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Functional neuroanatomy of the hypnotic state

Marie-Elisabeth Faymonville [a], Mélanie Boly [b], Steven Laureys [b,*]

[a] Department of Anesthesiology and Pain Clinic, University of Liège, Sart Tilman, Belgium
[b] Cyclotron Research Center and Department of Neurology, University of Liège, Sart Tilman B30, 4000 Liege, Belgium

Abstract

The neural mechanisms underlying hypnosis and especially the modulation of pain perception by hypnosis remain obscure. Using PET we first described the distribution of regional cerebral blood flow during the hypnotic state. Hypnosis relied on revivification of pleasant autobiographical memories and was compared to imaging autobiographical material in "normal alertness". The hypnotic state was related to the activation of a widespread set of cortical areas involving occipital, parietal, precentral, premotor, and ventrolateral prefrontal and anterior cingulate cortices. This pattern of activation shares some similarities with mental imagery, from which it mainly differs by the relative deactivation of precuneus. Second, we looked at the anti-nociceptive effects of hypnosis. Compared to the resting state, hypnosis reduced pain perception by approximately 50%. The hypnosis-induced reduction of affective and sensory responses to noxious thermal stimulation were modulated by the activity in the midcingulate cortex (area 24a′). Finally, we assessed changes in cerebral functional connectivity related to hypnosis. Compared to normal alertness (i.e., rest and mental imagery), the hypnotic state, significantly enhanced the functional modulation between midcingulate cortex and a large neural network involved in sensory, affective, cognitive and behavioral aspects of nociception. These findings show that not only pharmacological but also psychological strategies for pain control can modulate the cerebral network involved in noxious perception.

Keywords: Hypnotic state; Pain; Mental imagery; Functional connectivity; Positron emission tomography; Regional cerebral blood flow

1. Introduction

Hypnosis has long been known to be associated with heightened control over physical processes and has been used as a therapeutic tool since mankind's early history (DeBetz and Sunnen, 1985). It has been used in many medical and psychological problems (e.g., the treatment of pain, gastro-intestinal and dermatological pathologies, depression, anxiety, stress and habit disorders). Since 1992, we have used the anti-nociceptive effects of hypnosis routinely in more than 3300 surgical procedures such as thyroid and parathyroid surgery (Defechereux et al., 2000; Defechereux et al., 1998; Defechereux et al., 1999; Meurisse et al., 1999a; Meurisse et al., 1996; Meurisse et al., 1999b), plastic surgery (Faymonville et al., 1994; Faymonville et al., 1995; Faymonville et al., 1997; Faymonville et al., 1999) and peri-dressing change pain and anxiety in severely burned patients (Frenay et al., 2001). In patients undergoing surgery, hypnosis combined with local anesthesia and minimal conscious sedation (a technique called 'hypnosedation') is associated with improved intraoperative patient comfort and with reduced anxiety, pain, intraoperative requirements for anxiolytic and analgesic drugs, optimal surgical conditions and a faster recovery of the patient (for review see Faymonville et al., 1998).

In addition to its use in clinical settings, hypnosis can be used in neuroscience research, with the goal of learning more about the nature of hypnosis itself, as well as its impact on sensation, perception, learning, memory, and physiology. However, as its acceptance by the scientific community still is limited, the neural correlates of hypnotic

* Corresponding author. Tel.: +32 4 366 36 87; fax: +32 4 366 29 46.
E-mail address: steven.laureys@ulg.ac.be (S. Laureys).

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state remain poorly understood. One field where the efficacy of hypnosis has been the most extensively evaluated and validated is pain control. In the present chapter will first try to define hypnosis, describe our hypnotic procedure and than review our positron emission tomography (PET) studies on hypnosis in highly hypnotizable healthy volunteers. We will do so in three steps, discussing (1) changes in regional brain function; (2) modulation of pain perception; and (3) increases in cerebral functional connectivity.

2. What is hypnosis and how to induce it

There is not a generally accepted definition of hypnosis. For many authors it is seen as a state of focused attention, concentration and inner absorption with a relative suspension of peripheral awareness (Laureys et al., in press). We have all experienced similar states many times but do not usually call it hypnosis (e.g., being so absorbed in thought while doing something that we fail to notice what is happening around us). The Executive Committee of the American Psychological Association - Division of Psychological Hypnosis (1994) has constructed a definition from the multiplicity of positions of a number of researchers advocating differing theoretical perspectives. Their definition regards hypnosis as "a procedure during which a health professional or researcher suggests that a patient or subject experience changes in sensations, perceptions, thoughts, or behavior...". The hypnotic context is generally established by an induction procedure. Most hypnotic inductions include suggestions for relaxation. Our group then uses instructions to imagine or think about pleasant autobiographical experiences. Hypnosis has three main components: absorption, dissociation and suggestibility (Spiegel, 1991). *Absorption* is the tendency to become fully involved in a perceptual, imaginative or ideational experience. Subjects prone to this type of cognition are more highly hypnotizable than others who never fully engage in such experience (Hilgard et al., 1963). *Dissociation* is the mental separation of components of behavior that would ordinarily be processed together (e.g., the dream-like state of being both actor and observer when re-experiencing autobiographical memories). This may also involve a sense of involuntariness in motor functions or discontinuities in the sensations of one part of the body compared with another. *Suggestibility* leads to an enhanced tendency to comply with hypnotic instructions. This represents not a loss of will but rather a suspension of critical judgment because of the intense absorption of the hypnotic state. It is important to stress that hypnosis makes it easier for subjects or patients to experience suggestions or access memories, but cannot force them to have these experiences. Contrary to some depictions of hypnosis in the media, hypnotized subjects do not lose complete control over their behavior. They typically remain aware of who they are and where they are, and unless amnesia has been specifically suggested, they usually remember what transpired during hypnosis.

Four our PET research, the used hypnotic procedure was similar to the one used in clinical routine (Faymonville et al., 1995; Faymonville et al., 1997; Faymonville et al., 1999; Meurisse et al., 1999b). Hypnosis was induced using eye fixation, a 3 min muscle relaxation procedure, and permissive and indirect suggestions. Subjects were invited to re-experience very pleasant autobiographical memories. As in clinical conditions, they were continuously given cues for maintaining and deepening the hypnotic state. Just before scanning, subjects confirmed by a prearranged foot movement that they were experiencing hypnosis. Oculographic recording showed roving eye movements sometimes intermingled with few saccades. 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.

3. Brain function in the hypnotic state

In our first PET study on hypnosis, we explored its underlying brain mechanisms in healthy volunteers by determining the distribution of regional cerebral blood flow (rCBF), taken as an index of local neuronal activity, by use of the $H_2{}^{15}O$-technique (Maquet et al., 1999). The choice of the control task was difficult as, a priori, no cerebral state was close to the hypnotic state. Because the induction and maintenance of our hypnotic procedure relies on revivification of pleasant autobiographical memories, the closest situation was the evocation of autobiographical information, in the absence of the hypnotic state (i.e., in a state of normal alertness). To better understand the comparisons made for hypnosis, we first investigated this control condition. The results showed that listening to autobiographical material activates the anterior part of both temporal lobes, basal forebrain structures, and some left mesiotemporal areas (Fig. 1). This pattern is in agreement with another PET study of autobiographical memory (Fink et al., 1996).

During hypnosis, compared to our control task, a vast activation was observed that involved occipital, parietal, precentral, prefrontal, and cingulate cortices (Fig. 1). The neural network implicated in hypnosis and in the control task (i.e., evocation of autobiographical information in a state of normal alertness) did not overlap. These results show that the hypnotic state relies on cerebral processes different from simple evocation of episodic memory and suggest it is related to the activation of sensory and motor cortical areas, as during perceptions or motor acts, but without actual external inputs or outputs. In this respect, hypnosis is reminiscent of mental imagery (Kosslyn et al., 2001). The imagery content in hypnosis was polymodal. Although subjects predominantly reported visual impressions, somesthetic and olfactory perceptions were also mentioned. A lot of actions also appeared in the hypnotic experience of most of our subjects. In contrast, none of the subjects reported auditory imagery. When sounds were

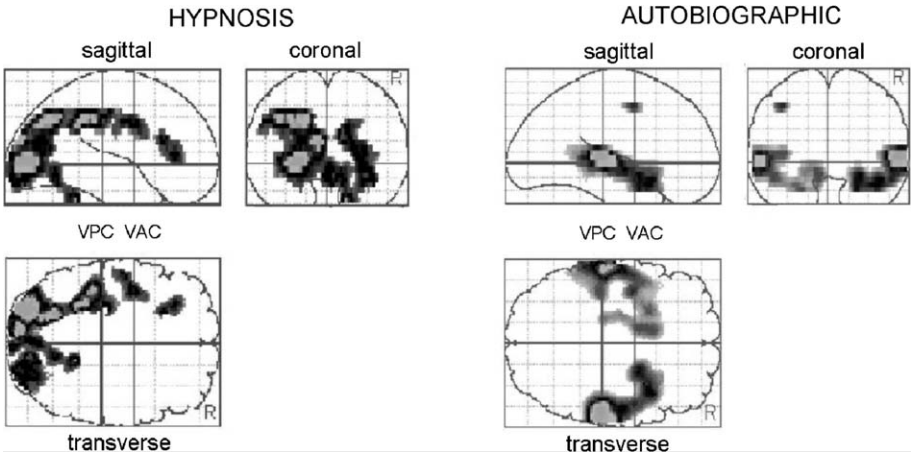

Fig. 1. Brain areas where regional cerebral blood flow (rCBF) is increased during hypnosis compared to mental imaging of autobiographical memories (control distraction task) (left) and brain areas where rCBF is increased during the mental imaging of autobiographical memories compared to the resting state (right). Results are displayed at $p < 0.001$. VAC and VPC identify anterior and posterior commissural planes, respectively. (Adapted from Maquet et al., 1999).

mentioned, they came from the actual experimental environment (mainly, the experimenter's voice). The visual mental imagery might take into account the activation of a set of occipital areas. More anteriorly, the activation of precentral and premotor cortices is similar to that observed during motor imagery (Decety, 1996), which could also have participated in the parietal activation. The activation of ventrolateral prefrontal cortex has also been observed in mental imagery tasks and would be involved in the programming of the building up of the mental image or in the maintenance of image in memory. Finally the activation in anterior cingulate cortex could reflect the attentional effort necessary for the subject to internally generate mental imagery.

Prominent decreased activity during hypnosis relative to the alert state was observed in the medial parietal cortex (i.e., precuneus). This area is hypothesized to be involved in the representation (monitoring) of the world around us (Gusnard and Raichle, 2001). Indeed, the precuneus shows the highest level of glucose use (the primary fuel for brain energy metabolism) of any area of the cerebral cortex in the so-called "conscious resting state". It is known to show task-independent decreases from the baseline during the performance of goal-directed actions. Evidence indicates that the functions to which this region of the cerebral cortex contributes include those concerned with both orientation within, and interpretation of, the environment (Vogt et al., 1992). Interestingly, the precuneus is one of the most dysfunctional brain regions in states of unconsciousness or altered consciousness such as coma (Laureys et al., 2001), vegetative state (Laureys et al., 1999), general anesthesia (Alkire et al., 1999), slow wave and rapid eye movement sleep (Maquet, 2000), amnesia (Aupee et al., 2001) and dementia (Matsuda, 2001), suggesting that it is part of the critical neural network subserving conscious experience.

4. Interaction between hypnosis and pain perception

We have previously shown the effectiveness of hypnosis in producing analgesia in two large clinical studies. A retrospective study first showed that hypnosis as an adjunct procedure to conscious intravenous sedation provides significant peri-operative pain and anxiety relief. These benefits were obtained despite a significant reduction in drug requirements (Faymonville et al., 1995). A prospective randomized study confirmed these observations (Faymonville et al., 1997).

In our second PET study, we explored the brain mechanisms underlying the modulation of pain perception proper to our clinical hypnotic protocol (Faymonville et al., 2000). During this procedure, hypnotized healthy volunteers and patients are invited to have revivification of pleasant life episodes, without any reference to the pain perception. This technique lowers both the unpleasantness (i.e., affective component) and the perceived intensity (i.e., sensory component) of the noxious stimuli (Faymonville et al., 2000; Faymonville et al., 1997). In our hands, it decreases both components of pain perception by approximately 50% compared to the resting state and by approximately 40% compared to a distraction task (mental imagery of autobiographical events).

Our group and others (Faymonville et al., 2000; Rainville et al., 1997; Rainville et al., 1999) have shown that this modulatory effect of hypnosis is mediated by the anterior cingulate cortex (ACC; the ventral part of the ACC named area 24′a). Indeed, the reduction of pain perception correlated with ACC activity specifically in context of hypnosis (Fig. 2). The ACC 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 (Devinsky et al., 1995). It can be

divided into two parts, based on structural, connection, and functional observations: the perigenual cortex and the midcingulate cortex (Vogt et al., 2004).

The ACC 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 (Paus, 2001). It is unlikely that opioid neurotransmission underlies the midcingulate cortical activation we observe under hypnosis although the ACC contains high concentrations of opioid receptors and peptides. Indeed, psychopharmacological studies showed that hypnotic analgesia was not altered by the administration of naloxone (Moret et al., 1991). It is also unlikely that the ACC might modulate pain perception during hypnosis through pure 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 (Derbyshire et al., 1998). 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. Pain is a multi-dimensional 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' (Jones et al., 1991). In order to further explore the antinociceptive effects of hypnosis we then assessed the hypnosis-induced changes in functional connectivity between ACC and the large neural network involved in the different aspects of noxious processing. Before we discuss the results from this third study, we will briefly explain what is meant by 'functional connectivity analyses' when using PET data.

Finally, assessing changes in cerebral functional connectivity, we could show that the midcingulate cortex (which mediates the hypnosis-induced reduction of pain perception (Faymonville et al., 2000; Rainville et al., 1997; Rainville et al., 1999)) is related to an *increased* functional modulation of the midcingulate cortex and a large neural network of cortical and subcortical structures known to be involved in different aspects of pain processing encompassing prefrontal, insular, and pregenual cortices, pre-SMA, thalami, striatum and brainstem (Fig. 3). These findings reinforce 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. The observed hypnosis-induced changes in connectivity between ACC and prefrontal areas may indicate a modification in distributed associative processes of cognitive appraisal, attention or memory of perceived noxious stimuli. Frontal increases in rCBF have previously been demonstrated in the hypnotic state (Faymonville et al., 2000; Maquet et al., 1999; Rainville et al., 1999). 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 (Treede et al., 1999). The anterior cingulate cortex has also a major role in motor function (Dum and Strick, 1991). 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 (Coghill et al., 1994; Derbyshire et al., 1997; Derbyshire et al., 1998; Jones et al., 1991). 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 (Brown and Marsden, 1998). The insular cortex and the anterior cingulate cortex are known to show the most consistent activation in functional imaging studies on pain perception. The insula is thought to take an intermediate position between the lateral (sensory-discriminative) and medial (affective-emotional) pain systems. It receives major input from the somatosensory system (Mesulam and Mufson, 1982), has direct thalamocortical nociceptive input (Craig et al., 1994) and through its projections to the amygdala, has been implicated in affective and emotional processes (Augustine, 1996). Our observation of an increased midcingulate-insular modulation during hypnosis is in line with its proposed role in pain affect (Rainville et al., 1999) and pain intensity coding (Craig et al., 2000). In the light of the 'somatic marker' hypothesis of consciousness (Damasio, 1994), 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. The observed increases in functional connectivity between the midcingulate cortex and the thalamus and midbrain during hypnosis could be related to pain-relevant arousal or attention (Kinomura et al., 1996). The thalamus has recently been shown to correlate with pain threshold whereas activation of midbrain correlated with pain intensity (Tolle et al., 1999). It is tempting to hypothesize a hypnosis-related subcortical gating on cortical activation that underlies the observed decreased subjective pain perception. 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 (Bandler and Shipley, 1994). The perigenual cortex, insula and thalamus are also known to be implicated in autonomic regulation (Augustine, 1996; Bandler and Shipley, 1994). The observed modulatory role of the midcingulate cortex on this network could explain the clinical finding that patients undergoing surgery during

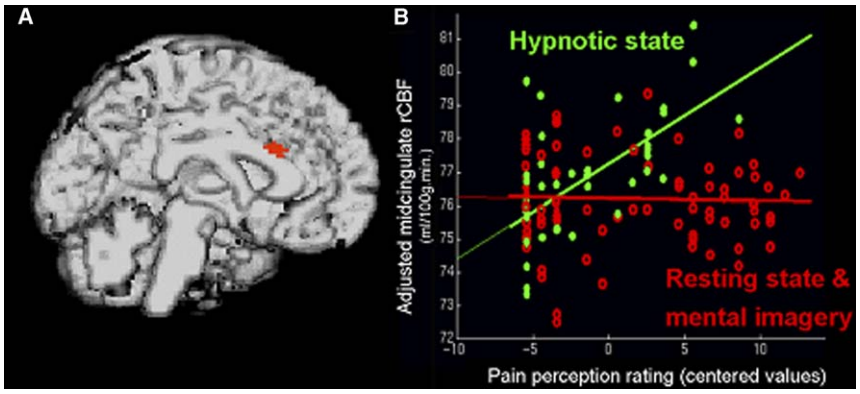

Fig. 2. (A) Brain area in which neural activity correlates linearly with pain sensation ratings, in the specific context of hypnosis: the ventral part of the midcingulate cortex (area 24′a) shown in red on a 3D rendered spatially normalized MRI. (B) Plot of changes in pain perception ratings versus changes in adjusted blood flow in midcingulate cortex. Note the difference ($p < 0.05$) in regression slopes between hypnosis (green dots) and control conditions (red open circles). (Adapted from Faymonville et al., 2000; Laureys et al., in press.)

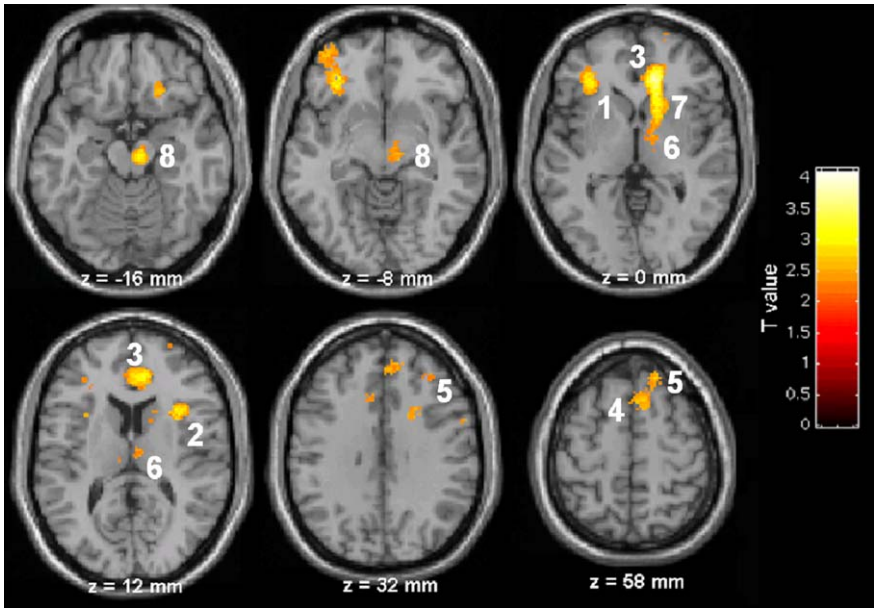

Fig. 3. Regions that showed hypnosis-related increased functional connectivity with midcingulate cortex: (1) left insula, (2) right insula, (3) perigenual cortex, (4) pre-supplementary motor cortex, (5) superior frontal gyrus, (6) right thalamus, (7) right caudate nucleus, (8) midbrain/brainstem. (Adapted from Faymonville et al., 2003).

the hypnotic state show modified autonomic responses and less defensive reactions in response to an aversive encounter (Faymonville et al., 1997).

5. Concluding remarks

In our experience, hypnosis can be seen as a particular cerebral waking state where the subject, seemingly somnolent, experiences a vivid, multimodal, coherent, memory-based mental imagery that invades and fills the subject's consciousness. The pattern of cerebral activation, measured by means of $H_2{}^{15}O$-PET, during the hypnotic state differs from that induced by simple mental imagery. The reduced nociception during hypnosis is mediated by an increased functional connectivity between the midcingulate cortex 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 painful stimuli.

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