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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.

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

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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 $\times$ 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: $0.96 \times 0.96 \times 1.35$ 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 ($P > 0.440$).

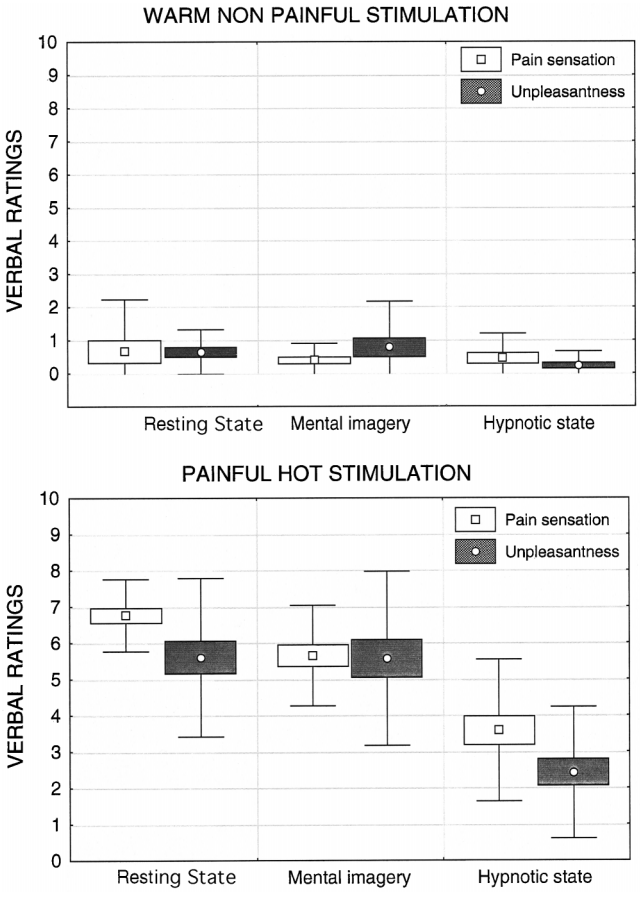


**Fig. 1. Ratings of noxious sensation and unpleasantness during the three states (RS = resting state; MI = mental imagery; HS = hypnotic state). Note that hot noxious stimuli had higher ratings than warm non-noxious ones. Ratings for noxious sensation and unpleasantness are not significantly different 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

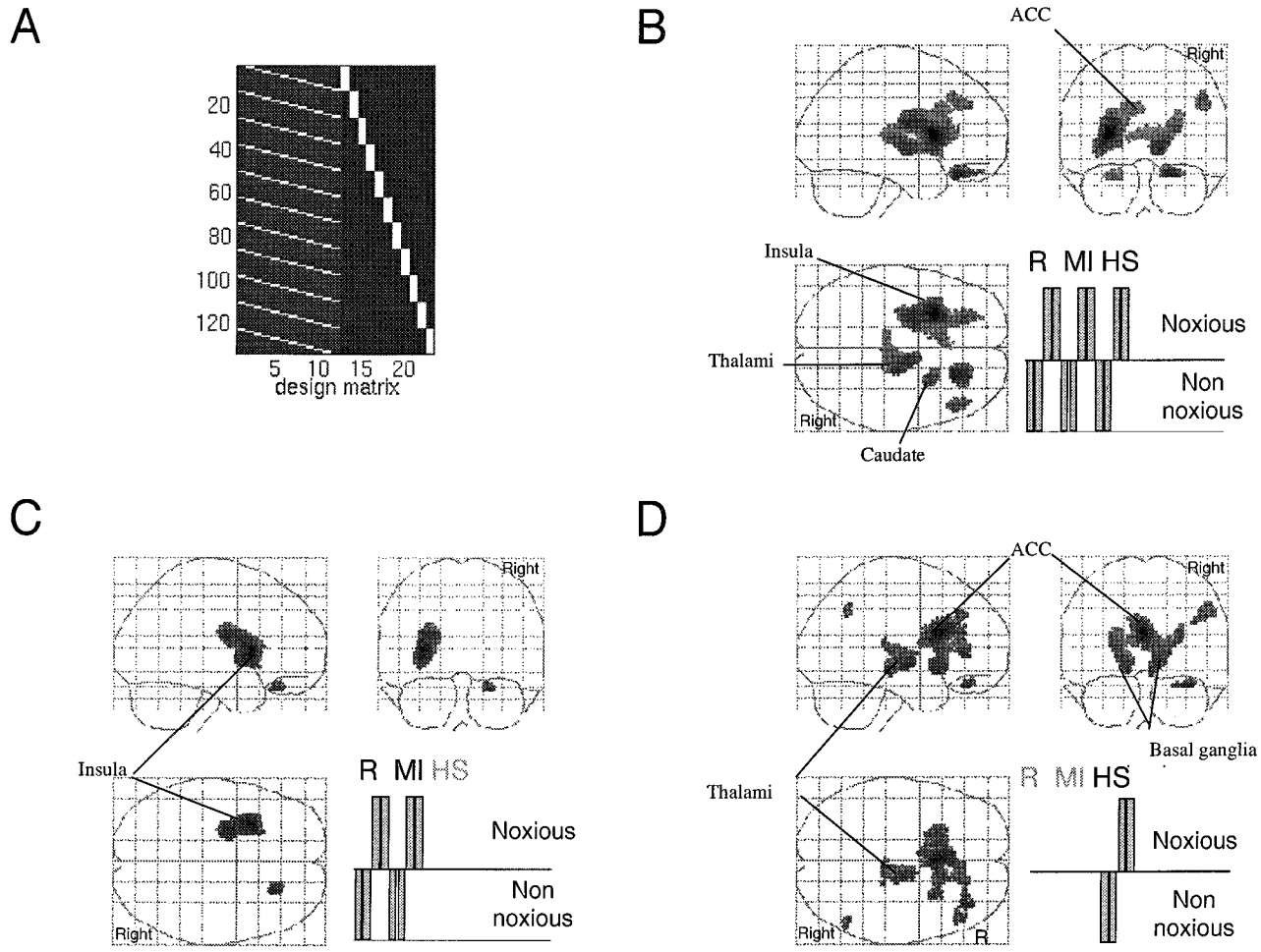


**Fig. 2. Categoric comparisons: main effect of noxious simulation. (*A*) The design matrix included 12 conditions (scans) for each subject. (*B*) All conditions; (*C*) non-HS states; (*D*) HS. The results are displayed in a transparent brain normalized to the reference space of Talairach and Tournoux,[9]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

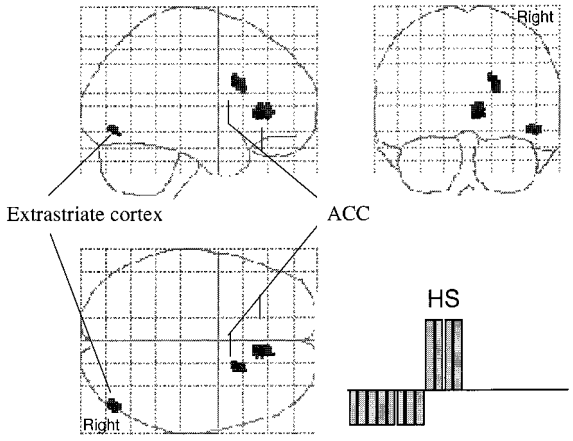


**Fig. 3. Categoric comparisons: main effect of state. Increases in the hypnotic state (HS) as compared with the other states. The design matrix is the same as in Fig. 2. The results are displayed in a transparent brain normalized to the references space of Talairach and Tournoux,[9] thresholded at $P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

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: $5.9 \pm 2.2$; after the HS: $5.3 \pm 2.3$). 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.

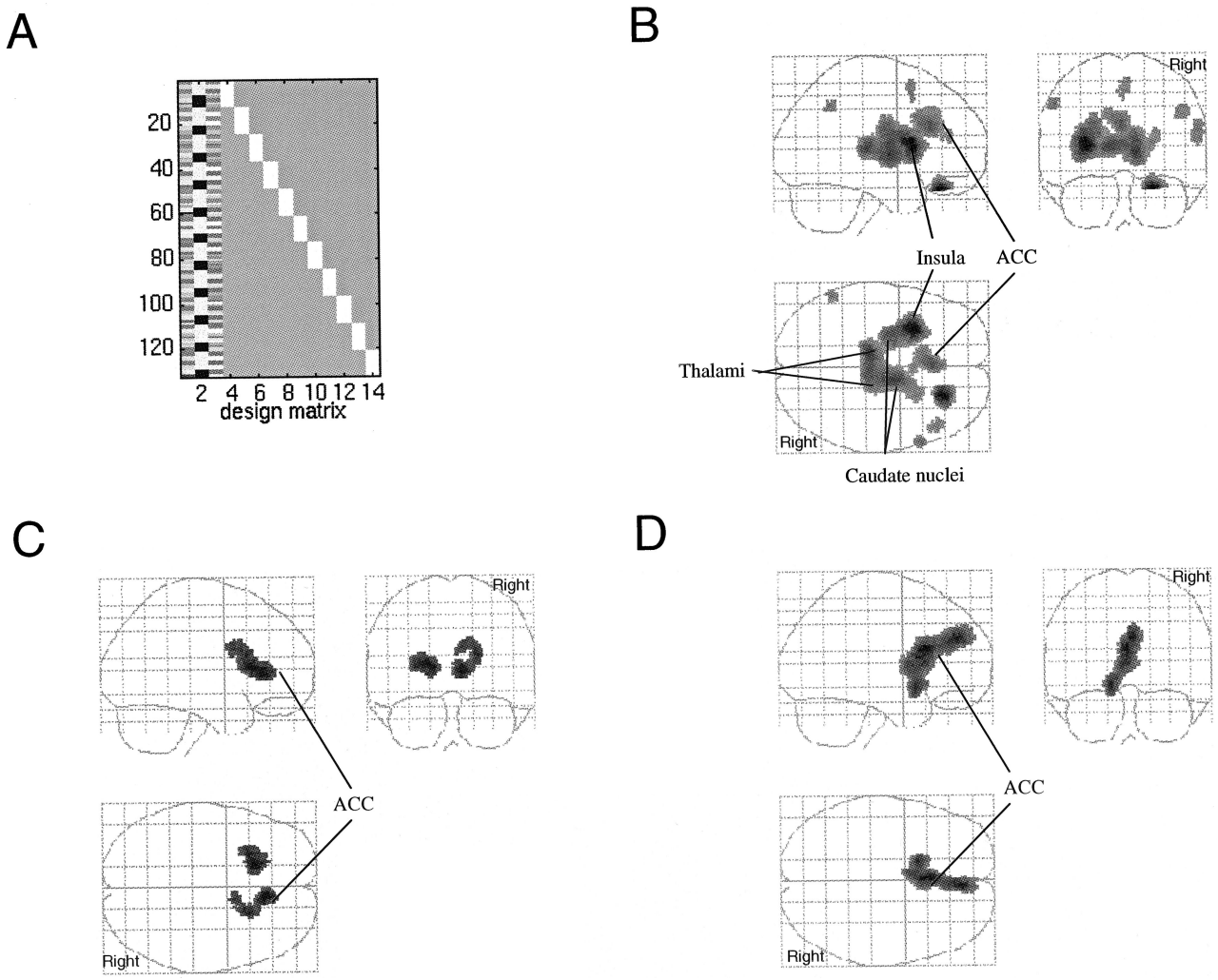


**Fig. 4. Multiple regression analysis. (*A*) The design matrix included three covariates of interest: the pain ratings, the experimental states, and a covariate representing the interaction between ratings of pain perception and the states (the hypnotic state *vs.* control states). (*B*) Main effects 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

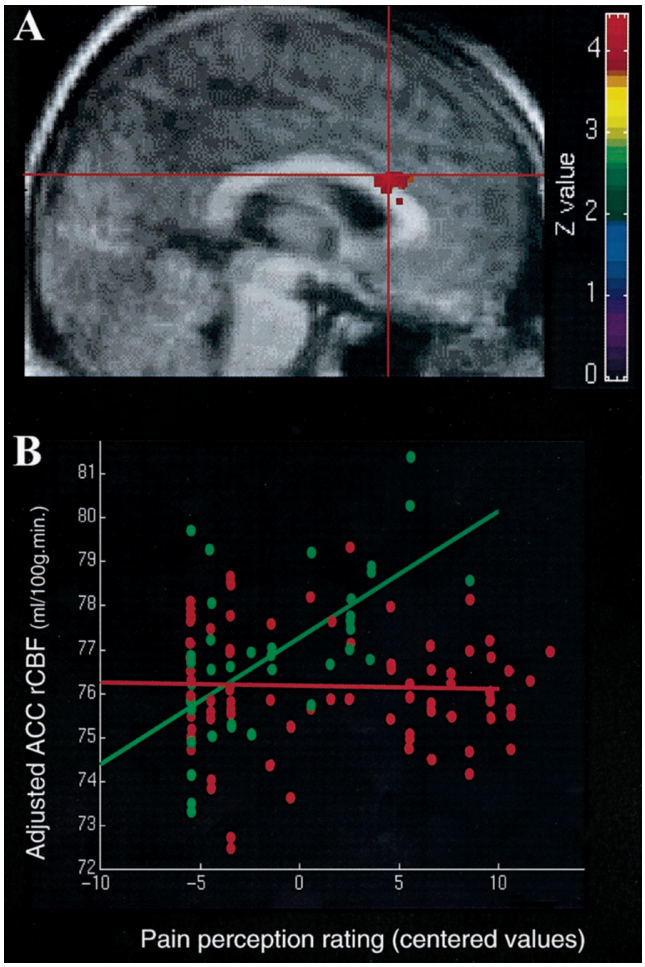


**Fig. 5. (*A*) Brain area in which blood flow increases in proportion to pain sensation ratings, in the specific context of the hypnotic state: the ventral part of the midcingulate cortex (tentatively area 24′a). Results are displayed on the subject's T1-weighted average magnetic resonance imaging scan, 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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