

Subject D had a reduction in VAS from 7 to 2 with dorsal PAVG DBS. Naloxone caused an increase in NPS to 6 without other side-effects. Significant power differences were found in both γ_{low} and γ_{high} bands (ANOVA, γ_{low} $p<0.005$, γ_{high} $p<0.005$). γ_{low} power was elevated with naloxone compared to both saline (Tamhane, $p=0.03$) and rest (Tamhane, $p<0.01$) and with saline compared to rest (Tamhane, $p=0.03$). γ_{high} power was increased by naloxone compared to both saline (Tamhane, $p=0.03$) and rest (Tamhane, $p<0.005$), with no significant difference between saline and rest.
Figure 8.2 shows mean power normalised against rest for the frequency bands δ (0-4Hz), θ (4-8Hz), α (8-12Hz), β (12-30Hz), γ_{low} (30-60Hz) and γ_{high} (60-90Hz). Subject B exhibited significantly elevated ventral PAVG δ oscillations with both naloxone and saline compared to rest. Both subjects C and D with dorsal PAVG electrodes revealed elevated γ oscillations with naloxone compared to both saline and rest, concomitant with pain exacerbation. Figure 8.3 illustrates changes in γ_{low} oscillations with time. Time was not a significant factor upon power for any frequency band in any subject.

8.5. Discussion

The novel findings from this LFP study were firstly that dorsal PAVG γ frequency band power was significantly increased by naloxone compared to both placebo and rest, concomitant with pain exacerbation. In contrast, ventral PAVG LFPs were unaltered in one subject and had elevated δ power in another with both naloxone and placebo delivery. Naloxone did not change pain levels in the ventral PAVG DBS subjects. The results suggest that dorsal PAVG analgesia may act by opioidergic mechanisms. In this context, elevated γ oscillations may signify awareness of increased pain and preparation for fight or flight as synchronous cortical γ oscillations are associated with attention

(Engel and Singer 2001; Jenkinson et al. 2012). This postulate is consistent with the preceding chapter's findings from human heart rate variability and LFP studies that ventral but not dorsal PAVG analgesia may act concomitant with augmentation of parasympathetic function (Pereira et al. 2010a). The observations together suggest that dorsal PAVG DBS may act via opioidergic mechanisms to relieve pain whereas ventral PAVG DBS may increase parasympathetic activity while reducing pain.

The finding that δ power increased in one patient may indicate a survival rhythm signifying passive coping as a response to chronic pain. δ oscillations relate to both appetitive and aversive behaviour. Functionally, they are also implicated in autonomic neuromodulation and in attention and orienting to motivationally salient external stimuli. They are thus involved in functions critical for survival (Knyazev 2012), and may be elevated by the external stimulus of intravenous bolus administration.

It seems that ventral PAVG DBS may engage analgesia commensurate with increased vagal output and passive coping behaviour whereas dorsal PAVG DBS may involve 'fight or flight' analgesia, perhaps with associated sympathomimetic effects, via an opioid mediated mechanism. Such dorsal and ventral streams may have greater functional anatomic connections to sensory/cognitive and limbic/emotive aspects of pain perception respectively.

As mentioned in the introduction, investigations into whether PAVG DBS acts by opioidergic mechanisms can be stratified into studies focused upon tolerance, cross-tolerance, naloxone administration and assessment of endogenous opioid levels. Tolerance is the attenuation of SPA over time, reported in both animals and humans (Mayer and Hayes 1975; Pereira and Aziz 2011; Young and Chambi 1987). The suggestion that tolerance is a consequence of opioid modulated PAVG DBS is

somewhat refuted by the observation that thalamic DBS also begets tolerance. Partial reversal of tolerance by L-tryptophan supplementation has also been demonstrated, arguing for serotoninergic mechanisms (Hosobuchi 1978b).

Cross-tolerance refers to the inhibition of opioid agonist action by PAVG DBS and vice-versa. Again, demonstrated in rodents (Mayer and Hayes 1975), daily morphine injections reduced SPA but tolerance to SPA did not reduce morphine efficacy, albeit in an acute pain paradigm. Patients tolerant to PAVG DBS have required increased opioid dosages (Hosobuchi and Wemmer 1977). However in one study, morphine administered to all 10 patients tolerant to PAVG DBS was effective and PAVG DBS effective in 15 of 19 patients tolerant to morphine (Young and Chambi 1987), suggesting lack of cross-tolerance.

Naloxone is a potent μ-opioid receptor antagonist that would be expected to attenuate SPA if opioid mediated. Only partial reversal of SPA by naloxone in seven of nine rodents has been described (Akil et al. 1976). An early case report showed dose-dependent reversal of PAVG DBS SPA by naloxone compared to placebo (Adams 1976), as did small case series (Hosobuchi et al. 1977). The only placebo-controlled, double-blind study in the field demonstrated similar degrees of reversal of PAVG DBS SPA by both naloxone and saline placebo in 22 human subjects and no change with either naloxone or saline in 8 subjects, thus concluding that PAVG DBS does not act by opioidergic mechanisms (Young and Chambi 1987).

Endogenous opioid depletion in rodents has reduced PAVG SPA (Millan et al. 1986). Endorphin and enkephalin levels in patients receiving PAVG DBS have been studied with variable results. PAVG DBS was initially reported to increase ventricular concentrations (Akil et al. 1978; Hosobuchi et al. 1979). However, the cerebrospinal

fluid measures were found to be artefact of the metrizamide contrast medium used in the ventriculographic stereotactic targeting of that era (Dionne et al. 1984; Fang et al. 1984; Fessler et al. 1984; Rachlin et al. 1984). Nevertheless morphine administration and naloxone reversal tests became favoured for distinguishing between 'nociceptive' pain predicted to be more responsive to presumably opioidergic PAVG DBS and 'deafferentation' pain predicted to respond best to VP thalamic DBS by many practitioners (Kumar et al. 1997), with notable exceptions (Meyerson 1983; 1988).

The hetereogeneity of past investigations into opioidergic mechanisms of PAVG DBS may also now be explained by a failure of those studies to distinguish between dorsal and ventral electrode placements (Akil et al. 1978; Hosobuchi et al. 1979; Kumar et al. 1997; Meyerson 1983; Young and Chambi 1987). Partial cross-tolerance may have occurred in patients in whom PAVG DBS was stimulating both dorsal and ventral streams.

Many aspects of the mechanisms of PAVG DBS SPA remain unanswered with higher brain regions are undoubtedly involved and few human studies distinguishing between dorsal and ventral streams. Elegant LFP studies have recorded from sensory thalamus while stimulating PAVG and demonstrated reduction of 0.2-0.4 Hz oscillations with SPA (Nandi et al. 2003; Nandi et al. 2002a). DBS has also differentiated between rostral and caudal PAVG delivering SPA predominantly to legs and face respectively, suggesting a rostrocaudally inverted somatotopy (Bittar et al. 2005c). However, these studies did not distinguish between dorsal and ventral PAVG. SPET and MEG have been used to image changes in brain activity during PAVG DBS. These showed that and insula are activated, which are medial components of the pain neuromatrix and are proposed to attribute emotional valence to pain (Kringelbach et al. 2007; Mohseni et al.

2010; Pereira et al. 2007a; Ray et al. 2009). Diffusion weighted probabilistic tractography of normal control subjects demonstrated strong connections to different cortical brain regions from ventral and dorsal PAVG and separate, adjacent dorsolateral medullary connections (Pereira et al. 2010a). This suggests distinct ascending and descending functional neuroanatomic pathways from ventral and dorsal PAVG likely to be involved in pain modulation. It should be noted that the DBS electrodes in this study were positioned more rostrally in PAVG, where nociceptive effects may be less pronounced than those seen more caudally in animal SPA studies (Behbehani 1995). However, a recent meta-analysis of neuroimaging data suggests that both pain and autonomic processing areas of the PAVG may be located more rostrally in humans (Linnman et al. 2012).

PAVG DBS for chronic pain is undertaken in specialist centres experienced in the technique in appropriately selected patients refractory to pharmacotherapy. Challenges to long-term efficacy and tolerance phenomena pervade DBS, spinal cord stimulation, motor cortex stimulation and other neurostimulatory treatments for this challenging patient group. At present, patient selection is guided by aetiology, clinical expertise and qualitative aspects of the chronic pain as determined by the McGill pain questionnaire (Pereira and Aziz 2011; Pereira et al. 2009a). Opioid responsiveness and naloxone challenges may prove useful pharmacological tests that may help to identify patients in whom to target dorsal PAVG DBS, augmenting current patient and DBS target selection methods. Larger studies and complementary autonomic experiments to evaluate their utility should be undertaken in this regard.

An obstacle yet to be surmounted in the quest to understand the mechanisms of analgesic stimulation is the lack of adequate animal models of chronic pain (Blackburn-

Munro 2004; Oliveras and Besson 1988). In addition to their limited homology in chronic pain paradigms, the smaller brains of rodent models increase targeting inaccuracies, in particular for small brainstem structures like the PAVG. This study is the first in humans to reveal electrophysiological evidence of PAVG changes, in particular dorsal γ oscillations, with naloxone induced reversal of SPA. It emphasizes the important opportunities presented by translational research into DBS in human subjects for studying mechanisms underlying efficacious analgesia. The limited number of subjects in the study leaves open the possibility of individual differences accounting for some variability in the results seen and encourages further larger studies of the effects of opioid agonists and antagonists upon PAVG LFPs. The PAVG and adjacent midbrain structures are rich in modulatory monoamines and such investigations would advance our understanding not only of DBS mechanisms, but also potentially enable insights into neurotransmitter function and pharmacotherapy for chronic pain.

Table 8.1. Summary of patient demographics, pain duration and aetiology and deep brain stimulation parameters.

Subject	Sex	Age at surgery (years)	Pain duration before surgery (years)	Pain aetiology	Amplitude (v)	Frequency (Hz)	Pulse width (μs)
A	M	58	3	Oral pain (facial)	2.9	50	120
B	M	58	8	Stroke	2.8	50	250
C	M	55	14	Amputation	3.0	50	300
D	M	59	13	Failed back surgery	1.5	15	210

Table 8.2. Summary of subject electrode positions in periventricular/periaqueductal grey (PAVG); % pain relief with surgery (mean VAS improvement); % pain exacerbation with naloxone administration (NPS - numeric pain score); frequency bands and conditions (R – rest, N – naloxone, S – saline) with statistically significant local field potential power differences (nsd - no significant difference).

Subject	PAVG	%VAS	%NPS	0-4 Hz	30-60 Hz	60-90 Hz
A	Ventral	23	0	nsd	nsd	nsd
B	Ventral	100	0	N vs R S vs R	nsd	nsd
C	Dorsal	60	250%	nsd	N vs R N vs S	N vs R N vs S
D	Dorsal	70	300%	nsd	N vs R N vs S S vs R	N vs R N vs S

Figure 8.1.1. Sagittal positions of all PAVG electrode contacts relative to the mid-commissural point (MCP) and red nucleus (RN). Periaqueductal (PAG) and periventricular grey (PVG) are outlined in black. AC, Anterior Commissure; PC, Posterior Commissure; SC, Superior Colliculi;

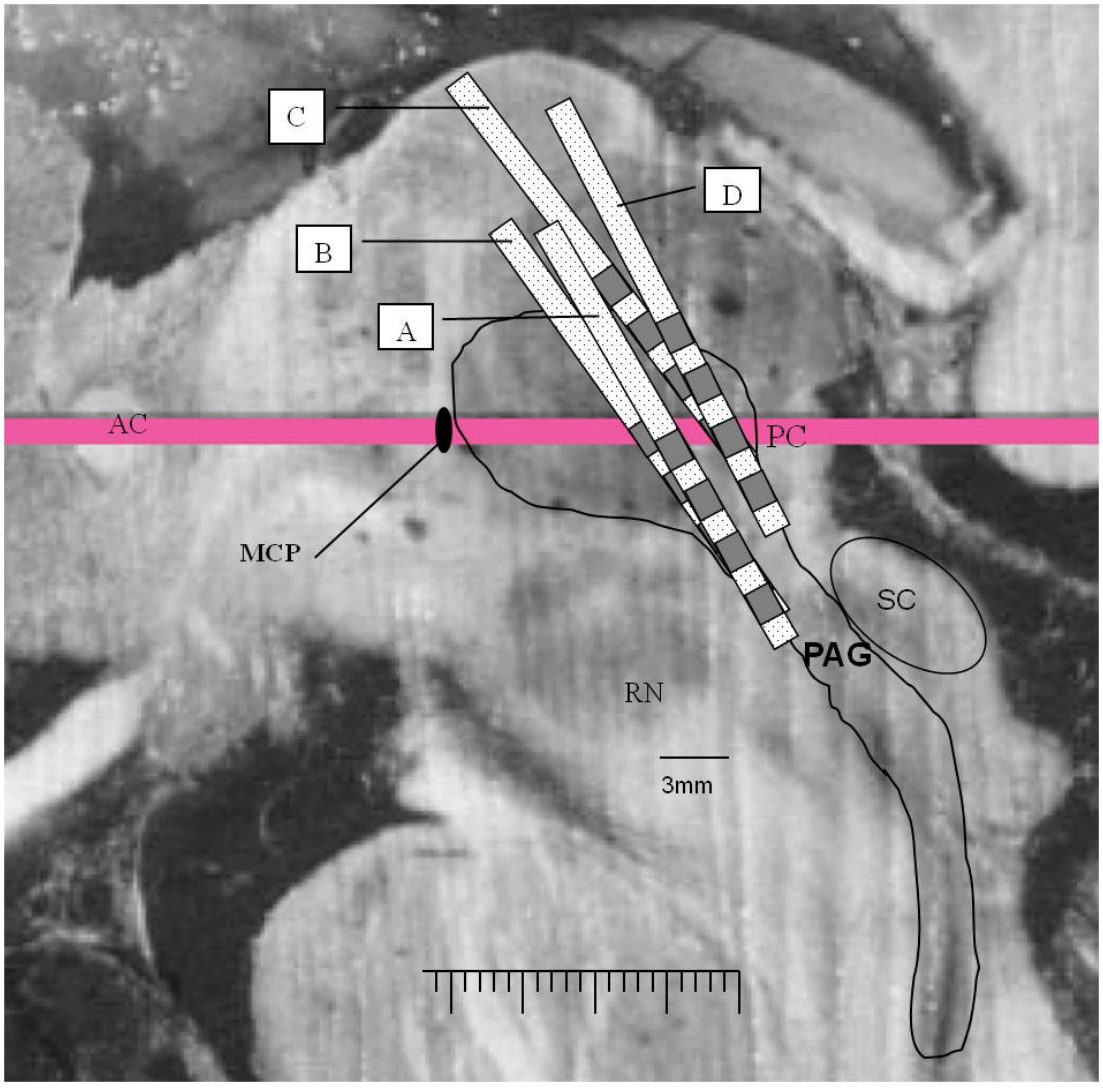


Figure 8.1.2. Coronal electrode positions relative to third ventricle (III), aqueduct of Sylvius (aq) and RN;

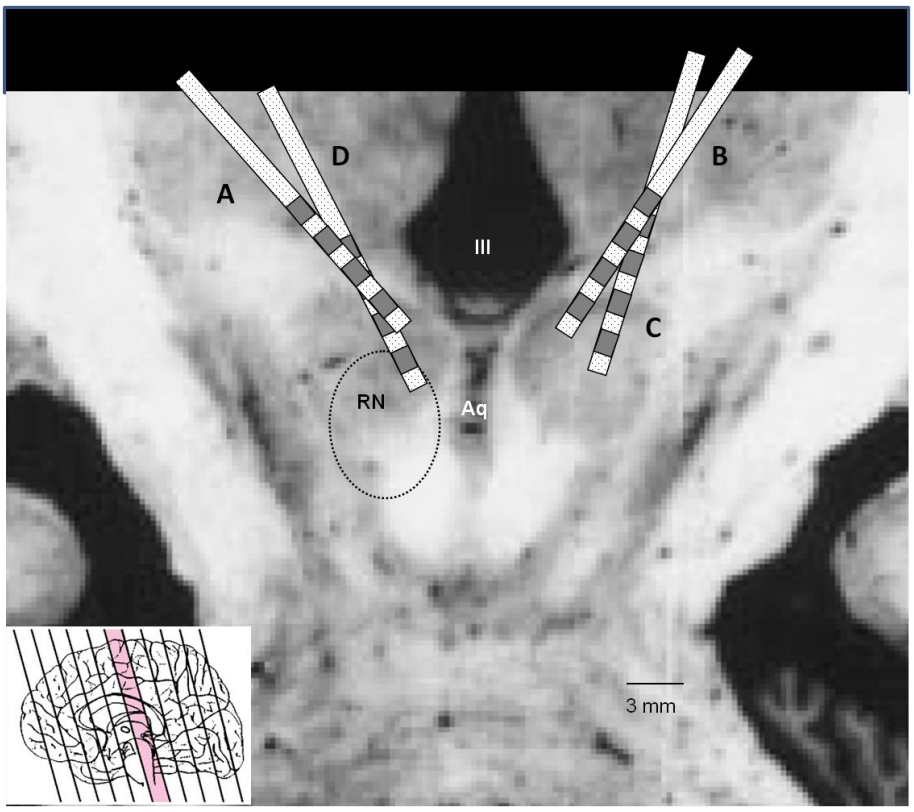


Figure 8.1.3. Higher axial (at level of PC);

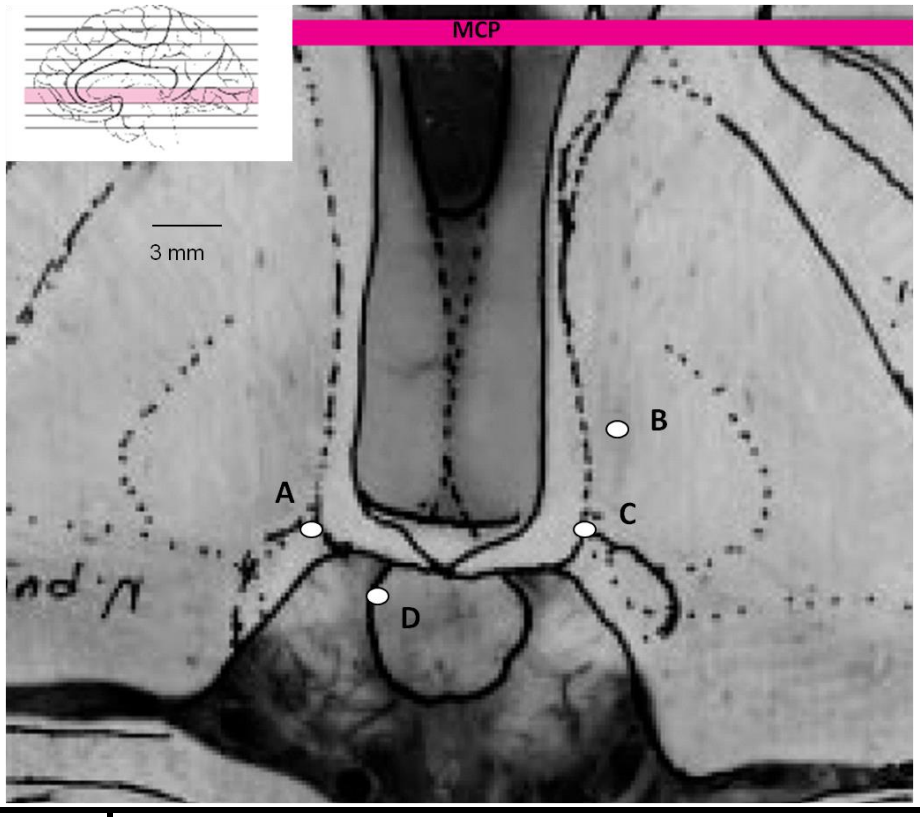


Figure 8.1.4. Lower axial (at level of SC) electrode positions relative to projected MCP, RN and SC. (background reprinted from Mai *et al*. Atlas of the human brain. San Diego: Academic Press, 1998, with permission from Elsevier).

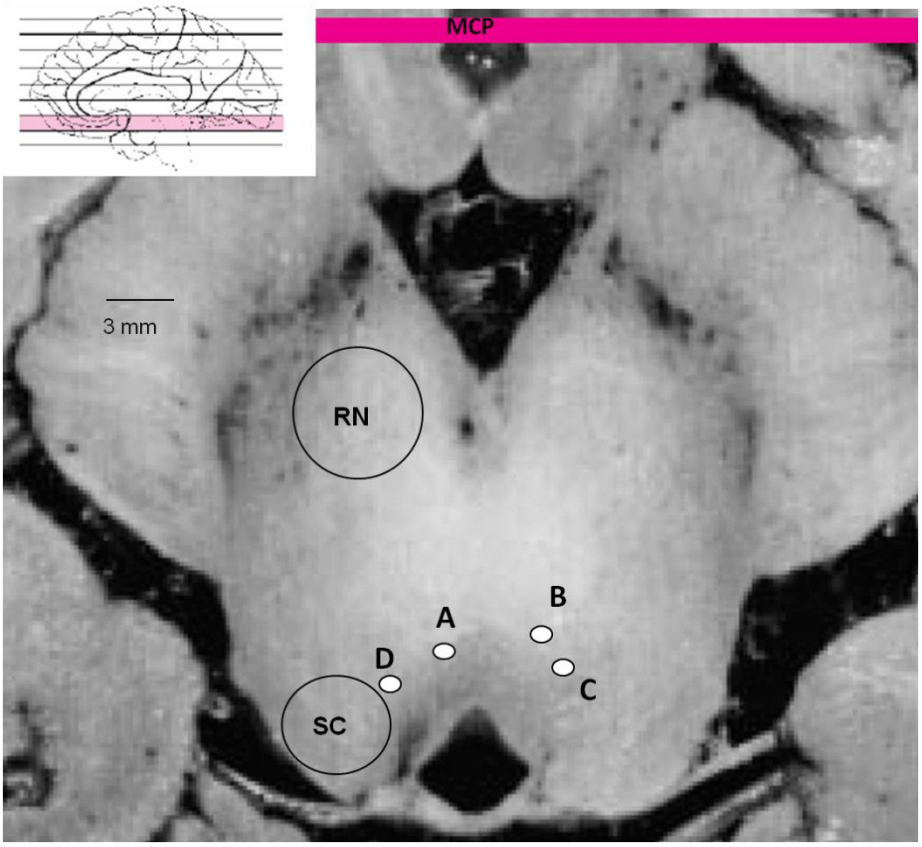


Figure 8.2. Mean power normalised against rest for the frequency bands δ (0-4Hz), θ (4-8Hz), α (8-12Hz), β (12-30Hz), γ_{low} (30-60Hz) and γ_{high} (60-90Hz). (A) subject B (ventral PAVG electrode) exhibited significantly increased δ oscillations with both naloxone and saline compared to rest. (B) subject C (dorsal PAVG electrode) showed significantly increased γ oscillations with naloxone versus both saline and rest in both low and high frequency bands. (C) subject D (dorsal PAVG electrode) had significantly increased γ oscillations with naloxone versus saline and rest, and saline versus rest in its low frequency band and naloxone versus both saline and rest in its high frequency band. Asterisks donate statistical significance, * donates $p<0.05$, ** donates $p<0.005$.

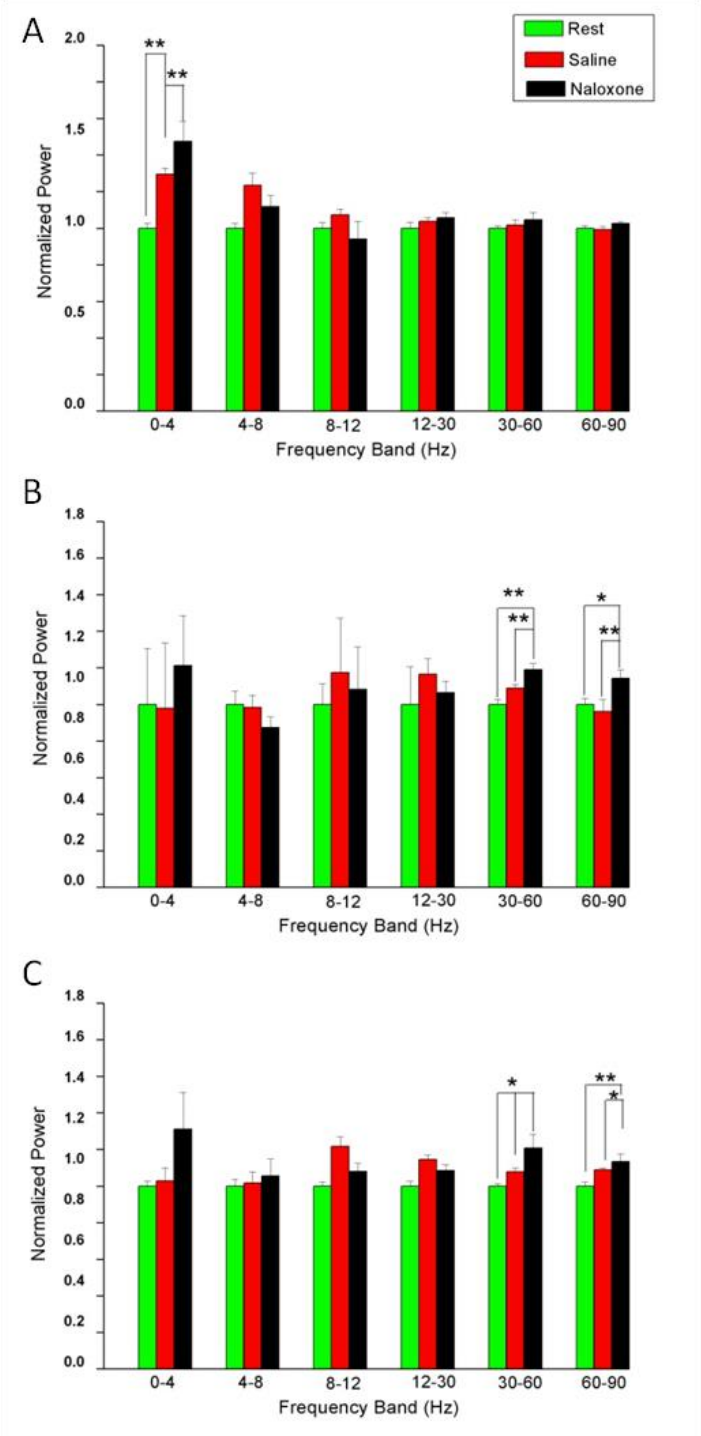
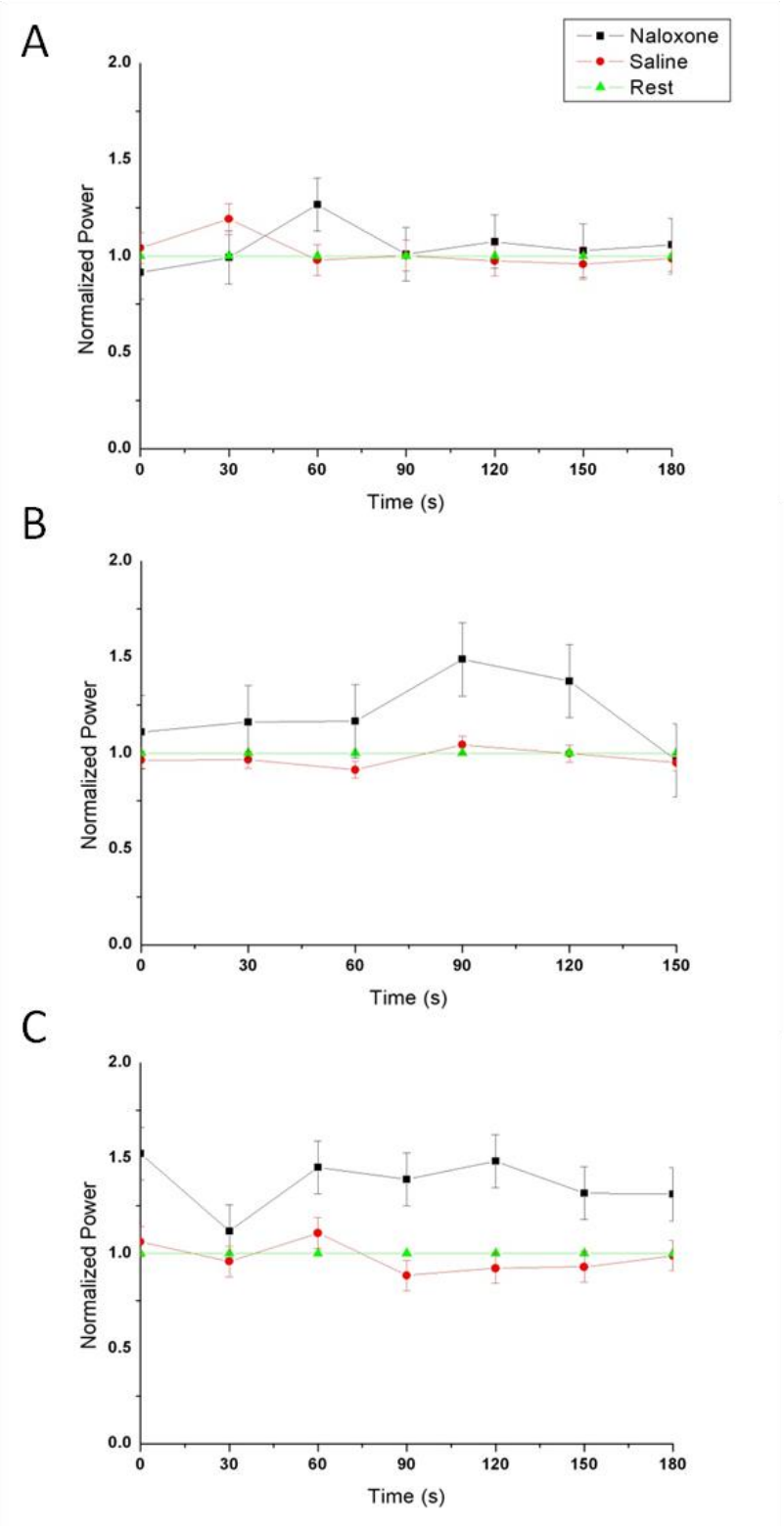


Figure 8.3. Mean γ_{low} (30-60Hz) band power versus time after injection of naloxone and saline normalised against rest. (A) subject B (ventral PAVG electrode) showed no significant difference between injections and rest. (B) subject C and (C) subject D with dorsal PAVG electrodes showed significantly elevated power after naloxone administration compared to both saline and rest states.



Chapter 9: Anterior cingulotomy improves malignant pain and dyspnoea

9.1. Summary

Bilateral anterior cingulotomy is a palliative procedure in continued use for cancer pain and human studies suggest the ACC is active in dyspnoeic states.

A case of debilitating thoracic wall pain due to malignant mesothelioma relieved by bilateral anterior cingulotomy is described and changes in dyspnoea investigated. Improvements in pain, dyspnoea and the extent to which either symptom bothered the patient were seen for two months after surgery before disease progression leading to death five months after surgery. Quality of life improvements were also seen for two months after surgery and pain relief was sustained from surgery to death. Arterial blood gas and lung function tests were unchanged by surgery, suggesting a reduction in pain and dyspnoea awareness by cingulotomy.

Bilateral anterior cingulotomy effectively relieved both pain and dyspnoea. The role of the in pain and autonomic control of respiration is discussed alongside the evidence for this palliative procedure for cancer pain.

9.2. Introduction

The ACC is a large medial brain region well delineated anatomically and much studied functionally over the past decade.(Vogt 2005) Human studies reveal reciprocal connections with prefrontal cortex suggesting roles in emotion and cognition.(Bush et al. 2000) Neuroimaging and electrophysiological studies in humans and animals delineate a limbic ventral ACC tier comprising Brodmann's areas 24a, 24b and 25, most active in emotional processing, with direct connections to amygdala and ventral striatum, and in behavioural arousal and motivational states with dense connections to midline thalamic and brainstem nuclei.(Paus 2001)

The ACC has been shown to be active in human pain by functional neuroimaging.(Pereira et al. 2007a; Peyron et al. 2000b) It is likely to be part of a central pain neuromatrix or medial pain system including thalamic nuclei and PAVG.(Bandler and Shipley 1994; Sewards and Sewards 2002) A similar neuromatrix also including the insula is involved in autonomic control,(Benarroch 2006) with demonstrable interactions between pain and autonomic function.(Green et al. 2006c) Thus, the postulated roles of the ventral ACC are self-monitoring, attribution of affect and initiation of homeostatic and voluntary responses to somatic pain.(Price 2000; Rainville 2002) The ACC therefore appears crucial to determining the emotional valency and thus the subjective intensity of pain.

Dyspnoea is a multidimensional sensation that commonly occurs in patients with terminal cardio-respiratory disease, leading to significant disability. Human functional MRI and positron emission tomography (PET) studies have correlated ACC activity with "air hunger", the subjective sensation of dyspnoea.(Corfield et al. 1995; Evans et al. 2002; Hashimoto et al. 2006; Liotti et al. 2001; Peiffer et al. 2001)

Cingulotomy, surgical ablation of part of the cingulate cortex, is a neurosurgical procedure currently undertaken for the treatment of medically refractory pain and psychiatric disorders with freehand resection (cingulectomy) first performed in 1948 by Cairns in Oxford.(Lewin 1972) The use of a stereotactic frame to target and radiofrequency thermocoagulation to ablate increased accuracy and reduced morbidity and mortality half a century ago.(Ballantine et al. 1967; Foltz and White 1962b) Malignant mesothelioma is cancer of the mesothelial cells lining the pleural surface. It is often aggressive and treatment resistant, with a median length of survival of nine to twelve months. The main risk factor is asbestos exposure, usually affecting elderly men and incidence is increasing. Presentation is often breathlessness and pleuritic chest pain.. Diagnosis is made clinically alongside imaging and cytology of effusions, or from fine needle aspirations of the pleura.(Robinson et al. 2005) There is currently no cure and most intervention is palliative.(Ceresoli et al. 2007) Here described is a patient with malignant mesothelioma who received palliative bilateral anterior cingulotomy for thoracic wall pain refractory to pharmacotherapy. The investigation sought to test the hypothesis that both pain and dyspnoea (air hunger) might be relieved.

9.3 Methods

A 67 year old retired roofer and ex-smoker with a 60 pack year history presented to his family practitioner with a three week history of left sided chest pain and progressive dyspnoea. Clinical examination and radiographs confirmed a left pleural effusion. Initial fluid cytology was negative for malignancy and infection. Two months later thoracoscopic drainage of 1800 ml blood stained fluid and pleural biopsy confirmed malignant mesothelioma. Over the following four months he complained of pleuritic

pain despite high dose gabapentin and amitriptyline consumption. His quality of life became poor as the pain rendered him housebound. His respiratory physicians referred him to neurosurgery for pain management.

The patient was assessed by a multi-disciplinary team consisting of pain specialists, neuropsychologists and neurosurgeons. Neuropsychological evaluation excluded psychiatric disorders and confirmed no cognitive impairment. There were no surgical contraindications such as coagulopathy or ventriculomegaly. Informed consent was obtained and the study was approved by the local ethics committee.

For surgery, a CRW base ring® (Radionics Inc., Burlington, MA) was applied to the patient's head under local anesthesia and 10 mg intravenous dexamethasone given. A stereotactic CT scan was performed with pre-operative T1-weighted MRI volumetrically fused to it as described elsewhere (Bittar et al. 2005a). Anterior cingulotomy targets were bilateral and 20 mm posterior to the tips of the frontal horns of the lateral ventricles, 10 mm lateral to the midline and 1-2 mm above the roofs of the lateral ventricles. Entry points at the coronal suture 15 mm lateral to the midline were planned and during an awake procedure under local anasethesia the frame was secured and a radiofrequency thermocoagulation electrode with a 10 mm uninsulated tip inserted after stab incision and 2.7mm twistdrill craniotomy.

Bilateral lesions were made to Brodmann area 24 by heating the electrode to 80 °C for 90 s. For each side a second lesion was made by withdrawing the tip 10 mm,. Thus two lesions one above the other, created a cylindrical effective lesion 20 mm in height and 8-10 mm in diameter across the ACC (figure 9.1). A third lesion may also be placed more laterally over the roof of the third ventricle but was not performed on this

occasion.(Cosgrove 2006) Operative time from skin incision to closure was 20 minutes, with stereotactic CT and planning time adding a further 30 minutes.

Quantitative assessment of pain, dyspnoea and health-related quality of life were performed before surgery and monthly afterwards alongside spirometry. Arterial blood gases were also sampled one month before and one month after surgery. A visual analog scale (VAS) was used to rate pain intensity having anchors of `no pain' (0) and `the worst pain you can imagine' (10). The patient recorded VAS twice daily in a pain diary over 14 days each month. The 28 VAS scores were reviewed to ensure consistency and the mean was then calculated. Quality of life was assessed by Euroqol five domain (EQ5D) quality of life questionnaire. Health state was also evaluated by EQ5D. Its two sections evaluate firstly the health state in five dimensions (mobility, self-care, usual activities, pain and anxiety) and secondly on a 'health' VAS, with '0' being the worst state they can imagine and 100 the best. EQ-5D scores were calculated as detailed elsewhere.(Kind et al. 1998) Dyspnoea was quantified by the dyspnoea component of the chronic respiratory questionnaire (CRQ) using a VAS with anchors of 0 and 100. This four part questionnaire assessed dyspnoea, pain and the extent to which both symptoms bothered the patient. It was administered daily for 10 days one month before surgery and daily for a week each month thereafter.(Guyatt et al. 1987) Paired sample t-tests were performed between timepoints with a *p*-value of <0.05 taken as statistically significant and <0.01 taken as highly significant.

9.4 Results

At 24 hours post operatively, the patient was mildly confused and incontinent of urine, as is often reported transiently after cingulotomy.(Cosgrove and Rauch 2003) This subsided with a further day of dexamethasone, after which he was discharged home without deficits. At one month follow up, he reported reduced pain replaced by a sensation of numbness over his chest wall, although he was not objectively numb to light touch or pinprick. He also reported being less bothered and troubled by the pain and his wife commented that he was much more relaxed and at ease. Quantitatively, his opioid requirements reduced considerably. His quality of life improved enormously from being housebound before surgery to mobilising independently and going on a Caribbean cruise six weeks after surgery. Figure 9.2 shows dyspnoea subscore VAS of the CRQ revealing highly significant ($p<0.01$) improvements in pain, dyspnoea and the extent to which they bothered the patient one month after surgery, sustained for a further month before disease progression. Table 9.1 shows arterial blood gases before and after surgery showing little change. Similarly table 9.2 reveals spirometry measures with time suggesting no objective changes in lung function. Figure 9.3 shows significant improvements in EQ5D in the two months after surgery ($p<0.05$) again followed by decline before death due to disease progression five months after surgery.

9.5 Discussion

Palliative bilateral anterior cingulotomy relieved pain and dyspnoea and reduced the extent to which either symptom bothered this terminally ill patient alongside enhancing quality of life for two months after surgery. Interestingly, pain VAS was at its lowest four months after surgery (figure 9.2). The finding suggests that the recurrence of dyspnoea and the patient's awareness of symptoms from three months after surgery were related to progression of the malignant mesothelioma that led to his demise, rather than loss of analgesic efficacy of the treatment. Furthermore, objective measures of lung function were unchanged by surgery, emphasising that subjective patient reported measures of dyspnoea alone were improved.

The ACC has roles in pain, emotion, attention and autonomic regulation. Human neuroimaging studies using PET, SPET and functional MRI have established the ACC's activity in pain.(Pereira et al. 2007a; Peyron et al. 2000b) The consensus is that the ACC is part of a central pain neuromatrix or medial pain system including thalamic nuclei and PAVG.(Bandler and Shipley 1994; Sewards and Sewards 2002) A similar neuromatrix also including the insula is involved in autonomic control,(Benarroch 2006) with demonstrable interactions between pain and autonomic function.(Green et al. 2006c) Thus, the postulated roles of the ventral ACC are self-monitoring, attribution of affect and initiation of homeostatic and voluntary responses to somatic pain.(Price 2000; Rainville 2002) The ACC therefore appears crucial to determining the emotional valency and thus the subjective intensity of pain. Furthermore, ventral ACC activity may be opioid modulated.(Derbyshire 2002) Ablative neurosurgery therefore aims, not to sever aberrant nociception, but to distract attention from and reduce the emotional valency of pain.

Reduction of pain awareness alone by cingulotomy may have relieved air hunger. The ACC is however implicated in respiratory control. In rodents, stimulation of the supragenual region led to inhibition of breathing, and subgenual stimulation facilitated respiration.(Vedyasova 2005) A PET study of brain activation in healthy humans, on induction of air hunger through breathing CO_2, reported activation of the ACC, amongst other regions, that correlated with reported breathlessness. The regional patterns of activation were in brain areas involved in primal emotions and basic vegetative systems including hunger, thirst, pain and sleep. The variables assessed were conscious awareness of CO_2 level changes and the subsequent urge to breathe, as opposed to chemical detection of altered pH of the neural interstitium, as a measure of hypercapnia.(Liotti et al. 2001) Thus, the ACC is implicated in altering the stream of consciousness to produce the urge to breath, perhaps by contributing to a subjective sensation of breathlessness, a postulate supported by other human studies.(Evans et al. 2002)

The increased metabolic neuronal activity revealed by functional neuroimaging studies may be excitatory or inhibitory, thus the role of the ACC requires further study. A structural investigation of combat veterans found that a measure of autonomic regulation, respiratory sinus arrhythmia magnitude, was positively correlated with right ACC volume, suggesting that smaller volume related to diminished autonomic regulation.(Woodward et al. 2008) Structural abnormalities in the ACC were also amongst those reported in a cohort of patients with congenital central hypoventilation syndrome.(Kumar et al. 2005)

The involvement of the ACC in pain processing, as well as in autonomic functions suggest that it has many roles.(Benarroch 2006; Critchley et al. 2003) Further research

in the area is needed to determine quantitatively the relationship between the ACC's activity, pain processing and respiratory function. Intra-operative LFP recording could be performed via the radiofrequency electrode, or by temporarily inserted DBS electrodes and post-operative magnetoencephalorgaphy undertaken in breathing paradigms.(Mohseni et al. 2012; Romer Thomsen et al. 2012) Combining functional neuroimaging, invasive neurophysiology and structural imaging may yield new insights into ACC function in dyspnoea and the effects of cingulotomy.(Herigstad et al. 2011) Palliative neurosurgery is an underused resource in cancer pain that is often intractable. DBS is an alternative to lesional surgery for pain but is less suited to patients with terminal cancer because of cost, longer surgical procedures and increased risks of infection and erosion with implantation in a less fit patient. Promising long-term results have been reported in non-cancer pain with sensory thalamic and PAVG DBS.(Boccard et al. 2013) Nevertheless, some patients have poor responses to or become tolerant to the treatment. Bilateral cingulotomy augmented by sensory thalamic DBS in post-stroke pain has also been described.(Kim et al. 2012) ACC DBS has been reported with moderate success,(Spooner et al. 2007) and rationales for DBS for the affective component of pain have been proposed with a view to targeting the anterior limb of the internal capsule.(Machado et al. 2012; Oluigbo et al. 2012) Recent investigations have also suggested DBS may improve breathing, and the ACC may therefore be a potential target for stimulation to improve dyspnoea.(Hyam et al. 2012a; Hyam et al. 2012b) Minor symptoms of headache, nausea, low-grade pyrexia, transient urinary incontinence and nausea are common after cingulotomy and usually last less than 48 hours. Other risks include seizures, ataxia, confusion, bleeding and infection but morbidity and mortality are minimal. A retrospective review of 800 cingulotomies at the

Massachusetts General Hospital found no deaths and no infections. 1% of patients had early post-operative seizures ameliorated by medication.(Abdelaziz and Cosgrove 2002; Cosgrove and Rauch 2003) Subtle attentional deficits have been reported concomitant with anxiolysis.(Cohen et al. 1999; Cohen et al. 2001) Cognitive impairments, amnesia, and functional deficits have generally been minimal and intelligence quotient has even reportedly increased.(Teuber et al. 1977)

Cingulotomy is not frequently performed for cancer pain. A comprehensive review of published cingulotomy series by Cosgrove and coworkers a decade ago suggested that in patients with pain of malignant origin, the procedure was useful in 80 (52%), but not in 73 patients (48%).(Abdelaziz and Cosgrove 2002) Historically, the first bilateral cingulotomies for cancer pain were performed by Foltz and White, reporting good or excellent relief in 9 of 11 patients.(Foltz and White 1962b) Fallaice et al. described 3 of 7 cancer pain patients improved for 3 days to 3 months, and Hurt and Ballantine reported 12 of 32 patients with marked or complete pain relief at up to 3 months' follow-up.(Hurt and Ballantine 1974) Hassenbusch found 6 of 12 patients with cancer pain gaining good or excellent analgesia after mean follow-up of 13 months, concluding it was useful as a palliative procedure for high grade or late stage malignancy and for severe pain of musculoskeletal origin, less beneficial for thalamic and other neuropathic pain syndromes.(Hassenbusch 1995; 1997) Wong et al. reported 3 patients with metastatic cancer pain improved by cingulotomy.(Wong et al. 1997) The largest reported case series of 35 patients with cancer pain by Ballantine, Cosgrove and colleagues reported 20 (57%) with satisfactory pain relief 3 months after surgery, with efficacious analgesia persisting in only 2 of 10 patients surviving longer.(Ballantine et al. 1995)

Neuromodulation may have superseded ablative brain surgery in most circumstances due not just to its superficial seductiveness and so-called reversibility, but also theoretically lower mortality rates and reductions in both serious complications such as haemorrhage and presumed adverse effects upon cognition. However, DBS confers higher costs, greater risks of infection due to the neuroprosthesis and of complications related to the frequently longer operative duration. Ablative stereotactic surgical procedures that continue to be practiced include pallidotomy for Parkinson's disease and dystonia,(Laitinen et al. 1992; Vitek et al. 1998) thalamotomy for tremor,(Speelman et al. 1998) cingulotomy and anterior capsulotomy for OCD and depression,(Feldman et al. 2001) and cingulotomy for cancer pain.(Cosgrove and Rauch 2003)

Ablation can always be considered if DBS fails, and may be appropriate as first-line surgical therapy rather than DBS where the efficacy of the former is better established – for example in psychiatric disorders.(Cosgrove and Rauch 2003) It is also of utility in those refractory to or unsuitable for DBS, for example cingulotomy for obsessive compulsive head bangers who may damage their indwelling neuroprostheses or palliatively for those with cancer pain in whom the tolerance effect seen several months later may occur beyond their limited lifespan. To quote a recent evidence based review of 'the case for cordotomy', "destructive procedures for cancer pain may play more than a historic role" with cingulotomy potentially conferring an advantage over cordotomy by improving dyspnoea.(Raslan et al. 2011)

Table 9.1. Arterial blood gases before and after surgery. $PaCO_2$, partial aterial pressure of carbon dioxide; PaO_2, partial arterial pressure of oxygen.

Time	pH	$PaCO_2$	PaO_2
1 month before surgery	7.44	5.45	11.40
1 month after surgery	7.41	5.64	11.90

Table 9.2. Spirometry results before surgery and after surgery then at monthly follow-up. FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

Time after surgery (months)	FEV1	FVC	FEV1/FVC
-1 (1 month before surgery)	1.9	2.4	0.79
0.5	1.8	2.4	0.74
1	1.8	2.4	0.74
2	1.8	2.3	0.78
3	1.8	2.2	0.80
4	1.7	2.1	0.80

Figure 9.1. T1-weighted MRI brain imaging showing bilateral anterior cingulotomies, A. axial, B. coronal, C. parasagittal, D. sagittal.

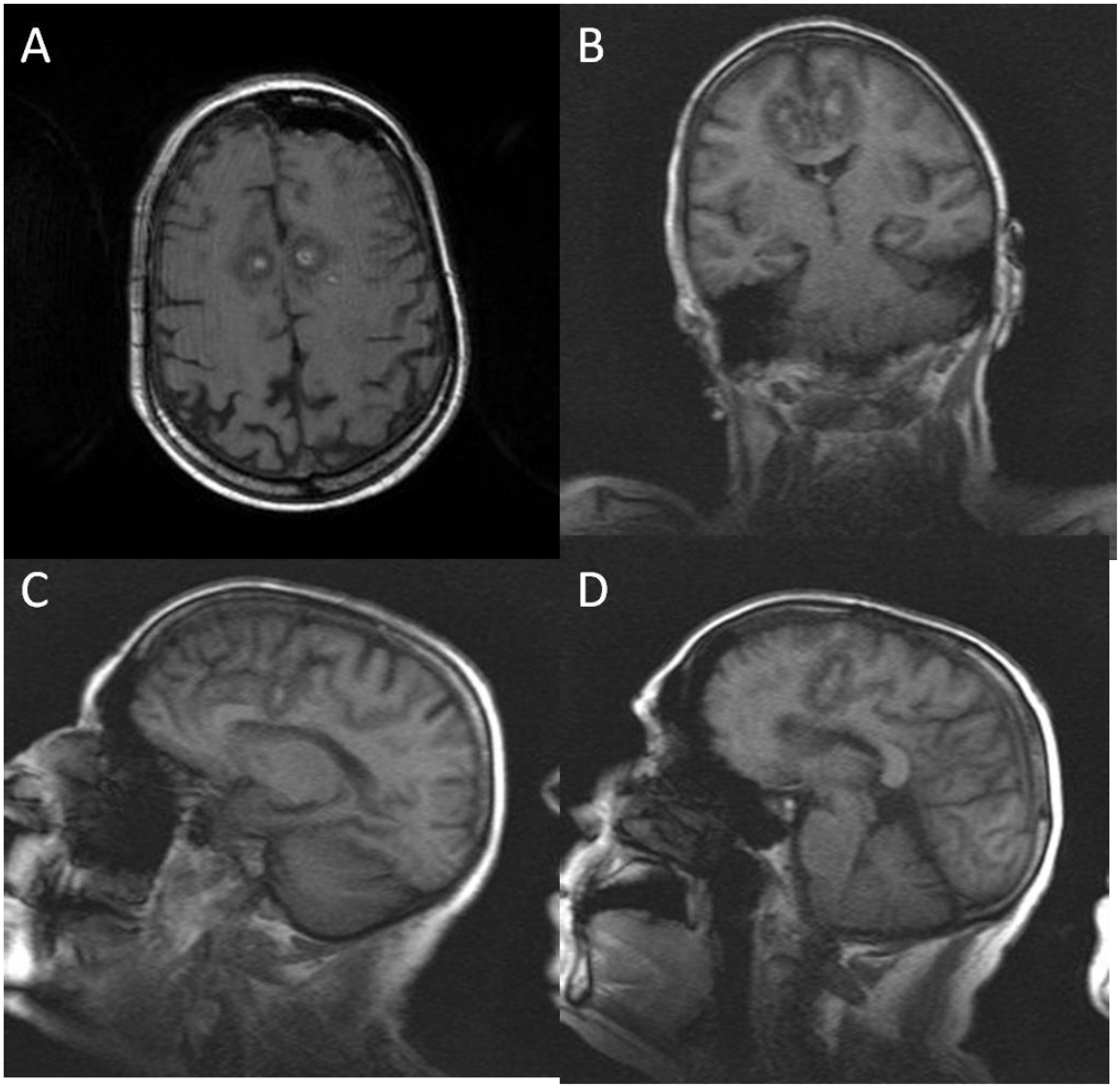


Figure 9.2. Dyspnoea CRQ visual analog scale (VAS) questionnaire scores for the four variables: perceived breathlessness; bothered by their breathlessness; chest pain; bothered by pain. The VAS scale is 0-100, 100 being most breathlessness or pain, or being most bothered by the breathlessness or pain.

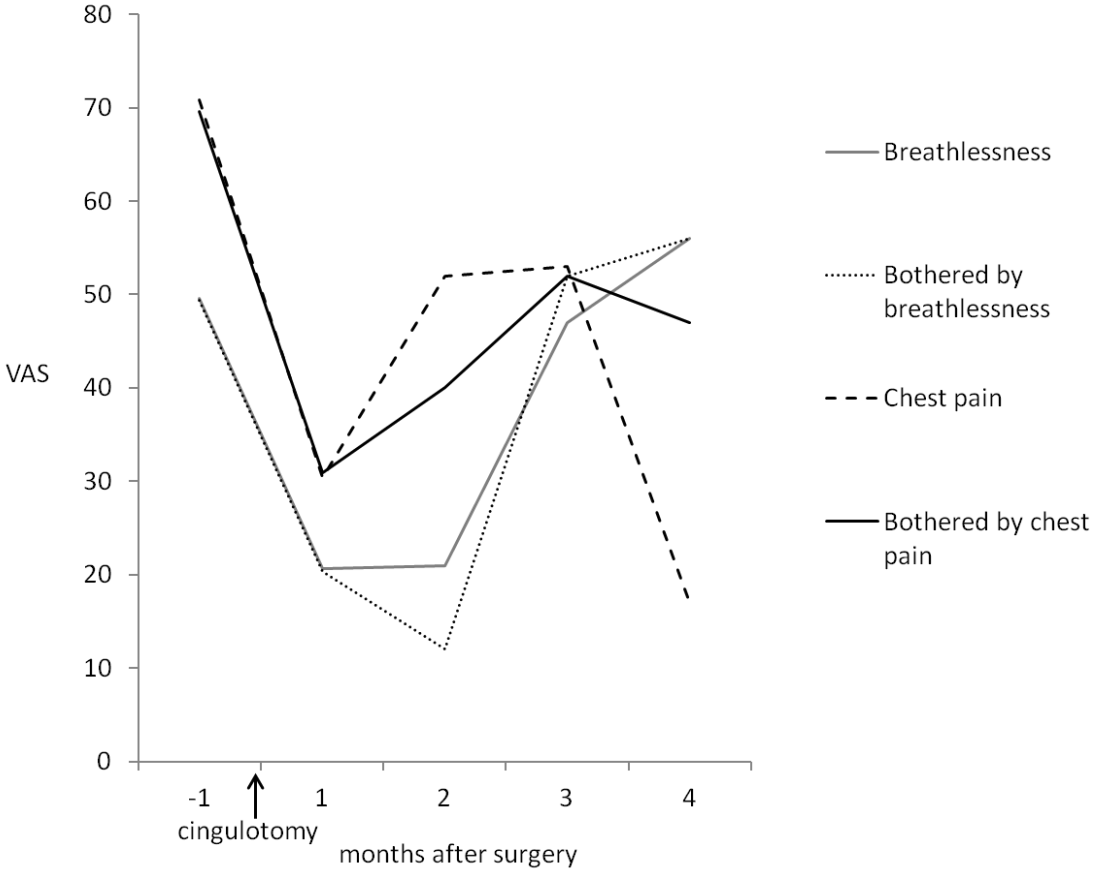
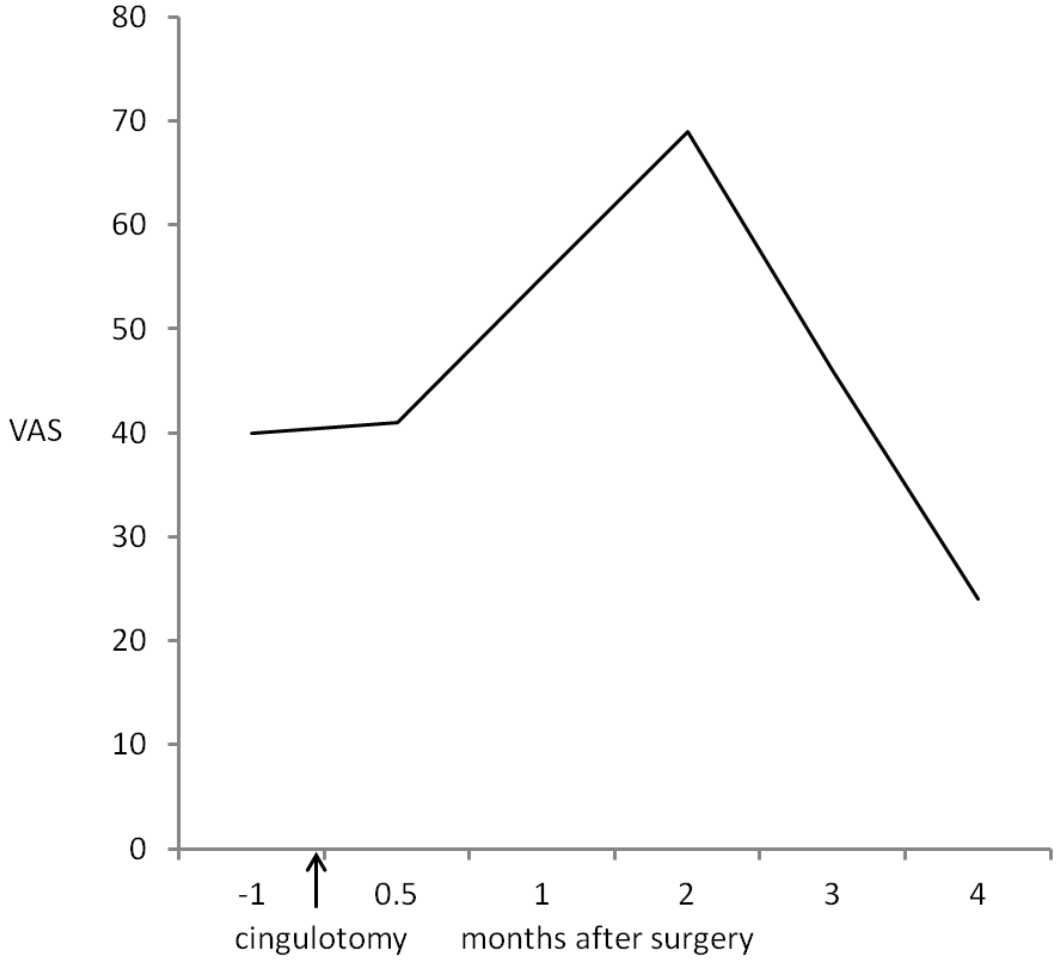


Figure 9.3. EQ5D health state scores over time. The VAS scale is 0-100, 0 being worst health state and 100 being best.



Chapter 10: Discussion

Although not a new therapy, DBS has evolved over the last decade, concomitant with advances in both stimulator technology and neuroimaging techniques, and by corollary improvements in efficacy and reductions in complications. Yet few centres have published detailed studies of patients treated for chronic pain during the last decade. Oxford results in chapter two suggest that DBS gives analgesia most consistently to patients with pain after amputation, either phantom or stump, BPA, cranial and facial pain including anaesthesia dolorosa and stroke. The larger Oxford patient experience of pain after stroke reveals greatest efficacy for stroke patients complaining of burning hyperalgesia (Owen et al. 2006a; Pereira et al. 2008d). The stroke subgroup therefore illustrates how important patient selection is to outcome.

The benefits of developing experience and expertise towards improving patient selection and clinical outcomes in functional neurosurgery are suggested by a second case series from Porto in chapter three. Here, excellent results are seen with VPL DBS alone for amputation pain and good outcomes also after BPA using VAS, MPQ and EQ5D, but also alternative pain outcome measures of BPI and UW-NPS. Such results suggest that DBS for pain should only be undertaken by centres and surgeons willing to acquire expertise and audit outcomes, as commented in national and European guidelines that I have been privileged to have opportunity to contribute to (Cruccu et al. 2007; NICE 2011).

The large variability of results in case series of DBS for pain to date reflects not just limitations in pain assessment tools and study design and execution, but moreover individual differences between patients as to what constitutes success. A good outcome may be the removal of a particular component of pain without quantitative reduction in

pain scores. Such pain relief may serve to unmask other types or components of pain elsewhere like muscular allodynia, as has been described after stroke (Kamano 2003). Thus, clinicians must characterise patients' pain qualitatively as well as quantitatively and investigators should endeavour to include quality of life measures in outcome assessment to overcome the limitations of using pain questionnaires alone.

As clinical indications and clinician and patient awareness of DBS continue to increase, costs of both the technology and its implantation will decrease, making the therapy more widely available. While it is unlikely that DBS will be as widespread and inexpensive as cardiac pacemakers, it may become comparable in cost to SCS. A priority is to demonstrate cost effectiveness by ensuring rigorous and evidence-based studies of DBS for pain and redressing the challenges of past failed trials. A combination of tailored evidence-based methods on intensively studied small cohorts should occur alongside the co-ordination of multi-centre clinical trials with standardised selection, implantation and outcome data collation protocols. Only then can DBS for pain become re-established as a widely used therapy.

Several microelectrode studies have delineated somatotopy of VP and assisted DBS targeting (Lenz et al. 1988). The objective characterization by LFPs and SSEPs of a rostrocaudally inverted somatosensory homunculus in the PAVG in chapter four appears an important anatomical finding that may guide the surgeon during patient self-reporting in awake surgery. SPET imaging findings in chapter five of sensory thalamic, PAG, anterior cingulate and insula activation with DBS also confirm their involvement in the pain neuromatrix and modulation by DBS. Future insights will arise from complementary information gathered using new technologies. DTI has shown connectivity between PAVG and thalamic structures and may elucidate differential

somatotopic connections (Owen et al. 2008; Sillery et al. 2005), and also have clinical utility to aid targeting in functional neurosurgery (Johansen-Berg and Behrens 2006). In chapter seven, it is used to suggest differential connections between dorsal and ventral PAG. MEG is an additional noninvasive functional electrophysiological tool that is beginning to improve our knowledge of analgesic mechanisms of DBS towards identifying predictors of efficacy and enhancing treatments (Kringelbach et al. 2007; Mohseni et al. 2012; Ray et al. 2009). Nevertheless, complimentary functional neuroimaging modalities such as SPET have roles in characterizing whole brain changes with DBS with excellent deep brain structure penetration compared to present MEG studies, albeit with more limited temporal resolution and characterization of metabolic correlates of neuronal function.

To improve selection, and thus efficacy, objective adjuncts to current pain assessments are desirable. Subjective preference for PAVG stimulation over VP for post-stroke pain together with correlations revealed between cardiovascular effects, analgesic efficacy of DBS and burning hyperaesthesia point towards autonomic measures as a potential objective markers (Green et al. 2006c). Chapters six and seven build upon Green and coworker's experimental distinction between dorsal PAG DBS elevating BP and ventral PAG DBS reducing it (Green et al. 2006b; Green et al. 2005a). ABPM is used in chapter six to show a sustained reduction of BP over 24 h by ventral PAG DBS. HRV is then utilized in chapter seven as a measure of vagal tone to suggest that ventral PAG DBS may augment parasympathetic tone concomitant with analgesia. The important roles of the PAG in both pain and autonomic function have been recently comprehensively reviewed by others to include findings published from this thesis (Benarroch 2012; Linnman et al. 2012).

Chapter eight revisits the contentious topic of whether PAG DBS is opioid mediated by LFP analysis during naloxone and placebo infusions and reaches the novel conclusion that dorsal but not ventral PAG DBS may be opioid mediated. The findings of chapters seven and eight therefore converge to a novel hypothesis that there exist separate dorsal and ventral analgesic streams in PAG, the former perhaps feeding more to sensory thalamic and dorsolateral pain pathways and the latter to a more ventromedial limbic pain processing route encompassing the ACC and involving autonomic modulation.

The ACC is mentioned in chapter one as an emerging target of DBS for pain without somatotopic localization. In chapter nine its potential is highlighted as a target for radiofrequency thermocoagulation lesioning for the treatment of terminal cancer pain. A case of mesothelioma gives opportunity to study the phenomenon of air hunger and its potential amelioration by cingulotomy. Concomitant pain and dyspnoea relief by the treatment is an intriguing result encouraging further investigation of the ACC in autonomic and respiratory control, which becomes increasingly possible as clinical trials of DBS for the affective aspects of pain commence (Machado et al. 2012).

Despite poorly conducted clinical case series labelled as trials two decades ago, DBS for pain retains promise in select patients, with potential for its eventual establishment. Breakthroughs may arise either from intensive study of autonomic changes with PAG DBS, leading to measurable autonomic predictors of efficacy, from pharmacological challenges of drugs such as naloxone or from non-invasive modalities such as SPET and MEG which may identify those patients with altered activity in target brain regions in particular paradigms of assessment. Such findings may lead to certain DBS targets being chosen on an individual patient basis to optimise success.

There remain groups of patients presently refractory to thalamic or PAVG DBS or whose pain, for example whole body pain lacking distinct somatotopy or pain after spinal cord injury, make them poor candidates for the procedure. Oxford has successfully implanted DBS into the ACC in such patients recently with the rationale of reducing the emotional valency of pain perception while not seeking to alter its nociceptive component. Such work draws upon a wealth of clinical literature of cingulotomy, as described in chapter nine. ACC DBS may not only become established as a viable novel target for the affective component of chronic pain but its use and related translational investigations could yield many neuropsychological insights into emotion, attention, autonomic and executive function.

At present, experience guides neurosurgeons broadly towards whom to offer DBS, which targets to select, and tentatively towards prognostication. For both thalamic and PAVG DBS targets for pain, the relative contributions of local interactions and wider functional neuroanatomical circuitry are yet to be fully understood. In addition, research attention should turn to focus upon improving patient selection. When successful, results from DBS for intractable pain are frequently spectacular and life transforming. The intensive experimental study of small groups of motivated patients generates hypotheses that create opportunities for improving therapies, combined with promising results from detailed open label studies that augur for a renaissance in randomised, controlled, clinical trials.

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Appendix 1. Systematic search methods

For the literature review in chapter 1, several electronic databases (MEDLINE - Pubmed using Entrez, EMBASE CINAHL, psychINFO, Scopus and Cochrane) were searched for systematic reviews. All databases were searched from inception date to December 2012. This search focused on indications for pain which encompassed amputation pain; post-stroke pain; neuropathic cephalalgia; failed back surgery syndrome; complex regional pain syndrome; peripheral neuropathies; post herpetic pain; intercostal neuralgia; brachial plexus damage and avulsion; peripheral nerve damage; spinal cord injury; central pain of brain origin; malignancy pain, multiple sclerosis pain and trigeminopathic facial pain. Search terms took the following form:

systematic reviews OR *meta-analysis* [or synonyms]

AND *indications* (*pain)* [or synonyms]

AND *deep brain stimulation* [or synonyms]

Search details are listed below. In addition, reviews and primary literature related to DBS for pain from textbooks and journals known to the authors were also examined. Reviews were used to further identify primary literature and references assessed for additional material. Given the search cut off dates of previous systematic reviews, an update search for published and electronic early release literature from January 2003 to December 2012 was undertaken. This was done by using appendix 5b from the Cochrane Handbook for guidance .

For tables 1.1.1 and 1.1.2, all study designs published in full (not abstract) form were included except case reports and small case series of less than six patients. Where there was more than one systematic review or more than one primary publication on the same series of patients, I took the most comprehensive and/or latest analysis.

DEEP BRAIN STIMULATION AND INDICATIONS AND SYSTEMATIC REVIEWS MEDLINE

1. SEARCH: DEEP-BRAIN-STIMULATION#.DE.
2. SEARCH: DBS
3. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$
4. SEARCH: ELECTRIC-STIMULATION#.DE.
5. SEARCH: ELECTRIC$ ADJ STIMULATION$
6. SEARCH: NEUROMODULATION$
7. SEARCH: 1 OR 2 OR 3
8. SEARCH: PAIN#.W..DE.
9. SEARCH: PAIN$4
10. SEARCH: NEURALGIA#.W..DE.

11. SEARCH: NEURALG$3
12. SEARCH: HEADACHE#.W..DE.
13. SEARCH: HEADACHE$
14. SEARCH: TRIGEMINAL-AUTONOMIC-CEPHALALGIAS#.DE.
15. SEARCH: CEPHALALG$
16. SEARCH: 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. SEARCH: SYSTEMATIC ADJ REVIEW$2
18. SEARCH: META ADJ ANALYSIS
19. SEARCH: META-ANALYSIS#.DE. OR META-ANALYSIS-PUBLICATION-TYPE#.DE.
20. SEARCH: META-ANALYSIS
21. SEARCH: 17 OR 18 OR 19 OR 20
22. SEARCH: BRAIN#.W..DE.
23. SEARCH: BRAIN$3
24. SEARCH: 22 OR 23
25. SEARCH: 4 OR 5 OR 6
26. SEARCH: 25 AND 24
27. SEARCH: 26 OR 7
28. SEARCH: 16 AND 21 AND 27

DEEP BRAIN STIMULATION AND INDICATIONS AND RCTS MEDLINE 2003 ONWARDS

1. SEARCH: DEEP-BRAIN-STIMULATION#.DE.
2. SEARCH: DBS
3. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$
4. SEARCH: ELECTRIC-STIMULATION#.DE.
5. SEARCH: ELECTRIC$ ADJ STIMULATION$
6. SEARCH: NEUROMODULATION$
7. SEARCH: 1 OR 2 OR 3
8. SEARCH: PAIN#.W..DE.
9. SEARCH: PAIN$4
10. SEARCH: NEURALGIA#.W..DE.
11. SEARCH: NEURALG$3
12. SEARCH: HEADACHE#.W..DE.
13. SEARCH: HEADACHE$
14. SEARCH: TRIGEMINAL-AUTONOMIC-CEPHALALGIAS#.DE.
15. SEARCH: CEPHALALG$
16. SEARCH: 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17. SEARCH: PT=RANDOMIZED-CONTROLLED-TRIAL
18. SEARCH: PT=CONTROLLED-CLINICAL-TRIAL
19. SEARCH: RANDOMIZED-CONTROLLED-TRIALS#.DE.
20. SEARCH: RANDOM-ALLOCATION#.DE.
21. SEARCH: DOUBLE-BLIND-METHOD#.DE.
22. SEARCH: SINGLE-BLIND-METHOD#.DE.
23. SEARCH: 17 OR 18 OR 19 OR 20 OR 21 OR 22
24. SEARCH: HUMANS#.W..DE.
25. SEARCH: ANIMALS#.W..DE.
26. SEARCH: 24 AND 25
27. SEARCH: 25 NOT 26
28. SEARCH: 23 NOT 27
29. SEARCH: PT=CLINICAL-TRIAL$
30. SEARCH: CLINICAL-TRIALS#.DE.
31. SEARCH: (CLINIC$2 NEAR TRIAL$1).TI.
32. SEARCH: (CLINIC$2 NEAR TRIAL$1).AB.
33. SEARCH: (SINGL$3 OR DOUBL$3 OR TREBL$3 OR TRIP$3) NEAR (BLIND$3 OR MASK$3)
34. SEARCH: 33.TI.
35. SEARCH: 33.AB.
36. SEARCH: 34 OR 35
37. SEARCH: PLACEBOS#.W..DE.
38. SEARCH: PLACEBO$.TI.
39. SEARCH: PLACEBO$.AB.
40. SEARCH: RANDOM$.TI.
41. SEARCH: RANDOM$.AB.
42. SEARCH: RESEARCH-DESIGN#.DE.
43. SEARCH: 29 OR 30 OR 31 OR 32 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 40.
44. SEARCH: 43 NOT 27

45. SEARCH: COMPARATIVE-STUDY#.DE.
46. SEARCH: EVALUATION-STUDIES#.DE.
47. SEARCH: FOLLOW-UP-STUDIES#.DE.
48. SEARCH: PROSPECTIVE-STUDIES#.DE.
49. SEARCH: CONTROL$4 OR PROSPECTIV$ OR VOLUNTEER$
50. SEARCH: 49.TI.
51. SEARCH: 49.AB.
52. SEARCH: 45 OR 46 OR 47 OR 48 OR 50 OR 51
53. SEARCH: 52 NOT 27
54. SEARCH: 28 OR 44 OR 53
55. SEARCH: YEAR=2006 OR YEAR=2005 OR YEAR=2004 OR YEAR=2003
56. SEARCH: BRAIN#.W..DE.
57. SEARCH: BRAIN$3
58. SEARCH: 56 OR 57
59. SEARCH: 4 OR 5 OR 6
60. SEARCH: 58 AND 59
61. SEARCH: 7 OR 60
62. SEARCH: 16 AND 54 AND 61
63. SEARCH: 62 AND 55

DEEP BRAIN STIMULATION AND INDICATIONS AND SYSTEMATIC REVIEWS EMBASE 1. SEARCH: BRAIN-DEPTH-STIMULATION#.DE.
2. SEARCH: DBS
3. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$1
4. SEARCH: ELECTROSTIMULATION#.W..DE. OR ELECTROSTIMULATION-THERAPY#.DE.
5. SEARCH: ELECTRIC$2 ADJ STIMULATION$1
6. SEARCH: NEUROMODULATION$
7. SEARCH: 1 OR 2 OR 3
8. SEARCH: PAIN#.W..DE.
9. SEARCH: PAIN$3
10. SEARCH: NEURALGIA#.W..DE.
11. SEARCH: NEURALG$3
12. SEARCH: HEADACHE#.W..DE.
13. SEARCH: HEADACHE$4
14. SEARCH: CEPHALALG$
15. SEARCH: 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16. SEARCH: SYSTEMATIC ADJ REVIEW$2
17. SEARCH: META ADJ ANALYSIS
18. SEARCH: META-ANALYSIS#.DE.
19. SEARCH: META-ANALYSIS
20. SEARCH: BRAIN#.W..DE.
21. SEARCH: BRAIN$3
22. SEARCH: 20 OR 21
23. SEARCH: 4 OR 5 OR 6
24. SEARCH: 22 AND 23
25. SEARCH: 24 OR 7
26. SEARCH: 16 OR 17 OR 18 OR 19
27. SEARCH: 15 AND 25 AND 26

DEEP BRAIN STIMULATION AND INDICATIONS AND RCTS EMBASE 2003 ONWARDS
1. SEARCH: BRAIN-DEPTH-STIMULATION#.DE.
2. SEARCH: DBS
3. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$1
4. SEARCH: ELECTROSTIMULATION#.W..DE. OR ELECTROSTIMULATION-THERAPY#.DE.

5. SEARCH: ELECTRIC$2 ADJ STIMULATION$1
6. SEARCH: NEUROMODULATION$
7. SEARCH: 1 OR 2 OR 3
8. SEARCH: PAIN#.W..DE.
9. SEARCH: PAIN$3
10. SEARCH: NEURALGIA#.W..DE.
11. SEARCH: NEURALG$3
12. SEARCH: HEADACHE#.W..DE.
13. SEARCH: HEADACHE$4

14. SEARCH: CEPHALALG$
15. SEARCH: 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16. SEARCH: RANDOMIZED-CONTROLLED-TRIAL#.DE.
17. SEARCH: CLINICAL-TRIAL#.DE.
18. SEARCH: RANDOMIZATION#.W..DE.
19. SEARCH: DOUBLE-BLIND-PROCEDURE#.DE.
20. SEARCH: SINGLE-BLIND-PROCEDURE#.DE.
21. SEARCH: 16 OR 17 OR 18 OR 19 OR 20
22. SEARCH: HUMAN#.W..DE.
23. SEARCH: ANIMAL#.W..DE.
24. SEARCH: 22 AND 23
25. SEARCH: 23 NOT 24
26. SEARCH: 21 NOT 25
27. SEARCH: CLINICAL-TRIAL#
28. SEARCH: CLINICAL-TRIAL#.DE.
29. SEARCH: (CLINIC$2 NEAR TRIAL$1).TI.
30. SEARCH: (CLINIC$2 NEAR TRIAL).AB.
31. SEARCH: (SINGL$3 OR DOUBL$3 OR TREBL$3 OR TRIP$3) NEAR (BLIND$3 OR MASK$3)

32. SEARCH: 31.TI.
33. SEARCH: 31.AB.
34. SEARCH: 32 OR 33
35. SEARCH: PLACEBO#.W..DE.
36. SEARCH: PLACEBO$.TI.
37. SEARCH: PLACEBO$.AB.
38. SEARCH: RANDOM$.TI.
39. SEARCH: RANDOM$.AB.
40. SEARCH: METHODOLOGY#.W..DE.
41. SEARCH: 27 OR 28 OR 29 OR 30 OR 32 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42. SEARCH: 41 NOT 25
43. SEARCH: COMPARATIVE-STUDY#.DE.
44. SEARCH: EVALUATION#.W..DE.
45. SEARCH: FOLLOW-UP#.DE.
46. SEARCH: PROSPECTIVE-STUDY#.DE.
47. SEARCH: CONTROL$4 OR PROSPECTIV$ OR VOLUNTEER$
48. SEARCH: 47.TI.
49. SEARCH: 47.AB.
50. SEARCH: 43 OR 44 OR 45 OR 46 OR 48 OR 49
51. SEARCH: 50 NOT 25
52. SEARCH: 26 OR 42 OR 51
53. SEARCH: YEAR=2006 OR YEAR=2005 OR YEAR=2004 OR YEAR=2003
54. SEARCH: BRAIN#.W..DE.
55. SEARCH: BRAIN$3
56. SEARCH: 54 OR 55
57. SEARCH: 4 OR 5 OR 6
58. SEARCH: 56 AND 57
59. SEARCH: 7 OR 58
60. SEARCH: 15 AND 52 AND 53 AND 59

DEEP BRAIN STIMULATION AND INDICATIONS AND SYSTEMATIC REVIEWS CINAHL
1. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$
2. SEARCH: DBS
3. SEARCH: ELECTRIC-STIMULATION#.DE.
4. SEARCH: ELECTRIC$ ADJ STIMULATION$
5. SEARCH: NEUROMODULATION$
6. SEARCH: 1 OR 2
7. SEARCH: PAIN#.W..DE.
8. SEARCH: PAIN$4
9. SEARCH: NEURALGIA#.W..DE.
10. SEARCH: NEURALG$3
11. SEARCH: HEADACHE#.W..DE.
12. SEARCH: HEADACHE$3
13. SEARCH: CEPHALALG$
14. SEARCH: 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13

15. SEARCH: SYSTEMATIC-REVIEW#.DE.
16. SEARCH: SYSTEMATIC ADJ REVIEW$2
17. SEARCH: META-ANALYSIS#.DE.
18. SEARCH: META ADJ ANALYSIS
19. SEARCH: META-ANALYSIS
20. SEARCH: 15 OR 16 OR 17 OR 18 OR 19
21. SEARCH: BRAIN#.W..DE.
22. SEARCH: BRAIN$3
23. SEARCH: 21 OR 22
24. SEARCH: 3 OR 4 OR 5
25. SEARCH: 23 AND 24
26. SEARCH: 6 OR 25
27. SEARCH: 14 AND 20 AND 26

DEEP BRAIN STIMULATION AND INDICATIONS AND RCTS CINAHL 2003 ONWARDS

1. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$
2. SEARCH: DBS
3. SEARCH: ELECTRIC-STIMULATION#.DE.
4. SEARCH: ELECTRIC$ ADJ STIMULATION$
5. SEARCH: NEUROMODULATION$
6. SEARCH: 1 OR 2
7. SEARCH: PAIN#.W..DE.
8. SEARCH: PAIN$4
9. SEARCH: NEURALGIA#.W..DE.
10. SEARCH: NEURALG$3
11. SEARCH: HEADACHE#.W..DE.
12. SEARCH: HEADACHE$3
13. SEARCH: CEPHALALG$
14. SEARCH: 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. SEARCH: CLINICAL-TRIALS#.DE.
16. SEARCH: RANDOM$ ADJ ALLOCATION$
17. SEARCH: DOUBLE-BLIND-STUDIES#.DE.
18. SEARCH: SINGLE-BLIND-STUDIES#.DE.
19. SEARCH: 15 OR 16 OR 17 OR 18
20. SEARCH: HUMAN$
21. SEARCH: ANIMAL$
22. SEARCH: 20 AND 21
23. SEARCH: 21 NOT 22
24. SEARCH: 14 NOT 23
25. SEARCH: PT=CLINICAL-TRIAL
26. SEARCH: CLINICAL-TRIALS#.DE.
27. SEARCH: (CLINIC$2 NEAR TRIAL$1).TI.
28. SEARCH: (CLINIC$2 NEAR TRIAL$1).AB.
29. SEARCH: (SINGL$3 OR DOUBL$3 OR TREBL$3 OR TRIP$3) NEAR (BLIND$3 OR MASK$3)

30. SEARCH: 29.TI.
31. SEARCH: 29.AB.
32. SEARCH: 30 OR 31
33. SEARCH: PLACEBOS#.W..DE.
34. SEARCH: PLACEBO$.TI.
35. SEARCH: PLACEBO$.AB.
36. SEARCH: RANDOM$.TI.
37. SEARCH: RANDOM$.AB.
38. SEARCH: STUDY-DESIGN#.DE.
39. SEARCH: 25 OR 26 OR 27 OR 28 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38
40. SEARCH: 39 NOT 23
41. SEARCH: COMPARATIVE-STUDIES#.DE.
42. SEARCH: EVALUATION-RESEARCH#.DE.
43. SEARCH: PROSPECTIVE-STUDIES#.DE.
44. SEARCH: CONTROL$4 OR PROSPECTIV$ OR VOLUNTEER$
45. SEARCH: 44.TI.
46. SEARCH: 44.AB.
47. SEARCH: 41 OR 42 OR 43 OR 45 OR 46
48. SEARCH: 47 NOT 23

49. SEARCH: 24 OR 40 OR 48
50. SEARCH: YEAR=2006 OR YEAR=2005 OR YEAR=2004 OR YEAR=2003
51. SEARCH: BRAIN#.W..DE.
52. SEARCH: BRAIN$3
53. SEARCH: 51 OR 52
54. SEARCH: 3 OR 4 OR 5
55. SEARCH: 53 AND 54
56. SEARCH: 6 OR 55
57. SEARCH: 14 AND 49 AND 50 AND 56

DEEP BRAIN STIMULATION AND INDICATIONS AND SYSTEMATIC REVIEWS PSYCHINFO
1. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$2
2. SEARCH: DBS
3. SEARCH: BRAIN#.W..DE.
4. SEARCH: BRAIN$3
5. SEARCH: 3 OR 4
6. SEARCH: ELECTRIC$3 ADJ STIMULATION$2
7. SEARCH: NEUROMODULATION$
8. SEARCH: 6 OR 7
9. SEARCH: 8 AND 5
10. SEARCH: 1 OR 2 OR 9
11. SEARCH: PAIN#.W..DE.
12. SEARCH: PAIN$4
13. SEARCH: NEURALGIA#.W..DE. OR TRIGEMINAL-NEURALGIA#.DE.
14. SEARCH: NEURALG$3
15. SEARCH: HEADACHE#.W..DE.
16. SEARCH: HEADACHE$3
17. SEARCH: CEPHALALG$
18. SEARCH: 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. SEARCH: SYSTEMATIC ADJ REVIEW$3
20. SEARCH: META-ANALYSIS#.DE.
21. SEARCH: META-ANALYSIS
22. SEARCH: META ADJ ANALYSIS
23. SEARCH: 19 OR 20 OR 21 OR 22
24. SEARCH: 10 AND 18 AND 23

DEEP BRAIN STIMULATION AND INDICATIONS AND RCTS PSYCHINFO 2003 ONWARDS
1. SEARCH: DEEP ADJ BRAIN ADJ STIMULATION$2
2. SEARCH: DBS
3. SEARCH: BRAIN#.W..DE.
4. SEARCH: BRAIN$3
5. SEARCH: 3 OR 4
6. SEARCH: ELECTRIC$3 ADJ STIMULATION$2
7. SEARCH: NEUROMODULATION$
8. SEARCH: 6 OR 7
9. SEARCH: 8 AND 5
10. SEARCH: 1 OR 2 OR 9
11. SEARCH: PAIN#.W..DE.
12. SEARCH: PAIN$4
13. SEARCH: NEURALGIA#.W..DE. OR TRIGEMINAL-NEURALGIA#.DE.
14. SEARCH: NEURALG$3
15. SEARCH: HEADACHE#.W..DE.
16. SEARCH: HEADACHE$3
17. SEARCH: CEPHALALG$
18. SEARCH: 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. SEARCH: RANDOM$8 ADJ CONTROL$4 ADJ TRIAL$2
20. SEARCH: CONTROL$4 ADJ CLINICAL$1 ADJ TRIAL$2
21. SEARCH: RANDOM$8 ADJ ALLOCAT$5
22. SEARCH: DOUBL$3 ADJ BLIND$4
23. SEARCH: SINGL$3 ADJ BLIND$4
24. SEARCH: 19 OR 20 OR 21 OR 22 OR 23
25. SEARCH: HUMAN$2
26. SEARCH: ANIMALS#.W..DE.
27. SEARCH: 25 AND 26

28. SEARCH: 26 NOT 27
29. SEARCH: 24 NOT 28
30. SEARCH: CLINICAL-TRIALS#.DE.
31. SEARCH: (CLIN$5 NEAR TRIAL$3).TI.
32. SEARCH: (CLIN$5 NEAR TRIAL$3).AB.
33. SEARCH: (SINGL$3 OR DOUBL$3 OR TREBL$3 OR TRIP$3) NEAR (BLIND$3 OR MASK$3)

34. SEARCH: 33.TI.
35. SEARCH: 33.AB.
36. SEARCH: 34 OR 35
37. SEARCH: PLACEBO#.W..DE.
38. SEARCH: PLACEBO$2.TI.
39. SEARCH: PLACEBO$2.AB.
40. SEARCH: RANDOM$8.TI.
41. SEARCH: RANDOM$8.AB.
42. SEARCH: EXPERIMENTAL-DESIGN#.DE.
43. SEARCH: 30 OR 31 OR 32 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42
44. SEARCH: 43 NOT 28
45. SEARCH: COMPAR$6 ADJ STUD$3
46. SEARCH: EVALUAT$5 ADJ STUD$3
47. SEARCH: FOLLOW$3 ADJ UP$1 ADJ STUD$3
48. SEARCH: PROSPECTIVE-STUDIES#.DE.
49. SEARCH: CONTROL$4 OR PROSPECTIV$4 OR VOLUNTEER$4
50. SEARCH: 49.TI.
51. SEARCH: 49.AB.
52. SEARCH: 45 OR 46 OR 47 OR 48 OR 50 OR 51
53. SEARCH: 52 NOT 28
54. SEARCH: 29 OR 44 OR 53
55. SEARCH: 10 AND 18 AND 54
56. SEARCH: YEAR=2006 OR YEAR=2005 OR YEAR=2004 OR YEAR=2003
57. SEARCH: 55 AND 56

DEEP BRAIN STIMULATION AND INDICATIONS COCHRANE

ID	Search	Hits
#1	MeSH descriptor **Deep Brain Stimulation** explode all trees	19
#2	(dbs):ti,ab,kw	57
#3	(deep brain stimulation*):ti,ab,kw	84
#4	MeSH descriptor **Electric Stimulation** explode all trees	1012
#5	(electric* stimulation*):ti,ab,kw	2982
#6	(neuromodulation*):ti,ab,kw	51
#7	MeSH descriptor **Brain** explode all trees	4687
#8	(brain*):ti,ab,kw	9908
#9	(#7 OR #8)	11689
#10	(#4 OR #5 OR #6)	3114
#11	(#9 AND #10)	344
#12	(#1 OR #2 OR #3)	116
#13	(#11 OR #12)	407
#14	MeSH descriptor **Pain** explode all trees	19599
#15	(pain*):ti,ab,kw	36801
#16	MeSH descriptor **Neuralgia** explode all trees	350
#17	(neuralg*):ti,ab,kw	516
#18	MeSH descriptor **Trigeminal Autonomic Cephalalgias** explode all trees	43
#19	(cephalalg*):ti,ab,kw	16
#20	(#14 OR #15 OR #16 OR #17 OR #18 OR #19)	41130
#21	(#13 AND #20)	56

Appendix 2. Electrode mapping techniques

These methods (used in chapters 4, 6, 7 and 8) I learnt from my thesis adviser Alex Green and this appendix is reproduced from his 2007 University of London MD thesis.

Images were filed in Dicom format and manipulated using MRIcro software. First, the scans were checked for slice uniformity (2mm in all cases) and then rotated about the coronal plane so that the AC and PC were in the same axial section (figure A2.2). The mid-commissural point (MCP) was then calculated in Talairach space i.e. it was assigned an X, Y, Z coordinate to be used as a reference to each electrode contact. The electrode contacts are visible, circular swellings and the position of each contact was calculated by taking the centre of this low signal as the position of the electrode (figure A2.3). In addition, the distance from the midline was calculated for each contact.

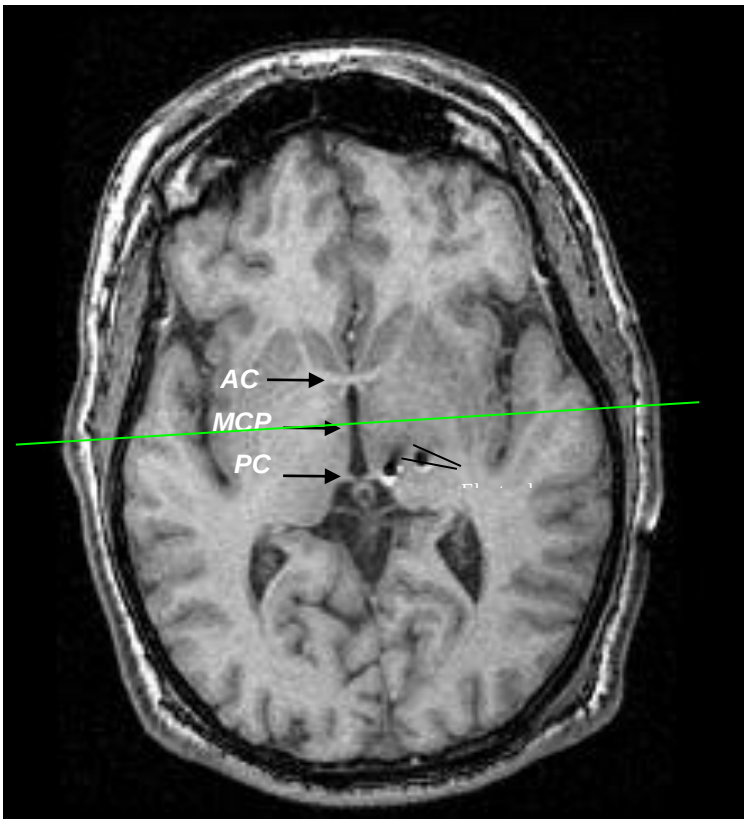


Figure A2.2. Calculating the Mid-comissural point. Axial section with the scan rotated about the coronal axis (green line) so that the mid-commissural point can be calculated. The PVG and VPL electrodes are visible. MCP = mid-commissural point. AC = anterior commissure. PC = posterior commissure

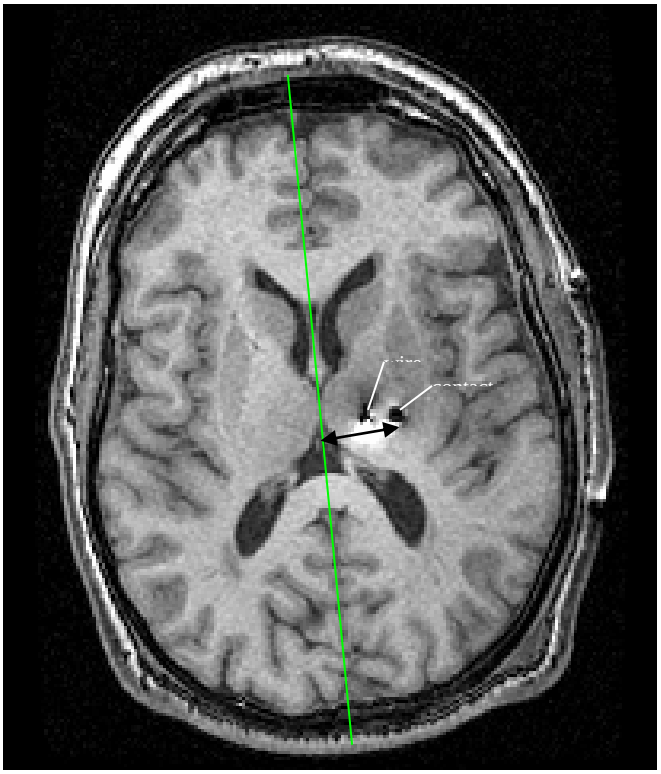
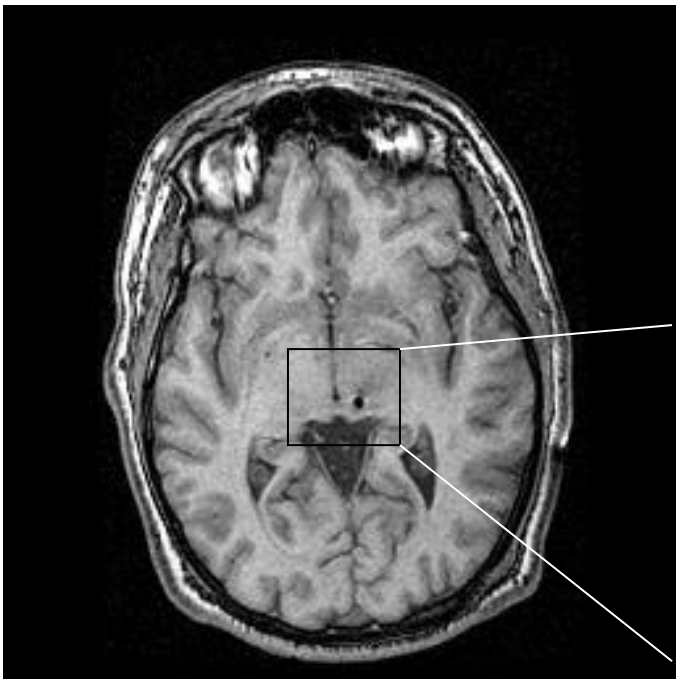


Figure A2.3. Calculating the Distance from the Midline. Axial section showing that the contacts can be distinguished from the wire, and calculation of the distance from the midline. Distance relative to the MCP was calculated using the X,Y,Z coordinates of the contacts (in mm) and basic trigonometry.

As a further validation of the coordinates thus obtained, the position of the contacts relative to the dorsum of the brainstem at the level of the lowest electrode (usually the superior colliculus) were also calculated (figure A2.4).



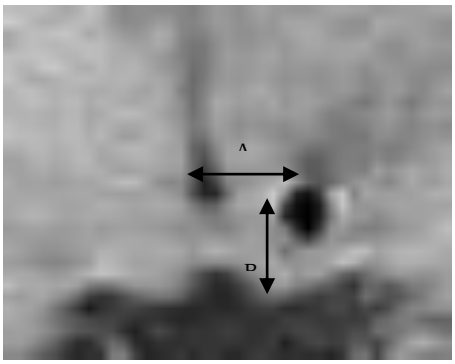


Figure A2.4.Calculating the distal contact. Relative position of centre of lowest contact of the PAG electrode to the dorsum of the brainstem ‘ B) and distance to the midline (‘A).

The coordinates obtained thus far would be enough to calculate the *angle* of the electrodes relative to the midline, in the coronal plane (termed *azimuth)* and relative to the AC-PC line in the sagittal plane (termed *declination*). However, in order to maximise accuracy of this technique, these angles were calculated using the MR images (figures A2.5 and A2.6) and used to plot the electrodes on the final picture (see below).

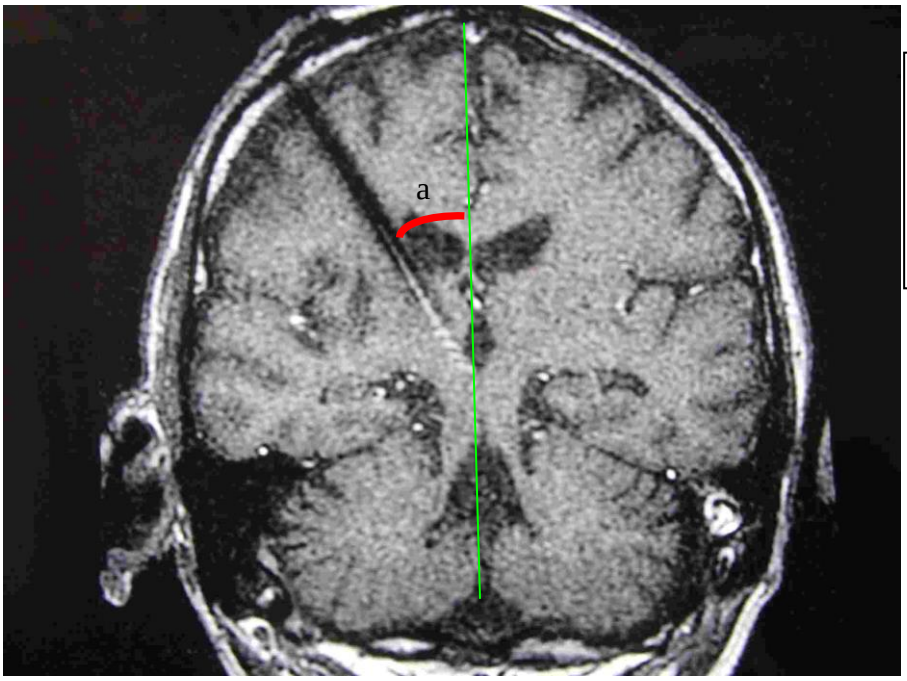


Figure A2.5. Calculating the azimuth (a) on the coronal MRI

In order to calculate the *declination*, a line is drawn between the AC and PC on a saggittal image. The angle of the electrode is then calculated relative to this line.

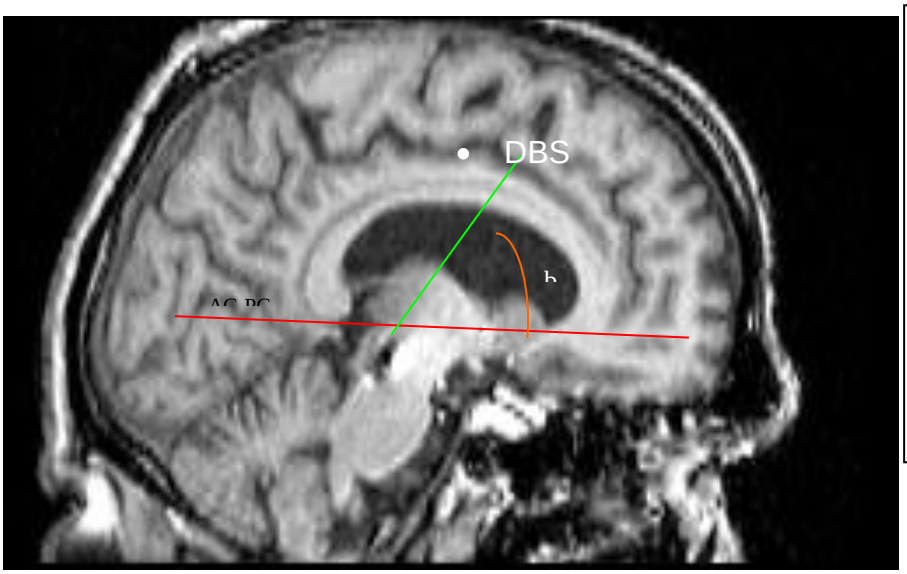


Figure A2.6. The *declination* (b) is calculated relative to the AC-PC line (the AC and PC are not visible in the same slice as the electrode, but the Y and Z coordinates are measured on the axial cuts and translated to the saggittal image).

Next, a standard saggittal section was taken from a brain atlas (Mai *et al*., 1998). The central portion, showing the position of the PAVG was then enlarged (figure A2.7). The electrodes of each patient were then plotted, using the relative distances to the mid-commissural point, dorsum of the brainstem etc as described above.

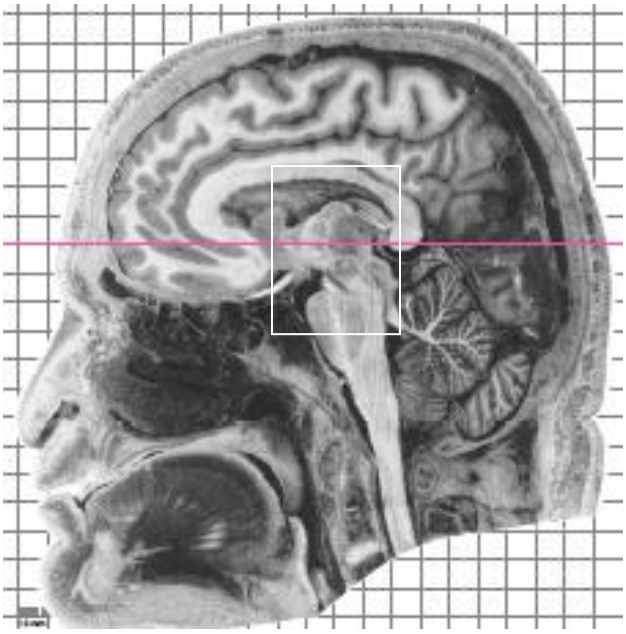


Figure A2.7: Sagittal section of the human brain, taken through the midline. The white box represents the enlarged area in figure A2.9. The pink line represents the AC-PC line.

Figure A2.9 shows the enlarged area with an outline of the PAVG. The red nucleus and the superior colliculus are also represented. The electrode was constructed to the same scale as the section in figure A2.9. The configuration of the electrode is shown in figure A2.8. All electrodes were Medtronic 3387® (Medtronic inc, Minneapolis) and consist of four cylindrical platinum-iridium contacts measuring 1.5mm in length with 1.5mm of insulated electrode in between each contact and 1.5mm at the tip. The wires from each of the four contacts are insulated from one another along the length of the electrode so that each contact can be stimulated separately (either positive or negative polarity). Either bipolar stimulation can be applied between any combination of contacts or monopolar between each of the contacts and the implantable pulse generator (in this study, bipolar was used).

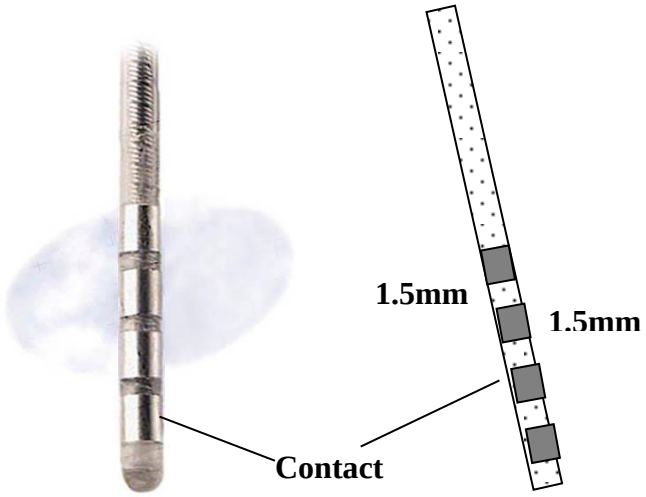


Figure A2.8. Configuration of the electrode. The electrode consists of 4 cylindrical contacts with separate, insulated wires (internally). Each contact measures 1.5mm in length with 1.5mm in between

In order to position each electrode on the atlas, first the positions of the deepest and most proximal contacts ('0' and '3' respectively) were plotted relative to the mid-commissural point and dorsum of the brainstem using a moveable scale bar. Lines were placed on the atlas at the relative positions from each landmark as well as the distance above and below the AC-PC line (see figure A2.9 for an example).The electrode was then placed on the picture and rotated so that the proximal and deepest contacts

corresponded to the lines. If there was any difference between the relative distance to the mid-commissural point or dorsum of the brainstem, the point taken was between these two lines (in no instance was this distance greater than the contact width). The angle of the electrode was then double-checked with the *declination* calculated on the saggittal scan (figure A2.6).

The electrode position was then plotted in the coronal plane (figure A2.10) as follows. The relative position of the contacts from the midline were calculated and this was verified with the *azimuth* (see figure A2.5 above). The distance of the contacts above and below the ACPC line were used to determine the depth of the electrode. In addition, the distance of the closest part of the electrode to the 3rd ventricle (yellow line in figure A2.10) was used to verify the position.

The position of the superior colliculus is superimposed on the atlas to show where this nucleus is, in relation to the section.

Finally, the position of each electrode relative to the PC, at the level of the PC, and relative to the superior colliculus, at the level of this nucleus were plotted on axial atlas images. The position of the PC was taken at its midline section.

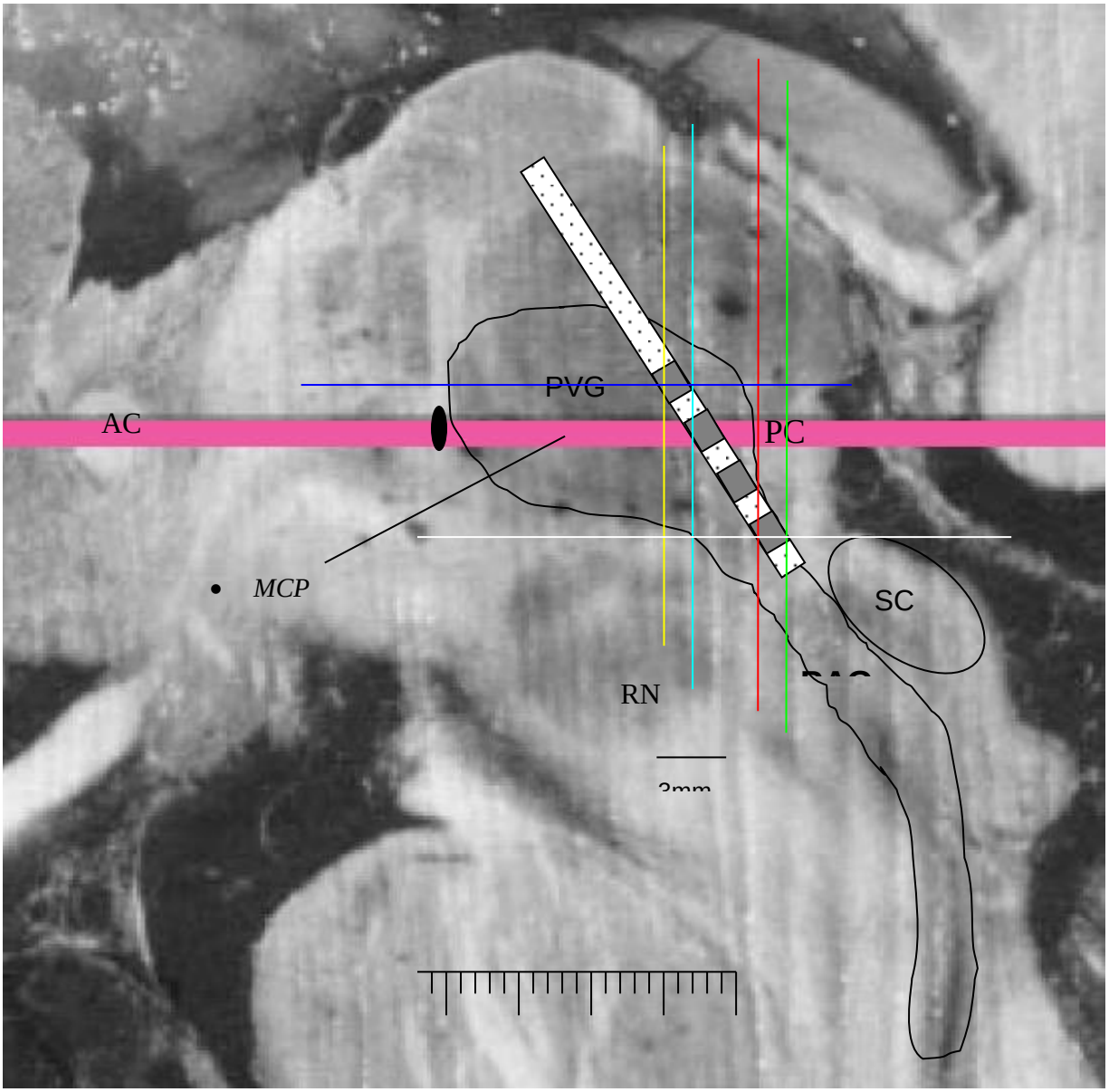


Figure A2.9. Placing the electrode on the atlas. Green line = distance of contact '0' to dorsum of brainstem. Red = distance from MCP. White= distance below ACPC line. Light blue = distance of contact '3' from dorsum of brainstem, yellow = distance from MCP, dark blue = distance above ACPC line. MCP= midcommissural point

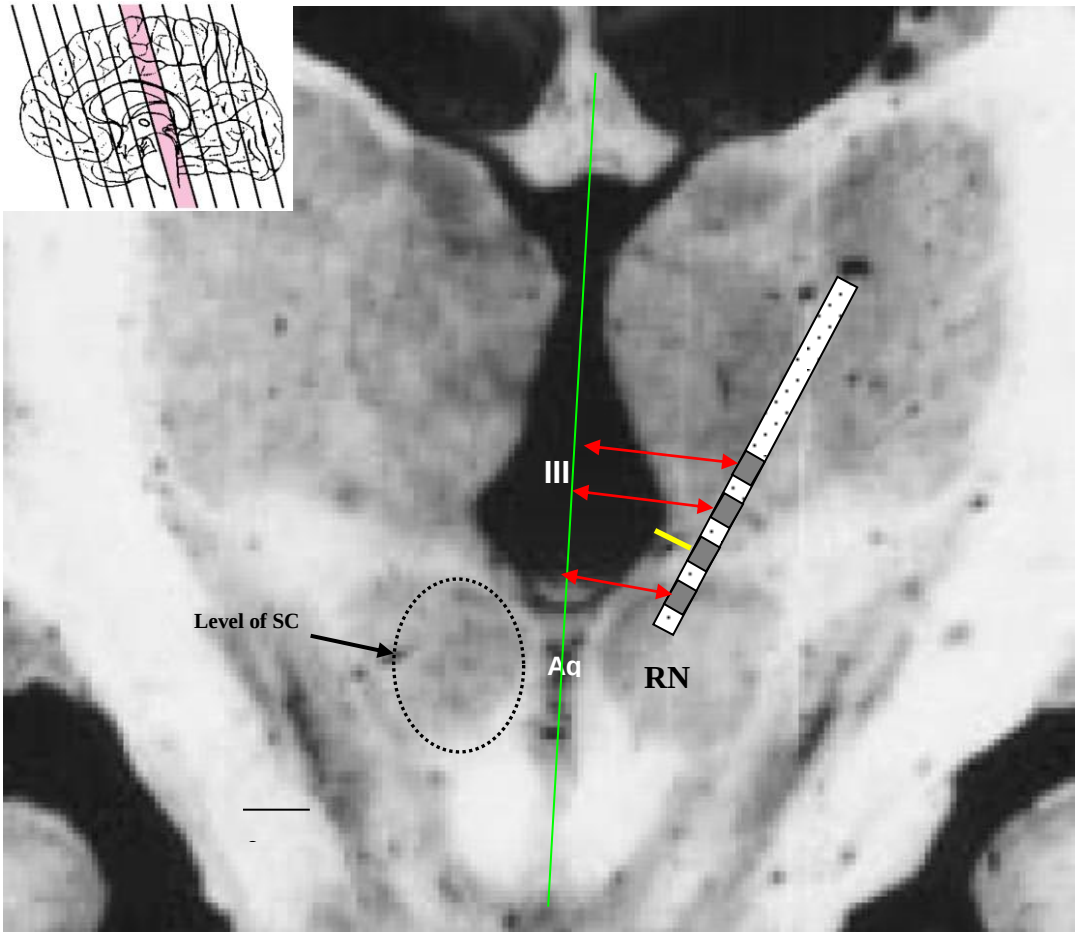


Figure A2.10. Positioning the electrode in the coronal plane. Green line = midline. Red lines= distance from midline.Yellow = distance to 3rd ventricle. RN = red nucleus. SC = superior colliculus. III = 3rd ventricle. Aq = aqueduct. Inset at top right = position of slice

Composite electrode positions were plotted for all the patients. The composite pictures were then used to verify the relative electrode positions of different patients, in 3 planes, to eradicate any errors.

In addition, the distance of contacts from the centre of the *red nucleus* was measured on the saggittal section (see figure A2.11). This was for two reasons. Firstly, this provides a better estimation of ventral vs. dorsal PAG than AP distance from mid-commissural point. Secondly, the red nucleus provides a visible target when planning the procedure (figure A2.11).

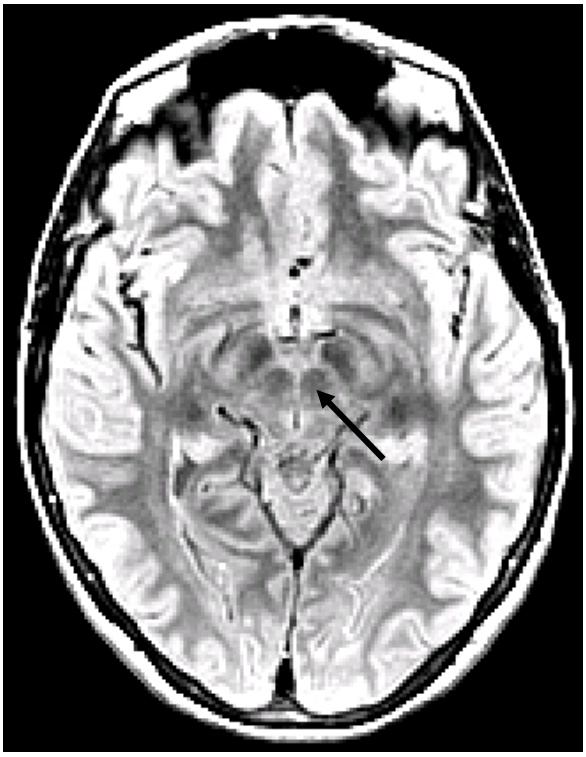


Figure A2.11. Red Nuclei
Axial T2 'Fluid Attenuated Inversion Recovery' ('FLAIR') sequence MRI showing the Red Nuclei (indicated on the left with a black arrow)

It is difficult to estimate the accuracy of this technique. However, the MRI slices are 2.0mm apart. The accuracy cannot be better than this. In fact, given the added inaccuracies of plotting the electrodes on a single atlas which is not necessarily in the exactly the same proportions as each patient, accuracy probably decreases to nearer 3mm. We have, in effect, 'normalised' each patient's brain by plotting the electrode positions relative to landmarks in at least three planes (AC, PC and midline).