Cerebral Mechanisms of Hypnotic Induction and Suggestion

Pierre Rainville
Université de Montréal

Robert K. Hofbauer and Tomáš Paus
McGill University

Gary H. Duncan
Université de Montréal

M. Catherine Bushnell
Université de Montréal and McGill University

Donald D. Price
University of Florida

Abstract

■ The neural mechanisms underlying hypnotic states and responses to hypnotic suggestions remain largely unknown and, to date, have been studied only with indirect methods. Here, the effects of hypnosis and suggestions to alter pain perception were investigated in hypnotizable subjects by using positron emission tomography (PET) measures of regional cerebral blood flow (rCBF) and electroencephalographic (EEG) measures of brain electrical activity. The experimental conditions included a restful state (Baseline) followed by hypnotic relaxation alone (Hypnosis) and by hypnotic relaxation with suggestions for altered pain unpleasantness (Hypnosis-with-Suggestion). During each scan, the left hand was immersed in neutral (35°C) or painfully hot (47°C) water in the first two conditions and in painfully hot water in the last condition. Hypnosis was accompanied by significant increases in both occipital rCBF and delta EEG activity, which were highly correlated with each other (r = 0.70, p < 0.0001). Peak increases in rCBF were also observed in the caudal part of the right anterior cingulate sulcus and bilaterally in the inferior frontal gyri. Hypnosis-related decreases in rCBF were found in the right inferior parietal lobule, the left precuneus, and the posterior cingulate gyrus. Hypnosis-with-suggestions produced additional widespread increases in rCBF in the frontal cortices predominantly on the left side. Moreover, the medial and lateral posterior parietal cortices showed suggestion-related increases overlapping partly with regions of hypnosis-related decreases. Results support a state theory of hypnosis in which occipital increases in rCBF and delta activity reflect the alteration of consciousness associated with decreased arousal and possible facilitation of visual imagery. Frontal increases in rCBF associated with suggestions for altered perception might reflect the verbal mediation of the suggestions, working memory, and top-down processes involved in the reinterpretation of the perceptual experience. These results provide a new description of the neurobiological basis of hypnosis, demonstrating specific patterns of cerebral activation associated with the hypnotic state and with the processing of hypnotic suggestions. ■

INTRODUCTION

The neural mechanisms underlying hypnotic experience and responses to hypnotic suggestions are largely unknown and even the most general hypotheses remain controversial. Right-hemispheric function has been emphasized (e.g., Carter, Elkins, & Kraft, 1982; Gabel, 1988) because of its presumed association with imaginative, holistic, or appositional thinking (Benton, 1972; Bogen, 1969), all believed to be characteristic of hypnosis. Evidence for predominant right-hemisphere involvement comes from behavioral observations that hypnotic states and/or high hypnotic susceptibility are associated with an increase in left lateral eye movements in response to

various challenges (Bakan, 1969; Gur & Gur, 1974) and stronger responsiveness to hypnotic suggestions on the left than the right side of the body (Sackeim, 1982). Other studies suggest that hypnosis produces performance shifts in favor of the left ear in dichotic listening tasks (Frumkin, Ripley, & Cox, 1978; Pagano, Akots, & Wall, 1988), in favor of the left hemifield in divided visual field studies (McCormack & Gruzelier, 1993), and in favor of the left hand in haptic discrimination (Gruzelier, Brow, Perry, Rhonder, & Thomas, 1984). Support for a right-hemisphere involvement in hypnosis also comes from psychophysiological studies that show greater suppression of the electrodermal orienting response on the left side of the body during hypnosis (Gruzelier & Brow, 1985; Gruzelier et al., 1984) and greater right-hemisphere suppression of the late components of visually evoked brain potentials in response to suggestions for obstructive hallucination (Spiegel, Cutcomb, Ren, & Pribram, 1985). However, numerous studies using the same or similar paradigms have produced contradictory results and have challenged the right-hemisphere dominance view (e.g., Crawford, Crawford, & Koperski, 1983; Jasiukaitis, Nouriani, & Spiegel, 1996; Levine, Kurtz, & Lauter, 1984; Otto-Salaj, Nadon, Hyot, Register, & Kihlstrom, 1992; Spanos, Pawlack, Mah, & D'Eon, 1980). Moreover, studies of electroencephalographic (EEG) correlates of hypnosis have produced mixed results, suggesting complex dynamic interactions between the two hemispheres (see the review by Crawford and Gruzelier, 1992). These equivocal results have questioned the validity of investigating hypnosis in terms of a unique process or cognitive mode lateralized to one hemisphere.

New concepts of hypnosis suggest the involvement of multiple cognitive processes and offer promising opportunities to further our understanding of the underlying neural correlates (e.g., Crawford & Gruzelier, 1992; Price, 1996). Recently, Jasiukaitis, Nouriani, Hugdahl, and Spiegel (1997) have emphasized that hemispheric activation during hypnosis may depend on the nature of the task involved in the hypnotic experience (also see Morgan, MacDonald, & Hilgard, 1974). For example, aspects of hypnosis such as the role of language in establishing hypnotic reality are likely to involve left-hemisphere functions. Moreover, the establishment of the hypnotic state and the response to various hypnotic challenges are likely to involve distinct cognitive and neural processes. To date, however, virtually all evidence bearing on these conflicting views has relied on EEG, visual evoked potentials, or autonomic and psychophysical data and does not allow a detailed analysis of local changes in brain activity. The present report uses positron emission tomography (PET) to separately examine changes in brain activity associated with both the hypnotic state and the response to hypnotic suggestions.

We have previously reported the effect of hypnotic suggestions to selectively alter pain unpleasantness on pain-evoked changes in regional cerebral blood flow (rCBF) to examine the relationship between pain affect and cerebral activity (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Consistent with previous studies, pain-related increases in rCBF were found in primary and secondary somatosensory cortical areas (S1 and S2), the anterior cingulate cortex (ACC), and the insular cortex (IC) (see Aziz et al., 1997; Casey et al., 1994; Casey, Minoshima, Morrow, & Koeppe, 1996; Coghill et al., 1994; Craig, Reiman, Evans, & Bushnell, 1996; Hsieh et al, 1996; Jones, Brown, Friston, Qi, & Frackowiak, 1991; Talbot et al., 1991). Hypnotic suggestions that altered the subjects' pain unpleasantness ratings but not their sensory ratings likewise altered activity in the ACC but not in the S1 cortex.

We now describe additional analyses of rCBF and EEG data acquired in that study that address three fundamental questions about cortical regions involved in the production of hypnosis and/or response to hypnotic suggestions: (1) What cortical regions are activated during the hypnotic state? (2) How does pain influence cortical regions activated during the hypnotic state? (3) What cortical regions are activated in response to hypnotic suggestions of altered perception?

The experimental design included three conditions: restful state (Baseline), hypnotic relaxation (Hypnosis), and hypnotic relaxation with suggestions for altered pain unpleasantness (Hypnosis-with-Suggestion) (Table 1). Hypnosis was induced following the Baseline condition using the instructions of the Stanford Hypnotic Susceptibility Scale Form A (SHSS-A). During each scan of the Baseline and Hypnosis conditions, the left hand of the subject was immersed in neutral (35°C) or in painfully hot water (47°C). In the Hypnosis-with-Suggestion condition the hypnotic state was maintained, and suggestions for increased or decreased pain unpleasantness were given before the beginning of each stimulus and scan. The same painful stimulus was applied during each scan of the Hypnosis-with-Suggestion condition. Brain electrical activity was also measured during each scan in 9 of 11 experimental PET sessions, with EEG scalp electrodes placed over the left and right frontal (F_3, F_4) and occipital regions (O_1, O_2).

RESULTS

Evidence for Production of Hypnotic States

All eight subjects selected to participate in the PET experiment had moderate to high hypnotic susceptibility scores, as assessed individually in a preliminary training session using 11 subtests of the SHSS-A (range: 8/11 to 11/11; median = 10). These relatively high scores were maintained during the PET experiment (range 8/11 to 11/11; median = 9). The test-retest reliability of the susceptibility scores across training and PET experiments was high and statistically significant (Spearman, $r = 0.79$, $p = 0.02$). These results provide critical evidence that a

Table 1. Experimental Conditions

Scan	Condition	State	Pain Modulation	Stimulus
1	Baseline	Restful awake	–	Neutral
2	Baseline	Restful awake	–	Painful
3	Baseline	Restful awake	–	Painful
4	Baseline	Restful awake	–	Neutral
5	Hypnosis	Hypnotic relaxation	–	Painful
6	Hypnosis	Hypnotic relaxation	–	Neutral
7	Hypnosis	Hypnotic relaxation	–	Neutral
8	Hypnosis	Hypnotic relaxation	–	Painful
9	Hypnosis-with-Suggestion	Hypnotic relaxation	High Unpleasantness	Painful
10	Hypnosis-with-Suggestion	Hypnotic relaxation	High Unpleasantness	Painful
11	Hypnosis-with-Suggestion	Hypnotic relaxation	Low Unpleasantness	Painful
12	Hypnosis-with-Suggestion	Hypnotic relaxation	Low Unpleasantness	Painful

[a] Stimulus order in scans 1–4 and 5–8, and pain-modulation suggestions order in scans 9–12 are reversed in half the subjects and sessions.

moderate to high hypnotic state was maintained throughout the Hypnosis and Hypnosis-with-Suggestion conditions in the PET scanning session. This evidence is further strengthened by the observation of selective and significant modulation of pain unpleasantness ratings in the Hypnosis-with-Suggestion condition (see Rainville et al., 1997). Relative to the unpleasantness ratings of the painful stimuli in the Hypnosis condition (see Table 1, mean rating ± *SD*: 54.8 ± 25.8, on a scale of 0 to 100), ratings increased by 43% (±39%) in the High ($t = 4.97$, p-corrected < 0.001), and decreased by 29% (±35%) in the Low unpleasantness suggestion condition ($t = -3.75$, p-corrected = 0.04). Ratings were comparable in the Hypnosis and Baseline conditions ($t = 2.19$, p-corrected = 0.12), indicating that the induction of hypnosis without specific suggestions for altered perception had little effect on pain sensations.

Hypnosis-Related Effects (Hypnotic Relaxation Alone vs. Restful Awake Baseline)

rCBF Subtraction

Evaluation of hypnosis-related changes in rCBF was done by subtracting, on a voxel-by-voxel basis, rCBF acquired in the Baseline condition from that obtained in the Hypnosis condition using both neutral and painful stimulus conditions (Hypnotic relaxation alone; see Table 1). The locations of significant peaks and clusters of voxels showing increased or decreased rCBF in response to hypnosis are shown in Figure 1 and Table 2. Increases in rCBF were found bilaterally in several regions of the occipital cortex and in the inferior frontal gyri. Other sites of significant increase included the caudal part of

the right anterior cingulate sulcus, the right anterior superior temporal gyrus, and the left insula (Table 2, part A, Figure 1). Significant decreases associated with hypnosis were found in the parietal cortex, with peaks in the right inferior parietal lobule, medial precuneus, and left posterior cingulate gyrus (Table 2, part B, Figure 1D). Other sites of significant decrease included the left medial superior frontal gyrus and the left posterior middle temporal gyrus.

Effect of Pain on Hypnosis-Related Changes in rCBF

The effect of pain on hypnosis was tested by comparing hypnosis-related changes in rCBF in the neutral and painful stimulation conditions. The stimulation condition influenced the hypnosis-related changes only in occipital and left temporal rCBF. A significant occipital cluster of 82 cm^3 with three significant peaks was observed in the neutral stimulation condition (Figure 1F, top). In the painful stimulation condition this increase was markedly reduced to a cluster of 9 cm^3 with a single significant peak. Another site of interaction was found in the left middle temporal gyrus, where the hypnosis-related decrease in rCBF was observed only in the neutral temperature condition (not shown). All other sites of hypnosis-related changes in rCBF listed in Table 2 did not show evidence of an interaction with stimulation condition.

EEG Activity

Hypnotic relaxation produced an increase in occipital delta activity in the neutral stimulation condition. EEG

data were compared for relative power across lobes (frontal, occipital), sides (right, left), stimulus temperature (neutral, painful), and hypnosis-related conditions (Baseline, Hypnosis) for each of five bandwidths (delta: 1.5 to 4.0 Hz, theta: 4.5 to 8.0 Hz, alpha: 8.5 to 12.0 Hz, beta: 12.5 to 30.0 Hz and gamma: 30.5 to 50.0 Hz). An interaction of hypnosis and stimulus temperature was observed in the delta band over the occipital lobe, as illustrated in Figure 2A ($F = 11.96, p = 0.015$; p-adjusted for five comparisons using Bonferroni correction). Occipital delta power increased with hypnotic relaxation in the neutral stimulus condition (simple effect of hypnosis: $F = 4.77, p = 0.04$) and decreased nonsignificantly in the painful condition ($F = 2.65, p = 0.12$). Analysis of other bands did not yield significant main effects of, or interaction with, condition or stimulus.

The effect in occipital delta power paralleled the hypnosis-related effect observed in occipital rCBF in the neutral stimulation condition. The relationship between rCBF and delta activity was thus further evaluated in a linear regression model (analysis of covariance, or ANCOVA). As delta activity increased, rCBF increased in the left and right occipital lobes and left post-central gyrus (occipital cluster size: 69.8 cm^3, maximum peak coordinates: $x = -20.1, y = -83.1, z = -13.5, t = +5.51$, Pearson-$r = +0.70$; postcentral cluster size: 8.1 cm^3, peak coordinates $x = -41.5, y = -34.9, z = +57.0, t = +4.78$, Pearson-$r = +0.77$). The occipital region showing this significant correlation is illustrated in Figure 2B. This region largely overlapped with the region of significant hypnosis-related increase in rCBF in the subtraction analysis (see Table 2, part A; Figure 1F). In addition, a near-significant negative correlation was observed in the thalamus, suggesting a decrease in thalamic rCBF with the increase in occipital delta activity ($x = -5.4, y = -12.6, z = 0.0; t = 4.35$, Pearson-$r = -0.65$, uncorrected $p = 0.0002$; p corrected over the entire brain volume = 0.10, see Methods).

Comparison of ACC Hypnosis- and Pain-Related Changes in rCBF

A strong lateralized increase in rCBF was found in the right ACC in response to hypnosis (Figure 1B.). Similar ACC activation has consistently been shown in response to experimental painful stimuli, and our previous report confirmed this effect, both within the Baseline and Hypnosis conditions (Aziz et al., 1997; Casey et al., 1994, 1996; Coghill et al., 1994; Craig et al., 1996; Davis, Taylor, Crawley, Wood, & Mikulis, 1997; Hsieh et al., 1996; Jones et al., 1991; Rainville et al., 1997; see also Talbot et al., 1991). However, the hypnosis-related increase in rCBF reported here was independent of changes produced by pain because it was observed in both neutral and painful stimulus conditions. Furthermore, although pain- and hypnosis-related ACC sites were anatomically close

within Brodmann's area 24, the pain-related peak was medial along the cingulate gyrus (left 1.3)[1] and the hypnosis-related peak was more lateralized in the cingulate sulcus (right 10.7; see Table 2). Moreover, there was little overlap between these two foci of rCBF increase as indicated by the negative t value found at the pain-related peak coordinates in the hypnosis-related subtraction analysis ($t = -1.85$). ANCOVAs were used to investigate further the possibility of a functional distinction between these two ACC sites, in relation to the two orthogonal experimental factors (Baseline versus Hypnosis and neutral versus painful stimulus).

We hypothesized that if the pain- and hypnosis-related changes in rCBF within the ACC reflected activity in the same anatomo-functional site, the covariation pattern of each site with other brain regions would be similar when analyzed across all experimental factors. This hypothesis was tested in two regression analyses to reveal brain regions with blood flow linearly related to the level found in either the hypnosis-related ACC site or the pain-related ACC site. Normalized rCBF values were extracted from two volumes of interest (VOIs) at the hypnosis- or pain-related site, from scans acquired in both Baseline and Hypnosis conditions, and under both the neutral and painful stimulation (see Table 1). These two VOIs were used as covariates in two separate voxel-by-voxel regression analyses (ANCOVA). Rather than sequentially factoring out the effects of either pain or hypnosis, as had been done in the standard subtraction-based analyses, each of these ANCOVA analyses allows the potential effects of both factors to influence the pattern of covariation relative to each VOI. Regions of significant hypnosis-related changes in rCBF listed in Table 2 were specifically searched for covariation with rCBF at the hypnosis- or pain-related ACC sites.

Results of these ANCOVA analyses revealed striking differences in the patterns of covariations associated with the hypnosis- and pain-related ACC sites. Regions of significant positive and negative correlation with rCBF at the hypnosis-related ACC site were found in each region listed in Table 2 where hypnosis produced an increase or decrease, respectively (see Appendix for a detailed listing of covariation sites). In particular, positive correlation sites were observed in the occipital lobe—the principal area of rCBF increase with hypnosis (Table 2, part A)—and negative correlation sites were found in the left posterior cingulate and right inferior parietal lobule—two regions of hypnosis-related decrease in rCBF (Table 2, part B). In sharp contrast, occipital rCBF correlated *negatively* and the left posterior cingulate and right parietal lobule rCBF correlated *positively* with rCBF in the nearby pain-related ACC site (Table 3). Other regions of significant correlation with rCBF in the pain-related ACC site lay outside the search volume of hypnosis-related changes (see Appendix). In general, these two adjacent regions within area 24 of the ACC both demon-

Table 2. Cerebral sites of significant hypnosis-related changes in rCBF (Hypnosis minus Baseline rCBF; combined neutral and painful stimulation conditions). Clusters are defined as significant groups of adjacent voxels with t values > 2.50. Significant peaks are described for each cluster (see Methods). Brain structures are identified based on the stereotaxic atlas of Talairach and Tournoux (1988) and on morphological landmarks on the merged PET-MRI images (x: lateral, y: anterior, z: superior). The most probable Brodmann's cytoarchitectonic area (BA) is given for cortical sites (Left: L., Right: R.; gyrus: g.; anterior: ant.; posterior: post.; superior: sup.; inferior: inf.).

Cluster Identification (Size)	Peak Location	x	y	z	t
A. Increases in rCBF					
1. Bilateral occipital (94.6cm^3)	L. fusiform g. (BA 19)	−29.5	−69.3	−13.5	6.51
	R. fusiform g. (BA 18)	38.9	−84.8	−6.0	4.94
	L. middle occipital g. (BA 19)	−30.8	−76.2	13.5	4.78
	R. fusiform g. (BA 19)	33.5	−77.9	−9.0	4.76
	R. middle occipital g. (BA 19)	20.1	−81.4	18.0	4.54
	L. lingual g. (BA 18)	−9.4	−86.5	−7.5	4.54
2. R. sylvian (40.6cm^3)	R. inf. frontal g. (BA 47)	45.6	32.2	−16.5	6.06
	R. sup. temporal g. (BA 38)	60.3	13.2	−12.0	5.94
	R. sup. temporal g. (BA 22)	63.0	8.1	3.0	5.79
	R. parietal operculum (BA 43)	63.0	−5.7	18.0	4.82
3. L. insula (12.9cm^3)	L. post. insula	−29.5	−21.2	21.0	4.55
4. L. dorso-lateral frontal (12.3cm^3)	L. inf. frontal g. (BA 44)	−27	15.0	27	5.06
	L. inf. frontal g. (BA 45)	−29.5	18.4	18.0	4.58
5. R. cingulate (7.2cm^3)	R. ant. cingulate g. (BA 24)	10.7	4.6	42.0	5.22
B. Decreases in rCBF					
6. R. temporo-parietal (23.6cm^3)	R. inf. parietal lobule (BA 40/7)	45.6	−50.4	42.0	−5.86
7. Medial parietal (20.4cm^3)	Post. cingulate g. (BA 31)	−4.0	−35.0	37.5	−7.24
	Precuneus (BA 7)	−4.0	−64.2	42.0	−4.68
	Precuneus (BA 7)	0.0	−62.4	51.0	−4.50
8. L. middle temporal g. (12.3cm^3)	L. middle temporal g. (BA 37)	−57.6	−57.3	1.5	−4.00[a]
9. L. medial prefrontal (11.8cm^3)	L. sup. frontal g. (BA 6)	−10.7	6.4	66.0	−4.35[a]

[a] Uncorrected-p < 0.001.

strated increases in rCBF in this study—one during hypnotic relaxation and the other during the presentation of painful stimuli; however, the results of the covariation analyses suggest that the increase in rCBF in these two ACC sites may reflect different functions.

Suggestion-Related Effects

rCBF Subtraction

The effects of suggestions were evaluated by subtracting rCBF values acquired in the Hypnosis condition with painful stimulus presentation from those observed in the Hypnosis-with-Suggestion conditions (High or Low pain unpleasantness; see Table 1). As indicated in Figure 3 and in part A of Table 4, suggestion-related increases in rCBF were widespread and predominant within medial superior and left dorsolateral aspects of the frontal lobes. Other cortical sites of significant increase in rCBF were found in the right dorsolateral frontal, the left medial posterior parietal, and the bilateral posterior parietal cortices. Additional peaks were found in the left red nucleus and nucleus accumbens. Significant decreases in rCBF were found in the right uncus, in bilateral posterior orbito-frontal regions, and in the left lateral cerebellum (Table 4, part B). Both suggestion conditions contributed to these effects, as indicated by the nonsignificant differ-
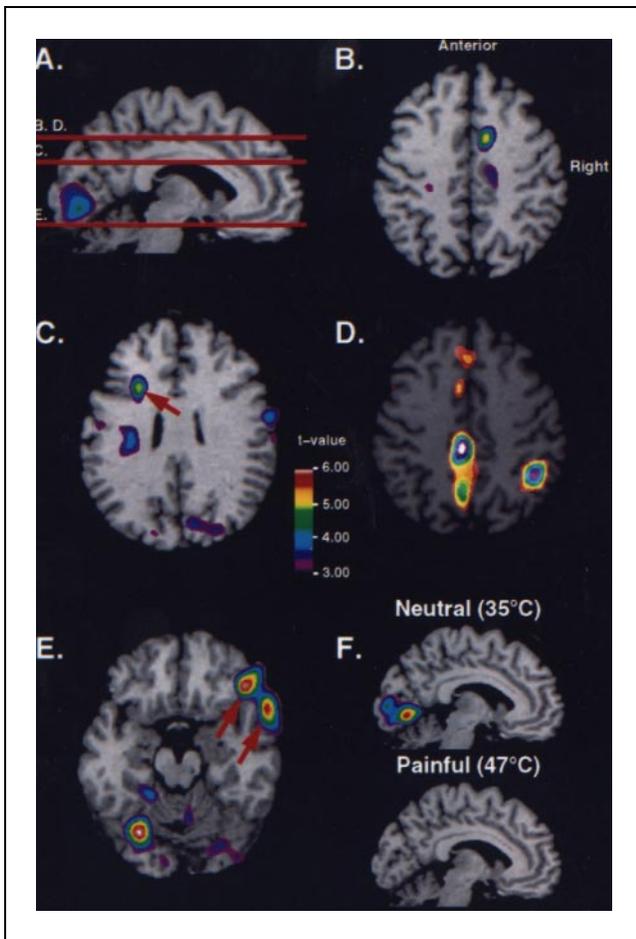
Figure 1. Statistical (*t*) maps of hypnosis-related increases in rCBF, across stimulation conditions, in occipital (A: left 6.7), right anterior cingulate (B: superior +42.0), left frontal (arrow in C: superior +27.0), right frontal and right temporal cortices (arrows in E: superior −16.5). Decreases in blood flow were found in right lateral and medial posterior parietal cortices (D: superior +42.0; *t* color scale reversed in D). When analyzed separately in each stimulation condition, the hypnosis-related increase in occipital rCBF was observed mainly in the neutral stimulation condition, as shown in F. Coordinates refer to the atlas of Talairach and Tournoux (1988).

ences found in the direct comparison of the High and Low pain unpleasantness conditions.

EEG Activity

There was no significant main effect of, or interaction with, the suggestion conditions in any of the five EEG bands analyzed separately (see Methods).

DISCUSSION

The paradigm used in this study allowed a distinction between changes associated with the induction of hypnotic states and changes associated specifically with responses to hypnotic suggestions to alter perceptual
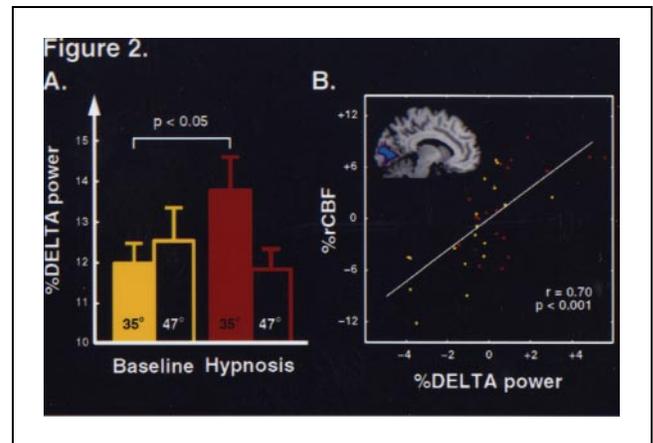

Figure 2. Relative power in delta EEG occipital activity increased significantly with hypnotic relaxation in the neutral (35°C) but not in the painful (47°C) stimulation condition (A). This effect parallels the interaction between hypnosis and stimulus condition in occipital rCBF changes (see Figure 1F). Result of the regression analysis (ANCOVA) testing the linear relation between occipital delta activity and rCBF in Baseline (yellow dots) and Hypnosis (red dots) scans in the neutral stimulation condition is shown in B (*n* = 18; 2 scans in each condition × 9 experimental sessions). The slope of the relationship was significant in bilateral occipital cortices (white line shows linear best fit). Inset shows the occipital region of significant regression (left 9.4).
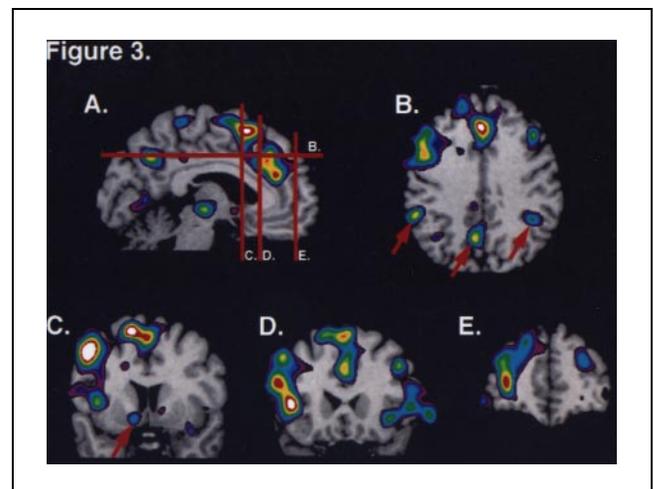

Figure 3. Statistical (*t*) maps of suggestion-related changes in rCBF show increases in medial (A: left 5.4) and dorsolateral frontal cortices (C: anterior +8.1; D: +21.8; E: +49.4), and in medial and lateral posterior parietal cortices (arrows in B: superior +37.5). Arrow in D shows significant subcortical increase in left nucleus accumbens.

experiences. The following discussion will focus on evidence for (1) the production of hypnotic states and reliable responses to hypnotic suggestions, (2) a pattern of cerebral activity associated with the hypnotic state,

Table 3. Regions of significant correlation with rCBF in the *pain-related ACC site* ($x = -1.3$, $y = +2.9$, $z = +39.0$) within the search volume defined by the regions of hypnosis-related changes in rCBF listed in Table 2 (total search volume equals the sum of cluster sizes in Table 2: 235.7cm^3; within this search volume, $t > 4.00$ was significant at $p < 0.05$; uncorrected-p <0.0006; Ci refers to the cluster identification number in Table 2). Positive correlations are found in regions where rCBF *decreased* with hypnosis, whereas a negative correlation is found in a region where rCBF *increased* with hypnosis. Other regions showing significant correlation with rCBF at the pain-related ACC, outside the hypnosis-related clusters of rCBF changes, are listed in Appendix. See Table 2 caption for further explanation.

Cluster Identification (Size)	Peak	x	y	z	t
A. Positive Correlation					
1. See note (174.7cm³)	R. inf. parietal lobule (BA 40) (C6)	52.3	−24.6	25.5	5.36
	Post. cingulate g. (BA 31) (C7)	−6.7	−28.0	45.0	4.23
	R. inf. parietal lobule (BA 40) (C6)	42.9	−47.0	51.0	4.06
B. Negative Correlation					
2. R. occipital (17.2cm³)	R. middle occipital g. (BA 19) (C1)	45.6	−72.8	7.5	−4.54

Note: A single cluster of voxels with $t > 2.5$ included all significant positive peak coactivation sites listed in Table 3 and Appendix.

(3) an interaction between pain and the hypnosis-related changes, (4) a functional distinction between hypnosis- and pain-related changes in ACC, and (5) a pattern of cerebral activity associated with responses to hypnotic suggestions of altered perception.

Evidence for Production of Hypnosis

Several lines of evidence indicate that hypnotic states were indeed produced by the intervention used in this study. Subjects selected to participate were highly responsive to a standardized protocol of hypnotic suggestions and showed similar moderate to high scores when tested during the PET scanning sessions. All subjects responded to the hypnotic suggestions for selective modulation of pain unpleasantness. In an independent pre-experimental session in which subjects with low, moderate, or high hypnotic susceptibility were tested using the same protocol, modulation of pain unpleasantness was significantly correlated with susceptibility scores (Rainville, Carrier, Hofbauer, Duncan, & Bushnell, submitted). Finally, subjects spontaneously reported having been in an altered state of consciousness, describing these states in terms that are commonly known to characterize hypnosis, including deep relaxation, automatic responding, and a suspension of usual orientation toward time.

Changes Associated with the Hypnotic State

Functional significance of the hypnosis-related changes in rCBF might relate to several processes suggested as key phenomena in the induction of hypnosis. In addition to the reported general relaxation, automatic responding,

and slight disorientation in time, such processes might include imagery, focused attention, *disattention* to irrelevant stimuli, and disorientation toward space or sense of self (see Crawford & Gruzelier, 1992; Price, 1996). Different sites of hypnosis-related rCBF changes are discussed separately.

Occipital Increase in rCBF

The most striking effect observed in hypnosis is the widespread increase in occipital rCBF. Similar effects have been described during visual imagery (D'Esposito et al., 1997; Kosslyn, Thompson, Kim, & Alpert, 1995). In the present study, subjects were not explicitly instructed to engage in such imaginative processes, but spontaneous visual imagery was reported in some subjects. This effect might also relate to the high levels of imagery vividness reported in highly hypnotizable subjects (Crawford, 1982). The mechanisms by which hypnosis may facilitate visual imagery processes could depend on the establishment of a state of deep relaxation.

In the absence of visual stimulation, increases in occipital rCBF have been reported during meditation (Kjaer, Lou, Nowak, Wildshiødtz, & Friberg, 1997), slow wave sleep (Hofle et al., 1997), and a gradual decrease in arousal in a prolonged auditory vigilance task (Paus et al., 1997). Moreover, occipital delta EEG activity was found to correlate positively with occipital and negatively with thalamic rCBF in response to hypnosis, a pattern similar to the results obtained in slow wave sleep (Hofle et al., 1997). The increase in occipital rCBF might relate to the deep relaxation or decreased arousal common to these states. Paus et al. (1997) interpreted the decrease in occipital rCBF following the initiation of an

Table 4. Cerebral sites of significant suggestion-related changes in rCBF (Hypnosis-with-Suggestion minus Hypnosis rCBF; all under painful stimulation condition). See Table 2 caption for further explanation.

Cluster Identification (Size)	Peak	x	y	z	t
A. Increases in rCBF					
1. Bilateral frontal lobes (228.5cm^3)	L. inf. frontal g. (BA 44/45)	−41.5	15.0	4.5	7.74
	L. middle frontal g. (BA 6/8)	−48.2	6.4	45.0	7.14
	L inf. frontal g. (BA 47)	−46.9	39.0	−10.5	7.10
	Medial sup. frontal g. (BA 6)	0.0	15.0	58.5	6.92
	L. frontal pole (BA 10)	−33.5	56.2	−1.5	6.84
	L. inf. frontal g. (BA 44/45)	−53.6	16.7	19.5	6.48
	L. sup. frontal g. (BA 6)	−13.4	8.1	63.0	6.42
	Ant. cingulate g. (BA 32)	0.0	28.7	34.5	6.33
	R. sup. frontal g. (BA 8)	12.1	32.2	48.0	5.88
	Ant. cingulate g. (BA 32)	−4.0	37.3	24.0	5.69
	L. precentral g. (BA 4)	−41.5	−14.3	60.0	5.30
	R. inf. frontal g. (BA 44/45)	50.9	18.4	1.5	5.24
	R. inf. frontal g. (BA 47)	36.2	25.3	−7.5	5.22
	R. middle frontal g. (BA 9)	42.9	23.6	34.5	5.15
	L. frontal pole (BA 9)	−18.8	54.5	25.5	4.61
	L. sup. frontal g. (BA 6)	−13.4	−17.7	64.5	4.60
2. Medial parietal (14.7cm^3)	Precuneus	−5.4	−62.4	36.0	5.23
3. L. Subcortical (10.0cm^3)	L. red nucleus	−5.4	−19.4	−4.5	5.01
	L. nucleus accumbens	−10.7	4.6	−7.5	4.75
4. L. parietal (10.0cm^3)	L. Supramarginal g. (BA 40)	−54.9	−43.5	33.0	5.53
5. R. parietal (7.4 cm^3)	R. inf. parietal lobule (BA 40)	41.5	−47.0	37.5	4.41[a]
6. L. parietal (6.1 cm^3)	L. inf. parietal lobule (BA 40/7)	−39.0	−62.4	42.0	4.33[a]
B. Decreases in rCBF					
7. Bilateral orbitofrontal/R. uncus (8.12 cm^3)	R. uncus	14.7	4.6	−19.5	−4.25[a]
	Post. g. rectus (BA 25)	−4.0	16.7	−22.5	−4.23[a]
	Post. g. rectus (BA 25)	6.7	20.1	−15.0	−4.17[a]
8. L. cerebellum/fusiform g. (4.43 cm^3; $p = 0.11$, *ns*)	L. lateral cerebellum	−25.5	−67.6	−19.5	−4.95

[a] Uncorrected-$p < 0.0005$.

auditory vigilance task as cross-modality suppression (also see Kawashima, O'Sullivan, & Roland, 1995). The reversal of this effect, as arousal decreased with time-on-task, was interpreted as a reduction of cross-modality suppression associated with a shift from the alert to the relaxed state of consciousness. The decrease in arousal associated with relaxation during the Hypnosis condition might produce a similar decrease in cross-modality suppression during the thermal stimulation, resulting in an increase in background synaptic activity in the visual cortex and, in turn, a facilitation of spontaneous visual imagery.

Effect of Pain on Hypnosis-Related Changes in Occipital rCBF

A reduction of the hypnosis-related increases in occipital rCBF and delta activity was observed under the painful

stimulation condition. This effect was paralleled by the spontaneous report, in some subjects, of a disturbing effect of pain on the hypnotic state. Reduction in occipital rCBF and delta activity during painful stimulation might reflect disruption of relaxation and/or imagery processes by pain. We have previously reported that hypnosis alone, without suggestions for altered pain perception, did not produce major changes on pain ratings or pain-related rCBF increases in the somatosensory, insular, and anterior cingulate cortices (Rainville et al., 1997). These contrasting results—a strong effect of pain on hypnosis and no major effect of hypnosis alone on pain—might reflect the primacy of pain-related processes over hypnosis-related processes. Previous psychophysical results on attentional modulation of pain perception support such reasoning. Miron, Duncan, and Bushnell (1989) showed that pain ratings and thermal discrimination performance were comparable when subjects were instructed to attend selectively to the thermal painful stimuli or to divide their attention to both painful and visual stimuli. This result supports the hypothesis that in the presence of competing processes, primacy of pain is likely, unless additional instructions and attentional effort are directed to other processes. Pain has been recently shown to produce a decrease in occipital rCBF that could reflect arousal-mediated cross-modality suppression (Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; Svensson, Minoshima, Beydoun, Morrow, & Casey, 1997). Following the above line of interpretation, the fundamental relevance of the pain signal is likely to produce preeminent cross-modality suppression on ongoing competing sensory or cognitive processes. The decreased arousal and facilitation of imagery processes hypothesized during the hypnotic relaxation would therefore be reduced under the painful stimulation condition.

Dissociation of Hypnosis- and Pain-Related Changes in ACC

Both hypnosis and pain led to increases in rCBF in the ACC. Hypnosis- and pain-related increases in rCBF were found in discrete regions in the caudal part of the ACC within area 24. The hypnosis-related increase was independent of pain because it was observed in both neutral and painful-stimulus conditions. The pain-related effect was also independent of hypnosis because it was observed in both the Baseline and Hypnosis conditions. The more medial, posterior, and ventral location of the pain-related site is consistent with results of a study directly comparing rCBF changes in the ACC produced by pain and by a cognitive task (Davis et al., 1997). Similarly, pain- and hypnosis-related changes in rCBF in the ACC might reflect different functions.

The ACC has been associated with various processes such as attention and processing selection (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990; Pardo,

Pardo, Janer, & Raichle, 1990; Petersen, Fox, Posner, Mintun, & Raichle, 1988), motor control (Picard & Strick, 1996), and facilitation/suppression of action and automatic motor responses (Paus, Petrides, Evans, & Meyer, 1993). The ACC contains many distinct subregions that are likely to show divergent functional interactions with other cortical regions (see Devinsky, Morrell, & Vogt, 1995; Paus, Koski, Caramanos, & Westbury, 1998; Vogt and Gabriel, 1993). Accordingly, contrasting patterns of covariation were associated with hypnosis- and pain-related ACC sites. Regions of hypnosis-related increase in rCBF correlated positively, and regions of hypnosis-related decrease in rCBF correlated negatively with rCBF in the hypnosis-related ACC site. In sharp contrast, regions correlated with the pain-related site in the ACC showed the reverse pattern of covariation or lay outside the regions of hypnosis-related changes. Reverse patterns of covariation were found in the occipital (negative correlation with pain-related ACC) and the medial and posterior parietal rCBF (positive correlation with pain-related ACC). In spite of their close proximity within the ACC, these two sites of increased rCBF may not reflect a single mechanism common to both hypnosis and pain. Instead, each demonstrates a contrasting relationship, through covariation, to other regions of the cerebral cortex that are involved in either the hypnotic state or the processing of painful stimuli, respectively. The nature of the functional role of the ACC in hypnosis remains to be elucidated.

Posterior Parietal Changes in rCBF

Processes involving spatial attention and orientation to external stimuli have been attributed to the posterior parietal cortices (Posner & Petersen, 1990). Furthermore, right posterior parietal cortices are likely to play a determinant role in higher-order body or *self*-representation (Bisiach & Berti, 1995). Hypnosis produced decreases in posterior parietal rCBF. Accordingly, rCBF at these sites was negatively correlated with rCBF at the hypnosis-related ACC site. In contrast, some parietal sites showed a positive correlation with pain-related ACC (see Table 3). In line with the above interpretations, pain probably produces an increase in arousal, orienting, and attention to external stimuli. We speculate that the decrease in rCBF observed in these posterior parietal cortical regions reflects decreased attention and orientation to irrelevant extrapersonal and somatic stimuli during the hypnotic state.

Changes Associated with Suggestions to Alter Perception

Suggestion-related changes in rCBF were assessed by comparing the Hypnosis-with-Suggestion condition to the Hypnosis condition in the presence of painful stimuli

(see Table 1). Because the hypnotic state was maintained throughout these two conditions, differences are interpreted as reflecting processes involved specifically in the response to the suggestions to alter perception. Such processes involve verbal working memory necessary to maintain the framework proposed in the suggestions active throughout the stimulation and top-down *reinterpretation* of the external event according to this internal representation (Price, 1996).

A strong increase in rCBF in the left inferior frontal gyrus and the left dorsolateral aspect of the frontal lobes was found in response to suggestions. Similar effects have been observed when subjects listen to lists of words or a story and have been associated with active verbal lexical-semantic processing (Klein, Milner, Zatorre, Meyer, & Evans, 1995; Petersen et al., 1988; Zatorre, Evans, Meyer, & Gjedde, 1992) and working memory (D'Esposito et al., 1995; Paulesu, Frick, & Frackowiack, 1993). The anterior language area showed increased rCBF in the present study and could be involved in the internal verbal rehearsal or maintenance of the suggestion content in working memory during the stimulation and scan. However, the frontal cluster of voxels showing this increase extended largely beyond the anterior language area and encompassed almost all the left as well as part of the right frontal lobe.

Reality testing has been suggested to describe the monitoring of present external events and to depend on prefrontal function (Knight & Grabowecky, 1995). The right frontal lobe may be involved mainly in *external* monitoring, whereas the left frontal lobe may have a larger role in internally generated reinterpretation of the painful stimulus and/or the general experimental context, consistent with previous explanations (Gazzaniga, 1989; Jasiukaitis et al., 1997; Phelps & Gazzaniga, 1992). The hypnotic suggestions for pain modulation given in the present experiment were precisely aimed at altering the *perceived external reality* by reinterpretation of the pain sensations as being more (in some scans) or less (in other scans) unpleasant. Although different types of hypnotic suggestions would probably lead to distinct patterns of activation, we suggest that frontal activation might be common to the actualization of various types of suggestions involving *alteration of the meanings of perceptual experiences.*

The specific systems on which suggestions act would most likely depend on their content. Interestingly, left posterior lateral and medial precuneus parietal foci of increased rCBF observed in response to suggestion corresponded to sites of *decreased* rCBF in the Hypnosis condition. This effect could reflect a reversal of some hypnosis-related effect in response to the suggestions of pain modulation. In addition, left posterior parietal cortices showed increased rCBF in response to suggestions. Following the above proposed line of interpretation, this activity in higher-order parietal association cortices could reflect the specific content of the suggestions involving reinterpretation of meanings associated with somatic sensations. These contrasting results strongly emphasize the importance of examining the effect of the hypnotic relaxation separately from the effect of specific suggestions.

CONCLUSION

Complex patterns of rCBF changes in response to hypnosis and suggestions were found to involve both the right and the left hemisphere. Bilateral occipital increase in rCBF during hypnosis might relate to deep relaxation or decreased arousal and reflect a decrease in cross-modality suppression. This mechanism might explain the facilitation of visual processes such as imagery during hypnosis. The marked reduction of this effect under painful stimulation and the negative correlation between pain-related ACC and occipital rCBF support the hypothesis that pain processes produce enhanced cross-modality suppression and might disrupt competing sensory or cognitive processes. Following hypnotic suggestions, massive rCBF increase in frontal cortices, mainly but not exclusively on the left side, could reflect the verbal mediation of the hypnotic suggestions, working memory processes, and top-down mechanisms involved in the reinterpretation of the sensory experience. These results provide a new description of the neurobiological basis of hypnosis, demonstrating a specific pattern of cerebral activation underlying the multiple cognitive processes involved in this intervention.

METHODS

Subjects

Eight subjects showing high hypnotic susceptibility on the SHSS-A (score > 8/11) and reliable modulation of pain unpleasantness in a preliminary training session were selected from a group of 22 volunteers to participate in the PET experiment (3 females, 5 males; 7 right- and 1 left-handed; mean ± *SD* age = 28.5 ± 11.2 years, range = 19 to 53 years). Hypnotic susceptibility assessment was repeated during the PET experiment by giving items of the SHSS-A between scans (French version of the SHSS-A taken from Bourassa & Leclerc, 1991). To allow for immobilization of the right arm for the I.V. line in the PET scanner, item 5 involving both hands (finger lock) was changed to fist lock, and item 7 (moving hands toward each other) was discarded. Posthypnotic amnesia was used as an additional susceptibility test for a maximum score of 11. Three subjects participated in two PET scanning sessions, and five subjects participated in one. The Montreal Neurological Institute Ethics Committee approved all procedures, and all subjects signed a consent form describing the nature of the stimuli and the scanning procedure and affirming their right to withdraw from the experiment at any time without prejudice.

Experimental Procedure

Subjects participated in three successive blocks of four scans consisting of restful Baseline, Hypnosis, and Hypnosis-with-Suggestion, as shown in Table 1. Subjects remained immobile in the scanner, eyes closed, with earplugs and inserted earphones connected to a microphone through which instructions were given between scans. The hypnotic state was induced after the fourth Baseline scan using the protocol included in the SHSS-A. The hypnotic state was maintained throughout the Hypnosis and Hypnosis-with-Suggestion conditions by repeating sections of the induction instructions between scans. In the first two conditions (Baseline and Hypnosis), the subject's left hand was immersed in neutral (35°C) or painfully hot (47°C) water for the duration of each scan. Stimulus order (35 or 47°C) was counterbalanced within sessions and reversed across subjects and sessions to minimize order effects. In the Hypnosis-with-Suggestion condition, suggestions for High or Low pain unpleasantness (adapted from Kiernan, Dane, Phillips, & Price, 1995) were given before each of two scans, and the painful stimulus was applied during each scan. The order of the suggestion conditions was reversed across subjects and sessions. After each scan in all conditions, subjects rated the intensity and the unpleasantness of the pain sensation on separate scales.

The hypnotic suggestions were designed to modulate the affective dimension of pain perception by reinterpreting/associating the pain sensation with positive affect or reemphasizing, amplifying, and generalizing its negative affective impact. The suggestions did not contain any direct reference to muscle relaxation/tension to prevent motor confounds as much as possible. These suggestions were effective in modulating pain unpleasantness ratings as well as pain-related cerebral activation in specific cortical regions (Rainville et al., 1997).

PET Imaging Methods

rCBF was measured using a high-resolution PET scanner operated in 3-D-acquisition mode (Siemens ECAT HR$^+$, 63 slices). Measurements of rCBF were done using the $H_2^{15}O$ bolus-injection method (10 millicuries per scan) without arterial blood sampling (Fox & Mintun, 1989; Fox, Mintun, Raichle, & Herscovitch, 1984; Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, Herscovitch, Mintun, & Markham, 1983). Stimulus onset was simultaneous with bolus injection, and 1-min acquisition scans started about 15-sec postinjection. Results are reported for the first 40 sec of data acquisition, which produced a higher signal-to-noise ratio in preliminary analyses and in previous studies in this laboratory. An interscan interval of 12 to 15 min allowed the tracer to decay to background levels and minimized sensitization to repeated painful stimulation. After completing the PET sessions, each subject underwent high-resolution ana-tomical magnetic resonance imaging (MRI) (160 1-mm sagittal slices acquired on a Philips 1.5T Gyroscan system). Each PET and MRI volume was reconstructed, aligned, and transformed (Collins, Neelin, Peters, & Evans, 1994) to fit into a standardized space (Talairach & Tournoux, 1988) to allow for intersubject averaging and anatomical localization of rCBF changes. PET volumes were smoothed (full width, half maximum, or FWHM = 14mm) and normalized to the average brain count, and experimental conditions were compared using the subtraction method and statistical t maps of rCBF changes (Worsley, Evans, Marrett, & Neelin, 1992). In addition to peak analyses, cluster analyses were performed in which statistical significance was based on the false-positive expectancy rate of a group of adjacent voxels with t values > 2.5 (Friston, Worsley, Frackowiak, Mazziotta, & Evans, 1994). With a given pooled standard deviation in rCBF, peak significance depends on the maximum amplitude of a peak, whereas cluster significance depends on both the volume of the cluster and the t values within the cluster. All the main effects reported are significant at $p < 0.05$ in cluster or peak analyses (t value > 4.5) after a correction for multiple comparison over the entire brain volume. This correction is considered conservative to the extent that gray matter represents about one-third (500 cc) of the total volume (1495 cc) searched. This correction gives an expected number of false positives of 0.016 over the gray matter volume and corresponds to an uncorrected $p < 0.0001$.

EEG Recording Procedure

EEG activity was recorded in 9 out of 11 scanning sessions in the seven right-handed subjects (three females, four males). Recording electrodes (Ag/AgCl) were placed at sites O1, O2, F3, and F4, and a reference electrode was placed at C_z according to the international 10–20 system (Jasper, 1958). Additional electrodes were used to measure horizontal eye movements and mentalis muscle activity. Impedance of all electrodes was below 10 kΩ and electrical activity was amplified (bandpass 0.3 to 60 Hz), sampled at 200 Hz, and stored using Monitor software (Stellate Systems) for off-line analysis. Records containing muscle artifacts were discarded, and EEG activity during each scan was analyzed using fast Fourier transform analysis (Rhythm software, Stellate Systems). Frequency bands were defined as follows: delta: 1.5 to 4.0 Hz, theta: 4.5 to 8.0 Hz, alpha: 8.5 to 12.0 Hz, beta: 12.5 to 30.0 Hz, and gamma: 30.5 to 50.0 Hz. Relative power was first compared across experimental conditions, side, and lobe for each of the five frequency band analyzed separately (ANOVA). Significance was set at $p < 0.05$ after applying a Bonferroni correction for five analyses (five bands). Only the significant effects of, or interaction with, experimental conditions are reported.

Regression and Covariation Analyses

Regression analyses were performed on a voxel-by-voxel basis (1) to test the relationship between EEG and rCBF results and (2) to evaluate patterns of covariation between different cerebral regions. The first regression tested a linear model between rCBF and relative EEG activity in a covariance analysis model (ANCOVA) with subject as the main effect and EEG activity as a covariate. Covariation analyses followed the same general principle with the rCBF measured in a given VOI$_i$ used as the covariate. In both analyses, subject effects were removed, and the slope of the relationship (EEG versus rCBF or VOI$_i$ versus rCBF) was estimated at each voxel. The standard deviation of the slope (pooled over the entire volume) was used to derive the corresponding t statistic (Worsley et al., 1992). The t regression maps were superimposed over the anatomical MRI volume to localize foci at which the slope of the relationship was significantly different from 0. In addition, r maps (Pearson-r) were derived to obtain the correlation coefficient at sites of significant regression.

Appendix

Regions of significant correlation with rCBF in (A) the hypnosis-related ACC site ($x = +10.7, y = +4.6, z = +42.0$) or (B) the pain-related ACC site ($x = −1.3, y = +2.9, z = +39.0$) not listed in Table 3. See title of Table 3 for further explanation. Almost all regions significantly correlated with rCBF in the hypnosis-related ACC site (A) were found within the regions of significant hypnosis-related changes listed in Table 2 (Ci), except for the R. thalamus, L. precentral g., and R. frontal pole (in italic). Regions correlated with rCBF in the pain-related ACC site (B) were outside the hypnosis-related clusters listed in Table 2 with the exception of sites listed in Table 3.

Cluster Identification (Size)	Peak	x	y	z	t
A. Covariation with rCBF in Hypnosis-Related ACC Site					
i. Positive Correlation					
L. inf. frontal/insula (45.4cm³)	L. insula (C3)	−33.5	−0.5	13.5	5.25
	L. inf. frontal g. (BA 45/47) (C4)	−26.8	27.0	9.0	5.21
	L. pre-central g. (BA 4)	−46.9	−2.2	7.5	4.95
	L. inf. frontal g. (BA 44) (C4)	−28.1	15.0	24.0	4.39
	L. inf. parietal lobule (BA 40) (C3)	−37.5	−29.8	25.5	4.20
Bilateral occipital/ cerebellum (43.4cm³)	L. cerebellum/fusiform g. (BA 19) (C1)	−22.8	−67.6	−19.5	5.08
	Medial lingual g. (BA 18) (C1)	−1.3	−74.5	4.5	4.88
	Cerebellum (C1)	4.0	−57.3	−18.0	4.66
	R. post. cuneiform g. (BA 19) (C1)	14.7	−79.6	18.0	4.22
	L. middle occipital g. (BA 19) (C1)	−30.8	−72.8	15.0	4.12
R. sylvian (32.9cm³)	R. parietal operculum (BA 43) (C2)	61.6	−7.4	12.0	5.11
	R. frontal pole (BA 10)	37.5	56.2	−13.5	4.55
	R. inf. frontal g. (BA 47) (C2)	42.9	30.4	−19.5	4.38
	R. sup. temporal g. (BA 22) (C2)	57.6	8.1	0.0	4.06

Appendix. Continued.

<table>
<tr><td colspan="6" align="center">*ii. Negative Correlation*</td></tr>
<tr><td>Medial parietal (12.4cm^3)</td><td>Precuneus (BA 31) (C7)</td><td>−5.4</td><td>−36.7</td><td>34.5</td><td>−5.86</td></tr>
<tr><td></td><td>Post. cingulate g. (BA 23/31) (C7)</td><td>−6.7</td><td>−47.0</td><td>30.0</td><td>−5.61</td></tr>
<tr><td>R. temporo-
parietal (10.2cm^3)</td><td>R. middle temporal g. (BA 37) (C6)</td><td>42.9</td><td>−60.7</td><td>22.5</td><td>−4.59</td></tr>
<tr><td></td><td>R. inf. parietal lobule (BA 40) (C6)</td><td>46.9</td><td>−52.1</td><td>43.5</td><td>−4.00</td></tr>
<tr><td>L. sup. frontal (7.5cm^3)</td><td>L. sup. frontal g. (BA 6) (C9)</td><td>−12.1</td><td>16.7</td><td>61.5</td><td>−4.56</td></tr>
<tr><td>L. post. temporal (6.4cm^3)</td><td>L. middle temporal g. (BA 37) (C8)</td><td>−56.3</td><td>−60.7</td><td>9.0</td><td>−4.31</td></tr>
<tr><td>Thalamus (6.4cm^3)</td><td>*R. thalamus*</td><td>10.7</td><td>−14.3</td><td>3.0</td><td>5.06</td></tr>
<tr><td colspan="6" align="center">*B. Sites of Covariation with rCBF in Pain-Related ACC not Listed in Table 3*</td></tr>
<tr><td colspan="6" align="center">*i. Positive Correlation*</td></tr>
<tr><td>See note (174.7cm^3)</td><td>Sup. frontal g. (BA 6)</td><td>−4.0</td><td>−10.8</td><td>57.0</td><td>6.30</td></tr>
<tr><td></td><td>L. putamen</td><td>−29.5</td><td>4.6</td><td>6.0</td><td>5.51</td></tr>
<tr><td></td><td>R. post-central g. (BA 2/7)</td><td>26.8</td><td>−34.9</td><td>55.5</td><td>5.43</td></tr>
<tr><td></td><td>R. pre-central g. (BA 4)</td><td>49.6</td><td>−4.0</td><td>12.0</td><td>5.32</td></tr>
<tr><td></td><td>R. post-central g. (BA 1/3)</td><td>18.8</td><td>−29.8</td><td>60.0</td><td>5.17</td></tr>
<tr><td></td><td>L. pre-central g. (BA 6)</td><td>−50.9</td><td>2.9</td><td>4.5</td><td>5.11</td></tr>
<tr><td></td><td>R. post. insula</td><td>38.9</td><td>−19.4</td><td>16.5</td><td>5.11</td></tr>
<tr><td></td><td>R. post-central g. (BA 1/3)</td><td>37.5</td><td>−22.9</td><td>58.5</td><td>5.01</td></tr>
<tr><td></td><td>R. pre-central g. (BA 4)</td><td>38.9</td><td>−16.0</td><td>49.5</td><td>4.97</td></tr>
<tr><td></td><td>R. sup. frontal g. (BA 6)</td><td>16.1</td><td>4.6</td><td>64.5</td><td>4.90</td></tr>
<tr><td></td><td>R. pre-central g. (BA 4)</td><td>32.2</td><td>−5.7</td><td>55.5</td><td>4.78</td></tr>
<tr><td></td><td>R. thalamus</td><td>21.4</td><td>−12.6</td><td>6.0</td><td>4.74</td></tr>
<tr><td></td><td>L. inf. parietal lobule (BA 40)</td><td>−63.0</td><td>−31.5</td><td>33.0</td><td>4.53</td></tr>
<tr><td></td><td>L. sup. parietal lobule (BA 7)</td><td>−18.8</td><td>−52.1</td><td>60.0</td><td>4.53</td></tr>
<tr><td></td><td>R. medial thalamus</td><td>6.7</td><td>−14.3</td><td>3.0</td><td>4.51</td></tr>
<tr><td></td><td>R. post. insula</td><td>34.8</td><td>−16.0</td><td>3.0</td><td>4.48</td></tr>
<tr><td></td><td>L. sup. frontal g. (BA 6)</td><td>−21.4</td><td>−12.6</td><td>64.5</td><td>4.47</td></tr>
<tr><td></td><td>L. thalamus</td><td>−13.4</td><td>−17.7</td><td>9.0</td><td>4.28</td></tr>
<tr><td colspan="6" align="center">*ii. Negative Correlation*</td></tr>
<tr><td>R. hippocampal g. (4.9cm^3)</td><td>R. hippocampal g. (BA 35)</td><td>17.4</td><td>−41.8</td><td>−9.0</td><td>−4.90</td></tr>
<tr><td>R. middle temporal g.
(4.4cm^3)</td><td>R. middle temporal g. (BA 21)</td><td>53.6</td><td>−9.1</td><td>−19.5</td><td>−4.76</td></tr>
<tr><td>Medial prefrontal
(13.7cm^3)</td><td>Frontal pole (BA 10)</td><td>1.3</td><td>63.1</td><td>−1.5</td><td>−4.50</td></tr>
</table>

Note: All positive peaks in the pain-related ACC-based coactivation analysis were included in one large cluster of voxels with $t > 2.5$. Coactivation is considered significant ($p < 0.05$) if $t > 4.00$ and the peak location lies within the search volume defined by the regions of hypnosis-related changes in rCBF listed in Table 2. Peaks reported outside this search volume are significant in a global search over the entire brain volume ($t > 4.50$).

Note

1. Baseline and Hypnosis Painful minus Baseline and Hypnosis Neutral; ACC peak rCBF increase: left 1.3, anterior +2.9, superior +39.0, $t = +4.87$, $p < 0.0001$.

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