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Cerebral activation during hypnotically induced and imagined pain

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The continuing absence of an identifiable physical cause for disorders such as chronic low back pain, atypical facial pain, or fibromyalgia, is a source of ongoing controversy and frustration among pain physicians and researchers. Aberrant cerebral activity is widely believed to be involved in such disorders, but formal demonstration of the brain independently generating painful experiences is lacking. Here we identify brain areas directly involved in the generation of pain using hypnotic suggestion to create an experience of pain in the absence of any noxious stimulus. In contrast with imagined pain, functional magnetic resonance imaging (fMRI) revealed significant changes during this hypnotically induced (HI) pain experience within the thalamus and anterior cingulate (ACC), insula, prefrontal, and parietal cortices. These findings compare well with the activation patterns during pain from nociceptive sources and provide the first direct experimental evidence in humans linking specific neural activity with the immediate generation of a pain experience.

Keywords: Functional magnetic resonance imaging; Hypnotically induced pain; Physically induced pain; Anterior cingulate cortex

Introduction

An extensive functional imaging literature has demonstrated that pain experience is mediated via activation of a network of cortical regions including the anterior cingulate cortex (ACC), insula, prefrontal regions, and primary (S1) and secondary (S2) somatosensory cortices (Derbyshire et al., 2002; Casey, 1999; Peyron et al., 2000; Price, 2000; Treede et al., 1999). The interpretation of these findings is complicated, however, by processes associated with the stimulus that are incidental to the actual sensory and emotional experience of pain. Such processes include motor inhibition or motor control responses and processes attributable to the innocuous components of the stimulus. A technique that provides for painful experience in the absence of stimulation would be valuable in the identification of brain regions that are critically and uniquely associated with the sensory and emotional components of pain.

Such a technique would also be valuable in identifying regions of the brain that may be actively generating pain disorders in patients where other abnormality cannot be demonstrated. Abnormal activation within the pain network has been postulated to cause or partially generate certain clinical pain disorders such as chronic low back pain, atypical facial pain, and fibromyalgia (Derbyshire et al., 1994, 2002; Gracely et al., 2002). Such disorders fall broadly under the umbrella of functional pain, defined as consisting of one or more symptoms that, after appropriate medical assessment, cannot be explained in terms of a conventionally defined medical disease (Wessely et al., 1999). This exclusory definition is clearly problematic because the possibility of future diagnosis based on objective findings remains open and unresolved (Derbyshire, 1999). Elevated spinal fluid substance P, abnormal single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) scans, and low serum growth hormone levels, as described in fibromyalgia patients (Bennett et al., 1997; Gracely et al., 2002; Mountz et al., 1995; Russell et al., 1994), might be precursors of a 'conventional' medical diagnosis. A model of functional pain based upon early or greater activation of central regions responsible for pain experience might also be integrated into a biomedical understanding of functional disorder (Croft, 2000; Derbyshire et al., 1994, 2002; Gracely et al., 2002).

Nevertheless, the known interconnection of stress, negative affect, and pain has led to suggestions that various stimuli ranging from injury elsewhere in the body to emotional and cognitive inputs from higher neural centers can expand, amplify, or create pain symptoms (Croft, 2000; Derbyshire, 2004). Taken together, these hypotheses and data raise the possibility that an experience of pain can originate exclusively within a subject's brain or mind rather than being necessarily dependent on the pathology of peripheral tissue.

The existence of a neural functional pain mechanism is supported by studies that have shown brain activation to be generally colinear with reported pain experience, rather than stimulus intensity, and by demonstration of specific modulation of brain activity via manipulation of affective and sensory dimensions of pain experience (Coghill et al., 2003; Croft, 2000; Derbyshire et al., 1997, 2002; Faymonville et al., 2003;

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Gracely et al., 2002; Rainville et al., 1997). The extent to which different cortical structures might actively generate a painful experience independent of peripheral input, however, is largely unknown and untested.

We have previously argued that although there are differences, in context and chronicity for example, there are common mechanisms underlying functional neurological symptoms, such as those seen in conversion disorder, and in comparable phenomena produced by suggestion in hypnosis (Oakley, 1999). In support of this view, similar patterns of brain activation have been demonstrated during attempted movement in a subject with a hypnotically induced (HI) lower limb paralysis (Halligan et al., 2000) and in a comparable conversion disorder patient (Marshall et al., 1997). There is also evidence that hypnotically induced paralysis is not only experienced as an involuntary effect but is mediated by different brain processes compared to the mere simulation or imitation of the same paralysis in hypnotized subjects (Oakley et al., 2003; Ward et al., 2003). These observations raise the possibility that a similar commonality in mechanism may exist in clinically encountered functional pain conditions and in the experience of hypnotically induced pain.

There is already some evidence that hypnotic suggestion can be used to produce the experience of pain in the absence of a physical stimulus with concomitant changes in galvanic skin response (GSR), heart rate, and respiration (Barber and Hahn, 1964; Dudley et al., 1966; Hilgard et al., 1974). More recently, we have investigated similarities in participants' experiences of hypnotically induced and physically induced (PI) pains (Whalley and Oakley, 2003), demonstrating the induction of a painful sensation in the absence of a physical stimulus. Functional imaging techniques offer the opportunity to objectively validate such self-report measures of pain. Activation of the pain network in the absence of noxious stimulation would support the possibility of direct central involvement in functional pain disorders.

In the present study, we used hypnosis as a cognitive tool to reveal cerebral mechanisms of pain generation in normal human volunteers (Rainville et al., 1997; Raz and Shapiro, 2002). A perceptual experience of pain was achieved with a hypnotic induction followed by the suggestion of painful heat without actual delivery of any stimulus (Whalley and Oakley, 2003). Cerebral cortical activity related to this hypnotically induced functional pain experience was measured using functional magnetic resonance imaging and compared with activation during actual delivery of noxious heat.

Materials and methods

Hypnosis

Functional pain was induced using a procedure adapted from Szechtman et al. (1998) and confirmed in the individuals chosen for these imaging experiments. Subjects were selected from a sample of 33 students at the University of Pittsburgh prescreened on the Harvard Group Scale of Hypnotic Susceptibility: Form A (Shor and Orne, 1962). Following a hypnotic induction, high scorers (>8) were tested for their ability to experience functional pain from an inactivated Medoc thermal probe attached to the palm of the right hand. From that group, five female and three male subjects, 21 to 50 years in age, who reported consistent pain experience in the absence of stimulation were selected for imaging with fMRI. Subjects were hypnotized upon entering the MR scanner using an induction described in detail elsewhere (Whalley and Oakley, 2003), and all experimental procedures were carried out following the hypnotic induction. After each scanning, block verbal ratings were taken concerning the intensity of the six previous pain experiences. Additional deepening instructions were provided to subjects immediately following the feedback of ratings, and reinforcement of the pain suggestion was provided before the initiation of each scanning block.

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 T 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). As in the evaluation procedure, the subjects were fitted with the thermal stimulator and told to expect noxious heat pulses to the palmar surface of their right hand interspersed by 30-s rest over 6 min. A single tap to the foot indicated arrival of the stimulus, and two taps indicated the beginning of the rest. Crucially, actual

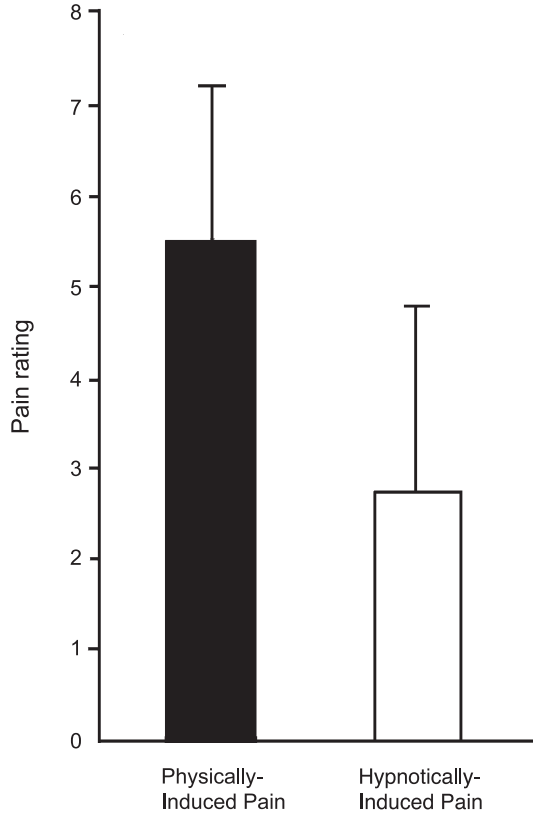

Fig. 1. Graph of the average pain ratings for the physically induced and hypnotically induced pain experience with standard deviations shown as error bars. Physically induced pain resulted in significantly greater pain ratings ($P < 0.001$).

noxious heat pulses (48.5°C) were delivered following only three of the six single taps. The other three single taps and all six double taps were accompanied by non-noxious heat (37.0°C). Functional data were collected in two blocks of 6 min each to derive 3 min of physically induced pain, 3 min of hypnotically induced pain, and 6 min of rest. The conditions (physically and hypnotically induced pain) were alternated within blocks, and the alternation was counterbalanced across blocks and subjects.

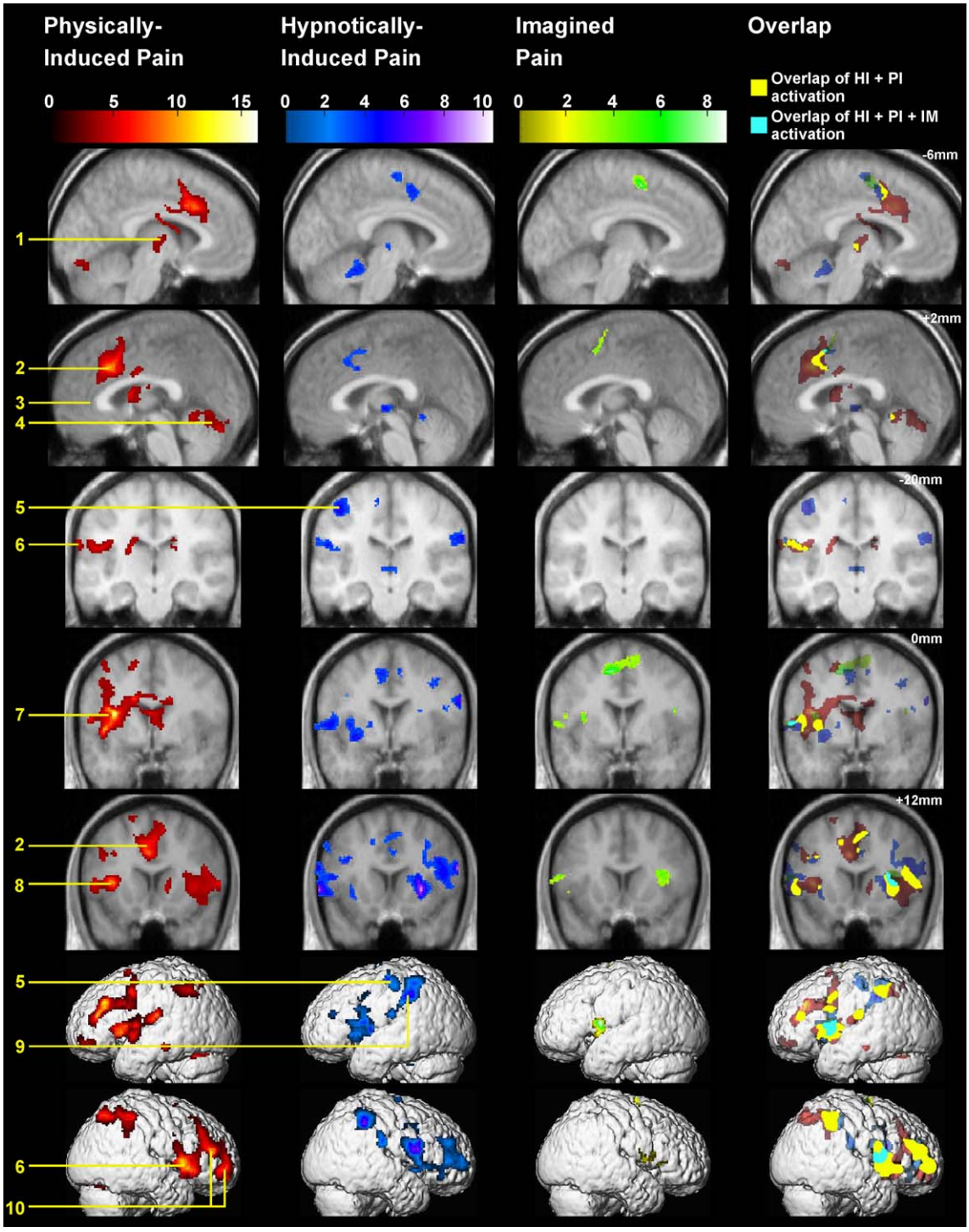

Fig. 2. Activated voxels during physically induced pain (left, red-yellow scale), hypnotically induced pain (middle, blue-purple scale), and the imagined condition (right, yellow-green scale). The effects are shown as SPMs superimposed on an averaged structural MRI derived from the subject's own structural scans. At the top are sagittal slices 6 and 2 mm lateral to the midline. Below are coronal slices 20 mm posterior (negative), on (0 mm), and 12 mm anterior (positive) to the anterior commissure. At the bottom are the surface projections. Regions of interest are numbered and significance detailed in tables 1–3.

A further block of functional data was collected with instructions to imagine the heat increasing to a painful level following a single tap to the foot. Subjects were explicitly told that the thermal probe would not be activated during this block and that they were to simply imagine the heat pain as clearly as possible following a single tap and to imagine the probe becoming deactivated following two taps. The probe temperature remained at 37.0 °C throughout. This block derived 3 min of imagined pain and 3 min of rest.

Data analysis

Data analysis was performed using SPM2 (Wellcome Trust Centre for the Study of Cognitive Neurology), described in detail elsewhere (Friston et al., 1995). In summary, head movement between scans was corrected by aligning all subsequent scans with the first. Each realigned set of scans from every subject was coregistered with his or her own hi-res structural MRI image 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 10 mm (FWHM). For each subject, a boxcar model with a hemodynamic delay function was fitted to each voxel to contrast the effects of interest with rest generating a statistical parametric map that was then assessed for significance at the second level for the group analysis shown in Fig. 2. Baseline drifts were removed by applying a high-pass filter and any artifact from the motion correction removed by applying the correction parameters as covariates of no interest. The random effects implementation corrects for variability between subjects so that outlying subjects cannot drive the result. Brain regions with a large statistic correspond to structures whose BOLD response shares a substantial amount of variance with the conditions of interest. Images were thresholded at an arbitrary $P < 0.01$ with an extent threshold of 50 contiguous voxels. Directed searches of activation were conducted on the thalamus, insula, S1, S2, and mid- and perigenual anterior cingulate (pACC), prefrontal, and inferior parietal cortices. The multiple comparisons problem of simultaneously assessing all the voxel statistics was addressed via correction for the total number of voxels reported active using the false discovery rate (Genovese et al., 2001), via a correction for voxels within a region of interest or spherical volume of 12-mm diameter centered upon the search region, or via the cluster threshold (Friston et al., 1994). These methods are consistent with those adopted elsewhere (Derbyshire, 2000; Derbyshire et al., 1997, 2002; Faymonville et al., 2003; Rainville et al., 1997) and provide a reasonable balance of protection against false-positive without artificially concealing the real profile of activation.

Results

Subjects rated the perceived intensity of each physically induced (PI) and hypnotically induced (HI) stimulus immediately following each scanning block using a verbal rating scale (0, no pain; 10, maximal pain). Average pain rating following actual delivered stimulation (PI) was 5.7 (range 3–10), and average rating without stimulation (HI) was 2.8 (range 1–9) and is illustrated in Fig. 1. This difference was statistically significant ($P < 0.001$). All of the subjects confirmed that they imagined the pain clearly in the imagined block, and only one reported actually experiencing pain (of a low intensity and only on some trials) in this condition. Four of the subjects reported a sensation of increased heat in the imagining condition. As no pain was actually expected in this condition, pain ratings were not solicited.

The profile of brain activation dependent upon these perceptual changes in pain intensity is illustrated in Fig. 2 and tabulated in Table 1. Activation of the thalamus, anterior cingulate cortex (A24/32′), cerebellum, S2, insula, inferior parietal cortex [Brodmann area (BA) 39/40], and prefrontal cortex (BA 9/10/46) are common to both physically and hypnotically induced pain, although generally with greater intensity and extent during actual stimulation. The imagined condition, in contrast, provided minimal activation in the ACC (A32′ extending into medial premotor cortex), insula, and S2. Activation in S1 was observed only during HI pain.

The differences in activation between these conditions were formally assessed and the results shown in Fig. 3 and Tables 2 and 3. HI pain resulted in marginally greater activity of the midinsula, S1, and orbitofrontal cortex (BA 11/47), while actual noxious stimulation produced greater activity of the thalamus and mid- (A24′) and perigenual anterior cingulate (A24), and prefrontal and inferior parietal cortices.

Greater activation throughout the pain matrix was evident for both hypnotically and physically induced pain relative to the imagined condition.

To directly assess the dependence of brain activation upon pain rating, the subjects with the highest and the lowest pain ratings during HI pain were analyzed separately, and the result is shown in Fig. 4. A subject with a matching average pain rating during actual stimulation was also analyzed separately for comparison. As might be predicted from previous work (Coghill et al., 2003; Derbyshire et al., 1997), higher subjective ratings are associated with greater cerebral activity. Critically, this effect is comparable whether the pain source is noxious heat or hypnotic suggestion.

Discussion

fMRI data were obtained during conditions of physically and hypnotically induced experiences of heat pain interleaved with periods of rest, revealing common activation of the thalamus, ACC, midanterior insula, and parietal and prefrontal cortices (see Table 1 and Fig. 2). These findings demonstrate the efficacy of suggestion following hypnotic induction in producing altered sensory experience, as has been demonstrated elsewhere, with specificity of the response to the stimulus under investigation (Faymonville et al., 2003; Rainville et al., 1997). Compared to the rest condition, pain from a nociceptive source and hypnotically induced pain both activated regions of the brain that have been variously described as belonging to a pain network or neuromatrix (Casey, 1999; Derbyshire, 2000; Peyron et al., 2000; Price, 2000; Treede et al., 1999).

In contrast, imagining the presence of a noxious heat stimulus resulted in only minimal activation of the pain network, extensive-

Table 1
Regions with increased BOLD relative to rest due to HI, PI, and imagined conditions separately

BOLD increases relative to rest														
(*x*, *y*, *z* coordinates) (region)					(*x*, *y*, *z* coordinates)					(*x*, *y*, *z* coordinates) (region)				
HI	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr	**PI**	*T* score	$P_{FDRcorr}$	Cluster Size	*P*corr	**Imagined**	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr
1. Thalamus														
(0, −16, 0)	5.7	0.10[b]	74	ns	(−18, −14, 10)	7.0	0.04[a]	9590	0.00	No response	–	–	–	–
					(8, 0, 4)	3.9	0.05[a]	9590	0.00	No response	–	–	–	–
2. ACC														
(−4, 4, 48)	4.2	ns	417	0.05	(−6, 10, 46))	6.3	0.06	9590	0.00	No response	–	–	–	–
(6, 8, 34)	4.3	ns	417	0.05	(8, 20, 32)	12.0	0.04	9590	0.00	No response	–	–	–	–
3. pACC														
No response	–	–	–	–	No response	–	–	–	–	No response	–	–	–	–
No response	–	–	–	–	No response	–	–	–	–	No response	–	–	–	–
4. Cerebellum														
(−12, −40, −30)	5.3	0.05[b]	187	ns	No response	–	–	–	–	No response	–	–	–	–
(8. 46, −10)	5.6	0.05[b]	118	ns	(14, −72, −16)	9.8	0.04	872	0.00	No response	–	–	–	–
5. S1														
(−30, −16, 60)	9.7	0.01[b]	332	ns	No response	–	–	–	–	No response	–	–	–	–
No response	–	–	–	–	No response	–	–	–	–	No response	–	–	–	–
6. S2/insula														
(−56, 16, −2)	9.7	0.01[a]	808	0.00	(−58, −28, −12)	6.7	0.06	110	ns	(−56, 8, 14)	5.6	0.04[b]	339	ns
No response	–	–	–	–	No response	–	–	–	–	No response	–	–	–	–

7. M. insula/putamen														
(−30, 0, −6)	5.7	0.05[b]	374	ns	(−38, 2, 18)	16.1	0.03	9590	0.00	No response	–	–	–	–
(28, 10, 4)	10.3	0.00[a]	2572	0.00	No response	–	–	–	–	(−34, 12, 8)	4.5	0.05[b]	248	ns
8. A. insula														
No response	–	–	–	–	(−34,12, 8)	9.1	0.04	9590	0.00	No response	–	–	–	–
(40, 18, 16)	7.4	0.03[a]	2572	0.00	(38, 14, 6)	5.6	0.05	9590	0.00	No response	–	–	–	–
9. Inf. parietal cortex														
(−46, −48, 60)	7.5	0.04[a]	1017	0.00	(−32, −52, 40)	6.7	0.06	1120	0.00	No response	–	–	–	–
(56, −42, 48)	7.0	0.07[a]	606	0.01	(30, −70, 56)	5.8	0.07	1452	0.00	No response	–	–	–	–
10. PFC (BA 9/46)														
(−50, 42, 24)	3.9	ns	56	ns	(−44, 34, 34)	15.1	0.03	9590	0.00	No response	–	–	–	–
(60, 14, 20)	8.3	0.01[b]	2572	0.00	No response	–	–	–	–	No response	–	–	–	–
11. PFC (BA 10/46)														
No response	–	–	–	–	(−48, 42, 18)	10.0	0.04	9590	0.00	No response	–	–	–	–
(40, 60, 4)	7.7	0.01[b]	2572	0.00	(−40, 54, −2)	7.2	0.05	9590	0.00	No response	–	–	–	–

The areas are tabulated in terms of the brain region, as illustrated in Fig. 2, and their Brodmann areas (BA). The *x, y, z* coordinates plot each peak (defined as the pixel with the highest *T* score within each labeled region) according to the MNI coordinate system (negative is left, posterior, and inferior; contralateral listed first for each region). *P* values are based on the false discovery rate (FDR)—see text for details. If a region reached significance for any comparison, then the region is tabulated for all comparisons and for both sides except where no voxels reached the display threshold ($P < 0.01$ uncorrected) indicated as no response. ACC indicates anterior cingulate cortex; pACC, perigenual anterior cingulate cortex; S1, primary sensory cortex; S2, secondary somatosensory cortex; M., mid; A., anterior; P., posterior; Inf., inferior; PFC, prefrontal cortex.

P values are corrected for the whole brain based on the false discovery rate (FDR) except where indicated.

[a] indicates correction made for the region wide voxels.

[b] indicates correction applied for 925 voxels within a spherical volume of 12 mm diameter. See text for details.

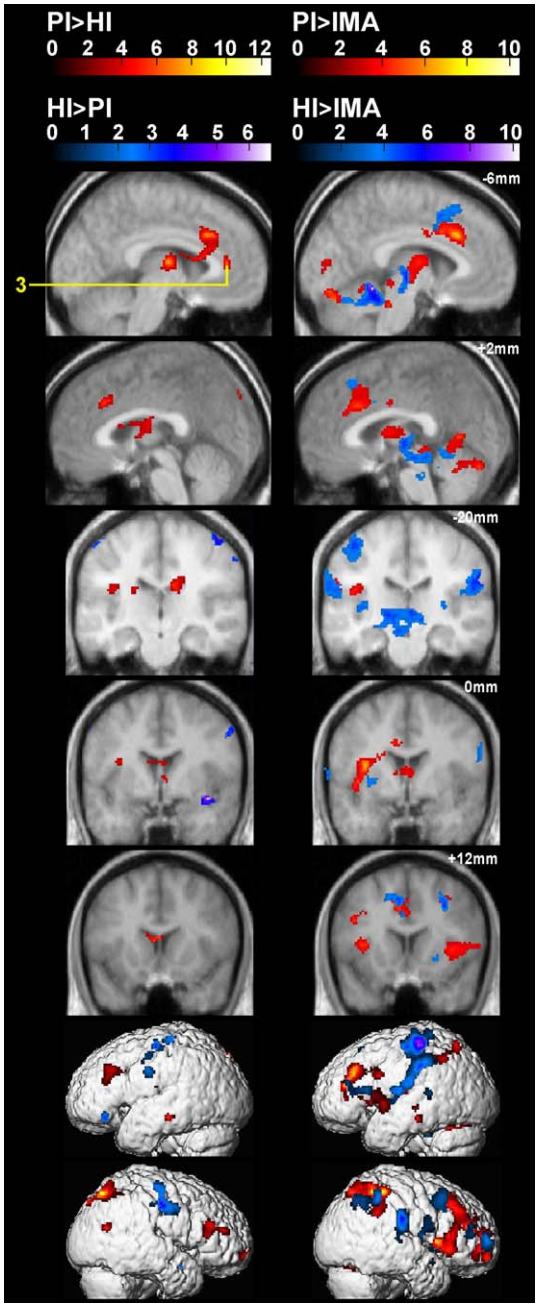

Fig. 3. Differences between the physically induced (PI) and hypnotically induced (HI) conditions to the left and the differences compared with the imagined (IMA) condition to the right. Image layout is as for Fig. 1.

ly reduced compared with both physically and hypnotically induced pain experience. These results are com- parable to those demonstrated using auditory sensation where physically presented and hypnotically hallucinated sounds resulted in activation of the right ACC, but imagining the same sound in hypnosis did not (Szechtman et al., 1998).

Although we used hypnosis here as a tool to produce the intended subjective effect, it is possible to interpret the pain experienced during the HI condition in terms of phenomena other than hypnosis per se, such as a form of conditioned response to the tap. In our experience, however, only highly hypnotizable individuals are able to routinely and repeatedly report hallucinated experience, such as the presence of pain in the absence of a stimulus, and high hypnotizables were directly selected for the current study. Nevertheless, we cannot be certain of the extent to which the hypnosis was responsible for creating the experience of pain until further studies with and without hypnotic induction are completed. Other research indicates that the hypnotic induction may be neither necessary nor sufficient to produce response to suggestion (Braffman and Kirsch, 1999), and nonhypnotic suggestion has been used to produce functional headaches in normal subjects (Schweiger and Parducci, 1981). None of this materially alters the interpretation of our findings. Activation observed during the hypnotically induced pain experience can be interpreted without the usual caveats concerning incidental sensory or motor processing that might be associated with an actual stimulus regardless of the precise influence of hypnosis in our study.

Although similar patterns were seen in the two conditions, higher levels of activation were found with physically induced pain compared with hypnotically induced pain in contralateral thalamus, ACC, and orbitofrontal cortex and in the ipsilateral parietal cortex. These larger responses can most easily be explained as being due to the more intense pain experience during PI but may also reflect the presence of peripheral sensory information (Coghill et al., 2003; Derbyshire et al., 1997).

Greater activation in the HI relative to PI condition incorporated bilateral S1 [overlapping with adjacent primary motor cortex (M1)] partly as a consequence of decreased response in the PI condition (decreases not shown). Variable S1 responses to noxious stimuli have been reported with a mix of both increases and decreases (Derbyshire, 2000; Derbyshire et al., 1997; Peyron et al., 2000). In general, S1 activation occurs in about 50% of pain studies and is usually within the appropriate somatotopical region (Derbyshire et al., 1997). Regions of S1 not currently engaged by the stimulus (such as the foot area when stimulating the hand) have been demonstrated as reducing blood flow possibly to enhance the spatial localization of the stimulus (Apkarian et al., 1992; Drevets et al., 1995). These spatial localization mechanisms may be more apparent when delivering an actual stimulus relative to the hypnotically induced pain experience.

Significant activation in the PI condition relative to HI also incorporates the perigenual ACC (pACC, A24 approaching A25). This effect follows decreased response in the HI condition. Decreased pACC activation has been previously reported during the anticipatory phase before delivery of stimulation that may be similar to the anticipation or internal monitoring of sensory information during HI (Porro et al., 2002).

Overall, however, Fig. 2 illustrates a considerable similarity in the processing of both hypnotically and physically induced pain but not with imagined pain. Fig. 4 further demonstrates predictable activation based on the perceptual report of pain experience independent of actual nociceptive input. These findings extend beyond the general suggestion of a neural network for pain by providing direct evidence that regional activation is specifically and actively involved in the generation of pain in the absence of stimulation. To our knowledge, this is the first demonstration of a functional pain experience

Table 2
Regions with significantly greater BOLD response during HI compared with PI (HI > PI) or vice versa (PI > HI)

Differences between HI and PI									
HI > PI	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr	PI > HI	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr
1. Thalamus, no difference	–	–	–	–	(−14, −14, 10)	11.05	0.02[a]	1474	0.00
2. mACC, no difference	–	–	–	–	(−4, 26, 34)	9.4	0.03[a]	1474	0.00
3. pACC, no difference	–	–	–	–	(−8, 36, 12)	8.4	0.03[b]	1474	0.00
4. Cerebellum, no difference	–	–	–	–	No difference	–	–	–	–
5. S2, no difference	–	–	–	–	No difference	–	–	–	–
6. M. insula (38, −2, 16)	6.6	0.06[b]	84	ns	No difference	–	–	–	–
7. A. insula, no difference	–	–	–	–	No difference	–	–	–	–
8. S1 (50, −14, 42)	5.6	ns	410	0.03	No difference	–	–	–	–
9. OFC (−42, 34, −12)	6.4	0.05[b]	63	ns	PFC (−42, 30, 34)	5.1	0.05[b]	160	ns
10. IPC, no difference	–	–	–	–	(32, −72, 54)	12.5	0.00[b]	1149	0.00

The areas are tabulated in terms of the brain regions as illustrated in Fig. 3. OFC indicates orbitofrontal cortex; IPC, inferior parietal cortex. Other details and abbreviations are as for Table 1.

measured with brain imaging in healthy normal controls. Direct evidence for such a mechanism being present in clinical functional pain must await further studies with chronic pain patients. Nevertheless, by providing a material basis for pain experience in the absence of injury or other physical stimulus, these findings support the possibility of direct cortical

Table 3
Regions with significantly greater BOLD response during HI compared with the imagined condition (HI > Imagined) and during PI compared with the imagined condition (PI > imagined)

Comparisons with imagined									
HI > Imagined	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr	PI > Imagined	*T* score	$P_{FDRcorr}$	Cluster size	*P*corr
1. Thalamus									
(−16, −24, −2)	5.6	0.03[b]	2050	0.00	(−12, −10, 14)	6.1	0.05[a]	839	0.00
(14, −14, 0)	7.2	0.03[b]	2050	0.00					
2. mACC									
(−4, 10, 46)	5.8	0.04[b]	471	0.02	(−8, 24, 32)	6.9	0.05[a]	789	0.00
					(10, 30, 26)	7.1	0.04[a]	789	0.00
3. pACC									
No difference	–	–	–	–	No difference	–	–	–	–
4. Cerebellum									
(−6, −46, −12)	10.3	0.00[b]	2050	0.00	(−26, −60, −24)	7.6	0.01[b]	1023	0.00
					(18, −70, −22)	10.5	0.00[b]	1023	0.00
5. S2					S2/ P. insula				
(−68, −4, −4)	8.7	0.01[b]	2708	0.00	(−42, −12, 18)	6.3	0.04[b]	921	0.00
6. P. insula					M. insula				
(−36, −26, 8)	6.1	0.03[b]	2708	0.00	(−34, 2, 16)	10.2	0.01[b]	921	0.00
7. A. insula									
No difference	–	–	–	–	(−36, 16, 12)	4.3	0.05[b]	921	0.00
					(38, 14, 6)	5.3	0.04[b]	2083	0.00
8. S1									
(−34, −28, 60)	10.2	0.02[a]	2708	0.00	No difference	–	–	–	–
9. PFC									
(−48, 28, 14)	4.2	0.08[b]	156	ns	(−46, 34, 34)	8.6	0.01[b]	495	0.04
(42, 58, 4)	7.5	0.01[b]	192	ns	(32, 60, 12)	6.9	0.04[b]	2083	0.00
10. IPC									
(38, −56, 42)	4.7	0.03[b]	330	ns	(−28, −50, 44)	7.7	0.06[a]	774	0.00
					(30, −50, 44)	9.0	0.03[a]	1845	0.00

The areas are tabulated in terms of the brain regions as illustrated in Fig. 3. P. Insula indicates posterior insula. Other details and abbreviations are as for Table 1.

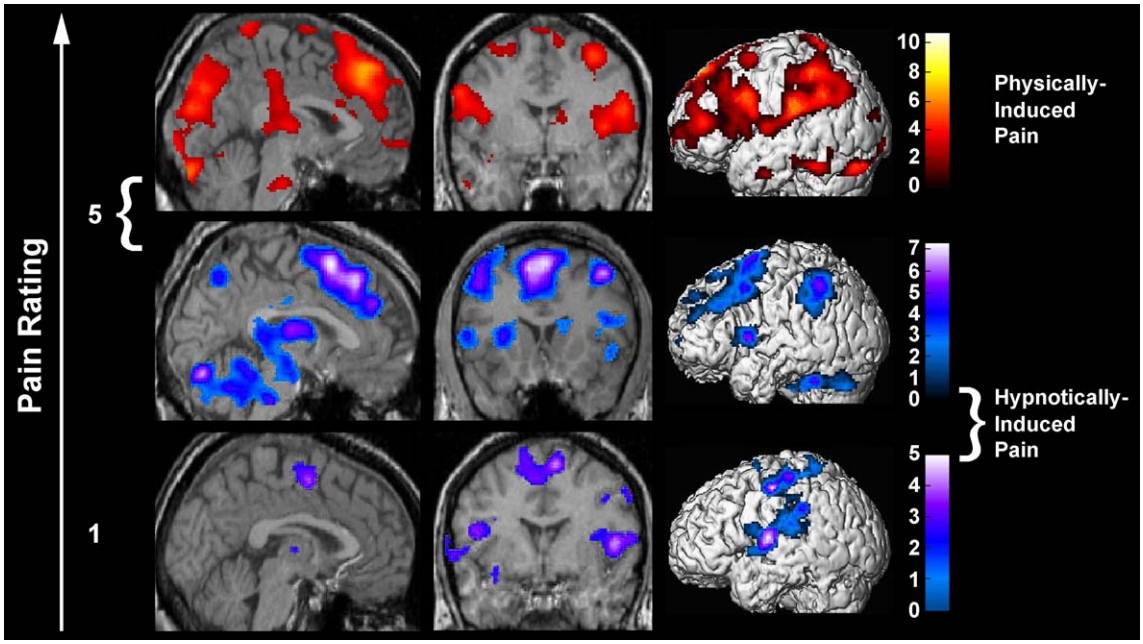

Fig. 4. Results from three individual subjects. At the bottom are activations during HI pain for the subject with the lowest average pain rating (average rating of six HI = 1), in the middle are results for the subject with the highest average rating (=5) for HI, and at the top are results from a single subject with a PI rating matching the highest HI rating (=5). The SPM results are shown superimposed on a left, contralateral, sagittal slice, a coronal slice, and projected onto the left surface of each subject's own brain.

involvement in the generation of some clinical functional pain disorders.

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