Research report

Increased cerebral functional connectivity underlying the antinociceptive effects of hypnosis

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Abstract

The neural mechanisms underlying the antinociceptive effects of hypnosis are not well understood. Using positron emission tomography (PET), we recently showed that the activity in the anterior cingulate cortex (midcingulate area 24a′) covaries with the hypnosis-induced reduction of affective and sensory responses to noxious thermal stimulation [Faymonville et al., *Anesthesiology* 92 (2000) 1257–1267]. In the present study, we assessed changes in cerebral functional connectivity related to the hypnotic state, compared to simple distraction and the resting state. Nineteen highly hypnotizable right-handed volunteers were studied using $H_2^{15}O$-PET. The experimental conditions were hot noxious or warm non-noxious stimulation of the right hand during resting state, mental imagery and hypnotic state. Using a psychophysiological interaction analysis, we identified brain areas that would respond to noxious stimulations under the modulatory action of the midcingulate cortex in, and only in, the hypnotic state. Hypnosis, compared to the resting state, reduced pain perception by 50%. Pain perception during rest and mental imagery was not significantly different. Analysis of PET data showed that the hypnotic state, compared to normal alertness (i.e., rest and mental imagery), significantly enhanced the functional modulation between midcingulate cortex and a large neural network encompassing bilateral insula, pregenual anterior cingulate cortex, pre-supplementary motor area, right prefrontal cortex and striatum, thalamus and brainstem. These findings point to a critical role for the midcingulate cortex in the modulation of a large cortical and subcortical network underlying its influence on sensory, affective, cognitive and behavioral aspects of nociception, in the specific context of hypnosis.
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1. Introduction

Hypnosis combined with slight conscious sedation (i.e., hypnosedation) and local anesthesia is now considered a valuable alternative to general anesthesia in specific indications [18,20,21,30,31,37]. Since 1992 we have used hypnosis routinely in more than 3300 surgical procedures. The underlying neuromodulatory effects of hypnosis remain, however, not fully understood. Studies of the antinociceptive effects of hypnosis have labored under a double burden: both hypnotic experience and pain experience are highly subjective phenomena. Factors that evoke pain reduction range from extrinsic psychosocial (e.g., interactions between clinician and patient) to intrinsic psychophysiological (e.g., modulation of pain signal transmission [47]). Recent positron emission tomography (PET) studies have demonstrated that the decreased perception of pain during hypnosis is related to changes in the activity (i.e., regional cerebral blood flow—rCBF) measured in the midcingulate cortex (area 24′ [19,48]). We here test the hypothesis that hypnosis-induced analgesia

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can be explained by an enhanced modulation between the midcingulate cortex and the large neural networks involved in sensory, affective and cognitive aspects of noxious processing. Using a psychophysiological interaction analysis [23], we assessed hypnosis-specific increases in functional connectivity between the midcingulate cortex, identified in our previous study [19], and the rest of the brain.

Complementary to the concept of functional segregation as a principle of organization of the human brain (i.e., localizing a function to a cerebral area), recent neuroimaging techniques have focused on functional integration (i.e., assessing the interactions between functionally segregated areas mediated by changes in functional connectivity). Functional connectivity is defined as the temporal correlation of a neurophysiological index (i.e., rCBF) measured in different remote brain areas. Anatomical connectivity (e.g., neuroanatomic tracer studies obtained in animals) is a necessary underpinning for the assessment of functional connectivity. A psychophysiological interaction means that the contribution of one area to another (i.e., regression slope) changes significantly with the experimental context [23]. The psychophysiological interaction analysis used in the present study, aims at explaining the activity in one cortical area in terms of an interaction between the influence of a chosen area (i.e., midcingulate cortex) and some experimental condition (i.e., being in a hypnotic state or not). Pain is a multidimensional experience including sensory-discriminative, affective-emotional, cognitive and behavioral components. Its cerebral correlate is best described in terms of neural circuits or networks, referred to as the 'neuromatrix' for pain processing, and not as a localized 'pain center' [25]. The aim of the present study is to explore the modulatory role of the midcingulate cortex on the activity of this 'neuromatrix' in the specific context of hypnosis.

2. Methods

2.1. Experimental protocol

The Ethics Committee of the Faculty of Medicine of the University of Liège approved the study. Written informed consent was obtained from all volunteers. The experimental protocol has been extensively described elsewhere [19]. For the aim of the present assessment of cerebral functional connectivity, which greatly depends upon the number of observations, we have nearly doubled the number of participants of the previously published population. Hence, from a cohort of 50 screened subjects, 19 young healthy right-handed unpaid volunteers (mean 28 ± 4 years; nine women) were selected because they were highly hypnotizable (score>8 of 12 on the Stanford Hypnotic Susceptibility Scale-Form C [24]). During the selection procedure, which took place several weeks before the experiment, detailed information about pleasant life experiences

that the subject wanted to use during hypnosis was obtained through a semi-structured interview. PET data were acquired during three kinds of states (hypnotic state, mental imagery or rest) and during two kinds of stimulation (hot noxious stimulation or warm non-noxious stimulation). Subjects were scanned twice in each of these six conditions. To avoid multiple hypnotic inductions, the fifth to eight scans were always made in the hypnotic state. The order of the two other states, and of the non-noxious and noxious stimulations, was pseudo-randomized.

In the hypnotic state condition, each subject was invited to re-experience very pleasant autobiographical memories. The hypnotic state was induced using eye fixation, a 3-min muscle relaxation procedure, and permissive and indirect suggestions. The exact words and details of the induction technique and specific suggestions and details during the course of the induction varied depending upon the experimenter's (M.E.F.) observation of subject behavior, and on her judgment of subject's needs (in a similar way to her extensive clinical experience with hypnosedation [18,20,21,37]). As in clinical conditions, subjects were continuously given cues for maintaining and deepening the hypnotic state. However, during the scans, the experimenter remained silent. Hypnotic state was considered to be present when roving eye movements were observed on oculography and if, just before the scan, the subject confirmed by a prearranged foot movement that he/she was experiencing a hypnotic state. Slow ocular movements are regularly observed in the hypnotic state in isolation or intermingled with few saccades [35]. This pattern of eye movements, in conjunction with the subject's behavior was used to differentiate hypnosis from other states. Polygraphic monitoring (electroencephalographic, electromyographic and oculographic recordings) further ensured that no sleep occurred during the experimental session.

During the mental imagery task, subjects were instructed to simply imagine a pleasurable autobiographical memory and were urged not to enter the hypnotic state. In the resting state participants were asked to relax and empty their mind. The experimenter remained silent during all scans. After each scan, subjects were asked to rate the noxious stimulus intensity on a scale from 0 (absent) to 10 (most intense imaginable).

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

PET data were acquired on a Siemens CTI 951 R 16/31 scanner in three-dimensional mode. The subject's head was stabilized by a thermoplastic facemask (Truscan Imaging, MA, USA) and a venous catheter was secured in

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

2.2. Analysis of PET data

We used statistical parametric mapping (SPM99; Welcome Department of Cognitive Neurology, Institute of Neurology, London, UK) to realign, coregister, spatially normalize, smooth (16 mm full width at half maximum) and analyze the PET data. Proportional scaling adjusted rCBF for changes in global flow. The effect of the covariates of interest was estimated according to the general linear model at each voxel [22]. The covariates consisted of the state effect (hypnotic state versus normal alertness state) and the rCBF of the reference region previously found to mediate the hypnosis-induced reduction of pain perception: the midcingulate cortex (area 24′a; coordinates −2, 18, 22 [19]). The activity in the reference region was modeled separately for the two states, allowing us to test for an interaction in terms of the difference in the regression slopes between the two states [34]. This analysis identified the brain areas that were functionally more related the reference area in the hypnotic state than in the normal alertness state (i.e., rest or mental imagery).

The assessment of functional integration using psychophysiological interaction analyses [23] is limited by the known structural neuroanatomical connections between the reference region and the rest of the brain. Until such information is available for humans, our hypotheses are based upon observations in monkeys. Hence, only brain areas known from tracer studies in animals to be connected to the midcingulate cortex were considered. In the non-human primate, this region is connected with supplementary and pre-supplementary motor area [17,39,58], insula [36,43,56], perigenual anterior cingulate cortex [53], prefrontal cortices (mainly mid-dorsolateral and middle orbitofrontal areas) [28,40,56], posterior parietal cortex [56], striatum [29], amygdala [4], thalamus (mediodorsal,

midline, intralaminar and anteromedial nuclei) [55] and brainstem [16,38,41,42]. Most of these projections are reciprocal, except for the brainstem where the periaquaductal gray only receives inputs from the midcingulate cortex. Areas of significant change within these sets of brain regions were determined using linear contrasts of the parameter estimates. The resulting set of voxel values for each contrast constituted a map of the t statistic [SPM{t}]. All SPM{t}s were transformed to the unit normal Z-distribution to create a statistical parametric map or SPM{Z}. Results were considered significant at small volume corrected $P<0.05$, using a 10 mm radius-spherical volume of interest on our predetermined regions of interest. This analysis relies on a fixed-effect model. In consequence, the results pertain only to the sampled population. The results should be extended to the general population with caution.

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

3. Results

As shown in Fig. 1, subjects' perception of pain during the resting condition (mean±standard deviation: 6.4±1.2) significantly decreased during the hypnotic state (3.2±1.1; $P<0.001$) but not during the mental imagery condition (5.6±1.0). Given that pain perception during rest and mental imagery did not significantly differ, PET data obtained during these conditions were pooled for further analyses.

Compared to normal alertness states (rest and mental imagery), the hypnotic state enhanced the functional modulation between midcingulate cortex (area 24′a, coordinates −2, 18, 22 mm, identified in a previous study
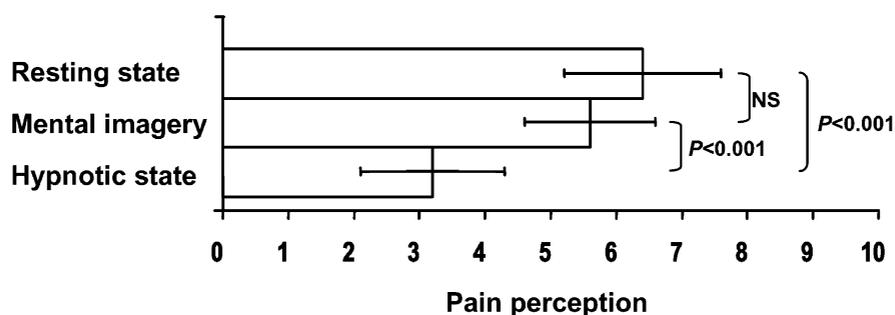

Fig. 1. Ratings of pain perception in the resting state, the mental imagery condition and in the hypnotic state. Values are means and standard deviations (NS=not significant).

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

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

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

[19]) and bilateral anterior insular cortices, pregenual anterior cingulate cortex (Brodmann's area 32), pre-supplementary motor area (pre-SMA; area 6), right prefrontal cortex (area 8), right thalamus, right striatum and brainstem (Table 1 and Fig. 2). At lower threshold for significance, left prefrontal cortex (area 10), right prefrontal areas 9 and 11 and mesiofrontal cortex (area 9) were also identified. Fig. 3 illustrates the changes in interaction (i.e.,

regression slope) between the activity measured in our seed region (i.e., midcingulate cortex) and in one of the identified brain regions (i.e., pregenual cortex), depending on the experimental condition (i.e., hypnotic state versus normal alertness).

Regions that *decreased* their functional relationships with the midcingulate cortex during hypnosis as compared to normal alertness were confined to bilateral occipital
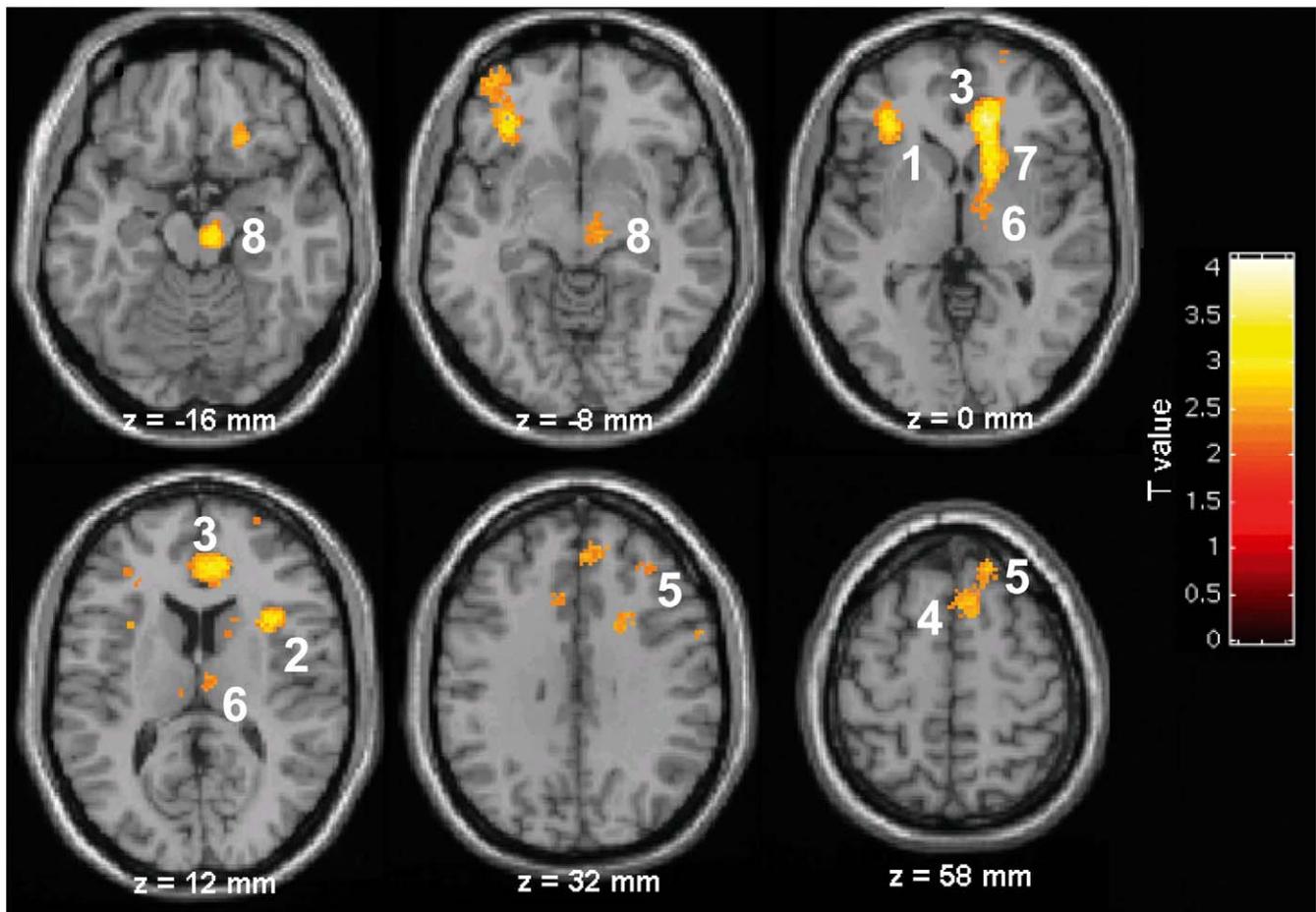

Fig. 2. Regions that showed an increased functional connectivity (i.e., differences in regression slopes of rCBF correlations, thresholded at *P*<0.001) with midcingulate cortex in hypnosis relative to normal alertness (rest and mental imagery). Numbers correspond to the numbering used in Table 1.
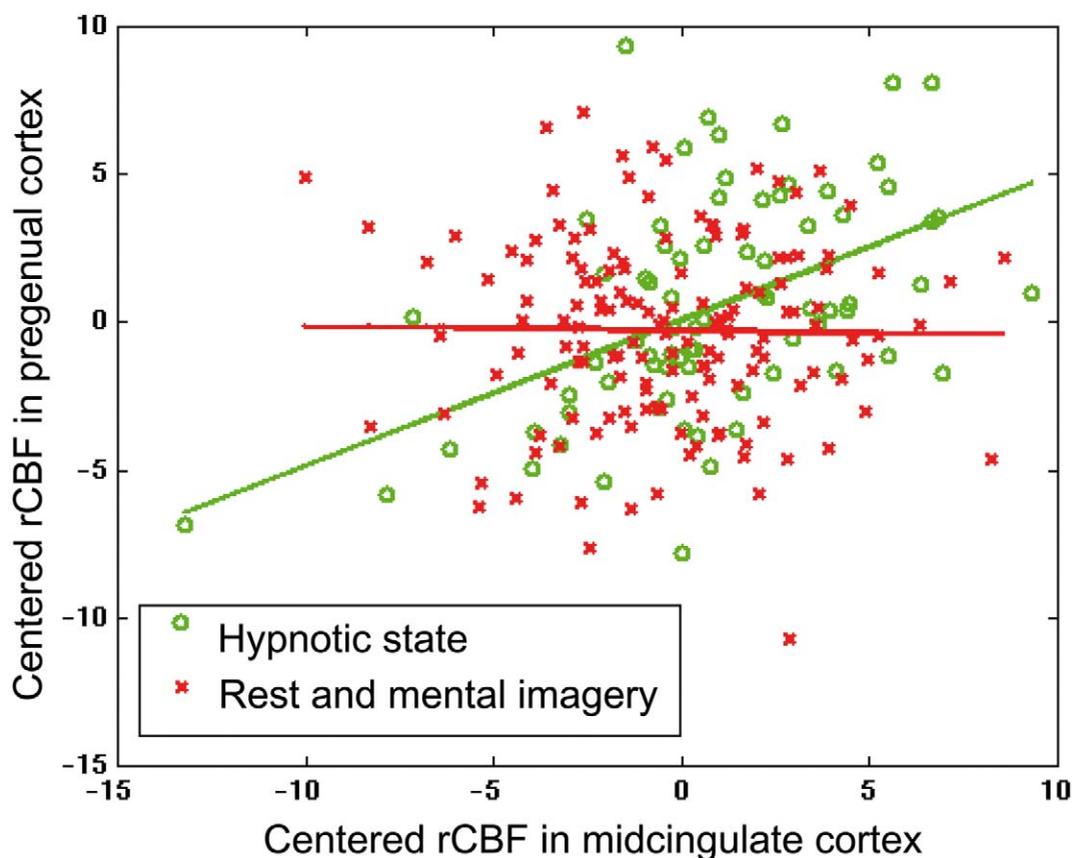
Fig. 3. Plot of the neural activity (regional cerebral blood flow, rCBF) in midcingulate cortex and pregenual cortex during hypnosis (green circles) and normal alertness (red crosses). Note the significant (small volume corrected *P*-value <0.005; *Z*-value=4.04) difference between the regression slopes relative to both experimental conditions as assessed by the SPM psychophysiological interaction analysis [23,32–34], reflecting the increase in functional modulation (i.e., increase in functional connectivity) between both brain regions in the specific context of hypnosis. Each point represents one PET measurement (19 subjects, 12 scans per subject, makes 228 measurements in total).

cortex (coordinates of peak voxels: 58, −68, 8; *Z*=3.72 and −18, −70, 14; *Z*=3.53). As these regions were not part of our a priori defined regions known to be structurally connected to the midcingulate cortex, they are only reported for completeness but will not be discussed further.

4. Discussion

The hypnotic procedure used in the present experimental setting, which is similar to the one used for clinical purposes [18,20,21,37], decreased pain perception by 50% compared to the resting state and by 43% compared to the mental imagery state. Participants were invited to have revivification of pleasant life episodes, without any reference to the pain perception. As reported previously, this technique lowers both the unpleasantness (i.e., affective component) and the perceived intensity (i.e., sensory component) of the noxious stimuli [19,20].

The anterior cingulate cortex can be divided into two parts, based on structural, connection, and functional observations: the perigenual cortex and the midcingulate cortex [16,54,57]. It is a functionally very heterogeneous region thought to regulate or modulate the interaction between cognition, sensory perception and motor control in relation to changes in attentional, motivational, and emotional states [16]. Previous studies from our own and other laboratories have shown that the midcingulate cortex mediates the hypnosis-induced reduction of pain perception [19,48,49]. We here show that this mediation of pain perception observed in the hypnotic state is related to an *increased* functional modulation of the previously identified midcingulate cortex and a large neural network of cortical and subcortical structures known to be involved in different aspects of pain processing encompassing insular, pregenual and prefrontal cortices, pre-SMA, thalami, striatum and brainstem.

The insular cortex and the anterior cingulate cortex are known to show the most consistent activation in functional imaging studies on pain perception [6,10,13,15,25,33,45,50]. The insula is thought to take an intermediate position between the lateral (sensori-discriminative) and medial (affective-emotional) pain systems. It receives major input from the somatosensory system [36], has direct thalamocortical nociceptive input [8] and through its projections to the amygdala, has been

implicated in affective and emotional processes [1]. The insula is considered to serve a sensory integrative function for pain, taste and other visceral sensations, as well as tactile and vestibular inputs [7]. Our observation of an increased midcingulate-insular modulation during hypnosis is in line with its proposed role in pain affect [49] and pain intensity coding [9]. In the light of the 'somatic marker' hypothesis of consciousness [11], the right insular cortex has been hypothesized to be involved in the mental generation of an image of one's physical state underlying the attribution of emotional attributes to external and internal stimuli. It is, however, important to stress that the used correlation analyses do not guarantee that the identified midcingulate-insular connectivity is direct (i.e., a third area, which shows context-sensitive responses, may be providing input to the two areas implicated in the psychophysiological interaction). The midline and intralaminar thalamic nuclei, for example, could project to both the anterior insula and midcingulate cortex and this might produce highly correlated activity between insular and midcingulate areas [57].

In the monkey, midcingulate cortex is connected to mid-dorsolateral frontal areas [3,56]. A recent meta-analysis of PET studies observed frequent co-activations of prefrontal cortices and anterior cingulate cortex in a variety of tasks demonstrating their functional connectivity in the human brain [28]. The anterior cingulate cortex has been hypothesized to facilitate the implementation of a selected action whereas the prefrontal cortex would compute and maintain on-line information necessary for the choice of the appropriate response [44]. Being able to feel unpleasantness and to assess pain reflects an experience of conscious awareness. Consciousness is in part the product of attentional processes that act in reference to temporal-spatial organizational networks in the brain [46]. The observed prefrontal areas may indicate distributed associative processes of cognitive appraisal, attention or memory of perceived noxious stimuli. Widespread frontal increases in rCBF have previously been demonstrated in the hypnotic state [19,35,49]. Frontal activation has also been reported in a series of studies on experimental pain but the precise role of particular regions in the central processing of pain remains to be elucidated [52].

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

The observed increases in functional connectivity between the midcingulate cortex and the thalamus and midbrain during the hypnotic state could be related to pain-relevant arousal or attention [27]. The thalamus has recently been shown to correlate with pain threshold whereas activation of midbrain correlated with pain intensity [51]. It is tempting to hypothesize a hypnosis-related subcortical gating on cortical activation that underlies the observed decreased subjective pain perception. The limited spatial resolution and smoothing of our data (16 mm) do not permit an accurate localization of these structures. Previous studies have shown that different forms of defensive or emotional reactions, analgesia and autonomic regulation are represented in different regions of the midbrain's periaqueductal gray [2]. The perigenual cortex, insula and thalamus are also known to be implicated in autonomic regulation [1,2]. In epileptic patients, electrical stimulation of the pregenual cortex diminished reflexes, movements and arterial blood pressure [26]. The observed modulatory role of the midcingulate cortex on this network could explain the clinical finding that patients undergoing surgery during the hypnotic state show modified autonomic responses and less defensive reactions in response to an aversive encounter [20].

The anterior cingulate cortex is abundantly innervated by a multitude of neuromodulatory pathways including opioid, dopaminergic, noradrenergic and serotoninergic systems and is known to contain high levels of substance P, corticotropin-releasing factor, neurotensin and prosomatostatin-derived peptides [44]. The neurotransmitter systems involved in the antinociceptive effects of hypnosis will be specifically explored in another experimental protocol.

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

Acknowledgements

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