CHAPTER 19

The cognitive modulation of pain: hypnosis- and placebo-induced analgesia

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Abstract: Nowadays, there is compelling evidence that there is a poor relationship between the incoming sensory input and the resulting pain sensation. Signals coming from the peripheral nervous system undergo a complex modulation by cognitive, affective, and motivational processes when they enter the central nervous system. Placebo- and hypnosis-induced analgesia form two extreme examples of how cognitive processes may influence the pain sensation. With the advent of modern brain imaging techniques, researchers have started to disentangle the brain mechanisms involved in these forms of cognitive modulation of pain. These studies have shown that the prefrontal and anterior cingulate cortices form important structures in a descending pathway that modulates incoming sensory input, likely via activation of the endogenous pain modulatory structures in the midbrain periaqueductal gray. Although little is known about the receptor systems involved in hypnosis-induced analgesia, studies of the placebo response suggest that the opioidergic and dopaminergic systems play an important role in the mediation of the placebo response.

Introduction

Placebo- and hypnosis-induced analgesia should be seen within the broader context of the conceptualization of pain. In 1965, Melzack and Wall proposed the “gate control” theory, according to which activation in large myelinated fibers is capable of inhibiting nociceptive information. This model struck against the contemporary belief that pain processing is a hard-wired process, mediated exclusively by pain-dedicated pathways. A few years later, Melzack and Casey described their theory about the multidimensional processing of pain. This theory added a rostral (cerebral) extension to the gate control theory, which focuses on activity in the spinal cord dorsal horn. According to Melzack and Casey (1968), pain is a complex multidimensional experience comprising sensory-discriminative, motivational-affective and cognitive-evaluative components. For the first time, the concepts of cognition and emotion were introduced to a field in which sensory physiologists had claimed the exclusive rights. Over the years, a number of assumptions have been added to Melzack and Casey’s scheme. One of these assumptions is that distinct anatomical pathways are involved in the sensory and affective pain dimension (Albe-Fessard et al., 1985; Bushnell and Duncan, 1989; Price, 1999). The sensory component of pain would involve the somatosensory thalamus and its projections to the primary and secondary somatosensory cortices and insula. The affective component on the other hand would involve the medial thalamus and its projections to the anterior cingulate and prefrontal cortices. Recent neuroimaging studies have endeavored to yield evidence for the

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DOI: 10.1016/S0079-6123(05)50019-0
selective activation of brain areas involved in the sensory-discriminative or affective dimension of pain (Rainville et al., 1997; Hofbauer et al., 2001) by using hypnotic suggestions specifically targeted at activating either system. While, according to the model by Melzack and Casey, cognitive and affective processing is performed in parallel with sensory processing, Price (2000) proposed a serial two-stage model in which the emotional component is the result of the interaction between a hard-wired sensory input and contextual processes. This model views pain perception as a self-contained process simply driven by a reliable sensory process. However, cognitive processes directly influence the operation of the sensory system. According to Wall (1991, 1996), nociceptive processing is not something purely dictated by the sensory characteristics of the stimulus but results from the interaction between the latter and the state of the nervous system at that particular time. The state of the nervous system depends both on past experiences and on the cognitive and emotional processes of the organism at the time of sensory input. A series of elegant animal studies by Dubner and co-workers in the 1980s provide strong experimental support for this view (Dubner et al., 1981, Duncan et al., 1987). These investigators recorded neuronal activity in the medullary dorsal horn of monkeys that had been trained for months to discriminate between noxious thermal stimuli of different temperatures applied to the face. A light signal preceding the noxious stimulus by a variable time announced the onset of the noxious stimulus to the animal. In naïve monkeys, changes in neuronal activity in the dorsal horn were only recorded, as expected, during the actual period of the application of the nociceptive stimulus. In sharp contrast, in monkeys that had been trained for several months in the thermal discrimination task, dorsal horn cells already started firing in response to the warning signal. In other words, the light stimulus had become a conditioned stimulus following repetitive pairings with the unconditioned (noxious) stimulus and now produced a conditioned response in the dorsal horn. This is one of the first examples of top-down modulation at such an early (dorsal horn) stage of pain processing. Hypnotic-induced analgesia and placebo analgesia are two other examples of this top-down modulation of pain modulation.

There is ample evidence that the modulation of pain is mediated by the midbrain periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM) (Fields and Basbaum, 1999). The RVM contains antinociceptive descending pathways targeting the spinal and trigeminal dorsal horn (Urban and Smith, 1994; Hudson et al., 2000). Although there are no known direct descending projections from the PAG to the spinal cord, it has been hypothesized that the analgesic effects of PAG are mediated through relays in the RVM and the dorsolateral pontine tegmentum (DLPT). The PAG and RVM function as a unit exerting global control over pain transmission neurons in the dorsal horn. Opioids injected into the PAG and RVM produce analgesia (Urban and Smith, 1994; Price and Fields, 1997; McGaraughty et al., 2003), which can be blocked by administration of the opioid antagonist naloxone into the same area (Wang and Wessendorf, 2002). Regions of the frontal lobe and the amygdala project via the hypothalamus and also directly to the PAG (An et al., 1998; Ongur et al., 1998).

Many of the ascending pain pathways terminate in cortical and subcortical areas, which are also at the origin of pain modulatory systems (Burstein et al., 1993; Bernard et al., 1996; Helmbetter et al., 1998; Fields and Basbaum, 1999; Price, 1999). These areas also play a major role in threat-elicted defensive-behavior, learning, and memory. This raises the following important questions: (1) which cognitive and environmental circumstances are able to trigger these pain inhibitory mechanisms? and (2) once they are triggered, how do they produce their analgesic effect?

Animal studies over the past three decades have shed some light on the answers to these questions. Activation of the endogenous pain modulatory circuits requires specific extrinsic environmental cues or conditions. For instance, Watkins and Mayer (1982) demonstrated that severe physical or psychological stressors such as inescapable footshock and whole body rotation can induce robust analgesic responses. Some, but not all, of these environmentally induced analgesic responses are blocked by naloxone, suggesting that both opioid and non-opioid systems must be involved. When the animals were later placed in the apparatus
where they had been submitted to the noxious stimulation, analgesia was induced. In other words, the environmentally induced analgesic response is prone to classical conditioning (Hayes et al., 1978; Price, 1999). These experimental findings may be of great relevance to placebo analgesia in humans. Cues associated with previous pain relief may become effective for evoking endogenous analgesic mechanisms because they were previously associated with an effective treatment. Furthermore, the findings call for the formulation of a pain theory that incorporates cognitive expectations and the state of the nervous system at the time of nociceptive processing.

In this chapter, we will discuss the mechanisms through which hypnosis and placebo may modulate pain perception. We will first try to give a definition of both concepts and we will summarize available data on the neurobiological mechanisms involved in these two forms of cognition-induced analgesia. This will be followed by a discussion of the relevant brain imaging literature.

Hypnosis

Hypnosis has long been known to be associated with heightened control over physical processes and has been used as a therapeutic tool since the early history of mankind (De Betz 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). At present, there is no 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. We have all experienced similar states many times, but do not tend to call it hypnosis (e.g., being so absorbed in thought while driving home that we fail to notice consciously 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. Faymonville and co-workers use instructions to imagine or think about pleasant autobiographical experiences to decrease pain perception in patients undergoing surgery (1997), and in healthy volunteers participating in functional brain imaging (2000). 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.

Since 1992, the university hospital of Liège has used "hypnosedation", a combination of hypnosis with local anesthesia and minimal conscious sedation, in over 4,800 patients, (Faymonville et al., 1997). Hypnosedation was shown to be a valuable, safe, efficient, and economic alternative to general anesthesia in specific indications such as thyroid and parathyroid surgery (Meurisse et al., 1996,
1999a, b, Defechereux et al., 1998, 1999, 2000), plastic surgery (Faymonville et al., 1994, 1995, 1997, 1999), and per-dressing change pain and anxiety in severely burned patients (Frenay et al., 2001). In patients undergoing surgery, the technique of 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. In our opinion, clinical hypnosis should be used only by properly trained and credentialed health care professionals who have also been trained in the clinical use of hypnosis and are working within the areas of their professional expertise.

In addition to its use in clinical settings, hypnosis is used in research, with the goals of learning more about the nature of hypnosis itself as well as its impact on central nervous system processes such as pain, perception, learning, and memory (e.g., Kosslyn et al., 2000). However, as its acceptance by the scientific community remains limited, the neural correlates of the hypnotic state remain poorly understood. One field where the efficacy of hypnosis has been the most extensively evaluated and validated is pain control. We will here review hypnosis-induced (i) changes in regional brain function, (ii) modulation of pain perception, and (iii) increases in cerebral functional connectivity as studied by means of positron emission tomography (PET).

**Hypnosis-induced changes in regional brain function**

Maquet et al. (1999) first explored the brain mechanisms underlying hypnosis in healthy volunteers by determining the distribution of regional cerebral blood flow (rCBF), by use of the H\textsubscript{2}\textsuperscript{15}O technique. The hypnotic procedure used was similar to the one used in clinical routine (Faymonville et al., 1995, 1997, 1999; Meurisse et al., 1999b) and was induced using eye fixation, a 3-minute 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.

The choice of the control task was difficult as, a priori, no cerebral state is close to the hypnotic state. Because the induction and maintenance of our hypnotic procedure relies on revivification of pleasant autobiographical memories, the closest situation is 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, the authors first investigated this control condition. Listening to autobiographical material activated the anterior part of both temporal lobes, basal forebrain structures, and some left mesiotemporal areas (Fig. 1, left panel). This pattern is in agreement with previous findings on autobiographical memory (Fink et al., 1996).

During hypnosis, compared to the control task, a vast activation was observed that involved occipital, parietal, precentral, prefrontal, and cingulate cortices (Fig. 1, right panel). 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 the subjects. In contrast, none of the subjects reported auditory imagery. When sounds were 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 (ACC) is thought to 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 (also see Vogt and Laureys, this volume and Lou et al., this volume). 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 (Binder et al., 1999; Gusnard and Raichle, 2001; Mazoyer et al., 2001; Raichle et al., 2001). 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., 1999), vegetative state (Laureys et al., 1999), general anesthesia (Alkire et al., 1999; also see Alkire et al., this volume; Fiset et al., this volume), slow wave and rapid eye movement sleep (Maquet, 2000; also see Maquet et al., this volume), amnesia (Aupee et al., 2001), and dementia (Salmon et al., 2000; Matsuda, 2001; also see Salmon et al., this volume), suggesting that it is part of the critical neural network subserving conscious experience.

**Hypnosis-induced changes in pain perception**

In a next step, Faymonville et al. (2000) investigated the brain mechanisms underlying the modulation of pain perception proper to their clinical hypnotic protocol. 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., 1997, 2000). Hypnosis 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) (Fig. 2).

Faymonville et al. (2000) and Rainville et al. (1997, 1999) showed that this modulatory effect of hypnosis is mediated by the ventral part of the ACC (Brodmann area 24'a). Indeed, the reduction of pain perception correlated with ACC activity specifically in the context of hypnosis (Fig. 3). 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; Bush et al., 2000). The ACC can be divided into a perigeniculate and midcingulate cortex on the basis of cytoarchitectonical structure, connectivity, and functional observations (Vogt et al., 2002); whereas the perigeniculate part is mostly involved in emotional processing, and the midcingulate part is more involved in cognitive processing.

The ACC is abundantly innervated by a multitude of neuromodulatory pathways including opioidergic, dopaminergic, noradrenergic, and serotonergic systems and contains high levels of substance P, corticotropin-releasing factor, neurotensin, and prosmatostatin-derived peptides (Paus, 2001). Although the ACC contains high

![Fig. 2. Ratings of pain perception in the resting state, the distraction task (mental imagery of biographical memories), and in the hypnotic state. Values are means and standard deviations (NS = not significant). Adapted from Faymonville et al. (2003).](image)

![Fig. 3. (A) Brain area in which blood flow increases in proportion to pain sensation ratings, in the specific context of hypnosis: the ventral part of the midcingulate cortex (area 24'a). (B) Plot of changes in pain perception ratings versus changes in adjusted blood flow in ACC. Note the difference ($p < 0.05$) in regression slopes between hypnosis (black dots) and control conditions (gray circles). Results are displayed on a 3-D rendered spatially normalized MRI scan. Adapted from Faymonville et al. (2000) and Laureys et al. (2004).](image)
concentrations of opioid receptors and peptides, it is doubtful whether opioid neurotransmission underlies the midcingulate cortical activation in hypnosis-induced reduction of pain perception. 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 was identified by Faymonville et al. (2000) has been related to pain perception, whereas the more anterior portions of the ACC are involved in attention-demanding tasks (Derbyshire et al., 1998; Petrovic and Ingvar, 2002). From an anatomical viewpoint, the midcingulate cortex is in a critical position to receive both the sensory and the affective aspects of a noxious stimulus from respectively the somatosensory areas and insula, and the amygdaloid complex and perigenual ACC. Since 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’ (Jones et al., 1991; Peyron et al., 2000).

**Hypnosis-induced changes in cerebral functional connectivity**

In order to further explore the antinociceptive effects of hypnosis, Faymonville et al. (2003) assessed hypnosis-induced changes in functional connectivity between the ACC and a large neural network involved in the different aspects of noxious processing. Before we discuss these results, we will briefly explain what is meant by ‘functional connectivity analyses’ when using PET data.

The functional role played by any component (e.g., neuronal population) of a connected system (e.g., the brain) is largely defined by its connections. 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 (Friston, 2002). A psychophysiological interaction analysis explains the activity in one cortical area in terms of an interaction between the influence of another area and some experimental condition (i.e., being in a hypnotic state or in a state of normal alertness). A psychophysiological interaction means that the contribution (i.e., regression slope) of one area to another changes significantly with the experimental context assessed with the general linear model as employed by statistical parametric mapping (Friston et al., 1997). The statistical analysis will identify brain regions that show condition-dependent differences in modulation with another (chosen) area. It is important to stress that one cannot guarantee that these connections are direct (i.e., they may be mediated through other areas) and that the two regions can have a common input (a third area, which shows context-sensitive responses, may be providing input to the two areas implicated in the psychophysiological interaction). Anatomical connectivity (e.g., neuroanatomic tracer studies obtained in animals) is a necessary underpinning for the assessment of functional connectivity.

Using a functional cerebral connectivity analysis, Faymonville et al. (2000) showed that the hypnosis-induced reduction of pain perception mediated by the midcingulate cortex (Rainville et al., 1997, 1999; Faymonville et al., 2000) relates to an increased functional modulation between this area and a large neural network of cortical and subcortical structures known to be involved in different aspects of pain processing, encompassing prefrontal cortex, pre-supplementary motor area (pre-SMA), insular and perigenual cortices, striatum, thalamus, and brainstem (Fig. 4).

These 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. As discussed above, frontal increases in rCBF have previously been demonstrated in the hypnotic state (Maquet et al.,
Fig. 4. During hypnosis an increase in activity in midcingulate cortex increases activity in a wide cortical and subcortical neural network (part of the ‘pain matrix’), much more so than is observed under control conditions (rest or distraction tasks). Regions that showed such hypnosis-related increased functional connectivity with midcingulate cortex (peak voxel marked by red crosshair in circle) are: left insula (1), right insula (2), perigenual cortex (3), pre-supplementary motor area (4), superior frontal gyrus (5), right thalamus (6), right caudate nucleus (7), and midbrain/brainstem (8). Adapted from Faymonville et al. (2003). See Plate 19.4 in Colour Plate Section.

1999; Rainville et al., 1999; Faymonville et al., 2000). Frontal activation has also been reported in a series of studies on experimental pain (Kupers et al., 2001, 2004; Witting et al., 2001; Bornhovd et al., 2002; Lorenz et al., 2003), but the precise role of particular regions in the central processing of pain remains to be elucidated (Coghill et al., 1999; Treede et al., 1999).

The ACC has also a major role in motor function (Fink et al., 1997). Its increased functional connectivity with pre-SMA and striatum during hypnosis may therefore allow the midcingulate cortex to organize the most appropriate behavioral response to the pain stimulus. Indeed, the basal ganglia encode and initiate basic movement patterns expressed through premotor and primary motor areas and show frequent activation to noxious stimuli (Jones et al., 1991; Coghill et al., 1994; Derbyshire et al., 1997; Derbyshire and Jones, 1998). 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 and the anterior cingulate cortices show the most consistent activation in functional imaging studies on pain perception (Peyron et al., 2002). The insula takes 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 is implicated in affective and emotional processes through its projections to the amygdala (Augustine, 1996). The 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 light of the ‘somatic marker’ hypothesis of consciousness (Damasio, 1994), the right anterior insular cortex has been hypothesized to be involved in the mental generation of an image of one’s physical state underlying the assignment of emotional attributes to external and internal stimuli.

The increased 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). Since thalamic and midbrain activity have been shown to correlate, respectively, with pain threshold and pain intensity (Tolle et al., 1999; Moerman and Jonas, 2002), it is tempting to hypothesize that hypnosis induces a subcortical gating of cortical activation, resulting in 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 PAG (Bandler and Shipley, 1994). The perigenual and insular cortices and thalam are also known to be implicated in autonomic regulation (Bandler and Shipley, 1994; Augustine, 1996). The modulatory role of the midcingulate cortex on this network could explain the clinical observation that patients undergoing surgery during the hypnotic state show modified autonomic responses and less defensive reactions in response to an aversive encounter (Paymonville et al., 1997).

Hypnosis can hence 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\textsuperscript{15}O-PET, during the hypnotic state differs from that induced by simple mental imagery. The reduced pain perception during hypnosis is mediated by an increased functional connectivity between the midcingulate cortex and insular, perigenual, 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.

**Placebo**

Like hypnosis, placebo is another example of a powerful form of top-down modulation of pain by cognitive processes. There are several striking similarities between the two. Just like there is no generally accepted definition for hypnosis, there is also no clear definition of placebo. It is indeed difficult or maybe even impossible to define the placebo and the placebo effect in a coherent and logical manner. For instance, Shapiro (1960) defined placebo as: “any therapeutic procedure (or that component of any therapeutic procedure) which is given deliberately to have an effect, or unknowingly, and has an effect on a symptom, syndrome, disease, or patient but which is objectively without specific activity for the condition being treated. The placebo effect is defined by the changes produced by placebos”. Consequently, the placebo is described as being: “without specific activity for the condition being treated”. Putting this phrase in place of the word itself, it then reads: “The placebo effect is defined as the changes produced by things without specific activity for the condition being treated”, a statement that does not make any sense. Because of the difficulty to provide a clear definition, some authors have suggested the abandonment the entire concept of placebo (Götzsche, 1994) or to rename placebo effects as “meaning responses”, by which is meant the physiologic and psychological effects of meaning in the origins or treatment of illness (Moerman and Jonas, 2002). A second characteristic that placebo has in common with hypnosis is that it has long been considered an unpopular topic that was largely neglected by the neuroscience community. Fortunately, this situation has changed in recent years during which we have witnessed an increased interest in the neurobiology of the placebo.
response, both for pain and other conditions such as Parkinson’s disease and depression (Fig. 5).

**Placebo: classes of explanation**

*Conditioning and expectation*
One of the main theories of placebo analgesia is that it is mediated by classical (Pavlovian) conditioning. Applied to placebo analgesia, active agents that reduce pain act as unconditioned stimuli (UCS) and the vehicles and settings in which they are delivered (pills, syringes, the medical setting, etc.) act as conditioned stimuli (CS). It follows that medical treatments act as acquisition phases or conditioning trials where vehicles and active agents are paired. The pairings enable the CS to produce therapeutic effects as conditioned responses (CR) (Wickramasekera, 1980; Suchman and Ader, 1992; Kirsch, 1997; Montgomery and Kirsch, 1997). Several investigators have provided empirical evidence in support of a role of conditioning in placebo analgesia in man (Laska and Sunshine, 1973; Voudouris et al., 1989, 1990; Amanzio and Benedetti, 1999). In addition, experimental studies of conditioned pharmacological responses revealed that animals with a history of drug administration are likely to show drug resembling behavior when a placebo is administered in a drug-associated context (Siegel, 1985).

Not everybody agrees with the purported role of classical conditioning in placebo analgesia (Brewer, 1974). For instance, placebo effects are sometimes not in accordance with the pharmacological property of the active conditioning drug, but are context and suggestion dependent. This has led to the adoption of an informational (cognitive) view of classical
conditioning to explain the placebo effect. According to this view, conditioning produces expectancies that certain events will follow other events. Conditioning depends on the information that the CS provides about the UCS (Rescorla, 1988). The unconditioned response (UCR) is seen as the anticipatory response preparing the organism for the occurrence of the anticipated US. In order for a stimulus to serve as a US, it has to be perceived and that what is perceived is the active drug's effect. Essentially what is learned is that drugs produce specific effects; consequently, conditioning is one way to obtain response expectancies. This implies that the drug response becomes the UCS rather than the UCR. It follows that the placebo effect is dependent on the strength of an individual's expectancies and not on how these expectancies have been formed (Evans, 1985; Kirsch, 1997; Montgomery and Kirsch, 1997; Price et al., 1999; De Pascalis et al., 2002).

Conditioning and expectancy might represent two separate dimensions of a common process. It is likely that each mechanism can be applied to explain placebo analgesia under different experimental conditions. Benedetti and colleagues (2003) tried to disentangle the respective roles of expectancy and conditioning in the placebo response. They showed that conditioning mediates the placebo effect when an unconscious physiological function like hormonal secretion is involved. However, even though a conditioning procedure has taken place, the placebo effect is mediated by expectancy when conscious physiological processes like pain and motor performance are involved. In other words, the placebo effect is learned at an unconscious or a conscious level depending on the system involved.

Endogenous opioids

The study gave placebo analgesia a biological underpinning and initiated a series of pharmacological studies, most of which confirmed Levine's findings (Amanzio and Benedetti, 1997, 1999; Benedetti et al., 1999). However, Greval et al. (1983) reported that placebo analgesia can occur without the involvement of the endogenous opioid system. Likewise, Grevert et al. (1983) showed that placebo analgesia was only partly blocked by naloxone. We recently also studied the involvement of the endogenous opioid system in two patients suffering from chronic low back pain (Kupers et al., in preparation). Both patients showed a profound and long-lasting placebo response to placebo infusions. Naloxone and saline were administered in a double-blind manner to test whether the placebo response was mediated by endogenous opioids. Naloxone (10 mg) failed to block the placebo response, suggesting that the placebo response in these patients was not mediated by the endogenous opioid system. In order to better understand the conditions that produce naloxone-reversible and naloxone-insensitive placebo effects, Amanzio and Benedetti (1999) evoked different types of placebo analgesic effects by using cognitive expectation cues, drug-conditioning or a combination of both. Their aim was to dissect placebo analgesia into opioid and non-opioid parts and determine their relation with expectancy and conditioning. The drug conditioning trials were carried out with either morphine or the non-steroidal anti-inflammatory drug ketorolac. Morphine conditioning generated a naloxone-reversible placebo effect. In contrast, when conditioning was done with the non-opioid ketorolac, the resulting placebo effect was not antagonized by naloxone. Expectancy cues presented alone without prior drug conditioning generated a small placebo effect that was completely blocked by naloxone. This demonstration that placebo analgesia can be dissected into opioid and non-opioid parts, depending on the procedure used to evoke the placebo effect, may resolve the old controversy of the role of opioids in placebo analgesia. The results further indicate that cognitive factors and conditioning are differently balanced in relation to placebo analgesia, activating either the opioid or non-opioid system. Whereas expectation triggers the endogenous opioid system,
conditioning procedures may activate either opioid or non-opioid systems.

A subsequent study by the same group (Benedetti et al., 1999) further elaborated on how endogenous opioids are activated by expectancy cues. They induced specific expectancies of analgesia directed toward different body parts. In brief, a noxious stimulus was simultaneously applied to four different body areas (arms and legs, left and right). A placebo cream was applied to one of the stimulated body parts and the subjects were informed that the cream was an analgesic (induction of expectations). The expectancy of an analgesic effect was exclusively directed toward the site where the placebo had been applied. The results showed a placebo analgesic effect that was restricted to the treated site and that was completely abolished by a hidden injection of naloxone. These data show that a spatially directed expectation produces a placebo effect that is somatotopically restricted to the body site that is the target of expectation. These data further indicate that placebo-activated endorphines act only on the expected target of action and not on the entire body. It can thus be hypothesized that a cognitive component in the form of spatial attention or spatial directed expectation plays a pivotal role in the activation of specific opioid systems (Benedetti et al., 1999; Price, 1999).

The role of opioids in placebo analgesia implies that the activation of the pain modulatory circuitry, including the PAG and the RVM, is triggered by psychological factors. Fields and co-workers already emphasized the role of expectation, arousal, and attention in the modulation by the PAG and RVM (Price and Fields, 1997). Furthermore, Soper and Melzack (1982) found that the PAG is functionally and somatotopically organized. That is, stimulation of different sites of the PAG produced an analgesic effect in different cutaneous areas. In other words, the spatially directed effect may be explained by the somatotopical organization of the PAG. Because the pain modulatory circuitry is influenced by opioids, it can be hypothesized that the endogenous opioid systems have a role in organizing the PAG and RVM (Benedetti et al., 1999).

There is evidence from studies on the placebo effect in patients with Parkinson’s disease (PD) that the opioid system is not the only neurotransmitter system involved in the placebo response. Another candidate is dopamine. de la Fuente-Fernández and colleagues (2001) used PET to study the involvement of the brain dopamine system in the placebo response in patients with PD. They used [11C]raclopride (RAC), which is an antagonist for the dopamine D2/D3 receptors. By calculating the displacement of the exogenously applied RAC following a pharmacological or behavioral challenge, one can estimate the amount of endogenously released dopamine. Six PD patients were scanned in a placebo-controlled, double-blind fashion following the administration of a placebo or an active dopaminergic drug (levodopa). Placebo administration caused a significant decrease in RAC binding potential in the dorsal striatum. Interestingly, the magnitude of the decrease in RAC binding potential following a placebo was comparable to that evoked by a therapeutic dose of levodopa. The authors also reported a positive correlation between the degree of dopamine release and the extent of the perceived placebo effect. In a following study, the same authors showed that placebo also releases dopamine in the nucleus accumbens (de la Fuente-Fernández et al., 2002a). The dopamine release in the ventral striatum may be caused by the expectation of reward — in casu, the anticipation of a therapeutic effect.

**Brain imaging findings**

Brain imaging studies over the past decade have greatly advanced our understanding of the mechanisms underlying placebo analgesia. Their contribution has been twofold. First, these studies showed that placebo-induced pain relief is associated with a concomitant decrease of brain activity in pain-related areas such as the thalamus, the insula, and the anterior cingulate cortex. This is important in view of the discussion whether reported pain reductions following placebos represent genuine analgesic effects or mere compliance with experimental instructions. Second, these studies pointed out a number of structures that may be at the origin of the placebo effect. Among these figure the dorsolateral, ventrolateral and orbital prefrontal cortices, the ACC, and the midbrain. Interestingly, the dorsolateral
prefrontal cortex has also been proposed to be an important structure in the endogenous modulation of pathological pain (Lorenz et al., 2003).

Using PET, Petrovic and colleagues (2002) scanned a group of healthy volunteers following the administration of a short acting opioid (remifentanil), placebo, or no drugs. Subjects were scanned during non-painful and painful tonic heat stimulation of the dorsum of the left hand. Pain ratings following placebo administration were significantly lower than when no drugs were given. The placebo response was associated with a significant rCBF increase in the orbitofrontal and ACCs, areas that were also reliably activated by the opioid remifentanil. When the results were analyzed for the high and low placebo responders separately, it was found that only the high placebo responders activated the rostral ACC (rACC) during remifentanil analgesia. This suggests that there exists a relationship between how effectively opioids activate the rACC and how well subjects respond to placebo during pain. In other words, placebo responders seem to have a more efficient opioid system. This hypothesis is supported by data from a study by Lasagna et al. (1954) showing that 95% of individuals responding to a placebo report pain reduction following the injection of morphine, whereas only 54% of the individuals not responding to a placebo report pain reduction following the injection of morphine. A regression analysis of the PET data from Petrovic’s study further showed that in the pain-opioid and pain-placebo conditions, activity in the rACC varied with activity in an area near the PAG and the pons. This suggests that higher cortical areas may take control over descending pain modulatory systems during opioid- and placebo analgesia. As mentioned above, cognitive factors such as expectation and desire for pain relief contribute a lot to the occurrence of the placebo response. The ACC and lateral orbitofrontal cortex may play an important role in this cognitive modulation of pain via their projections to the PAG, an area involved in descending inhibitory control of pain.

Wager et al. (2004) used fMRI to study the brain mechanisms involved in placebo analgesia. In two separate experiments, they addressed the following questions: (1) which pain-responsive areas of the brain show reduced activity following a placebo? and (2) which areas in the brain show increased activity following the administration of a placebo? Whereas the previous PET study tried to answer the second question, it did not address the first one. To increase the likelihood of the occurrence of a placebo response, the authors used a conditioning procedure. The results showed that placebo significantly reduced the BOLD response in the rACC, contralateral insula, and thalamus, areas that are part of the so-called pain-matrix (Peyron et al., 2000). In order to answer the second question, the authors compared brain activity in the anticipation period of pain under the control and placebo conditions. The results revealed that activity in the dorsolateral and orbital prefrontal cortices, ACC and PAG was significantly higher following a placebo compared to the control condition. In addition, the increased prefrontal activity correlated with the placebo-induced reductions in pain-evoked activity in thalamus, insula, and ACC. The increased activity in the prefrontal cortex is in line with the hypothesis that brain areas involved in generating and mediating expectation contribute to placebo-analgesia; whereas the above-mentioned brain imaging studies used acute, experimentally induced pain. A recent study by Lieberman et al. (2004) investigated placebo analgesic responses in patients with irritable bowel syndrome. The experimental setup of the study was different from the previous studies. Before and after a 3-week placebo regimen, patients were scanned at rest and during controlled rectal stimulation. In line with the results of the placebo response in acute pain, the placebo response was associated with significantly increased activity in the prefrontal cortex. In contrast with the previous results (Petrovic et al., 2002; Wager et al., 2004), the increased activity occurred in the ventrolateral and not in the dorsolateral or orbitofrontal part of the prefrontal cortex. Interestingly, the stereotactic coordinates of the ventrolateral prefrontal activation in the Lieberman study (x = 30, y = 33, z = -5) is nearly a right-hemispheric mirror image of the hypnosis-induced rCBF increase (x = -28, y = 26, z = 8) in the left ventrolateral prefrontal cortex in the study by Maquet et al. (1999). A second difference with the previous
Fig. 6. (A) Time course of the placebo response in a chronic pain patient. Before placebo, average pain rating was around 7 on a 10-point visual analogue scale (VAS). The patient’s pain was significantly reduced by placebo during the 50 days she was followed by the pain clinic. On two occasions, indicated by the arrows, the placebo administration was stopped and the original pain reappeared, indicating that natural course of the disease or regression to the mean are unlikely to explain the pain improvement. The data also indicate that placebo analgesia can last over extended periods. (B) Effect of naloxone on the placebo response in a chronic pain patient. Naloxone (10 mg, i.v.) or saline was administered in a double-blind manner in a patient with placebo analgesia. The left bar (before) shows average pain ratings before placebo. Patient’s average pain ratings during the 30 days of placebo administration dropped significantly (placebo). Naloxone did not abolish the placebo response in this patient. (C) rCBF changes in the anterior cingulate cortex in a chronic pain patient during a placebo response (Kupers et al., unpublished results).

Studies is that the placebo response was not associated with increased activity in the ACC. In contrast, activity in ACC was significantly reduced and the reduction in this region correlated negatively with activity in the ventrolateral prefrontal cortex. Our own preliminary findings in patients with neuropathic pain argue for a possible role of the orbitofrontal cortex in the placebo response (Fig. 6).

Fig. 7 shows a composite image of the activations induced by placebo and hypnosis in the higher discussed papers. As can be seen, ACC and prefrontal cortex are activated in both forms of cognition-induced analgesia.
Fig. 7. Both hypnosis- and placebo-induced modulation of pain perception seems to be mediated by the ACC (red circles). Note that mean peak coordinates from hypnosis- and placebo-induced pain modulation studies, using very different methodology, are within 5 mm from each other (x = 2, y = 22, z = 28 versus x = 6, y = 17, z = 31 mm, respectively). Hypnosis: (A) Suggestion-related changes in rCBF during pain perception: the image shows rCBF changes for the subtraction hypnosis-with-suggestion minus hypnosis-without-suggestion, both under painful stimulation (coordinates of peak voxel: x = 7, y = 20 and z = 29 mm). From Rainville et al. (1997). (B) Pain-related activity associated with hypnotic suggestions of high unpleasantness (painfully hot/high unpleasantness minus neutral/hypnosis control condition; peak voxel: x = 0, y = 29, z = 34 mm). From Rainville et al. (1999). (C) rCBF increases in proportion to pain sensation ratings, in the specific context of the hypnotic state (difference in pain ratings versus rCBF regression slopes between the hypnotic state and control conditions (i.e., non-hypnotic mental imagery and resting state; peak voxel: x = 2, y = 18, z = 22 mm). From Faymonville et al. (2000). Placebo: (D) rCBF increases with increased intestinal discomfort in placebo-treated patients with chronic abdominal pain (irritable bowel syndrome): a greater reduction in rCBF response to visceral stimulation from pre- to post-placebo was associated with greater self-reported symptom improvement (peak voxel: x = 8, y = 19, z = 34 mm). From Lieberman, M. D., Jarcho, J. M., Berman, S., Nahboff, B. D., Suyenobu, B. Y., Mandelkern, M. and Mayer, E. A. (2004). Neuroimage, 22: 447–455. (E) Activated areas in high placebo responders (healthy volunteers) during heat pain and opioid treatment minus heat pain only (peak voxel: x = 3, y = 18, z = 34 mm). From Petrovic et al. (2002). (F) Pain regions showing correlations between placebo effects in reported pain (control minus placebo) and placebo effects in neural pain (i.e., measured activity in pain related brain areas) (control minus placebo) (peak voxel: x = 6, y = 14, z = 26 mm). From Wager et al. (2004). See Plate 19.7 in Colour Plate Section.

**Conclusion**

It has taken a long time before the scientific community finally accepted that hypnosis and placebo are worth being studied scientifically. Therefore, our knowledge about the mechanisms mediating these powerful effects is still fragmentary. Brain imaging studies have investigated the brain circuitry that is involved in hypnosis- and placebo-induced forms of pain modulation. Brain structures that are involved in these cognitive-induced forms of analgesia are the ACC, and the dorsolateral and orbitofrontal prefrontal cortices. Functional brain connectivity studies further suggest that the anterior
cingulate and prefrontal cortices exert their effects by modulating activity in the midbrain periaqueductal gray, a structure that is of utmost importance in the endogenous modulation of pain. Taken together, these findings reinforce the idea that psychological interventions can relieve pain by modulating activity in an interconnected network of cortical and subcortical regions that are implicated in the processing of noxious information.

Acknowledgments

S. L. is Research Associate at the Fonds National de la Recherche Scientifique de Belgique (FNRS). This research was supported by research grants from the University of Liège, the Centre Hospitalier Universitaire Sart Tilman of the University of Liège and the Danish Medical Research Council.

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