NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 25 (2005) 1161–1167

Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture

Jérémie Pariente,[a,*] Peter White,[b] Richard S.J. Frackowiak,[a] and George Lewith[b]

[a]Wellcome Department of Imaging Neuroscience, 12 Queen Square, WC1N 3BG London, UK
[b]Complementary Medicine Research Unit, Aldermoor Health Centre, Aldermoor Close, SO16 5ST Southampton, UK

Received 16 August 2004; revised 9 January 2005; accepted 11 January 2005
Available online 2 March 2005

Both specific and non-specific factors may play a role in acupuncture therapy for pain. We explored the cerebral consequences of needling and expectation with real acupuncture, placebo acupuncture and skin-prick, using a single-blind, randomized crossover design with 14 patients suffering from painful osteoarthritis, who were scanned with positron emission tomography (PET). The three interventions, all of which were sub-optimal acupuncture treatment, did not modify the patient's pain. The insula ipsilateral to the site of needling was activated to a greater extent during real acupuncture than during the placebo intervention. Real acupuncture and placebo (with the same expectation of effect as real acupuncture) caused greater activation than skin prick (no expectation of a therapeutic effect) in the right dorsolateral prefrontal cortex, anterior cingulate cortex, and midbrain. These results suggest that real acupuncture has a specific physiological effect and that patients' expectation and belief regarding a potentially beneficial treatment modulate activity in component areas of the reward system.

Keywords: Expectancy; Belief; Acupuncture; PET; Pain

Introduction

Many acupuncture trials demonstrate no efficacy or minimal superiority over placebo/control despite clinical effectiveness. Little is understood about the complexities of the interaction between acupuncture, placebo, patient, and practitioner. This relative ignorance may be responsible for the confusing results of acupuncture trials (Birch et al., 1996) and the lack of clarity emerging from the subsequent systematic reviews (White et al., 2002).

Cho et al., in a neuroimaging study, showed that stimulation of specific acupuncture points on the foot, traditionally used to treat the eye, causes activation of the visual cortical areas in the same way as direct stimulation of the eye by light (Cho et al., 1998). Alimi et al. found that stimulation of an auricular acupuncture point representing the hand causes a cerebral response similar to direct stimulation of the hand, but this effect is not consistent (Alimi et al., 2002). Wu et al. report a differential brain response to acupuncture and penetrating sham acupuncture (Wu et al., 1999a,b). While Cho suggests that both acupuncture and sham acupuncture reduce activation of areas associated with pain perception (Cho et al., 2002). Hsieh noted differential patterns of brain activation with needling at the same site to produce pain and 'deqi' (the specific needling sensation associated with acupuncture) (Hsieh et al., 2001). Hui et al. suggest that subject expectation may influence anterior cingulate activity and this pattern of activation is not modified by previous experience of acupuncture (Hui et al., 2002). However, it may be difficult to generalize about the clinical effects of acupuncture from these studies, as they were carried out in pain-free healthy volunteers.

The placebo (Streitberger) needle (SN) (Streitberger and Kleinhenz, 1998) gives the impression of skin penetration without piercing the skin, it acts like a stage dagger with the needle disappearing into the needle shaft. The belief that real acupuncture (RA) has occurred has been confirmed (Kleinhenz et al., 1999), but we have no understanding of the physiological effect of SN. Non-specific placebo effects include the natural history of illness, the therapeutic relationship, the process and rituals involved in treatment, patient expectation, suggestibility, and conditioning (Araujo, 1998; Peck and Coleman, 1991; Sheppeard and Wigley, 1984). We have defined these effect sizes clinically and suggest that the non-specific effects are 3 or 4 times greater than the specific effects of acupuncture in a randomized, controlled, single blind assessment of acupuncture for chronic mechanical neck pain (White et al. submitted for publication). This is a similar ratio of specific to non-specific effect sizes to that found with pharmacological treatment of depression (Kirsch et al., 2002), reinforcing the impact and importance of belief and expectancy on outcome in chronic benign conditions.

Procedurally, we defined overt placebo (OP) as a skin prick with a blunt needle with patients aware that they were being given an 'inert' intervention. We manipulated belief by using the SN

* Corresponding author. Fax: +44 207 813 1420.
E-mail address: j.pariente@fil.ion.ucl.ac.uk (J. Pariente).
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2005.01.016

which gives the same physical sensation as the blunt needle but in the consistent and reliable expectation of positive therapeutic benefit. We argued that if expectation is of minor therapeutic importance, overt placebo and the Streitberger needles would show similar cerebral effects, especially if both were different to real acupuncture. On the other hand, differential cerebral responses to all three types of stimulation would suggest that both expectation and a specific acupuncture effect may both be important for effective therapy.

Methods

Patients

Patients were recruited from Southampton General Hospital orthopedic department. All patients were diagnosed with 1st metacarpophalangeal (MCP) osteoarthritis (OA) pain. This pain is known to respond to acupuncture (Dickens and Lewith, 1989). Patients abstained from normal analgesia or alcohol for a day prior to scanning and were otherwise without pain. No patient had a history of neurological or psychiatric illness and all gave written informed consent to the study. The study was approved by the National Hospital for Neurology and Neurosurgery and The Institute of Neurology Joint Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee (London, United Kingdom).

Outcomes

We compared brain activation maps based on regional cerebral blood flow (rCBF) distributions obtained by $H2^{15}O$ PET scanning in three conditions: (RA), (SN), and (OP).

We also examined a number of behavioral factors for comparison with the brain scanning results. All clinical outcomes have been used in other studies and are well validated, repeatable, and reliable:

- Pain in the 1st MCP measured on a 0–100 mm visual analogue scale (VAS).
- Holistic Health Questionnaire (HCAMQ) (Finnigan, 1991; Lewith et al., 2002). This single questionnaire has two subscales, one measuring belief in complementary and alternative medicine (CAM) and the other attitudes to holistic health. It can be scored as a single scale, higher scores indicating a more positive attitude towards CAM (score range 14–84).
- Needle Sensation Questionnaire (NSQ) (Park et al., 2002). This consists of 25 descriptive words specifically defining needling sensation during acupuncture and scores 0–75 maximum.
- Credibility Rating (CR). The Borkovec and Nau scale has been used to rate the credibility and expectation of acupuncture placebo controls in a number of studies (White et al., 2003; Vincent, 1990; Vincent and Lewith, 1995). Two questions are asked before treatment (how confident are you that this treatment can alleviate your complaint? how logical does this treatment seem to you?) and two questions after treatment (how confident would you be in recommending this treatment to a friend who suffered the same complaint? how successful do you think this treatment would be in alleviating other complaints?). Each question was measured on a 0–6 Likert scale with 6 being the most credible.

Experimental procedure

Each patient underwent each of the following three interventions in random order during a single PET session. Before the first intervention, an evaluation was performed including a VAS of pain, the HCAMQ, and the first part of the CR. Following each intervention, patients completed a VAS pain score, a NSQ, and the second part of the CR.

Prior to any manipulation, a baseline scan at rest was performed (scan 0 at 0 min). The acupuncture point (Liangyue et al., 1990) situated in the muscle bulk between the 1st and 2nd metacarpals was then found and marked with a plastic O-ring on the skin and held in place with a sticking plaster. This enabled a non-penetrating needle (SN and OP) to be held in place to give consistency across all three interventions.

- Real acupuncture (RA). Sterile, single-use, copper-handled needles were used (25 mm long × 0.25 mm diameter) from Asia-Med Co, Munich (Germany). A needle was inserted through the sticking plaster into the acupuncture point and 'deqi' was obtained in all patients by needle manipulation. After insertion, the needle was left in situ for 4 min and then rotated to further elicit 'deqi'. A second manipulation was carried out 4 min later and the first scan for this condition was acquired (scan 1 at 8 min). The needle was left in place with no further stimulation for the second scan (scan 2, at 16 min) and was then removed just before the two last image acquisitions (scan 3 and scan 4, respectively at 24 and 32 min). The needle was in place for 24 min.
- Streitberger needle (SN). This needle was supplied by Asia-Med Co, Munich (Germany), and resembles a real needle. Its construction is different insomuch as it works in the same way as a 'stage dagger', i.e., as the blunt tip is pushed against the skin the shaft moves into the handle, giving the appearance that it has pierced the skin. Needles are sterile, blister packed, and single use. It is inserted through the plaster and manipulated as with RA. The manipulation and scan sequence were exactly as in RA (scans 5–8).
- Overt placebo (OP). These needles exactly resemble the real needles; however, the tips are blunt. Each needle is single use, sterile, and individually packed. The manipulation and the scan sequence were the same as for RA and SN (scans 9–12).

RA and SN interventions were blinded. In OP, subjects were told that the needle would not pierce the skin and that it did not have therapeutic value but was acting as a baseline. The order of interventions was randomized.

PET procedures and data analysis

Each subject had 13 PET scans in 150 min. Scans were obtained using a SIEMENS/CPS ECAT EXACT HR+ (model 962) PET scanner (Siemens/CTI, Knoxville, TN, USA). Participants received before each scan a 20-s intravenous bolus of $H_2^{15}O$ at a concentration of 55 MBq/ml and at a flow rate of 10 ml/min through a forearm cannula located in the non-painful arm. For each subject, a T_1-weighted structural MRI was obtained with a 1.5-T Sonata scanner (Siemens, Erlangen, Germany).

The data were analyzed blinded to the order of interventions with statistical parametric mapping (SPM) using SPM2 software (Wellcome Department of Imaging Neuroscience, London, UK;

http://www.fil.ion.ucl.ac.uk/spm) (Frackowiak et al., 1997) implemented in Matlab 6.5 (Mathworks Inc. Sherborn, MA, USA) using standardized procedures including realignment, spatial normalization (voxel size = 2 mm^3), smoothing, and analysis of covariance (ANCOVA). The smoothing kernel was a 3D Gaussian filter of 8 mm. The SPM analysis was conducted in two different ways: (1) images were analyzed as they were acquired ("non-flipped images" (NF); (2) after flipping images from the 6 patients who had intervention to the right hand along the anterior–posterior axis following normalization onto a bilaterally symmetrical template ("flipped images" (F)). Condition and subject effects were estimated according to the general linear model at each voxel. To test hypotheses about regionally specific condition effects, these estimates were compared using linear compounds or contrasts. The rexsulting set of voxel values for each contrast was represented as an SPM of the t statistic and then converted to a Z statistic map (SPM_Z).

Behavioral data were correlated with analysis of variance and Chi-squared tests as appropriate.

Results

14 right-handed patients (11 females and 3 males), aged between 48 and 63 (mean age 59.4, SD = 5.7), were recruited. Six patients had first MCP joint osteoarthritis (OA) of the right and 8 of the left thumb. Four subjects had previously been treated with acupuncture, 10 were acupuncture naive.

Behavioral results

Pain

There was no difference in pre vs. post treatment pain for RA, SN, and OP. Subject's pre-existing pain was not altered during this study as a result of the 3 interventions. However, this is not surprising bearing in mind that only one treatment on one occasion was used, therefore we had no expectation of any response, with respect to chronic pain, from this regime (Ezzo et al., 2000).

Table 1
Comparison of behavioral results

		RA	SN		OP	
Credibility scores		–	Q1	Q2	Q1	Q2
comparison,	RA	–	0.20	0.53	<0.05	<0.05
P values (χ^2)	SN	–	–	–	0.07	0.05
Was treatment real?,	RA	–	0.067		<0.05	
score comparison,	SN	–	–		<0.05	
P values (1)						
Needle sensation	Mean (SD)	12.28 (7.44)	5.14 (6.70)		3.57 (5.89)	
scores	95% CI	7.9–16.6	1.3–9.0		0.2–6.9	
Sensations of pain,	RA	–	0.367		0.931	
score comparison	SN	–	–		0.136	
P values (2)						

Scores of credibility, belief, and needle sensation compared across the three interventions (P value given for each comparison). RA: real acupuncture; SN: blind placebo; OP: overt placebo; SD: standard deviation.
(1) The question of was the intervention real?
a. RA 14 = Yes, 0 = No;
b. SN 11 = Yes, 3 = No;
c. OP 3 = Yes, 11 = No
(2) Difference in pain pre to post intervention
a. RA = 1.5mm difference (S.E = 7.9)
b. SN = 9.6mm (S.E = 4.0)
c. OP = 0.714mm (S.E = 4.2)

Credibility

Credibility ratings were compared using χ^2 tests (Table 1). There were no statistical differences between scores for RA and SN. OP was significantly different from RA and SN, though the answers to question 1 only approached significance at $P < 0.07$ for SN.

Skin penetration

All 14 subjects believed that their skin had been penetrated with both RA and SN. One patient believed the skin had been pierced with OP. The analysis with and without data from this patient did not alter the results and these data were therefore included in analyses.

Perception of reality of treatment

The question "Did you think the treatment you just had was real?" elicited similar answers for both RA and SN (Table 1). No one receiving OP believed it had been real treatment.

Needle sensation

The mean scores for needle sensation are shown in Table 1. There were no statistical differences between RA and SN scores ($P > 0.2$). OP did not elicit significantly different sensations from the other two interventions (RA $P > 0.206$, SN $P > 0.3$).

Other potential confounds

An analysis of covariance (ANCOVA) showed that order of treatment, previous experience of acupuncture, and holistic health beliefs had no significant influence on how patients answered questions on the belief that their skin had been pierced and whether the treatment had been real (Table 2).

PET results

A group analysis was carried out including all 14 patients. Images analysis was performed both on flipped (F) and non-flipped (NF) data; the former to examine for lateralized and the later bilateral effects. No differences were found between the four repeat scans collected within each intervention so they were treated as repetitions and averaged. SPM maps were thresholded at $P < 0.001$ uncorrected and a small volume correction (SVC) was applied. The levels of significance and spatial coordinates of activations with literature references justifying our choice of areas interrogated are given in Table 3.

Categorical analysis

RA vs. SN

We found a relative activation with RA in the posterior insula/SII (Flipped −F; −54 −16 4 −peak voxel; $Z = 3.85$ −Z score) and anterior insula (F; −30 24 −4; $Z = 3.95$) ipsilateral to the side of treatment (see Fig. 1a). Non-flipped data showed a trend to bilateral insula activation confirming the highly lateralized nature of the response.

Table 2
Analysis of covariance between behavioral scores

Covariate	Question relating to:	
	Needle penetration	Reality of treatment
HHQ	0.822	0.955
Experience	0.996	0.969
Order	0.699	0.705

Behavioral scores: analysis of covariance (ANCOVA) (P value): needle penetration, belief, holistic health questionnaire (HHQ), previous acupuncture experience, and order of treatment.

RA vs. OP

There were relative activations in the insula (F; −34 8 0; Z = 3.86), the dorsolateral prefrontal cortex (DLPFC, BA 6) (F; 20, 2, 50; Z = 4.21), in the rostral part of the anterior cingulate cortex (rACC) (NF; 12 20 46; Z = 3.72), and in the midbrain (NF; 0 −24 −4; Z = 3.38).

SN vs. OP

We found relative activations in the DLPFC (F; 20 4 58; Z = 4.57), in the rostral ACC (NF; 0 18 36; Z = 4.12), and in the midbrain (NF; 0 −24 −4; Z = 3.52).

A conjunction analysis

A conjunction analysis was performed on (RA vs. OP) and (SN vs. OP), where OP was randomly divided into two independent groups. This conjunction identifies activations common to both interventions. Relative activations in the DLPFC (F; 20 4 58; Z = 4.57), rACC (NF; 0 16 38; Z = 4,07), and in the midbrain (NF; −4 −24 −6; Z = 3.5) were found, but there was no activation in the ipsilateral insula (F and NF) (Fig. 2).

Correlation analysis

We performed a correlation analysis to investigate the relationship between needling sensation and brain activity in all three interventions (P < 0.05, corrected for multiple comparisons). There was a correlation between needle sensation induced by RA and activity in the two thalami in their posterior parts (F; −18 −26 14; Z = 5.1 and F; 16 −30 10; Z = 5.46). Post hoc, we separated 10 pain-related factors (“ache”, “boring”, “burning”, “electric”, “hurting”, “pricking”, “sharp”, “stinging”, “tender”, “throbbing”) from the 25 explored by the Needle Sensation Questionnaire (NSQ). We found a positive correlation between these summed scores and activity in the insula contralateral to the site of

Table 3
Spatial coordinates and levels of significance of the activations

Flipped images							
Contrasts	Structure	Side	Coordinates in Talairach's space			Statistical significance	
	Anatomical structure		x	y	z	Z max	Correction
Categorical analysis							
RA-SN > 0	Posterior insula/SII	L	−54	−16	4	3,85	(1)
RA-OP > 0	Insula	L	−34	8	0	3,86	(2)
	DLPFC	R	20	2	50	4,21	(1)
	ACC	R	10	2	44	4,17	(1)
	Midbrain	R	4	−22	−4	3,63	(1)
SN-OP > 0	DLPFC	R	20	4	58	4,37	(1)
	rACC	R	10	12	44	3,34	(1)
	Midbrain	R	4	−22	−4	3,92	(1)
Conjunction analysis							
RA-OP > 0 and SN-OP > 0	DLPFC	R	20	4	58	4,57	(1)
	rACC	R	2	16	38	4,11	(1)
	Midbrain	R	4	−24	−4	4,17	(1)
Correlations analysis							
RA and Needle Sensation	Thalamus	R	16	−30	10	5,46	(1)
	Thalamus	L	−18	−26	14	5,1	(1)
RA and the 10 pain-related needle sensations	Orbitofrontal cortex	R	16	32	−28	5,83	(1)
	Anterior insula	R	34	20	8	5,41	(1)
SN and needle sensation	Orbitofrontal cortex	R	22	36	−10	5,02	(1)
OP and needle sensation	Orbitofrontal cortex	R	6	32	−26	4,64	(1)

Non flipped images							
Contrasts	Structure	Side	Coordinates in Talairach's space			Statistical significance	
	Anatomical structure		x	y	z	Z max	Correction
Categorical analysis							
RA-OP > 0	ACC	R	12	20	46	3,72	(1)
	Midbrain	L	0	−24	−4	3,38	(1)
SN-OP > 0	ACC		0	18	36	4,12	(1)
	Midbrain	L	0	−24	−4	3,52	(1)
Conjunction analysis							
RA-OP > 0 and SN-OP > 0	ACC	R	0	16	38	4,07	(1)
	Midbrain	L	−2	−24	−6	3,5	(1)

(1) P < 0.05, corrected for multiple comparison at the cluster level; (2) ns: non-significant; RA: real acupuncture; SN: blind placebo; OP: overt placebo.

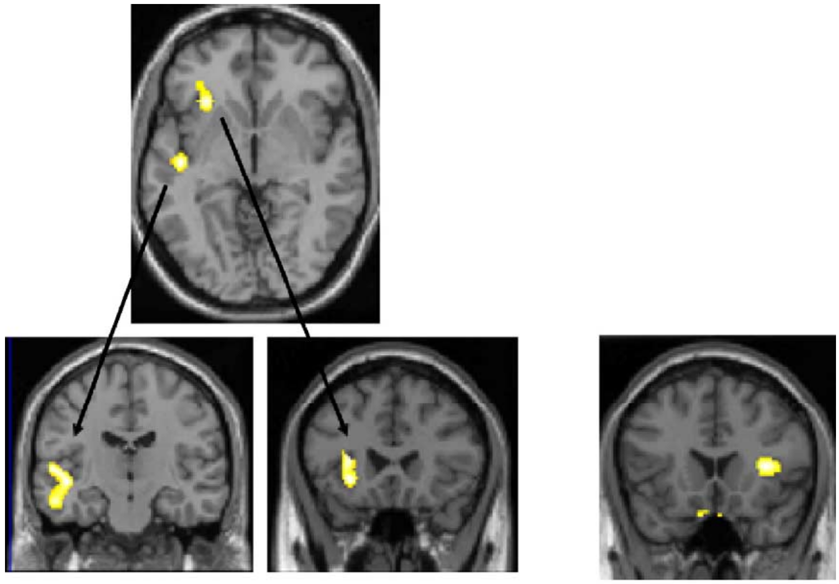

Fig. 1. Ipsilateral and controlateral insulae. (a) RA vs. SN comparison. Activation maps (flipped images) are overlaid on a structural image. Left part of the brain is on the left side of the image. Relative hyperactivation of the posterior insula/SII ipsilateral to the acupuncture intervention (RA) is shown (SPM maps thresholded at $P < 0.01$ uncorrected for illustration; see Table 3 for details). (b) Correlation analysis between the 10 most pain-related needle sensation felt during real acupuncture (RA) and the regional cerebral blood flows (rCBF) (flipped images) are overlaid on structural images. Left part of the brain is on the left side of the image. Pain-related sensation during needling is correlated to the rCBF in the insula contralateral to the intervention (SMP maps thresholded at $P < 0.05$, corrected for multiple comparison; see Table 3 for details).

intervention (F; 34 20 8; $Z = 5.41$) (Fig. 1b) and in the left orbitofrontal cortex (OFC) (F; 16 32 −28; $Z = 5.83$). No correlations were found with activity in the ipsilateral insula.

Discussion

We investigated the effect of three acupuncture-related interventions: RA, SN, and OP. RA elicited a specific relative activation of the ipsilateral insula to needling that was not correlated with the sensation of being needled. When patients expected a "real treatment" (RA and SN), activations were found in the DLPFC, in the rACC, and in the midbrain. These areas have together been linked to pain modulation (Rainville et al., 1999; Wager et al., 2004) and reward expectation (Schultz, 2002). Patients were in pain throughout the study and pain was not significantly modified by any of the three interventions.

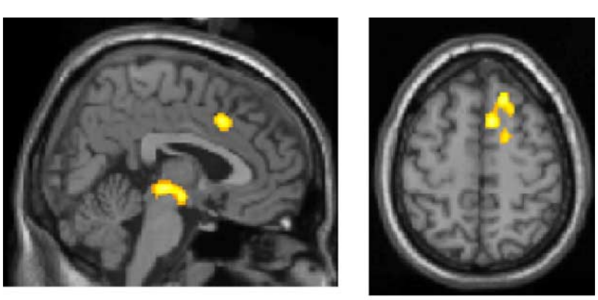

Fig. 2. Conjunction analysis between RA and SN vs. OP. Activation maps in the context of expectation of receiving a real treatment are overlaid on a structural image. Analysis was carried out on flipped images for picture (a) and on non-flipped images for picture (b). Left part of the brain is on the left side of the image. SPM maps thresholded at $P < 0.01$ uncorrected for illustration. See Table 3 for details. (a) Rostral part of the anterior cingulate cortex and midbrain periaqueductal grey (PAG) region; (b) dorsolateral prefrontal cortex activation; RA: real acupuncture; SN: blind placebo; OP: overt placebo.

The specific effect of acupuncture

As RA and SN were perceived as equally credible, the observed differences between them constitute a specific physiological effect of acupuncture. Ipsilateral activation of the insula has been reported in previous acupuncture studies (Hsieh et al., 2001; Zhang et al., 2003). This difference cannot be explained by a difference in needle sensation as RA and SN needling were perceived as identical. It is also possible that the difference between the SN and the RA condition represents the difference between combined stimulation of the extero- end enteroceptive systems as compared to sole exteroceptive activation (Craig, 2003). However, ipsilateral activation of SII/insular cortices has previously been described after electrical nerve stimulation in patients recovering from stroke regardless of the responsiveness of the contralateral SI/SII (Forss et al., 1999) and acute and chronic pain activate the SII/insular cortex (Peyron et al., 2000). This finding confirms that processing of somato-sensory information can occur in both ipsilateral and contralateral SII/insulae. Acupuncture may be modulating activity in the ipsilateral insula either through a crossed spino-thalamo-cortico-limbic pathway through the corpus callosum (Price, 2000) or through a direct uncrossed spino-thalamo-limbic pathway (spino-parabrachio-thalamo-insular pathway) (Craig, 2003; Nishijo et al., 1997; Wu et al., 1999a,b). This ipsilateral, uncrossed, visceroceptive autonomic pathway seems crucial for acupuncture as lesions of the parabrachial nucleus reduce the effects of acupuncture in rats (Wang et al., 1991).

The non-specific effects of acupuncture

We provide behavioral and physiological data that validate SN as a placebo control for acupuncture in clinical trials involving treatment of chronic pain. Needling sensation is believed by acupuncturists to be therapeutically important. All three interventions created needling sensation, an observation that has not previously been reported in OP conditions. Needling sensation scores for SN were intermediate between the other two interventions, but closer to OP, supporting the suggestion that RA elicits a different physiological response than either of the control conditions. SN is as believable to our subjects as RA in terms of potential pain relief. Patients were convinced that the SN needle penetrated their skin, regardless of order of treatment and previous experience of acupuncture. The only difference between SN and OP was activation in DLPFC, rACC, and midbrain suggests a possible mechanism for the placebo response to acupuncture. Moreover, DLPFC, rACC, and the midbrain were activated concomitantly by the two credible, potentially pain relieving interventions (RA and SN).

Current available evidence suggests the DLPFC is involved in the cognitive regulation of pain. Lorenz et al. proposed that the DLPFC exerts an active control on pain perception by modulating cortico-cortical and cortico-subcortical pathways (Lorenz et al., 2003). Peyron et al. have shown that one of the DLPFC role–involved in a more general attentional network–is to direct attention away from pain (Peyron et al., 2000). It is also possible that DLPFC generates and maintains the expectation of pain relief specifically in the context of placebo-induced analgesia in which specific expectation may trigger the midbrain opioid system through a top-down effect (Wager et al., 2004).

The ACC is known to have two functionally distinct components: the most caudal part is involved in pain perception and its unpleasant nature (Rainville et al., 1999; Vogt et al., 1996) whereas the rostral ACC (rACC) is important for conditions modulating pain experience (Petrovic et al., 2002a) or contextual modulation of experience of pain (Price, 2000). Activation of the rACC has been described during expectation of pain (Hutchison et al., 1999), modulation of pain processing (Petrovic and Ingvar, 2002), or when empathizing with another's pain (Singer et al., 2004). The rACC is also known to be involved in primary reward or in the context of expectation of a reward (Fuente-Fernandez and Stoessl, 2002; Kaasinen et al., 2004; O'Doherty et al., 2002a). The reward expectation process involving the rACC is reported to be mediated by dopaminergic nigro-striatal system (Fuente-Fernandez et al., 2001; O'Doherty et al., 2002a; Schultz, 2002). On the other hand, Petrovic et al. have shown the rACC plays a key role both in placebo-induced analgesia and in opioid analgesia. The activity the rACC is correlated with activity in the brain stem opioid system—periaqueductal grey matter (PAG) in both of these analgesic processes (Petrovic et al., 2002a). The involvement of the brainstem opioid system in the placebo effect has been confirmed by another placebo analgesia study showing PAG increased activity (Wager et al., 2004). The activation of the opioid system during placebo analgesia is reversed after naloxone (Benedetti et al., 1999; Levine et al., 1978). These studies strongly suggest a related neural mechanism in opioid and placebo analgesia. In the present study, patients were expecting a pain relief during both RA and SN conditions. This is linked to the expectation of a particular reward for patients suffering from a chronic painful condition and thus adds substantially to our understanding of acupuncture treatment, particularly as most previous imaging studies have involved healthy volunteers. We found the rACC to be activated by the two interventions believed capable of improving patients' symptoms, but not by the OP condition. Concomitantly, we report activation in the midbrain in the same two conditions. We therefore suggest that the rACC activation found in RA and SN is linked to the expectation of therapeutic benefit and exerts a top-down effect on the midbrain which is at the same site of activation (PAG) reported by Petrovic et al. (2002a). Though there is a clear role for the dopaminergic system in appetitive expectation and reward, the collocation of these activations suggests that, in the context of pain, the (DLPFC and) rACC may interact not only with dopaminergic nigrostriatal neurons, but also with opioid PAG-located neurons, the latter in the expectation of pain relief rather than non-specific reward. We speculate that the first step of the pain relief/expectation phenomenon takes place in DLPFC which in turn acts on the midbrain as does the rACC.

We have shown that acupuncture does have a demonstrable physiological effect over and above simple skin prick which might go some way to explaining its mode of action, possibly through the visceroceptive pathway. SN does not elicit the same activation and is therefore fundamentally different from real acupuncture. It is therefore reasonable to suggest that SN may be an effective acupuncture placebo. We have also demonstrated that expectation of and belief in treatment have a physiological effect on the brain that appears to mediate a potentially powerful non-specific clinical response to acupuncture.

Acknowledgments

We would like to thank Peter Belward from the Physiotherapy Department and Mrs. D. Warwick and D. Hargreaves from the Orthopaedic and Trauma Department at Southampton General Hospital for their help with recruitment. Dr. Lewith's post is funded by a grant from the Maurice Laing Foundation. Dr. White is a Department of Health CAM post-doctoral research fellow. RSJF is funded by a Wellcome Trust program grant and JP by the French Foreign Office (Bourse Lavoisier).

References

Alimi, G., Geissmann, A., Gardeur, D., 2002. Auricular acupuncture stimulation measured on fMRI. Med. Acupunct. 13, 18–21.

Araujo, M., 1998. Does the choice of placebo determine the results of clinical studies on acupuncture. Res. Complement. Med. 5, 8–11.

Benedetti, F., Arduino, C., Amanzio, M., 1999. Somatotopic activation of opioid systems by target-directed expectations of analgesia. J. Neurosci. 19, 3639–3648.

Birch, S., Hammerschlag, R., Berman, B.M., 1996. Acupuncture in the treatment of pain. J. Altern. Complement. Med. 2, 101–124.

Cho, Z., Chung, S., Jones, J., Park, J., Park, H., Lee, H., Wong, E., Min, B., 1998. New findings of the correlation between acupoints and corresponding brain cortices using functional MRI. Proc. Natl. Acad. Sci. 95, 2670–2673.

Cho, Z., Oleson, T., Alimi, D., Niemtzow, R., 2002. Acupuncture: the search for biologic evidence with fMRI and PET techniques. J. Altern. Complement. Med. 8, 399–401.

Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13, 500–505.

Dickens, W., Lewith, G., 1989. Single-blind, controlled and randomised clinical trial to evaluate the effect of acupuncture in the treatment of trapezio-metacarpal osteoarthritis. Comp. Med. Res. 3, 5–8.

Ezzo, J., Berman, B.M., Hadhazy, V., Jadad, A., Lao, L., Singh, B.B., 2000. Is acupuncture effective for the treatment of chronic pain? A systematic review. Pain 86, 217–225.

Finnigan, M., 1991. Complementary medicine: attitudes and expectations, a scale for evaluation. Comp. Med. Res. 5, 79–82.

Forss, N., Hietanen, M., Salonen, O., Hari, R., 1999. Modified activation of somatosensory cortical network in patients with right-hemisphere stroke. Brain 122 (Pt. 10), 1889–1899.

Frackowiak, R.S.J., Friston, K.J., Frith, C.D., Dolan, R.J., Mazziotta, J.C., 1997. Human Brain Function. Academic Press, San Diego.

Fuente-Fernandez, R., Stoessl, A.J., 2002. The placebo effect in Parkinson's disease. Trends Neurosci. 25, 302–306.

Fuente-Fernandez, R., Ruth, T.J., Sossi, V., Schulzer, M., Calne, D.B., Stoessl, A.J., 2001. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 293, 1164–1166.

Hsieh, J., Tu, C., Chen, F., Chen, M., Yeh, T., Cheng, H., Wu, Y., Liu, R., Ho, L., 2001. Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study. Neurosci. Lett. 307, 105–108.

Hui, K., Lui, J., Makris, N., Chan, S., Napadow, V., Kong, J., Kwong, K., 2002. Acupuncture modulatory effects by whole brain MRI: response distinct from pain. Boston International Scientific Conference on Complementary, Alternative and Integrative Medicine Research (4-12-2002).

Hutchison, W.D., Davis, K.D., Lozano, A.M., Tasker, R.R., Dostrovsky, J.O., 1999. Pain-related neurons in the human cingulate cortex. Nat. Neurosci. 2, 403–405.

Kaasinen, V., Aalto, S., Nagren, K., Rinne, J.O., 2004. Expectation of caffeine induces dopaminergic responses in humans. Eur. J. Neurosci. 19, 2352–2356.

Kirsch, I., Moore, T.J., Scoboria, A., Nicholls, S.S., 2002. The emperor's new drugs: an analysis of antidepressant medication data submitted to the FDA. In Prevention and Treatment; available online at http://www.journalsapa.org/prevention/volume5/pre0050023a.html.

Kleinhenz, J., Streitberger, K., Windeler, J., Gussbacher, A., Mavridis, G., Martin, E., 1999. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. Pain 83, 235–241.

Kleinhenz, J., Streitberger, K., Windeler, J., Gussbacher, A., Mavridis, G., Martin, E., 1999. Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. Pain 83, 235–241.

Levine, J.D., Gordon, N.C., Fields, H.L., 1978. The mechanism of placebo analgesia. Lancet 2, 654–657.

Lewith, G., Hyland, M., Shaw, S., 2002. Do attitudes and beliefs about complementary medicine affect treatment outcome? American Journal of Public Health 92, 1604–1606.

Liangyue, D., Yijun, G., Shuhui, H., Xiaoping, J., Yang, L., Rufen, W., Wenjing, W., Xuetai, W., Hengze, X., Xiuling, X., Xinnong, Y. (Eds.), 1990. Chinese Acupuncture and Moxibustion. Foreign Languages Press, Beijing.

Lorenz, J., Minoshima, S., Casey, K.L., 2003. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 126, 1079–1091.

Nishijo, K., Mori, H., Yosikawa, K., Yazawa, K., 1997. Decreased heart rate by acupuncture stimulation in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerve. Neurosci. Lett. 227, 165–168.

O'Doherty, J.P., Deichmann, R., Critchley, H.D., Dolan, R.J., 2002. Neural responses during anticipation of a primary taste reward. Neuron 33, 815–826.

Park, H., Park, J., Lee, H., Lee, H., 2002. Does deqi (needle sensation) exist? Am. J. Chin. Med. 30, 45–50.

Peck, C., Coleman, G., 1991. Implications of placebo theory for clinical research and practice in pain management. Theor. Med. 12, 247–270.

Petrovic, P., Ingvar, M., 2002. Imaging cognitive modulation of pain processing. Pain 95, 1–5.

Petrovic, P., Kalso, E., Petersson, K.M., Ingvar, M., 2002. Placebo and opioid analgesia—imaging a shared neuronal network. Science 295, 1737–1740.

Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis (2000). Neurophysiol. Clin. 30, 263–288.

Price, D.D., 2000. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–1772.

Rainville, P., Hofbauer, R.K., Paus, T., Duncan, G.H., Bushnell, M.C., Price, D.D., 1999. Cerebral mechanisms of hypnotic induction and suggestion. J. Cogn. Neurosci. 11, 110–125.

Schultz, W., 2002. Getting formal with dopamine and reward. Neuron 36, 241–263.

Sheppeard, H., Wigley, R.D., 1984. Acupuncture an effective placebo? [letter]. N.Z. Med. J. 97, 499.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Streitberger, K., Kleinhenz, J., 1998. Introducing a placebo needle into acupuncture research. Lancet 352, 364–365.

Vincent, C., 1990. Credibility assessment in trials of acupuncture. Comp. Med. Res. 4, 8–11.

Vincent, C., Lewith, G., 1995. Placebo controls for acupuncture studies. J. R. Soc. Med. 88, 199–202.

Vogt, B.A., Derbyshire, S., Jones, A.K., 1996. Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. Eur. J. Neurosci. 8, 1461–1473.

Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303, 1162–1167.

Wang, Q., Mao, L.M, Han, J.S., 1991. The role of parabrachial nucleus in high frequency elecroacupuncture analgesia in rats. Chin. J. Physiol. Sci. 7, 363–367.

White, P., Lewith, G., Berman, B.M., Birch, S., 2002. Reviews of acupuncture for chronic neck pain—pitfalls in conducting systematic reviews. Rheumatology (Oxford) 41, 1224–1231.

White, P., Lewith, G., Hopwood, V., Prescott, P., 2003. The placebo needle, is it a valid and convincing placebo for use in acupuncture trials. A randomised, single blind, cross-over trial. Pain 106, 401–409.

Wu, M., Hsieh, J., Xiong, J., Yang, C., Pan, H., Chen, Y., Tsai, G., Rosen, B., Kwong, K., 1999. Central nervous pathway for acupuncture stimulation: localisation of processing with fMRI of the brain—Preliminary experience. Radiology 212, 133–141.

Wu, M.T., Hsieh, J.C., Xiong, J., Yang, C.F., Pan, H.B., Chen, Y.C., Tsai, G., Rosen, B.R., Kwong, K.K., 1999. Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain—preliminary experience. Radiology 212, 133–141.

Zhang, W.T., Jin, Z., Cui, G.H., Zhang, K.L., Zhang, L., Zeng, Y.W., Luo, F., Chen, A.C., Han, J.S., 2003. Relations between brain network activation and analgesic effect induced by low vs. high frequency electrical acupoint stimulation in different subjects: a functional magnetic resonance imaging study. Brain Res. 982, 168–178.