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# Brain activity during pain relief using hypnosis and placebo treatments

## A literature review

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## Abstract

*Placebo treatment and hypnosis are both examples of top-down regulation and are used to treat pain. However, it is unclear whether hypnosis produces anything more than a placebo effect when measuring brain activity changes. This literature review examines research articles published from 1997 onwards regarding the neurophysiology of pain relief during hypnosis or placebo treatments using functional brain imaging (fMRI or PET). The focus was on acute produced nociceptive pain. There seems to be both similarities and clear differences in the brain activity changes between hypnosis and placebo treatments. These results show that hypnosis is not equal to common placebo in terms of brain activity thus questioning the suggestion that the pain reducing properties of hypnosis are just one form of placebo effect.*

**Keywords**: *hypnosis, pain, placebo effect*

## Introduction

Pain is categorized as a separate sense with both an emotional and a sensory component. Its main purpose is to warn about the potential damage of bodily tissues and to motivate action to prevent such damage. Pain sensation is processed at several levels before it becomes a perception. Previous experiences, mood, expectations and stress are only a few of the factors that are known to modify pain perception (Ploghaus, Becerra, Borras & Borsook, 2003; Villemure & Bushnell, 2009). This kind of modification is called the top-down regulation, which means that we have a neurobiological system which, when activated by, for instance, expectations, may cause neurophysiological changes that affect perceiving of pain.

There are several ways of how the top-down regulation can modulate pain, such as through the use of placebos or hypnosis. However, the research of these two is often done in parallel and their neurobiological relation or even similarity is yet unclear. So far the only known study conducted on both treatments has shown that highly hypnotizable individuals report feeling less pain during hypnosis than during placebo condition (McGlashan, Evans & Orne, 1969). This result implies that the effects of placebo and hypnosis are at least to some extent separate processes.

Opinions about the nature of hypnosis are strongly divided in scientific circles (Kallio & Revonsuo, 2003). Some consider its effect to be based on an altered state of consciousness, dissociation or trance. Others say the outcomes of hypnotic treatment are nothing but the influences of social psychological factors like meeting expectations and role play. There are also those who see both sides to be correct in certain conditions.

Views on placebo treatment also vary (Kupers, Faymonville & Laureys, 2005). One perspective is that the effects are due to conditioning and previous experience. Another is that placebo effects are based on expectations, no matter how those were formed. Attitudes towards placebo treatment are often more negative than those towards hypnosis, because placebo condition always requires some amount of deceiving, which is ethically dubious.

The development of brain imaging techniques has increased the interest to research phenomena such as hypnosis and placebo effects, which were previously seen as purely psychological. By using modern functional imaging techniques, brain activity changes can be localized from blood oxygenation level in functional magnetic resonance imaging (fMRI) and through glucose uptake rate in positron emission tomography (PET).

In this literature review, the latest research (1997–2009) in the fields of hypnotic and placebo analgesia was examined in a narrative manner. The focus was on the alleviation of acute experimentally produced nociceptive pain, which differs from chronic clinical pain in respect to brain functioning (Apkarian, Bushnell, Treede & Zubieta, 2005). Another criteria for the chosen articles was the use of functional brain imaging techniques such as fMRI and PET. The purpose was to compare the localized activation changes in placebo and hypnosis treatments and to find out whether hypnosis differs from placebo in terms of neurophysiology. This issue is not known to have been investigated before.

First, placebo and hypnosis are examined from the viewpoint of the scientific research. Next, similarities and differences found in the activity of distinct brain areas and neurotransmitters are reviewed. Finally the results are summarised and proposals for future research are made.

## Definition and research of placebo and hypnosis

Placebo treatment is often used in medical research as a control state when the power of the real treatment is to be extracted from the overall clinical effect. All procedures are preserved, but the ingredient designed to be efficient is replaced with an inactive one. Placebo effect refers to the patient's experience of therapeutic efficacy without any active medication being given. In the studies of placebo effect, the placebo is used as the main condition and the control condition is otherwise the same, but the participant is specifically told that the treatment is inert and unable to, for example, soothe pain.

The state of hypnosis is usually reached by deep relaxation or special induction, after which various types of suggestions might be used. These can be for instance commands, propositions or descriptions of pleasant autobiographical memories that do not contain any message of pain relief (Faymonville et al., 2000; Vandenhuyse et al., 2009). The control condition is often the alert resting state.

In both placebo use and hypnosis, the direction of the effect can be altered by means of proper suggestions. When, in placebo condition, the treatment is said to enhance pain and the participant reports a greater sensation of pain, it is called the nocebo effect (reviewed in Benedetti, Lanotte, Lopiano & Colloca, 2007). Likewise, in hypnosis, the intensity of perceived pain can be increased (Derbyshire, Whalley, Stenger & Oakley, 2009).

Placebo and hypnosis pain treatments differ greatly. In placebo research, a diversity of aids, such as creams and pills, are used. Therefore the impact of previous knowledge and experience of medical treatments can not be excluded from the placebo effect. In addition, the use of these aids leads to physical sensations, which are known to reduce perceived pain (Bellieni et al., 2007). The same does not apply to hypnosis. In contrast, in hypnosis treatments visualization is mainly used which results in activation of visual

cortex (Faymonville et al., 2000; Rainville et al., 1999). This is not seen in placebo research.

The researchers of placebo effect sometimes use additional conditioning (Bingel, Lorenz, Schoell, Weiller & Büchel, 2006; Wager et al., 2004). This means that before the actual brain imaging experiment the participant gets the same treatment as in the experiment, but the stimuli used to produce pain are milder in the placebo condition than in the control condition. Consequently the person is assured that the treatment works and, as a result, the obtained placebo effect is greater (Vase, Riley & Price, 2002). This kind of convincing is not used in the studies of hypnosis.

To study pain in an experimental, laboratory setting, it usually has to be induced in participants. In studies of both placebo and hypnosis this may be done using hot water (Kong et al., 2006; Wager et al., 2004), electrocutaneous stimulation (Wager et al., 2004), laser light (Vandenhuyse et al., 2009), thermal stimulator (Faymonville et al., 2000), intravenous injection of hypertonic solution (Zubieta et al., 2005) or in case of irritable bowel syndrome (IBS) patients by rectal distention (Craggs, Price, Perlstein, Verne & Robinson, 2008; Liebermann et al., 2004).

The easiest way to find out the level of pain experienced by the participants is to ask them to rate it. In placebo and hypnosis research categorical scales are used, for example a scale of 0—10, where zero refers to no pain and ten to highest possible pain. People have individual differences in pain thresholds and the purpose of research is not to cause damage. Therefore at the beginning of an experiment, individual pain limits are defined and pain stimuli kept within those limits in all conditions.

In the studies of placebo effect, the participant's suggestibility is evaluated. This is usually done after the experiment by examining how much the belief in treatment efficacy decreased the participant's pain ratings; that is, whether the participant experienced a placebo effect or not. In the research of hypnosis, only the person's hypnotizability is explored, applying standardized questionnaires. The level of suggestibility is not evaluated. However, there is evidence that it might be essential for localization of the brain activity changes (Scott et al., 2008; Wager et al., 2004). At the same time it has been found that hypnotizability and suggestibility are relatively stable and independent traits (De Pascalis, Ray, Tranquillo & D'Amico, 1998).

When evaluating the functional changes of the brain, it is important to remember that there are certain differences, some of which are listed above, in placebo and hypnosis treatments' procedures which could appear as differences in brain activity. Then again, the similarity in the neural activity patterns may be partially explained by the common rules of pain research, such as the induced pain being expected and its cognitive evaluation required, rather than by resemblance of the treatments.

## Brain structures involved in pain reduction

The pain pathways proceed from pain receptors through the spine to the brain where they separate. The recognition, interpretation and evaluation of pain signals continue in different parts of the brain. One pathway goes through the thalamus towards the somatosensory cortex where the origin, quality, magnitude and length of the pain perception are processed (Hofbauer, Rainville, Duncan & Bushnell, 2001; Hunt & Mantyh, 2001). The valence and emotional significance are evaluated and the response of the autonomic nervous system is mostly generated on another path, which proceeds from medulla to thalamus, amygdala, hippocampus, cingulate cortex and prefrontal cortex (Hunt & Mantyh, 2001; Rainville, Duncan, Price, Carrier & Bushnell, 1997; Singer et al., 2004).

The entity of those brain structures activity of which changes during the pain experience is called the pain network (reviewed in Apkarian et al., 2005 and Peyron, Laurent & García-Larrea, 2000). The primary and secondary somatosensory cortex, insula, anterior cingulate cortex (ACC) and thalamus are those parts of the pain network whose functional alterations are seen in imaging

studies mainly during the pain sensation. Here these structures will together be referred to as the pain processing regions. The prefrontal cortex is associated with the anticipation of, focusing attention to and cognitive evaluation of pain. The cooperation of different structures of the pain network produces the pain perception.

## The pain network

In studies of the placebo effect, pain alleviation is always seen to be related to activity changes in the pain processing regions (Craggs et al., 2008; Kong et al., 2006; Liebermann et al., 2004; Price, Craggs, Verne, Perlstein & Robinson, 2007; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2005; Zubieta and Stohler, 2009). In the study of Wager et al. (2004) participants' hands were treated with a cream which was said either to be an efficient analgesic or just an inert control product. The pain was caused by mild electrocutaneous stimulation. Using fMRI the researchers found out that the reduction of perceived pain was associated with a reduction of activity in thalamus, insula, ACC and amygdala.

Similar results were obtained in a PET study of IBS-patients (Price et al., 2007). The participants' neural activity changes were monitored while the bowel was mechanically distended. Placebo cream use was associated with diminished activity in thalamus, insula, ACC and somatosensory cortex. In a longitudinal study of the same kind, IBS-patients kept a diary of their symptoms in between the experiments (Liebermann et al., 2004). It appeared that decrease of activity in cingulate cortex and prefrontal cortex in placebo condition correlated with smaller amount of symptoms reported by the patients.

Reduced pain ratings during the pain treatment with hypnosis are also associated with functional changes in the pain processing regions of the brain (Faymonville et al., 2000; Faymonville et al., 2003; Rainville et al., 1999; Vandenhuyse et al., 2009). Vandenhuyse et al. (2009) used laser beams that are known to activate only the pain receptors to cause pain to the participants' hands. The exact place was changed slightly every time to avoid sensitization and habituation. Participants were given suggestions encouraging a retrieval of some pleasant autobiographical memories which did not contain any message relating to analgesia. EEG activity was monitored by the researchers so that participants could be prevented from falling asleep. Decrease of the reported pain was associated with smaller activity in thalamus, insula, ACC, somatosensory cortex, motor cortex and basal ganglia.

In some studies of pain relief the activity of the pain processing regions is found to decrease (Price et al., 2007; Wager et al., 2004) while in others it seems to increase (Bingel et al., 2006; Craggs et al., 2008; Kong et al., 2006). These differences in the results may have several explanations. One of the proposed reasons is whether the final analyses are done only on the data of the participants who experienced the placebo effect (Wager et al., 2004) or also those whom the treatment did not seem to affect (Kong et al., 2006). However, Kong et al. (2006) compared the results of both groups and noticed that the direction of activity changes remained the same. The researchers concluded that the variation of the results in the field illustrates the view that there are several placebo effects – for instance one that is mediated by the opioids and another one that is not – instead of one.

The second explanation for the variations in the results might be the nature of blood circulation changes, which are linked to the increased synaptic activity and energy consumption. Therefore both excitatory and inhibitory processes are seen, as both consume energy, and the exact functional meaning of detected changes can not be evaluated (Peyron et al., 2000). In this case, the greatest impact of functional brain imaging is the localization of those changes.

In addition to changes in the pain processing regions, activity is found to increase in the prefrontal cortex during both placebo treatments (Craggs et al., 2008; Kong et al., 2006; Liebermann et al., 2004; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2005; Zubieta et al., 2009) and hypnosis (Faymonville et al., 2000; Faymonville et al.,

2003; Rainville et al., 1999; Vandenhuyse et al., 2009). In a PET-study of placebo made by Zubieta et al. (2005) the pain was produced by injections of hypertonic solution into participants' jaw muscle for 40–60 minutes so that their pain ratings remained the same. Before the experiment they had an injection of physiological solution which in the placebo condition was said to be a powerful analgesic. Participants were asked to rate how much they expect the pain to be alleviated by this treatment. The activity increased in the dorsolateral parts of the prefrontal cortex as well as in ACC, insula and nucleus accumbens. The bigger the pain relief one expected, the greater was the growth in functionality in one's prefrontal cortex.

Wager et al. (2004) also noticed that the activity in prefrontal cortex was associated with anticipation of pain relief. In that study, the pain was caused by gradually heating and cooling water in order to distinguish the start of the pain, its peak and the late phase. A warning light was shown just before the water started to warm up. It appeared that larger activity in prefrontal cortex after the warning light correlated with decrease in reported pain and smaller activation of the pain processing regions – ACC in the start phase and insula and thalamus in the late phase. These results support the view that top-down pain alleviation requires the pain signals to continue for a certain period of time to start working to its full magnitude. This would explain why the placebo effect is greater with longer lasting stimuli (Vase, Petersen, Riley & Price, 2009).

In the study of hypnotic analgesia, Faymonville et al. (2000) compared the ratings of pain induced on the hand by thermal stimulator, given while at rest, during pleasant recollection or during pleasant recollection under hypnosis. It appeared that only hypnosis affected the pain perception. PET-imaging showed that activity changes in ACC, medial prefrontal cortex, visual cortex and caudate nucleus during hypnosis correlated with decrease in the reported pain. Vandenhuyse et al. (2004) also found that functional connectivity between prefrontal cortex, insula and somatosensory cortex increased during hypnotic pain relief.

All in all the changes in activity in the pain processing regions in both hypnosis and placebo treatment imply that the pain perception is actually diminished by the treatments and the effects are not due to some sort of response bias. The additional activation of prefrontal cortex means that cognitive evaluation and attention are most likely to play an important part in placebo and hypnosis induced analgesia. The correlation of prefrontal activity changes with expectations for and the magnitude of pain relief might mean that efficacy of both treatments is based on changing the expectations of the participants.

## Other brain structures

Based on the presented evidence of the similarities of neural activation changes, the analgesic power of hypnosis could be largely explained by the placebo effect. However, a closer look at the study results shows that there are also some significant differences.

In the research of placebo analgesia the decrease of pain ratings is often associated with activity changes in those parts of the limbic system that are not included in the pain network. These are the amygdala (Bingel et al., 2006; Craggs et al., 2008; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2009), hypothalamus (Zubieta et al., 2009) and hippocampus (Craggs et al., 2008; Kong et al., 2006). Furthermore, alterations are seen in the periaqueductal grey (PAG) (Bingel et al., 2006; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2009) and nucleus accumbens (Scott et al., 2008; Zubieta et al., 2005; Zubieta et al., 2009). Similar changes have seldom been detected in the studies of hypnosis. In a PET-study by Scott et al. (2008), placebo treatment was related to increase of activity in PAG and decrease of it in ACC, amygdala and nucleus accumbens. The functional change in nucleus accumbens alone explained almost a quarter of variability in the pain ratings. In another study the functional connectivity between ACC, amygdala and PAG was found to increase in the placebo condition (Bingel et al., 2006).

Table 1. *Brain areas activated in hypnosis and placebo treatments*

| Brain area | Hypnosis | Placebo |
|---|---|---|
| Somatosensory cortex | x | x |
| Insula | x | x |
| Thalamus | x | x |
| ACC | x | x |
| Prefrontal cortex | x | x |
| Amygdala | | x |
| Hypothalamus | | x |
| Hippocampus | | x |
| PAG | | x |
| Nucleus accumbens | | x |
| Occipital cortex | x | |
| Basal ganglia | x | |

Kong et al. (2006) used fake acupuncture with needles set in the spots inactive according to the theory of meridians. Acupuncture was chosen as an interesting alternative because Western people do not have much experience of and thus are less familiar with it. FMRI was used to image the brain activity changes before and after the treatment when rating painful stimuli. After the treatment the functionality was seen to increase in ACC, insula, prefrontal cortex, hippocampus and pons. Greater activity of amygdala and hippocampus in the placebo condition was also seen in the study of IBS-patients (Craggs et al., 2008).

Conversely, in the research of hypnosis treatment, diminished pain ratings are associated with activity changes not only in the pain network, but also in the occipital cortex (Faymonville et al., 2000; Rainville et al., 1999) and basal ganglia (Faymonville et al., 2000; Faymonville et al., 2003; Vandenhuyse et al., 2009). This does not seem to happen during placebo treatment. For example the functional connectivity was seen to increase between ACC, insula, thalamus, prefrontal cortex and basal ganglia and to decrease between ACC and visual cortex during hypnotic analgesia (Faymonville et al., 2003).

Placebo treatment and hypnosis cause activity changes in both similar and different brain regions (Table 1). The placebo effect is related to the function of the limbic system areas that are involved in processes such as emotions and memory and autonomic processes. It is also related to the activity of PAG, which is rich in opioid receptors, and the activity of nucleus accumbens, which is informally known as the craving center. At the same time in hypnosis parts of the brain that pertain to movement regulation and imagery processing are activated.

## The role of neurotransmitters

The most researched neurotransmitter systems in pain alleviation are opioidergic, involving endogenous opioids and their receptors, and dopaminergic, which relates to dopamine and its receptors. The research of the placebo effect shows that dopaminergic activity is increased during the placebo analgesia (Scott et al., 2008; Zubieta et al., 2009). Scott et al. (2008) used dopamine tracer and PET-scanning and discovered that raised dopaminergic activity in nucleus accumbens was associated with lower pain ratings.

There is some indirect evidence of dopaminergic mediation of the pain relieving effect of hypnosis too. The level of hypnotizability was found to be related to a higher amount of dopamine metabolites in the spinal fluid (Spiegel & King, 1992) and to the genes involved in the regulation of dopamine secretion (reviewed in Raz, Fan & Posner, 2006). Unfortunately these results do not tell

us anything about the dopaminergic activity during the actual hypnosis treatment.

It has long been known that the amount of opioids released in the body increases during painful experiences (Levine, Gordon & Fields, 1978). Nowadays opioidergic activity is examined closer using PET and opioid tracers. These methods show that placebo treatment increases this activity in the ACC, insula, prefrontal cortex, amygdala, nucleus accumbens and PAG (Scott et al., 2008; Wager et al., 2007; Zubieta et al., 2005). However, when opioidergic activity is studied with the opioid antagonist naloxone the results are inconsistent. Some studies showed that the placebo effect is blocked by naloxone (reviewed in Sauro & Greenberg, 2005); but there are also results suggesting that naloxone has no effect on placebo efficacy (Vase, Robinson, Verne & Price, 2005). These kinds of contradictory results support the view of several placebo effects instead of one (reviewed in Stewart-Williams & Podd, 2004). One placebo effect might be based on conscious expectations and mediated by opioids, while another one, perhaps based on acquired conditioning, may not be mediated by them and therefore not affected by naloxone (Amanizio & Benedetti, 1999).

In a few studies conducted on the role of opioids in the hypnotic analgesia no effect of naloxone was found (Goldstein & Hilgard, 1975; Moret et al., 1991). This means that opioidergic activity does not seem to mediate the effect of hypnosis on pain perception. However this conclusion needs to be tested further, at least with bigger sample sizes.

According to results obtained until now and presented here dopamine plays an important role both in placebo and hypnosis effects. The significance of opioids, which are well-known as the body's own pain killers, is unclear. More research is needed especially on the neurochemistry of hypnosis.

## Conclusions

### Summary

Many similarities have been found between hypnotic and placebo analgesia. First of all, functional brain imaging studies show that neither of the treatment effects are due to response bias. This conclusion is based on the observation that decreased pain ratings are associated with activity changes in the pain network of the brain. This network comprises of somatosensory cortex, ACC, insula, thalamus and prefrontal cortex and its activity is known to be changed along with the pain experience (Apkarian et al., 2005; Peyron et al., 2000). Second, there are some results which suggest that both placebo and hypnosis effects are mediated by dopaminergic activity and caused by changes in expectations.

On the other hand, the evidence gathered so far shows that there are also major differences in the brain activity between hypnosis and placebo effects. During the placebo treatment decreased pain ratings are associated with functional changes in several parts of the limbic system, such as amygdala, hypothalamus and hippocampus, which are known to participate in memory, emotions and autonomic processes (Bingel et al., 2006; Craggs et al., 2008; Kong et al., 2006; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2009) as well as in the PAG (Bingel et al., 2006; Scott et al., 2008; Wager et al., 2004; Zubieta et al., 2009) and the nucleus accumbens known to be involved in craving (Scott et al., 2008; Zubieta et al., 2005; Zubieta et al., 2009). Instead, hypnotic pain relief causes changes of activity in the occipital areas concerned with imagery processing (Faymonville et al., 2000; Rainville et al., 1999) and basal ganglia which take part for example in the voluntary movement regulation (Faymonville et al., 2000; Faymonville et al., 2003; Vandenhuyse et al., 2009).

Based on these results it can be concluded that the analgesic effect which treatment with hypnosis may have on acute produced pain is probably more than just placebo effect in terms of brain functionality. This supports the previous result according to which placebo and hypnosis are different processes of top-down regulation (McGlashan et al., 1969). However, the recent knowledge is insufficient to make assumptions on whether the state of hypnosis can be described as altered

consciousness or are the results rather the manifestation of differences in treatment procedures between placebo and hypnosis. In the latter case hypnosis could be regarded as simply another form of placebo treatment.

## Discussion

At the present time the study of the placebo effect and hypnosis seems to have different approaches: in the field of placebo the focus is set on the neurochemical processes, while study of hypnosis is most often an investigation of its efficacy as a treatment in clinical practice. The nature of hypnosis is highly debated (Kallio & Revonsuo, 2003), and currently there is insufficient scientific evidence to support or reject either viewpoint. However comparing hypnosis and placebo treatments in the same study might bring new insight on the matter.

Another direction for future research would be to examine the role of different treatment elements in the alleviation of pain. For instance, how important are hypnotic induction and its deepening for the magnitude of pain alleviation? Or how much do quality and quantity of suggestions affect the decrease in the perceived pain? Conditioning is seen as an important part of the placebo effect (Amanizio & Benedetti, 1999); however, the reputation of hypnosis also creates certain expectations. Can this be interpreted as conditioning and what part does it play in the effect of the hypnotic pain treatment? The additional conditioning used in the placebo studies could also be exploited in the research of hypnosis.

There is a lot of inconsistency in both placebo and hypnosis research. The comparability of study results would be increased if some common standards were found. For instance hypnotizability and suggestibility are qualities that should be measured systematically and used in the data analysis, because they might confound the results (Scott et al., 2008; Wager et al., 2004).

The interaction of the body and the mind is complex. In a spiritual trance, some martial arts or life-threatening situations the perception of pain is sometimes reported to disappear completely. Even simple relaxation or distraction is often enough to gain an analgesic effect. Placebo effect and hypnosis are thus only two forms of the mind-body coaction.

The significance of pain is assimilated early in life. Gradually we learn the limits of our body, internalize the ways to avoid pain and the commonly accepted ways to react to it; we realize the role of pain in punishing and bringing pleasure. The pain produced in the laboratory settings is different from the pain in every-day life which usually comes unexpectedly. Still, by means of scientific study pain alleviation can be better modelled, understood and applied. The goal of pain research on hypnosis and the placebo effect is to utilize the obtained knowledge in the treatment of pain, to be able to use more efficiently our own abilities and resources to diminish the suffering.

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