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Chapter 18

Hypnosis for cingulate-mediated analgesia and disease treatment

D. TRUJILLO-RODRÍGUEZ[1], M.-E. FAYMONVILLE[2]*, A. VANHAUDENHUYSE[2], AND A. DEMERTZI[1,3]

[1]*Physiology of Cognition Research Lab, GIGA-Consciousness, GIGA Institute B34, University of Liège, Liège, Belgium*

[2]*Algology Department, Liège University Hospital and Sensation and Perception Research Group, GIGA-Consciousness, University of Liège, Liège, Belgium*

[3]*Fonds National de la Recherche Scientifique, Brussels, Belgium*

Abstract

Hypnosis is a technique that induces changes in perceptual experience through response to specific suggestions. By means of functional neuroimaging, a large body of clinical and experimental studies has shown that hypnotic processes modify internal (*self-awareness*) as well as external (*environmental awareness*) brain networks. Objective quantifications of this kind permit the characterization of cerebral changes after hypnotic induction and its uses in the clinical setting. Hypnosedation is one such application, as it combines hypnosis with local anesthesia in patients undergoing surgery. The power of this technique lies in the avoidance of general anesthesia and its potential complications that emerge during and after surgery. Hypnosedation is associated with improved intraoperative comfort and reduced perioperative anxiety and pain. It ensures a faster recovery of the patient and diminishes the intraoperative requirements for sedative or analgesic drugs. Mechanisms underlying the modulation of pain perception under hypnotic conditions involve cortical and subcortical areas, mainly the anterior cingulate and prefrontal cortices as well as the basal ganglia and thalami. In that respect, hypnosis-induced analgesia is an effective and highly cost-effective alternative to sedation during surgery and symptom management.

THE MERITS OF HYPNOSIS IN CLINICAL APPLICATIONS

The use of hypnosis by the medical community has increased exponentially in the past years. This increase can be attributed to a growing awareness of hypnosis as a valuable clinical tool as well as to more intense research experimental work highlighting its measurable effects (Jensen et al., 2017). Hypnosis can be defined as "a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestions" (Elkins et al., 2015). As such, hypnosis can be viewed as a particular cerebral waking state during which the individual, seemingly somnolent, experiences vivid, multimodal, coherent, memory-based mental imagery.

Hypnosis is an effective complementary technique in several areas of care. A widely used application is during surgery (Faymonville et al., 1999, 2000). It can be also used to address a large number of clinical conditions at both acute and chronic stages of disease expression, ranging from treatment of phobias and affective disorders (e.g., depression or posttraumatic stress disorder) to neuropsychiatric disorders, such as dissociative identity disorder, psychosis, anorexia nervosa, and somatic symptom disorder (Lynn et al., 2010). As an alternative

*Correspondence to: Marie-Elisabeth Faymonville, M.D., Ph.D., Domaine Universitaire du Sart Tilman, Department of Algology and Palliative Care, CHU Liège—B35, Liège, 4000 Belgium. Tel: +00-324-366-8033, Fax: +00-324-366-7013, E-mail: mfaymonville@chu.ulg.ac.be

approach for multiple medical conditions, hypnosis has also a well-established evidence of treating and managing a spectrum of painful conditions (Vanhaudenhuyse et al., 2015, 2018), such as dilation and curettage (Fathi et al., 2017), irritable bowel syndrome (Gonsalkorale et al., 2003; Surdea-Blaga et al., 2016), phantom limb (Oakley and Halligan, 2002), migraine (Flynn, 2018), cancer-related pain (Vickers and Cassileth, 2001; Carlson et al., 2018), and pain related to multiple sclerosis (Amatya et al., 2018). A common denominator for these interventions is the involvement of the cingulate cortex (Vogt and Brent, 2009). By and large, findings from functional neuroimaging point to a critical role of the cingulate cortex as the key cerebral structure mediating hypnosis-related alteration of sensory, affective, cognitive, and behavioral aspects of subjective experience. Indeed, diffuse functional disorders including fibromyalgia, trigeminal neuralgia, and diffuse low back pain have no apparent organic basis in peripheral organ structure or chemistry and appear to result primarily from dysfunction of nervous system structures, with prominent impairment of cingulate functions. Hence, it might be reasonable to consider the role of hypnotic intervention in pain and psychiatric diseases as a parallel model to drug development. Just as a molecule is synthesized with greater specificity for a particular receptor subtype, similarly different hypnotic methodologies can be altered to generate activity in particular parts of the brain. Therefore, the treatment of acute and chronic diseases requires continual refining to enhance the specificity of hypnosis for particular outcomes (Faymonville et al., 2009).

THE SUBJECTIVE DIMENSIONS OF HYPNOSIS

Hypnosis leads to a change in baseline mental activity after an induction procedure experienced at the subjective level as an increased disattention to environmental stimuli alongside a reduction in spontaneous thinking (Oakley and Halligan, 2009). In other words, hypnosis is a way to modify the content of conscious awareness by filtering both sensations and thoughts involving receptive concentration. Hypnotic procedure is characterized by three main dimensions: (i) *absorption*, which is a tendency to become fully involved in an experience being ideational, imaginative, or perceptual, (ii) *dissociation*, which involves a mental severance of the behavioral components of the experience that normally are processed together, causing a feeling of motor uncontrollability, and (iii) *suggestibility*, which is mediated by high responsiveness to social cues leading the individual to comply with hypnotic instructions (Spiegel, 1991; Vanhaudenhuyse et al., 2014). Hypnotic suggestibility, also commonly referred to as *hypnotizability*, is considered a stable trait (Piccione et al., 1989) that can be observed outside hypnosis (Rubichi et al., 2005). It ranges from low to high (Varga et al., 2012) depending on the recruitment of attentional networks (Cojan et al., 2015) and can be predicted by rating the subject's self-level of focused attention, the dissociation between the own bodily sensation and the actual environment, and the difference between the subject's estimated time compared to the actual duration of an induced neutral hypnotic experience. Without any specific suggestion, merely with eye fixation and muscle relaxation (i.e., neutral hypnosis), it is possible to identify high and low hypnotizable subjects, considering the dissociation score in the same way it is categorized by a traditional standardized scale (Vanhaudenhuyse et al., 2019).

To develop a hypnotic state, guided instructions are required. As an example, a 3-min induction with progressive muscle relaxation and eye fixation precedes invitations to the subject to reexperience pleasant autobiographic memories while permissive and indirect suggestions and cues are given to deepen and maintain the hypnotic state (Vanhaudenhuyse et al., 2009a,b). This state is further characterized by a modulation of some other properties of phenomenal self-consciousness, such as mental ease, orientation toward space and time, monitoring, and sense of self-agency, as the responses are experienced like being produced without deliberation (Rainville and Price, 2003). Indeed, hypnosis disrupts the personal sense of agency and deludes the source and feasibility of the experienced sensations (Polito et al., 2013). It is believed that during the hypnotic session the dissociation experienced by the subject correlates with the level of hypnotic suggestibility (Vanhaudenhuyse et al., 2019) as it is observed with a standardized form of the Stanford Hypnotic Susceptibility Scale (Weitzenhoffer and Hilgard, 1959). As such, it is not the physical responses to suggestions that are visible *per se* but rather the subjective experience, which accompanies the suggested behaviors. Therefore, the self-rated responses need to be clearly specified in behavioral terms, mainly because the resulting scores reflect the hypnotic effect only to a certain degree. As behavior limitedly reflects alterations in the individual's phenomenological experience, various scales addressing the veridicality of the suggested experience have been developed (Lush et al., 2018). Objective quantifications of the responsiveness to suggestions are of paramount importance to understand the specific neural substrates underpinning the hypnotic phenomena. Such observations of perceptual modifications and inner experiences of individuals during a hypnotic state further allow the development of theoretical models addressing the phenomenology of hypnosis.

HYPNOSIS CAN BE OBJECTIVELY MEASURED

Improvements in functional neuroimaging and electrophysiology techniques have allowed researchers to articulate objective evidence of hypnotic induction. Although hypnosis does not have a specific neural correlate, we can quantify its influences on brain activity in different ways. Functional magnetic resonance imaging (fMRI), for example, enables us to estimate different intensities of functional connectivity, i.e., the correlations between spatially remote neurophysiologic events (Friston, 2011). Using fMRI, for example, hypnotizability has been shown to have higher functional connectivity within the executive control network, which includes, among others, the anterior cingulate and paracingulate cortex as well as the anterior insula. At the same time, a right frontoparietal network of areas had lower functional connectivity with right lateral fronto-striatal-thalamic regions (Huber et al., 2014). These right-sided systems are involved in receiving peripheral somatosensory input and process mainly somesthetic and pain signals (Vogt, 2005). Further observations evidenced that the right frontoparietal network partly overlapped with a right ventral fronto-parietal network, which is generally responsible for reorienting attention toward unexpected but salient environmental stimuli and which was suppressed when attention was allocated to prevent reorienting to distracting events (Huber et al., 2014). Studies of these kinds provide unique insights into the mechanisms of hypnosis and its neural underpinnings, which may be eventually used not only to understand hypnosis as a phenomenon *per se* (intrinsic hypnosis) but also to use hypnosis as a means to study other cognitive functions (instrumental hypnosis) (Oakley and Halligan, 2009).

Cortical networks and hypnosis

By means of fMRI, several systems have been consistently identified in healthy individuals (Damoiseaux et al., 2006) relevant for conscious cognition during resting conditions, that is, when the subject is not engaged in any particular task (Heine et al., 2012). One of them, the default mode network (DMN) is defined as a set of specific brain regions involving the precuneus/posterior cingulate cortex, mesiofrontal/anterior cingulate cortex, and temporoparietal junction (Raichle et al., 2001). These regions are primarily involved when individuals are not focused on external tasks but are engaged in internally focused mentation including autobiographic memory retrieval and mind-wandering (Buckner et al., 2008). The DMN activity has been shown to attenuate during externally cued tasks (Greicius et al., 2008), potentially reflecting higher-order cognitive function (Heine et al., 2012). The DMN typically shows negative correlations with a set of frontoparietal regions, otherwise known as DMN anticorrelations (Fox et al., 2005). These networks can be also viewed as an (i) *extrinsic system* that is oriented and associated with environmental awareness and an (ii) *intrinsic system* that is oriented and associated with self-related stimulus-independent awareness (Soddu et al., 2009). In our previous fMRI-behavioral study, under hypnosis, we found reduced functional connectivity in the extrinsic system, almost at zero level (Demertzi et al., 2011). These reductions were further relevant for subjective reportability where subjects self-rated switches between the internal and external awareness less frequently. Indeed, subjects reported being in a sustained absorbed state of internal awareness longer than paying attention to their environment, taking more time to respond with button presses, and they had a higher number of lapses in their responses (Demertzi et al., 2015; Fig. 18.1). It has been hypothesized that whereas the extrinsic system hyperfunction is expected to relate to a state of total sensory-motor absorption, the hypofunctionality of extrinsic network along with intrinsic hyperfunction might be evidence of the subjective experience of disengagement from external environment leading to a state of "self-centered absorption." This state is translated into a complete detachment from the external world, limiting sensory input or reducing motor output (Soddu et al., 2009). Another study, though, reported that the induction of hypnosis in high hypnotizable subjects during the resting state leads to a reduced anterior default mode activity without affecting activity in other cortical regions (McGeown et al., 2009). These differences may be partly explained by the different experimental designs in combination with the distinct instructions for hypnotic suggestions. It, therefore, seems that the suggestions used influence cerebral organization in a way to reflect their specific context (e.g., invitation to revive autobiographical memories elicits a differential pattern of connectivity as compared to pure hypnosis or invitations to move a body part). This expands the possibilities of study for the understanding of the absorption and dissociation phenomena during hypnosis in the resting state and the physiologic implications of spontaneous activity in sensory cortices, such as primary visual areas (Wang et al., 2008).

In terms of other networks, it has been observed that despite any differences in whole-brain connectivity, there was a coactivation of the left dorsolateral prefrontal cortex (DLPF) and the midcingulate cortex (MCC) in high but not in low hypnotizable individuals in the salience network (Hoeft et al., 2012). The salience network is an extensive set of regions anchored by limbic anterior cingulate and frontoinsular cortices with widespread connectivity with subcortical structures

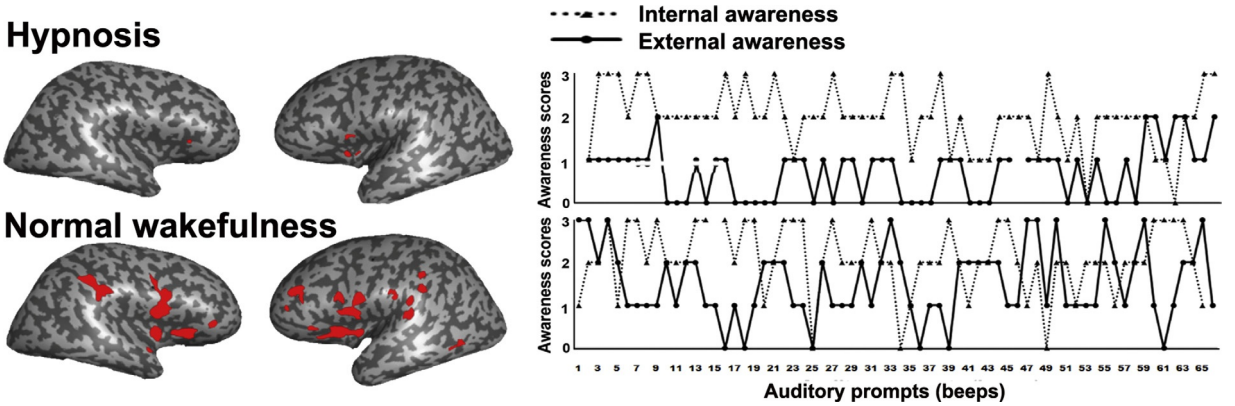

Fig. 18.1. Hypnosis induces quantifiable changes at different levels. At the cerebral level, hypnosis with suggestions to revive pleasant autobiographical memories relates to reduced connectivity in a set of lateral frontoparietal regions, typically mediating the perception of the external environment (left top panel). This dissociation is further mirrored at the behavioral level, where subjects report longer periods of increased internal awareness during a thought-sampling task. The task concerned the presentation of auditory beeps, which were interrupting the subjects' ongoing stimulus-independent thinking, and prompted them to provide ratings on the external and internal awareness states (right top panel). In normal waking conditions, in contrast, where no dissociative suggestions are delivered, frontoparietal connectivity is preserved (left bottom panel). Similarly, behavioral ratings about internal-external awareness follow an interchangeable flow with no particular dominance across time in the typical waking state (right bottom panel). Figure adapted from Demertzi, A., et al., 2011. Hypnotic modulation of resting state fMRI default mode and extrinsic network connectivity. Prog Brain Res 193, 309–322.

(Seeley et al., 2007). This network is responsible for sensory integration and cognitive control (Ham et al., 2013), switching between the externally oriented cognition of the central executive network and the internally oriented cognition of the DMN (Menon and Uddin, 2010). Using fMRI to study the recruitment of attentional networks during a cognitive task in high and low hypnotizable participants, it has been observed that in highly hypnotizable subjects the right inferior frontal gyrus was more connected to the DMN, suggesting that interactions between internally and externally driven processes may allow higher flexibility in attention and support the ability to dissociate (Cojan et al., 2015).

Taken together, research shows that hypnotic induction leads to an alteration of cerebral functional organization by disrupting interrelations between regions through an interpersonal context. Initiated by the intervention of the hypnotist (Gruzelier, 2000), these modifications might reflect a change in brain state that is specific to the hypnotic induction in subjects with high susceptibility to its effects (McGeown et al., 2009). The mediation of the cingulate cortex is critical and these hypnosis-related increases in functional connectivity align with our studies showing enhanced functional connectivity of the anterior midline structures during hypnosis (Faymonville et al., 2003).

THE CINGULATE CORTEX IN HYPNOSIS

The anterior cingulate cortex (ACC) is a functionally complex structure that has extensive projections to prefrontal cortex, anterior insular cortex, amygdala, hypothalamus, and several nuclei in the midbrain and brainstem as part of the central autonomic network (Cersosimo and Benarroch, 2013). It controls sympathetic and parasympathetic functions intervening in neuromodulatory pathways including opioidergic, serotonergic, and noradrenergic systems (Paus, 2001). This region plays an important role in cognitive control (Bush et al., 2000; van Veen and Carter, 2002), conflict monitoring (Botvinick et al., 1999), motor coordination (Wenderoth et al., 2005), and self-conscious emotional reactivity (Sturm et al., 2013). The ACC is divided into subgenual (sACC) and pregenual (pACC) parts, whereas the midcingulate cortex (MCC) is subdivided into an anterior (aMCC) and a posterior part (pMCC) adjacent to the posterior cingulate cortex (Stevens et al., 2011), (see Chapter 1 for cingulate parcellations).

Functionally, the aMCC shares direct and reciprocal connections with the dorsal anterior insular lobe, the lateral prefrontal cortex, and premotor and supplementary areas, as part of a highly complex attentional network often referred to as the cognitive division. The sACC has enormous projections to hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex and modulates autonomic, visceromotor, and endocrine responses correspondent to an affective division (Bush et al., 2000). Indeed, while the ACC has been generally considered to be involved in the affective component of pain stimulation (Vogt, 2005), the sensory-discriminative and affective responses associated with pain unpleasantness (Kulkarni et al., 2005), as well as in the development of chronic pain after injury (Zhao et al., 2018), MCC activation has been associated with high cognitive processes like

response selection, vicarious pain, and motor regulation rather than pain perception (Misra and Coombes, 2015; Yesudas and Lee, 2015). This role of MCC in cognitive processing of pain information is supported by a number of studies that show an increasing activation of MCC during attentional shifts to the noxious stimuli as well as during inhibition of motor reactions triggered by painful stimulation (Legrain et al., 2009) or when observing pain in others (Grice-Jackson et al., 2017), concluding that conscious experiences of pain stimulation are supported by specific patterns of functional connectivity between pain-related and regulatory regions and not only by increased activity within the pain neuromatrix itself.

The functional segregation of the cingulate cortex subregions and its mediation in cognitive processes involving motor planning (Devinsky et al., 1995; Picard and Strick, 1996), response selection (Turken and Swick, 1999), motor learning (Jueptner et al., 1997), conflict detection, and error monitoring (Swick and Turken, 2002) have been also confirmed during functional resting-state studies (Fellows and Farah, 2005; Taylor et al., 2009; Yu et al., 2011).

The cingulate cortex poses as a critical modulator during surgical procedures. It alters nociceptive signaling during the hypnotic state, which in turn depends on the level of hypnotizability and, hence, the depth of the induced state. In clinical terms, an important effect that can be (self)induced through the hypnotic process, involving the activity of the cingulate cortex, is the reduction of conscious perception (awareness) of sensory input (Feinstein et al., 2004), changes in pain modulation and in the perceived unpleasantness of painful stimuli (Rainville et al., 1997), and changes in mental relaxation and mental absorption (Rainville et al., 2002). On the other hand, suggestion of pain (Porro et al., 2002) and hypnotic suggestions to induce pain (Derbyshire et al., 2004) can affect the internal monitoring of sensory information triggered by anticipation even in the absence of an actual noxious stimuli and can induce specific neural activity.

The effectiveness of pain relief during hypnosis has been evaluated with psychophysical measures of pain intensity and unpleasantness in resting, distraction, and hypnotic states. Studies in pain modulation examining brain activity during hypnosis have shown a modified activity in the area 24a′, which is a part of the anterior midcingulate cortex and located rostral to the posterior midcingulate cortex (Vogt and Palomero-Gallagher, 2012). In a study using hypnotic suggestions (Rainville et al., 1997), powerful expectations of increased as well as decreased unpleasantness of experimental painful stimulation were induced, reporting that only specific suggestions of increased or decreased unpleasantness changed the pain ratings. This behavioral effect is associated with the modulation of the aMCC activity and a modulation of pain unpleasantness. In one of our previous PET studies, we determined the main effects of noxious stimulation and hypnotic state by means of a factorial design by considering the *state* (hypnosis, resting state, mental imagery) and the type of *stimulation* (warm non-noxious vs hot noxious stimuli applied to the right palm of the hand at the base of the thumb) as factors. Hypnosis based on the recall of a pleasant life experience modulated both unpleasantness and pain intensity of noxious stimuli in the aMCC as indicated by self-ratings of pain intensity (Faymonville et al., 2000). The interaction analysis showed that the activity in aMCC was related to pain intensity and unpleasantness in a distinctive way under hypnosis compared to normal wakefulness, increasing blood flow proportionally to pain sensation and increases in pain unpleasantness ratings (Fig. 18.2).

Data obtained from clinical and lesion studies as well as neurophysiologic single neuron activity studies showed that MCC activity codes the intensity of noxious stimulation in mammals (Foltz and White, 1962; Sikes and Vogt, 1992; Tsai et al., 2010; Agarwal et al., 2016). Evidence provided from structural and functional imaging studies also conclusively show that MCC has a role in the coding for noxious stimuli; in addition, opposing pain/avoidance and reward/approach functions have been reported (Vogt, 2016; Warbrick et al., 2016). A study addressing the dissociable neural responses related to the intensity of noxious stimuli and pain awareness showed that a region in the aMCC exhibits functional responses that were not related to pain intensity but to basic somatosensory processing (Büchel et al., 2002). Stimulus-related activations were adjacent to the rostral cingulate premotor area, highlighting the strategic link of stimulus processing and response generation in this region.

One important cognitive factor in pain processing is the expectation related to pain stimulation and the degree of certainty associated with this expectation. Subjective certainty that a particular aversive event is imminent has been associated with the emotional state of fear and decreased pain sensitivity, inhibiting withdrawal from noxious stimuli (Rhudy and Meagher, 2000) with different arousal levels (Rhudy and Meagher, 2003). Behavioral studies supporting the view that emotional states modulate pain reactivity have shown that, in contrast, uncertainty about the nature of the approaching stimuli can be associated with anxiety as well as an increased somatic and environmental attention, leading to increased pain sensitivity (Ploghaus et al., 2001). Several functional imaging studies suggest that fear and the anticipation of pain (e.g., conditional analgesia) enhance responses to nonpainful somatosensory stimulation in the ACC (Sawamoto et al., 2000) triggering descending opioid and nonopioid analgesic systems (Lichtman and Fanselow, 1991) subserved by both cortical- and

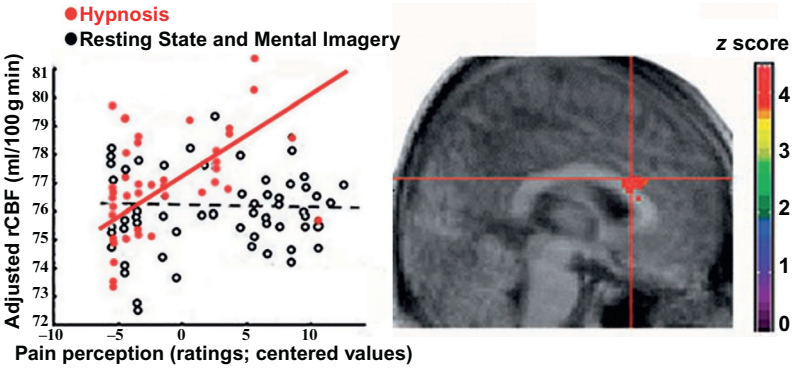

Fig. 18.2. Hypnosis mediates perception of pain. Subjective ratings about pain perception, after hot noxious stimulation applied to right thenar eminence, were lower in hypnosis as compared to a control condition of mental imagery and resting state (^{15}O-water positron emission tomography). The interaction analysis showed that the activation of the anterior midcingulate area 24a' was related to pain perception and unpleasantness differently in hypnosis (red slope) than in control situations (black dashed slope), pointing to the critical role of the anterior MCC for the hypnotic modulation of pain. Figure adapted from Faymonville, M., et al., 2000. Neural mechanisms of antinociceptive effects of hypnosis. Anesthesiology 92, 1257–1267 with permission from Wolters Kluwer Health.

spinal-level mechanisms. The altered perception of somatic stimulation is possibly related to changes in the level of arousal and to cognitive modulation of the pain neuromatrix (Porro et al., 2003). Pain perception thus depends on the expectation of the sensory consequences elicited by noxious stimuli, which relies on attention and anticipation networks (Peyron et al., 1999) and may be associated with emotions produced by disequilibrium of the internal state of the body.

Taken together, structural and functional studies allow us to conclude that although different subregions of the cingulate cortex play a fundamental role in pain processing and associated behaviors, it is the aMCC that appears pivotal to the mechanism of hypnoanalgesia. Cognitive modulation of pain-related MCC activation has been shown in multiple conditions, including hypnosis, decreasing both unpleasantness (i.e., affective component) and perceived intensity (i.e., sensory component) of acute noxious stimuli compared to the resting state.

CEREBRAL MECHANISMS OF HYPNOSIS

The subjective sensations of individuals during hypnosis are essential to correctly estimate the intensity of the hypnotic experience. However, behavioral responses to hypnotic suggestion are not sufficient to characterize the phenomenology of hypnosis partly because an external observer might not be able to identify modifications of perception. In the recent years, proposed neurophysiologic models emphasize the crucial involvement of the frontal regions in mediating both hypnosis and hypnotizability.

Transient hypofrontality hypothesis

It is proposed that the effects of hypnosis are related to frontal functional inhibition and impairment in error detection, selective inhibition, dissociation, and disconnection, which take place after the induction process (Gruzelier, 2006). The observed differences in hypnotizability are in part due to the dissimilar attentional abilities and the nonhypnotic, baseline condition seen in individuals with low and high hypnotic suggestibility, suggesting that hypnosis involves the supervisory, attentional control system of the prefrontal cortex. In the specific case of hypnoanalgesia, inhibitory feedback circuits further cooperate in the regulation of thalamocortical interaction (Crawford et al., 1993). Depending on the given instructions and the cognitive flexibility of the hypnotizable subject, some frontal functions bilaterally may conceivably be enhanced while left frontal functions appear to be selectively more prone to alteration (Gruzelier, 2006). Indeed, hypnotic induction and suggestion produce a widespread increase in regional cerebral blood flow (rCBF) in the frontal cortices predominantly on the left side (Rainville et al., 1999). It is possible that verbal mediation of the suggestions, working memory, and top-down processes involved in the reinterpretation of the perceptual experience play a role in these rCBF changes in frontal cortices. The transient hypofrontality hypothesis, therefore, suggests that the multiple altered states of consciousness are principally due to transient prefrontal cortex deregulation. The phenomenological characteristics of each one of these states result from the differential viability and specificity of various frontal circuits. During some cognitive states, the required extensive neural activation, such as integrating sensory inputs, performing motor patterns, and coordinating autonomic responses, results in a simultaneous transient diminishing of neural activity in the prefrontal cortex. This hypothesis suggests that during hypnosis the focused attention is the cognitive mechanism by which

several prefrontal circuits decrease their activity by removing their contribution to the current conscious experience. The cognitive function supported especially by the dorsolateral prefrontal cortex (e.g., critical reflection, willed action, independent thinking, and initiative) are indeed affected in hypnosis (Dietrich, 2003). In other words, during hypnosis, suggestions become the predominant content in the working memory buffers without going through the higher cognitive filters provided by the dorsolateral prefrontal circuits.

Early studies confirm the decreased prefrontal activation during hypnosis (Kaiser et al., 1997; Nordby et al., 1999; Iani et al., 2009). The observed disruption of functional connectivity within distributed areas in anterior and left-sided brain areas is consistent with transient hypofrontality and left-hemisphere inhibition (Gruzelier, 2000). In a study addressing the question of how suggestions of analgesia could modulate the subjective perception of pain, EEG gamma activity (32–100 Hz) over prefrontal scalp sites predicted subject pain ratings in the nonhypnotic condition (Croft et al., 2002). This relation was not affected in low hypnotizable subjects, while it was absent during hypnosis and hypnoanalgesia in high hypnotizable subjects, suggesting that hypnosis interferes with gamma oscillations in frontal regions. A study using event-related fMRI and EEG coherence measures compared conflict-related neural activity in the ACC and control-related activity in the lateral frontal cortex during Stroop task (Egner et al., 2005). Hypnosis decoupled cognitive control from conflict-monitoring processes of the frontal lobe, confirming a decrease in functional connectivity (i.e., EEG gamma band coherence) between frontal midline and left lateral areas in highly susceptible subjects.

According to some authors, hypnosis may result from inhibitory influences on the secondary somatosensory cortex/insula regions from the right lateral prefrontal cortex and a breakdown of coherent large-scale cortical oscillations organized and controlled by regions in the frontal cortex (Jensen et al., 2017). Regional decreases in ventromedial prefrontal cortex (VMPFC) activity have been described by means of functional neuroimaging studies (Maquet et al., 1999; Rainville et al., 2002). Hypnosis seems to be characterized by increased frontal alpha, decreased central, frontal, and parietal gamma bilaterally, and increased occipital gamma (Fingelkurts et al., 2007). These particular properties further point to the involvement of the prefrontal cortex in hypnotic analgesia by asking a patient to intentionally ignore an injurious stimulus. The pain sensation must first be recognized and then selectively blocked by conscious awareness modulation. This suggests top-down processes for hypnoanalgesia during which increased rCBF in the orbitofrontal cortex might reflect attention system efforts to keep the emotional salience of the sensation from reaching the consciousness (Crawford et al., 1993). Top-down working models of hypnotic relaxation induction involve (i) a thalamocortical attentional network engaging a left frontolimbic focused attention network, underpinning sensory fixation and concentration on the induction, (ii) induction of frontolimbic inhibitory systems through suggestions of relaxation whereby anterior executive functions are suspended and directed by the induction, and (iii) engagement of right-sided posterior functions through passive imagery and dreaming (Gruzelier, 1998). In support of the top-down theories, another prominent group of studies emphasizes the correlation between hypnosis and deactivation in the medial prefrontal cortex. Under invariant conditions of passive visual stimulation, the state of attentional absorption following a hypnotic induction has been associated with reduced activity in the DMN and increased activity in prefrontal attentional systems (Deeley et al., 2012). Recent findings suggest that high hypnotic suggestibility is associated with atypical brain connectivity profiles. High suggestible participants showed decreased brain activity in the anterior parts of the DMN during hypnosis, whereas in low suggestible people the hypnotic induction produced no detectable changes in these regions but instead deactivated areas involved in alertness (McGeown et al., 2009).

The dissociated control theory of hypnosis

The dissociated control theory of hypnosis (Bowers, 1992) proposes that hypnotic ability is not a one-dimensional response. For high hypnotizable subjects, hypnotic suggestions may often directly activate subsystems of cognitive control so that hypnotic inductions reduce frontal control of behavioral schemas. By this, a direct engagement of behavior by the hypnotist's suggestions is induced (Kirsch and Lynn, 1998). This theory is indirectly supported by rCBF studies reporting that increases in the right pregenual ACC area 32 were evoked during hypnosis using pleasant life experiences, while parts of medial and lateral prefrontal areas had a reduction in rCBF (Maquet et al., 1999). Hallucination of auditory stimuli during hypnosis activates area 32 in a similar way to actually hearing such stimuli, but not similar to imagined hearing (Szechtman et al., 1998; Woody and Szechtman, 2000). Taken together, the theory of hypnosis as a dissociated experience proposes that pain and the cognitive efforts to reduce it are cut off from consciousness by an amnesia-like barrier. However, other evidence shows that hypnotic analgesia can occur with little or no cognitive effort to reduce pain, hence challenging the dissociation theory of hypnosis (Miller and Bowers, 1993).

Hypnotic block of thalamocingulate processing

By means of functional cerebral connectivity, it has been shown that the hypnosis-induced reduction in pain

processing is mediated by the aMCC (Rainville et al., 1997, 1999; Faymonville et al., 2000; Vanhaudenhuyse et al., 2009a,b) and it is related to an increased functional modulation between the MCC and a large neural network of cortical and subcortical structures involved in different aspects of pain processing. The reported role of the aMCC in the modulation of this network could explain our clinical finding that patients undergoing surgery during the hypnotic state show modified autonomic responses and less defensive reactions in response to an aversive stimulus (Faymonville et al., 1997). The functional hypnotic circuit has been derived from clinical information along with imaging studies with different paradigms and neurophysiologic assessment of the functions of the particular components of the circuit. The hypnotic induction begins with the driving of pACC by the imagery of pleasant autobiographic events that drives much of the periaqueductal gray (PAG) and descending noxious inhibitory system (DNIS) along with the aMCC (Faymonville et al., 2009). The specific connection patterns in the functional circuit include area 24, which is involved in the unpleasantness of nociceptive stimuli (Ploner et al., 2002; Kulkarni et al., 2005) leading to the assumption that the active region during hypnosis in the circuit model is focused on area 32 (Vogt and Palomero-Gallagher, 2012). Area 32 projects to area 24a′/b′ (Arikuni et al., 1994) and these two areas have correlated activity. Both areas project to a large extent to the striatum and may be involved in the reward systems that could be active during hypnosis. These cingulate areas and the dysgranular insula project to the periaqueductal gray (PAG) induce a diffuse analgesia via the DNIS (Faymonville et al., 2009). Nociceptive inputs to the medial pain system are transmitted through the midline, mediodorsal, and intralaminar thalamic nuclei (MITN) in order to drive cortical pain events (Vogt and Brent, 2009).

It is possible that the insula activates in a manner similar to that of area 32, since a general sense of the body state is activated with pleasant living experiences (Wicker et al., 2003). The insula and aMCC receive parallel input from the MITN (Vogt and Sikes, 2000). Spinal projection neurons convey nociceptive information to higher centers in the brain, where non-noxious and noxious signals can be perceived (D'Mello and Dickenson, 2008). In mammals, differential longitudinal distributions have been found over the length of the spinal cord. Pyramidal and multipolar cells together predominate in the enlargements, whereas fusiform cells predominate in thoracic segments (Zhang and Craig, 1997). Spinothalamic tract projection neurons are inhibited via widely distributed spinothalamic tract fibers originating in the PAG (Zhang et al., 2015) possibly via a nucleus raphe magnus inhibition of spinal cord dorsal horn neurons (Fields et al., 1977). There are two blocks of pain processing through the MITN. One of them is mediated by the thalamus activity and its projections to nociceptive cortical centers where the sensation of pain is coded and the pain is perceived. The other one is mediated by inhibition of nociceptive projections out of the spinal cord resulting in a functional inhibition. This is the fundamental mechanism of hypnosis-mediated block of nociceptive transmission during a surgical intervention.

HYPNOSIS AS AN ALTERNATIVE TO OTHER ANESTHETIC TECHNIQUES

Over the last decades, hypnosis in combination with pharmacologic light sedation has witnessed widespread use as an alternative strategy for pain management during surgical procedures. This happened due to the success of interdisciplinary clinical teams in addressing multiple medical conditions with the use of hypnosis, such as plastic surgery or endocrine pathologies (e.g., thyroid and parathyroid surgery) (Faymonville et al., 1997, 1999; Meurisse et al., 1999). It is reported that since 1992, the Department of Anesthesia of the University Hospital of Liège has used hypnosedation in more than 9500 patients, combining hypnosis with conscious intravenous sedation and local anesthesia for both major and minor surgeries (Vanhaudenhuyse et al., 2014). Hypnosedation has proved to be a safe and effective alternative to general anesthesia in specific conditions (Tefikow et al., 2013). The advantage of hypnosedation during a surgical procedure is that the induction of hypnosis allows the patient to calm preoperative emotional distress and to be distracted from the procedure while it reduces pain and unpleasant sensations. With the active participation of the patient and with the assistance of the clinician (anesthesiologist-hypnotist), there are improvements in the peri- and postoperative comfort, faster and better recoveries, as well as better bleeding control and less fatigue (Mortazavi et al., 2010). Hypnosedation is reported also to increase relaxation by reducing intraoperative anxiety and relieving operational pain better than conventional intravenous sedation. This leads to a significant reduction in midazolam and alfentanil requirements in the surgery room (Faymonville et al., 1995). The extent that the phenomena are experienced and observed depend upon the depth of the hypnotic state and hypnotic susceptibility (Faymonville et al., 2009). As a result, only around 0.2% of the patients operated under hypnosedation require to convert to general anesthesia due to positional discomfort during neck hyperextension and lack of complete relief (Meurisse et al., 1999).

Despite the consistent advantages of hypnosedation in pain management and postoperational recovery and even

its socioeconomic implications (Faymonville et al., 1999), general anesthesia is primarily used in medical practice in a variety of applications including surgical operation with incision, dental surgery, invasive procedures, and intensive care (White, 2008). Potentially life-threatening effects of drugs used to induce pharmacologic unconsciousness include cardiovascular complications and side effects, most commonly manifested as hypotension, bradycardia, and other arrhythmias (Fulton and Sorkin, 1995), severe metabolic acidosis and circulatory collapse (Marik, 2004), and oxygenation and ventilation failure leading to abnormally elevated carbon dioxide levels in the blood and hypoxia (Hedenstierna and Edmark, 2005; von Ungern-Sternberg et al., 2007). Unlike general anesthesia, hypnosis is a very safe and well-tolerated intervention with minimal side effects during or after the hypnotic process that may impair optimal mental function. Throughout the entire procedure, the anesthesiologist talks to the patient to maintain the hypnotic state while vital parameters are constantly monitored; hence, careful observation permits the immediate detection of any sign of discomfort in the patient, to adapt conscious sedation and possibly administer local anesthesia at the operative site (Mortazavi et al., 2010). The reported negative effects include minor complaints such as dizziness, headache, or nausea during the experimental set (Coe and Ryken, 1979), unexpected or unwanted thoughts, feelings, or behaviors as a reaction to an inadvertently given suggestion (Levitt and Hershman, 1963), difficulties in awakening from hypnosis in clinical situations or resistance to suggestions (Orne, 1965), and to a lesser extent anxiety or panic (Judd et al., 1985). The hypnotic state–induced during surgery has been replicated for research purposes (Maquet et al., 1999; Faymonville et al., 2000; Vanhaudenhuyse et al., 2009a,b) to study functional brain activity of volunteers exposed to inflicted pain during hypnosis.

MECHANISMS OF HYPNOSIS TO INDUCE ANALGESIA

In some cases, specific suggestions to alleviate pain are administered during hypnosis (hypnoanalgesia). Pain is a multifaceted experience produced by the output of a specific and widely distributed neural network rather than directly by sensory input, as suggested by the body-self neuromatrix theory of pain (Melzack, 2001). Hence, pain can be modified by experience. Hypnosis-induced analgesia for disease treatment and surgical procedures must be seen in the wider context of the pain neuromatrix because its output pattern is determined by multiple factors, of which the somatic sensory input is only a part. According to the observations in PET studies, there is evidence of multiple brain areas in which hypnosis modulates cerebral responses to a variety of noxious stimuli (i.e., regions recruited in pain experience, such as anterior cingulate and insular cortex, secondary somatosensory cortex, and dorsolateral prefrontal cortex). An early study investigating the effect of hypnosis and suggestions in pain perception demonstrated peak increases in rCBF in the caudal part of the right anterior cingulate sulcus and bilaterally in the inferior frontal gyri along with rCBF decreases in the right inferior parietal lobule, the left precuneus, and the posterior cingulate gyrus (Rainville et al., 1999). This finding supports the existence of an activation pattern in an extensive set of cortical areas, primarily left-sided, involving cingulate, occipital, parietal, precentral, premotor, and ventrolateral prefrontal cortices measuring increases in rCBF (Maquet et al., 1999). In a study with no specific suggestions for pain relief, pain perception was still modulated under hypnosis. Both intensity and unpleasantness of noxious stimulations were decreased during hypnosis and it covaried with a significant activation of the right extrastriate area (Brodmann Area 19) in the occipital lobe and the midcingulate area 24a (Fig. 18.2). These findings confirm a differential modulation in midcingulate activity in response to noxious stimuli in the specific context of the hypnotic state as compared with alert states where the main effect of noxious stimulation was observed in the left insular cortex and left orbitofrontal cortex (Faymonville et al., 2000).

The analgesic effect of the hypnotic procedure is not restricted to the cerebral cortex, as multiple subcortical regions are recruited in pain experience. Hypnoanalgesia effects altering the flow of noxious signals throughout the pain neuromatrix are evident from depletions in the nociceptive spinal reflex (R-III) supporting physiologic changes in the central nervous system associated with hypnoanalgesia (Kiernan et al., 1995) similar to those related to the hypnotic or sedative effect of anesthetics such as propofol (von Dincklage et al., 2009). These findings support a role in the suppression of movement during surgical procedures. It has been suggested that there are multiple cerebral mechanisms implicated in hypnotic analgesia as observed in healthy volunteers that show reductions in the R-III nociceptive spinal reflex (involving spinal cord antinociceptive responses), but they also show reductions in pain sensation beyond changes in R-III response, with further reductions in unpleasantness regardless of hypnotic suggestibility (Kiernan et al., 1995). Seen together, this evidence indicates the presence of several mechanisms serving to prevent pain awareness once nociceptive information has reached higher brain centers.

During hypnoanalgesia, highly hypnotizable subjects show rCBF augmentation in the somatosensory cortex

and the orbitofrontal cortex as opposed to low-hypnotizable subjects (Crawford et al., 1993). Using a thulium-YAG laser to induce pain, we explored brain activation and connectivity within the pain neuromatrix when comparing painful and nonpainful stimulation (Vanhaudenhuyse et al., 2009a,b). As expected, activity within the pain neuromatrix was significantly decreased during hypnosis where both painful and nonpainful range failed to elicit any cerebral activation. Behaviorally, the effect of hypnosis on pain perception was significantly more pronounced. Further analysis of cortical interactions revealed that after painful stimulation in the left hand, the contralateral thalamus, bilateral striatum, and ACC are more activated in normal wakefulness compared to hypnosis. This activation suggests that there is a top-down modulation during hypnotic suggestion modifying the functional connectivity between the somatosensory and forebrain areas. Such direct experimental evidence in humans has served to our understanding of the modulation of brain activity and basic mechanisms of pain. Yet, a lot remains to unravel the implications of interactions between distal regions of the brain in the experience of subjective cognitive processes.

CONCLUSIONS

In the past two decades hypnosis has received extensive recognition and acceptance of its therapeutic interventions. Based on the understanding of its neurophysiologic underpinnings, research supports the efficacy of hypnosis for managing a number of clinical problems and symptoms. The pivotal role of the cingulate cortex in hypnosis provides a target for therapeutic and surgical interventions. Research evidence highlights especially the role of the subgenual portion of the ACC and the prefrontal cortex in hypnotic responses. Hypnoanalgesia targets the midcingulate region; thus, future applications aiming at this area may lead to even more effective means of truncating nociceptive processing. Such progress reinforces the notion that not only pharmacologic but also psychologic strategies for relieving pain can modulate the interconnected network of cortical and subcortical regions to alleviate the perception of pain during surgery.

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Further Reading

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