OPEN

Suggestions to Reduce Clinical Fibromyalgia Pain and Experimentally Induced Pain Produce Parallel Effects on Perceived Pain but Divergent Functional MRI–Based Brain Activity

Stuart W.G. Derbyshire, PhD, Matthew G. Whalley, PhD, Stanley T.H. Seah, BA, and David A. Oakley, PhD

ABSTRACT

Objective: Hypnotic suggestion is an empirically validated form of pain control; however, the underlying mechanism remains unclear.

Methods: Thirteen fibromyalgia patients received suggestions to alter their clinical pain, and 15 healthy controls received suggestions to alter experimental heat pain. Suggestions were delivered before and after hypnotic induction with blood oxygen level–dependent (BOLD) activity measured concurrently.

Results: Across groups, suggestion produced substantial changes in pain report (main effect of suggestion, $F_{2, 312} = 585.8$; $p < .0001$), with marginally larger changes after induction (main effect of induction, $F_{1, 312} = 3.6$; $p = .060$). In patients, BOLD response *increased* with pain report in regions previously associated with pain, including thalamus and anterior cingulate cortex. In controls, BOLD response *decreased* with pain report. All changes were greater after induction. Region-of-interest analysis revealed largely linear patient responses with increasing pain report. Control responses, however, were higher after suggestion to increase or decrease pain from baseline.

Conclusions: Based on behavioral report alone, the mechanism of suggestion could be interpreted as largely similar regardless of the induction or type of pain experience. The functional magnetic resonance imaging data, however, demonstrated larger changes in brain activity after induction and a radically different pattern of brain activity for clinical pain compared with experimental pain. These findings imply that induction has an important effect on underlying neural activity mediating the effects of suggestion, and the mechanism of suggestion in patients altering clinical pain differs from that in controls altering experimental pain. Patient responses imply that suggestions altered pain experience via corresponding changes in pain-related brain regions, whereas control responses imply suggestion engaged cognitive control.

Key words: chronic pain, functional magnetic resonance imaging, experimental pain, hypnosis, alternative therapy, brain.

INTRODUCTION

Targeted suggestions after a hypnotic induction are well established as an adjunctive procedure in clinical practice (1,2) and have been increasingly used as a research tool in cognitive neuroscience (3,4). In particular, several reviews and meta-analyses have demonstrated the efficacy of hypnotically suggested analgesia in reducing chronic pain, acute surgical pain, and acute nonsurgical pain (5–12).

aMCC = anterior mid-cingulate cortex, **BA** = Brodman area, **BOLD** = blood oxygen level dependent, **FM** = fibromyalgia, **FSL** = FMRIB software library, **HADS** = Hospital Anxiety And Depression Scale, **HGSHS** = Harvard Group Scale of Hypnotic Susceptibility, **ICA** = independent components analysis, **MRI** = magnetic resonance imaging, **pACC** = perigenual anterior cingulate, **PAG** = periaqueductal gray, **ROI** = region of interest, **S1** = primary somatosensory cortex, **S2** = secondary somatosensory cortex

Approximately 75% of the population report significant pain reduction after hypnotic analgesia suggestion for both clinical and experimentally induced pain regardless of the noxious source (10,11). Indeed, in some patients, hypnotic suggestion can have a startling effect on pain experience allowing surgery, childbirth, or bone marrow aspiration without further anesthetic intervention (13–15).

The effects produced by hypnotic suggestion can also be produced by the same suggestions given without hypnosis (16), leading to considerable debate regarding the role of the typical hypnotic induction (17–21). Previous studies have demonstrated (*a*) the efficacy of nonhypnotic suggestions and (*b*) that behavioral differences when suggestions are delivered with or without a formal induction are relatively small (22).

Broadly speaking, there have been 2 explanations offered as to why a hypnotic induction procedure might modestly increase suggestibility (20). The first invokes the role of sociocognitive factors such as expectancy, beliefs, role-enactment, and demand characteristics associated with a hypnotic context. The word *hypnosis*, for example, triggers lay beliefs and expectations of powerful influences on experience. Consequently, a standard suggestion script described as "hypnotic" increased responsiveness to suggestion, including increased analgesia, compared with using the identical script described as "relaxation" (23,24). The second explanation invokes an altered mental state (or "state of consciousness") created by the hypnotic induction, characterized by focused attention and absorption, and involving an altered state of brain function. From this neurocognitive perspective, hypnotic interventions are qualitatively different from other behavioral interventions because the hypnotic induction creates a special state, which facilitates responses to suggestion (20,25).

Neuroimaging studies allow for novel exploration of the effects of hypnotic inductions. One method is to examine the resting state of brain activity ("default mode") after a hypnotic induction procedure, and this has been shown to be different from comparable nonhypnotic conditions (26–30). Attentional and executive control has also been shown to differ in hypnosis (31) and between high and low hypnotizable participants (32). Few studies have taken care to compare identical suggestions in and out of a hypnotic context, but when this has been done, hypnosis seems to have additive effects on suggestion. Suggested analgesia and hyperalgesia, for example, produces similar changes in pain experience with or without an induction (33). Brain imaging, however, has indicated greater responses to suggested analgesia and hyperalgesia after an induction (33). Similar findings have also been reported when participants were asked to drain color from a colored image or add color to a gray image (34). Highly hypnotizable participants could perform both tasks in and out of hypnosis but were slightly more able to do so during hypnosis. Brain imaging data collected at the same time, however, indicated greater responses to the suggested changes in color vision after an induction.

Here, we aimed to further pursue the understanding of hypnotic analgesia using both a normal population with an experimentally induced noxious heat stimulus and clinical pain patients. Currently, hypnosis is used in clinical settings as an adjunctive treatment to control acute pain during invasive surgery (13) and as a replacement for anesthesia during invasive dental treatment (15). In addition, hypnosis in the UK is an approved treatment to control the discomfort associated with irritable bowel syndrome (35–37). Previously, we demonstrated highly successful immediate control of chronic fibromyalgia pain using hypnosis, which correlated with regions of the brain known to be involved in acute pain experience (33). Behavioral studies have also demonstrated that heat pain can be modified using hypnosis in normal controls (35), and functional magnetic resonance imaging (fMRI) studies have indicated the involvement of pain-related regions in both normal controls and patients with chronic pain (33,38–40). Thus, it was expected that suggestion of more or less pain from a fixed noxious heat would produce comparable activation to that previously observed with suggested increased and decreased fibromyalgia pain (33). The demonstration of similar activation during the modification of chronic and acute pain would support similar mechanisms underlying the effects of hypnosis on chronic and acute pain or similar mechanisms driving chronic and acute pain or both.

Unlike our previous report (33), the current report uses the stepwise design to contrast BOLD changes when suggesting low versus high pain. This approach allows us to more fully explore the hypothesized step-changes in activation as pain is moved hypnotically from a medium to low level and from a medium to high level. For completeness and direct comparison, the current report also includes the same analysis conducted using our previous data (33). This analysis was not reported previously (33).

METHODS

Participants

Patients with a primary diagnosis of fibromyalgia and included on the University of Pittsburgh Rheumatology Registry were invited to participate via letter. Healthy controls were recruited using flyers posted around the University of Pittsburgh campus. Subsequently, 46 patients with fibromyalgia and 43 healthy controls were prescreened on the Harvard Group Scale of Hypnotic Susceptibility: Form A (HGSHS:A 23) using both objective and subjective scoring methods (41). Of these, 13 patients (all women; mean age, 51.4 years) and 15 controls (7 men; mean age, 25.3 years) were selected for the scanning phase of the study on the basis of high hypnotic suggestibility (scoring >8 of 12 on the HGSHS:A—objective scores) and the ability to respond to suggestions for pain control (see below). Data from all participants were collected over a period of 2 years (June 2002 to June 2004). All participants gave informed consent, and the study was approved by the University of Pittsburgh Institutional Review Board.
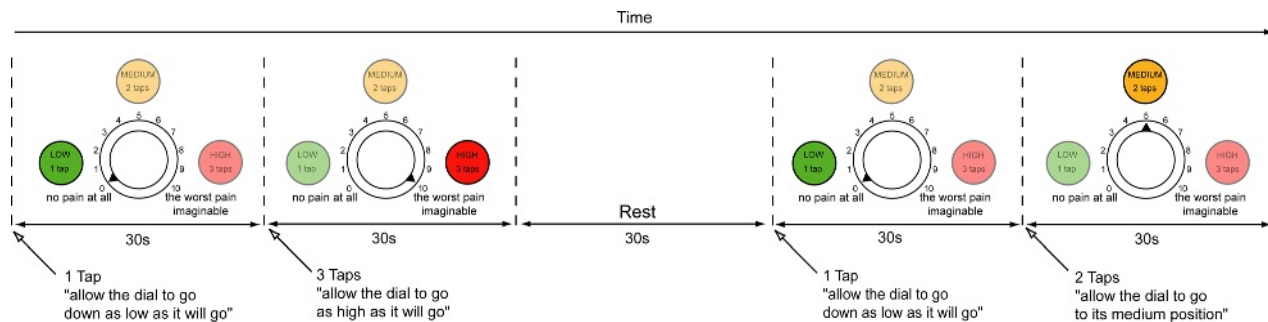
FIGURE 1. Functional MRI procedure for controls is illustrated. Each participant was asked to view, in their mind's eye, a dial representing the heat pain. They were asked to move the dial as close to zero as possible after one tap to the foot, as close to 5 as possible after 2 taps, and as close to 10 as possible after 3 taps. Each tapping signal began a 30-second scanning period during which the subjects controlled the heat pain using the dial and moved the heat pain experience as instructed.

Behavioral Measures

Before scanning all participants rated as highly hypnotically suggestible were screened for their ability to control pain using standardized imagery. The patients were asked to visualize a dial representing their main source of fibromyalgia pain. The healthy controls had a thermal probe attached to their right hand and were asked to visualize a dial representing pain from the probe. The probe delivered a series of 60-second heat stimuli to the palm of their right hand. The temperature was calibrated individually to produce a rating of 5/10 on the visualized pain dial (Fig. 1), labeled from 0 (no pain at all) to 10 (most pain imaginable). The dial image was then used for both groups to rapidly alter and anchor pain experience to a high, medium, or low level according to verbal suggestions delivered to each participant during hypnosis.

The participants were informed that hypnotic suggestions would be given to allow the dial to move up and down, producing a concomitant change in their fibromyalgia or heat pain sensation. Control participants were explicitly informed that the heat stimulus itself would remain constant. Fibromyalgia patients were asked to concentrate on their main source of pain. All participants were then hypnotized individually using an eyes-closed induction including relaxation suggestions and descent imagery as described in detail elsewhere (42).

After the hypnotic induction, participants were asked to bring the dial to mind and to notify the experimenter of its current position. For the controls, the heat probe was then activated. Suggestions were given for the dial and the corresponding pain to be turned up as high as possible. 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 participants. This procedure was repeated to give participants practice with these suggestions before the hypnosis was terminated and the subjects debriefed.

To ensure consistency in the level pain control and the imagery used in both groups in the scanning stage of the study, participants who reported that they spontaneously used distractive/dissociative techniques of pain control (eg, finding themselves on a pleasant beach and unaware of the pain), rather than the dial imagery provided, or who could not demonstrate

adequate pain control, were excluded. The remaining 13 patients and 15 controls who reported dial changes of 6 points or more (from maximum to minimum) in their pain experience, without the use of distraction or dissociation, were selected for scanning.

Participants in both groups completed the Hospital Anxiety and Depression Scale (HADS) (43). The HADS is a short self-report screening tool that was developed to indicate anxiety and depressive states in patients with physical illness, but has also been used extensively with normal controls (44).

Imaging Procedure

Brain activation was inferred based on measurement of the blood oxygen level–dependent (BOLD) contrast (45). These measurements were acquired at 3 T using a reverse spiral technique (TE, 25 ms; TR, 1.5 s; flip angle, 60 degrees; matrix, 64×64) described in detail elsewhere (46,47). 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 repetition time of 1.5 seconds. 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.
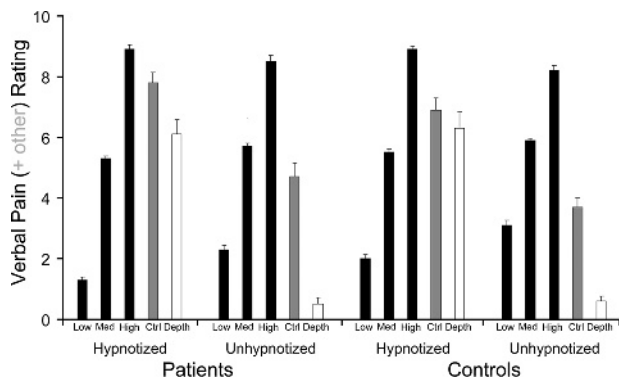
Seven patients were hypnotized upon entering the fMRI scanner using the same induction as during screening (hypnosis condition). After the collection of 2 runs of fMRI data, hypnosis was terminated and 2 further runs of data were collected (no-hypnosis condition). One hundred sixty volumes were collected in each of these 4 runs. Each run lasted 4 minutes and included two 30-second periods of high pain, two 30-second periods of low pain, and four 30-second periods of medium pain. There was no rest period. For the remaining 6 patients, the procedure was the same except that the order of the 2 conditions was reversed. Normal controls had the thermal probe attached to their right hand upon entering the scanner. Temperatures calibrated to 5/10 on the pain dial, as for the screening session, were

TABLE 1. Questionnaire Data and Initial Pain Ratings

	HAD A (SE)*	HAD D (SE)*	HGSHS:A O (SE)	HGSHS:A S (SE)	Pain (SE)[a]
FM (n = 13)	9.5 (1.1)	7.7 (1.3)	9.8 (0.3)	37.1 (1.0)	4.1 (0.6)
Control (n = 15)	5.5 (1.1)	2.1 (0.8)	10.3 (0.3)	38.2 (1.2)	5.8 (0.3)

[a] The patients were significantly more anxious ($t = 2.6$; $p = .016$; 95% CI, 0.8–7.2) and depressed ($t = 3.5$; $p = .002$; 95% CI, 2.1–8.2) than the controls; the prescan pain levels were greater for controls ($t = 2.2$; $p = .035$; 95% CI, 0.1–3.3).

Table shows the mean anxiety (HAD A), depression (HAD D), HGSHS:A objective (HGSHS:A O), and subjective (HGSHS:A S) and prescan pain scores. Standard error (SE) is shown in brackets.

FIGURE 2. Average reported fibromyalgia pain (left) and thermal pain in the control participants (right) during the low, medium, and high suggestions (0, no pain; 10, maximum pain) with and without hypnosis. Post hoc reported control over pain and depth of hypnosis for each group and condition is shown in gray and white, respectively. Error bars show standard errors.

delivered at the appropriate times. Eight participants were hypnotized upon entering the fMRI scanner (hypnosis condition). After the collection of 2 runs of fMRI data, hypnosis was terminated and 2 further runs of data were collected (no-hypnosis condition). One hundred volumes were collected in each of these 4 runs, which lasted 150 seconds each and included one 30-second period of high pain, one 30-second period of low pain, and two 30-second periods of medium pain. For the remaining 7 controls, the procedure was the same except that the order of the hypnosis/no-hypnosis conditions was reversed.

As in the screening procedure, all participants were told to visualize the dial labeled from 0 to 10, representing their current level of maximal fibromyalgia pain or heat pain. For the purposes of fMRI data collection, verbal suggestion was replaced by nonverbal signals in the form of a simple sequence of taps to the participant's left foot. One tap conveyed the suggestion that the participant should use the dial to reduce their pain experience, getting as close to zero as possible. Two taps indicated that the participant was to experience their pain in the middle range of the dial, as close to 5 as possible. Three taps indicated that the participant was to increase their pain experience to as close to 10 on the dial as possible. Two runs of fMRI data were collected from each participant in both conditions (hypnosis and no-hypnosis), and identical suggestions were used throughout. The runs for the patients are described in our previous report. A typical heat pain fMRI run for the controls is illustrated in Figure 1.

After each run, the participant gave verbal ratings of pain intensity for the previously experienced low, medium, and high pain trials and a measure of how hypnotized they felt on a 0 to 10 scale of hypnotic depth, where 0 is equal to not at all hypnotized and 10 is as deeply hypnotized as you have ever been before (48). All participants had prior experience of a hypnotic induction procedure as part of the HGSHS: A and in the pain control screening procedure as a reference point for the hypnotic depth rating. At the end of the MR session, participants 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 to 10 scale (0, no control; 10, maximum control).

Data Analysis

Data analysis was performed using the FMRIB Software Library (FSL release 5.07, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain), described in detail elsewhere (49). In summary, functional brain
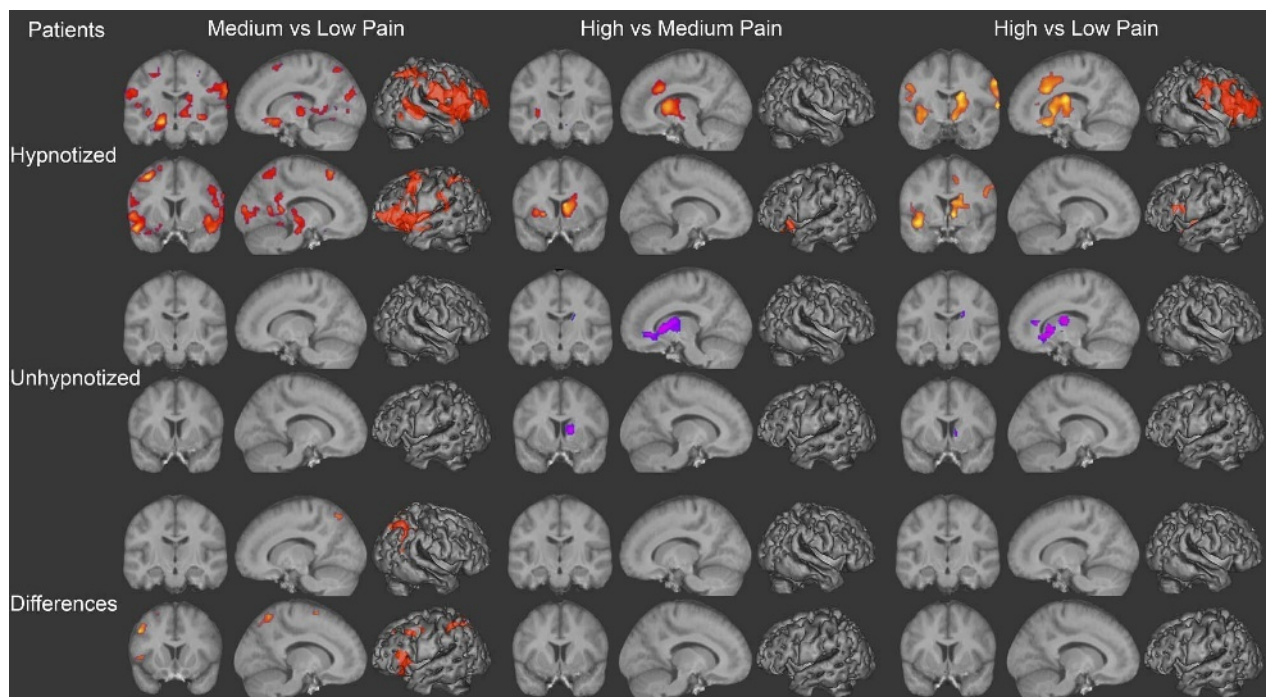
FIGURE 3. BOLD activation for the contrasts of medium with low, high with medium and high with low pain epochs during hypnotic (red-orange scale) and non-hypnotic (purple-blue scale) suggestion and the differences between hypnotic and non-hypnotic suggestion. Clusters of voxels that exceeded Z score >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 fibromyalgia 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 sagittal slices right lateral (top) and left lateral (bottom) to the midline. To the right are right surface (top) and left surface (bottom) projections.

TABLE 2. Increased BOLD Response When Contrasting Medium With Low, High With Medium, and High With Low Hypnotically Suggested Changes in Fibromyalgia Pain Experience

Med Versus Low		High Versus Med		High Versus Low	
Brain Area (x, y, z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score
Brain stem/PAG		Brain stem/PAG			
(−4, −26, −16)	3.2	(8, −8, −12)	4.6	—	—
Thalamus		Thalamus		Thalamus	
(−18, −26, 0)	3.1	(6, −4, −2)	4.8	(10, 0, 0)	3.2
(14, −16, 0)	2.8	—	—	—	—
		Caudate		Caudate	
—	—	(8, 6, 14)	4.6	(16, −6, 20)	3.5
		Lentiform nucleus			
—	—	(−22, 2, 0)	4.4	—	—
Hippocampus/Amygdala		Hippocampus/Amygdala			
(−22, −20, 14)	3.4	(−22, −2, −14)	3.4	—	—
A insula		A insula			
(−54, 0, −2)	4.6	(−30, 14, −8)	3.9	—	—
(48, 14, −4)	3.9	—	—	—	—
				Mid Insula	
—	—	—	—	(−38, −2, −8)	3.5
		aMCC		aMCC	
—	—	(10, 18, 32) (BA 24)	3.6	(16, 20, 30)	3.3
Frontal cortex				Frontal cortex	
(−56, 22, 32) (BA 9)	4.4	—	—	(−52, 20, 18) (BA 44/45)	3.3
(48, 24, 20) (BA 46)	3.5	—	—	(46, 52, −2) (BA 44/10)	3.8
				Premotor Cx	
—	—	—	—	(62, −12, 38) (BA 6)	3.6
S1					
(−46, −34, 52)	4.0	—	—	—	—
(54, −34, 44)	3.7	—	—	—	—
S2				S2	
(−56, −4, 18)	4.3	—	—	(66, −8, 8)	3.4
Inf temporal cortex					
(52, −62, 0) (BA 37)	4.9	—	—	—	—
Inf parietal cortex					
(−46, −36, 52) (BA 40)	4.6	—	—	—	—

PAG = periaqueductal gray; A insula = anterior insula; aMCC = anterior mid anterior cingulate cortex; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; Inf = inferior.

Table 2 Regions with increased BOLD response when contrasting the different intensities of hypnotically suggested changes in fibromyalgia pain experience. The areas are tabulated in terms of the brain region, as illustrated in Figure 3, and their approximate cytoarchitecture (BA = Brodman area). The x, y, and z coordinates plot each peak (defined as the pixel with the highest Z-score within each tabulated region) according to the Montreal Neurological Institute coordinate system (negative is left, posterior and inferior).

images from every participant were first preprocessed by extracting the skull and other nonbrain regions using FMRIB's brain extraction tool, whereas motion correction was performed using FMRIB's Linear Image Registration Tool (50) on each echo planar image volume. To increase the signal-to-noise ratio and accommodate variability in functional anatomy, each image was then smoothed in X, Y, and Z dimensions with a Gaussian filter of 8-mm full-width-half-maximum. Data were filtered with a high-pass temporal filter of 100 seconds to remove temporal noise and drift of fMRI data. For the group-level analyses, functional data of each participant were first coregistered to individuals' anatomical images and then coregistered to a template brain in Montreal Neurological Institute space using FMRIB's Linear Image Registration Tool (FLIRT, 51). The calculated transformation matrix parameters were then applied to the functional data set to perform group-level analyses in Montreal Neurological Institute

TABLE 3. Increased BOLD Response When Contrasting Medium With Low, High With Medium, and High With Low Nonhypnotically Suggested Changes in Fibromyalgia Pain Experience

| Med Versus Low		High Versus Med		High Versus Low	
Brain Area (x, y, z Coordinates) (Region)	Z-Score	(x, y, z Coordinates) (Region)	Z-Score	(x, y, z Coordinates) (Region)	Z-Score
		Thalamus		Thalamus	
—	—	(6, −6, 0)	3.9	(14, −4, 16)	3.4
		Caudate		Caudate	
—	—	(10, 16, 2)	3.6	(12, 12, 4)	3.3
		pACC		pACC	
—	—	(12, 32, −4)	3.5	(4, 32, 14) (BA 24)	3.0

pACC = perigenual anterior cingulate cortex. All other details are as for Table 2.

Regions with increased BOLD response when contrasting the different intensities of nonhypnotically suggested changes in fibromyalgia pain experience. All other details are as shown in Table 2.

standard space. Comparisons of the conditions (high vs medium, high vs low, and medium vs low) were separately generated for each run using a series of paired t tests. Repeated contrasts of the same conditions were then combined using a fixed-effects single-group average. Group analyses were then conducted using a mixed-effect (FMRIB's Local Analysis of Mixed Effects 1 + 2) single-group average to determine the group mean of the differential BOLD responses to the low, medium, and high pain epochs with and without a hypnotic induction. Further group analysis was performed using a mixed-effect (FMRIB's Local Analysis of Mixed Effects 1 + 2) 2-group t test to examine differences between patients and controls (see Supplemental Digital Content 1, http://links.lww.com/PSYMED/A310). For all analyses, clusters of voxels that exceeded a Z score >2.3 and

$p < .05$ (corrected for multiple comparisons) were considered statistically significant. Additional region of interest (ROI) analysis was also performed and is described in more detail in supplementary materials.

The analysis was performed in 2 complete passes. The first pass included an independent components analysis 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 independent components analysis results were examined for each participant, and components that were obviously noise (such as participant motion, physiological or machine noise) were rejected. The original data were then filtered to remove the components
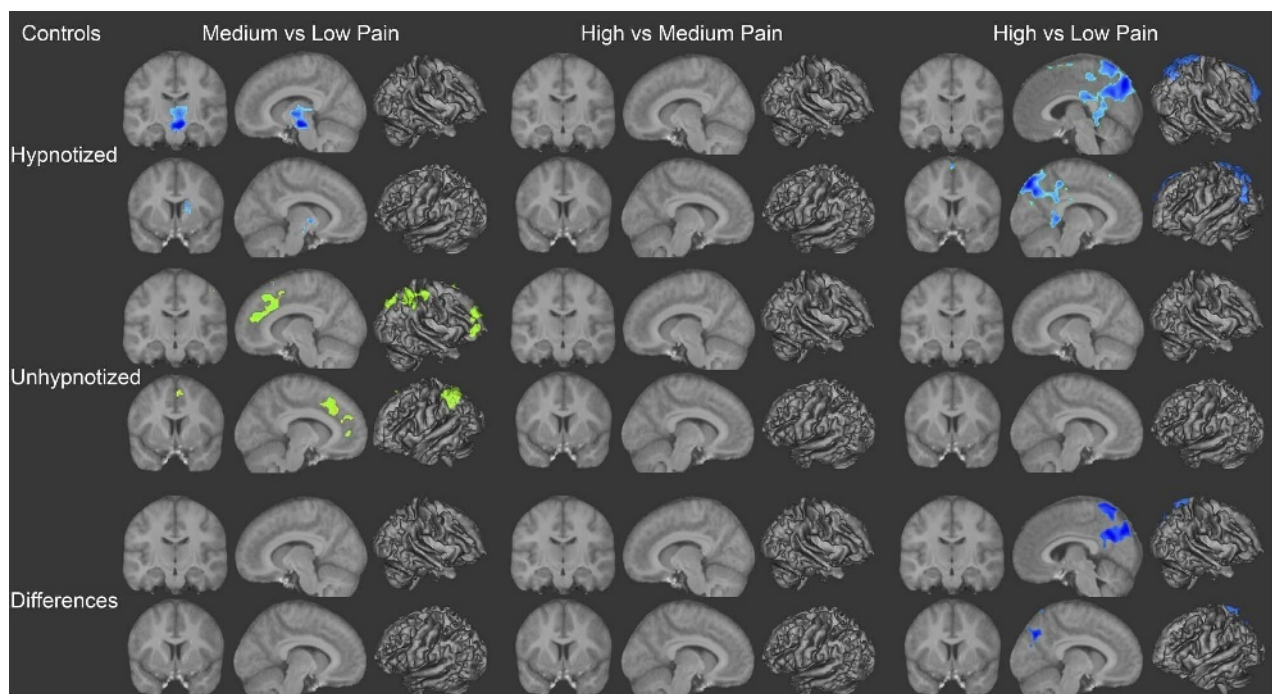
FIGURE 4. Blood oxygen level–dependent deactivation for the contrasts of medium with low, high with medium, and high with low pain epochs during hypnotic (blue-green scale) and nonhypnotic (green-yellow scale) suggestion and the differences between hypnotic and nonhypnotic suggestion. Regions of significant deactivation are shown superimposed on an averaged structural MRI derived from the control's own structural scans. All other details are as shown in Figure 3.

TABLE 4. Decreased BOLD Response When Contrasting Medium With Low, High With Medium, and High With Low Hypnotically Suggested Changes in Experimental Heat Pain Experience

Medium Versus Low		High Versus Medium		High Versus Low	
Brain Area (x, y, z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score
Brain Stem/PAG		No significant voxels			
(8, −18, −14)	−4.3		—		—
Thalamus					
(8, −6, 2)	−3.8				—
Caudate					
(14, 8, 18)	−3.0				—
	—			Superior Parietal Cortex	
				(−6, −80, 48) (BA 7)	−4.3
				(4, −78, 44) (BA 7)	−4.2
				PCC	
	—			(0, −28, 26) (BA 23)	−3.9
				Frontal Cortex	
				(−20, 30, 40) (BA 9)	−3.4
	—			(30, 44, 30) (BA 9)	−3.8
				Supplementary Motor Cortex	
	—			(0, 8, 68) (BA 6)	−3.2
				aMCC	
	—			(−8, 20, 32) (BA 24)	−2.8
				(2, 16, 46) (BA 32)	−3.6
				(10, 12, 34) (BA 24)	−3.7

Regions with *decreased* BOLD response when contrasting the different intensities of hypnotically suggested changes in heat pain experience for the control participants. All other details are as shown in Table 2.

identified as being a result of noise and the analysis repeated using the filtered data. In total, 441 components (30%) were identified as noise when the participants were hypnotized and 416 (29%) when the participants were not hypnotized.

RESULTS

Behavioral Ratings

Table 1 shows the questionnaire data and pain ratings recorded before scanning.

The patients were significantly more anxious ($t(26) = 2.6$; $p = .016$; 95% confidence interval [CI], 0.8–7.2) and depressed ($t(26) = 3.5$; $p = .002$; 95% CI, 2.1–8.2) than the controls. The prescan pain levels (spontaneous pain for the FM patients and pain in response to the previously calibrated thermal stimulus for the controls) were greater for controls ($t(26) = 2.2$; $p = .035$; 95% CI, 0.1–3.3). The objective and subjective measures of hypnotizability did not differ between the groups.

Figure 2 illustrates the average pain ratings during fMRI scanning for the fibromyalgia patients and controls with

and without a hypnotic induction during suggestions of low, medium, and high pain. There are obvious stepwise increases and decreases in pain report, with the suggestions of increasing and decreasing pain, with only small differences between the hypnotized and unhypnotized conditions and between the groups. A linear mixed-effects model was used to assess the main effect of suggestion, hypnosis, and group, and any interactions. There was a highly significant effect of suggestion ($F_{2,312} = 585.8$; $p < .0001$), a marginally significant effect of hypnosis ($F_{1,312} = 3.6$; $p = .060$) and no significant effect of group ($F_{1,312} = 2.6$; $p = .11$). There was a marginally significant effect of repetition across the 2 blocks of fMRI acquisition ($F_{1,312} = 3.6$; $p = .058$).

There was a significant interaction of hypnosis and suggestion, which can be observed from Figure 2 as a consequence of the low pain being lower and the high pain being higher in the hypnotized compared to unhypnotized condition ($F_{2,312} = 9.6$; $p < .0001$). Ratings were collapsed across groups and repeat for post hoc inspection. Post hoc analysis revealed a significantly lower pain report during low and medium suggestion when hypnotized compared to

TABLE 5. Decreased BOLD Response When Contrasting Medium With Low, High With Medium, and High With Low Nonhypnotically Suggested Changes in Experimental Heat Pain Experience

Med Versus Low		High Versus Med		High Versus Low	
Brain Area (x, y, Z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score	Brain Area (x, y, z Coordinates) (Region)	Z-Score
aMCC		No significant voxels		No significant voxels	
(6, 20, 36) (BA 24)	−4.1		—		—
(6, 46, 22) (BA 32)	−3.9				
pACC					
(−10, 46, 2) (BA 24)	−3.4				
Supplementary Motor Cortex					
(6, 30, 48) (BA 6)	−4.0				
Frontal Cortex					
(50, 42, 22) (BA 9)	−3.9				
Inf Parietal Cortex					
(−48, −56, 44) (BA 40)	−4.1				
(38, −46, 44) (BA 40)	−3.5				

Regions with *decreased* BOLD response when contrasting the different intensities of nonhypnotically suggested changes in heat pain experience for the control participants. All other details are as shown in Table 2.

unhypnotized (low: $t(51) = 3.7$; $p = .001$; 95% CI, 0.4–1.2; medium: $t(51) = 2.0$; $p = .046$; 95% CI, 0.0–0.6) and significantly higher pain report during high suggestion when hypnotized compared to unhypnotized ($t(51) = 2.5$; $p = .018$; 95% CI, 0.1–1.0).

There was also a significant interaction of suggestion with group ($F_{2,312} = 3.3$; $p = .038$), which can be observed from Figure 2 as a likely consequence of the low pain being higher in the controls compared with the patients. Ratings were collapsed across hypnosis and repeat for post hoc inspection. Post hoc analysis revealed a significantly higher pain report during low suggestion in the control participants compared to the patients ($t(110) = 2.2$; $p = .028$; 95% CI, 0.1–1.4).

Figure 2 also illustrates post hoc reports of control over the pain (0, no control; 10, complete control) and the perceived depth of hypnosis (0, not hypnotized at all; 10, as deeply hypnotized as you have ever been before). Control over the pain is noticeably higher for the hypnotized versus unhypnotized conditions and is similar for both groups. A repeated-measures analysis of variance confirmed the main effect of hypnosis ($F_{1,24} = 61.6$; $p < .001$) with no significant effect of group ($F_{1,24} = 1.4$; $p = .249$) or interaction of hypnosis with group ($F_{1,24} < 1$). Similarly, the rating of hypnotic depth is considerably higher for the hypnotized versus unhypnotized conditions and similar for both groups. A repeated-measures analysis of variance confirmed the main effect of hypnosis ($F_{1,24} = 202.2$; $p < .001$) with no significant effect of group ($F_{1,24} < 1$) or interaction of hypnosis with group ($F_{1,24} < 1$).

## Brain Activation According to Condition and Group

Figure 3 illustrates brain activation in the fibromyalgia patients when contrasting medium pain epochs with low pain epochs and high pain epochs with medium epochs and high pain epochs with low epochs. Details of the activated regions are provided in Tables 2 and 3.

When the patients were hypnotized, increases in BOLD can be observed in the brainstem (including the periaqueductal gray), thalamus, mid anterior cingulate cortex, insula, prefrontal cortex, and sensory cortices but not consistently across all contrasts. When the patients were not hypnotized, activation is notably reduced but differences only reached formal significance when comparing hypnotized with unhypnotized scans for the contrast of medium versus low pain.

Figure 4 illustrates the same contrasts in the control participants. Unlike the fibromyalgia patients, only significant decreases in BOLD response were observed for medium versus low and high versus low pain contrasts. High versus medium pain did not reveal any significant differences. Details of the activated regions are provided in Tables 4 and 5.

Figure 5 provides a visual summary of the percentage BOLD changes averaged from a series of ROIs, selected based on our previous work ((33) and detailed in Supplemental Digital Content 1, http://links.lww.com/PSYMED/A310). The summary shows the mean percentage BOLD changes for the hypnosis and nonhypnosis conditions in patients and controls, alongside an idealized representation of the expected result if the BOLD effects had a
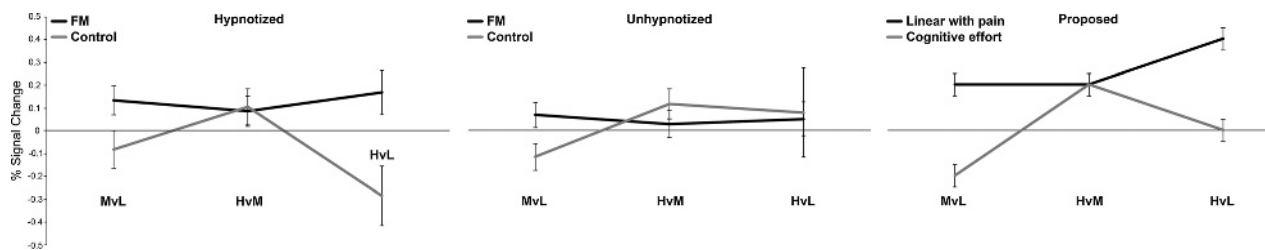
FIGURE 5. Average percent change across all ROIs for the hypnotized and the unhypnotized contrasts. To the right is an idealized representation of how the data would look if they exactly followed a linear relationship with perceived pain or was being driven by the cognitive effort of pushing pain down for the low conditions and pushing it up for the high conditions. Error bars show standard errors.

linear relationship with pain experience or were responding to the effort of increasing pain during the high suggestion and during the low suggestion epochs.

In summary, BOLD responses to suggested changes in fibromyalgia pain are most consistent with a pattern that might be expected if the BOLD changes were increasing linearly with subjective pain experience, and that effect is stronger when patients were hypnotized. Blood oxygen level–dependent responses to suggested changes in thermal heat pain in normal controls are most consistent with a pattern that might be expected if the BOLD changes were increasing as the subjects attempted to reduce or increase their pain experience from baseline using cognitive strategies. That effect is especially notable when the control subjects were required to reduce their pain and was stronger when hypnotized.

DISCUSSION

Similar to previous reports (33,37,51), both controls and patients reported large changes in pain experience after both hypnotic and nonhypnotic suggestion of increasing or decreasing pain experience. The hypnotic suggestions did produce larger changes, in both groups, and the added benefit of hypnotic suggestion trended toward significance overall. There was also a significant interaction of hypnosis with suggestion, which followed lower pain ratings when suggestions to reduce pain were delivered under hypnosis. Nevertheless, although significant differences were demonstrated, the absolute differences were small, especially compared to the large changes that followed both hypnotic and nonhypnotic suggestion. Overall, therefore, the behavioral data indicate little difference between hypnotic and nonhypnotic suggestion.

The behavioral data were also largely equivalent for both controls and patients, with the only difference being a significantly greater low pain rating in the controls compared with that in the patients. Interpretation of this minimal difference should be treated cautiously, as the 2 groups differed substantially in demographics and their past and current experience of pain. In addition, pain ratings were collected retrospectively, which compromises accuracy for both groups and introduces the possibility of a further

interaction of recall ability with patient status. Accepting those problems, the behavioral data indicate only marginal differences between hypnotic and nonhypnotic suggestion and between the effects of suggestion in patients and controls. These findings are consistent with previous reports and our hypotheses, and are also consistent with the view that whatever mechanism might be involved in altering pain experience with suggestion, it is the same for both the patients and the controls. Consequently, we also hypothesized that differences in brain activation when comparing hypnotic and nonhypnotic suggestion and when comparing patients with controls would also be marginal.

In contrast to these expectations, the fMRI data indicate that something quite different happened in the patients compared with the controls. For the patients, comparing higher levels of reported pain with lower levels of reported pain produced activation in areas generally associated with pain experience, including the thalamus, anterior cingulate cortex, anterior insula, and S1 and S2 (52–55). No areas of significant deactivation were found. For the controls, however, the same contrasts produced significant deactivations in the thalamus, posterior and anterior cingulate cortices, and parietal and prefrontal regions. No areas of significant activation were found. This distinct difference in activation pattern strongly suggests that whatever brain mechanism might underlie the alteration of pain experience in patients and controls, the mechanism is not the same. Broadly, the increases seen in patients are consistent with increasing pain involving increasing activation as might be expected. The decreases seen in controls, in contrast, mean that activation increased as the participants brought their pain down, which suggests that the brain activation changes are a consequence of increased cognitive effort as participants moved their pain down.

Both groups were given permissive suggestions to "allow" their pain to move as the dial moved. The intention was for the change in pain experience to be felt as effortless and happening by itself, an effect argued to be characteristic of suggestion and termed *the classic suggestion effect* (56). In an effort to maintain the consistency of suggestion, participants who reported using alternate strategies, such as distraction or dissociation, were excluded from scanning.

The activation pattern observed in the patients is broadly consistent with the patients experiencing a shift in pain, with pain regions increasing as pain experience increased. This finding is consistent with our previous report and is discussed in more detail elsewhere (33).

The activation pattern in the controls, in contrast, is not consistent with their reported changes in pain experience. Increasing pain does not reveal increasing activation in pain-related areas but rather, decreasing activity in areas that are broadly associated with cognition, as well as pain (57,58). Examining the pattern of activity more closely using ROI analysis to plot the BOLD differences across conditions revealed a pattern close to linear with increasing pain for patients but closer to increasing effort with suggested changes in pain experience for controls. Despite our instructions, and efforts to exclude participants that did not comply, it is possible that the controls spontaneously adopted effortful cognitive strategies to alter their pain experience after suggestion.

The activation patterns consistent with the above interpretations were more apparent for both groups after a formal hypnotic induction. This finding replicates our previous observations (33) and implies that whatever neural mechanism might be involved in mediating suggested changes in experience, a formal induction acts to strengthen the effects of suggestions. Whether that strengthening exceeds what might be expected based on the larger changes in pain experience after the hypnotic induction is difficult to decide. There is no simple means to translate neural activity into experience or vice versa. It is also potentially relevant clinically that the presence of a hypnotic induction procedure increased the sense of control over pain for both the clinical and experimental pain groups.

Interpretation of the activation patterns observed in both groups is limited by the lack of behavioral data that might indicate more precisely the strategies used. It is possible that the patients moved their pain more effortlessly because they have a longer history with pain, are used to their pain fluctuating, and have previously used similar strategies to move their pain. It is possible that the controls, in contrast, used strategies associated with distraction or other attention-based mechanism despite being instructed not to. In addition, despite both being selected for high hypnotizability, both groups may have mobilized very different expectations regarding the influence of hypnosis and suggestion, resulting in the different brain activation patterns observed. It is also the case that the pain experienced by controls was reported as significantly more intense at baseline than the pain of the patients and heat pain is likely to differ in many other ways from fibromyalgia pain; several studies point to potential mechanistic differences between chronic and experimental pain (59–61). Differences in pain intensity and quality might generate different pain alteration strategies during suggestion. Although the patterns of activity provide some support for the idea of effortlessness in patients and effortfulness in controls, there is considerable variability in BOLD activation within both groups and across the ROIs examined (see Supplemental Digital Content 1, http://links.lww.com/PSYMED/A310). Consequently, other interpretations are possible (62). Previous studies have demonstrated that highly hypnotizable participants use various cognitive strategies (63,64), and similar hypnotic responses may originate from different cognitive routes that may not precisely differ according to a metric of effort (65).

Despite the possibility of other interpretations, however, it is clear that the pattern of BOLD activity in the controls differs substantially from that observed in the patients. That difference implies a very different mechanism of suggestion in controls compared with patients, which would not have been evident from the behavioral data. Overall, the fMRI data, however they may be precisely interpreted, clearly revealed something not visible in the behavioral data.

REFERENCES

1. Kirsch I, Montgomery G, Sapirstein G. Hypnosis as an adjunct to Cognitive-Behavioral Psychotherapy: a meta-analysis. J Consult Clin Psychol 1995;63:214–20.
2. Lynn SJ, Rhue JW, Kirsch I. Handbook of Clinical Hypnosis, 2nd ed. Washington, DC: American Psychological Association; 2010.
3. Halligan PW, Oakley DA. Hypnosis and cognitive neuroscience: bridging the gap. Cortex 2013;49:359–64.
4. Oakley DA, Halligan PW. Hypnotic suggestion: opportunities for cognitive neuroscience. Nat Rev Neurosci 2013;14:565–76.
5. Birnie KA, Noel M, Parker JA, Chambers CT, Uman LS, Kisely SR, McGrath PJ. Systematic review and meta-analysis of distraction and hypnosis for needle-related pain and distress in children and adolescents. J Pediatr Psychol 2014;39:783–808.
6. Castel A, Cascón R, Padrol A, Sala J, Rull M. Multicomponent cognitive-behavioral group therapy with hypnosis for

the treatment of fibromyalgia: long-term outcome. J Pain 2012;13:255–65.

7. Elkins G, Johnson A, Fisher W. Cognitive hypnotherapy for pain management. Am J Clin Hypn 2012;54:294–310.

8. Hawkins RMF. A systematic meta-review of hypnosis as an empirically supported treatment for pain. Pain Rev 2001;8:47–73.

9. Iserson KV. An hypnotic suggestion: review of hypnosis for clinical emergency care. J Emerg Med 2014;46:588–96.

10. Montgomery GH, David D, Winkel G, Silverstein JH, Bovbjerg DH. The effectiveness of adjunctive hypnosis with surgical patients: a meta-analysis. Anesth Analg 2002;94:1639–45.

11. Montgomery GH, DuHamel KN, Redd WH. A meta-analysis of hypnotically induced analgesia: how effective is hypnosis? Int J Clin Exp Hypn 2000;48:138–53.

12. Patterson DR, Jensen MP. Hypnosis and clinical pain. Psychol Bull 2003;129:495–521.

13. Faymonville ME, Meurisse M, Fissette J. Hypnosedation: a valuable alternative to traditional anaesthetic techniques. Acta Chir Belg 1999;99:141–6.

14. Fredericks LE. Hypnosis as the sole anesthetic. In: Fredericks LE, editor. The Use of Hypnosis in Surgery and Anesthesiology. Charles C Thomas: Springfield, Illinois, 2001: 99–118.

15. Gow MA. Dental extractions and immediate implant placements using hypnosis in place of traditional local anaesthetics. Contemp Hyp 2010;27:268–77.

16. Hull CL. Hypnosis and Suggestibility: An Experimental Approach. Crown House Publishing 1933;2002.

17. Kihlstrom JF. Hypnosis. Ann Rev Psychol 1985;36:385–418.

18. Kirsch I. Wagstaff's definition of hypnosis. The Journal of Mind–Body Regulation 2014;2:124–5.

19. Kirsch I, Cardena E, Derbyshire SW, Dienes Z, Heap M, Kallio S, Potter C. Definitions of hypnosis and hypnotizability and their relation to suggestion and suggestibility: a consensus statement. Contemp Hyp 2011;28:107–15.

20. Kirsch I, Lynn SJ. The altered state of hypnosis. Changes in the theoretical landscape. Am Psychol 1995;50:846–58.

21. Wagstaff GF. The semantics and physiology of hypnosis as an altered state: towards a definition of hypnosis. Contemp Hyp 1998;15:149–65.

22. Braffman W, Kirsch I. Imaginative suggestibility and hypnotizability: an empirical analysis. J Pers Soc Psychol 1999;77:578–87.

23. Gandhi B, Oakley DA. Does 'hypnosis' by any other name smell as sweet? The efficacy of 'hypnotic' inductions depends on the label 'hypnosis'. Conscious Cogn 2005;14:304–15.

24. Hylands-White N, Derbyshire SWG. Modifying pain perception: is it better to be hypnotisable or feel that you are hypnotised? Contemp Hyp 2007;24:143–53.

25. Mazzoni G, Venneri A, McGeown WJ, Kirsch I. Neuroimaging resolution of the altered state hypothesis. Cortex 2013;49:400–10.

26. Deeley Q, Oakley DA, Toone B, Giampietro V, Brammer MJ, Williams SC, Halligan PW. Modulating the default mode network using hypnosis. Int J Clin Exp Hypn 2012;60:206–28.

27. Demertzi A, Soddu A, Faymonville ME, Bahri MA, Gosseries O, Vanhaudenhuyse A, Phillips C, Maquet P, Noirhomme Q, Luxen A, Laureys S. Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity. Prog Brain Res 2011;193:309–22.

28. McGeown WJ, Mazzoni G, Venneri A, Kirsch I. Hypnotic induction decreases anterior default mode activity. Conscious Cogn 2009;18:848–55.

29. Pyka M, Burgmer M, Lenzen T, Pioch R, Dannlowski U, Pfleiderer B, Ewert AW, Heuft G, Arolt V, Konrad C. Brain correlates of hypnotic paralysis—a resting-state fMRI study. Neuroimage 2011;56:2173–82.

30. Lipari S, Baglio F, Griffanti L, Mendozzi L, Garegnani M, Motta A, Cecconi P, Pugnetti L. Altered and asymmetric default mode network activity in a "hypnotic virtuoso": an fMRI and EEG study. Conscious Cogn 2012;21:393–400.

31. Egner T, Jamieson G, Gruzelier J. Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. NeuroImage 2005;27:969–78.

32. Cojan Y, Piguet C, Vuilleumier P. What makes your brain suggestible? Hypnotizability is associated with differential brain activity during attention outside hypnosis. Neuroimage 2015;117:367–74.

33. Derbyshire SW, Whalley MG, Oakley DA. Fibromyalgia pain and its modulation by hypnotic and non-hypnotic suggestion: an fMRI analysis. Eur J Pain 2009;13:542–50.

34. McGeown WJ, Venneri A, Kirsch I, Nocetti L, Roberts K, Foan L, Mazzoni G. Suggested visual hallucination without hypnosis enhances activity in visual areas of the brain. Conscious Cogn 2012;21:100–16.

35. Palsson OS, Turner MJ, Johnson DA, Burnett CK, Whitehead WE. Hypnosis treatment for severe irritable bowel syndrome: investigation of mechanism and effects on symptoms. Dig Dis Sci 2002;47:2605–14.

36. Whitehead WE. Hypnosis for irritable bowel syndrome: the empirical evidence of therapeutic effects. Int J Clin Exp Hypn 2006;54:7–20.

37. Whorwell PJ, Prior A, Colgan SM. Hypnotherapy in severe irritable bowel syndrome: further experience. Gut 1987;28:423–5.

38. Abrahamsen R, Dietz M, Lodahl S, Roepstorff A, Zachariae R, Østergaard L, Svensson P. Effect of hypnotic pain modulation on brain activity in patients with temporomandibular disorder pain. Pain 2010;151:825–33.

39. Derbyshire SW, Whalley MG, Stenger VA, Oakley DA. Cerebral activation during hypnotically induced and imagined pain. Neuroimage 2004;23:392–401.

40. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 1997;277:968–71.

41. Shor RE, Orne EC. Harvard Group Scale of Hypnotic Susceptibility, Form A. Palo Alto, CA: Consulting Psychologists Press; 1962.

42. Whalley MG, Oakley DA. Psychogenic pain: a study using multidimensional scaling. Contemp Hyp 2003;20:16–24.

43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.

44. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale—a review of validation data and clinical results. J Psychosom Res 1997;42:17–41.

45. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 1990;87:9868–72.

46. Noll DC, Cohen JD, Meyer CH, Schneider W. Spiral K-space MR imaging of cortical activation. J Magn Reson Imaging 1995;5:49–56.

47. Stenger VA, Boada FE, Noll DC. Three-dimensional tailored RF Pulses for the reduction of susceptibility artifacts in T(*)(2)-weighted functional MRI. Magn Reson Med 2000;44:525–31.

48. Oakley DA, Deeley Q, Halligan PW. Hypnotic depth and response to suggestion under standardized conditions and during fMRI scanning. Int J Clin Exp Hypn 2007;55:32–58.

49. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23(suppl 1):208–19.

50. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17: 825–41.

51. Raij TT, Numminen J, Närvänen S, Hiltunen J, Hari R. Brain correlates of subjective reality of physically and psychologically induced pain. Proc Natl Acad Sci U S A 2005;102: 2147–51.

52. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463–84.

53. Derbyshire SW, Osborn J. Modeling pain circuits: how imaging may modify perception. Neuroimaging Clin N Am 2007; 17:485–93.

54. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–91.

55. Derbyshire SWG. The use of neuroimaging to advance the understanding of chronic pain: from description to mechanism. Psychosom Med 2014;76:402–3.

56. Weitzenhoffer AM. Hypnotism and altered states of consciousness. In: Sugarman A, Tarter RE, eds. Expanding Dimensions of Consciousness, New York: Springer; 1978.

57. Gazzaniga MS. The Cognitive Neurosciences, 3rd ed. Cambridge, MA: Bradford Books; 2004.

58. Shallice T. From Neuropsychology to Mental Structure. Cambridge, MA: Cambridge University Press; 1988.

59. Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. Psychosom Med 2015;77(3):333–41.

60. Lloyd DM, Findlay G, Roberts N, Nurmikko T. Illness behavior in patients with chronic low back pain and activation of the affective circuitry of the brain. Psychosom Med 2014;76:413–21.

61. Rosselló F, Muñoz MA, Duschek S, Montoya P. Affective modulation of brain and autonomic responses in patients with fibromyalgia. Psychosom Med 2015;77(7):721–32.

62. Landry M, Raz A. Hypnosis and imaging of the living human brain. Am J Clin Hypn 2015;57:285–313.

63. McConkey KM, Barnier AJ. High hypnotisability: unity and diversity in behaviour and experience. In: Heap M, Brown RJ, Oakley DA, editors. The Highly Hypnotizable Person: Theoretical, Experimental and Clinical Issues. New York, NY: Routledge; 2004; 61–84.

64. McConkey KM, Glisky ML, Kihlstrom JF. Individual differences among hypnotic virtuosos: a case comparison. Austral J Clin Exp Hyp 1989;17:131–40.

65. Cardeña E. Hypnos and psyche, or how hypnosis has contributed to the study of consciousness. Psychology of Consciousness: Theory, Research, and Practice 2014;1:123–138.