Annexe 8

Functional neuroanatomy of hypnotic state

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Functional Neuroanatomy of Hypnotic State

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Background: *The aim of the present study was to describe the distribution of regional cerebral blood flow during the hypnotic state (HS) in humans, using positron-emission tomography (PET) and statistical parametric mapping.*

Methods: *The hypnotic state relied on revivification of pleasant autobiographical memories and was compared to imaging autobiographical material in "normal alertness." A group of 9 subjects under polygraphic monitoring received six $H_2{}^{15}O$ infusions and was scanned in the following order: alert–HS–HS–HS with color hallucination–HS with color hallucination–alert. PET data were analyzed using statistical parametric mapping (SPM95).*

Results: *The group analysis showed that hypnotic state is related to the activation of a widespread, mainly left-sided, set of cortical areas involving occipital, parietal, precentral, premotor, and ventrolateral prefrontal cortices and a few right-sided regions: occipital and anterior cingulate cortices.*

Conclusions: *The pattern of activation during hypnotic state differs from those induced in normal subjects by the simple evocation of autobiographical memories. It shares many similarities with mental imagery, from which it differs by the relative deactivation of precuneus.* Biol Psychiatry 1999;45:327–333 © *1999 Society of Biological Psychiatry*

Key Words: Cerebral blood flow, positron-emission tomography, statistical parametric mapping, hypnosis, mental imagery

Introduction

Hypnosis has been used as a therapeutic tool since mankind's early history (De Betz and Sunnen 1985). Nevertheless, its acceptance by the scientific community remains limited. Consequently, the neural correlates of hypnotic state (HS) remain poorly understood. One field where the efficacy of HS has been objectively evaluated and validated is pain control (Faymonville et al 1995). Since 1992, more than 1350 patients underwent surgical procedures with a specific anesthetic method combining local anesthesia, conscious sedation, and hypnosis (Faymonville et al 1995, 1996, in press). This procedure was proposed instead of general anesthesia. We showed that the HS procedure significantly increased patient (and surgeon) comfort.

To better understand what happens in patients in the HS during surgery, we decided to explore the brain mechanisms underlying the HS in healthy volunteers by determining the distribution of regional cerebral blood flow (rCBF), taken as an index of local neuronal activity. The HS was induced in the same way as it is in patients during surgery (eye fixation, progressive muscular relaxation, and evocation of pleasant life experience). Regional cerebral perfusion was determined by positron-emission tomography (PET), with $H_2{}^{15}O$ infusions. Data were analyzed using statistical parametric mapping (SPM).

The study reported here should be considered as a first step in our approach to HS; it focuses on HS processes per se. The analgesic effects of HS are specifically explored in another experimental protocol.

Methods and Materials

Subjects' Selection

This study was approved by the Ethical Committee of the Faculty of Medicine of the University of Liège.

Young healthy right-handed subjects were considered for selection, after they gave their written informed consent. All of them were people working in the operating theater, and they applied spontaneously to participate to the experiment. From a cohort of 30 screened subjects, 15 were selected because they were scored as highly hypnotizable subjects (score >8) on the Stanford scale–form C (Hilgard et al 1963). During the selection procedure, which took place several weeks before the experimental session, subjects were asked to recall souvenirs they wanted to be used on the scanner.

PET Acquisitions

EXPERIMENT 1. Nine subjects (7 female, 2 male; mean age 30.7 years; age range 23–38) participated in the study. Before the scanning session, electrodes were put in place to monitor electroencephalogram (EEG) (C3–A2 and C4–A1), horizontal

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electro-oculogram (EOG), and chin electromyogram (EMG). A venous catheter was inserted under local anesthesia in a left antebrachial vein. The subject's head was stabilized by a thermoplastic face mask secured to the head-holder (Truscan imaging, MA). Earphones were adapted to the subject's head. Verbal communications were made at a distance via a microphone at all times. A transmission scan was performed to allow a measured attenuation correction. In both experiments, six emission scans were acquired. Each consisted of two frames: a 60-sec background frame and a 120-sec frame. The slow intravenous water ($H_2{}^{15}O$) infusion was begun just before the second frame to observe the head curve rising within the first 10 sec of this frame. Thirty millicuries (1110 MBq) were injected for each scan, in 10 cc saline, over a period of 60 sec. The infusion was totally automated so as not to disturb the subject during the scanning periods. Data were acquired by a Siemens CTI 951 R 16/31 scanner in 2D mode. Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity. The final in-plane image resolution was 8.7 mm full width at half maximum (FWHM) (Degueldre and Quaglia 1992).

Each subject was scanned twice in each of three conditions, under continuous polygraphic monitoring. In the first condition (I: alert state with autobiographical information), the subjects were studied while listening to sentences containing pleasant information taken from their own past. Subjects were instructed to imagine what happened to them in the described situations. The subjects were urged not to try to enter a hypnotic state. In the second condition (II: hypnotic state), the subjects were scanned after the hypnotic state was induced. Hypnotic state was considered to be present when roving eye movements were observed on oculography and if, just before the scan, the subject responded by a foot movement that he felt in HS. During the hypnotic state, subjects were invited to have revivification of pleasant life experiences. In the third condition (III: hypnosis with forced color hallucinations), while in hypnotic state, the subject was asked to focus on their preferred colors and to view settings and objects in these colors. Scan was also acquired after the subject manifested by a foot movement that he actually succeeded in attaining the targeted colors.

To avoid multiple hypnotic inductions that would have unduly lengthened the experimental procedure, the acquisitions during HS were blocked in the middle of the session. In consequence, the order of injections was I, II, II, III, III, I for all subjects. Subjects were scanned with eyes closed throughout the experimental procedure. Ambient noise was reduced to a minimum, and ambient light was dimmed. The same experimenter (MEF) spoke to the subjects in all conditions.

EXPERIMENT 2. This experiment was designed to evaluate the distribution of regional cerebral blood flow during revivification of personal memories, which served as the control situation in experiment 1.

Six subjects (4 female, 2 male; mean age 29.3 years; age range 24–39) participated in this experiment, during which we contrasted the autobiographical condition to a resting condition. In the first condition (IV: rest), subjects were scanned in a resting state and were asked to empty their mind. The second condition (V: autobiographical) exactly replicated the control condition of the first experiment. The third condition (VI) was part of a larger study on language processing and will not be discussed here. In this condition, the subjects heard the auditory stimuli presented during condition V, played backward on a tape.

The order of injection respected a Latin square design (IV, V, VI, VI, V, IV) and was counterbalanced over subjects. Subjects were scanned with eyes closed throughout the experimental procedure. Ambient noise was reduced to a minimum, and ambient light was dimmed. Data acquisition was identical to experiment 1, except that no polygraphic recording was obtained.

Data Analysis

PET data were analyzed using the statistical parametric mapping software (SPM95 version; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, U.K.) implemented in MATLAB (Mathworks Inc., Sherborn, MA). In short, data from each subject were realigned using a least square approach and the first scan as a reference (Friston et al 1995a). Following realignment, all images were transformed into a standard space (Friston et al 1995a; Talairach and Tournoux 1988) and then smoothed using a 12-mm FWHM isotropic kernel. A design matrix was specified, according to the general linear model (Friston et al 1995b). It included the global activity as confounding covariate (Friston et al 1990). The condition effects were first estimated at each and every voxel. The analysis used linear contrasts to identify the brain regions where rCBF was significantly increased (II+III−I) or decreased (I−II−III) in hypnosis as compared to normal alertness. The areas more active during hypnosis with color hallucination than during hypnosis alone (III−II) were also looked for. Finally, the analysis looked for areas more active while listening to autobiographical evocation than at rest (V−IV).

The resulting set of voxel value for each contrast constituted a map of the t statistic (SPM{t}). The SPM{t} were then transformed to the unit normal distribution (SPM{Z}) and thresholded at $p < .001$ ($Z = 3.09$). The resulting foci of activation were finally characterized in terms of peak height over the entire volume analyzed, [$p(_{Zmax > u})$], which corresponds to a corrected p value $< .05$ (Friston et al 1991, 1994, 1995b).

Results

Experiment 1

All subjects readily entered the HS when HS induction was begun. They remained in the HS until the end of the fifth scan, as requested by the experimental protocol.

During the experimental session, EEG recordings did not show any sign of sleep (spindles, K complexes). During HS, the waking alpha rhythm was fragmented and replaced by periods of slower (theta) activities. Oculograms systematically showed slow roving eye movements. EMG recordings were characterized by a decreased muscular tone.

During HS with color hallucination, all subjects reported having successfully obtained the desired color.

Table 1. Localization[a] and Statistical Results[b] Concerning the Local Maxima of the Brain Areas Where rCBF Is Significantly Higher or Lower in Hypnotic State than during Imaging Autobiographical Material in "Alert" State

Side	Cerebral area	BA	x	y	z	Z score	p (corrected)
Increases in HS							
Left	Occipital cortex	18	−24	−96	−4	4.30	.032
			−30	−76	0	4.71	.006
			−24	−82	0	5.05	.001
		19	−30	−68	−4	4.37	.024
			−20	−62	36	5.37	<.001
		37	−50	−56	−20	4.92	.002
Right	Occipital cortex	18	2	−78	−4	4.73	.006
			6	−70	−8	4.24	.039
Left	Inferior parietal lobule	40	−24	−48	28	5.66	<.001
			−40	−34	32	4.88	.003
Left	Precentral cortex	4	−48	−8	32	4.63	.008
		4/6	−36	−4	32	4.39	.022
		4/43	−42	−10	20	4.27	.035
			−26	−22	36	4.44	.018
Left	Prefrontal cortex	45	−28	26	8	5.45	<.001
			−24	22	16	5.16	.001
			−28	12	20	4.61	.009
Right	Anterior cingular cortex	24/32	14	32	16	4.43	.019
Right	Cerebellum		16	−52	−28	5.85	<.001
			10	−64	−12	4.96	.002
Decreases in HS							
Left	Temporal cortex	20	−56	−16	20	4.71	.006
		21	−46	0	20	4.91	.003
			−60	−34	8	4.23	.041
		38	−26	16	20	5.29	<.001
			−40	8	20	4.47	.017
		39	−46	−64	4	4.41	.021
Right	Temporal cortex	21	48	0	16	7.11	<.001
			60	−24	4	5.28	<.001
		22	56	−30	4	5.12	.001
Medial	Prefrontal cortex	8	−6	34	4	5.10	.001
			−4	26	8	4.86	.003
			−6	12	8	4.17	.050
		9	−4	50	4	4.82	.004
		10	0	50	8	4.22	.042
Right	Premotor cortex	6	42	2	4	5.64	<.001
Medial	Precuneus	7	−2	−56	4	5.70	<.001
Right	Cerebellum		18	−82	−28	4.35	.026

[a]Coordinates are defined in the stereotactic space of Talairach, relative to anterior commissure. x represents the lateral distance from midline (positive = right); y is the anteroposterior distance from anterior commissure (positive = anterior); z represents the rostrocaudal distance from the bicommissural plane (positive = rostral).

[b]The areas are significant at a threshold of $p = .001$, by reference to unit normal distribution ($Z = 3.09$), and at a threshold of corrected $p < .05$ (corrected p, the probability that the regional rCBF variation could have occurred by chance over the entire volume analyzed).

Significant increases in rCBF during hypnosis (conditions II and III) as compared to normal alertness (condition I) were observed in four regions (Table 1, Figure 1A). The largest excursion set was left-sided and involved extrastriate visual cortex [Brodmann's area (BA) 18, 19, 37], inferior parietal lobule (BA 40), precentral and adjacent premotor (BA 6) cortex, and the depth of ventrolateral prefrontal cortex (BA 45), close to the insular cortex. The second area was right-sided and involved deep cerebellar nuclei and prestriate cortex (BA 18). The two last areas are the right anterior cingulate cortex (BA 24/32) and left occipitotemporal cortex (BA 37). Significant decreases in rCBF during hypnosis as compared to normal alertness (Table 1, Figure 1B) were observed in left temporal cortex (BA 20, 21, 38, 39), right temporal cortex (BA 21, 22), medial prefrontal cortex (BA 8, 9, 10), posterior cingulate (BA 39) and adjacent precuneus (BA 7), right premotor cortex (BA 6/8), and right cerebellar hemisphere. No significant rCBF variations were detected between hypnosis with and without forced color hallucination.

The comparison of conditions III and II (effects of color hallucinations during HS) provided no significant results.

ery tasks (Kosslyn et al 1996) and would be involved in the programming of the building up of the mental image or in the maintenance of image in memory. In this respect, the left-sided lateralization is not easily explained. We do not feel that prefrontal activation could reflect subvocal subjects' vocalization, because orofacial movements are usually less frequent in hypnosis. Finally a right-sided activation of anterior cingulate cortex would probably reflect the attentional effort necessary for the subject to internally generate mental imagery (Devinsky et al 1995; Posner and Petersen 1990).

Some cortical areas are significantly less active during hypnosis that during the alert state. These temporal deactivations might simply emphasize that autobiographical evocation is, in contrast to HS, characterized by a prominent activation of anterior temporal lobe structures (experiment 2 and Fink et al 1996). Alternatively, the deactivation of anterior parts of both temporal lobes could also indicate that subjects did not resort to auditory mental imagery, which is known to activate temporal areas (Zatorre et al 1996). It could also be explained by the experimental conditions. The examiner's speech rate was lower during the hypnosis than during alert conditions. This parameter is known to influence the activity of left superior temporal cortex (Price et al 1992). Likewise, processing of pitch (which was lower and more monotonous during HS) depends on right hemisphere structures (Zatorre et al 1992; Zatorre and Samson 1991).

The deactivation of precuneus has been reported during visual discrimination tasks, when visual stimulus is physically present (Shulman et al 1996). In contrast, precuneus is usually activated in tasks requiring mental imagery (Kosslyn et al 1996), long-term memory (Grasby et al 1993), and visual attention (Corbetta et al 1993). The deactivation of precuneus is certainly an important metabolic feature distinguishing hypnotic state from alert visual mental imagery.

The mesial frontal deactivation remains speculative, as the function of this part of the prefrontal cortex remains fragmentary. Such deactivation has been reported in several tasks, such as visual discrimination (Shulman et al 1996) and mental arithmetics (Ghatan et al 1996). It would reflect the interruption of tasks going on during alert condition, irrelevant to the HS, such as unconstrained monitoring of environment, emotional state, or thought processes.

Comparison with Other Internally Generated Mental Experiences

Hypnotic state should be distinguished from other types of internally generated, polymodal perceptuomotor experiences, the functional anatomy of which has recently been approached with PET: dreams during REM sleep in normal subjects (Maquet et al 1996), and hallucinations in schizophrenic patients (Silbersweig et al 1995).

In the present study, no subjects presented polygraphic evidence of slow sleep (sleep spindles, K complexes, or large-amplitude slow waves) or REM sleep (especially complete atonia). The distribution of regional cerebral blood flow during HS is mainly cortical and does not seem to activate the pons, the thalami, and amygdaloid complexes, in contrast to what has been observed in REM sleep with dreaming (Maquet et al 1996).

Likewise, HS differs from the schizophrenic hallucinations (estimated on a group of patients) by the absence of subcortical and paralimbic activation and by the activation of lateral prefrontal cortex (Silbersweig et al 1995).

Conclusions

Taken together, these results suggest that, in our experimental conditions, HS is a particular cerebral waking state where the subject, seemingly somnolent, experiences a vivid, multimodal, coherent, memory-based mental imagery that invades and fills the subject's consciousness.

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Annexe 9

Neural mechanisms of antinociceptive effects of hypnosis

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Neural Mechanisms of Antinociceptive Effects of Hypnosis

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Background: **The neural mechanisms underlying the modulation of pain perception by hypnosis remain obscure. In this study, we used positron emission tomography in 11 healthy volunteers to identify the brain areas in which hypnosis modulates cerebral responses to a noxious stimulus.**

Methods: **The protocol used a factorial design with two factors: state (hypnotic state, resting state, mental imagery) and stimulation (warm non-noxious *vs.* hot noxious stimuli applied to right thenar eminence). Two cerebral blood flow scans were obtained with the ^{15}O-water technique during each condition. After each scan, the subject was asked to rate pain sensation and unpleasantness. Statistical parametric mapping was used to determine the main effects of noxious stimulation and hypnotic state as well as state-by-stimulation interactions (*i.e.*, brain areas that would be more or less activated in hypnosis than in control conditions, under noxious stimulation).**

Results: **Hypnosis decreased both pain sensation and the unpleasantness of noxious stimuli. Noxious stimulation caused an increase in regional cerebral blood flow in the thalamic nuclei and anterior cingulate and insular cortices. The hypnotic state induced a significant activation of a right-sided extrastriate area and the anterior cingulate cortex. The interaction analysis showed that the activity in the anterior (mid-)cingulate cortex was related to pain perception and unpleasantness differently in the hypnotic state than in control situations.**

Conclusions: **Both intensity and unpleasantness of the noxious stimuli are reduced during the hypnotic state. In addition, hypnotic modulation of pain is mediated by the anterior cingulate cortex. (Key words: Functional neuroimaging; pain; statistical parametric mapping.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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HYPNOSIS combined with slight conscious intravenous sedation (hypnosedation) and local anesthesia offers a valuable alternative to traditional general anesthesia.[1–4] In our center, the technique has been used in more than 1,800 surgical interventions since 1992. The effectiveness of hypnosis in producing analgesia has been demonstrated by two clinical studies. A retrospective study first showed that hypnosis as an adjunct procedure to conscious intravenous sedation provides significant perioperative pain and anxiety relief. These benefits were obtained despite a significant reduction in drug requirements.[1] A prospective randomized study confirmed these observations.[2]

In a recent positron emission tomography (PET) study aimed at differentiating cortical areas involved in pain affect, Rainville *et al.*[5] used hypnotic suggestions to alter selectively the unpleasantness of remained noxious stimuli, without changing the perceived intensity. In these conditions, anterior cingulate cortex (ACC) activity was shown to be selectively correlated with unpleasantness. However, our experimental design differed in that volunteers were asked to rate unpleasantness and perceived intensity of noxious stimuli without a specific demand to

maintain either one or the other constant. By this it is meant that subjects were not asked to actively induce analgesia but only to recall pleasant life experiences, without any reference to pain perception.[1,2] The rationale of the present study was to explore the brain mechanisms underlying the modulation of pain perception proper to our clinical hypnotic protocol.

Materials and Methods

Subjects

This study was approved by the Ethical Committee of the Faculty of Medicine of the University of Liège. Healthy right-handed drug-free unpaid volunteers were considered for selection after written informed consent was obtained. From a cohort of 30 screened subjects, 11 (4 women, 7 men; mean age, 31.7 yr; age range, 27–55 yr) were selected because they were scored as highly hypnotizable subjects (score > 8 of 12) according to a French version of the Stanford Hypnotic Susceptibility Scale–Form C.[6] During the selection procedure, which took place several weeks before the experimental session, detailed information about pleasant life experiences that the subject wanted to use during the experiment was obtained through a semistructured interview.

Experimental Design

Experimental Conditions. The experiment followed a factorial design with two factors: stimulation (warm non-noxious *vs.* hot noxious) and state (resting state [RS], mental imagery [MI], hypnotic state [HS]).

In the first condition (RS), the subjects were asked to empty their minds and remain immobile. In the second condition (MI), during the interscan interval, the subjects listened to sentences containing pleasant information taken from their own past. Subjects were instructed to vividly imagine a pleasurable autobiographical memory. The subjects were urged not to try to enter in the HS. During 90-s scanning periods, the experimenter remained silent. Subjects confirmed by a foot movement that they used MI. In the third condition (HS), the subjects were scanned after the HS was induced. This condition started with a 3-min induction procedure involving muscle relaxation. 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 HS. They were continuously given cues for maintaining an HS. However, during the scans, the experimenter remained silent. The HS was considered to be present when roving eye movements were observed on oculography and if, just before the scan, the subjects responded by a prearranged foot movement that he/she felt in the HS. Slow ocular movements are regularly observed in the HS in isolation or intermingled with few saccades. This pattern of ocular movements, in conjunction with the subject's behavior, was used to differentiate the HS from other states. Polygraphic recordings ensured that no sleep occurred during the experimental session.

Each subject was scanned twice in both levels of stimulation (non-noxious and noxious) in each of the three states (12 scans per subject). After each measurement, the subjects were asked to verbally rate the noxious stimulus intensity and unpleasantness on a scale from 0 to 10 (for sensation, 0 = no pain sensation, 10 = most intense painful sensation imaginable; for unpleasantness, 0 = not at all unpleasant, 10 = most unpleasant imaginable). To avoid multiple hypnotic inductions, the fifth to eighth scans were always made in HS. The order of the other two states, and of the non-noxious and noxious stimulations, was pseudorandomized over subjects. Subjects were warned that scans started but were not told in which order the different stimulations would occur. Subjects were instructed to keep their eyes closed throughout the experimental session. Ambient noise was reduced to a minimum, and ambient light was dimmed.

Thermal Stimulation. Thermal stimuli were delivered by a Marstock thermal stimulator (Somedic: thermotest Type I; Senselab, Upsala, Sweden) that delivers calibrated and reproducible thermal stimulations *via* a water-cooled probe (2.5 × 5 cm). The thermode was applied to the thenar eminence of the right hand. The stimuli consisted of a ramp increase from 35°C to the predetermined level during 5 s, a plateau at this temperature for 5 s, and linear return to the baseline temperature for 5 s. This sequence was repeated six times during the scanning period. Thermal stimulation started 10 s before the second frame of the scans.

Before the PET studies, target temperatures that were reproducibly experienced as warm and non-noxious (typically 39°C) or hot and noxious (typically 47°C) were carefully established for each subject before the study. Once established, these individual (non-noxious and noxious) temperatures were used during the corresponding scans. Practice sessions were conducted so that the anxiety and emotional reactions associated with a novel experimental situation or unexpected noxious stimuli would be reduced.

PET and Magnetic Resonance Imaging Acquisitions. Before the scanning session, electrodes were put in place to monitor electroencephalograph (C3–A2 and C4–A1), horizontal electrooculogram, and chin electromyogram. A venous catheter was inserted during local anesthesia in a left antebrachial vein. The subject's head was stabilized by a thermoplastic face mask secured to the head holder (Truscan Imaging, Anapolis, MA). Earphones were adapted to the subject's head, and verbal communications were made at a distance *via* a microphone. Direct visual observation was maintained at all times. A transmission scan was performed to allow a measured attenuation correction. Twelve emission scans were acquired at 8-min intervals in three-dimensional mode using a CTI 951 16/32 scanner (Siemens, Erlangen, Germany). Each scan consisted of two frames: a 30-s background frame and a 90-s frame. The slow intravenous water ($H_2{}^{15}O$) infusion was begun just before the second frame to observe the head curve rising within the first 10 s of this frame. Six to eight millicuries (222–296 MBq) were injected for each scan, in 10 ml saline, over a period of 20 s. The infusion was totally automated so as not to disturb the subject during the scanning periods. Data were reconstructed using a Hanning filter (cutoff frequency: 0.5 cycle/pixel) and corrected for attenuation and background activity.

A high resolution (voxel size: 0.96 × 0.96 × 1.35 mm) T1-weighted structural magnetic resonance imaging scan was obtained for each subject on a 1.5 T imager (Magnetom, Siemens) a few days after the PET session.

PET Data Analysis

Positron emission tomography data were analyzed using the statistical parametric mapping software (SPM96 version; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom[7]) implemented in MATLAB (Mathworks Inc., Sherborn, MA). In short, data from each subject were realigned using a least square approach and the first scan as a reference.[8] PET data were then coregistered to individual T1-weighted magnetic resonance imaging scans. After realignement, all images were transformed into a standard space[8,9] and then smoothed using a 16-mm full width at half-maximum isotropic kernel.

Two separate statistical analyses were performed. The first one was based on categoric comparisons, and the second used a multiple regression approach. For categoric comparisons, the design matrix[10] included the 12 conditions (scans) for each subject. For the regression analysis, the design matrix consisted of three covariates of interest: the pain ratings, the experimental states, and a covariate representing the interaction between ratings of pain perception and the states (the HS *vs.* control states). The state regressor consisted of dummy variables (−1 for RS and MI scans and 1 for the HS scans). The use of pain ratings and states as regressors allowed the assessment of main effects of pain perception and the HS condition, respectively. These two covariates were centered, orthogonalized, and multiplied, element by element, to form the third covariate, which thus represented a state-by-stimulation interaction covariate. The rationale of similar types of analysis was described by Friston *et al.*[11] In essence, this analysis looks for a difference in the slope of regression between cerebral blood flow (CBF) and pain ratings between the HS and the other states.

In both types of analysis, the design matrix also included the block effect as a confounding covariate.[12] Global flow normalization was performed by proportional scaling. Furthermore, the RS and MI were considered together and contrasted to the HS. The collapse of these states into a single one was considered when behavioral data showed no significant difference in pain ratings between them (see Results).

The resulting set of voxels for each contrast constituted a map of the t statistic (SPM{t}). The SPM{t} were then transformed to the unit normal distribution (SPM{z}). Whatever the analysis, the first step was to identify the main effects of pain and hypnosis. In these contrasts, hypotheses existed as to which brain areas should be found activated. Results were thus considered significant at $Z = 3.09$ ($P < 0.001$, uncorrected). Based on previous literature, the main effect of noxious stimulation was considered in upper midbrain, thalamic nuclei, lentiform nuclei, primary and secondary somatosensory cortexes, the insula, and the ACC. On the basis of our previous study,[13] the effect of hypnosis was suspected to occur bilaterally in the occipital regions and the ACC or on the left side in parietal, motor areas, and the ventrolateral prefrontal cortex.

However, the particular interest of the present study was in the state-by-stimulation interaction, looking for the brain areas that would be more (or less) activated by noxious stimulation during the HS than in other states. For this purpose, we considered the analysis as exploratory and used a more conservative level of significance (*i.e.*, $P < 0.05$ corrected for multiple comparisons at the voxel level).[10]

Results

Behavioral Data

The average temperature used for warm non-noxious and noxious stimulation was, respectively, 39.1°C ± 0.3 and 47.2°C ± 1.1 (mean ± SD).

Figure 1 shows ratings of unpleasantness and pain sensation after thermal non-noxious and noxious stimulation in RS, MI, and HS. A three-way analysis of variance with state (RS, MI, and HS) and thermal stimulation (non-noxious *vs.* noxious) as independent factors, and rating (unpleasantness *vs.* pain intensity) as within-subject variables, revealed no significant effect of the rating variable [$F(1,126) = 1.07$; $P > 0.30$], indicating that the rating scale for unpleasantness did not differ from the one for pain intensity. The interaction between state and thermal stimulation on ratings was significant [$F(2,126) = 9.66$; $P < 0.001$], demonstrating that subjects experienced noxious stimulation differently when at rest, distracted, or in the HS. A Tukey honest significant difference *post hoc* test showed that the state effect was only significant for the HS *versus* RS ($P < 0.001$) and *versus* MI ($P < 0.001$) but not for MI *versus* RS ($P > 0.440$).

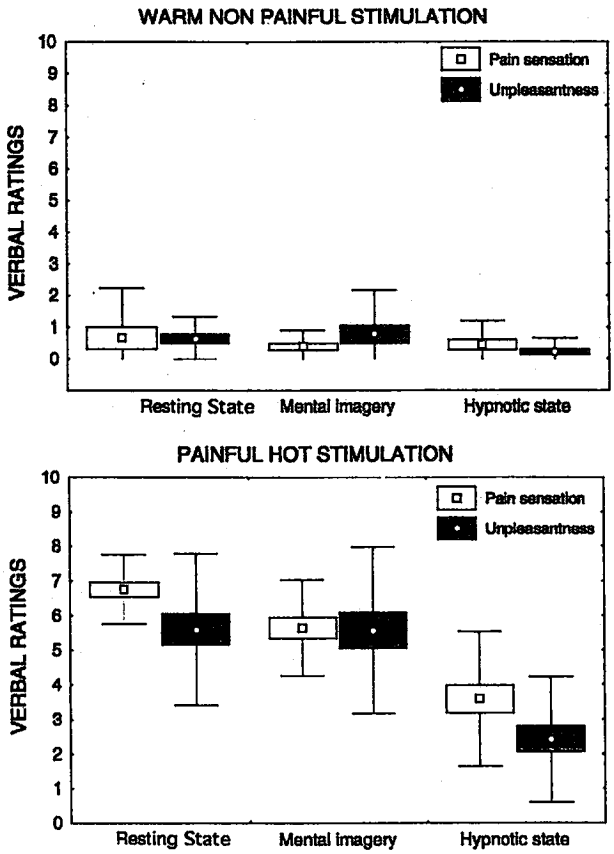

Fig. 1. Ratings of noxious sensation and unpleasantness during the three states (RS = resting state; MI = mental imagery; HS = hypnotic state). Note that hot noxious stimuli had higher ratings than warm non-noxious ones. Ratings for noxious sensation and unpleasantness are not significantly different from each other. For noxious hot stimuli, ratings are significantly lower during the HS than during RS or MI, whereas RS and MI ratings are not significantly different from each other. Boxes and whiskers represent, respectively, SEMs and SDs.

PET Data

Categoric Comparisons. The SPM had 110 residual degrees of freedom, a smoothness estimate of 13.2 × 14.3 × 14.7 mm and was composed of 193,799 voxels (*i.e.*, 553.6 resolution elements).

When all conditions were considered together, the main effect of pain, as compared with non-noxious stimulation, consisted of an activation in both thalamic nuclei (predominantly on the right side), in the right caudate nucleus, and in a region encompassing the left insula and the ACC (fig. 2B and table 1). Other regions that were not expected *a priori* were also significantly activated: the right dorsolateral prefrontal cortex (Brodmann's area [BA] 8), and the orbitofrontal cortex on both sides.

When the analysis concerned only "alert" states (RS and MI), the main effect of noxious stimulation was observed in the left insular cortex (fig. 2C and table 1). The left orbitofrontal cortex was also activated, although it was not included in our *a priori* hypotheses.

In the HS, activation was observed in response to noxious stimulation in an area encompassing the ACC (both BA 24 and 32), right caudate, left caudate, and left putamen (fig. 2D and table 1). Further activation was found in a region involving the right thalamus and extending caudally to the upper midbrain. Other regions were also found activated but were not predicted *a priori*: the right orbitofrontal cortex, the right dorsolateral prefrontal cortex (BA 9), and the right inferior parietal lobule (BA 40).

The comparison between the HS and the other two states (RS and MI) showed activation in the right extrastriate area (BA 19; fig. 3 and table 1). More anteriorly, activated sites were present in the right ACC, one of which crossed the border between the ACC and the corpus callosum.

The state-by-stimulation interaction (table 1) looked for brain areas that would be more activated by hot noxious (as compared with non-noxious) stimuli, in the context of the HS (as compared with RS and MI). This

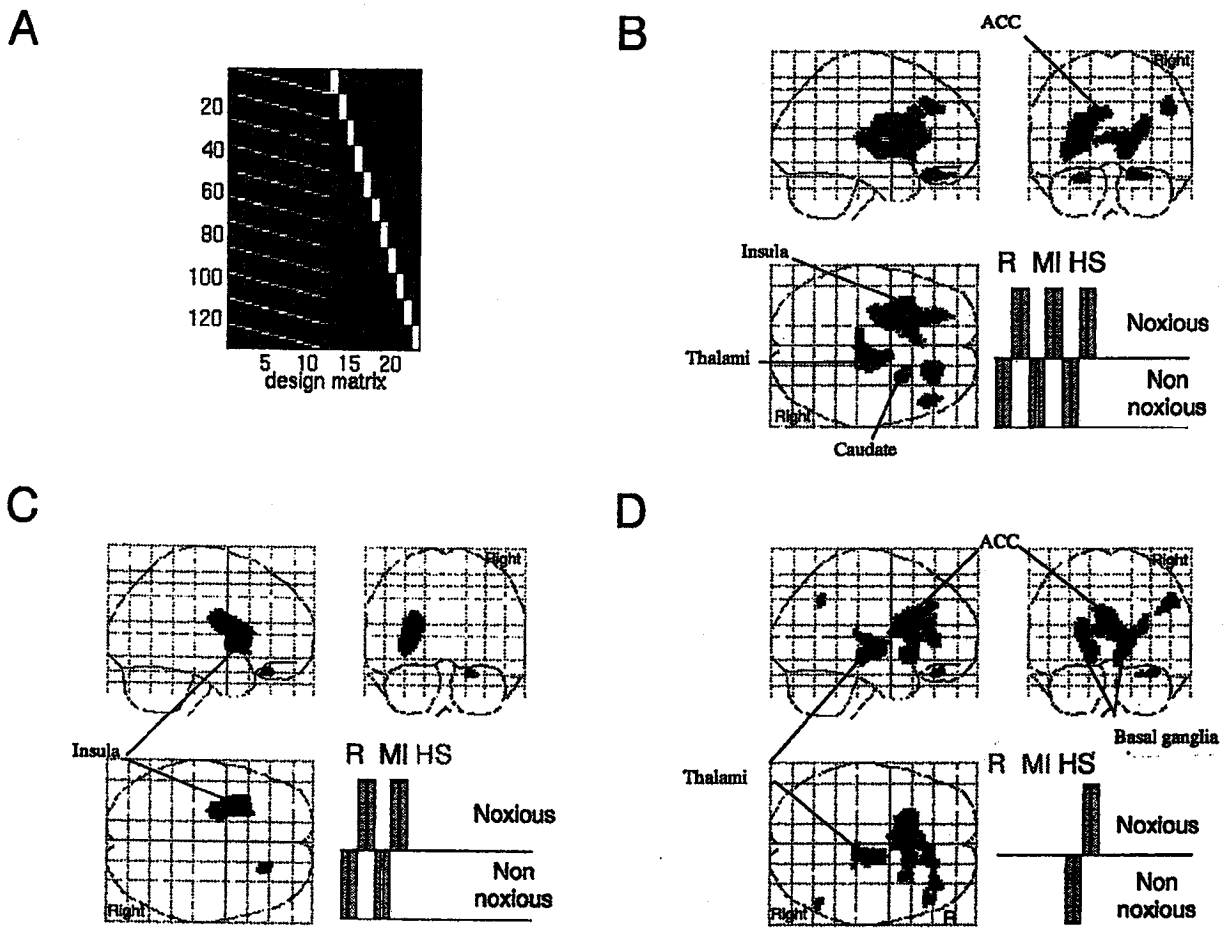

Fig. 2. Categoric comparisons: main effect of noxious simulation. (*A*) The design matrix included 12 conditions (scans) for each subject. (*B*) All conditions; (*C*) non-HS states; (*D*) HS. The results are displayed in a transparent brain normalized to the reference space of Talairach and Tournoux,[9] thresholded at $P < 0.001$.

analysis did not show any significant activation at the chosen level for this contrast ($P < 0.05$, corrected for multiple comparisons at the voxel level). However, at the uncorrected level $P < 0.001$, a region across the ACC and corpus callosum ($P = 0.13$ at voxel level; $Z = 4.25$; $x = -2$ mm; $y = 16$ mm; $z = 14$ mm) as well as a medial polar prefrontal area ($Z = 3.38$; $x = 0$ mm; $y = 60$ mm; $z = 26$ mm) were found activated (not shown). No region was found less activated in the HS than in other states during pain perception.

Regression Analysis. The SPM had 118 residual degrees of freedom, a smoothness estimate of 13.4 × 14.5 × 14.9 mm, and was composed of 193,799 voxels (*i.e.*, 539.2 resolution elements).

Using subjects' pain sensation ratings as regressor, the main effect of noxious stimulation was characterized by a significant activation of an area involving both thalami and caudate nuclei (fig. 4B and table 2). The left insula and the ACC were also found activated. Other (unexpected) regions were found activated in the right orbitofrontal cortex, the right dorsolateral prefrontal cortex (BA 44/46 and 9), and left parietal cortex (BA 40). This mode of analysis does not permit the separate evaluation of the effect of noxious stimulation in alert states and HS.

Significant regression was found with the state covariate in the ACC, indicating an increased CBF in these regions in the HS as compared with RS and MI (fig. 4C and table 2). This activation area continued caudal to the ventral striatum. The left caudate nucleus was also significantly activated.

Table 1. Results from the Categorical Comparisons

Side	Region	x	y	z	Z score
Increases in rCBF caused by noxious stimulation (all conditions)*					
Left	Insula	−28	14	10	5.16
Left	Anterior cingulate cortex	−8	22	30	3.39
Right	Thalamus	18	−22	8	3.76
Left	Thalamus	−10	−26	8	3.34
Right	*Dorso-lateral prefrontal cortex*	*4*	*34*	*38*	*3.83*
Right	*Orbito-frontal cortex*	*−24*	*38*	*−24*	*3.93*
Left	*Orbito-frontal cortex*	*24*	*32*	*−24*	*4.91*
Right	*Caudate nucleus*	*24*	*10*	*18*	*3.90*
Increases in rCBF caused by noxious stimulation (R and MI)*					
Left	Insula	−30	12	8	4.61
Right	*Orbito-frontal cortex*	*24*	*32*	*−24*	*3.99*
Increases in rCBF caused by noxious stimulation (the HS alone)*					
	Anterior cingulate cortex (BA 24)	−2	18	22	4.52
	Anterior cingulate cortex (BA 32)	2	28	22	3.77
Right	Thalamus	12	−14	0	3.77
Left	Putamen	−24	16	8	3.67
	Mesencephalon	4	−28	−8	3.64
Right	*Orbito-frontal cortex*	*34*	*36*	*−22*	*3.74*
Right	*Dorso-lateral prefrontal cortex*	*46*	*34*	*36*	*3.54*
Right	*Inferior parietal lobule*	*50*	*−58*	*42*	*3.27*
Right	*Caudate nucleus*	*6*	*14*	*10*	*3.57*
Left	*Caudate nucleus*	*−10*	*4*	*18*	*3.35*
Increases in rCBF caused by the HS as compared to both R and MI state					
Right	Anterior cingulate cortex (BA 24)	8	34	2	3.73
Right	Anterior cingulate cortex	18	14	24	3.52
Right	Extrastriate cortex	50	−74	−10	3.51
Interaction state by stimulation†					
	Anterior cingulate cortex/corpus callosum	*−2*	*16*	*14*	*4.25*
	Medial prefrontal cortex	*−2*	*16*	*14*	*4.25*

* In italics, the regions significant at $P < 0.001$ (uncorrected) that were not expected to be activated.

† In italics, the regions that were significant at $P < 0.001$ but did not survive correction for multiple comparisons at the voxel level ($P < 0.05$).

Finally, a significant interaction between pain sensation ratings and state (fig. 4D and table 2) was observed in a region involving the ACC ($P = 0.047$: Z = 4.51; BA 24; x = −2; y = 18; z = 22). This region spreads rostral to area 32, reaching the vicinity of medial BA 9 and caudal toward the corpus callosum. The voxel with maximum Z value is located in the supracallosal part of the midcingulate cortex (fig. 5A). In the specific context of hypnosis, and in contrast to the control states, the ACC regional CBF increases proportionally to pain sensation (fig. 5B). Similar results were observed using pain unpleasantness ratings. Again, no region was found less activated in the HS than in other states during the application of noxious stimuli.

DISCUSSION

Authenticity of HS

It is clear that our experimental protocol relies critically on the recognition of the HS and its differentiation from control states, in particular MI. Three arguments corroborate the presence of the HS in our subjects during scanning. First, the recording of slow ocular movements has proven a valuable parameter in our clinical and research protocols. These eye movements cannot be willfully mimicked.[14] At the very least, their recording rules out the presence of a simulated state. Second, the subject's behavior is characterized by an intense muscular relaxation, a decrease in heart and respiratory rates,

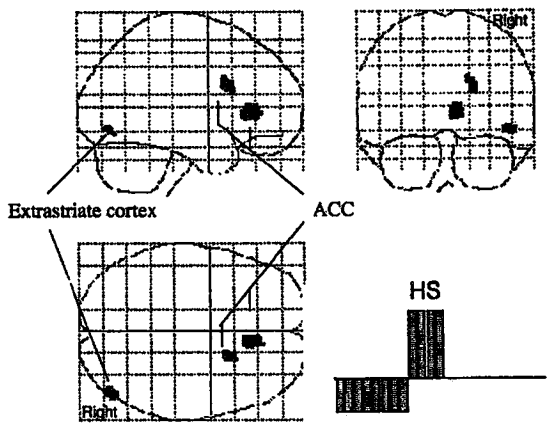

Fig. 3. Categoric comparisons: main effect of state. Increases in the hypnotic state (HS) as compared with the other states. The design matrix is the same as in Fig. 2. The results are displayed in a transparent brain normalized to the references space of Talairach and Tournoux,[9] thresholded at $P < 0.001$.

and a sluggishness in verbal and motor response that are more marked than at rest or during MI. In this respect, our subjects' behavior corresponded to our clinical observation. Third, a statistically significant decrease in pain ratings was observed during the HS only, a finding that is in agreement with our clinical practice.[2,15] Furthermore, our subjects testified that they were in the HS before each scan and confirmed their hypnotic experience during debriefing. Each of these points, taken in isolation, does not prove the presence of the HS in our subjects, but together they form a body of arguments that, by their cooccurrence, strongly suggest that this was indeed the case.

Main Effects of Noxious Stimulation

When all conditions are considered together, regional CBF increases in response to noxious stimulation in various brain areas related to pain perception: thalamic nuclei and anterior cingulate and insular cortices. These three sites are most commonly reported as activated during noxious stimulation.[16] We did not observe any significant activation of somatosensory areas (SI and SII), but these cortical regions are not systematically reported in the literature.[17] More specifically, the lack of activation may be related to our mode of stimulation, which includes a tonic aspect and does not optimize SI/SII activation.[17-19]

The thalamic activation, although bilateral, was predominantly ipsilateral to the stimulation. Most studies of pain perception with PET reported contralateral thalamic activation, although it may also be lacking.[16] However, Adler *et al.*[20] and Rainville *et al.*[5] (quoted by Derbyshire *et al.*[17]) found bilateral thalamic activation, the latter with a reportedly ipsilateral predominance. Likewise, ipsilateral thalamic activation was observed for mildly painful stimulation and not for more painful stimuli.[16] The reason for this particular thalamic distribution may also be related to the tonic mode of noxious heat stimulation, as suggested by Derbyshire *et al.*[17]

When alert states are considered in isolation, the insular cortex controlateral to the noxious stimulation was the only cortical area to be significantly activated. The insular cortex is among the brain areas that are most frequently reported as activated in response to noxious stimulation.[16,17,19,21-23] More intriguing is the lack of activation in other brain areas, in particular the thalamic nuclei and the ACC. This is in contrast to other reports of functional neuroanatomy of the central processing of noxious stimuli.[5,16,17] These negative results may be caused by various factors. Despite the restricted number of observations per subject in alert states (eight scans per subject), a lack of statistical power is unlikely to be relevant here because there were 110 residual degrees of freedom in our (categoric) design matrix. Furthermore, significant activation in ACC was found in the HS alone, where the number of observations is even fewer (four scans per subject). We already pointed out the effect of a tonic, rather than phasic, noxious stimulation on the regional CBF increases as detected by SPM. The intensity of the stimulation is also of importance. For instance, the thalamic nuclei and the ACC are not activated by "just painful" stimuli but were activated by "moderately painful" stimulations.[16] This factor is probably not relevant in the present study because the target temperature for non-noxious and noxious stimulations was set for each subject before the scanning session. As indicated by subjects' ratings, the non-noxious and noxious stimuli could be easily discriminated. Finally, a carry-over of the antinociceptive effect of the HS during the post-HS control scans remains possible. Indeed, pain ratings for post-HS scans tended to be lower than pre-HS values, although this variation was not significant (e.g., for noxious sensation, before HS: 5.9 ± 2.2; after the HS: 5.3 ± 2.3). In addition, in our clinical studies, postoperative pain was significantly lower in the hypnosis group despite a standardized prescription of postoperative analgesics.[2] In these conditions, mixing pre-HS and post-HS scans may have averaged out some regional activations.

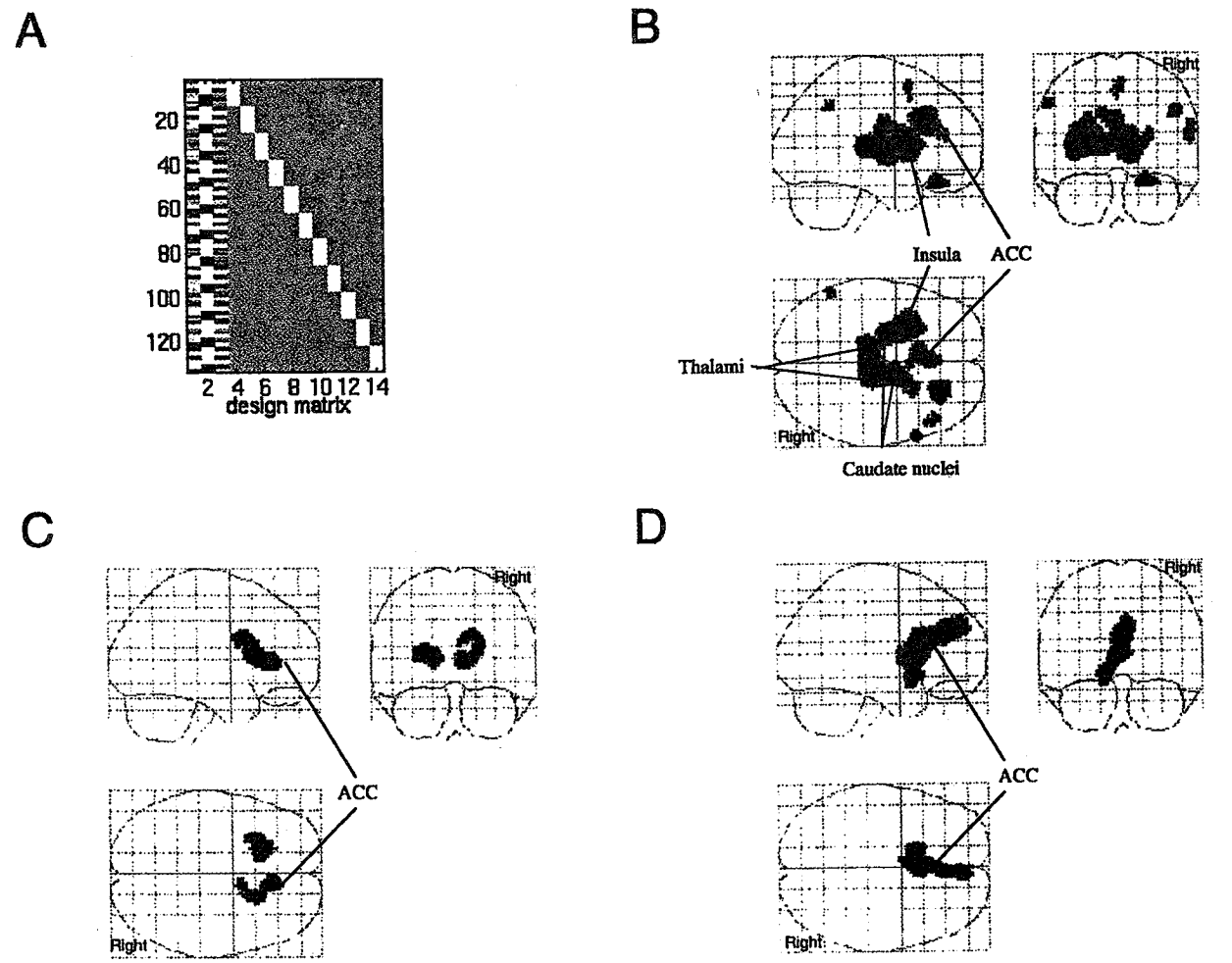

Fig. 4. Multiple regression analysis. (*A*) The design matrix included three covariates of interest: the pain ratings, the experimental states, and a covariate representing the interaction between ratings of pain perception and the states (the hypnotic state *vs.* control states). (*B*) Main effects of pain perception. (*C*) Main effect of state (increases in the hypnotic state as compared with the two other states). (*D*) State-by-condition interaction. The results are displayed in a transparent brain normalized to the reference space of Talairach and Tournoux[9] thresholded at $P < 0.001$.

Main Effects of the HS

We previously reported that the functional neuroanatomy of the HS was characterized by the activation of a widespread, mainly left-sided, set of cortical areas involving occipital, parietal, precentral, premotor, ventrolateral prefrontal cortices, and a few right-sided regions: occipital and anterior cingulate cortices.[13] These results were recently confirmed by another group.[24] In the present study, regional CBF distribution during the HS differed from alert states only by a significant activation of a right-sided extrastriate area and the ACC. The differences in activation patterns are likely to be a result of the experimental conditions. In our previous experiment, subjects in the HS were verbally accompanied during the entire hypnotic session, including during the scanning periods. The only instructions were to enter the HS and let the HS imagery invade their consciousness. In the present experiment, during the hypnotic session, the experimenter remained silent during the scanning periods, and thermal stimuli were administered. It is probable that, in these conditions, and although the subjects were not explicitly instructed to do so, most of the mentation in the HS was directed toward reducing pain perception. This would explain the predominant activation of the ACC, but we currently have no means to substantiate this.

Table 2. Results from the Regression Analysis

Side	Region	x	y	z	Z score
Increases in rCBF due to pain ratings*					
Left	Insula	−30	10	16	4.94
	Anterior cingulate (BA 32)	−2	26	30	4.08
	Anterior cingulate (BA 24)	−6	12	30	3.23
Left	Thalamus	−12	−24	10	4.26
Right	Thalamus	10	−6	4	4.39
Right	*Orbito-frontal cortex*	*22*	*34*	*−24*	*4.76*
Right	*Dorso-lateral prefrontal cortex (BA 44/46)*	*62*	*18*	*22*	*3.62*
Right	*Dorso-lateral prefrontal cortex (BA 9)*	*50*	*30*	*34*	*3.43*
Left	*Parietal cortex (BA 40)*	*−56*	*−54*	*44*	*3.64*
Right	*Caudate nucleus*	*14*	*14*	*10*	*3.36*
Left	*Caudate nucleus*	*−20*	*−4*	*16*	*3.60*
Increases in rCBF due to the HS as compared to both R and MI states*					
Right	Anterior cingulate cortex (BA 24)	8	34	6	3.89
Right	*Caudate nucleus*	*14*	*22*	*4*	*3.18*
Left	*Caudate nucleus*	*−18*	*24*	*12*	*3.95*
Interaction state by stimulation					
	Anterior cingulate cortex	−2	18	22	4.51

* In italics, the regions significant at $P < 0.001$ (uncorrected) that were not expected to be activated.

These results shed further light on brain function in the HS. The HS does not rely on a stereotyped brain organization, as is the case for well-defined states of vigilance such as sleep stages.[25,26] On the contrary, in the HS, brain work may be directed at will to certain tasks. In our case, perception of noxious stimulation was at the center of subjects' concern. Other cognitive tasks may be generated during the HS, such as memory recall and automatic writing. Each of these cerebral functions is likely to correspond to a different brain activation pattern in the HS. This suggestion is in good agreement with the results of Grond *et al.*,[27] showing that hypnotically induced catalepsy was related to increased glucose metabolism in the sensorimotor cortex.

State-by-stimulation Interaction: The Effect of the HS on Pain Perception

The results of the interaction analysis, especially using a multiple regression approach, confirmed a differential modulation in midcingulate (ACC) activity in response to noxious stimuli, in the specific context of HS, as compared with control states. The CBF in the ACC increases steeply in relation to pain ratings, in the specific context of the HS. Given our experimental setting, this result would suggest that ACC activity plays a role in decreasing pain ratings.

The mechanisms by which the midcingulate cortex may modulate response to noxious stimuli remain unclear. To explore the neural network that the ACC might affect, we performed psychophysiologic interaction analyses,[11] looking for regions that would respond to noxious stimulations under the modulatory action of the ACC specifically in the HS. No significant results were obtained by these analyses, possibly because of the small number of observations. Consequently, the physiologic significance of the midcingulate activation in the HS during noxious stimulation remains putative.

It is unlikely that opioid neurotransmission underlies the midcingulate activation we observed under the HS, although the ACC contains high concentrations of opioid receptors and peptides.[28,29] Indeed, psychopharmacologic studies showed that hypnotic analgesia was not altered by the administration of naloxone.[30] Furthermore, Adler *et al.*[20] showed that fentanyl, an opioid agonist that has powerful analgesic properties, causes an activation rather than a deactivation of midcingulate cortex. In other words, under fentanyl administration, ACC blood flow increases while pain perception decreases, in contrast to what is observed in the HS.

It is also unlikely that the ACC might modulate pain perception during the HS through attentional mechanisms. The midcingulate cortex that we show activated in our study has been related to pain perception, whereas the more anterior portions of the ACC are involved in attention-demanding tasks.[31,32] These anatomic considerations suggest that attentional processes

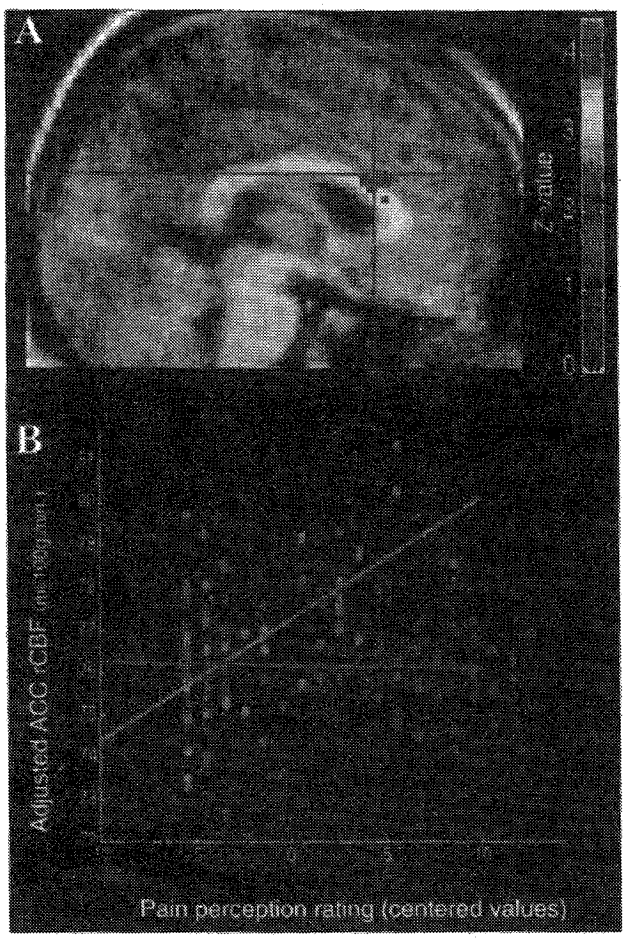

Fig. 5. (*A*) Brain area in which blood flow increases in proportion to pain sensation ratings, in the specific context of the hypnotic state: the ventral part of the midcingulate cortex (tentatively area 24'a). Results are displayed on the subject's T1-weighted average magnetic resonance imaging scan, normalized to the same standardized space. (*B*) Plot of adjusted anterior cingulate cortex blood flow *versus* pain perception ratings. The results show that there is a significant difference ($P = 0.047$, voxel level) in pain ratings *versus* regional cerebral blood flow regression slopes between the hypnotic state (green) and control conditions (red).

were probably not responsible for the analgesia during the HS.

From the anatomic standpoint, the ACC is anatomically and functionally heterogeneous.[33,34] Anatomically speaking, the midcingulate cortex is in critical position to receive both the sensory noxious aspects from the somatosensory areas and insula, and the affective component of noxious stimuli, encoded in amygdaloid complexes and pregenual ACC.[35] Functional relationships with nearby premotor areas of the medial frontal cortex (motor-related cingulate areas, supplementary motor area) might also allow the midcingulate cortex to organize the most appropriate behavioral response, taking into account the affective component of stimuli to the pain perception.

Comparison with the Data of Rainville et al.[5]

A recent PET study explored the neuroanatomic correlates of "pain affect" during hypnosis.[5] The investigators specifically used hypnotic suggestions to increase or decrease noxious unpleasantness, seemingly without affecting pain sensation by separating sensory and affective pain perception. It should be emphasized that these behavioral results are in contrast to those of Kiernan *et al.*,[15] who showed that intensity and unpleasantness remain highly correlated during the HS ($r = 0.88$). Nevertheless, during HS, Rainville *et al.*[5] observed significant changes in pain-evoked activity within the ACC in the HS, consistent with the encoding of perceived unpleasantness. In the authors' view, this suggested "a specific encoding for noxious unpleasantness in the ACC." Our results confirm that noxious unpleasantness during the HS is related to ACC activity, in keeping with this previous PET study. Indeed, the coordinates of the ACC activation (coordinates: −2, 18, 22 mm) are close to those of Rainville *et al.*[5] (coordinates: −1, 25, 29 mm; distance in y and z direction = 7 mm).

However, using our hypnotic technique, we were able to show that the HS reduces both noxious perception and unpleasantness. This effect is specific to the HS and cannot be accounted for by the subject being distracted from noxious stimuli: as a control, MI did not significantly decrease pain ratings. The decrease in both affective and sensory aspects of pain perception is, of course, critical for hypnosis that is used to reduce perioperative pain. Furthermore, in HS, the ACC responds to both perceptive and affective aspects of pain sensation.

Consequently, our functional data extend the results of Rainville *et al.*[5] by showing that both affective and sensory responses to noxious stimulation are reduced in the specific context of HS, and this reduction is mediated by the ACC.

In conclusion, pain perception by normal subjects can be modified by the HS. This modulatory effect of the HS seems mediated by the midcingulate cortex activity. Indeed, the reduction of pain perception correlated with ACC activity specifically in the HS.

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Annexe 10

Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis

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Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis

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Abstract

The neural mechanisms underlying the antinociceptive effects of hypnosis are not well understood. Using PET, we recently showed that the activity in the anterior cingulate cortex (midcingulate area 24a') covaries with the hypnosis-induced reduction of affective and sensory responses to noxious thermal stimulation (Faymonville et al., Anesthesiology 92, 1257-67, 2000). In the present study, we assessed changes in cerebral functional connectivity related to the hypnotic state, compared to simple distraction and the resting state.

Nineteen highly hypnotizable right-handed volunteers were studied using $H_2{}^{15}O$-PET. The experimental conditions were hot noxious or warm non-noxious stimulation of the right hand during resting state, mental imagery and hypnotic state. Using a psychophysiological interaction analysis, we identified brain areas that would respond to noxious stimulations under the modulatory action of the midcingulate cortex in, and only in, the hypnotic state.

Hypnosis, compared to the resting state, reduced pain perception by 50%. Pain perception during rest and mental imagery was not significantly different. Analysis of PET data showed that the hypnotic state, compared to normal alertness (i.e., rest and mental imagery), significantly enhanced the functional modulation between midcingulate cortex and a large neural network encompassing bilateral insula, pregenual anterior cingulate cortex, pre-supplementary motor area, right prefrontal cortex and striatum, thalamus and brainstem.

These findings point to a critical role for the midcingulate cortex in the modulation of a large cortical and subcortical network underlying its influence on sensory, affective, cognitive and behavioral aspects of nociception, in the specific context of hypnosis.

1. Introduction

Hypnosis combined with slight conscious sedation (i.e., hypnosedation) and local anesthesia is now considered a valuable alternative to general anesthesia in specific indications [18,20,21,30,31,36]. Since 1992 we have used hypnosis routinely in more than 3300 surgical procedures. The underlying neuromodulatory effects of hypnosis remain, however, not fully understood. Studies of the antinociceptive effects of hypnosis have labored under a double burden: both hypnotic experience and pain experience are highly subjective phenomena. Factors that evoke pain reduction range from extrinsic psychosocial (e.g., interactions between clinician and patient) to intrinsic psychophysiological (e.g., modulation of pain signal transmission; [46]. Recent positron emission tomography (PET) studies have demonstrated that the decreased perception of pain during hypnosis is related to changes in the activity (i.e., regional cerebral blood flow – rCBF) measured in the midcingulate cortex (area 24'; [19,47]. We here test the hypothesis that hypnosis-induced analgesia can be explained by an enhanced modulation between the midcingulate cortex and the large neural networks involved in sensory, affective and cognitive aspects of noxious processing. Using a psychophysiological interaction analysis [23], we assessed hypnosis-specific increases in functional connectivity between the midcingulate cortex, identified in our previous study [19], and the rest of the brain.

Complementary to the concept of functional segregation as a principle of organization of the human brain (i.e., localizing a function to a cerebral area), recent neuroimaging techniques have focused on functional integration (i.e., assessing the interactions between functionally segregated areas mediated by changes in functional connectivity). Functional connectivity is defined as the temporal correlation of a neurophysiological index (i.e., rCBF) measured in different remote brain areas. Anatomical connectivity (e.g., neuroanatomic tracer studies obtained in animals) is a necessary underpinning for the assessment of functional

connectivity. A psychophysiological interaction means that the contribution of one area to another (i.e., regression slope) changes significantly with the experimental context [23]. The psychophysiological interaction analysis used in the present study, aims at explaining the activity in one cortical area in terms of an interaction between the influence of a chosen area (i.e., midcingulate cortex) and some experimental condition (i.e., being in a hypnotic state or not). Pain is a multidimensional experience including sensory-discriminative, affective-emotional, cognitive and behavioral components. 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" [25]. The aim of the present study is to explore the modulatory role of the midcingulate cortex on the activity of this "neuromatrix" in the specific context of hypnosis.

2. Materials and methods

Experimental protocol

The Ethics Committee of the Faculty of Medicine of the University of Liège approved the study. Written informed consent was obtained from all volunteers. The experimental protocol has been extensively described elsewhere [19] and will only be summarized here. For the aim of the present assessment of cerebral functional connectivity, which greatly depends upon the number of observations, we have added 8 more subjects to this previously published population. Hence, 19 young healthy right-handed volunteers (mean 28 ± 4 years; 9 women) were included. All subjects were highly hypnotizable (score > 8 of 12 on the Stanford Hypnotic Susceptibility Scale-FormC; [24]. PET data were acquired during three kinds of states (hypnotic state, mental imagery or rest) and during two kinds of stimulation (hot noxious stimulation or warm non-noxious stimulation). Subjects were scanned twice in each of these six conditions. To avoid multiple hypnotic inductions, the fifth to eight scans were always made in the hypnotic state. The order of the two other states, and of the non-noxious and noxious stimulations, was pseudo-randomized.

The hypnotic state was induced by a muscle relaxation procedure after which the subjects were invited to re-experience pleasant autobiographical memories. Similar to our extensive clinical experience with hypnosedation [18,20,21,36], permissive and indirect suggestions were used to develop and deepen the hypnotic state. During the mental imagery task, subjects were instructed to vividly imagine a pleasurable autobiographical memory. In the resting state participants were asked to empty their mind and remain immobile. Electroencephalographic, electromyographic and oculographic recordings ensured that no sleep occurred during the experiment and that roving eye movements were present during hypnosis [34]. Before and after scanning, subjects confirmed by a prearranged foot movement that they were in the demanded state. The experimenter remained silent during scans. After each scan, subjects were asked to rate the noxious stimulus intensity on a scale from 0 (absent) to 10 (most intense imaginable).

Stimuli were delivered by a Marstock thermode (Somedic, Senselab, Upsala, Sweden) applied to the thenar eminence of the right hand. Before the PET studies, target temperatures that were reproducibly experienced as hot and noxious (typically 47°) or warm and non-noxious (typically 39°), were carefully established for each subject. Training sessions were conducted so that anxiety and emotional reactions associated with a novel experimental situation would be reduced.

PET data were acquired on a Siemens CTI 951 R 16/31 scanner in 3D mode. The subject's head was stabilized by a thermoplastic facemask (Truscan imaging, MA) and a

venous catheter was secured in a left antebrachial vein. A transmission scan was acquired for attenuation correction. Changes in rCBF were estimated using the $H_2{}^{15}O$ infusion method [32]. T1-weighted magnetic resonance imaging (MRI) (0.96 x 0.96 x 1.50 mm voxel size) was performed on a 1.5T Magnetom scanner (Siemens, Erlangen, Germany).

Analysis of PET data

We used statistical parametric mapping (SPM99; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK) to realign, coregister, spatially normalize, smooth (16 mm full width at half maximum) and analyze the PET data. Proportional scaling adjusted rCBF for changes in global flow. The effect of the covariates of interest was estimated according to the general linear model at each voxel [22]. The covariates consisted of the state effect (hypnotic state versus normal alertness state) and the rCBF of the reference region previously found to mediate the hypnosis-induced reduction of pain perception: the midcingulate cortex (area 24'a; coordinates -2, 18, 22; [19]. The activity in the reference region was modeled separately for the two states, allowing us to test for an interaction in terms of the difference in the regression slopes between the two states [33]. This analysis identified the brain areas that were functionally more related the reference area in the hypnotic state than in the normal alertness state (i.e., rest or mental imagery).

The assessment of functional integration using psychophysiological interaction analyses [23] is limited by the known structural neuroanatomical connections between the reference region and the rest of the brain. Until such information is available for humans, our hypotheses are based upon observations in monkeys. Hence, only brain areas known from tracer studies in animals to be connected to the midcingulate cortex were considered. In the non-human primate, this region is connected with supplementary and pre-supplementary motor area [17,38,56], insula [35,42,54], perigenual anterior cingulate cortex [52], prefrontal cortices (mainly mid-dorsolateral and middle orbitofrontal areas) [28,39,54], posterior parietal cortex [54], striatum [29], amygdala [4], thalamus (mediodorsal, midline, intralaminar and anteromedial nuclei) [53] and brainstem [16,37,40,41]. Most of these projections are reciprocal, except for the brainstem where the periaquaductal gray only receives inputs from the midcingulate cortex. Areas of significant change within these sets of brain regions were determined using linear contrasts of the parameter estimates. The resulting set of voxel values for each contrast constituted a map of the t statistic [SPM{T}]. Results were considered significant at small volume corrected $P < 0.05$, using a 10 mm radius-spherical volume of interest on our predetermined regions of interest.

Results from classical subtraction analyses (e.g. identifying the main effects of pain and hypnosis) or state-by-stimulation interaction analyses (e.g., identifying brain areas that were activated more by noxious stimulation during hypnosis than in other states) have previously been reported in detail [19], and will not be discussed here. Behavioral data were analyzed using ANOVA models, with a significance threshold fixed at $P<0.05$.

Results

As shown in figure 1, subjects' perception of pain during the resting condition (mean ± standard deviation: 6.4 ± 1.2) significantly decreased during the hypnotic state (3.2 ± 1.1) but not during the mental imagery condition (5.6 ± 1.0). Given that pain perception during rest and mental imagery did not significantly differ, PET data obtained during these conditions were pooled for further analyses.

> Insert fig1.

Compared to normal alertness states (rest and mental imagery), the hypnotic state enhanced the functional modulation between midcingulate cortex (area 24'a, coordinates –2, 18, 22 mm, identified in a previous study; [19] and bilateral anterior insular cortices, pregenual anterior cingulate cortex (Brodmann's area 32), pre-supplementary motor area (pre-SMA; area 6), right prefrontal cortex (area 8), right thalamus, right striatum and brainstem (Table 1 and Fig. 2). At lower threshold for significance, left prefrontal cortex (area 10), right prefrontal areas 9 and 11 and mesiofrontal cortex (area 9) were also identified. Figure 3 illustrates the changes in interaction (i.e., regression slope) between the activity measured in our seed region (i.e., midcingulate cortex) and in one of the identified brain regions (i.e., pregenual cortex), depending on the experimental condition (i.e., hypnotic state versus normal alertness). Regions that decreased their functional relationships with the midcingulate cortex during hypnosis as compared to normal alertness were confined to bilateral occipital cortex (coordinates of peak voxels: 58, -68, 8; Z=3.72 and -18, -70, 14; Z=3.53). As these regions were not part of our a priori defined regions known to be structurally connected to the midcingulate cortex, they are only reported for completeness but will not be discussed further.

> Insert table 1, fig 2 and 3.

Discussion

The hypnotic procedure used in the present experimental setting, which is similar to the one used for clinical purposes [18,20,21,36], decreased pain perception by 50% compared to the resting state and by 43% compared to the mental imagery state. Participants were invited to re-experience pleasant life episodes, without any reference to the pain perception. As reported previously, this technique lowers both the unpleasantness (i.e., affective component) and the perceived intensity (i.e., sensory component) of the noxious stimuli [19,20].

The anterior cingulate cortex can be divided into two parts, based on structural, connection, and functional observations: the perigenual cortex and the midcingulate cortex [16,52,53,54]. It is a functionally very heterogeneous region thought to regulate or modulate the interaction between cognition, sensory perception and motor control in relation to changes in attentional, motivational, and emotional states [16]. Previous studies from our own and other laboratories have shown that the midcingulate cortex mediates the hypnosis-induced reduction of pain perception [19,47,48]. We here show that this mediation of pain perception observed in the hypnotic state is related to an increased functional modulation of the previously identified midcingulate cortex and a large neural network of cortical and subcortical structures known to be involved in different aspects of pain processing encompassing insular, pregenual and prefrontal cortices, pre-SMA, thalami, striatum and brainstem.

The insular cortex and the anterior cingulate cortex are known to show the most consistent activation in functional imaging studies on pain perception [6,10,13,15,25,44,49,55]. The insula is thought to take an intermediate position between the lateral (sensori-discriminative) and medial (affective-emotional) pain systems. It receives major input from the somatosensory system [35], has direct thalamocortical nociceptive input [8] and through its projections to the amygdala, has been implicated in affective and emotional processes [1]. The insula is considered to serve a sensory integrative function for pain, taste and other visceral sensations, as well as tactile and vestibular inputs [7]. Our observation of an increased

midcingulate-insular modulation during hypnosis is in line with its proposed role in pain affect [48] and pain intensity coding [9]. In the light of the 'somatic marker' hypothesis of consciousness [11], the right insular cortex has been hypothesized to be involved in the mental generation of an image of one's physical state underlying the attribution of emotional attributes to external and internal stimuli. It is, however, important to stress that the used correlation analyses do not guarantee that the identified midcingulate-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 psychophysiological interaction). The midline and intralaminar thalamic nuclei, for example, could project to both the anterior insula and midcingulate cortex and this might produce highly correlated activity between insular and midcingulate areas [57].

In the monkey, midcingulate cortex is connected to mid-dorsolateral frontal areas [3,54]. A recent meta-analysis of PET studies observed frequent co-activations of prefrontal cortices and anterior cingulate cortex in a variety of tasks demonstrating their functional connectivity in the human brain [28]. The anterior cingulate cortex has been hypothesized to facilitate the implementation of a selected action whereas the prefrontal cortex would compute and maintain on-line information necessary for the choice of the appropriate response [43]. Being able to feel unpleasantness and to assess pain reflects an experience of conscious awareness. Consciousness is in part the product of attentional processes that act in reference to temporal-spatial organizational networks in the brain [45]. The observed prefrontal areas may indicate distributed associative processes of cognitive appraisal, attention or memory of perceived noxious stimuli. Widespread frontal increases in rCBF have previously been demonstrated in the hypnotic state [19,34,48]. Frontal activation has also been reported in a series of studies on experimental pain but the precise role of particular regions in the central processing of pain remains to be elucidated [51].

The frontal-midcingulate circuit may modulate the cognitive appraisal and the inhibitory control on the pain-relevant affective signals from the limbic system [16]. The right-sided preponderance lends support to the hypothesis that the non-dominant hemisphere is preferentially involved in the negative emotion of pain [12]. The anterior cingulate cortex has a major role in motor function [17]. Its increased functional relationships with pre-SMA and striatum during hypnosis may allow the midcingulate cortex to organize the most appropriate behavioral response taking into account the affective component of stimuli to the pain perception. Indeed, the basal ganglia encode and initiate basic movement patterns expressed through premotor and primary motor areas and show frequent activation to noxious stimuli [6,14,15,25]. The basal ganglia are not exclusively linked to motor function but have also been proposed to support a basic attentional mechanism facilitating the calling up of motor programs and thoughts [5].

The observed increases in functional connectivity between the midcingulate cortex and the thalamus and midbrain during the hypnotic state could be related to pain relevant arousal or attention [27]. The thalamus has recently been shown to correlate with pain threshold whereas activation of midbrain correlated with pain intensity [50]. It is tempting to hypothesize a hypnosis-related subcortical gating on cortical activation that underlies the observed decreased subjective pain perception. The limited spatial resolution and smoothing of our data (16 mm) do not permit an accurate localization of these structures. Previous studies have shown that different forms of defensive or emotional reactions, analgesia and autonomic regulation are represented in different regions of the midbrain's periaqueductal gray [2]. The perigenual cortex, insula and thalamus are also known to be implicated in autonomic regulation [1,2]. In

epileptic patients, electrical stimulation of the pregenual cortex diminished reflexes, movements and arterial blood pressure [26]. The observed modulatory role of the midcingulate cortex on this network could explain the clinical finding that patients undergoing surgery during the hypnotic state show modified autonomic responses and less defensive reactions in response to an aversive encounter [20].

The anterior cingulate cortex is abundantly innervated by a multitude of neuromodulatory pathways including opioid, dopaminergic, noradrenergic and serotoninergic systems and is known to contain high levels of substance P, corticotropin-releasing factor, neurotensin and prosomatostatin-derived peptides [43]. The neurotransmitter systems involved in the antinociceptive effects of hypnosis will be specifically explored in another experimental protocol.

In conclusion, the reduced nociception during hypnosis, compared to normal alertness, seems mediated by an increased functional connectivity between the midcingulate cortex (area 24'a) and insular, pregenual, frontal and pre-SMA regions as well as brainstem, thalamus and basal ganglia. These findings point to a critical role for the midcingulate cortex in hypnosis-related alteration of sensory, affective, cognitive and behavioral aspects of nociception. It reinforces the idea that not only pharmacological but also psychological strategies for relieving pain can modulate the interconnected network of cortical and subcortical regions that participate in the processing of noxious stimuli.

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Abbreviations

PET, positron emission tomography; rCBF, regional cerebral blood flow; SMA, supplementary motor area; SPM, statistical parametric mapping.

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TABLE 1. Cerebral areas that showed a significant increase in functional connectivity between midcingulate cortex during hypnotic state compared to normal alertness (rest and mental imagery).

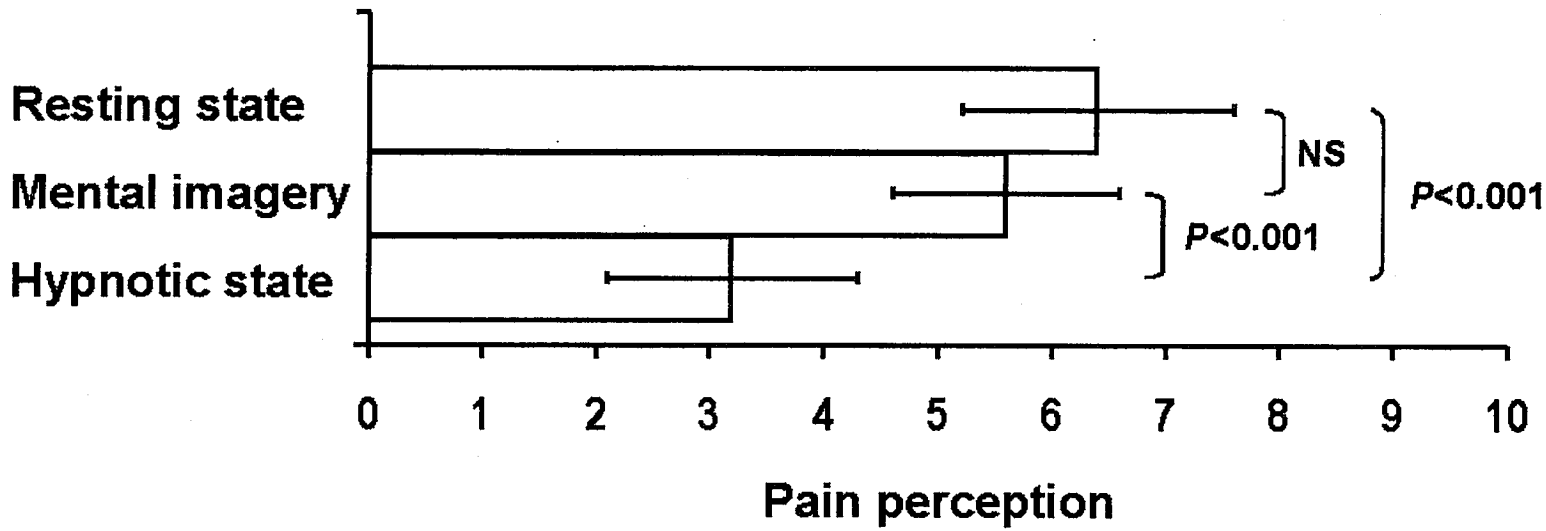
Region	***x***	***y***	***z***	***Z*-value**	***P-value***
1. Insula (L)	-32	34	4	3.35	< 0.001**
2. Insula (R)	34	16	12	3.13	0.001*
3. Pregenual cortex (BA 32/24)	14	40	4	4.04	< 0.001**
4. Pre-SMA (BA 6)	6	16	64	3.25	0.001*
5. Superior frontal gyrus (R-BA 8)	22	40	50	3.16	0.001*
6. Thalamus (R)	14	-6	2	3.03	0.001*
7. Caudate nucleus (R)	14	20	0	3.23	0.001*
8. Midbrain / brainstem	8	-18	-16	3.18	0.001*

Note: **Small volume corrected *P*-value < 0.005; *Small volume corrected *P*-value < 0.05; L = left; R = right; BA = Brodmann's area; SMA = supplementary motor area

FIG. 1. Ratings of pain perception in the resting state, the mental imagery condition and in the hypnotic state. Values are means and standard deviations (NS = not significant).

FIG. 2. Regions that showed an increased functional connectivity (i.e., differences in regression slopes of rCBF's correlations, thresholded at $P<0.001$) with midcingulate cortex in hypnosis relative to normal alertness (rest and mental imagery). Numbers correspond to the numbering used in Table 1.

FIG. 3. Plot of the neural activity (regional cerebral blood flow, rCBF) in midcingulate cortex and pregenual cortex during hypnosis (green circles) and normal alertness (red crosses). Note the difference between the regression slopes relative to both experimental conditions, reflecting the increase in functional modulation (i.e., increase in functional connectivity) between both brain regions in the specific context of hypnosis. Each point represents one PET measurement (19 subjects, 12 scans per subject, makes 228 measurements in total).


Resting state
Mental imagery
Hypnotic state
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P<0.001
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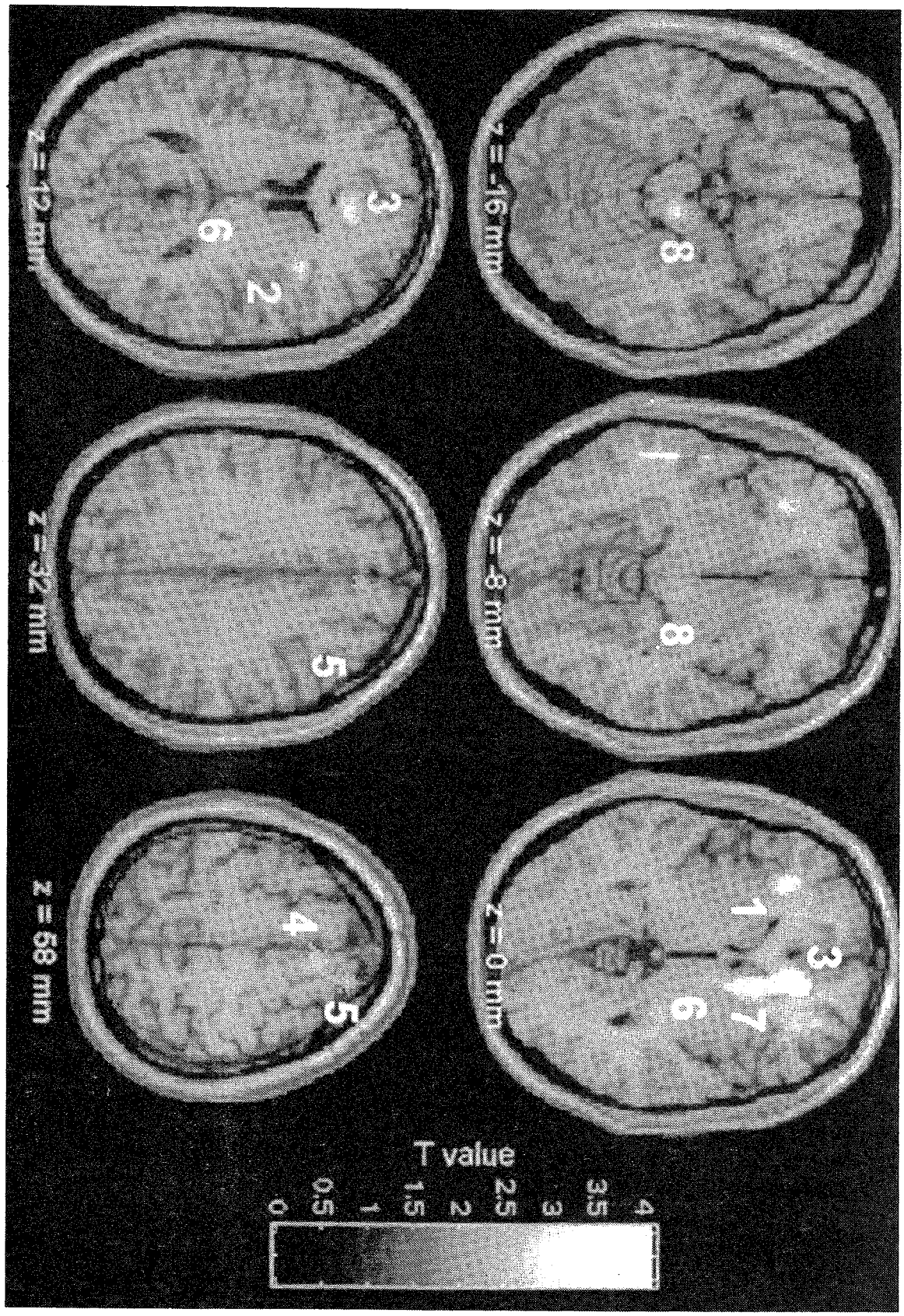
Pain perception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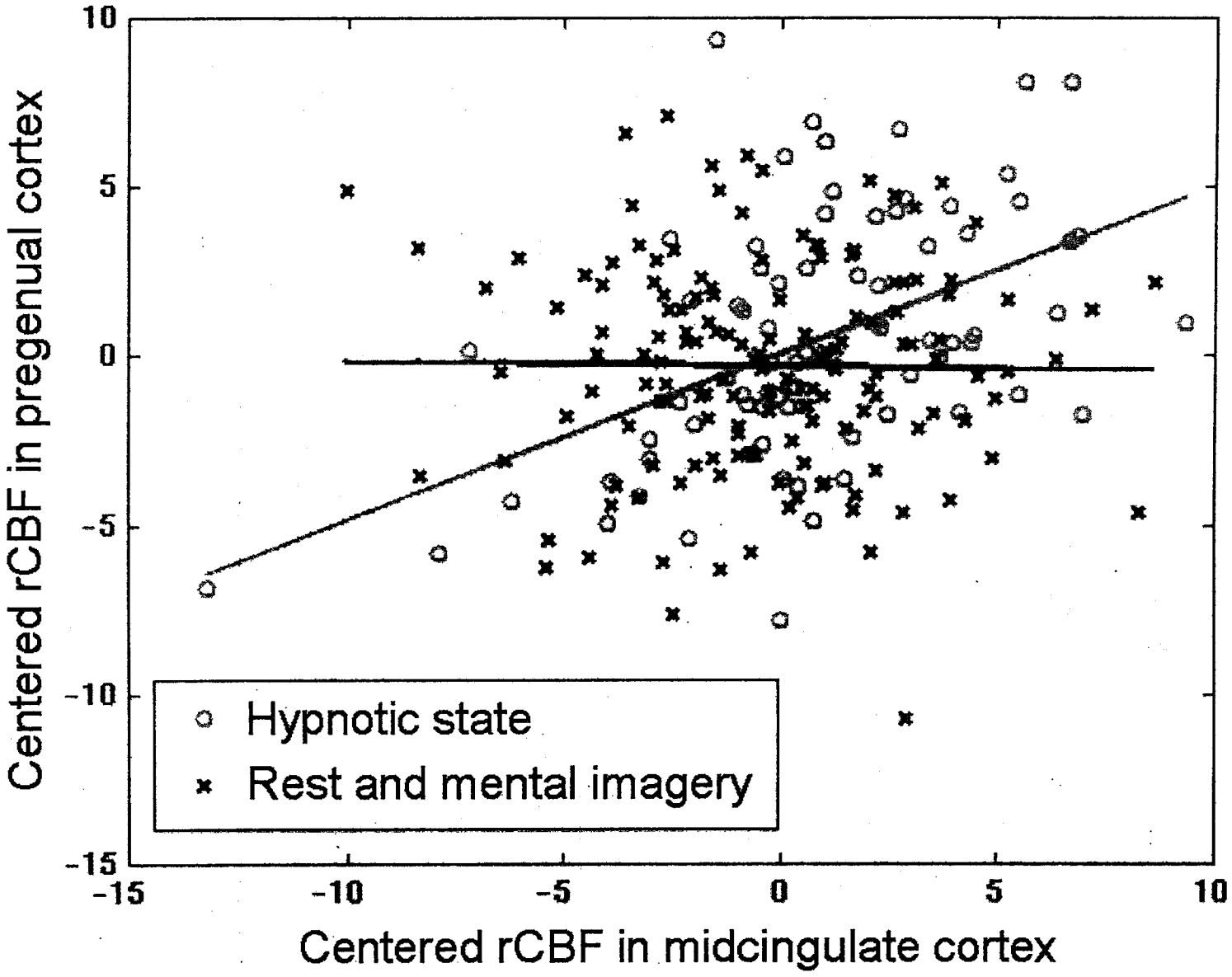
Centered rCBF in pregenual cortex
Centered rCBF in midcingulate cortex
10
5
0
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Hypnotic state
Rest and mental imagery