NeuroImage 47 (2009) 1047–1054

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Pain and non-pain processing during hypnosis: A thulium-YAG event-related fMRI study

A. Vanhaudenhuyse [a], M. Boly [a,b], E. Balteau [a], C. Schnakers [a], G. Moonen [b], A. Luxen [a], M. Lamy [d], C. Degueldre [a], J.F. Brichant [d], P. Maquet [a,b], S. Laureys [a,b,*], M.E. Faymonville [c]

[a] Coma Science Group, Cyclotron Research Center, University of Liège, Belgium
[b] Department of Neurology, University Hospital of Liège, Belgium
[c] Clinic of Pain, University Hospital of Liège, Belgium
[d] Department of Anesthesiology, University Hospital of Liège, Belgium

ARTICLE INFO

Article history:
Received 15 January 2009
Revised 5 May 2009
Accepted 8 May 2009
Available online 19 May 2009

ABSTRACT

The neural mechanisms underlying the antinociceptive effects of hypnosis still remain unclear. Using a parametric single-trial thulium-YAG laser fMRI paradigm, we assessed changes in brain activation and connectivity related to the hypnotic state as compared to normal wakefulness in 13 healthy volunteers. Behaviorally, a difference in subjective ratings was found between normal wakefulness and hypnotic state for both non-painful and painful intensity-matched stimuli applied to the left hand. In normal wakefulness, non-painful range stimuli activated brainstem, contralateral primary somatosensory (S1) and bilateral insular cortices. Painful stimuli activated additional areas encompassing thalamus, bilateral striatum, anterior cingulate (ACC), premotor and dorsolateral prefrontal cortices. In hypnosis, intensity-matched stimuli in both the non-painful and painful range failed to elicit any cerebral activation. The interaction analysis identified that contralateral thalamus, bilateral striatum and ACC activated more in normal wakefulness compared to hypnosis during painful versus non-painful stimulation. Finally, we demonstrated hypnosis-related increases in functional connectivity between S1 and distant anterior insular and prefrontal cortices, possibly reflecting top-down modulation.

Introduction

Nociceptive processing results from the interaction of sensory and affective components of pain, i.e. interactions between sensory characteristics of the stimulus and the state of the nervous system based on past experiences and on cognitive as well as emotional processes of the organism at the time of sensory input (Price et al., 1999; Wall, 1992). Sensory processes refer to the quality, intensity, and spatio-temporal characteristics of the sensation while affective-motivational processes relate to its negative valence and aversiveness (Melzack and Wall, 1965). Since pain is a multidimensional experience, its cerebral correlate is best described in terms of neural circuits or networks, referred to as the "neuromatrix" for pain processing, and not as a localized "pain center" (Jones et al., 1991; Peyron et al., 2000). Neuroimaging studies have brought evidence for two distinct cerebral networks involved in the perception of pain. The sensory component of pain would involve the somatosensory thalamus (lateral thalamic nuclei) and its projections to the primary and secondary somatosensory cortices. The affective component would involve the medial thalamic nuclei and its projections to the anterior cingulate and prefrontal cortices (Hofbauer et al., 2001; Rainville et al., 1997) with the insula playing an intermediate position between both components of processing (Augustine, 1996; Craig et al., 1994).

Under most circumstances, the sensory and affective components of pain are highly correlated; as pain increases, it usually becomes more unpleasant. However, in some situations such as in hypnosis, these components are dissociated (Faymonville et al., 1995, 1997, 1999, 2003; Rainville et al., 1997, 1999a). Hypnosis can be defined as "a procedure during which a health professional or researcher suggests that a patient or subject experience changes in sensations, perceptions, thoughts, or behavior" (The Executive Committee of the American Psychological Association, 1994). The hypnotic context is generally established by an induction procedure including suggestions for relaxation (Faymonville et al., 1997).

Since 1992, the University Hospital of Liège has used "hypnosedation", a combination of hypnosis with local anesthesia and minimal conscious sedation, in over 6500 patients (Vanhaudenhuyse et al., 2008). Hypnosedation was shown to be a valuable, safe and efficient alternative to general anesthesia in thyroid or parathyroid surgery (Defechereux et al., 1999, 2000; Meurisse et al., 1996; Meurisse, 1999), plastic surgery (Faymonville et al., 1995, 1997, 1999) and in the

* Corresponding author. Coma Science Group, Cyclotron Research Center, University of Liège, Sart Tilman-B30, 4000 Liège, Belgium. Fax: +32 4 366 29 46.
E-mail address: steven.laureys@ulg.ac.be (S. Laureys).
URL: http://www.comascience.org (S. Laureys).

1053-8119/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2009.05.031

severely burned (Frenay et al., 2001; Sharar et al., 2008). It has also been used as a treatment for chronic pain patients (Elkins et al., 2007; Grondahl and Rosvold, 2008; Jensen et al., 2008; Oneal et al., 2008).

The aim of this study was to investigate how the hypnotic state changes non-painful and painful laser-induced brain activation as compared to normal wakefulness by means of event-related fMRI.

Material and methods

Subjects

Thirteen healthy volunteers (8 males, age 24 ± 2 years; mean ± standard deviation) without history of neurological or psychiatric disease, gave written informed consent to participate in the study approved by the Ethics Committee of the Medical School of the University of Liège. It was performed in accordance with the Declaration of Helsinki (1997) and the International Association for the Study of Pain (IASP) Ethical Guidelines for Pain Research in Humans (Charlton, 1995). All subjects were instructed to take neither alcohol nor analgesic drugs during the 24 h preceding the experiment. Subjects were selected because they were highly hypnotizable (score 8 of 12 on the Stanford Hypnotic Susceptibility Scale-Form, Hilgard et al., 1963). During the selection procedure, which took place several weeks before the experiment, detailed information about pleasant life experiences that the subject wanted to use during hypnosis was obtained through a semi-structured interview as described elsewhere (Faymonville et al., 2003).

Stimuli and task

The stimulation procedure has been described elsewhere (Boly et al., 2007; Buchel et al., 2002). In short, we used a thulium-YAG laser (Baasel Lasertech, Starnberg, Germany) to apply computer-controlled brief radian pulses to the dorsum of the left hand of the subjects. The thulium-YAG laser emits calibrated near-infrared radiation (wavelength, 1.92 μm; spot diameter, 5 mm; pulse duration, 1 ms, distance 20 cm from the left hand) with a penetration depth of 360 μm into the human skin. The laser stimulus allows a precise restriction of the emitted heat energy to the termination area of primary nociceptive afferents without damaging the epidermis or affecting the subcutaneous tissue. It delivers brief (1 ms) stimuli with defined energy levels and activates only nociceptors, not the vibrotactile sensory system (Ploner et al., 2000). MEG studies have shown that vibrotactile stimuli evoke short-latency responses in the primary somatosensory cortex, while the latencies of laser-evoked responses in the primary somatosensory cortex were three times longer, without an initial short-latency component (Ploner et al., 2000; Timmermann et al., 2001). The temperature rise in the superficial skin after laser stimuli is fast enough to elicit activation of thinly myelinated A delta nociceptors and unmyelinated C nociceptors. At low intensities, laser stimuli elicit a sensation of light touch. At higher intensities, the induced sensation is similar to a pinprick. The stimulation site was changed slightly after each stimulus to avoid sensitization and habituation.

Two sessions were performed on 2 different days: one during normal wakefulness and one during hypnotic state. The order of the 2 sessions was randomized. The hypnotic state was induced in the same way as it is in our patients during surgery (Faymonville et al., 1995, 1997, 1999) and as in our previous PET studies on hypnosis (Maquet et al., 1999; Faymonville et al., 2000, 2003). The hypnotic instruction encompassed a 3-min induction procedure involving progressive muscle relaxation and eye fixation. Subjects were then invited to reexperience their pleasant autobiographical memory. As in clinical conditions, permissive and indirect suggestions were used to develop and deepen the hypnotic state. They were continuously given cues for maintaining a hypnotic state. The exact words and details of the induction technique and specific suggestions and details during the course of the induction varied depending upon the experimenter's (M.E.F.) observation of subject behavior, and on her judgment of subject's needs (in a similar way to her extensive clinical experience with hypnosedation; for review see Vanhaudenhuyse et al. (2008)). However, during scanning, the experimenter remained silent and the hypnotic state was considered to be present when subjects responded by a prearranged foot movement that he/she felt in the hypnotic state. The subjects were instructed to interrupt the experiment if they were going out of the hypnotic state.

During each session, 200 laser stimuli were administered with target intensities randomly ranging around 300, 400, 500 and 600 mJ (Buchel et al., 2002) and with a randomized inter-stimulus interval ranging from 8 to 12 s. After each stimulus, subjects rated their sensory perception on a five-point scale as described elsewhere (Boly et al., 2007; Buchel et al., 2002): P0, no perception; P1, perceived not painful; P2, mild; P3, moderate and P4, severe pain. The subject indicated their ratings on a keyboard with their right hand. To better separate motor response from non-painful- or pain-related activity, subjects were prompted by a tone (600 Hz sine wave, 250 ms) to respond at a randomized interval of 3–5 s after the laser stimulation.

fMRI data acquisition

Functional MRI time series were acquired on a 3 T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit-receive quadrature head coil. Multislice T_2*-weighted functional images were acquired with a gradient-echo planar imaging sequence using axial slice orientation and covering the whole brain (32 slices, FoV = 220 × 220 mm^2, voxel size 3.4 × 3.4 × 3 mm^3, 30% interslice gap, matrix size 64 × 64 × 32, TR = 2130 ms, TE = 40 ms, FA = 90°). The three initial volumes were discarded to avoid T_1 saturation effects. For anatomical reference, a high-resolution T_1-weighted image was acquired for each subject (T_1-weighted 3D magnetization-prepared rapid gradient-echo sequence, TR = 1960 ms, TE = 4.43 ms, inversion time (TI) = 1100 ms, FoV = 230 × 173 mm^2, matrix size = 256 × 192 × 176, voxel size = 0.9 × 0.9 × 0.9 mm^3).

Data analysis

Laser intensities data

Student's *t*-tests were used to compare laser intensities between normal wakefulness and the hypnosis sessions. Differences were considered significant at $p<0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 14.0). No differences were found for non-painful laser intensities in normal wakefulness and in hypnotic state (mean laser intensity ± standard deviation 294 ± 30 mJ; 298 ± 23 mJ; respectively; $t = 0.7$), as well as for painful laser intensities (534 ± 8 mJ; 532 ± 14 mJ; $t = 0.4$).

Behavioral data

A repeated measures ANOVA compared sensation scores in normal wakefulness and hypnotic state, separating stimuli into low non-painful (i.e., <450 mJ) and high noxious range (i.e., ≥450 mJ) intensities. Data were analyzed using SPSS 14.0.

fMRI data

Functional data were preprocessed and analyzed using Statistical Parametric Mapping software SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/; Wellcome Department of Imaging Neuroscience, London, U.K.). The first three fMRI volumes were discarded to allow for signal equilibration. Preprocessing steps included realignment and adjustment for movement-related effects, spatial normalization into standard stereotactic Montreal Neurological Institute (MNI) space, and spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum (Friston et al., 1995a). Functional images were then

analyzed with a mixed-effects model, aiming at showing stereotypical effect in the population from which the subjects are drawn (Penny and Holmes, 2003). The mixed-effects model was implemented in two processing steps accounting for fixed and random effects, respectively.

fMRI analysis was not based on the subject's perception but on physical properties of the stimulus, due to the fact that in hypnotic state subjects don't have perception of pain sensation. To evaluate perception of painful stimulations during hypnosis we hence, for each subject in normal wakefulness, retrospectively sorted laser stimuli in such a way that laser energy for perceived and unperceived stimuli (P0 and P1 scores) were intensity-matched (user-independent automated procedure performed using Matlab). A similar procedure was applied for the pain intensity study (P2 and P3 scores) (as described in Boly et al. (2007)). We found that non-painful sensations were matched with intensities under 450 mJ, while painful sensations were matched with intensities ≥450 mJ. In the second step, we could compare sensation scores in normal wakefulness and hypnotic state, separating stimuli into low non-painful (i.e., <450 mJ) and high noxious range (i.e., ≥450 mJ) intensities (Fig. 1).

For each subject and each condition (normal state and hypnotic state), a first-level intra-individual fixed effects analysis aimed at modeling the data to partition the observed neurophysiological responses into components of interest, confounds, and errors by using a general linear model (Friston et al., 1995b). The onsets of laser stimulations in the low and high intensity ranges were convolved with the canonical hemodynamic response function as implemented in SPM5. Laser stimuli were thus incorporated as regressors of interest in the design matrix. Motor responses were modeled in a supplementary regressor. Movement parameters derived from realignment of the functional volumes (translations in the x, y, and z directions and rotations around the x, y, and z axes) were included as covariates of no interest in the design matrix. High-pass filtering using a cut-off period of 128 (Desseilles et al., 2009; Majerus et al., 2008)) between activity in the right primary somatosensory (S1) cortex and distant brain regions involved in non-painful and painful processing, as a function of the subjects state (i.e., normal wakefulness versus hypnosis). Using psychophysiological interaction (PPI), we determined whether the correlations between activity in S1 and other brain regions differed between states (Friston et al., 1997; Gitelman et al., 2003). The choice of S1 was driven by results obtained by previous studies on sensory perception in hypnosis (Derbyshire et al., 2004; Raij et al., 2005; Rainville et al., 1997). Activity from S1 was obtained by extracting the first eigenvalue of a 6 mm radius sphere around the peak coordinates obtained by our functional localizer in sensory stimulation in normal wakefulness at the group level (i.e., $x=46$ $y=-38$ $z=52$) as described elsewhere (Boly et al., 2009). Two types of new linear models were constructed for each subject, using three regressors (plus the realignment parameters as covariates of no interest, as in the initial model). One regressor represented the subject state (i.e., normal wakefulness versus hypnosis). The second regressor was the activity in the reference area. The third regressor represented the interaction of interest between the first (psychological) and second (physiological) regressors. Significant contrasts for this psychophysiological regressor indicated a state-dependant change in the regression coefficients between any reported brain area and the reference region. We smoothed the contrast images (6 mm FWHM Gaussian kernel) in order to improve statistic across subjects by increasing the overlap between activated areas of each subject, and balancing the existing inter-subject anatomical variability (Mikl et al., 2008; White et al., 2001). The calculation of the effective smooth is $\sqrt{(8^2+6^2)}=10$ mm. These smoothed contrast images were then entered in a second-level (random effects) analysis. A one-sample t-test was performed to assess the differences in functional connectivity between normal wakefulness and hypnosis. Statistical inferences were then obtained at the population level.

In normal wakefulness, results on non-pain and pain perception were thresholded at $p<0.05$ family wise error (FWE) corrected for multiple comparisons at the whole brain level. The identified regions were used for thresholding the results obtained in hypnosis, for the comparison between hypnosis and normal wakefulness, the interaction analysis and the PPI analysis results were thresholded at $p<0.05$ corrected for small volumes (sphere with 10 mm radius) centered on our functional localizer (i.e., coordinates previously identified in normal wakefulness for non-pain and pain processing, see Tables 1 and 2).

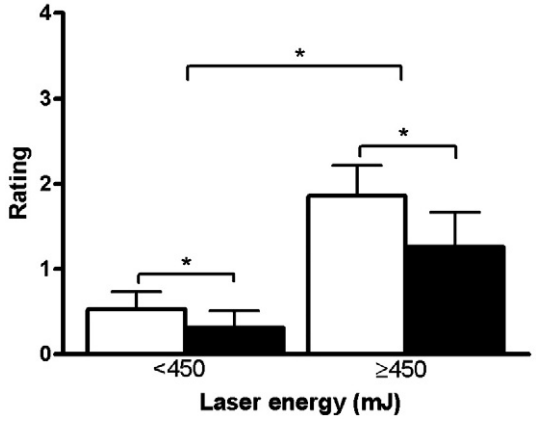

Fig. 1. Subjective ratings in non-painful (<450 mJ; left) and noxious (≥450 mJ; right) intensity ranges for normal wakefulness (mean ± standard deviation mean 0.52 ± 0.21; 0.31 ± 0.19; respectively; *Significant at $p<0.001$; white) and the hypnotic state (1.80 ± 0.36; 1.26 ± 0.40; *Significant at $p<0.001$; black) in 13 healthy volunteers.

Results

Behavioral data

Mean administered stimulation intensities were 303 ± 28; 400 ± 23, 498 ± 24 and 506 ± 26 mJ (mean ± standard deviation). As compared to normal wakefulness, subjects' ratings of perception decreased during the hypnotic state for both non-painful (mean ± standard deviation 0.52 ± 0.21; 0.31 ± 0.19; $p<0.001$; respectively) and noxious stimuli (1.80 ± 0.36; 1.26 ± 0.40; $p<0.001$). An interaction analysis showed that the effect of hypnosis was larger for the noxious as compared to the non-painful intensity ranges ($F=30.4$; $p<0.001$).

fMRI data

Non-painful stimuli

In normal wakefulness, non-painful intensity stimuli resulted in activation of right S1, bilateral insula and brainstem (encompassing periaqueductal gray matter) (Table 1; Fig. 2 — upper row). In the hypnotic state, sensory stimuli of comparable intensity to those applied during normal wakefulness (mean laser intensity in hypnosis was 298 ± 23 mJ and in normal waking was 294 ± 30 mJ; $t=0.7$) failed to elicit any cerebral activation (Fig. 2 — middle row). Comparison of activation patterns between both states showed that all above mentioned areas (i.e., right S1, bilateral insula and brainstem — encompassing periaqueductal gray matter) activated significantly less in hypnosis than in normal wakefulness (Fig. 2 — lower row).

Painful stimuli

In normal wakefulness, pain intensity stimuli resulted in activation of the brainstem (encompassing periaqueductal gray), right thalamus, bilateral striatum, right S1, bilateral insula, anterior cingulate cortex, right middle frontal gyrus and right premotor cortex (Table 2, Fig. 3 — upper row). In the hypnotic state, intensity-matched sensory stimuli

Table 1
Peak voxels of non-painful activation in normal wakefulness and in the hypnotic state and regions showing significant differences between wakefulness and hypnosis.

Regions	x (mm)	y (mm)	z (mm)	z-value	p-value
Activation in normal wakefulness					
Brainstem	−6	−22	−12	5.15	0.031[a]
Left insula	−58	−34	12	5.86	0.001[a]
Right insula	46	−16	−4	5.55	<0.0001[a]
Right primary somatosensory cortex	46	−38	52	4.77	<0.0001[b]
Activation in the hypnotic state					
No brain activation was identified					
Regions less activated in hypnosis compared to normal wakefulness					
Brainstem	0	−22	−16	4.61	<0.0001[b]
Left insula	−54	−42	8	4.34	<0.0001[b]
Right insula	46	−14	−6	4.83	<0.0001[b]
Right primary somatosensory cortex	48	−36	52	3.13	0.011[b]
Regions less activated in normal wakefulness compared to hypnosis					
No brain activation was identified					

[a] Family-wise error (FWE) corrected for multiple comparisons for the whole brain volume.
[b] Small volume correction (10 mm sphere) for multiple comparisons based on coordinates identified in normal wakefulness.

failed to elicit any cerebral activation (Fig. 3 — middle row). Comparison of activation patterns between both states showed that all above mentioned areas (i.e., brainstem, right thalamus, bilateral striatum, right S1, bilateral insula, anterior cingulate cortex, right middle frontal gyrus and right premotor cortex) activated significantly less in hypnosis than in normal wakefulness (Fig. 3 — lower row).

Interaction analyses

Brain regions activating more in normal wakefulness as compared to hypnosis during painful as compared to non-painful stimulation were identified in thalamus, bilateral striatum and ACC (Table 3). Inversely, no brain area showed higher activity in hypnosis compared to normal wakefulness in painful versus non-painful stimulation.

Psychophysiological interaction analyses

Functional connectivity was shown to be higher in hypnosis as compared to normal wakefulness between right S1 and left insular and right prefrontal cortices (Table 4). Inversely, S1 functional connectivity was not higher in normal wakefulness as compared to hypnosis with any brain region.

Discussion

In the present study, differences between hypnotic and control conditions should be considered. We here placed subjects into a hypnotic trance in the same way as our patients during surgery (Faymonville et al., 1995, 1997, 1999) but did not deliver any suggestions for pain relief. However, presentation of the word 'hypnosis' may automatically trigger lay beliefs and expectations that may have influenced our observed behavior (Gandhi and Oakley, 2005; Hylands-White and Derbyshire, 2007). Even if we did not suggest pain relief due to the hypnotic state, it cannot be excluded that this might have occurred implicitly. Another critical issue is that hypnosis was internally generated and that no output was required from our subjects. In consequence, we had to find a solution to ascertain the presence of the hypnotic state. First, there was no difference between clinical appearance of our subjects and patients undergoing surgical interventions or burn debridement under hypnosis (Faymonville et al., 1995, 1997, 1999). Second, before starting of EPI scan sequences, subjects were requested to manifest, via a prearranged foot movement, that they actually felt themselves to be in hypnosis. Finally, they were interviewed afterwards about their hypnotic experience. All subjects reported that they fell into a hypnotic state starting from the foot movement and remained in this state throughout the scanning procedure. Subjects reported having experienced vivid, detailed, and colorful revivifications of pleasant memories, having actually mentally reenacted them. Behaviorally, the effect of hypnosis on sensory perception was significantly more pronounced for pain (i.e., 38% decrease compared to normal wakefulness) as compared to its effect on non-pain ratings (i.e., 33% decrease). These results differ from Rainville et al. (1997) who observed no change induced by hypnosis on ratings of either pain intensity or unpleasantness. They reported that only specific suggestion of increased or decreased unpleasantness changed the pain ratings. Our hypnosis induction technique decreased non-pain and pain ratings without using explicit suggestions related to the stimuli.

The fMRI data showed that stimuli in the non-painful range activated brainstem, contralateral S1 and bilateral insular cortices. In line with previous studies, painful range stimuli activated additional areas encompassing right thalamus, bilateral striatum, anterior cingulate, contralateral premotor and dorsolateral prefrontal cortices (for review see e.g., Tracey (2008)). In the hypnotic state, both non-painful and painful intensity-matched stimuli failed to elicit any cerebral activation. The interaction analysis identified that contralateral thalamus, bilateral striatum and ACC activated more in normal wakefulness versus hypnosis during painful as compared to non-painful stimulation. These results confirm the known role of ACC in pain perception (e.g., Coghill et al., 1994; Craig et al., 1996; Derbyshire et al., 1997; Laureys et al., 2002; Ploghaus et al., 1999) as well as its modulatory role in hypnosis-induced analgesia (Rainville et al., 1997, 1999a,b; Faymonville et al., 2000, 2003). Our data also point to subcortical targets of "hypnoanalgesia" in thalamus and striatum. Because the thalamus represents the major cortical relay for afferent pain fibers, its involvement is predicted by theories of hypnosis that hypothesize inhibition of afferent sensory pain transmission (Faymonville et al., 2003). The thalamus (and ACC) was also shown to correlate with the magnitude of placebo-induced analgesia (Wager et al., 2004). Villemure and Bushnell (2009) recently showed

Table 2
Peak voxels of pain activation in normal wakefulness and in the hypnotic state and regions showing significant differences between normal wakefulness and hypnosis.

Regions	x (mm)	y (mm)	z (mm)	z-value	p-value
Activation in normal wakefulness					
Brainstem	0	−22	−14	5.91	<0.0001[a]
Right thalamus	6	−18	16	5.55	0.004[a]
Left striatum	−14	10	8	5.33	0.012[a]
Right striatum	16	6	−2	5.67	0.002[a]
Left insula	−60	−34	10	5.52	0.004[a]
Right insula	40	−14	14	5.28	0.01[a]
Right primary somatosensory cortex	48	−34	52	5.60	0.003[a]
Anterior cingulate cortex	−6	18	44	5.41	0.008[a]
Right middle frontal gyrus	34	48	12	5.37	0.01[a]
Right premotor cortex	36	14	60	5.19	0.025[a]
Activation in the hypnotic state					
No brain activation was identified					
Regions less activated in hypnosis compared to normal wakefulness					
Brainstem	8	−18	14	4.07	0.003[b]
Right thalamus	10	−18	14	4.21	0.001[b]
Left striatum	−14	12	10	5.15	<0.0001[b]
Right striatum	18	8	2	5.16	<0.0001[b]
Left insula	−54	−40	6	3.89	0.003[b]
Right insula	34	−14	12	3.90	0.001[b]
Right primary somatosensory cortex	46	−40	52	3.87	0.003[b]
Anterior cingulate cortex	−4	24	46	4.01	<0.001[b]
Right middle frontal gyrus	36	50	12	4.98	<0.0001[b]
Right premotor cortex	36	6	54	3.99	0.001[b]
Regions less activated in normal wakefulness compared to hypnosis					
No brain activation was identified					

[a] Family-wise error (FWE) corrected for multiple comparisons for the whole brain volume.
[b] Small volume correction (10 mm sphere) for multiple comparisons based on coordinates identified in normal wakefulness.

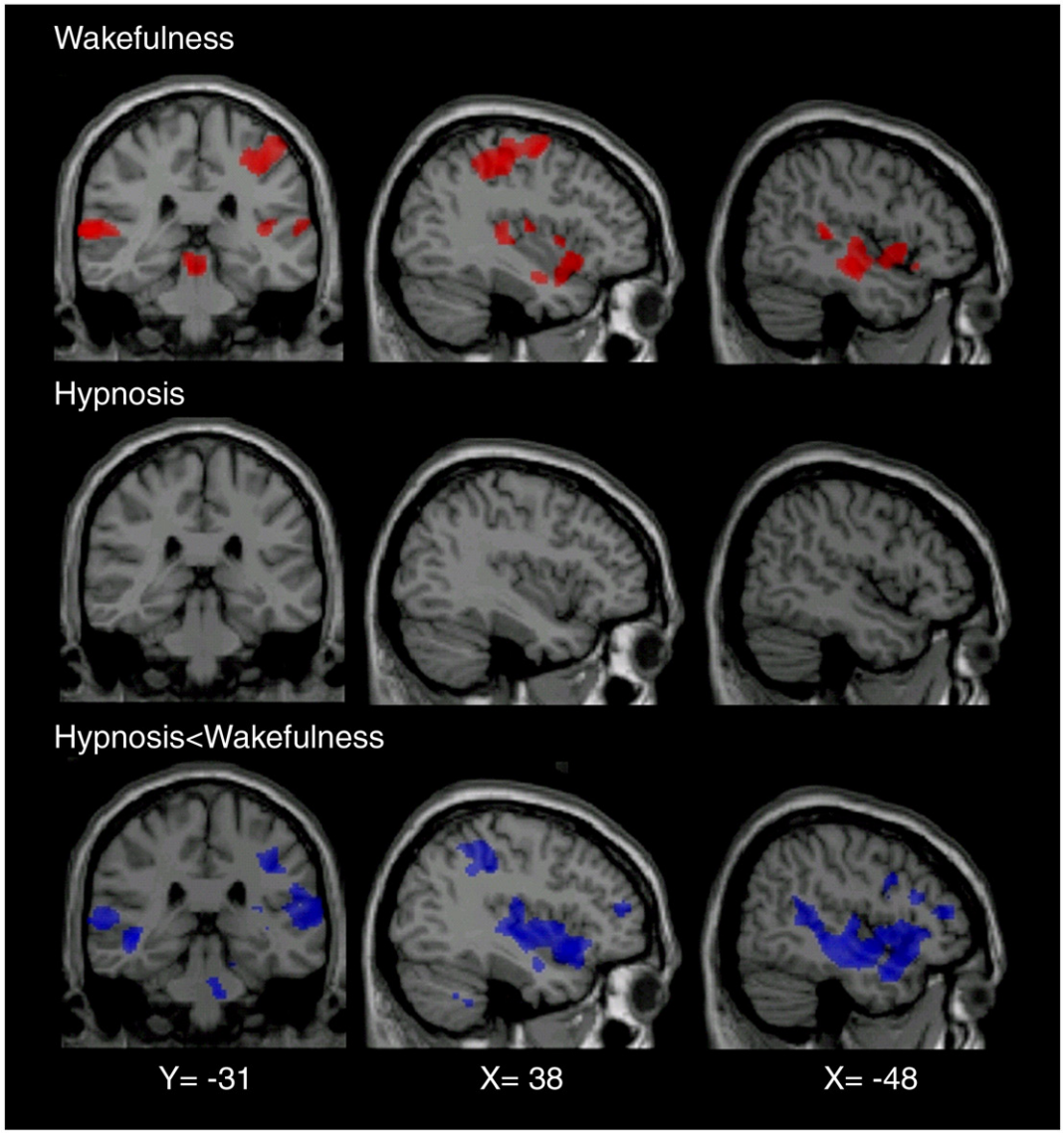

Fig. 2. Upper row. Brain regions showing significant ($p<0.05$) activation during non-painful stimulation (<450 mJ) in normal wakefulness (mean laser intensity 294 ± 30 mJ). For display, results were thresholded at uncorrected $p<0.00001$ (note that all identified regions except S1 survived FWE correction for multiple comparisons). Middle row. In the hypnotic state, sensory stimuli of comparable intensity to those applied during normal wakefulness failed to elicit any cerebral activation. Lower row. Brain regions showing significant differences with activation induced by identical stimuli in the hypnotic state (mean laser intensity 298 ± 23 mJ). For display, results were thresholded at uncorrected $p<0.001$ (note that all identified regions survived SVC correction for multiple comparisons based on a priori knowledge obtained in normal wakefulness).

involvement of thalamus and ACC in mood-related analgesia. Since the induction technique used in the present study in addition to being distracting, probably also alters emotions and attention, the observed changes in brain activation could be a combination of modulation by mood and by attention. The basal ganglia are known to encode and initiate basic movement patterns expressed through premotor pathways and are frequently reported in neuroimaging studies of pain (Coghill et al., 1994; Derbyshire et al., 1997; Derbyshire and Jones, 1998; Jones et al., 1991). They have also been proposed to support a basic attentional mechanism facilitating the calling up of motor programs and thoughts (Brown and Marsden, 1998). Joint with the observed decreases in premotor cortices activation in hypnosis, our results suggest that hypnosis, may diminish anxiety, defensive and emotional reactions to pain by reducing the activation of both cortical (encompassing ACC) and subcortical areas (encompassing thalamus and striatum) (Faymonville et al., 1997).

Finally, we demonstrated that hypnosis, compared to normal wakefulness, increased functional connectivity between S1 and distant insular and prefrontal cortices, possibly reflecting top-down modulation. The insula shows the most consistent activation in functional imaging studies on pain perception (Coghill et al., 1994; Craig et al., 1996; Derbyshire et al., 1997; Jones et al., 1991; Laureys et al., 2002; Ploghaus et al., 1999) and takes an intermediate position between the lateral (sensory-discriminative) and medial (affective-emotional) components of pain processing (Mesulam and Mufson, 1982). Increased S1-insular modulation during hypnosis is in line with its proposed role in pain affect (Rainville et al., 1999b) and pain intensity coding (Craig et al., 2000). However, it is important to stress that the used correlation analyses do not guarantee that the identified S1-insular connectivity is direct (i.e., a third area, which shows context-sensitive responses, may be providing input to the two areas implicated in the PPI) nor does it inform on the directionality of this modulation. The observed prefrontal areas may indicate distributed associative processes of cognitive appraisal, attention or memory of perceived stimuli (Courtney et al., 1998). Widespread frontal increases in rCBF have previously been demonstrated in the hypnotic state (Faymonville et al., 2000; Maquet et al., 1999; Rainville et al., 1999b). Neuropsychological studies suggest that the efficiency of the frontal

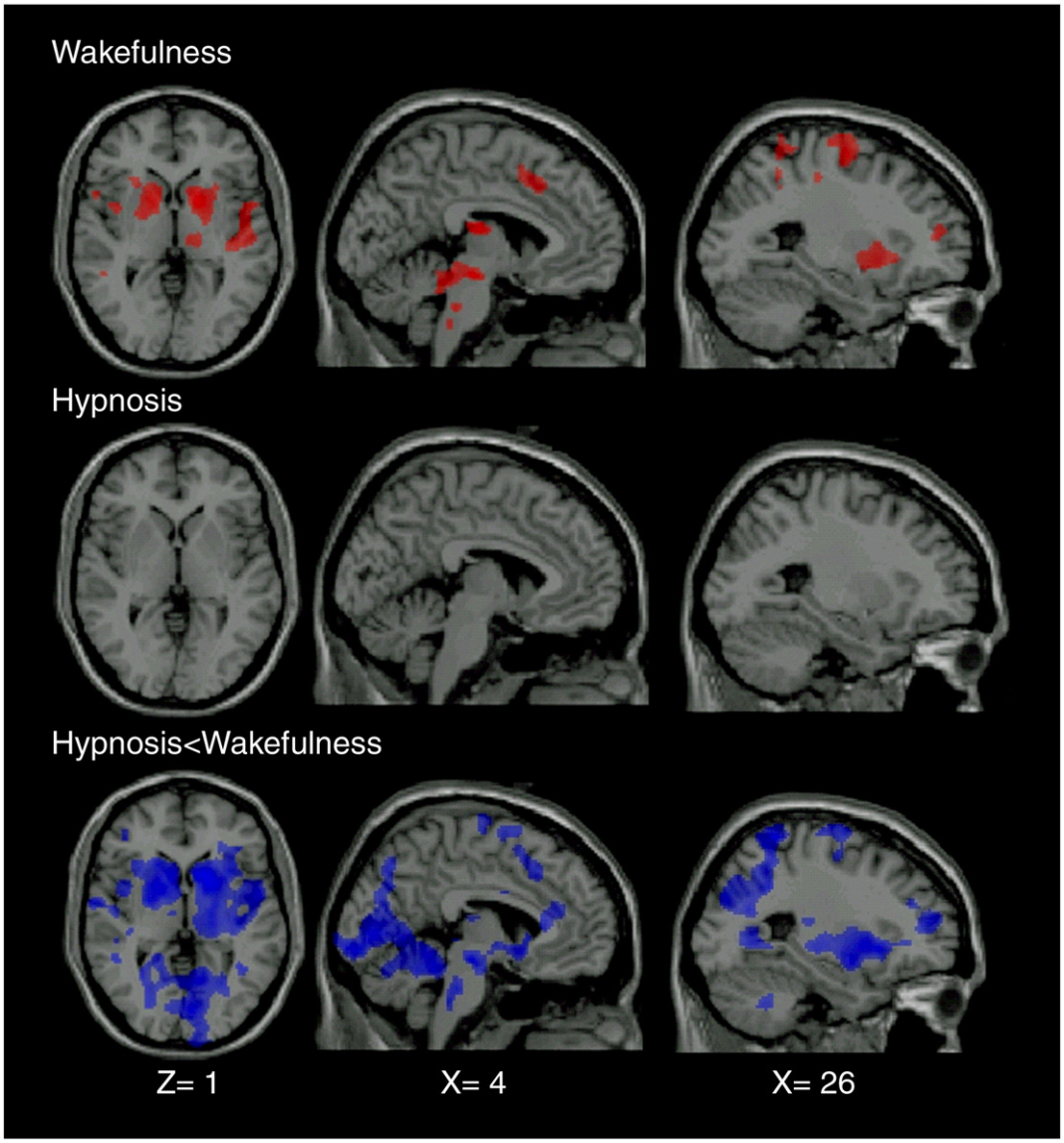

Fig. 3. Upper row. Brain regions showing significant ($p<0.05$) activation during noxious stimulation ($\geq$450 mJ) in normal wakefulness (mean laser intensity 534 ± 8 mJ). For display, results were thresholded at uncorrected $p<0.00001$ (note that all identified regions survived FWE correction for multiple comparisons). Middle row. In the hypnotic state, intensity-matched sensory stimuli failed to elicit any cerebral activation. Lower row. Brain regions showing significant differences with activation induced by identical stimuli (mean laser intensity 532 ± 14 mJ) in hypnotic state. For display, results were thresholded at uncorrected $p<0.001$ (note that all identified regions survived SVC correction for multiple comparisons based on a priori knowledge obtained in normal wakefulness).

attentional system may influence hypnotic susceptibility and thus, the perception of environmental stimulations during hypnosis (Egner et al., 2005; Kaiser et al., 1997; Kallio et al., 2001). The observed right-sided preponderance lends support to the hypothesis that the non-dominant hemisphere is preferentially involved in the negative emotion of pain (Davidson, 1992).

In conclusion, the reduced perception of both non-painful and painful ratings of the applied laser stimuli during hypnotic state compared to normal wakefulness is reflected by a decreased functional activation of not only anterior cingulate, insular, prefrontal and premotor cortices but also of downstream brain regions

Table 3
Interaction analysis identifying brain regions activated differently in normal wakefulness as compared to hypnosis during painful as compared to non-painful stimulation.

Regions	*x* (mm)	*y* (mm)	*z* (mm)	*z*-value	*p*-value
Normal wakefulness > hypnosis					
Thalamus	4	−10	12	3.43	0.009[a]
Right striatum	24	2	−6	3.76	0.004[a]
Left striatum	−20	8	6	3.29	0.007[a]
Anterior cingulate cortex	4	12	58	3.31	0.019[a]
Hypnosis > normal wakefulness					
No brain activation was identified					

[a] Small volume correction (10 mm sphere) for multiple comparisons based on coordinates identified in normal wakefulness.

Table 4
Psychophysiological interaction analyses identifying hypnosis-related changes in functional connectivity of primary somatosensory cortex.

Regions	*x* (mm)	*y* (mm)	*z* (mm)	*z*-value	*p*-value
Normal wakefulness > hypnosis					
No brain activation was identified					
Hypnosis > normal wakefulness					
Left insula	−64	−30	8	3.37	0.013[a]
Right middle frontal gyrus	26	48	6	3.09	0.033[a]

[a] Small volume correction (10 mm sphere) for multiple comparisons based on coordinates identified in normal wakefulness.

encompassing brainstem, thalamus, striatum and primary somatosensory cortex. Hypnosis-induced analgesia related to a decreased activation of ACC, striatal and thalamic areas in pain as compared to non-pain stimulation. Our findings point to a critical role for the cortical pain neuromatrix (encompassing ACC) but also of hierarchically "lower-level" brain areas (encompassing the thalamus and basal ganglia) in a hypnosis-induced decrease of sensory, affective, cognitive and behavioral aspects of sensory perception. Functional connectivity studies suggest an increased top-down modulation from anterior insular and prefrontal areas on primary somatosensory cortex. It reinforces the idea that not only pharmacological but also psychological strategies for relieving pain can modulate the cortico-cortical networks that participate in the processing of sensory external stimuli.

Acknowledgments

This research was funded by the Belgian National Funds for Scientific Research (FNRS), the European Commission, the James McDonnell Foundation, the Mind Science Foundation, the French Speaking Community Concerted Research Action (ARC-06/11-340), the Fondation Médicale Reine Elisabeth and the University of Liège. A. V. was funded by ARC 06/11-340, M.B. and E.B are research fellow at the FNRS, S.L., P.M. and C.P. are senior research associate at the FNRS.

References

Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res. Rev. 22, 229–244.
Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., Phillips, C., Peigneux, P., Maquet, P., Laureys, S., 2007. Baseline brain activity fluctuations predict somatosensory perception in humans. Proc. Natl. Acad. Sci. U. S. A. 104, 12187–12192.
Boly, M., Tshibanda, L., Vanhaudenhuyse, A., Noirhomme, Q., Schnakers, C., Ledoux, D., et al., 2009. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum. Brain Mapp. (April 6).
Brown, P., Marsden, C.D., 1998. What do the basal ganglia do? Lancet 351, 1801–1804.
Buchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., 2002. Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. J. Neurosci. 22, 970–976.
Charlton, E., 1995. Ethical guidelines for pain research in humans. Committee on Ethical Issues of the International Association for the Study of Pain. Pain 63, 277–278.
Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., Duncan, G.H., 1994. Distributed processing of pain and vibration by the human brain. J. Neurosci. 14, 4095–4108.
Courtney, S.M., Petit, L., Haxby, J.V., Ungerleider, L.G., 1998. The role of prefrontal cortex in working memory: examining the contents of consciousness. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 353, 1819–1828.
Craig, A.D., Bushnell, M.C., Zhang, E.T., Blomqvist, A., 1994. A thalamic nucleus specific for pain and temperature sensation. Nature 372, 770–773.
Craig, A.D., Reiman, E.M., Evans, A., Bushnell, M.C., 1996. Functional imaging of an illusion of pain. Nature 384, 258–260.
Craig, A.D., Chen, K., Bandy, D., Reiman, E.M., 2000. Thermosensory activation of insular cortex. Nat. Neurosci. 3, 184–190.
Davidson, R.J., 1992. Anterior cerebral asymmetry and the nature of emotion. Brain Cogn. 20, 125–151.
Defechereux, T., Meurisse, M., Hamoir, E., Gollogly, L., Joris, J., Faymonville, M.E., 1999. Hypnoanesthesia for endocrine cervical surgery: a statement of practice. J. Altern. Complement. Med. 5, 509–520.
Defechereux, T., Degauque, C., Fumal, I., Faymonville, M.E., Joris, J., Hamoir, E., Meurisse, M., 2000. Hypnosedation, a new method of anesthesia for cervical endocrine surgery. Prospective randomized study. Ann. Chir. 125, 539–546.
Derbyshire, S.W., Jones, A.K., 1998. Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. Pain 76, 127–135.
Derbyshire, S.W., Jones, A.K., Gyulai, F., Clark, S., Townsend, D., Firestone, L.L., 1997. Pain processing during three levels of noxious stimulation produces differential patterns of central activity. Pain 73, 431–445.
Derbyshire, S.W., Whalley, M.G., Stenger, V.A., Oakley, D.A., 2004. Cerebral activation during hypnotically induced and imagined pain. NeuroImage 23 (1), 392–401.
Desseilles, M., Balteau, E., Sterpenich, V., Dang-Vu, T.T., Darsaud, A., Vandewalle, G., Albouy, G., Salmon, E., Peters, F., Schmidt, C., Schabus, M., Gais, S., Degueldre, C., Phillips, C., Luxen, A., Ansseau, M., Maquet, P., Schwartz, S., 2009. Abnormal neural filtering of irrelevant visual information in depression. J. Neurosci. 29, 1395–1403.
Egner, T., Jamieson, G., Gruzelier, J., 2005. Hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe. NeuroImage 27, 969–978.
Elkins, G., Jensen, M.P., Patterson, D.R., 2007. Hypnotherapy for the management of chronic pain. Int. J. Clin. Exp. Hypn. 55, 275–287.
Faymonville, M.E., Fissette, J., Mambourg, P.H., Roediger, L., Joris, J., Lamy, M., 1995. Hypnosis as adjunct therapy in conscious sedation for plastic surgery. Reg. Anesth. 20, 145–151.
Faymonville, M.E., Mambourg, P.H., Joris, J., Vrijens, B., Fissette, J., Albert, A., Lamy, M., 1997. Psychological approaches during conscious sedation. Hypnosis versus stress reducing strategies: a prospective randomized study. Pain 73, 361–367.
Faymonville, M.E., Meurisse, M., Fissette, J., 1999. Hypnosedation: a valuable alternative to traditional anaesthetic techniques. Acta Chir. Belg. 99, 141–146.
Faymonville, M.E., Laureys, S., Degueldre, C., DelFiore, G., Luxen, A., Franck, G., Lamy, M., Maquet, P., 2000. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology 92, 1257–1267.
Faymonville, M.E., Roediger, L., Del Fiore, G., Delgueldre, C., Phillips, C., Lamy, M., Luxen, A., Maquet, P., Laureys, S., 2003. Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis. Cogn. Brain Res. 17, 255–262.
Frenay, M.C., Faymonville, M.E., Devlieger, S., Albert, A., Vanderkelen, A., 2001. Psychological approaches during dressing changes of burned patients: a prospective randomised study comparing hypnosis against stress reducing strategy. Burns 27, 793–799.
Friston, K.J., Ashburner, J., Frith, C., Poline, J., Heather, J., Frackowiak, R., 1995a. Spatial realignment and normalization of images. Hum. Brain Mapp. 2, 165–189.
Friston, K.J., Holmes, A.P., Poline, J.B., Grasby, P.J., Williams, S.C., Frackowiak, R.S., Turner, R., 1995b. Analysis of fMRI time-series revisited. NeuroImage 2, 45–53.
Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6, 218–229.
Gandhi, B., Oakley, D.A., 2005. Does 'hypnosis' by any other name smell as sweet? The efficacy of 'hypnotic' inductions depends on the label 'hypnosis'. Conscious Cogn. 14, 304–315.
Gitelman, D.R., Penny, W.D., Ashburner, J., Friston, K.J., 2003. Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. NeuroImage 19, 200–207.
Grondahl, J.R., Rosvold, E.O., 2008. Hypnosis as a treatment of chronic widespread pain in general practice: a randomized controlled pilot trial. BMC Musculoskelet. Disord. 9 (124).
Hilgard, E.R., Lauer, L.W., Morgan, A.H., 1963. Manual for Standard Profile Scales of Hypnotic Susceptibility. Forms I and II, Palo Alto, CA.
Hofbauer, R.K., Rainville, P., Duncan, G.H., Bushnell, M.C., 2001. Cortical representation of the sensory dimension of pain. J. Neurophysiol. 86, 402–411.
Hylands-White, N., Derbyshire, S., 2007. Modifying pain perception: is it better to be hypnotisable or feel that you are hypnotised? Contemp. Hypn. 24, 143–153.
Jensen, M.P., Barber, J., Hanley, M.A., Engel, J.M., Romano, J.M., Cardenas, D.D., Kraft, G.H., Hoffman, A.J., Patterson, D.R., 2008. Long-term outcome of hypnotic-analgesia treatment for chronic pain in persons with disabilities. Int. J. Clin. Exp. Hypn. 56, 156–169.
Jones, A.K., Brown, W.D., Friston, K.J., Qi, L.Y., Frackowiak, R.S., 1991. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc. Biol. Sci. 244, 39–44.
Kaiser, J., Barker, R., Haenschel, C., Baldeweg, T., Gruzelier, J.H., 1997. Hypnosis and event-related potential correlates of error processing in a stroop-type paradigm: a test of the frontal hypothesis. Int. J. Psychophysiol. 27, 215–222.
Kallio, S., Revonsuo, A., Hamalainen, H., Markela, J., Gruzelier, J., 2001. Anterior brain functions and hypnosis: a test of the frontal hypothesis. Int. J. Clin. Exp. Hypn. 49, 95–108.
Laureys, S., Faymonville, M.E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., Degueldre, C., Aerts, J., Luxen, A., Franck, G., Lamy, M., Moonen, G., Maquet, P., 2002. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. NeuroImage 17, 732–741.
Majerus, S., Belayachi, S., De Smedt, B., Leclercq, A.L., Martinez, T., Schmidt, C., Weekes, B., Maquet, P., 2008. Neural networks for short-term memory for order differentiate high and low proficiency bilinguals. NeuroImage 42, 1698–1713.
Maquet, P., Faymonville, M.E., Degueldre, C., Delfiore, G., Franck, G., Luxen, A., Lamy, M., 1999. Functional neuroanatomy of hypnotic state. Biol. Psychiatry 45, 327–333.
Melzack, R., Wall, P.D., 1965. Pain mechanisms: a new theory. Science 150, 971–979.
Mesulam, M.M., Mufson, E.J., 1982. Insula of the old world monkey. III: Efferent cortical output and comments on function. J. Comp. Neurol. 212, 38–52.
Meurisse, M., 1999. Thyroid and parathyroid surgery under hypnosis: from fiction to clinical application. Bull. Mem. Acad. R. Med. Belg. 154, 142–150 (discussion 150–144).
Meurisse, M., Faymonville, M.E., Joris, J., Nguyen Dang, D., Defechereux, T., Hamoir, E., 1996. Endocrine surgery by hypnosis. From fiction to daily clinical application. Ann. Endocrinol. (Paris) 57, 494–501.
Mikl, M., Marecek, R., Hlustik, P., Pavlicova, M., Drastich, A., Chlebus, P., et al., 2008. Effects of spatial smoothing on fMRI group inferences. Magn. Reson. Imaging 26 (4), 490–503.
Oneal, B.J., Patterson, D.R., Soltani, M., Teeley, A., Jensen, M.P., 2008. Virtual reality hypnosis in the treatment of chronic neuropathic pain: a case report. Int. J. Clin. Exp. Hypn. 56, 451–462.
Penny, W., Holmes, A., 2003. In: Frackowiak R.F.K., Frith C., Dolan R., Price C., Zeki S., Ashburner J., Penny W. (Academic, London) (Ed.), Hum. Brain Funct., p. 1114.
Peyron, R., Laurent, B., Garcia-Larrea, L., 2000. Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol. Clin. 30, 263–288.
Ploghaus, A., Tracey, I., Gati, J.S., Clare, S., Menon, R.S., Matthews, P.M., Rawlins, J.N., 1999. Dissociating pain from its anticipation in the human brain. Science 284, 1979–1981.
Ploner, M., Schmitz, F., Freund, H.J., Schnitzler, A., 2000. Differential organization of touch and pain in human primary somatosensory cortex. J. Neurophysiol. 83, 1770–1776.

Price, D.D., Milling, L.S., Kirsch, I., Duff, A., Montgomery, G.H., Nicholls, S.S., 1999. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain 83, 147–156.
Raij, T.T., Numminen, J., Narvanen, S., Hiltunen, J., Hari, R., 2005. Brain correlates of subjective reality of physically and psychologically induced pain. Proc. Natl. Acad. Sci. U. S. A. 102 (6), 2147–2151.
Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971.
Rainville, P., Carrier, B., Hofbauer, R.K., Bushnell, M.C., Duncan, G.H., 1999a. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain 82, 159–171.
Rainville, P., Hofbauer, R.K., Paus, T., Duncan, G.H., Bushnell, M.C., Price, D.D., 1999b. Cerebral mechanisms of hypnotic induction and suggestion. J. Cogn. Neurosci. 11, 110–125.
Sharar, S.R., Miller, W., Teeley, A., Soltani, M., Hoffman, H.G., Jensen, M.P., Patterson, D.R., 2008. Applications of virtual reality for pain management in burn-injured patients. Expert Rev. Neurother. 8, 1667–1674.
The Executive Committee of the American Psychological Association — Division of Psychological Hypnosis, 1994. Definition and description of hypnosis. Contemp. Hypn. 11, 142–162.
Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R., Schnitzler, A., 2001. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J. Neurophysiol. 86, 1499–1503.
Tracey, I., 2008. Imaging pain. Br. J. Anaesth. 101, 32–39.
Vanhaudenhuyse, A., Boly, M., Laureys, S., Faymonville, M.E., 2008. Neurophysiological correlates of hypnotic analgesia. Contemp. Hypn. 25 (3).
Villemure, C., Bushnell, M.C., 2009. Mood influences supraspinal pain processing separately from attention. J. Neurosci. 29, 705–715.
Wager, T.D., Rilling, J.K., Smith, E.E., Sokolik, A., Casey, K.L., Davidson, R.J., Kosslyn, S.M., Rose, R.M., Cohen, J.D., 2004. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science 303, 1162–1167.
Wall, P.D., 1992. The placebo effect: an unpopular topic. Pain 51, 1–3.
White, T., O'Leary, D., Magnotta, V., Arndt, S., Flaum, M., Andreasen, N.C., 2001. Anatomic and functional variability: the effects of filter size in group fMRI data analysis. NeuroImage 13 (4), 577–588.
World Medical Association declaration of Helsinki, 1997. Recommendations guiding physicians in biomedical research involving human subjects. JAMA 277, 925–926.