Assessing the Relationship Between Proposed Psychological and Neurobiological Mechanisms for the Placebo Effect and Hypnosis: A Review

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Abstract

**TITLE:** Assessing the Relationship Between Proposed Psychological and Neurobiological Mechanisms for the Placebo Effect and Hypnosis: A Review

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**Purpose:** Mental processes, such as those involved in the placebo effect and hypnosis, can lead to clinical improvements like analgesia. Comparing the psychological and neurobiological mechanisms behind the placebo effect and hypnosis can help clarify the relationship between these processes.

**Methods:** A targeted Medline and Google Scholar literature review of publications written in English was performed, using the following key words: “placebo mechanisms,” “placebo neurobiology,” “hypnosis mechanisms,” “hypnosis neurobiology,” “hypnosis theories,” from 1945 to January 2016.

**Results:** The placebo effect and hypnosis potentially share several psychological mechanisms, including expectations, evaluation of physical and interpersonal context, anxiety reduction, motivation, reward, and somatic focus. Neurobiologically, placebo and hypnotic analgesia have been shown to modulate key areas of the “pain matrix,” including the prefrontal cortex, the anterior cingulate cortex, the insula, the somatosensory cortices, the thalamus, and the midbrain.

**Conclusions:** Given the several shared psychological and neurobiological mechanisms underlying the placebo effect and hypnosis, they may at times appear to be the same. However, the variety of placebo effects and hypnotic responses differ sufficiently in psychological, phenomenological, and neurobiological ways to suggest that they are different mental processes. These findings have important clinical and research implications.
Table of Contents

Section 1: Introduction

Section 2: Student Role

Section 3: Methods and Structure of Paper

Section 4: Results

• Review of Neurobiology of Pain

• Review of Mechanisms of the Placebo Effect
  • Definition and History
  • Clinical Evidence
  • Proposed Mechanisms

• Review of Mechanisms of Hypnosis
  • Definition and History
  • Clinical Evidence
  • Proposed Mechanisms

Section 5: Discussion

• Comparative Analysis of Proposed Mechanisms for the Placebo Effect and Hypnosis

• Evaluation of Gaps in the Literature, Recommendations for Further Study, and Implications for Clinical Trial Design

• Clinical Implications

• Limitations

• Conclusions

• Acknowledgements
Introduction
The scientific advances of the last several decades have revolutionized our understanding of how mental processes can contribute to clinical improvement or to clinical worsening. Critical to this advancement has been a better understanding, through psychology and neuroscience, of the prevalence and mechanisms of placebo effects in clinical and experimental contexts. Simultaneously, we have further elucidated the mechanisms through which clinical hypnosis leads to clinical improvement. Although comparisons of the mechanisms of the placebo effect and hypnosis have been done in the past, to my knowledge there has not been a review comparing the psychological and the neurobiological mechanisms of the placebo effect and hypnosis in almost a decade. Given the research advances that have occurred since then, there is a need for an updated review of these two fields. If the placebo effect and hypnosis both reflect “top-down” mental processes that contribute to health and wellness, how are their proposed psychological and neurobiological mechanisms related? Answering this question has significant clinical and research implications for how we understand and treat various kinds of illnesses and how we promote healing in medicine.

Student Role
I performed the literature review and wrote the entire manuscript. My mentors advised me along the way, providing me with reading suggestions, ideas to pursue, and organizational suggestions. They also kindly reviewed the manuscript, gave me valuable feedback, and made edits.

Methods and Structure of Paper
I performed a targeted Medline and Google Scholar literature review of publications written in English, using the following key words: “placebo mechanisms,” “placebo neurobiology,” “hypnosis mechanisms,” “hypnosis neurobiology,” “hypnosis theories,” from 1945 to January 2016. I also expanded my literature review by reading relevant citations from the articles I found through my search criteria. In addition, I consulted various experts in the field for suggestions on papers I should read, including my two mentors for this project: Ted J. Kaptchuk and Arthur J. Barsky.
Given that most of the work in the fields of the placebo effect and hypnosis has been done in the areas of pain and analgesia, my review will mostly focus on mechanisms relating to these conditions. As a result, I will start by briefly reviewing our current understanding of the neurobiology of pain. For each of the two processes that I am reviewing, I will then define concepts and provide a brief history, review clinical evidence of their effect, and discuss their proposed mechanisms. This will be followed by a comparative analysis of the proposed mechanisms, as well as a discussion of implications for research and clinical practice.

Results

Neurobiology of Pain
Our understanding of pain has improved significantly during the last century, as we went from understanding pain as a simple transmission of nociceptive information to seeing it as a complex process involving sensory-discriminative, affective-motivational, and cognitive-evaluative components.(1) Pain has been theorized to depend on the state of the nervous system, “which depends both on past experiences and on the cognitive and emotional processes of the organism at the time of sensory input.”(2) Neurologically, nociceptive information is transmitted from the periphery via nerve fibers to the dorsal root horn of the spinal cord, then to the thalamus via the ascending spinothalamic tract, and subsequently to various brain regions like the primary (S1) and secondary (S2) somatosensory cortices, the anterior cingulate cortex (ACC), the insula cortex, and the prefrontal cortex (PFC).(3) Through neuroimaging studies like fMRI and PET, the above brain regions have come to be known as the “pain matrix”—a series of brain regions that activate during pain.(4)

The prefrontal cortex, and the “dorsolateral aspect (DLPFC) in particular, acts to maintain and appropriately update internal representations of goals and expectations, which modulate processing in other brain areas.”(5) The ACC is “thought to regulate or modulate the interaction between cognition, sensory perception and motor control in relation to changes in attentional, motivational, and emotional states.”(6) The insula receives information from the thalamus, somatosensory cortex, and the amygdala, playing a key role in pain affect and in coding the intensity of pain.(6) The prefrontal cortex connects to the midbrain periaqueductal gray (PAG), which also receives signals from the amygdala, hypothalamus, and nucleus accumbens. The
PAG, in turn, sends signals through the rostroventral medulla (RVM) to the spinal cord, being an important part of the network involved in the descending modulation of pain.(7)

**Placebo Effect**

**Definition and History**

Placebos are inert substances or treatments that are given in a specific context and that by definition lack inherent properties that directly affect physiology. Traditionally, the term *placebo response* has been used to describe the clinical effect observed in an individual following the administration of a placebo, whereas the term *placebo effect* has been used to describe the overall effect and phenomenon of individuals experiencing clinical improvement following the administration of a placebo. However, the evolution of the field of placebo studies has led to an expansion of these definitions beyond the effect of the simple administration of a placebo and into the broader clinical effect of the therapeutic encounter.(8) The physical, interpersonal, and historical contexts in which medical interventions are delivered—ranging from the pills, instruments, and words used to the therapeutic relationship and the patient’s own treatment history—are now seen as the broader intervention leading to the placebo effect.

The word and concept of *placebo* has a fascinating history that informs how its modern understanding came to be. A Latin word meaning “to please,” the word *placebo* has early roots in St. Jerome’s translation of a line in Psalm 116 as “I shall please (*Placebo*) the Lord in the land of the living.” The association of the word *placebo* with fake or inert interventions began in medieval times, when paid mourners would sing Psalm 116 and would be called “placebos” because of their false mourning. (9) By the 16th and 17th centuries, the concept of using placebo or “fake” controls emerged during investigations of demonic possessions via the use of “real and effective” vs “fake” holy objects to identify those truly possessed by their responses to these objects.(10) In the 18th century, a commission led by Benjamin Franklin to investigate the existence of the “animal magnetism” proposed by Mesmer designed placebo-controlled experiments. In these experiments, patients would be exposed to “mesmerized” objects without being told and to “non-mesmerized” objects while being told that they were mesmerized, in the fashion of crossover studies. While the Franklin commission did not find evidence of animal
magnetism, they concluded that the clinical effects observed from mesmerism were due to the effects of the imagination. (10)

It is therefore not surprising that with the rise of modern medicine in the late 19\textsuperscript{th} and early 20\textsuperscript{th} centuries, placebos were considered inert treatments commonly and deceptively given to patients “to please” them rather than to actually physiologically benefit them, or as aids in differentiating patients with “true” illness from those with psychological troubles. It was not until the post-WWII era with the rise of the double-blind randomized controlled trial (RCT) that placebos began to be seen as efficacious interventions with unknown physiological mechanisms that deserved scientific investigation. (11)(12) Since then, much has been learned about the psychological and neurobiological mechanisms underlying the placebo effect, which I will review in this paper.

**Clinical Evidence**

Given the exponential growth of RCTs since the mid-20\textsuperscript{th} century, significant treatment responses in placebo-control arms of such trials have been documented across a vast array of interventions targeted at diverse clinical conditions. While many have equated these treatment effects to the placebo effect, these in reality represent a conglomerate of factors such as natural history, regression to the mean, methodological biases (e.g. response bias), and the actual placebo effect. (13)(14) To separate and quantify the placebo effect, an additional “no-intervention” control arm must be added to trials, such that the difference between the placebo- and no-intervention-control arms equals the placebo effect. Trials that have been designed in this way have shown significant placebo effects in conditions like depression, Parkinson’s disease, chronic pain, and asthma. (7) Placebo effect sizes range from small to matching the effect of drugs and interventions, and have been implicated in improving quality of life, decreasing disability, and even decreasing mortality in the case of cardiovascular disease. (7)(15)(16) Overall, compared to the therapeutic effects of active medications, placebo effects tend to last less, be more variable across people, and have lower average effect magnitude. (13) Moreover, placebo effects on autonomic, immune, and endocrine systems have been documented and genetic determinants of the placebo response are beginning to be understood. (7)(17)
**Proposed Mechanisms**

1. **Psychological Mechanisms**

The most commonly proposed and studied psychological mechanisms for the placebo effect are expectancy and conditioning, along with a variety of modulating processes such as reward, desire, somatic focus, anxiety reduction, therapeutic alliance, social observational learning, and learning from prior clinical experiences. The overall consensus in the literature is that several of these processes likely interact with each other, often in a way that influences expectations and subsequently the placebo response.

Expectancy has been defined as “the experienced likelihood of an outcome or an expected effect.”(18) In the medical setting, expectancy manifests as the patient’s perceived likelihood of benefit derived from environmental stimuli (e.g. medical office setting, instruments, etc) and interpersonal interactions (e.g. therapeutic alliance, verbal suggestions, etc).(14) Personality traits or mood states affecting factors such as baseline optimism or skepticism in face of an uncertain benefit may also modulate the strength of people’s positive expectations in response to the aforementioned external stimuli.(19) Overall, this anticipation of improvement can subsequently manifest as clinical improvement. Nowhere has this been demonstrated as thoroughly as in the study of how expectation of pain relief improves experimental and clinical pain.(20) (21)

The effect of expectation seems to have a dose-response relationship to pain improvement, as shown by Price et al in a study demonstrating increasing analgesia with increasing verbal suggestion of placebo strength (control, weak, strong).(22) In addition, a clinical study by Collo et al showed that altering the expectation of post-operative patients about the strength of the pain medication being received intravenously changed the demand for pain medications, with less demand the stronger the suggestion of analgesic strength.(23) A few studies that have tried to quantify the effect of expectancy on placebo analgesia have calculated it be responsible for 25-49% of the variance in post-placebo pain.(24)(22)

Other studies have explored the interaction between desire and expectation and have found the interaction to be a significant predictor of placebo analgesia in some conditions.(25)(26)(27)
Desire can be thought of as the degree to which someone wants a certain outcome (e.g. pain relief); this is different, albeit related, to the degree to which someone expects that a certain intervention is going to work (expectancy). Longer, more intense types of experimental pain (e.g. ischemic arm pain), which in theory produce a larger desire in the person to be relieved of the pain than brief low-intensity pain, lead to strong placebo effects. The interaction between desire and expectation is put forth by Price and Barrell’s desire-expectation model, although Geers et al propose a similar model positing that placebo responses are more likely when the confirmation of an expectation meets a goal the patient has.

Some have proposed that the expectation of a positive outcome is a form of reward, with neurobiological evidence to substantiate the claim. In this sense, the positive psychological feelings associated with rewards may be partially responsible for the reported subjective clinical improvement seen with placebos.

Kirsch points out that expectations carry a degree of specificity that is required to explain the range of placebo responses in a way that general processes like hope, faith, anxiety reduction, rapport, trust, or generalized endorphin release cannot do alone. In a study that illustrates this, Kirsch et al applied a painful stimulus to parts of the body that were untreated and treated with a placebo anesthetic, and obtained placebo responses specifically in treated parts. Given these findings, Kirsch argues that any global processes (e.g. change in affect) cannot alone account for placebo responses.

Beyond expectancy, classical conditioning has been proposed as a mechanism that explains unconscious contributors to the placebo effect. Patients are assumed to have prior experiences where they associated an unconditioned stimulus (e.g. getting an effective medication) with a conditioned stimulus (e.g. overall context of therapeutic encounter, such as receiving a pill or injection from physician in a white coat in a hospital). When presented with the conditioned stimulus again, this time with a placebo treatment, the patient develops a conditioned response (e.g. clinical improvement with placebo). In a classic study by Kirsch and Montgomery, however, the effect of conditioning was mediated by the subjects’ expectations. Although there is a role for conditioning in the placebo effect, it is likely not exactly the classical,
Pavlovian type. The increase in the magnitude of placebo analgesia in over 10 extinction trials does not support a classical conditioning stimulus substitution model. (24) Furthermore, some studies have shown that when subjects have outcome expectations about a treatment that contradict the unconditioned response (i.e. the true effect of the drug), expectations predominate. (31) In cases involving conditioning with medications that affect immune and endocrine processes, however, conditioning seems to overpower the expectations of subjects. For example, some conditioning studies have shown that placebos can result in changes in immune (interleukin-2 and interferon gamma) and endocrine factors (growth hormone) after conditioning with cyclosporine A and sumatriptan, respectively. (33)(13) These changes occurred irrespective of subjects actively expecting or not expecting these changes to take place.

In addition to conditioning, various researchers have proposed an effect for other forms of learning on the placebo response. A person’s memories of experiences of illness, treatment, recovery, or failure to recover have been shown to influence his or her propensity to have a placebo response. (34) These memories represent a form of learning and influence the expectations that a future treatment will be effective. (13)

Individuals do not learn only from their own experiences, but also from observations of the social environment. In an experiment, subjects who witnessed someone else have an analgesic effect from a placebo intervention had a placebo response comparable in magnitude to the placebo response of subjects who had been personally conditioned to experience analgesia. (35)

While a focus on how others react can influence an individual’s placebo response, so can a focus on his own bodily sensations after receiving a placebo. This has often been called somatic focus or self-monitoring, and it has been postulated to be at work when an individual pays attention to signs or symptoms of clinical improvement and interprets these as proof that the placebo treatment is working. (18)(36) Whether these signs or symptoms are actual new changes or simply “background noise” of normal bodily sensations that get misattributed as treatment effects, they can lead to a “self-confirming feedback” that can strengthen factors like expectancy and the overall placebo response. (8)(18)
II. Neurobiological Mechanisms

Our understanding of the placebo effect has been greatly advanced by scientific inquiry into its biological mechanisms, especially in the areas of pain and Parkinson’s disease. In my review I will integrate pharmacological mechanistic studies and more recent neuroimaging studies showing neurobiological correlates of the placebo effect. Overall, studies across a variety of placebo interventions and illnesses have shown that there isn’t a single biological mechanism for the placebo effect, but different ones depending on the circumstances.(13)

The best understood mechanism for the placebo effect is its activation of the endogenous opioid system in cases of placebo analgesia. Levine et al published a pivotal study in 1978 that showed that placebo analgesia could be reversed by the opioid antagonist naloxone, launching a new era of scientific study of the placebo effect.(37) Given that not all cases of placebo analgesia were completely reversed by naloxone, Amanzio and Benedetti designed an experimental ischemic arm pain study investigating the reversibility of placebo analgesia via naloxone in two settings. In one setting, they induced placebo analgesia through expectations or pharmacological conditioning with an opioid (morphine), while in the other setting through a non-opioid (ketorolac) medication. They found that placebo analgesia induced through the positive expectation of receiving a powerful painkiller or through pharmacological conditioning with morphine was completely reversible by naloxone. Interestingly, placebo analgesia induced through combined positive expectation and conditioning with ketorolac was only partially reversible with naloxone, while analgesia induced through conditioning with ketorolac alone was not reversible with naloxone. These results showed that positive expectations of pain relief and opioid conditioning produce analgesia through the endogenous opioid system, while conditioning with non-opioids (ketorolac) produces analgesia through a different mechanism.(21) More recently, placebo analgesia induced through ketorolac conditioning was found to be reversible with a CB1 cannabinoid receptor antagonist, suggesting a role for the endocannabinoid system in non-opioid placebo analgesia.(38)

A different line of study investigating the role of cholecystokinin (CCK) has substantiated both the role of the opioid system and that of anxiety reduction in placebo analgesia. CCK, which is elevated by anxiety, has been found to inhibit endogenous opioid release. A CCK antagonist
(proglumide) has been shown to augment placebo analgesia while the CCK type 2 receptor agonist (pentagastrin) has been found to decrease placebo analgesia. (39)(40) Given these findings, some have postulated that positive expectations of pain relief reduce anxiety, which in turn reduces pain through mechanisms like decreased CCK. (41)

While pharmacological studies have been crucial in understanding the placebo effect, the rise of neuroimaging has expanded our ways of understanding its mechanisms. In particular, a better understanding of the neurobiological correlates of pain and analgesia has enhanced our capacity to assess how the placebo effect interacts with the “pain matrix.” As discussed earlier in this paper, the “pain matrix” is a series of brain regions that have been shown to be functionally involved in the experience of pain, primarily the prefrontal cortex, the anterior cingulate cortex, the insula, the somatosensory cortices, the thalamus, and the midbrain. Overall, many placebo analgesia studies have shown decreased activity in areas of the pain matrix, including the thalamus, the insula, the dorsal anterior cingulate cortex, the secondary somatosensory cortex (S2), and the periaqueductal grey (PAG). (7) At the same time, these studies have shown increased activity in areas that modulate expectations, evaluations, and information about context, such as the ventromedial and dorsolateral prefrontal cortices, the orbitofrontal cortex, the rostral ACC (rACC), the nucleus accumbens, the PAG, and the rostroventral medulla (RVM). (7)(42)(43)

One of these studies was a positron emission tomography (PET) study that showed greater regional cerebral blood flow (rCBF) in the rostral anterior cingulate cortex (rACC) and PAG with both an exogenous opioid (remifentanil) analgesia and placebo analgesia, suggesting a shared neuronal mechanistic network between these two interventions. (42) Another study using fMRI showed reduced activation during placebo analgesia in the rACC, insula, and thalamus, while showing increased activity in the dorsolateral and orbitofrontal prefrontal cortices during the expectation of pain relief. (5) Moreover, Zubieta et al conducted a PET study using a radiotracer with affinity for mu-opioid receptors that found increased mu-opioid activity during placebo analgesia in the subgenual and pregenual rACC, insula, dorsolateral prefrontal cortex (DLPFC), and nucleus accumbens. In addition, they showed that the greater the magnitude of expectation of analgesia, the greater the mu-opioid activation in the DLPFC. (43) These results
were confirmed by an interesting study that found that the open administration of remifentanil (i.e. positive expectations) was more effective than the hidden administration, with accompanying activation of the DLPFC and the pregenual ACC. (44)

Such studies employing the open and hidden administration of active medications have strongly highlighted the importance of cognitive awareness of and engagement with treatment in the therapeutic response obtained. The open administration of a placebo analgesic (e.g. saline) has been shown to produce post-operative analgesia equivalent to that achieved via a hidden intravenous administration of 6-8 mg of morphine, with similar results seen with other analgesics like buprenorphine, tramadol, and ketorolac. (45)(13) Moreover, cases in which patients have reduced capacity to form expectations, such as in diseases affecting cognition and the frontal lobes, have shown that expectations are essential for placebo responses. (13) Benedetti et al followed patients with Alzheimer’s disease over a year to investigate the effect of cognitive decline on placebo analgesic response. After this period, they found an indirect correlation between decline in cognitive status and placebo analgesia. (46) Repetitive transcranial magnetic stimulation (rTMS) at low frequencies that inhibit the prefrontal cortex has also been shown to eliminate placebo analgesia. (47) The administration of naloxone leads to reduced fMRI prefrontal cortex activity and decreased analgesia, providing further support for the crucial role of this region in endogenous opioid analgesia. (48)

In addition to the endogenous opioid system, the role of the dopamine system and of reward in the placebo effect has also been demonstrated through various studies. It has been shown that the expectation of reward leads to the tonic activation of dopaminergic neurons in the prefrontal cortex, the nucleus accumbens, and the caudate/putamen. (49) During placebo analgesia, there is evidence of increased dopamine D2/D3 and mu-opioid receptor binding in the nucleus accumbens, an essential component of the brain’s reward network. (50) In placebo studies of patients with Parkinson’s disease whose motor function improves with placebos, increased dopamine release in the nucleus accumbens has also been observed with placebo treatment, leading some to speculate that the expectation of reward is a shared mechanism of placebo effects across various conditions. (51)(13)
While most of the research on the mechanisms of the placebo effect has focused on the brain, there is evidence of pain modulation at level of the spinal cord during placebo analgesia. Using fMRI, Eippert et al showed decreased activation in the dorsal horn of the spinal cord at the level of the incoming nociceptive signal. These researchers subsequently suggested a plausible mechanism for placebo-induced descending inhibitory control of pain based on their results and on neuroimaging studies showing activation of the DLPFC, rACC, hypothalamus, periaqueductal gray (PAG), and the rostroventral medulla (RVM) during placebo analgesia. In essence, they suggested that the DLPFC engages the rACC, which projects to subcortical regions like the PAG and RVM, which in turn send inhibitory signals to the dorsal root horn of the spinal cord. These inhibitory signals at the level of the spinal cord then result in reduced ascending nociceptive signal transmission via the spinothalamic tract to the thalamus.

Overall, neurobiological research in recent decades has significantly advanced our understanding of the mechanisms behind the placebo effect. Various neural networks and neurotransmitters have been implicated in placebo analgesia, with increasing validation for psychological mechanisms such as expectations, conditioning, reward, and anxiety reduction.

**Clinical Hypnosis**

**Definition and History**

Clinical hypnosis has been defined as “a procedure during which a health professional or researcher suggests that a client, patient, or subject experience changes in sensations, perceptions, thoughts, or behavior.” A more recent definition from the American Psychological Association defines hypnosis as “a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion.” The intervention of hypnosis typically involves the hypnotic induction phase (where a hypnotic state is created), the hypnotic state (during which suggestions are given), and the post-hypnotic state (during which some effects of hypnotic suggestions may be reflected). Price and Barrell describe the hypnotic state as one generally characterized by a sense of calm relaxation, sustained focused attention, suspended judgment, altered sense of time, place or self, and perceived automaticity or effortlessness of hypnotic responses. While hypnosis involves a relative suspension of judgment to allow for the incorporation of suggestions, the subject
continues to have control over this process. In the end, hypnosis scholars state that clinical hypnosis is ultimately self-hypnosis.(55)

Hypnosis has had a complicated history within the medical field, as it has had a difficult time disentangling itself from early associations with discredited and mystical theories of its mechanisms. The word hypnosis has its origin in Hypnos, the Greek god of sleep and dreams, although hypnosis does not involve sleep but rather a state of “attentive receptive concentration.”(56) In the 18th century, Franz Anton Mesmer put forth his theory of magnetism suggesting that people and objects had a magnetic force that could be used therapeutically in a way that was later denominated hypnosis by James Braid. Hypnosis then went on to be used as a technique to investigate and treat hysteria (modern-day conversion disorder) by the likes of Jean Martin Charcot, Pierre Janet, Sigmund Freud, and Josef Breuer. Modern hypnosis research began in the 1920s with the work of Clark Hull at Yale and by the 1960s standard hypnotizability scales had been created by researchers at Stanford.(56) Hypnotizability is a measure of people’s capacity to respond to hypnotic suggestions, and when measured with standardized scales it has been shown to be an individual trait that is stable across 25 years and approximately normally distributed in a population.(56) As a result, most hypnosis studies tend to compare groups of subjects who score high on standardized hypnotizability scales (“highs”) with those who score low (“lows”).

To this day, the continued professional and public association of hypnosis with mind control, mysticism, and hypnosis stage shows has made scientific study of the field more difficult. Nonetheless, the development of technologies in neuroscience, such as neuroimaging, as well as developments in the field of cognitive neuroscience have reestablished hypnosis as an area of clinical and neuroscientific interest.(56)

Clinical Evidence
Hypnosis has been studied as a therapeutic intervention for a wide variety of clinical conditions and its effectiveness has been demonstrated.(57) Two meta-analyses have confirmed the effectiveness of hypnosis in reducing acute and chronic pain.(58,59) Evidence also exists supporting its effectiveness in treating anxiety, depression, PTSD, anorexia nervosa, migraines,
Proposed Mechanisms

I. Psychological Mechanisms

Attempts to understand hypnosis have yielded a variety of theoretical perspectives that conceptualize hypnosis from different angles, with no one perspective being widely accepted as the dominant perspective. Instead, many hypnosis scholars see the various perspectives as often being complementary, rather than mutually exclusive. In broad terms, theories of hypnosis consider intrapersonal and/or interpersonal mechanisms that explain the differences in hypnotizability across people, the hypnotic state itself, and the observed or subjectively experienced responses to hypnotic suggestions.

It is recognized that there is wide variability in hypnotizability among people that can remain stable over time, although scholars disagree on the degree to which hypnotizability can be modified. What factors influence hypnotizability? Several character traits are associated with hypnotizability, such as capacity for absorption, openness to experience, fantasy proneness, and cognitive flexibility. Studies consistently show a mild to moderate relationship between an individual’s capacity for absorption and hypnotic responses. Absorption can be defined as the “tendency to become fully involved in a perceptual, imaginative, or ideational experience” or as “a personality construct reflecting a disposition to enter states of narrowed attention and a blurring of boundaries between oneself and the object of perception.” Both absorption and fantasy proneness (“deep, profound, and longstanding involvement in fantasy and imagery” in everyday life) are related concepts often placed under the broader personality construct of “openness to experience.” Some researchers have also proposed that high hypnotizables have an increased ability to adapt their cognitive processes, such as shifting attention and awareness to something at the expense of other things. In other words, “highs can both better focus and sustain
their attention as well as better ignore irrelevant stimuli in the environment,” an aptitude that can enhance their ability to experience hypnotic analgesia, for example. (65)

Beyond the concept of hypnotizability, the mechanisms for the broader phenomena of hypnosis and hypnotic responses are elaborated by two main schools of thought—neodissociation and sociocognitive theories. The neodissociation theory, as advocated by Ernest Hilgard and others, “is based on the idea that there exists multiple cognitive systems or cognitive structures in hierarchical arrangement under some measure of control by an executive ego…or central control structure.” (62) During hypnosis, these systems may dissociate from each other, especially from the “central control structure.” In the case of hypnotic analgesia, the pain subsystem may be modulated by the hypnotist’s suggestions, which the subject temporarily allows to partially replace his own executive control. This kind of dissociation could explain why hypnotic subjects often report a sense of automaticity, effortlessness, or nonvolition while carrying out different kinds of hypnotic suggestions like arm levitation. (62) Bowers and Davidson propose that the fact that “not all action is consciously initiated, intended, or controlled” supports the idea that hypnotic responses can occur through non-volitional and dissociative mechanisms. (62) Neodissociation theories thus argue that the hypnotic state is a real and important component of achieving a hypnotic response. A number of studies show that more analgesia is seen with hypnotic inductions and with greater hypnotizability, but neither seems necessary nor sufficient to produce analgesia. (28)

In line with the neodissociation theory, Price et al suggest that hypnotic analgesia is facilitated by the hypnotic state because of the suspension of judgment and the sense of automaticity that characterizes it. (28) Hypnotic suggestions of analgesia tend to either target the sensory-discriminative or affective-motivational components of pain. In the sensory-discriminative realm, suggestions are made for patients to alter the intensity or quality (e.g. sharp, dull, numb) of the pain, at times including dissociative suggestions (e.g. not feeling the painful body part, imagining being in different context, etc). In the affective-motivational realm, suggestions are made for patients to move away from experiencing the pain as unpleasant, harmful, or threatening. (28) Some have hypothesized that greater hypnotic involvement is required to alter the intensity of pain, given the larger analgesic effects seen in some studies with suggestions to
modulate the affective component of pain. In fact, achieving hypnotic analgesia with sensory-discriminative suggestions is more correlated with high hypnotizability, given the greater ability of highs for hypnotic involvement. (28) Overall, it seems that the more difficult the suggestion, the higher the degree of hypnotizability required—with simple suggestions (e.g. ideomotor and mild analgesia) not requiring high levels of hypnotizability to manifest when compared with complex suggestions (e.g. post-hypnotic amnesia and total cessation of pain during painful stimulation).(60) These ideas, however, presuppose that hypnotizability is a trait and that the hypnotic state is a true and distinct mental entity.

Sociocognitive theorists, on the other hand, argue that “social and situational aspects of the hypnotic context, along with subjects’ attitudes, expectations, and beliefs about hypnosis, must be considered in any theory of hypnosis.” These theorists are thus less likely to attribute the effects of hypnosis to an altered or special state of consciousness and less likely to think these can only be achieved through hypnotic induction. At the same time, they are more likely to see hypnotizability as malleable. (28)(31) Spanos, for example, considers the subjective experience of automaticity to be just a reflection of how subjects cognitively interpret how they respond to the hypnotic suggestions. Indeed, sociocognitive theorists in general think that subjects are actively trying to experience the hypnotic suggestions through role enactment using cognitive skills such as attention modulation and imagery, while interpreting their hypnotic experience based on what was expected of and suggested to them. In line with these theories, one study found a mild-to-moderate correlation between the motivation/desire of subjects to have a hypnotic response and their hypnotic response.(66) Of note, all of these theories do not imply that subjects are lying to please the hypnotist, but that the suggestions given in a specific context influence how subjects appraise their experience.

Kirsch, one of the sociocognitive theorists, proposes that hypnotic suggestions generate the expectation in the subject that the suggestion being given by the hypnotist will manifest, akin to the expectation of pain relief that develops when a subject takes a placebo “powerful pain-killer.”(31) This expectation, in turn, leads to the specific hypnotic response, even if non-volitionally. Various studies have tried to measure subjects’ expectations and how they affect hypnotic response, with the results generally varying depending on the condition being studied.
and the degree of hypnotizability of the subject. (60) Jensen et al. controlled for expectancy through meditational analysis (i.e. a methodology that controls for a potential mediator of an outcome to assess the extent to which the outcome changes) and showed partial mediation for various types of pain. (60)

Overall, many of these psychological theories of hypnosis acknowledge that the hypnotic response is influenced by interpersonal and contextual factors, and that even if there is a goal-driven process at play, subjects may also not be aware of these processes. Indeed, there are several models that seek to integrate the various perspectives. (62) McGlashan et al theorized in the late 1960s that the hypnotic response consisted of nonspecific effects from receiving treatment (i.e. placebo effect) plus the effects from cognitive processes associated with hypnotic suggestions during the hypnotic state. (67) More recently, Jensen et al proposed a biopsychosocial model of hypnosis building on the work of Banyai and others in an effort to capture the many complex factors that together may better explain hypnosis. (60)

II. Neurobiological Mechanisms
Studies investigating the mechanisms underlying hypnosis have generally focused on the neurobiological correlates of the hypnotic state itself, of high hypnotizability, and of responses to specific suggestions. (63) With the development of cognitive neuroscience, hypnosis has also been used as a method for creating certain mental states in order to study cognition, emotion, perception, memory, and other psychological processes. (56) Overall, the neurobiological correlates of hypnosis in highs have been consistently different than those in lows across many studies. Most of the neurobiological research on hypnosis has utilized EEG and neuroimaging technologies, although there are some important pharmacological studies.

One of the leading questions in the field of hypnotic analgesia has been the role, if any, of the endogenous opioid system. Various studies have found that naloxone does not reverse hypnotic analgesia, suggesting that non-opioid mechanisms are involved. (68)(69)(70) Moreover, hypnotic analgesia repeatedly induced in a hypnotizable person tends to have a faster rate of onset and termination than that produced by endogenous opioids. (28) There is only one study from 1979 that found that naloxone partially reversed hypnotic analgesia under stressful experimental
circumstances that may normally result in endogenous opioid release. (71) Given the lack of strong support for the role of opioids, dopamine has been proposed as a possible neurotransmitter mediator of hypnotic analgesia. One study by Spiegel and King demonstrated increased levels of homovanillic acid (HVA), a dopamine breakdown product, in the cerebrospinal fluid of subjects experiencing hypnotic analgesia. (72) Although the mechanism of hypnotic analgesia at the neurochemical level remains unclear, much more is known at the level of functional brain activity.

Since the process of hypnosis typically includes various distinct phases (i.e. induction, hypnotic suggestions, post-hypnotic state), neurobiological correlates depend on the phases being studied and on the particular suggestions being given. Gruzelier proposed a three phase neurobiologic mechanistic model for one style of hypnosis, consisting of 1) induction phase characterized by increased cognitive focus and concurrent frontolimbic activation 2) relaxation phase characterized by reduced frontolimbic activation and increased subject receptivity to suggestions 3) hypnotic suggestion phase characterized by changes in brain regions associated with the particular suggestions (e.g. imagery suggestions activate right temporoposterior regions). (73) While not all hypnotic encounters have a relaxation phase or other aspects of this model, the main takeaway is the general idea that the neurobiology of hypnosis depends on the specifics of the intervention.

Hypnotic analgesia, in particular, has overall been associated with changes in the “pain matrix,” including the prefrontal cortex, thalamus, ACC, insula, and somatosensory cortices. (74) Given the relative involuntariness experienced by hypnotic subjects when carrying out hypnotic suggestions, researchers have theorized that there is a reduced activation of frontal brain regions typically associated with executive control during hypnosis. Research has indeed shown that reduced activity in frontal brain regions can enhance the hypnotic response, although this depends on the particular suggestions. An rTMS study showed that inhibiting the dorsolateral prefrontal cortex using low frequencies led to increased hypnotic responses (e.g. arm levitation, rigid arm and taste hallucination). (75) Another study found that alcohol, which leads to impairments in frontal lobe executive functioning, also led to increased hypnotic responses. (76) Nevertheless, when a hypnotic suggestion involves processes that are normally mediated by
activation of frontal brain regions, such as in inhibiting pain, these regions can become activated. (77) Indeed, some PET studies have shown increased regional cerebral blood flow (rCBF) in the orbitofrontal cortex and other frontal cortical regions during hypnotic analgesia. (77)(78)

The anterior cingulate cortex also shows varied activation depending on the particular suggestion given. A series of important studies by Rainville et al showed that hypnotic suggestions are able to selectively modulate the motivational-affective and sensory-discriminative aspects of pain. When subjects were given hypnotic suggestions to experience pain as highly unpleasant, ACC activity was much higher than with suggestions of low unpleasantness, while somatosensory cortex (S1) activity remained the same. (79) In another PET study with a similar design, subjects were given hypnotic suggestions for high and low pain intensity, with greater activity seen in S1 with high intensity suggestions. (80) Given that the ACC is a complex structure, it is important to note that Rainville et al found that the experience of pain activated a more caudal part of the ACC, while hypnotic analgesia activated a more rostral part. (42) They also found that subjects in a hypnotic state had increased occipital cortex activity and reduced posterior parietal cortex activity.

Another PET study by Faymoville et al showed that hypnotic suggestions to remember pleasant autobiographical memories reduced pain unpleasantness and pain intensity, with activation of the mid-ACC. (81) A subsequent study by the same research group found increased functional connectivity between the mid-ACC and the bilateral insula, pregenual cingulate cortex, right prefrontal cortex, pre-supplementary motor area, thalamus, and brain stem. (6) According to the authors, “these findings point to a critical role for the midcingulate cortex in the modulation of a large cortical and subcortical network underlying its influence on sensory, affective, cognitive and behavioral aspects of nociception, in the specific context of hypnosis.” (6) It is also interesting to note that remembering pleasant autobiographical memories during hypnosis has been shown to activate a very different neural network compared to such recollection during a normal alert state, suggesting specific attributes of the hypnotic state itself. (82)(83)

The importance of the specific suggestions on neurocorrelates is further demonstrated by a series
of interesting EEG ERP (event related potential) studies on positive and negative hallucinations. One study showed that suggestions to not smell in the presence of olfactory stimuli activated the P3 components; this is an example of a negative hallucination, which is not sensing something that is actually there. On the other hand, a study with suggestions to imagine a cardbox blocking a specific visual stimulus led to a decrease of the P3 components; this is an example of a positive hallucination, which is sensing something that is not actually there. Although subjects in both studies did not perceive their respective physical stimuli, the measured ERPs were in opposite directions.(63)

EEG studies have been an important part of the effort to understand the neurocorrelates of hypnotizability and the hypnotic state. Studies have fairly consistently shown higher baseline EEG theta wave levels among high hypnotizables compared to low hypnotizables, as well as greater changes among “highs” in the levels of various waves during hypnotic induction and hypnotic responses.(60) Another area that was explored through EEG studies was the theory that hypnosis was mediated via right hemisphere lateralization given the possibility of functional differences between the right and left hemispheres; the available evidence has not supported this theory. A study comparing stroke patients suffering from left or right hemisphere injuries did not find any differences in hypnotizability.(84) However, highly hypnotizable subjects have been shown to have greater left or right hemisphere activation during tasks that were specifically designed to activate left or right hemispheres, respectively.(85) These results have been used to support the theory that baseline cognitive flexibility (i.e. the ability to “shift easily between analytic (left hemisphere) and holistic (right hemisphere) modes of processing”) is related to hypnotizability.(63)

While most of the neurobiological research on hypnosis has focused on the brain, there is some evidence for the role of descending sensory modulation to the level of the spinal cord in hypnotic analgesia. The spinal cord R-III nociceptive flexion reflex, which is correlated with intensity of pain, decreases with hypnotic analgesia.(86)
Overall, the available research to date has demonstrated distinct neurobiological changes associated with hypnosis, with evidence of modulation of the “pain matrix” during hypnotic analgesia.

**Comparative Analysis of Mechanisms for the Placebo Effect and Clinical Hypnosis**

It has not escaped scholars of the placebo effect and of hypnosis that the two processes appear upon reflection to be similar in some ways. In this paper, I have presented an up to date review of the psychological and neurobiological mechanisms proposed for these two processes, with a natural focus on the most studied outcome in both fields—analgesia.

Psychologically, hypnosis and the placebo effect share many potential mechanisms. Theorists in both fields acknowledge the influence of the context (e.g. physical, interpersonal, historical) on the responses observed clinically and experimentally. Personality traits affecting factors such as baseline optimism or skepticism in face of an uncertain benefit may modulate the strength of people’s positive expectations and placebo responses, similar to how the personality construct of “openness to experience” can influence hypnotizability and hypnotic responses. The motivation or desire to experience a certain hypnotic suggestion or to experience a certain clinical relief may influence the likelihood that hypnotic and placebo responses may occur.

Although the role of reward has been more thoroughly theorized and experimentally studied with placebo analgesia, it is plausible that the expectation of reward (i.e. pain relief) is also present during analgesic hypnotic suggestions. Similarly, the impact of somatic focus or self-monitoring in leading to a “self-confirming feedback” that augments the placebo effect could also be occurring while a hypnotic subject is processing the hypnotic suggestions.

Both placebo and hypnotic responses show a remarkable specificity for modulating detailed aspects of a variety of conditions, as seen with regional analgesia. In addition, these responses are often fined-tuned to the details of the hypnotic suggestion or of the information a person receives or intuits from a particular “placebo” context. Kirsch argues that cognitive expectations carry the degree of specificity needed to produce the observed outcomes, as opposed to more global processes like anxiety reduction. According to him, hypnotic inductions provide an
interesting meeting point between the placebo effect and hypnosis. Since many different types of hypnotic inductions (including opposing ones like eye-fixation vs eye rolling, and relaxation vs alertness) lead to the same state of increased suggestibility, then hypnotic inductions may be placebos. In other words, the inductions themselves, like placebo pills, would not inherently work were it not for the context and expectancies that accompany them leading to the hypnotic state and the placebo effect, respectively.(31) The creation of positive expectations in a routine or experimental clinical setting through a placebo and positive hypnotic suggestions are thus both forms of cognitive modulation.

While hypnotizability can be reliably tested via standardized scales and be stable across decades, there is no reliable way yet to determine placebo responsiveness. Studies that assessed hypnotic analgesia and placebo analgesia in the same subjects have shown that the effects are different depending on hypnotizability.(67) For subjects with low hypnotizability, the hypnotic and placebo responses are comparable and mild-moderate in magnitude. For highly hypnotizable subjects, however, the hypnotic response is significantly larger than the placebo response, suggesting different mechanisms. Price et al suggest that the differences in the psychological experience of hypnosis and the placebo effect are likely responsible for the different outcomes. They suggest that hypnosis involves an internally-focused state in which expectations are self-generated in a way that feels automatic. On the other hand, they suggest that the placebo response relies on the subject developing expectations about the therapeutic power of the intervention and of the people delivering it.(28)

Could there be a component of hypnosis during encounters in which placebo effects are produced? As previously stated, hypnosis can be defined as “a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion.”(54) Since hypnotic inductions are not necessarily required for hypnotic responses to occur, it is feasible that patients enter a state of focused attention and enhanced suggestibility during clinical encounters that could mimic what we normally understand as the hypnotic state. Even if this is a possibility, there does seem to be a phenomenologically different process going on at least part of the time during hypnosis and during encounters in which placebo effects take place. During a “placebo encounter,” a subject is in an alert state, in a
particular context infused with prior associations, and in communication with a person who may say something along the lines of, “this pill is a strong analgesic.” Upon taking the pill, the subject experiences pain relief. During hypnosis, the subject is typically relaxed, with eyes closed, knowingly participating in an activity focused on guiding them to a certain experience, and in communication with a person who may say something along the lines of, “you are starting to feel the intensity of the pain decrease, almost as if you are feeling increasing comfort.” Whether there is a conscious attempt at experiencing the suggestion being heard or whether the outcome being suggested is experienced as happening effortlessly, the subject is typically deeply absorbed and focused on the experience of pain and pain relief. Even taking into account the sociocognitive factors that could influence how subjects describe how the analgesia was experienced, the differences in what a hypnotic subject and a subject in the placebo context report seem significant enough to signal different neurocognitive processes at play.

Neurobiologically, there isn’t a single mechanism for either placebo effects or hypnotic responses as these generally depend on the particular intervention and suggestions. There is strong evidence of the involvement of endogenous opioids in placebo analgesia, which is not the case with hypnotic analgesia. Other neurochemicals, like dopamine, endocannabinoids, and CCK have also been implicated as part of the mechanism of placebo analgesia, while their potential role in hypnotic analgesia is unknown. Unfortunately, there are only a few studies with small sample sizes studying the role of opioids or other neurochemicals in hypnotic analgesia.

The neuroimaging studies that exist for placebo and hypnotic analgesia have remarkably overlapping results. Both types of phenomena affect the pain matrix, with demonstrated reduced activity in the ACC, insula, thalamus, somatosensory cortices, PAG, and other important regions. At the same time, both analgesia-producing interventions have at times been associated with increased activity in areas that modulate expectations, appraisals, and information processing, such as the prefrontal cortex. As Kupers et al point out, “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).”(2) Although placebo responses tend to decrease in states of decreased frontal brain region activity (e.g. in Alzheimer’s
disease and with rTMS stimulation), hypnotic responses sometimes increase under such conditions. In addition to evidence of modulation of pain at the level of the brain, both placebo and hypnotic analgesia also seem to have a component of pain modulation at the level of the spinal cord.

Overall, the placebo effect and hypnotic responses share several psychological and neurobiological mechanisms and may under certain circumstances appear the same. Taken as a whole, the variety of placebo effects and hypnotic responses differ sufficiently in psychological, phenomenological, and neurobiological ways to indicate that the placebo effect and hypnosis are different mental processes.

**Evaluation of Gaps in the Literature, Recommendations for Further Study, and Implications for Clinical Trial Design**

The fields of placebo and hypnotic studies have rich research traditions and given the similarities of the phenomena they study, both fields could benefit from adapting experimental approaches used more commonly in one but not the other.

There is clearly a role for learning (e.g. conditioning, memories, social learning, etc) in the placebo effect. Since previous experiences with physical pain and/or the healthcare system are almost ubiquitous, studies examining the effect of an intervention to improve health are bound to illicit prior associations with such interventions. If positive, these associations can translate into a robust placebo effect. In the case of clinical hypnosis, patients are faced with a clinical intervention that is not common and to which they likely have no prior experience, reducing the amount of prior learning that can influence the intervention. There is, however, an overall context with environmental cues that parallels more common healthcare encounters. I wonder how learning could modulate hypnotic responses in studies where subjects are repeatedly exposed to hypnosis over time. If this were to increase the expectation of pain relief and if the placebo effect were to be a part of the hypnotic effect, then perhaps this learning would add a greater placebo effect to the hypnotic response with different neurochemical correlates (e.g. opioid or dopamine release). This, in theory, could be tested via naloxone administration or via neuroimaging with radiotracers that could detect opioid or dopamine release.
Moreover, studies of hypnotic analgesia could benefit from using the preconditioning protocols of many placebo studies. In these protocols, subjects would go through a round of hypnosis where the experimenter gradually decreases painful stimulation as analgesic suggestions are vocalized, creating a belief in the subject that hypnosis works. In subsequent rounds of hypnosis, it would be interesting to see the effect of this preconditioning on the degree of analgesia achieved when compared to a control group without preconditioning. Specifically, would the effect increase just as the placebo response increases post-preconditioning?

Hypnotic researchers could also study the effect of social observational learning in hypnosis. A study could have a subject who is actually an actor go through hypnosis and experience analgesia while being observed by other subjects. The impact of social learning could be seen if the hypnotic responses of these subjects are compared to those of a control group who didn’t see the actor.

During all of these studies, adding a component of neuroimaging would make findings richer and nuanced. Furthermore, adding pharmacological protocols that have been used in placebo studies to hypnosis studies could help us better understand hypnosis and its relationship to the placebo effect. Examples of such pharmacological studies are using naloxone, endocannabinoid antagonists, CCK agonists and antagonists, and radiotracers indicating release of various neurotransmitters. There also need to be more neuroimaging studies of the spinal cord during hypnotic analgesia to assess for nociceptive modulation at that level. In addition, it would be very interesting to study the effects of hypnosis on endocrine and immune factors. Following the example of McGlashan et al’s 1969 study comparing hypnosis and placebo in the same experiment, we need more head-to-head comparisons of the effects of these interventions.

To further advance our understanding of the placebo effect, we need more translational placebo research to harness the therapeutic benefit of the placebo effect in clinical populations in ethical ways. What aspects of the therapeutic encounter are most important and how, when, and to what extent must they be used to yield maximum health benefits? In particular, more open label placebo studies where no deceit is involved could open the way for new therapeutic
interventions. Furthermore, hypnosis research has separated analgesic goals into the reduction of pain intensity and pain unpleasantness using different suggestions, a research approach that may be useful in placebo analgesia studies to delineate the various mechanisms at play. For example, it would be interesting to study the neuroimaging correlates of taking a placebo pill that “makes you comfortable, as if the pain doesn’t bother you” versus a placebo pill that “reduces the intensity of your pain.”

Our understanding of the placebo effect has significant implications for research design, which many scholars have discussed at length. In this paragraph, I will summarize the implications discussed by Benedetti et al in a review article that focused on how the evidence behind the role of learning and conditioning in producing placebo responses has significant implications for research design.(13) In essence, any study design that involves sequential administration of a placebo or active treatment is prone to shape the physiological response of subjects. In enriched design trials, the selection of responders to active treatment and their subsequent separation into active and placebo arms may produce strong placebo responders due to prior conditioning and positive expectations. On the other hand, excluding placebo responders in placebo-run-in designs essentially only leaves subjects with prior negative conditioning and expectations who are less likely to show a robust response to treatment. Crossover studies also present similar challenges, given the learning that occurs via sequential treatment with placebo or active drug. Given that we don’t know the degree to which most drugs and interventions can lead to placebo responses through conditioning (as occurs with opioids, cyclosporine, sumatriptan, etc), it is unclear what the magnitude of the above-mentioned effect distortions is across different treatments. Furthermore, there is evidence from social observational learning studies that show that communications between subjects in clinical trials could affect the placebo effect. Trials should also assess whether subjects believe that they are in the active or placebo arm, as this could help isolate the effect of expectations on results seen in both trial arms.(88)(13)

Clinical Implications

In a 2014 article, Benedetti et al presented a series of clinical implications from placebo research, which I will summarize in this paragraph. Placebo studies using hidden administration of medications have shown that awareness of receiving treatment and expectations regarding that
treatment are a significant component of the overall treatment effect. The clear implication of these studies is the vital importance of doctor-patient communication for optimal clinical improvement to occur. Furthermore, the evidence of decreased placebo responses in patients with Alzheimer’s disease may have implications about effective dosing of medications for patients with prefrontal dysfunction in the context of poor ability to form positive expectations. Moreover, the observed sustained efficacy that occurs after substituting an active medication with placebo has implications for reducing active medication intake in patients. (13) The use of placebos in clinical practice, however, must occur in an ethically adequate way that does not involve deception.

In regards to hypnosis, it is time for this well-researched intervention to be more widely used to help patients. Significant efforts must be made to help remove the historical and cultural stigma associated with clinical hypnosis. While not every patient can benefit equally from hypnosis given the diversity in hypnotizability, some benefit is possible for many people suffering from various illnesses. Specifically, hypnosis may prove useful for conditions for which we do not have many other effective therapeutic options, such as chronic pain. The research observation that improving affective components of pain through hypnotic suggestions do not require high degrees of hypnotizability imply that a significant number of patients could benefit from hypnosis.

Overall, a main clinical implication of the research on the placebo effect and hypnosis is that there exist mental processes in people that can be used therapeutically to improve their health and wellness, and that we should learn to harness these processes in clinical practice

**Limitations**

The most significant limitation of this paper is the possibility that I may have missed important papers when I reviewed the literature in a targeted way. I tried to reduce the impact of this limitation by consulting experts in the fields I reviewed (two of which are my mentors) on important papers I may have missed through my literature search and through reading citations of articles.
Conclusions

The placebo effect and hypnosis represent two types of mental processes that have been demonstrated to improve health across a variety of conditions. In particular, they have been shown to be effective in reducing pain. In this paper, I reviewed the psychological and neurobiological mechanisms that have been proposed for the placebo effect and hypnosis, with a special focus on pain and analgesia. Overall, placebo and hypnotic responses potentially share several psychological mechanisms, including expectations, evaluation of physical and interpersonal context, anxiety reduction, motivation, reward, and somatic focus. Neurobiologically, placebo and hypnotic analgesia have been shown to modulate key areas of the “pain matrix,” including the prefrontal cortex, the anterior cingulate cortex, the insula, the somatosensory cortices, the thalamus, and the midbrain.

Taken as a whole, the variety of placebo effects and hypnotic responses differ sufficiently in psychological, phenomenological, and neurobiological ways to indicate that the placebo effect and hypnosis are different mental processes.

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