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Review

# Recent Insight on How the Neuroscientific Approach Helps Clinicians

Audrey Vanhaudenhuyse [1,*], Anne-Sophie Nyssen [2], Marie-Elisabeth Faymonville [1]

1. Algology Department of the University Hospital of Liège and Sensation & Perception Research Group from GIGA Consciousness, University of Liège, Liège, Wallonia, Belgium; E-Mails: avanhaudenhuyse@chuliege.be; mfaymonville@chuliege.be
2. Laboratory of Cognitive Ergonomics and Work Intervention and Sensation & Perception Research Group from GIGA Consciousness, University of Liège, Liège, Wallonia, Belgium; E-Mail: asnyssen@uliege.be

* **Correspondence:** Audrey Vanhaudenhuyse; E-Mail: avanhaudenhuyse@chuliege.be

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**Abstract**

Hypnosis is a modified state of consciousness widely used to decrease pain perception in research protocols and clinical practice. In recent decades, hypnosis has been increasingly proposed to patients to re-engage their resources and capacities to modulate pain and emotional distress and to improve their treatment and recovery of well-being. Neuroimaging research helps clinicians to understand better how hypnosis works in terms of brain modulation. Hypnotic suggestions dramatically influence the self and environmental consciousness networks as well as the attentional and somatosensorial networks. This explains why the subjects feel disengaged from their external surroundings combined with the modification of sensations related to their body and spontaneous thoughts. In this review, we aim to articulate the clinical and neuroimaging findings related to hypnosis in the context of perception of external (pain) stimuli. We intend to shed light on several mechanisms related to this specific modified state of consciousness that will help in designing randomized and controlled studies in the future.

**Keywords**
Hypnosis; fMRI; EEG; pain; clinical application

## Recent Insight on How the Neuroscientific Approach Helps Clinicians

Hypnosis is a therapeutic technique and an active experience focused on the abilities of the patient. Hypnosis has three main components—absorption, dissociation, and suggestibility—that go beyond simple relaxation, coping strategies, or placebo effects [1]. It includes cognitive and behavioral components that allow patients to use their mind to influence their body sensations [2, 3]. Absorption, dissociation, and suggestibility form the basis for hypnotizability, i.e. the capacity of the patient to be immersed in a hypnotic environment. The therapist may suggest this environment, but a patient may also experience it during self-hypnosis without therapeutic intervention. Precisely, hypnotizability is defined as an individual's ability to experience suggested alterations in physiology, sensations, emotions, thoughts, or behavior during hypnosis [4]. In this article, we review the evidence of brain activity modulation during hypnosis and the growing interest of clinical studies interesting hypnosis to improv conditions of patients.

## 1. Hypnosis, a Non-Ordinary State of Consciousness

During hypnosis, people may experience a range of phenomena, including increased absorption and dissociation, as well as decreased self-agency and self-monitoring, reduced spontaneous thoughts, and a suspension of space and time orientation. In previous studies, we observed that participants reported greater dissociation and absorption and reduced spontaneous thoughts during hypnosis, when compared to normal wakefulness and mental imagery [5, 6]. Although hypnosis does not have a specific neural correlate, we can quantify its influences on brain activity in different ways [7]. First, the neural activity of the two main consciousness networks, self/internal and environmental/external, markedly changes during hypnosis. During the ordinary conscious state, there is a negative correlation between environmental and self-awareness subjective rate; additionally, there is brain activation related to these two types of awareness [8]. On the contrary, during hypnosis, subjects reported higher scores for self-awareness and lower scores for environmental awareness (Figure 1) [6]. Concerning neuroimaging, the neural counterpart of subjective modulation of feelings during hypnosis is still controversial and discussed among researchers. There is reduced functional connectivity in the external control network during hypnosis, linked to environmental awareness [5, 9]; however, modulation of the self/internal control network is less clear. Some authors have found reduced connectivity in the posterior midline and parahippocampal structures of the default mode network (DMN) involved in self-related processing, combined with increased connectivity in its lateral parietal and middle frontal cortex areas [5]. Others have reported increased activity in posterior regions of the DMN as well as decreased activity in its anterior areas [10, 11]. Finally, some have shown reduced connectivity in DMN and increased activity in attentional/extrinsic systems in lateral prefrontal regions [12, 13]. Thus, there is a lack of clarity regarding the modulation of resting-state networks during hypnosis. Despite this, we can assume that hypnosis modifies the connection that an individual has with himself and all the surrounding components, by modulating self and environment awareness subjective and neural responses.

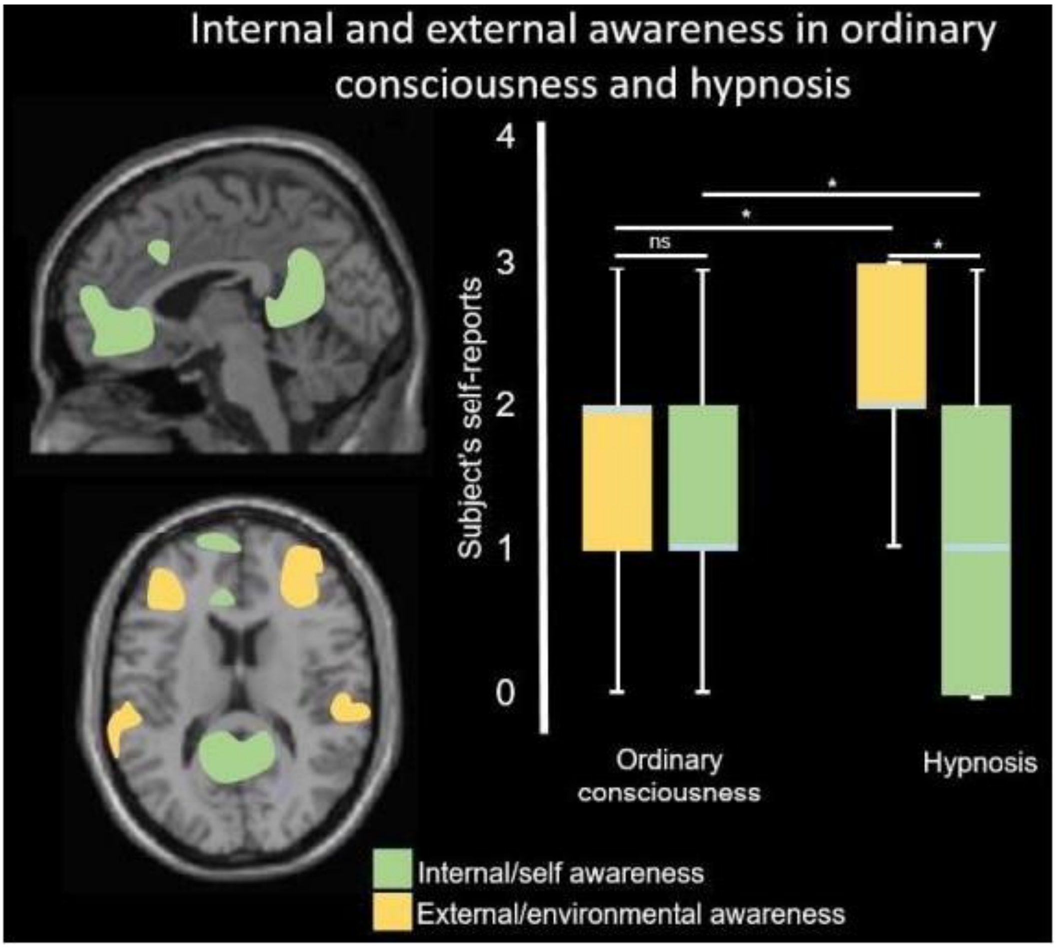


**Figure 1** Neural correlates of the two components of consciousness, internal/self-awareness in green and external/environmental awareness in yellow, during the ordinary state of consciousness. The graph illustrates reports of subjects for internal/self and external/environmental awareness during ordinary consciousness and hypnotic states (bars represent medians). *: significant at $p < 0.001$, ns: not significant. This figure was adapted from Demertzi et al. and Vanhaudenhuyse et al. [6, 8].

Researchers have used functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and event-related potential (ERP) studies to decode cognitive processes under hypnosis. EEG reports are inconsistent, making it difficult to conclude a single EEG signature of hypnosis (EEG rythms in ordinary consciousness are illustrated in Figure 2). Some studies reported an increase in alpha rhythms and theta activity, while others have found a decrease in theta activity during hypnosis (for a review, see [14]). An EEG case study on a highly hypnotizable subject reported specific decreases in beta, delta, and gamma amplitudes. This indicates increased independence of brain processes to maintain a state of alertness. The same study also reported an increase in theta and alpha amplitudes, mostly in occipital areas, reflecting the intensification of attentional processes [14]. The authors hypothesized that the subject could be in a relaxed state during hypnosis, along with a state that facilitated information processing. Others reported an increase in alpha activity, consistent with enhanced relaxation, and a reduction in visual activity, specific to the hypnotic state [15]. Some studies demonstrated a reduction in the ERP response during the hypnotic procedure, suggesting diminution of perception of stimuli, whereas other studies failed to detect such changes in ERP responses [1, 16].

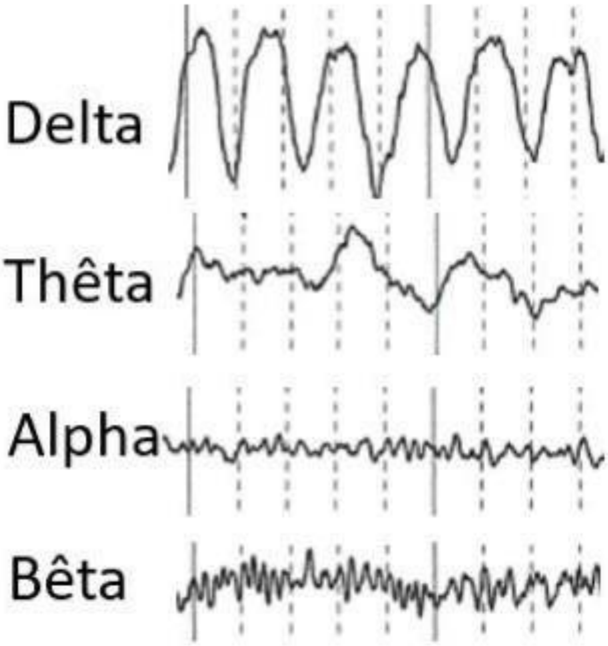


**Figure 2** Illustrative examples of EEG rhythms.

The efforts to understand hypnotic phenomena usually contrast with the responses across the levels of hypnotic susceptibility, also called hypnotizability. Hypnotizability is the individual's ability to experience suggested alterations in physiology, sensations, emotions, thoughts, or behavior during hypnosis [17]. It ranges from low to high, depending on the recruitment of attentional networks [18]. It is usually assessed by a protocol encompassing induction and suggestion, followed by evaluation of the number of suggestions an individual successfully experiences and reports after the hypnotic induction procedure [19]. Recently, we reported that it is possible to identify low and highly hypnotizable subjects, without any specific suggestion (i.e., neutral hypnosis). We achieved this by considering the dissociation score in the same way that is categorized by a traditional standardized scale [20]. Some authors demonstrated that training in self-hypnosis, relaxation, or neurofeedback improves the level of hypnotizability [21]. Structural MRI studies have revealed anatomical differences in brain structure size in frontal areas between low and highly hypnotizable subjects [22, 23]. Additionally, they revealed a larger rostrum of the corpus callosum in highly hypnotizable subjects than in subjects with low hypnotizability [24]. The corpus callosum is involved in the allocation of attention and transfer of information between prefrontal cortices. Therefore, the authors suggested that highly hypnotizable subjects might have more effective frontal attentional systems that implement control, monitor performance, and inhibit unwanted stimuli from conscious awareness [24]. However, this claim needs to be confirmed by other studies. One study reported greater grey matter volume in the medial frontal cortex and anterior cingulate cortex (ACC) combined with lower connectivity in the DMN during hypnosis. They hypothesized these to facilitate greater hypnotic depth [23]. In addition to these structural findings, a functional MRI study revealed differential processing between low and highly hypnotizable subjects. First, in contrast to the low hypnotizable subjects, those with high hypnotizability seemed to have greater functional connectivity between the left dorsolateral prefrontal cortex and the salience network; the former is involved in executive control processing, and the latter is involved in detecting, integrating, and filtering relevant somatic and emotional information [25]. However, this study lacks congruence in coupling executive and salience networks with structural correspondences in highly hypnotizable subjects [25]. Hypnotizability is positively correlated with functional connectivity between the posterior cingulate cortex and precuneus, and both the lateral visual network and the left frontoparietal network [22]. A positive correlation also exists between the executive control network and the right postcentral parietal cortex [22]. A negative correlation exists between the right frontoparietal network and the right lateral thalamus [22]. Other studies showed that the highly hypnotizable subjects recruited more of their right inferior frontal gyrus, whereas the low hypnotizable subjects recruited of their parietal cortex and ACC, during selective attention conditions (even outside of hypnosis). These regions are more connected to the DMN in highly hypnotizable subjects [18]. Based on these results, the authors hypothesized a close dialogue between internally and externally driven processes that may permit higher flexibility in attention and underlie a greater ability to dissociate in those individuals. Finally, Egner et al. displayed that highly hypnotizable subjects are characterized by an increased ACC activation during a congruent/incongruent attentional task, after a hypnotic induction [26]. They suggested that these results indicated an alteration in the attentional efficiency of their subjects as compared to baseline and low hypnotizable subjects.

Studies have revealed higher theta power in highly hypnotizable subjects, especially in the frontal and temporal areas [15, 27] as well as in the left parietal and occipital regions [28]. Also, highly hypnotizable subjects showed a significant difference in the EEG phase synchronization in the delta, theta, and beta bands (mostly in the frontal lobe), compared to medium or low hypnotizable subjects [29]. Mismatch negativity (MMN) is a negative component of ERP elicited by any change or 'mismatch' in the sequence of monotonous auditory stimuli in inattentive subjects. Studies have used MMN to evaluate the attention deficit toward auditory stimuli during hypnosis. MMN was larger in hypnosis compared to the baseline condition, reflecting enhancement of pre-attentive processing related to hypnosis condition [30, 31]. However, it was also larger in subjects with low hypnotizability, suggesting that MMN could not be attributed to distinctive hypnotic processes, despite its relation to the hypnosis condition [30]. These results can be discussed with the findings where MMN amplitude decreased only in the highly hypnotizable subjects during amusia hypnotic suggestions (i.e., inability to recognize melodies or rhythms), whereas subjects with low hypnotizability displayed no difference [32]. Others found no evidence for the effect of hypnosis on MMN amplitude in highly hypnotizable subjects [33]. The hypnotic suggestion of alexia (i.e., incapacity to read, as measured with a Stroop task) modulated the late positive complex amplitude. This amplitude was greater for congruent conditions (e.g., the word "yellow" inked in yellow) than incongruent conditions (e.g., the word "blue" inked in green) in subjects with high hypnotizability [34]. Altogether, these results show that hypnosis somehow modulates attentive auditory and visual mechanisms. However, some discrepancies appear between studies, and we need to interpret the results carefully since the number of subjects included is limited. Finally, the application of low frequency repetitive transcranial magnetic stimulation (rTMS) to the left dorsolateral prefrontal cortex enhanced subjective response to hypnotic suggestions, supporting theories postulating that diminished function in the frontal cortex is related to hypnotic response [35].

Theories about hypnosis are usually related to top-down processes and self-related mechanisms of modulation. Landry, Lifshitz, and Raz [36] proposed a meta-analysis that details processes related to these theories and gives a unique explanation of hypnosis brain mechanisms that remain challenging. However, most studies reported the involvement of the insula, ACC (involved in the salience network), prefrontal, posterior parietal areas (involved in the central executive network), medial prefrontal and lateral parietal cortices, midline structures, and parahippocampal areas (involved in the DMN). According to the authors, modulation of these brain areas is related to several processes observed during hypnosis—(a) focused attention on suggestions and absorption possibly allowing subjects to develop vivid imaginary experiences, (b) modification of sense of control related to automaticity, (c) integration of internal and external information resulting in modulation of self and environmental awareness, and (d) decrease of mind-wandering.

## 2. Hypnosis in Medicine and Surgery: the Origins of Interest in a Neuroscientific Approach

### *2.1 Hypnosis as a Support for Sedation*

The development of hypnosis as a scientific endeavor has occurred within the last two centuries. The documented use of hypnosis as an adjunct to surgery dates back to the 1830s; Jules Cloquet performed a mastectomy, and John Elliotson performed major surgical procedures with hypnosis as the only anesthetic technique. James Esdaile, a famous surgeon, worked in India and published more than 300 major surgical cases under hypnosis. He observed that the use of “mesmerism anesthesia” decreased surgical shock, improved morbidity, and decreased the mortality rate during surgery from 40% to merely 5% [37]. The medical establishment showed a great deal of hostility toward this promising surgical approach, censuring it. Almost simultaneous to Esdaile’s reports, the discovery of ether in 1846 and chloroform in 1847 suppressed the interest in psychological mechanisms of pain reduction as well as in utilizing the patient’s abilities as an influencing factor in recovery. Hypnosis subsequently became discredited, whereas inhaled anesthetic agents were rapidly adopted. During the 19$^{th}$ century, Carpenter and Tuke were among the first to draw attention to the mind’s ability to interact with the body and to alter perceptions and feelings. Likewise, Moll and Forel argued that hypnosis had important medical and therapeutic applications [38]. Since the end of World War II, interest in the clinical application of hypnosis has been waxing and waning. It was used sporadically as a complementary technique rather than an alternative to general anesthesia. Anesthesiologists paid little attention to hypnosis until 1955, when the British Medical Association accepted hypnosis in the management of acute pain [39].

More recently, there is a renewed interest in hypnosis due to the trend toward greater prominence of conscious sedation during surgery. Several studies have described the effects of hypnosis during surgery. It may be used more often in conjunction with local anesthesia and analgesics. The usefulness of hypnosis in the relief of pain was demonstrated early in the 19th century before the introduction of chemical anesthetics. Major operations, often limb amputations, were performed painlessly with “a mesmeric trance” as the only anesthetic; the term “hypnosis” was introduced later [37]. Since 1992, hypnosedation has been used to perform surgeries in Liège, Belgium. Hypnosedation is a technique combining hypnosis with light conscious intravenous sedation and local anesthetic drug [40]. The University Hospital of Liège was a pioneer in elaborating retrospective and prospective randomized studies comparing general anesthesia and hypnosedation in a surgical setting [40–46]. Firstly, it is important to note that hypnosis should be considered as a tool to be used with discrimination in surgical settings, only when circumstances are appropriate. The exclusion criteria for hypnosedation are psychopathology, deafness, and allergies to local anesthetics. Adherence and motivation of the patient, surgeon, and all the medical staff present during the surgery are also of the highest importance for this procedure. Hypnosedation can be used in various situations—thyroid surgery, endovascular procedures, breast and prostate biopsy, colectomy, hysteroscopic placement of implants for sterilization, tooth extraction, skin tumor removal, childbirth, glioma surgery, and burn dressing changes [9]. This technique is associated with improved peri- and post-operative comfort as well as with better conditions during the performance of surgery compared to general anesthesia. Studies revealed that hypnosedation is associated with reduced anxiety, emotional distress, pain, and nausea, as well as diminished intraoperative requirements for anxiolytic and analgesic drugs. Some authors also demonstrated a faster recovery with a significant decrease in the delay before restarting professional activity [42]. A recent study highlighted that prostate cancer patients receiving brachytherapy under hypnosedation reported reduced need for medication, shorter duration of urinary catheter use, and quicker recovery compared to patients receiving the therapy under general anesthesia [47]. In addition, a non-randomized study showed the potential benefits of hypnosedation on post-mastectomy chronic pain [48]. Meta-analysis highlighted several benefits of hypnosis in surgery. It was an effective adjunctive technique for a wide variety of surgical procedures. The patients in hypnosis groups had better outcomes than other patients. There were no differences between the methods of hypnotic induction. Positive effects were observed for emotional distress and medication consumption [49, 50]. In addition, a hypnotic suggestion for pain relief was equally effective in reducing pain in both, clinical and experimental setups. Therefore, it may be an effective and safe alternative to pharmacological intervention [51, 52]. Finally, a recent meta-analysis highlighted the analgesic effect of hypnosis for acute pain perception, efficacy modulation due to the subject's hypnotic suggestibility as well as the use of direct analgesic suggestion. It also revealed that hypnotic intervention could deliver meaningful pain relief for most people and may be an effective and safe alternative to pharmacological intervention [52].

### *2.2 Hypnosis During Childbirth and Labor*

The history of hypnosis in the clinical setting is notable for its early adoption in procedures relating to childbirth. The 20$^{th}$ century witnessed several such case reports in Europe, peaking in the 1950s. In this context, hypnotic suggestions focused on increasing feelings of safety, relaxation, and comfort, reframing the experience from one of pain to one of achievement, and potentially developing sensations of anesthesia such as numbing [53]. However, improvements in pharmacological analgesia in obstetric care in the 1960s led to the decline of hypnosis. Fortunately, in the past decades, various complementary medicines, including hypnosis, have gained renewed popularity for assisting women during labor and childbirth [54]. Hypnosis assisted women in coping with physical and psychological symptoms during pregnancy, labor, and the postpartum period. In particular, it can lead to decreased nausea and hyperemesis gravidarum, reduced epidural and surgical intervention, pain relief, shorter length of labor, increased postpartum psychological well-being, and decreased postpartum depression [55]. A randomized controlled study conducted on over 1000 women demonstrated a significantly better childbirth experience, including decreased pain, in women who learned self-hypnosis compared to groups undergoing relaxation and standard care [56]. During pregnancy, hypnosis aided to reduce stress, anxiety, depressive symptoms, and nausea and vomiting [55, 57, 58]. These studies highlight that non-pharmacological approaches, such as hypnosis, can facilitate enhanced feelings of satisfaction, competence, and control in women. A meta-analysis of randomized trials with a total of 2954 women showed that hypnosis may reduce the overall use of analgesia during labor, but not epidural use. Also, it did not find clear differences between women using hypnosis and those who did not with respect to satisfaction with pain relief and a sense of coping with labor or birth [54].

### *2.3 Hypnosis to Relieve Pain in Severely Burned Patients*

Hypnosis has also significantly benefited patients with severe burns in the alleviation of pain and anxiety, particularly during care procedures (i.e., removal of dressings, washing, debridement, and application of new dressings) [59]. While pharmacological approaches are recommended as a first-line treatment for procedural pain, studies reported that some patients did not benefit from medication or still experienced significant pain despite medication use [60]. Studies demonstrated that pain and anxiety perception decreased during dressing changes when hypnosis was used in adult and pediatric patients [61, 62]. A recent randomized, double-blind, controlled study evaluated the efficacy of hypnosis in significantly reducing the quality of background pain (i.e., burning or throbbing discomforts which affect patients daily while resting) and pain anxiety (i.e., pain-related anticipatory anxiety) in burned patients [63]. When integrated into their pain management procedures, hypnosis also improved opioid efficacy and wound outcomes of burned patients, while reducing hospital costs [64]. In addition, the integration of this technique in care significantly reduced the stress of nurses, when facing patients who are in pain, disoriented, agitated, and anxious during post-burn care [65].

### *2.4 Hypnosis to Manage Chronic Pain*

Hypnosis may be effective in reducing short- and long-term headaches in migraine sufferers [66]. In addition, self-hypnosis combined with self-care activities may benefit chronic pain patients, in a variety of biological, psychological, and social dimensions. When compared with physiotherapy or psychoeducation treatments, six sessions of self-hypnosis/self-care treatment decreased pain intensity, pain interference, anxiety, and depression with an improved quality of life [67]. Self-hypnosis/self-care intervention in chronic pain patients led to significant modifications in coping strategies due to the observed benefits [68]. A meta-analysis focused on hypnosis effect in fibromyalgia (6 controlled trials; 239 patients) concluded that hypnosis is effective in relieving both pain and sleep problems [69]. Another meta-analysis (12 clinical studies; 669 patients) revealed that hypnosis is moderately more efficacious than standard care or psychological intervention, specifically for adult patients not suffering from headaches [70].

### *2.5 Hypnosis in Oncology*

In 2017, a meta-analysis concluded that hypnosis was not rigorously studied with randomized, controlled trials in oncology [71]. This pushed some researchers to conduct robust studies to assess the potential of hypnosis in this particular clinical context. Initial studies in oncological patients showed that hypnosis is more efficient in relieving pain than other interventions, such as yoga or cognitive-behavioral therapy [72–74]. Hypnosis in oncology has also shown efficacy in helping patients to cope with sleep disturbances and management of stress, anxiety, and grief [75]. Besides, the gender of patients could influence these positive effects, although these observations need to be tested on a larger population [76]. Finally, a recent pilot study demonstrated the feasibility and personal interest in learning self-hypnosis for children with cancer and their parents [77].

### *2.6 Hypnosis and Dental Care*

The field of dentistry showed an increased interest in the hypnosis much later. The technique can be used to reduce anxiety in phobic patients as well as to reduce pain and anxiety during dental surgery. Case reports and controlled studies have displayed several positive effects of hypnosis in dentistry—prevention of avoidance behavior and lack of dental treatment, reduction of extreme fear, anxiety, and pain, reduction in bleeding during tooth extractions, and more effective healing of wounds [78–81].

There are a plethora of clinical reports on the beneficial effects of hypnosis on patients. Despite this, scientists need neurophysiological studies to shed light on the central mechanisms of hypnosis. In the further sections, we summarize the literature to explain how this modified state of consciousness allows individuals to modify their perception of external stimuli.

## 3. Hypnosis to Alleviate Acute Pain—A Neurological Perspective

Improvements in functional neuroimaging have allowed researchers to articulate objective evidence of hypnotic procedures to reduce pain. Painful stimuli activate several brain regions called the pain matrix—the primary (S1) and secondary (S2) somatosensory cortices, the insular cortex (IC), the ACC, and thalamic nuclei—modulating the perception of pain [82]. There are numerous, widely heterogeneous ways to study pain reduction during hypnosis. Methods used to produce painful simulation include high temperature, laser, and nerve stimulation; methodologies used include positron emission tomography (PET) and fMRI; protocols employed are presence or absence of baseline, a hypnotic suggestion for increased or decreased pain, and mental imagery. Various studies have proven that hypnosis has a direct effect on the pain neuromatrix. Painful stimulation in a normal, alert state resulted in brain activation within a network encompassing cortical and subcortical brain areas, namely, ACC, premotor, dorsolateral, prefrontal, primary somatosensory and bilateral insular cortices, thalamus, bilateral striatum, and brainstem. However, the same painful stimulus perceived under hypnosis failed to elicit any cerebral activation [83]. The modulatory effect of hypnosis was shown to be mediated by an increased modulation of the ACC and a cortical and subcortical network, encompassing prefrontal/superior frontal gyrus, insular, and pregenual cortices, pre-SMA, thalami, striatum and brainstem in the context of hypnosis [84–87] (Figure 3). In addition, there exists a hypnosis-related increase in functional connectivity between the primary somatosensory cortex (S1) and the anterior insular and prefrontal cortices [83]. Other studies reported that only specific suggestions of increased or decreased unpleasantness changed the pain ratings, in association with modulation of the ACC activity and modulation of pain unpleasantness [86]. A meta-analysis of functional neuroimaging studies of pain perception under hypnosis identified that analgesic suggestion is associated with an increase in the activation of right lateralization in the ACC and insula and a decrease in the midline thalamic nuclei [88]. Using specific hypnotic-focused analgesia (i.e., local analgesia produced during deep hypnosis by focusing attention on a mental image of the absence of pain [89]), a recent study showed that during hypnosis the sensory component of pain (related to S1, S2, insula, and parietal operculum) was reduced more than the affective component (related to ACC, amygdala, hippocampus, hypothalamus and temporal cortex)[89]. Other studies demonstrated additional effects of hypnosis modulation on the affective component of pain. This discrepancy could be explained by the script used for the suggestions of analgesia. Conversely, other studies showed that suggesting painfulness in the absence of actual pain stimulation activates brain areas associated with activation of the brain's pain circuit, similar to real pain stimulation [90, 91].

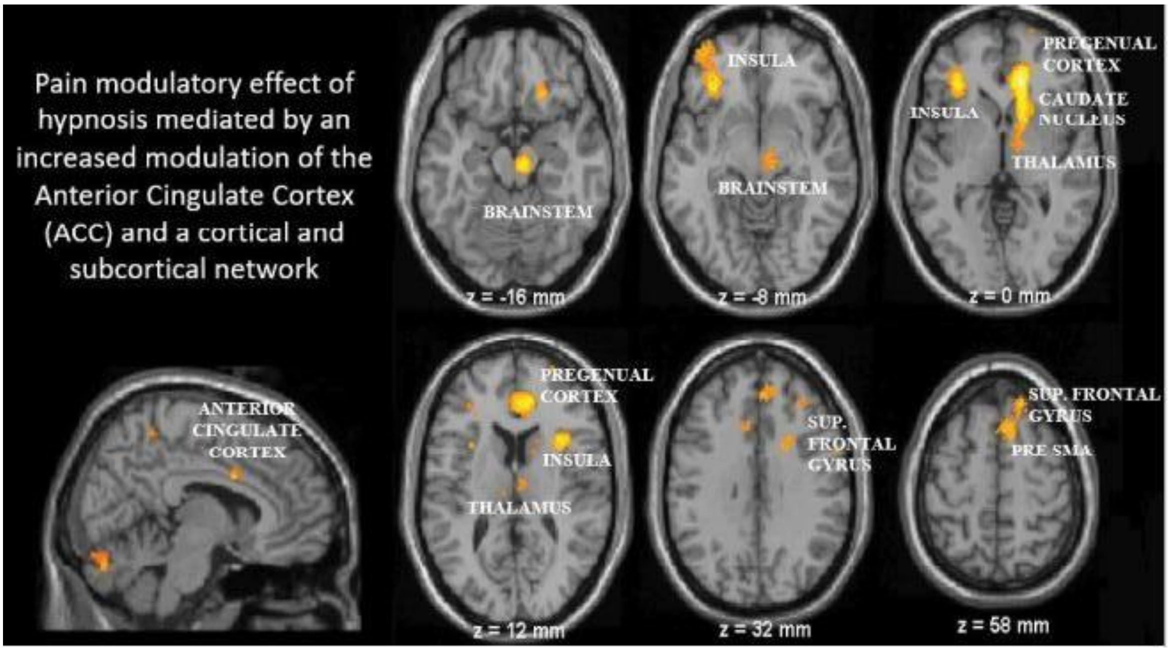


**Figure 3** The pain modulatory effect of hypnosis is mediated by an increased modulation of the anterior cingulate cortex and a cortical and subcortical network, encompassing the prefrontal/superior frontal gyrus, insular, and pregenual cortices, pre-supplementary motor area (pre-SMA), thalami, caudate nucleus, and brainstem. This figure was adapted from an earlier study [92].

Pain modulation during hypnosis can be understood concerning the specific role of some brain areas involved in pain perception processing. Firstly, studies have shown that the ACC is related to coding of the intensity of noxious stimulation, opposing pain/avoidance and reward/approach functions, somatosensory processing, fear, and the anticipation of pain [7]. Secondly, there is reported increased functional connectivity during hypnosis between the mid-cingulate cortex, thalamus, and brainstem [87, 93]. This might be related to pain-relevant arousal or attention mechanisms. Thirdly, the reported decreases in premotor cortex activation in hypnosis suggests that hypnosis may diminish anxiety, defensive, and emotional reactions to pain by reducing activation of both cortical and subcortical areas [94]. Besides, the increased modulation of activity in the insula is related to its role in the pain affect and pain intensity coding [95]. Finally, frontal activity modulation may reflect disruption in the cognitive attentional, appraisal, and memory systems that can influence the perception of environmental stimulation during hypnosis [83, 84].

EEG and ERP studies are key to understand sensorial and pain processing during hypnosis. They allow recording of the fast succession of brain events associated with the administration of sensory stimuli. A study tested whether hypnosis affects the early (sensory processing) or the later (affective integration) stages of sensorial processing. The researchers found reduced activity of the early (N20) and the late (P100, P150, P250) components in brain areas including S1 (N20), S2 (P100), right anterior insula (P150), and cingulate cortex (P150/P250) [96]. They suggested that hypnosis modulation of pain perception is reflected in both, somatosensorial processing with decreases in N20 (i.e., first stages of pain cerebral processing) and affective and conscious processing with decreases in P150 (related to somatosensory conscious perception), P100 (prerequisite for consciousness) and P250 (later stage of somatosensory perception associated with the affective integration of the stimulation). Other studies also reported a decrease in amplitude for the P250 component during hypnosis and painful stimulation [97]. Another study showed that a hypoalgesic hypnotic suggestion induced a decrease in amplitude in highly hypnotizable subjects. Similarly, it reported an increase in amplitude by a hyperalgesic suggestion of both, N140 (mainly in left frontal and frontocentral areas) and P200 (left frontocentral, central, and bilateral centroparietal and parietal areas) waves [98]. These results could be explained by an enhanced capacity of subjects to focus their attention to form the mental images designed to reduce/amplify pain sensations during hypo/hyperalgesia. Finally, magnetoencephalography (MEG) during hypnosis revealed a reduction of activity in the beta band around 214–413 ms post non-painful stimulus mainly in the right insula, combined with a reduction in the alpha band around 253–500 ms in the left inferior frontal gyrus [99].

Regarding hypnosis for pain modulation, higher hypnotic suggestibility correlated with greater relief from hypnotic intervention. Although, subjects with medium suggestibility also obtained significant relief from hypnosis [100]. We need to note that only 20–30% of individuals score either high or low in hypnotizability [36]. Thus, high hypnotic suggestibility is not necessary for successful hypnotic pain intervention.

Together, these results may indicate that brain modulation reported during hypnosis could reflect an alteration of afferent somatic perceptions in the process of cognitive-based pain control. They also suggest that highly hypnotizable subjects may have a specific capacity to enhance disengagement regarding sensorial information.

## 4. Neuroimaging to Explain the Clinical Benefits in Patients

A growing body of literature is focusing on the brain activity counterparts to clinical reports of patients who benefited from hypnosis. As discussed earlier, patients with different etiologies reported subjective positive effects of hypnosis. PET studies in chronic pain patients under hypnosis reported modulation of activity in the bilateral cingulate gyrus, right thalamus, left inferior parietal cortex, bilateral PCC, anterior cingulate gyrus, and insula [101, 102]. An fMRI study in fibromyalgia patients highlighted greater activation in the cerebellum, anterior ACC, anterior and posterior insula, and inferior parietal cortex correlating with reported changes in pain after hypnotic suggestions [103]. A similar study in patients with temporomandibular disorder reported activation in the posterior insula related to hypnotic suggestions of pain reduction [104]. With a hypnotic suggestion, pain matrix activation decreased in fibromyalgia patients similar to healthy control subjects [105]. ERP studies illustrated how hypnosis modulates brain function in chronic pain patients. First, in chronic pain patients under hypnosis, the differences in ratings of pain intensity and unpleasantness were accompanied by decreased N2–P2 components [106]. A pilot study in multiple sclerosis patients with chronic pain supported an interest in additional techniques to enhance responses to hypnosis treatment. This was in addition to the enhanced benefits of hypnosis treatments observed with neurofeedback and mindfulness on subjective variables, such as pain intensity, pain interference, pain acceptance, sleep, and depression. Hypnosis, combined with other techniques, impacted the EEG brain responses, mostly delta, theta, beta, and gamma rhythms [107]. Some authors proposed to study electrical brain activity before hypnotic treatment to predict its usefulness in modulating pain in spinal cord injury patients. Theta activity immediately before treatment was positively associated with response to hypnosis, with higher levels of it prospectively predicting subsequent pain reduction with the hypnosis procedure [108]. These results have implications for enhancing response to pain treatment by either better patient/treatment matching or influencing brain activity before treatment.

Few neuroimaging studies have been conducted with other populations of patients. People who suffer from dental phobia display symptoms that make dental treatments difficult or impossible; hypnosis is, therefore, used as an alternative intervention. An fMRI study reported that during hypnosis, dental phobia patients showed a significantly reduced activation in the left amygdala, bilateral ACC, insula, and hippocampus (involved in fear processing) [109]. Researchers observed patients undergoing a mastectomy and sentinel node biopsy with a combination of self-hypnosis and local sedation (i.e., hypnosedation). They reported complex changes in brain electrical activity measured with the bispectral index (BIS) [110] and an increased EEG activity in occipital regions related to visual imagery [111].

## 5. Conclusion

In the context of clinical practice, there is growing evidence of interest in hypnosis for pain management in various populations of patients. Although higher hypnotic suggestibility correlates with greater pain relief, people with medium suggestibility also manage pain better through hypnosis. Regarding the small proportion of the population (20–30%) considered having low suggestibility, there are no guidelines suggesting a clear strategy to be adopted. In our clinical experience, we never test hypnotizability before practicing hypnosis in either surgical contexts or the management of chronic diseases. Thus, we conclude that even low hypnotizable patients can gain benefits from hypnosis. The specific context of surgery allows anesthesiologists to increase the comfort of patients by administrating intravenous analgesic drugs in addition to hypnosis suggestion. Until now, no one has investigated whether low hypnotizable patients require increased analgesic drugs. However, additional non-pharmacological techniques, such as hypnosis combined with virtual reality, could potentially improve the efficacy of hypnosis for such patients. Studies are needed to validate this hypothesis in clinical practice. Neuroimaging research drastically increases our understanding of how hypnosis modulates pain and emotional distress in these patients. Hypnosis modifies brain activation as well as brain functional networks. These networks may be involved in self and environmental awareness (DMN and external control network), attentional processing (dorsolateral prefrontal cortex), anxiety processing (amygdala), and sensorial external stimulation (somatosensorial cortices, insula, ACC). These observations may be the first pieces of a rather intricate puzzle of the complex mind-body relationship mechanisms. Through these first studies, hypnosis has acquired a legitimate position in academic and medical fields, as a recognized modified state of consciousness with a specific, complex neural signature. Future research should explore more robust studies designed with randomized and controlled paradigms on larger cohorts to characterize the complexity of this social, cognitive, neurobiological, and interpersonal state of consciousness and its clinical applications.

Finally, a few clinical studies have assessed the effects of the type of hypnotic suggestion on the subjective feelings of individuals. One study reported that hypnosis combined with analgesia suggestion was more effective than hypnosis combined with relaxation suggestions in decreasing pain in 45 chronic pain patients [112]. Globally, positive suggestion to improve comfort leads to decrease in pain [113]. But, we still need comparative studies on large cohorts of patients to clarify which suggestions are more effective than others in the clinical context. Notably, some experimental studies conducted with healthy subjects demonstrated that the type of suggestion could differently affect pain perception [95, 114]. Also, the current research lacks consistent testing of the effects of hypnosis on resting-stage brain networks. Some researchers used pleasant autobiographical memories as a hypnotic suggestion [5, 115], while another used neutral hypnosis [10]. Thus, research in hypnosis lacks rigorous studies using large samples and randomized, controlled designs. Studies of this kind, comparing different types of hypnotic suggestions, would help us understand how different types of suggestions affect the global consciousness status, subjective reports, and pain perception in healthy volunteers and patients.

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## Author Contributions

A.V. wrote the manuscript. M-E.F. and A-S.N. reviewed the reviewed the manuscript and contributed to the editing of the manuscript.

## Competing Interests

The authors have declared that no competing interests exist.

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