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Fibromyalgia pain and its modulation by hypnotic and non-hypnotic suggestion: An fMRI analysis

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ABSTRACT

The neuropsychological status of pain conditions such as fibromyalgia, commonly categorized as 'psychosomatic' or 'functional' disorders, remains controversial. Activation of brain structures dependent upon subjective alterations of fibromyalgia pain experience could provide an insight into the underlying neuropsychological processes. Suggestion following a hypnotic induction can readily modulate the subjective experience of pain. It is unclear whether suggestion without hypnosis is equally effective. To explore these and related questions, suggestions following a hypnotic induction and the same suggestions without a hypnotic induction were used during functional magnetic resonance imaging to increase and decrease the subjective experience of fibromyalgia pain. Suggestion in both conditions resulted in significant changes in reported pain experience, although patients claimed significantly more control over their pain and reported greater pain reduction when hypnotised. Activation of the midbrain, cerebellum, thalamus, and midcingulate, primary and secondary sensory, inferior parietal, insula and prefrontal cortices correlated with reported changes in pain with hypnotic and non-hypnotic suggestion. These activations were of greater magnitude, however, when suggestions followed a hypnotic induction in the cerebellum, anterior midcingulate cortex, anterior and posterior insula and the inferior parietal cortex. Our results thus provide evidence for the greater efficacy of suggestion following a hypnotic induction. They also indicate direct involvement of a network of areas widely associated with the pain 'neuromatrix' in fibromyalgia pain experience. These findings extend beyond the general proposal of a neural network for pain by providing direct evidence that regions involved in pain experience are actively involved in the generation of fibromyalgia pain.

1. Introduction

A network of cortical regions, including the anterior cingulate cortex (ACC), insula, prefrontal regions and primary (S1) and secondary (S2) somatosensory cortices, mediates pain experience (Apkarian et al., 2005; Derbyshire, 1999, 2000, 2003; Treede et al., 1999). Abnormal activation within this pain network may cause or partially generate functional pain disorders including fibromyalgia (Gracely et al., 2002).

Fibromyalgia is a functional somatic syndrome, one of a cluster of disorders sharing common characteristics and possible etiological background without known physical disease (Wessely et al., 1999; Barsky and Borus, 1999; Brown, 2004). The persistence and intractability of the functional disorders, in the apparent absence of peripheral disease, has led to an increasing interest in the possibility of a central etiology and the use of functional imaging to test central hypotheses (Gracely et al., 2002, 2004; Cook et al., 2004; Derbyshire et al., 1994, 2002; Naliboff et al., 2001). Pain research has provided a model of fibromyalgia, for example, based on early activation, or greater activation, of central regions responsible for pain experience (Gracely et al., 2002, 2004; Croft, 2000).

Functional imaging of pain in patients, however, has been dominated by the study of responses to noxious experimental stimuli rather than the patients' own pain (Henningsen, 2003). The use of experimental noxious stimuli to probe the neural generators of functional disorder confounds any explanation of the disorder based on the possibility of direct central generation (Apkarian et al., 2005). Modulation of pain experience with suggestion avoids this confound. Furthermore, hypnotic suggestion induces highly responsive individuals to alter their sensory experience in an expeditious, impromptu fashion, without elaborate technical preparation, ideal for use with functional imaging. Patterns of neural activation during hypnotic modulation of experimental (Rainville et al., 1997) and clinical pain (Willoch et al.,

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2000) are very similar to the patterns observed during direct physical manipulation.

Previously, we used hypnosis to reveal the cerebral mechanisms of suggested pain in normal volunteers (Derbyshire et al., 2004). A perceptual experience of pain was achieved with a hypnotic induction followed by the suggestion of painful heat, but without actual heat delivery. Functional magnetic resonance imaging (fMRI) measured cerebral cortical activity related to the pain experience and revealed activation consistent with the self-report of pain. A further study independently replicated our findings (Raij et al., 2005). For the current study we extend our hypnotic technique to examine brain activation dependent on direct and immediate changes in fibromyalgia pain experience.

Suggestions for pain control following a hypnotic induction procedure are highly effective (Montgomery et al., 2000; Hawkins, 2001; Patterson and Jensen, 2003) but the delivery of a formal hypnotic induction may have less impact on responsiveness to suggestion than previously thought (Kirsch and Braffman, 2001; Gandhi and Oakley, 2005; Milling et al., 2005). Pain relief following suggestion, therefore, might be similar regardless of any formal hypnotic procedures, questioning the role of the hypnotic induction in increasing responsiveness to suggestions. Here we directly address this issue by comparing suggestions of pain relief and augmentation with and without hypnosis.

2. Methods

2.1. Subjects and screening

Letters were sent out to 397 patients included on the University of Pittsburgh Rheumatology Registry with a primary diagnosis of fibromyalgia. Ninety-two patients responded and 46 patients (four male) took part in the initial screening stage of the study. Average age of the screened patients was 52.4 (range 21–74). All patients gave informed consent and the study was approved by the University of Pittsburgh Institutional Review Board.

2.2. Hypnosis

The 46 patients were prescreened on the Harvard Group Scale of Hypnotic Susceptibility: Form A (Shor and Orne, 1962). High scorers (>8 out of a total possible score of 12) were further screened for the ability to experience significant hypnotic analgesia. During the second screening session patients were shown a diagram of a dial (see Fig. 1), labeled from 0 (no pain at all) to 10 (as bad as my pain gets). Patients were informed that the dial was to represent their level of fibromyalgia pain at any particular moment during the experiment. The dial image was employed to rapidly alter and anchor fibromyalgia pain at a high, medium or low level according to verbal suggestions delivered to each patient during hypnosis.

The patients were informed that hypnotic suggestions would be given to allow the dial to move up and down, producing a concomitant change in their fibromyalgia pain sensation. They were then hypnotised individually using an induction described in detail elsewhere (Whalley and Oakley, 2003). Following the hypnotic induction, patients were asked to bring the dial to mind and to notify the experimenter of its current position. Suggestions were given for the dial and the corresponding fibromyalgia pain sensation to be turned up as high as the patient could allow it to go, dial ratings were then recorded. Suggestions were then given to turn the dial down as low as possible and dial ratings were again recorded. The order of these suggestions was counterbalanced across patients. This procedure was repeated in order to give patients practice with these suggestions before the hypnosis was terminated and the patients debriefed.

Patients who reported that they spontaneously used distractive/dissociative techniques of pain control (e.g. finding themselves on a pleasant beach and unaware of the pain), rather than the dial imagery provided, were excluded. Patients who reported dial changes of 6 points or more (from maximum to minimum) in their fibromyalgia pain experience, without the use of distraction or dissociation, were selected for scanning.

Thirteen patients were selected for the scanning phase of the study, all were female. The average age of this group was 51.4 (range 21–63). Mean Harvard score was 9.7 (SD 0.92). Seven of the 13 participants also reported suffering from irritable bowel syndrome. Six of the patients were currently taking medications including antidepressants, benzodiazepines and opiates, three had been off all medication for a period of at least 7 days prior to the scan and four were not currently prescribed any medication at the time of study (Table 1). These patients completed the hospital anxiety and depression (HAD) scale (Zigmond and Snaith, 1983), a short self-report screening tool that was developed to indicate anxiety and depressive states in patients with physical illness (Herrmann, 1997).

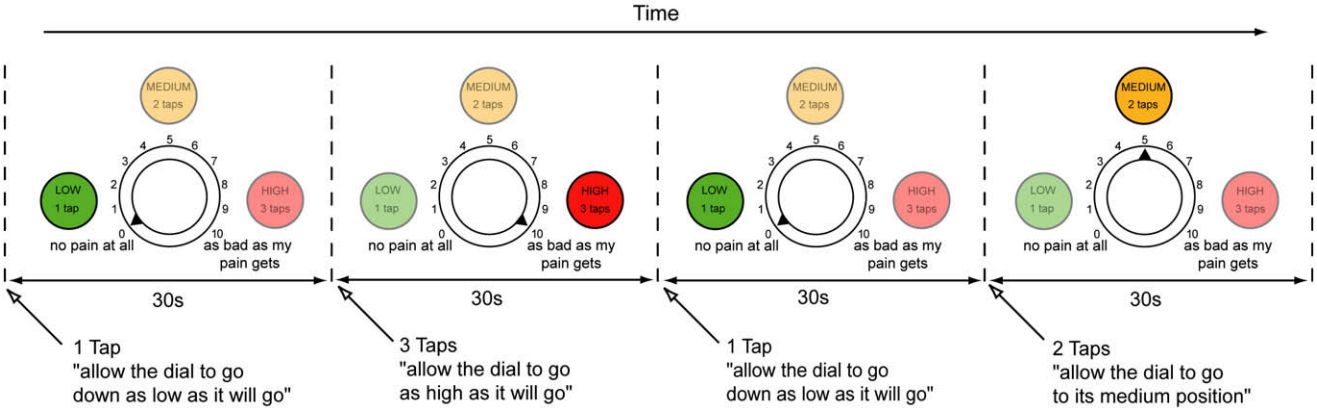

Fig. 1. Illustrates the fMRI procedures. Each patient was asked to view, in their mind's eye, a dial representing their own pain. They were told that their current experience of fibromyalgia pain was yoked to the reading on the dial and that as a consequence changes in the dial setting would be accompanied by corresponding changes in their pain experience. They were asked to move the dial as close to zero as possible following one tap to the foot, as close to five as possible following two taps, and as close to ten as possible following three taps. Each tapping signal began a 30 s scanning period during which the patients controlled their pain using the dial and moved their pain as instructed. The four conditions shown above were presented twice in each fMRI block to yield 4 min of data (2 min of low pain, 1 min of high pain and 1 min of medium pain). Two blocks of data were collected in the hypnosis condition and two in the no-hypnosis condition to yield four blocks of data for each patient.

Table 1
Shows the medication use for each patient

Patient	Antidepressant	Benzodiazepine	Opiate
1	Sertraline[b] 25 mg once daily Desipramine 100 mg once daily	Diazepam 5–15 mg daily, as needed	None
2	Nortriptyline 25 mg three times daily	Clonazepam 1 mg once daily	Fentanyl patch[a]
3	Venlafaxine 75 mg three times daily	None	None
4	None	None	None
5	None	None	None
6	None	None	None
7	Paroxetine 40 mg once daily	None	None
8	Venlafaxine[a] 75 mg twice daily Paroxetine[a] 40 mg once daily Trazadone[a] 100 mg once daily	None	None
10	Fluoxetine[a] 40 mg once daily	Lorazepam 4 mg once daily	Methadone[b]
11	Trazadone 50 mg once daily	None	None
12	None	None	None
13	Venlafaxine 75 mg twice daily	None	None

[a] Drug not taken during the 7 days before the study.
[b] Drug not taken during the 14 days before the study.

2.3. Imaging procedure

Brain activation was inferred based on measurement of the blood oxygen level dependent (BOLD) contrast (Ogawa et al., 1990). These measurements were acquired at 3 Tesla using a reverse spiral technique (TE = 25 ms, TR = 1.5 s, flip angle = 60°, 64 × 64 matrix) described in detail elsewhere (Noll et al., 1995; Stenger et al., 2000). Briefly, the single-shot reverse spiral imaging protocol, designed for the LX MRI system, allows for the acquisition of 24 3.2 mm thick 64 × 64 slices with a 20 cm field of view in a TR of 1.5 s. This protocol provides nearly full brain coverage with isotropic voxel dimensions (3.2 mm on a side) in a time rapid enough to produce well defined hemodynamic time courses. The reverse spiral technique and gradient compensation methods for spirals were designed to reduce susceptibility artifacts that can occur in brain regions adjacent to air cavities, such as the orbitofrontal cortex and perigenual cingulate cortex which are next to the frontal sinus.

Seven patients were hypnotised upon entering the fMRI scanner using the same induction as during screening (hypnosis condition). After the collection of two blocks of fMRI data hypnosis was terminated and two further blocks of data were collected (no-hypnosis condition). One hundred and sixty volumes were collected in each of these four blocks. For the remaining six patients the procedure was the same except that the order of the two conditions was reversed. As in the screening procedure, patients were told to visualize the dial labeled from 0 to 10 representing their current level of fibromyalgia pain. For the purposes of fMRI data collection, verbal suggestion was replaced by non-verbal signals in the form of a simple sequence of taps to the patient's left foot. One tap conveyed the suggestion that the patient should use the dial to reduce their fibromyalgia pain experience, getting as close to zero as possible. Two taps indicated that the patient was to experience their fibromyalgia pain in the middle range of the dial, as close to 5 as possible. Three taps indicated that the patient was to increase their fibromyalgia pain experience to as close to 10 on the dial as possible. fMRI data were collected in two blocks of 4 min each in both conditions (hypnosis and no-hypnosis) to derive 4 min of low pain, 2 min of medium pain and 2 min of high pain in each condition. The fMRI procedures are illustrated in Fig. 1.

After each block the participant gave verbal ratings of pain intensity for the previously experienced low, medium and high pain trials and a measure of how hypnotised they felt on a 0–10 scale of hypnotic depth, where 0 = not at all hypnotised and 10 = as hypnotised as possible (Oakley et al., 2007). At the end of the MR session, subjects were debriefed and asked to rate how much control they felt they had over their pain in the hypnosis and no-hypnosis conditions using a 0–10 scale (0 = no control, 10 = maximum control).

2.4. Data analysis

Data analysis was performed using the FMRIB Software Library (FSL release 4.1 – Oxford Centre for Functional Magnetic Resonance Imaging of the Brain), described in detail elsewhere (Smith et al., 2004). In summary, head movement between scans was corrected by aligning all subsequent scans with the first. Each re-aligned set of scans from every subject was coregistered with his or her own hi-res structural MRI image, with the non-brain components edited out, and reoriented into the standardized anatomical space of the average brain provided by the Montreal Neurological Institute (MNI). To increase the signal to noise ratio and accommodate variability in functional anatomy, each image was smoothed in X, Y and Z dimensions with a Gaussian filter of 8 mm (FWHM).

A box-car model with a hemodynamic delay function, weighted according to the level of pain reported, was fitted to each voxel, generating a statistical image corresponding to the hypothesized changes in pain experience. Baseline drifts were removed by applying a high-pass filter. Brain regions with a large statistic correspond to structures whose BOLD response shares a substantial amount of variance with the hypnotically induced changes in the patients own experience of fibromyalgia pain. The multiple comparisons problem of simultaneously assessing all the voxel statistics was addressed via cluster based thresholding. Clusters of voxels that exceeded a Z score > 2.3 and $P < 0.05$ (corrected for multiple comparisons) were considered statistically significant. Differences between hypnotic and non-hypnotic suggestion were assessed using a within-participants t-test to compare the suggestibility conditions.

The analysis was performed in two complete passes. The first pass included an independent components analysis (ICA) that provides images of BOLD change conforming to structure within the data that is not predicted *a priori*. Some structure is expected to derive from the design of the experiment, and is hypothesized, but other sources of structure can be due to unknown patient effects and to noise. The ICA results were examined for each subject and components that were obviously noise (such as patient motion, physiological or machine noise) were rejected. The original data was then filtered to remove the components identified as being a result of noise and the analysis repeated using the filtered data. In total, 269 components were identified as noise when the patients were hypnotised and 238 when the patients were not hypnotised. This difference was not significant.

Final analysis was performed using a fixed effects approach that only includes the variability within subjects and thus provides results that are more sensitive to small changes within this group but with interpretation restricted to the group under study. Studies of functional pain necessarily involve patients with a heterogeneous disorder characterized by a wide range of non-specific symptoms and often receiving a wide variety of medications. The current study also involved a highly select group of patients who responded to hypnotic suggestion with changes in their experience of pain. Variability in the patient sample, and the restrictive criteria for recruitment, are good reasons for considering our findings a

proof of principle that should not be generalized beyond the group studied until further research confirms and extends our findings.

Region of interest (ROI) analysis was also performed for the midbrain, thalamus, cerebellum, cingulate cortex, insula, S1, S2, inferior parietal cortex and frontal cortex as the main regions of the pain neuromatrix described in previous meta-analyses (Apkarian et al., 2005; Derbyshire, 1999, 2000, 2003). ROIs were drawn using MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html) and were then used as masks in FSL running FEATquery to extract the mean percentage change in BOLD signal for each ROI when patients were in the hypnosis or the no-hypnosis condition.

2.5. Drug effects

To assess the influence of centrally acting drugs on the profile of brain activation, the seven medication free subjects (those currently not taking their medication and those currently not prescribed medication) were analyzed separately and compared to the patients currently taking medication. To formally assess the overlap in activation from these two subgroups, a conjunction analysis, described in detail elsewhere (Friston et al., 1999, 2005; Nichols et al., 2005), was implemented manually. A conjunction determines whether both group slopes of BOLD response against pain are significantly different from zero. This is in contrast to whether the average intergroup slope is different from zero, which could be driven by one group alone. A conjunction is the minimum of two statistic images or, equivalently, conjunction regions are the intersection of suprathreshold regions across two statistic images. A voxel only appears as significant in the conjunction if both groups have significant activation and is, therefore, a measure of significant shared responses in two groups. The conjunction image, however, is a binary map thresholded at the intensity level and does not include cluster based thresholding.

3. Results

3.1. Behavioural ratings

Depression ratings averaged slightly above normal (mean depression rating = 7.7 (SD = 4.6), range 1–13) as did ratings of anxiety (mean anxiety rating = 9.5 (4.1), 2–15). On average, moderate fibromyalgia pain was reported by the patients upon arrival for the study (0 – no pain; 10 – maximal pain) but the range of pain was broad (mean pain rating = 4.1 (SD = 3.1), range 0–9).

When the patients were hypnotised (hypnosis condition), average pain ratings (0 – no pain; 10 – maximal pain) following low, normal and high conditions were 1.3 (SD = 0.8), 5.3 (0.6) and 8.9 (1.1), respectively. When the patients were not hypnotised (no-hypnosis condition) the respective ratings were 2.3 (1.8), 5.7 (1.0) and 8.5 (1.7). A repeated measures ANOVA was used to assess the main effect of suggestion (high, medium or low) and hypnosis and any interactions. There was a highly significant effect of suggestion ($F_{2,24} = 196.4$, $p < 0.001$) but not of hypnosis. Hypnosis and suggestion did, however, interact due to there being a significantly greater reduction in reported pain during the 'low' suggestion in the hypnosis condition compared to the no-hypnosis condition ($F_{2,24} = 7.7$, $p = 0.003$). Patient reports of perceived control over their pain were significantly higher during hypnosis (7.8 (2.2) vs. 4.7 (2.8); $t = 3.4$, $p = 0.005$, 95% CI [2.5, 3.7]). These data are illustrated in Fig. 2 as well as average measures of fibromyalgia pain at baseline (when arriving at the research centre) and measures of hypnotic depth when hypnotised and not hypnotised. Ratings of hypnotic depth were significantly higher when patients were hypnotised (6.1 (2.5) vs. 0.5 (1.3); $t = 7.9$, $p < 0.001$, 95% CI [5.3, 6.7]).

3.2. Brain activation correlated with changes in pain report following suggestion with and without hypnosis

Highly significant and widespread BOLD increases correlating with patient's pain reports were apparent during suggestion with and without hypnosis and are documented in Table 2 and illustrated in Fig. 3. When the patients were hypnotised BOLD responses were significantly greater in several regions including the cerebellum, anterior midcingulate cortex and anterior and posterior insula compared to the unhypnotised condition. Greater activity when patients were not hypnotised were demonstrated in right thalamus, left MCC, bilateral primary sensory cortex (S1) and left prefrontal cortex.

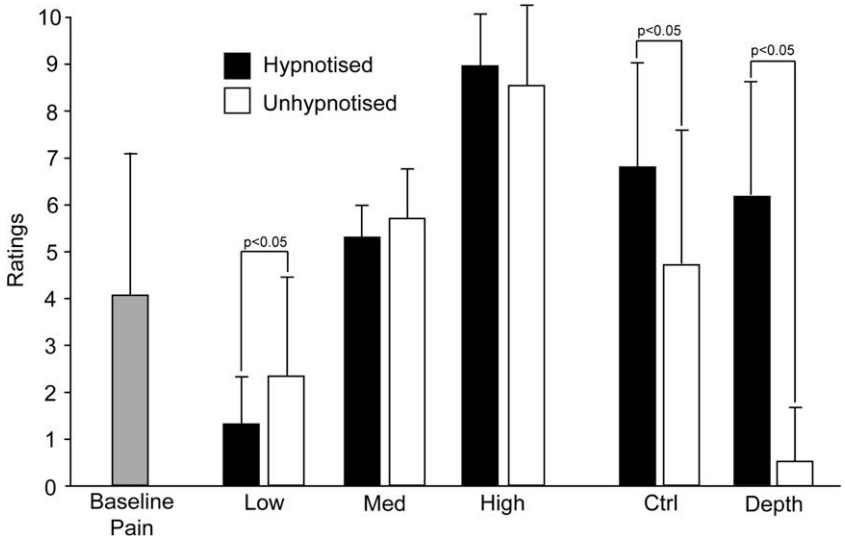

Fig. 2. Shows the reported fibromyalgia pain rating at baseline (upon arrival at the imaging centre) in grey and shows the reported fibromyalgia pain during the low, medium and high suggestions (0 – no pain, 10 – maximum pain) with (black) and without (white) hypnosis. Average ratings of the control over pain (0 – no control, 10 – complete control) and depth of hypnosis (0 – not hypnotised, 10 – complete immersion in hypnosis) are also shown with and without hypnosis. Significant differences ($p < 0.05$) between conditions are indicated.

Table 2
The regions with increasing or decreasing (*italicized*) BOLD response dependent upon changes in reported fibromyalgia pain experience with and without hypnosis

Figure label	Hypnotised			Unhypnotised	
	Brain area (*x*, *y*, *z* coordinates) (region)	Side	*Z*-score	Brain area (*x*, *y*, *z* coordinates) (region)	*Z*-score
1	Pons/midbrain				
	(4, −20, −20)	M	4.1	(2, −22, −24)	3.2
2	Thalamus				
	(−2, −6, 0)	L	3.1	(−22, −30, 10)	3.7
	(18, −4, 10)	R	4.4	(18, −14, 2)	5.4
3	Cerebellum				
	(−14, −58, −18)	L	3.9	(−8, −56, −12)	6.2
	(12, −50, −14)	R	4.0	(4, −62, −14)	4.2
4	sACC				
	(14,46, −8) (BA 32)	R	4.5	(10,36, −6) (BA 24/32)	3.1
	(6,24, −18) (BA 25)	R	3.4		*−3.1*
	(14,40,2) (BA 24/32)	*R*	*−2.7*	*(−14,44, −14) (BA 25/11)*	
5	aMCC			MCC	
	(−4,14,30) (BA 24/32)	L	3.0	(−16,16,38) (BA 32)	3.1
	(2,36,20) (BA 24/32)	R	3.8	–	
6	Posterior insula				
	(−48, −20,14)	L	3.5	*(−52, −16,8)*	*−4.1*
	(34, −32,8)	R	3.3		
7	S2				
	(−58, −28,10)	L	5.1	(−64, −26,16)	3.0
	(54, −16,12)	R	4.4	(70, −34,20)	4.5
8	S1				
	(−28, −36,64)	L	3.5	(−52, −40,44)	3.0
	(26, −36,62)	R	4.4	(30, −28,68)	
				(64, −22,40)	*−3.0*
9	Anterior insula				
	(−30,0, −8)	L	5.4	(−30,26, −4)	4.7
	(40,10, −2)	R	5.2	(46,16, −18)	3.9
10	Inferior parietal cortex				
	(−60, −38,40) (BA 40)	L	4.5	(−40, −56,46) (BA 40)	
	(52, −52,44) (BA 40)	R	4.5	–	
11	Prefrontal cortex				
	(−52,14,8) (BA 44/45)	L	4.5	(−40,50, −10) (BA 10/47)	4.7
	(−28,54,4) (BA 10/46)	L	3.7	(48,36, −12) (BA 10/47)	5.2
	(36,62,2) (BA 10)	R	4.8		

The areas are tabulated in terms of the brain region, as illustrated in Fig. 5, and their approximate cytoarchitecture (BA = Brodman's area). The *x*, *y*, *z* coordinates plot each peak (defined as the pixel with the highest *Z*-score within each tabulated region) according to the MNI coordinate system (negative is left, posterior and inferior). sACC = subgenual anterior cingulate cortex; MCC = mid anterior cingulate cortex; aMCC = anterior MCC; S2 = secondary somatosensory cortex; S1 = primary somatosensory cortex.

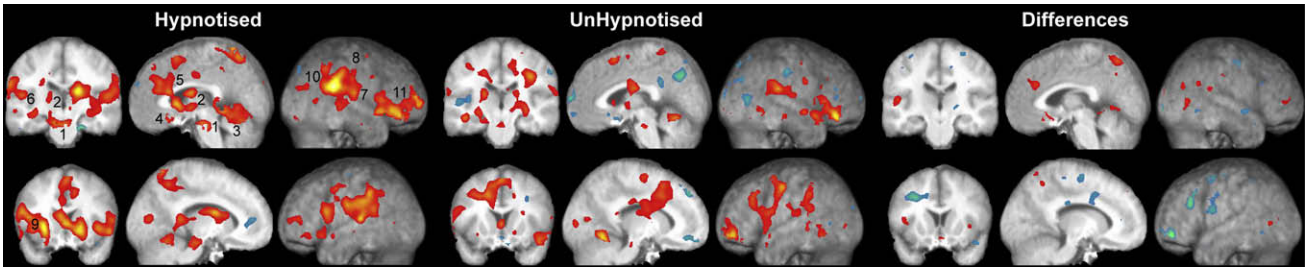

Fig. 3. BOLD activation weighted by suggestion to reduce or increase fibromyalgia pain report during hypnosis (left), without hypnosis (middle) and the difference between these conditions (right). Clusters of voxels that exceeded a *Z* score > 2.3 and *P* < 0.05 (corrected for multiple comparisons) were considered statistically significant and are shown superimposed on an averaged structural MRI derived from the patient's own structural scans. At the left of each condition are coronal slices showing the posterior insula (top) and the anterior insula (bottom). In the middle are saggital slices right lateral (top) and left lateral (bottom) to the midline. To the right are right surface (top) and left surface (bottom) projections. 1 = midbrain region of the pons; 2 = thalamus; 3 = cerebellum; 4 = subgenual anterior cingulate cortex (sACC); 5 = midcingulate cortex; 6 = posterior insula; 7 = secondary somatosensory cortex (S2); 8 = primary somatosensory cortex (S1); 9 = anterior insula; 10 = inferior parietal cortex; 11 = prefrontal cortex.

The percentage changes in BOLD activation are graphed and plotted in Fig. 4 and demonstrate that in every ROI, except left MCC, there was greater BOLD signal change when patients were hypnotised compared with unhypnotised.

3.3. Drug effects on the brain activation responses

Patients on medication did not differ significantly in age from those not on medication (46.5 (13.6) vs. 55.7 (6.7); $t = 1.5$, $p = 0.2$, 95% CI [−22.9,4.6]) and no behavioural differences between these two groups reached significance including baseline pain rating (3.5 (2.9) vs. 5.1 (3.5); $t = 0.8$, $p = 0.4$, 95% CI [−6.2,3.0]), depression (7.5 (5.3) vs. 7.8 (4.2); $t = 0.1$, $p = 0.9$, 95% CI [−6.5,5.8]), anxiety (9.0 (3.8) vs. 10.0 (4.6); $t = 0.4$, $p = 0.7$, 95% CI [−6.5,4.5]) and hypnotisability (10.3 (0.8) vs. 10.2 (1.2); $t = 1.4$, $p = 0.2$, 95% CI [−2.1,0.5]). Fig. 5 demonstrates common activation in the midbrain, thalamus, cerebellum, anterior cingulate cortex, posterior insula, anterior insula, S2 and PFC for both the medication free patients and those currently using medication during hypnosis. Common activation is less apparent when the patients were not hypnotised with nota-

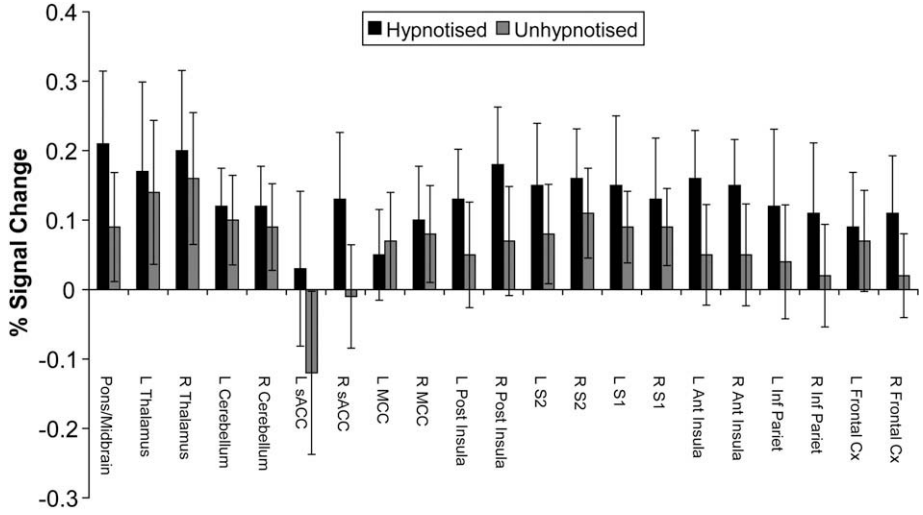

Fig. 4. Percentage changes in BOLD activation graphed for each ROI as illustrated and tabulated in Table 2.

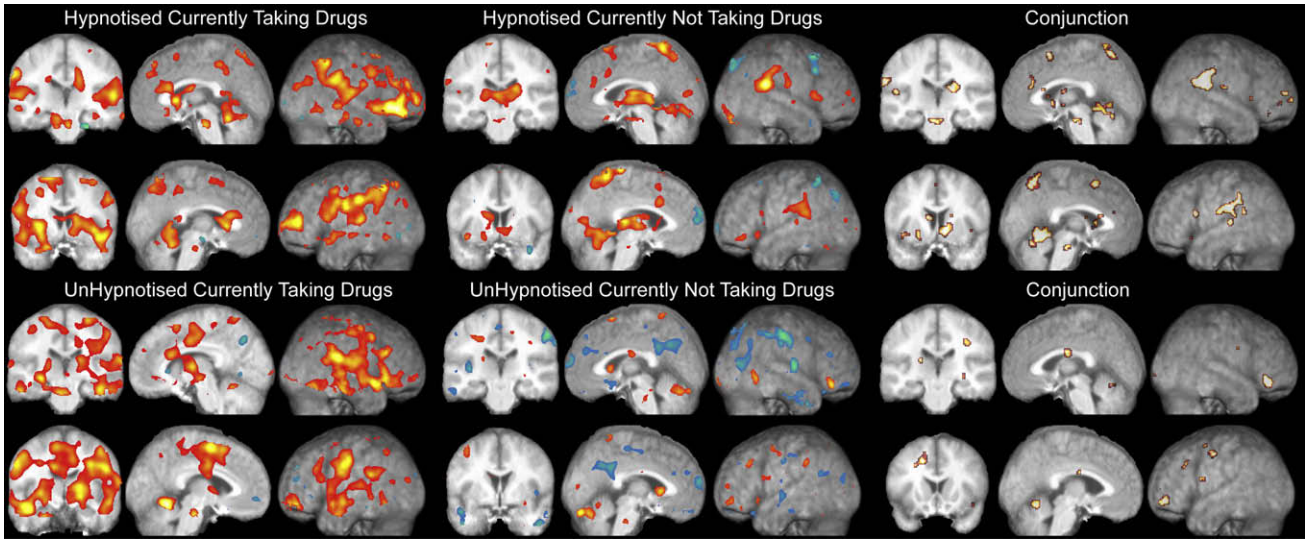

Fig. 5. shows activation in the medication free fibromyalgia patients (left), those taking medication (middle) and the conjunction of activation in those two groups (right) during the hypnotised (top) and unhypnotised (bottom) conditions.

bly greater activation in the patients currently taking drugs. There is particularly obvious dissociation in the thalamus, insula, S2 and inferior parietal cortex.

4. Discussion

fMRI data were obtained during suggested changes in fibromyalgia pain experience with and without hypnosis. Suggestion was highly effective in changing subjective pain reports, regardless of whether a formal hypnotic induction had taken place, but patients reported significantly more control over their pain and a greater ability to reduce their pain during the low pain conditions when hypnotised. Consistent with these findings, activation of cortical and subcortical structures commonly associated with the pain "neuromatrix" were significant in both 'hypnosis' and 'no hypnosis' conditions but greater activation peaks were associated with the hypnosis condition in the cerebellum, aMCC, posterior and anterior insula, inferior parietal cortex and right prefrontal cortex. In the unhypnotised condition, there was greater activation in the thalamus, MCC, S1and left prefrontal cortex. ROI analysis demonstrated that average activation in all regions except the left MCC was increased when the patients were hypnotised compared with unhypnotised. These findings support the view that suggestion can produce significant changes in fibromyalgia pain report and demonstrate the increased efficacy of these suggestions in producing both altered sensory experience and corresponding modulation of brain activity when they follow a hypnotic induction procedure. This result extends previous findings and demonstrates the specificity of (hypnotic) suggestion in altering responsiveness to the stimulus under investigation (Rainville et al., 1997; Willoch et al., 2000; Derbyshire et al., 2004; Kosslyn et al., 2000; Oakley, 2008; Raij et al., 2005; Szechtman et al., 1998). The reported changes in pain experience are also consistent with previous work indicating the utility of hypnotic techniques in the treatment of fibromyalgia (Haanen et al., 1991; Castel et al., 2007).

We propose that activation of neural structures comprising the pain matrix is dependent upon changes in the experience of fibromyalgia pain rather than the demand characteristics of the

experiment. Volitional responses to the demands of the experiment might be expected to activate supervisory neural structures such as the prefrontal cortex and medial ACC (Spence et al., 2003; Oakley et al., 2003). These structures were activated during our procedure and may mediate some of the cognitive processing thought to underlie hypnotic modulation of pain (Miltner and Weiss, 2007; Faymonville et al., 2006; Wik et al., 1999; Crawford et al., 1993). Nevertheless, the additional involvement of the thalamus, insula, midcingulate and somatosensory cortices is highly consistent with modulation of pain experience (Derbyshire et al., 1997, 2004; Coghill et al., 1999, 2003) and with other demonstrations of pain control during fMRI (deCharms et al., 2005).

Our findings are also directly relevant to current debate regarding the role of hypnosis in influencing responsiveness to suggestion (Kirsch and Braffman, 2001; Gandhi and Oakley, 2005; Raz et al., 2006) and support the view that formal hypnotic induction can alter the strength or character of a subsequent suggestion providing for an increased behavioural and neural response. Intriguingly, the regions demonstrating significantly greater activation during suggestion with hypnosis vs. without hypnosis were mainly right lateralised (see Table 3). This finding is broadly consistent with views that emphasise a greater involvement of right hemisphere processes in hypnosis in highly hypnotizable individuals (e.g. Crawford and Gruzelier, 1992; Gruzelier, 1998). It should be emphasized, however, that the differences between behavioural and neural responses when hypnotised and unhypnotised were differences in degree rather than type. The general pattern of BOLD response and changes in pain experience were comparable whether the patients had heard a formal induction or not.

As well as investigating the relative effects of hypnotic and non-hypnotic suggestion this study also explored the brain correlates of pain perception that might underlie fibromyalgia pain in this group, though it was not designed to elucidate the distinct perceptual roles for each of the activations found. Speculation as to the role of each neural activation is, therefore, properly restrained. Nevertheless, specific comment on the thalamic activation is warranted because of observations in previous studies (Cook et al., 2004; Gracely et al., 2004). The thalamus is a major gateway for noxious information (Apkarian and Hodge, 1989) and as we have argued above activation of the thalamus in this study is particularly compelling evidence for a change in pain experience directly related to pain report. Previous studies, however, have suggested reduced thalamic activation in patients with fibromyalgia (Cook et al., 2004; Gracely et al., 2004) that can be normalized (increased) using hypnosis for pain relief (Wik et al., 1999). By necessity, these previous studies used somatic noxious stimulation to provoke brain activation and thus confounded fibromyalgia pain with acute pain experience (Cook et al., 2004; Gracely et al., 2004). In addition, previous hypnotic manipulation of fibromyalgia pain used a baseline measure of brain activity that did not involve hypnosis (Wik et al., 1999). Consequently, the contribution of hypnosis itself, and of somatic stimulation, to the pattern of brain activation remains unclear. Our study tackles these confounds by manipulating fibromyalgia pain directly by the same suggestion with and without hypnosis. Our data indicate that thalamic and cortical activation are involved in the increased experience of fibromyalgia pain during suggestion with and without a hypnotic induction.

Studies of functional pain necessarily involve patients with a heterogeneous disorder characterized by a wide range of non-specific symptoms and often receiving a wide variety of medications (Wessely et al., 1999; Barsky and Borus, 1999). This study also

Table 3
The regions with increasing BOLD response dependent upon hypnotically suggested changes in fibromyalgia pain experience greater than those from suggestion without hypnosis and vice versa

Figure label	Hypnotised > unhypnotised			Unhypnotised > hypnotised	
	Brain area (*x*, *y*, *z* coordinates) (region)	Side	*Z*-score	Brain area (*x*, *y*, *z* coordinates) (region)	*Z*-score
1	Pons/midbrain				
	No significant difference	M	–	No significant difference	–
2	Thalamus				
	No significant difference	L	–	–	–
		R	–	(18, −14, −2)	3.5
3	Cerebellum				
	–	L	–	No significant difference	–
	(10, −52, −4)	R	3.5		–
4	sACC				
	(0,22, −12) (BA 25/11)	M	3.6	No significant difference	–
5	aMCC			MCC	
	–	L	–	(−6,0,28) (BA 24)	3.5
	(4,36,26) (BA 24/32)	R	3.2	–	–
6	Posterior insula				
	(−52, −20,10)	L	3.2	No significant difference	–
	–	R	–		–
7	S2				
	No significant difference	L	–	No significant difference	–
		R	–		–
8	S1				
	–	L	–	(−36, −14,62)	3.3
	(62, −26,38)	R	2.5	(48, −8,50)	3.6
9	Anterior insula				
	(−44,14,10)	L	2.8	No significant difference	–
	(38,10,0)	R	3.5		–
10	Inferior parietal cortex				
	–	L	–	No significant difference	–
	(60, −42,22) (BA 40)	R	3.1		–
11	Prefrontal cortex				
	–	L	–	(40,52, −8) (BA 10/47)	4.4
	–	L	–	(−42,26,34) (BA 9)	3.6
	(40,40,6) (BA 10/46)	R	3.0	–	–

All other details as for Table 1.

involved a highly select group of patients who responded to hypnotic suggestion with changes in their experience of pain. Because of the variability in the patient sample, and the restrictive criteria for recruitment, our demonstration that hypnosis can be used to modulate fibromyalgia pain with congruent changes in brain activation can be considered a proof of principle but generalization beyond the group studied should be approached with caution. Fixed effects analysis, which only considers variability in the group under study, demonstrated widespread and highly significant BOLD activation during hypnotic modulation of fibromyalgia pain that was generally attenuated when the patients were not hypnotised. ROI analysis of our data indicates that hypnosis provided greater modulation in every region except the left MCC.

It was not possible to find patients matching our criteria who were all currently medication free or willing to become medication free. Consequently some of our patients were receiving medication that may influence the BOLD response. This possibility was directly assessed via analysis of patients on or off medication at the time of study. Patients taking medication, and those who were medication free, demonstrated common activation in the midbrain, thalamus, cerebellum, anterior cingulate cortex, posterior insula, anterior insula, S2 and PFC when hypnotised. Patients on medication had generally greater levels of activation, which is consistent with the possibility that they were taking medication because they could experience greater levels of fibromyalgia pain on a day to day basis. Our findings are consistent with prescribed medication having little or no effect on brain activation mediating the hypnotic alteration of pain experience. Consistency in activation, however, was less apparent when the patients were not hypnotised. One possibility is that patients able to be off drugs suffer less pain and discomfort and so were less able to focus on their pain outside a hypnotic context. Additional psychometric measurements, however, including baseline pain rating, anxiety, depression, hypnotic depth and hypnotizability did not produce significant differences but these findings should be viewed with caution given the small numbers of patients in the drug and drug free groups.

The small number of patients also cautions against interpretation of BOLD differences between the drug and drug free groups. Fibromyalgia patients are typically heterogenous with extensive and variable medication histories and current prescription patterns; we have no *a priori* basis for interpreting differences between patients on and off medication using our current procedures. For these reasons we caution that any interpretation of these subgroups remains speculative. A similar argument applies to other subdivisions of the data that we might have performed. For example, it could be interesting to observe differences between patients with and without an IBS diagnosis. It is, however, inherent to fibromyalgia that patients report symptoms overlapping with other diagnoses (Wessely et al., 1999). An IBS diagnosis can reasonably be considered a part of the syndrome and so dissociating IBS from fibromyalgia is not necessarily useful and predicting and interpreting differences between patients with and without IBS would be difficult.

In summary, Fig. 3 extends our knowledge of pain processing in fibromyalgia by providing a map of activations underlying patients' own pain rather than their responses to external noxious events. This finding in a clinical pain population is compatible with prior evidence that intensity of the perceptual experience is tied to the strength of activity in the pain matrix (Coghill et al., 2003). Critically, the reported activations correlate with patient's reports of changes in their experience of their fibromyalgia pain, not pain due to an external stimulus, linking regional activation specifically to the modulation of fibromyalgia pain in this group. In addition, our results provide evidence that appropriate suggestion can relieve fibromyalgia pain with and without a formal hypnotic induction. Pain relief was significantly greater, however, when suggestion followed a hypnotic induction. Overall, the BOLD activation patterns were more consistent with changes in pain report in hypnosis though the differences were somewhat variable. These findings imply a therapeutic benefit from both hypnotic and non-hypnotic suggestion but with some additional benefit that is unique to suggestion following a hypnotic induction.

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