



## Stimulating the human midbrain to reveal the link between pain and blood pressure

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### Abstract

The periaqueductal grey area (PAG) in the midbrain is an important area for both cardiovascular control and modulation of pain. However, the precise relationship between pain and blood pressure is unknown. We prospectively studied 16 patients undergoing deep brain stimulation of the rostral PAG for chronic pain. Pre-operatively, post-operatively, and at 1 year, pain scores were assessed using both visual analogue scores and the McGill Pain Questionnaire. Patients were tested post-operatively to determine whether electrical stimulation of the PAG would modulate blood pressure. We found that the degree of analgesia induced by deep brain stimulation of the rostral PAG in man is related to the magnitude of reduction in arterial blood pressure. We found that this relationship is linear and is related to reduced activity of the sympathetic nervous system. Thus stimulation of the PAG may partly control pain by reducing sympathetic activity as predicted by William James over a century ago.

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*Keywords:* Pain; Deep brain stimulation; Blood pressure; McGill Pain Questionnaire; Visual analogue score; Periaqueductal grey; PAG

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### 1. Introduction

In 1884 William James suggested that pain sensations are at least partly due to autonomic reactions changing local blood flow and blood pressure (James, 1884). Craig (2002) has argued that ‘interoception’ (sensation of the physiological condition of the body) should be defined as the sense of the physiological condition of the entire body, not just the viscera. This hypothesis questions the traditional notion that pain and temperature are simply somatosensory aspects of touch but are part of a wider homeostatic mechanism that integrates pain with emotions to provide a sense of ‘how you feel’. The periaqueductal grey area (PAG) in the midbrain is

an important area for both cardiovascular control and modulation of pain (Fields et al., 1983; Hosobuchi, 1986; Young and Rinaldi, 1997; Vanegas and Schaible, 2004; Green et al., 2005). In rats, stimulation of the ventral PAG is associated with reduction in arterial blood pressure (ABP) and analgesia (Johnson et al., 2004) whereas dorsal stimulation is associated with increased ABP (Carrive and Bandler, 1991). These midbrain sites are inextricably coupled and are part of the ‘defence’ reaction that an animal uses to combat danger (Reis et al., 1967). Similarly, in the human, we have recently shown that blood pressure can be modulated (up or down) by stimulating the rostral PAG in patients with chronic pain (Green et al., 2005). Moreover, the direction of the change in blood pressure depends on whether the electrode is in dorsal or ventral PAG.

Although the precise relationship between pain and blood pressure has not been fully elucidated, that it is

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a complex relationship and is altered in chronic pain patients is well accepted. For example, in these patients, *pain sensitivity* (defined as the level of stimulus required to produce a subjective feeling of pain) *positively correlates* with blood pressure, the opposite of the relationship in pain-free individuals (Bruehl et al., 2002). The aim of this study was to correlate blood pressure changes following electrical stimulation of the rostral PAG with changes in the patients' resulting sensations of pain. We have shown that the degree of analgesia induced by *deep brain stimulation* of the rostral PAG in man is related to the magnitude of reduction in ABP. We found that this relationship is linear and is due to reduced activity of the sympathetic nervous system. Thus stimulation of the PAG may partly control pain by reducing sympathetic activity as predicted by William James over a century ago (James, 1884).

In this study, we used both *visual analogue scores* (VAS) and the *McGill Pain Questionnaire* (MPQ) to quantify and to give a qualitative measure of the pain. The VAS method has been extensively used and validated

(McCarthy et al., 2005). The MPQ is a widely used pain scoring method (Melzack, 1975) that has been validated by other authors (Cohen and Tate, 1989; Mystakidou et al., 2002). It also allows us to look specifically at the 'burning' component of the pain that is common in these patients.

## 2. Methods

Sixteen patients undergoing deep brain stimulation for pain were entered prospectively into the study after informed consent and approval from the local Ethics Committee. All patients suffered from chronic neuropathic pain. Table 1 shows the demographics of the patients and the aetiology of the pain. There were 13 male and 3 female patients. Mean age was 52 years (median 54.5). All patients had a PAG deep brain stimulator and four had a second electrode inserted into the ventroposterolateral (VPL) nucleus of the thalamus (turned off during this study). None of the six thalamic or one pontine stroke (see Table 1) were in the vicinity of the electrodes and in fact the closest thalamic infarct was 4 mm from the wire of a passing electrode (and further from the electrical contacts).

Table 1  
Demographics

Patient group	Number (Fig. 1)	Age	Sex	Origin of pain	Deep brain stimulator location	Medication (omitted on day of testing)	Hypertensive?
Group 1 (decreased BP)	1	39	M	Thalamic haemorrhage	Left PAG	Nil	X
	2	53	M	Right brachial plexus injury 32 years ago	Left PAG and VPL	Nil	X
	3	39	M	Phantom limb (L arm)	R PAG and VPL	Amitriptylline 50 mg nocte	X
	4	71	M	Thalamic infarct	Left PAG	Bendroflumethazide 2.5 mg od Atenolol 50 mg od	✓
	5	40	M	Post surgical supraorbital pain	Right PAG and VPL	Amitriptylline 50 mg nocte	X
	6	35	F	Right occipital neuralgia	Left PAG	Co-codamol 8/500 qds Zopiclone 7.5 mg nocte	X
	7	51	M	Thalamic haemorrhage	Left PAG	Nil	X
Group 2 (increased BP)	8	74	M	Thalamic haemorrhage	Right PAG	Nil	X
	9	34	F	Spinal cord injury	Bilateral PAG	MST 180 mg	X
	10	60	M	Thalamic haemorrhage	Left PAG	Nil	X
Group 3 (no change in BP)	11	59	M	Pontine haemorrhage	Right PAG and VPL	Co-codamol 8/500 qds	X
	12	56	F	Phantom limb (legs)	Bilateral PAG	Co-codamol 32/500 qds	X
	13	34	M	Post-traumatic head pain	R PAG	Zopiclone 7.5 mg nocte Acetaminophen 1 g qds	X
	14	67	M	Cortical infarction	Right PAG	Furosemide 40 mg od Nicorandil 30 mg bd, Amlodipine 5 mg od Tamulosin HCL 0.4 mg od ISMN 30 mg od Perindopril 2 mg od	✓
	15	60	M	Thalamic haemorrhage	Right PAG	Indapamide SR 1.5 mg om Irbesartan 300 mg om Citalopram 20 mg om Tramadol 100 mg om Diazepam 10 mg om	✓
	16	56	M	Left phantom leg	Right PAG	Co-codamol 8/500 qds	X

PAG, periaqueductal grey; VPL, ventroposterolateral nucleus.

### 2.1. Surgical technique

Details of our surgical technique have been described elsewhere (Bittar et al., 2005). In brief, Medtronic 3387<sup>®</sup> electrodes were stereotactically implanted under local anaesthetic. Intra-operative electrode localisation was aided by a feeling of warmth in the area of pain, during PAG stimulation, and parasthesia during thalamic stimulation, as described by others (Hosobuchi, 1986; Young and Rinaldi, 1997). We did not elicit fear or anxiety in any patient, as previously reported (Nashold et al., 1969).

### 2.2. Measurements

During lab-based recordings, non-invasive continuous finger arterial pressure was measured with an Ohmeda Finapres 2300 (BOC Healthcare, USA). The blood pressure was calibrated using a sphygmomanometer and the pressure transducer and finger cuff were positioned at heart level. The finger pressure was digitised at 4 kHz with 16-bit resolution (CED 1401 Mark II, Cambridge Electronic Design, Cambridge, UK) using Spike II software<sup>®</sup> (version 5.0, Cambridge Electronic Design, Cambridge, UK).

### 2.3. Study design

Experiments to determine blood pressure change and VAS were performed in the week after the initial placement of the electrode. All sessions were carried out on a single day. Each experiment was performed more than 2 h after any meal and room temperature was kept constant at 22 °C. Patients delayed opioid (one patient) or antihypertensive medication (three patients) until after the experiment. They also abstained from caffeine. The deep brain stimulator was initially turned off for at least 10 min prior to experiments.

Experiments were started with the patient sitting for 5 min. The first session consisted of a 12-min rest period with the stimulator turned off, while recording cardiovascular variables. Subsequent sessions consisted of six randomly ordered ‘on’ or ‘off’ periods lasting for 9 min per session. Between each of these ‘on’ or ‘off’ sessions, there was a 9-min rest period with stimulation off to allow cardiovascular variables to return to baseline. The person recording the data and the patient were blinded as to whether the stimulator was on or off. The patient was asked to provide a visual analogue score (0–100, 0 = no pain, 100 = worst pain ever experienced) to estimate pain level, during each session. The stimulator settings used were those that provided the optimal analgesia for each individual patient (see below). Frequency ranged from 5 to 80 Hz, amplitude from 2.5 to 5 V, and pulse width from 150 to 450  $\mu$ s.

### 2.4. Determining optimal stimulator parameters

This occurred prior to each experiment and usually lasts for 2–3 days. A full range of combinations of contacts, frequencies (5–80 Hz), pulse width (120–450  $\mu$ s) and amplitude (0.5–5 V) are trialled. The final parameters chosen are those that provide best subjective analgesia, often helped by looking at VAS. In this study, only the contacts that provided best analgesia were stimulated during the cardiovascular measurements. In all

cases, these were the chronic settings that were being used at one year, except that voltage was subsequently increased in three cases. The effect of location of stimulation and blood pressure is the subject of another study (Green et al., 2005) and is therefore not presented here.

### 2.5. Recording of McGill's Pain Questionnaire scores

Pre-operatively, and at one year, each patient completed a McGill Pain Questionnaire (MPQ) on both occasions, in the presence of a specialist nurse. For analysis of data, we used the Ranked Pain Rating Index (PRI(R)) as described by Melzack (Melzack, 1975). In this method of scoring, each word in a category is assigned a number, depending on its severity. Using this method, we calculated overall pain rating index – PRI (R) – (out of 78), sensory PRI(R) (out of 42), affective PRI (R) (out of 14), evaluative PRI (R) (out of 5) and miscellaneous PRI (R) (out of 17). In addition, as we were particularly interested in the burning component of pain, we scored question 7 separately. Question 7 gives the patient the opportunity to select one of four words of increasing severity (hot, burning, scalding, and searing) and they were thus assigned a score of 0–4.

### 2.6. Signal processing and statistical analysis

One-way analysis of variance of BP with time was performed on all raw data segments for each session to determine significant change from baseline BP ( $p < 0.05$ ). For each session, data were averaged every 30 s and the mean values were taken to give the average across all three of the ‘stimulation on’ or three ‘stimulation off’ sessions in each patient. These were then compared to the mean change in visual analogue score for each patient. To assess the contractility of the heart, and therefore to provide a measure of central sympathetic drive, we calculated the blood pressure changing rate,  $dP/dt$  (see Section 4). This was derived by differentiating the continuous blood pressure waveform. The maximum  $dP/dt$  (maximum slope of the blood pressure curve) was then extracted.

To assess whether blood pressure,  $dP/dt$ , and pulse pressure were related to changes in pain scores, linear regression analysis was performed. For long-term changes, using the McGill's Pain Questionnaire, pre-operative and one-year MPQ scores for each group were compared and linear regression analysis was applied to test any relationship between reduction in blood pressure and degree of analgesia. As ‘question 7’ or the burning component of pain consists of a scale of one to four, we did not consider linear regression analysis to be valid. We therefore divided the patients into three groups depending on whether their blood pressure significantly changed with stimulation (significant change was regarded as two-tailed  $p < 0.05$  using analysis of variance of blood pressure with time). We then compared the mean pre-operative and one-year scores for each group using the Wilcoxon Signed Ranks Test for non-parametric data with a two-tailed  $p$ -value of  $< 0.05$  taken as significant.

To assess changes in the sympathetic and parasympathetic components of SBP, *auto-regressive power spectral analysis of SBP* was performed (see (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) for methodology) after filtering out

frequencies below 0.023 Hz to detrend the signal. The power of the low and high frequency components was computed as the integral of the bands from 0.05 to 0.15 and 0.15 to 0.4 Hz. The logarithm of the LF and HF measures was further analysed using a *t*-test.

Signal processing was performed in *Matlab*<sup>®</sup> (v6.1, MathWorks Inc., Natick, Ma., USA) and statistical analysis was performed in SPSS (Version 11, SPSS Inc, IL, USA). Graphs were plotted using Origin<sup>®</sup> (v7. 0300, Northampton, MA, USA). All *p* values are two-tailed.

### 2.7. Post-operative localisation of electrodes

Electrode positions were plotted on a brain atlas (Mai et al., 1998) using the post-operative MRI and a manipulation program (MRicro version 1.38, Chris Rorden). First, the scan was rotated such that the Anterior and Posterior commissures (AC and PC, respectively) were on the same slice. The mid-commissural point was then calculated, followed by the position, in Talairach space, of the electrode contacts. The contacts are visible, circular thickenings in the low signal on the axial scan. The centre of each contact was taken as the position of the electrode and this corresponds to the centre of the contacts in Fig. 1. Using the coronal and sagittal scans, the angles of the electrode to the midline and AC-PC line, respectively, were calculated. Once plotted on the brain atlas, the relative position of the lowest contact to the posterior wall of the superior colliculus was verified, as was the relative position of the upper electrode to the mid-commissural point. As a further verification, the relative positions of the electrodes from all patients were compared, to rule out inconsistencies among the groups.

## 3. Results

### 3.1. Blood pressure changes

Seven out of 16 patients had a significant decrease in systolic blood pressure with stimulation (mean reduction =  $13.1 \pm 6.1$  mmHg). Four patients had a significant increase (mean =  $11.7 \pm 6.0$  mmHg). The remaining five patients had no significant changes in BP.

### 3.2. Visual analogue scores (short-term changes)

Using one-way ANOVA of VAS versus change in BP, mean pre-operative VAS scores were not found to be significantly different in the three groups of decrease, increase or no change in BP with stimulation ( $p > 0.5$  in all comparisons). VAS (within one week of surgery) were compared to changes in blood pressure during six 9-min stimulation periods for each patient (three 'on' and three 'off'). Linear regression analysis of change in VAS (%) versus change in systolic blood pressure showed that there is a significant linear relationship between reduction in blood pressure and reduction in VAS ( $r^2 = 0.62$ ,  $p = 0.0105$ ,  $n = 16$  – see Fig. 2A). Similar analysis revealed that fall in  $dP/dt$  was also strongly correlated with reduction in VAS ( $r^2 = 0.62$ ,  $p < 0.008$ ,  $n = 16$  – Fig. 2C) but that

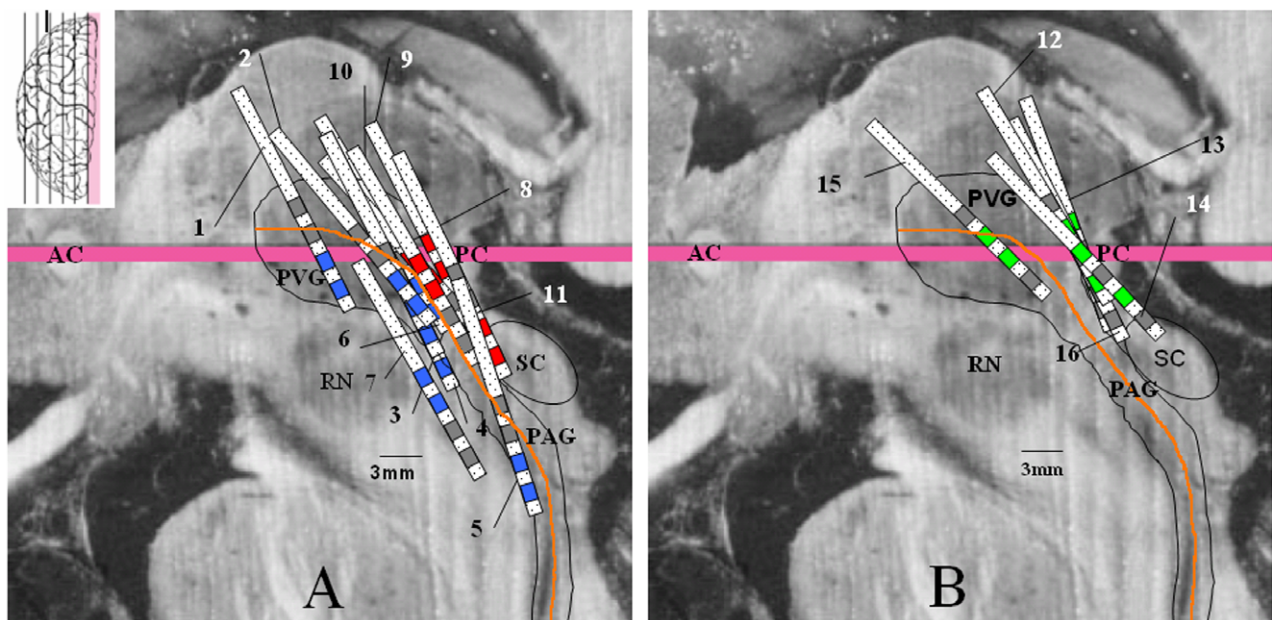


Fig. 1. Post-operative electrode location. (A) Sagittal view of the midbrain showing the superimposed electrode positions in those patients in whom BP significantly changed with stimulation. The electrode contacts that provided optimum pain relief are coloured and are both those that were studied and those used for chronic stimulation. Contacts that reduced BP are shown in blue, those that increased BP are red. Inset shows the level of the AC-PC line. The orange line indicates the approximate level of the aqueduct and therefore the distinction between ventral and dorsal PAG. (B) Location of electrodes that had no effect on BP (the contacts used are coloured green). RN, red nucleus; SC, superior colliculus; AC, anterior commissure; PC, posterior commissure (with pink line joining the two); PAG, periaqueductal grey; and PVG, periventricular grey. Patient numbers refer to those in Table 1. Background reprinted from Mai et al. ©1998, with permission from Elsevier.

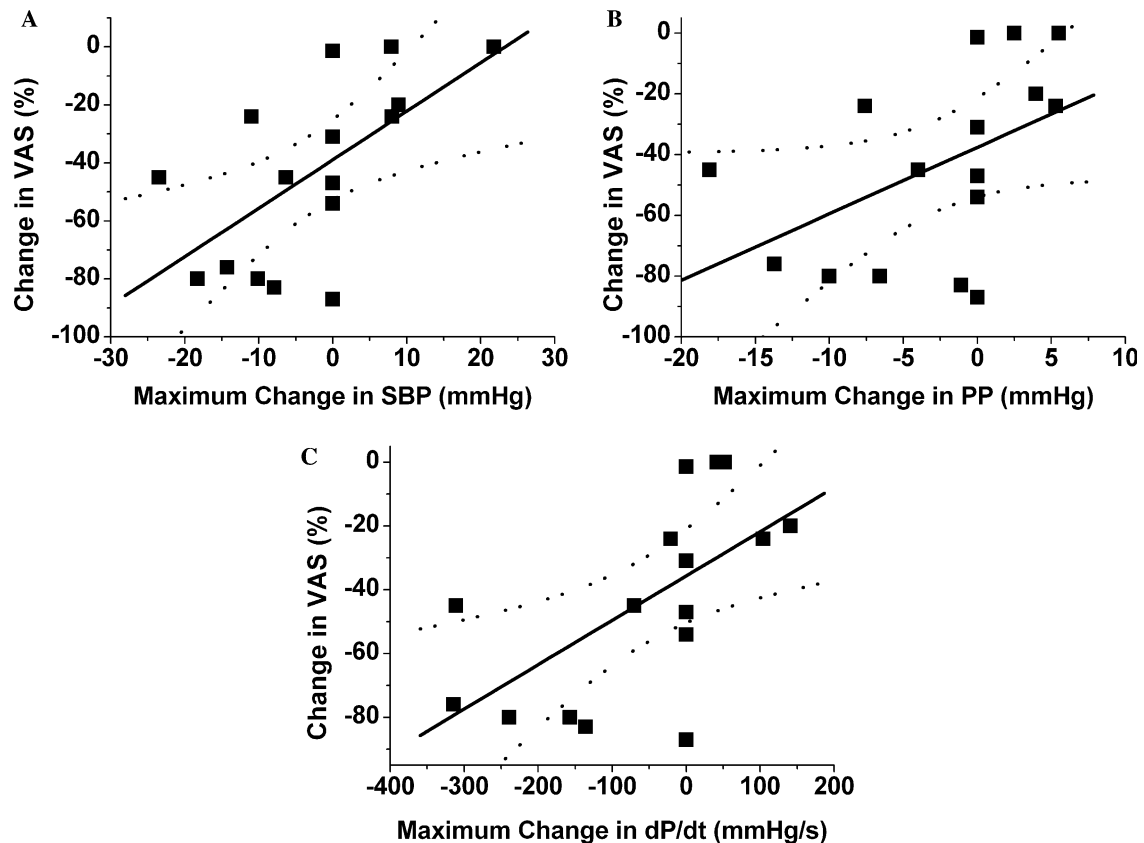


Fig. 2. Comparison of visual analogue scores with cardiovascular variables. (A) Average changes in VAS (%) significantly correlated to systolic blood pressure (A,  $r^2 = 0.62$ ,  $p = 0.01$ ,  $n = 16$ ) and  $dP/dt$  changes (C,  $r^2 = 0.62$ ,  $p = 0.01$ ,  $n = 16$ ), but weakly associated with pulse pressure changes with stimulation (B,  $r^2 = 0.48$ ,  $p = 0.06$ ,  $n = 16$ ). Solid lines = linear regression, Outer dashed lines = upper and lower 95% confidence intervals. VAS, visual analogue score; SBP, systolic blood pressure.

changes in pulse pressure were only weakly correlated ( $r^2 = 0.48$ ,  $n = 16$  – Fig. 2B). Autoregressive power spectral analysis of systolic blood pressure variability

revealed that in the group with decreased blood pressure, there was a significant reduction ( $p < 0.001$ ,  $n = 7$ ) in the logarithm of the low frequency component (Fig. 3A).

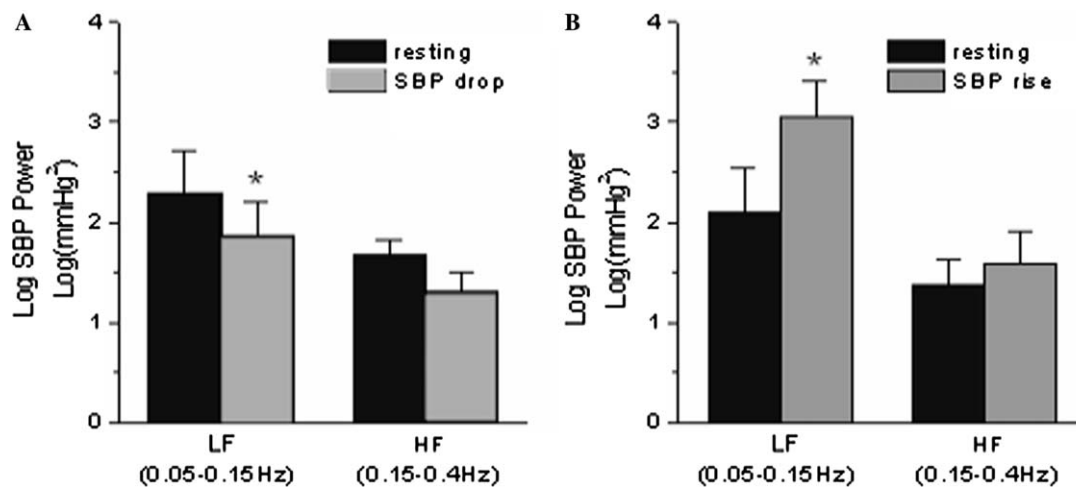


Fig. 3. Power spectral analysis of systolic blood pressure (A) in those patients with a significant reduction in systolic blood pressure with stimulation, there was a significant decrease ( $p < 0.001$ ) in the low frequency component (0.05–0.15 Hz) of systolic blood pressure variability. (B) Similar results for patients with increases in systolic blood pressure ( $p < 0.001$ ). Error bars indicate one standard deviation of the mean.  $n = 7$  for drop and  $n = 4$  for rise group. \* Denotes statistical significance.

The converse was true for increases in blood pressure ( $p < 0.001$ ,  $n = 4$ , Fig. 3B). This implies that blood pressure changes are related to changes in sympathetic activity (see Section 4).

### 3.3. McGill Pain Questionnaire – long-term results

To test whether this association between blood pressure changes and pain relief lasts for a long time, we compared blood pressure changes (taken within the first week post-operatively) to improvements in pain scores at one year, using the McGill Pain Questionnaire (Fig. 4). Pre-operatively, one-way ANOVA of all MPQ categories versus change in BP (decrease, increase or no change) revealed that there was no significant difference in starting values between each group for each category ( $p > 0.2$ ).

At one year, we found that total pain remained lowest, having reduced from a mean pain score of 34 (SD = 13) pre-operatively to a mean of 12.2

(SD = 9.5) one year post-operatively ( $p = 0.003$  Wilcoxon Signed Ranks Test,  $n = 7$ ) in those whose BP had decreased on stimulation (seven patients). The *no change in BP* group reduced from a mean of 28.5 (SD = 5.1) pre-operatively to 14 (SD = 7.0) post-operatively ( $p = 0.055$ ,  $n = 5$ ). Although there was an improvement in total pain score in the *increased BP* group from a mean of 41.5 pre-operatively to 36.8 post-operatively, this was not significant (Fig. 4A).

Analysis of the sensory component of the MPQ (scored out of 42) shows a similar decrease in the total scores (Fig. 4B). In the *decreased BP* group, mean reduced from 19.4 (SD = 7.9) pre-operatively to 6.2 (SD = 5.5) post-operatively ( $p < 0.05$ , Wilcoxon Signed Ranks Test). In the *no change* group, mean decreased from 15.3 (SD = 3.6) pre-operatively to 7.7 (SD = 0.6) post-operatively ( $p < 0.05$ , Wilcoxon Signed Ranks Test). Again, there was a reduction from 22.5 (SD = 9.5) to 18.0 (SD = 10.7) in the *increased BP* group but this was not significant. Although there was

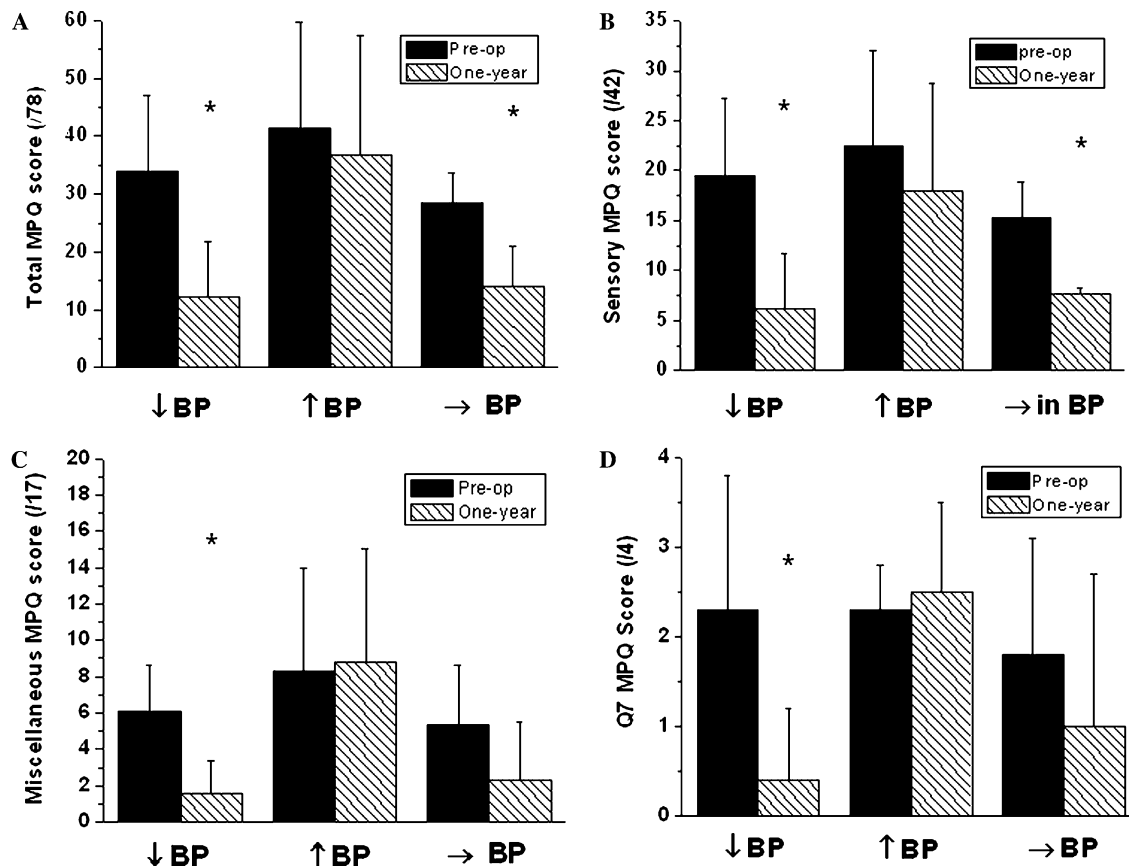


Fig. 4. Long-term changes in McGill Pain Questionnaire (MPQ) scores compared to BP changes. (A) Changes in MPQ scores at one year, compared to pre-operatively, depending on whether BP increased (BP ↑), decreased (BP ↓) or remained unchanged (BP →) in the laboratory. Comparisons were made using the Wilcoxon Signed Ranks Test. \* Indicates significance ( $p < 0.001$ ). Error bars denote one standard error of the mean. (B and C) similar results for the sensory and miscellaneous component of the MPQ. (D) Similar results for Question 7 which gives a patient the choice of one out of four words that describe ‘burning’ sensation, in increasing severity (0–4). These results show that those patients who had a decrease in blood pressure obtained the best analgesia over the long-term. Stimulation appears to work particularly well on the burning component of pain, which may have a vascular component.

a reduction in the affective and evaluative components in all groups, due to a wide variation between patients, none of these were found to be significant.

In the miscellaneous section, pre-operative scores reduced with weak significance ( $p = 0.066$ ) only in the *decreased BP* group (6.1 (SD = 2.5) pre-operatively versus 1.6 (SD = 1.8) post-operatively) but not in the other two groups. See Fig. 4C for a representation of these results.

Analysis of question 7 of the MPQ (related to ‘burning’ sensation) showed that all but two patients studied had *burning* pain pre-operatively (one in the ‘no change in BP’ group, the other in the ‘decreased BP’ group did not have *burning*). Post-operatively, in contrast, only one patient had *burning* pain in the *decreased BP* group, one in the *no change in BP* group, and all of the patients in the *increased BP* group. Thus, the burning component of pain reduced in the *decreased BP* group but not in the *increased BP* group. Fig. 4D shows that, using a quantitative score of 1–4 for the burning component, there was only a significant reduction in the burning component of pain in the *decreased BP* group, but not the other two.

The mean score dropped from 2.3 pre-operatively to 0.4 post-operatively. It therefore appears that there is a relationship between reduced BP and improvement of burning pain.

As with short-term changes there was a linear correlation between reduction in blood pressure and percentage reduction in MPQ score at one year ( $r^2 = 0.69$ ,  $p = 0.002$ ,  $n = 16$ ; Fig. 5A). There were also strong linear correlations with both the *sensory* and *miscellaneous* subsets of the MPQ score at one year, that describe the qualitative aspects of a patient’s pain ( $r^2 = 0.67$ ,  $p = 0.004$ ,  $n = 16$  for *sensory*; Fig. 5B,  $r^2 = 0.68$ ,  $p = 0.003$ ,  $n = 16$  for *miscellaneous*; Fig. 5C). Thus, it appears that reduction in blood pressure on deep brain stimulation is associated with prolonged pain relief for at least a year.

### 3.4. Electrode location and analgesic effect

Fig. 1 shows the electrode positions, as determined by the post-operative MRI scans. Note that these are an approximation as every brain is slightly different

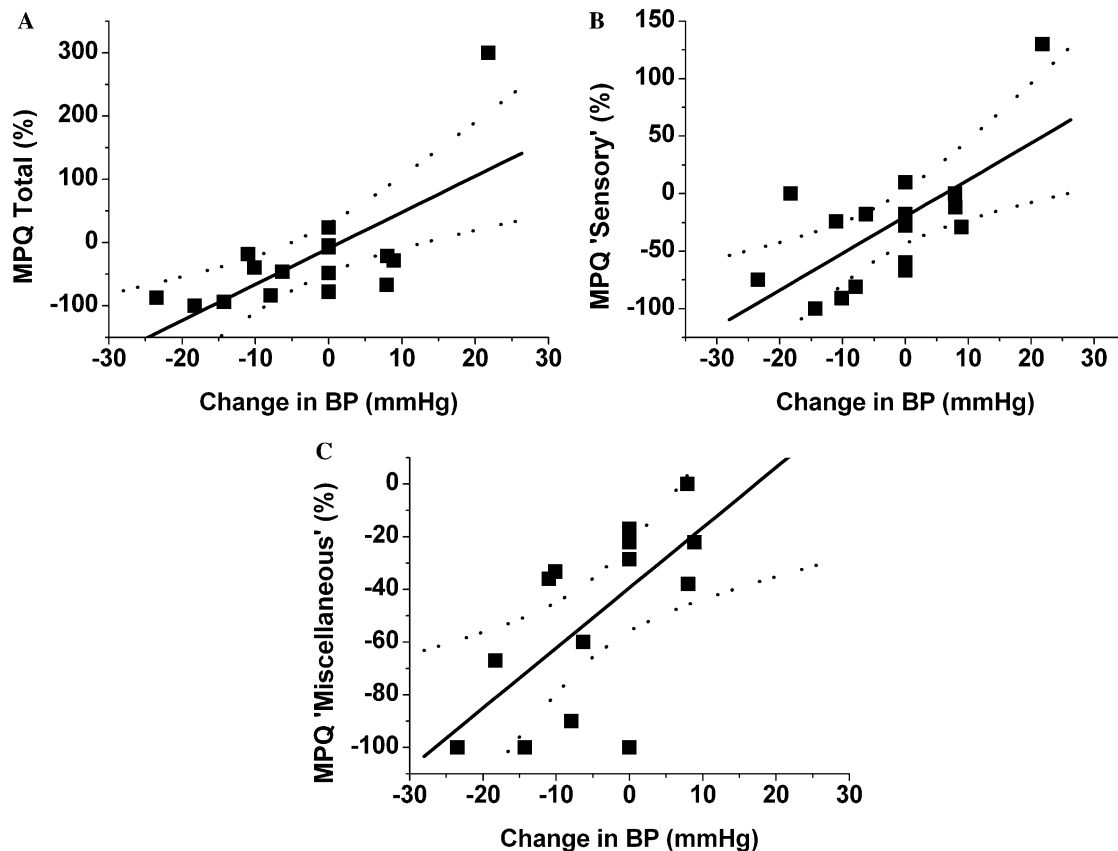


Fig. 5. Long-term Changes in MPQ scores compared to BP changes. (A) Changes in MPQ scores at one year, compared to pre-operatively, significantly correlated to changes in blood pressure ( $r^2 = 0.69$ ,  $p = 0.002$ ,  $n = 16$ ). Solid lines, linear regression; outer dashed lines, upper and lower 95% confidence intervals. (B and C) similar results for the ‘sensory’ and ‘miscellaneous’ components of the MPQ. ( $r^2 = 0.67$ ,  $p = 0.004$ ,  $n = 16$  for *sensory*;  $r^2 = 0.68$ ,  $p = 0.003$ ,  $n = 16$  for *miscellaneous*) These results show that decrease in blood pressure correlates to analgesia over the long-term.

and there are errors inherent in plotting all electrodes onto one image. We estimate an error of 2–3 mm using this technique. We have previously shown that electrodes in ventral PAG reduce blood pressure and those in dorsal PAG increase blood pressure (Green et al., 2005). Comparison of changes in VAS between the 8 most ventral and 8 most dorsal electrodes (as in Fig. 1) revealed a mean reduction in VAS of 56.6% in the ventral group and 33.6% in the dorsal group. This difference was found to be significant ( $p = 0.036$ , Wilcoxon,  $n = 16$ ).

### 3.5. Comparison of absolute values of pain and blood pressure

Linear regression analysis was performed on the absolute values of pain and blood pressure in each patient (Fig. 6). For each patient with a change in blood pressure during stimulation there are therefore two data points – stimulation on versus stimulation off, with corresponding VAS. For those with no significant change in

BP, there is only one data point for each pain score. The results show that there is no significant correlation between absolute systolic blood pressure, pulse pressure or  $dP/dt$  and pain scores for any of these variables (see legend for  $r^2$  values).

### 3.6. Comparison of short-term versus long-term pain scores

Short-term improvements in VAS (i.e. within one week of surgery) were compared to one-year MPQ scores (Fig. 7). Regression analysis showed that there is a significant correlation between early efficacy and improvement in long-term pain score.

## 4. Discussion

Pain processing in the central nervous system is complex and involves many areas, but there are some areas that have been shown to be important both in pain processing and blood pressure control. These include the

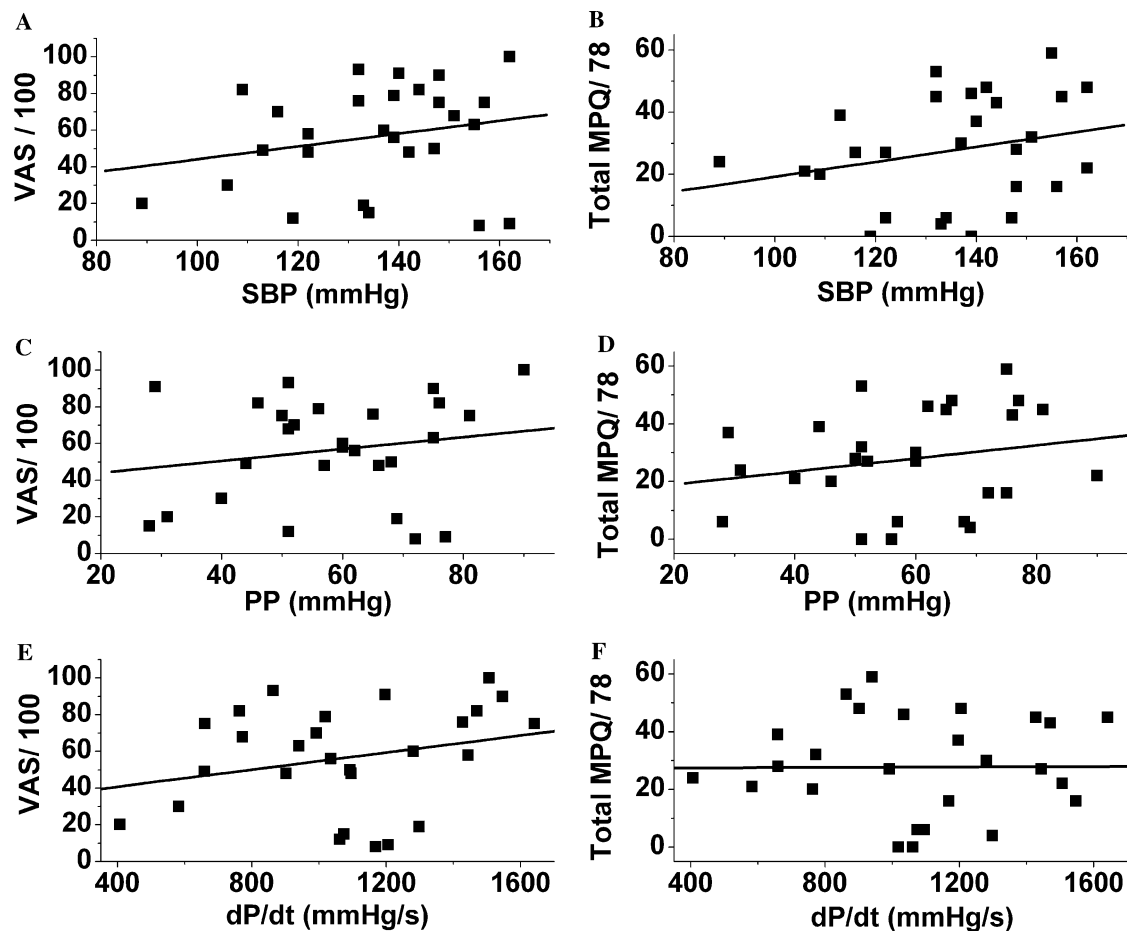


Fig. 6. Comparison of absolute BP and pain variables. None of the comparisons showed any significant correlation; (A) systolic blood pressure (SBP) versus VAS ( $r^2 = 0.22$ ,  $p > 0.25$ ,  $n = 27$ ). (B) SBP versus MPQ score ( $r^2 = 0.26$ ,  $p > 0.19$ ,  $N = 27$ ). (C) Pulse pressure versus VAS ( $r^2 = 0.18$ ,  $p > 0.35$ ,  $n = 27$ ). (D) Pulse pressure versus MPQ score ( $r^2 = 0.21$ ,  $p > 0.29$ ,  $n = 27$ ). (E)  $dP/dt$  versus VAS ( $r^2 = 0.26$ ,  $p > 0.18$ ,  $n = 27$ ). (F)  $dP/dt$  versus MPQ score ( $r^2 = 0.007$ ,  $p > 0.97$ ,  $n = 27$ ).

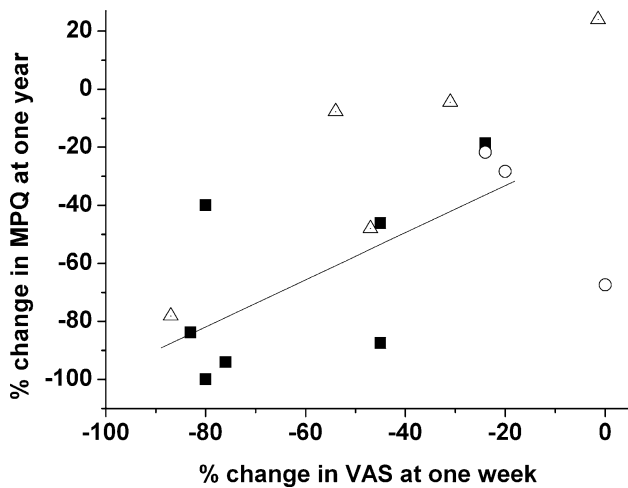


Fig. 7. Comparison of short-term VAS with long-term MPQ scores. There was a significant correlation ( $r^2 = 0.6$ ) between initial improvement in VAS (% reduction in VAS) and percentage reduction in long-term MPQ score. Note that two patients had an increase in MPQ score, one of which is not shown as the increase was 300% (with reduction of VAS of 0%). ■, patient with reduction in BP on stimulation; ○, no change in BP; △, increase in BP.

*nucleus tractus solitarius* (this is the first relay station of the baroreceptor afferents), the *locus coeruleus* and the *periaqueductal grey* region (Ghione, 1996). That there is a relationship between *acute* pain and raised blood pressure is well established, the mechanism being a combination of increased arousal and increased sympathetic activity (Maixner et al., 1990; Nordin and Fagius, 1995). The relationship between *chronic* pain and blood pressure, however, is much more complicated. In pain-free individuals, there appears to be an inverse relationship between resting BP and pain sensitivity. For example, hypertensive subjects do not feel pain as intensely as normotensives (Ghione et al., 1988; Sheps et al., 1992; Ghione, 1996; Bradley et al., 2002).

Dworkin et al. (1979) showed, in rats, that this effect is mediated by the baroreceptors and proposed that, not only could the stimulation of baroreceptors explain the hypalgesia of hypertension, but that hypertension may be a learned behaviour to minimise the effects of stress. In contrast to this inverse relationship of BP and pain sensitivity, *chronic pain patients* have been shown to lose, or even reverse, this relationship i.e. pain sensitivity positively correlates with BP (Maixner et al., 1997; Bragdon et al., 2002; Bruehl et al., 2002).

Our results show that the degree of pain relief achieved by stimulating the rostral PAG correlates with the magnitude of blood pressure changes; the greater the reduction in blood pressure during stimulation, the greater the analgesic effect (Fig. 2A). The fact that absolute BP variables did not correlate with pain scores suggests that it is the *reduction in BP* rather than the absolute blood pressure that is important. These findings could not be deduced from animal experiments,

because they cannot report their feeling of pain. Young and Rinaldi (1997) previously reported elevation of heart rate with intraoperative PVG stimulation ( $32 \pm 12$  beats per minute) as well as elevation of SBP and DBP ( $71 \pm 21$  and  $47 \pm 10$  mmHg, respectively) with stimulation at a threshold generally higher than that used to produce analgesia. As this effect was consistent, it was used to aid electrode localisation in over 120 patients. As their electrode localisation appears similar to ours, it is likely that their high amplitude of stimulation was exciting dorsal PAG in preference to ventral PAG. Their improved results in patients with cardiovascular changes are in agreement with our results, in that if the electrode is in the 'cardiovascular area', it can be used to reduce BP.

Does the reduction in blood pressure itself lead to analgesia; is it another consequence of the change in sympathetic nervous system activity; or is it due to another output of the PAG? Peripheral blood flow is increased in neuropathic pain conditions (Archer et al., 1984) and reduction of cutaneous blood flow is associated with pain relief (Tanaka et al., 2004). Thus reduction in ABP is not itself likely to reduce pain directly, but its effect of reducing local blood flow might. To test this, we compared changes in pain scores to changes in pulse pressure, a validated marker of peripheral vasodilatation (Laskey et al., 1990). Our results show that analgesic effects were only weakly correlated to reductions in pulse pressure (Fig. 1B) i.e. that pain relief was not strongly associated with local vasoconstriction. More importantly, correlation of the rate of change of systolic blood pressure ( $dP/dt$ ), a good index of cardiac contractility, implies that the blood pressure changes were likely to have been centrally mediated (Brinton et al., 1997). The reduction in  $dP/dt$  correlated significantly with the patients' relief of pain (Fig. 1C). Thus the reduction in blood pressure was probably largely cardiac in origin, and possibly mediated by a reduction in central sympathetic drive.

To elucidate the underlying mechanisms of these blood pressure changes further, we analysed blood pressure variability (BPV) by autoregressive power spectral analysis in the patients with increases and in those with decreases in blood pressure. The power of Mayer's wave c. 0.1 Hz on the BPV spectra provides another, albeit crude, index of sympathetic nervous activity (Pagani et al., 1997). We found that there was a significant reduction in power at this frequency in those with reduced blood pressure, and an increase in those with increased blood pressure (Fig. 1D). This again suggests that our patients' blood pressure changes were accompanied by changes in sympathetic nervous system activity. This is consistent with studies which have shown that sympathetic ganglion blockade can often reverse neuropathic pain (Treede et al., 1992).

Using the McGill's Pain Questionnaire, we have also shown that those patients with the greatest magnitude of

blood pressure reduction in the laboratory had the best results from deep brain stimulation in the long-term. This may be because of the long-term blood pressure changes (although these were not measured in this study) or it could be that acute blood pressure changes imply that the electrode is in the optimal position. Our comparison of short-term VAS and long-term MPQ scores suggests that long-term improvements are a reflection of early success, although there is still room for minor parameter adjustments leading to further improvements in some cases.

The 'defence' reaction in the rat is part of an integrated response that aids survival in the wild (Hunsperger, 1956). There are two components to this reaction. Firstly, 'freezing' behaviour that is associated with hypotension, bradycardia, and non-opioid related analgesia and can be induced by ventral PAG stimulation (Abrahams et al., 1960; Duggan and Morton, 1983; Lovick, 1992). Secondly, a 'fight or flight' response that is associated with hypertension, tachycardia and opioid related analgesia and can be induced by dorsal PAG stimulation (Lovick, 1985; Carrive and Bandler, 1991). Thus this basic survival response in animals couples the cardiovascular system to the modulation of pain. Our results provide evidence, for the first time, that similar responses may exist in the human.

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