Psychological and neurological factors of placebo analgesia

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Abstract

Placebo analgesia is defined as an inert substance or a sham physical treatment that could reduce pain experiences. Psychological context, such as verbal suggestion and visual cues, plays an important role in placebo analgesia. The potentially beneficial effect of placebos is mediated by diverse processes, including psychological and neurological mechanisms. The main psychological mechanisms indicated to play a role are learning trough conditioning and expectations. These factors activate the brain to release certain neurotransmitter in several brain areas, which could be the underling mechanism of the placebo effect. Interestingly, changed activation during placebo analgesia takes place in brain areas involved in the descending modulatory pain pathway. Neurotransmitters indicated to be involved in placebo analgesia are opioids, dopamine and endocannobinoids. Another interesting factor in placebo analgesia research is the huge variation in effect size, there are high and low responders. Individual differences in personal traits, brain structure, genetics, gender and age could influence the proneness to placebo analgesia effects. Knowledge about the beneficial effects and underlying mechanisms of placebo analgesia could have important implications to improve the effectiveness of real medicine.

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Introduction

Placebo is derived from the Latin root 'placere' (to please) and is usually defined as an inert substance or a sham physical treatment which may result in reduced symptoms (Colloca et al., 2014; Geuter, Koban & Wager, 2017). Although, according to other researchers this description of placebo is not complete. The psychological context, including verbal suggestions, symbols and rituals, also play an important role and should be taken into account for placebo effects (Benedetti, Piedimonte & Frisaldi, 2018). An explanation for the existence of placebo effect can be found in possible adaptations of the body that are optimal given the environment. The nervous system enables the body to focus on important goals and actions, for example suppress pain while running away from danger (Crombez et al., 2012; Wager & Fields, 2013).

Placebos have a long history, since the beneficial effects of man's first medication probably depend on the placebo effect (Shapiro, 1959). Haygart (1801) recognized the placebo effect for the first in a clinical trial. In this clinical trial was found that a successful tool invented to reduce pain was nothing more than a sham treatment. Much later, during the Second World War, Henry Beecher demonstrated the placebo effect in practice. While treating wounded soldiers, he ran out of the pain killer morphine. He replaced it by inert saline, but told the soldiers that they received morphine. Surprisingly, 40 percent of the soldiers reported reduced pain (Gross, 2017).

Although the effectiveness of placebo was indicated, the word placebo was applied in research to the control group with an inert substance to compare and determine effects of real medicine (Caen et al., 1999; Diehl et al., 1938). In this way, the placebo effect was not isolated but used to investigate therapeutic effects of medicine. An additional group without treatment should be included to examine placebo effects when testing the effects of drugs. Since Beecher (1955) proposed that placebos could have important clinical effects, research regarding placebos increased extensively. Various study designs have been used to investigate placebo analgesia effects (Wager & Atlas, 2015). More recent studies concerning the underlying psychology and neurobiology of placebos have yielded a greater appreciation of the potentially beneficial effects of placebos (Belcher et al., 2018; Colloca, Enck & DeGrazia, 2016).

Indicated beneficial effects of placebos are investigated across a wide array of disorders and conditions, including pain, Parkinson disease, depression and cognitive performance (Geuter, Koban & Wager, 2017). Although placebos could relief symptoms, evidence suggests that they are unlikely to cure underlying diseases (Kaptchuk & Miller, 2015). This essay focuses on analgesia effects of placebos, since pain serves a good model to study placebo effects for several reasons. One reason is that underlying mechanisms that modulate and induce pain are well described in literature and those mechanisms are implicated in placebo analgesia (Millan, 2002; Ossipov, Dussor & Porreca, 2010). Another reason is that pain relieving effects of placebos are extensively investigated in the healthy and clinical population (Schafer, Geuter & Wager, 2018).

The potentially beneficial effects of placebos are mediated by diverse processes, including psychological and neurological mechanisms. Important factors for psychological mechanisms are learning trough conditioning and expectations (Benedetti 2014, Enck et al. 2013, Wager & Atlas, 2015). These factors activate the brain to release several neurotransmitters in different brain areas, which could be the underlying mechanism of the placebo effect. In the context of placebo analgesia effects, various neurotransmitters are indicated to play a role, including opioids, dopamine and endocannobinoids (Skyt et al., 2020; Zunhammer et al., 2018). However, discrepancies exist in literature about the exact psychological and neurological mechanisms.

Therefore, the aim of this essay is to determine and describe the neurological and psychological mechanisms that are involved in placebo analgesia effects. First, pain perception will be explained, followed by placebo research including physiological and neurological factors. In the last section individual differences regarding proneness of placebo analgesia will be discussed. The beneficial effects of placebo analgesia could have important implications to improve the effectiveness of real medicine. As a result, reduced doses of medication will lead to desired therapeutic effects and reduction of side effects.

Pain perception

According to the International Association for the Study of Pain (IASP), pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (Bonica, 1979). The function of pain is to motivate an individual to withdraw from a damaging situation, to protect healing body parts and to avoid comparable situations in the future (Cervero, 2012). Specific ascending and descending pathways are involved in the perception of pain, called nociception.

The ascending pathway of pain sends possible threat signals from the body to the spinal cord and brain, also called bottom-up (figure 1A). This pathway starts with damaged cells, including inflammatory cells that release several substances that activate nocireceptors. Nocirecpetors on the afferent nerve fibers are called the first order neurons. The axons of those nerve cells enter the dorsal horn of the spinal cord and release substance P. Substance P stimulates secondary order nerves in the dorsal horn and the signal travels via the spinothalamic tract to the brainstem and thalamus (Purves et al., 2004). The second order neuron has also synaptic contacts with other regions of the brainstem, such as the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) (Damien et al., 2018). The thalamus projects via third order neurons to the somatosensory cortex, where the information is interpreted as pain (Purves et al., 2004). In addition, the thalamus signals to other structures including the frontal cortex, anterior cingulate cortex (ACC) and insular cortex. The latter connects with limbic structures such as the amygdala and the perirhinal complex. This pathway is related to the judgment of the unpleasantness of pain (Damien et al., 2018). Pain experience is a complex process, since many brain areas are involved.

The number of nociceptive stimuli does not always correlate with the sensory experience of pain. Even when the pain stimulus is similar, pain experiences may vary dramatically between individuals (Ossipov, Dussor & Porecca, 2010). An explanation for changed pain experience can be found in the existence of a descending modulatory pain system, also called top-down regulation (figure 1B). Functional and anatomical studies in animals and humans have provided indications for the descending pathway. In this pathway PAG receives input from multiple higher level brain areas, including the amygdala, hypothalamus and the rostral ACC (rACC) (Hadjipavlou et al., 2006; Schafer, Geuter & Wager, 2018; Zemel & Blier, 2016). PAG communicates with the RVM. Finally, efferents of the RVM project to nociceptive neurons in the dorsal horn of the spinal cord, where they can inhibit nociceptive signals (Damien et al., 2018; Ossipov, Dussor & Porecca, 2010).

The descending connection between higher level brain areas and the spinal cord could represent the background by which cognitive and emotional variables influence the experienced pain. Examples of such cognitive and emotional variables are emotional state, attention and distraction, past experiences, memories and degree of anxiety (Ossipov, Dussor & Porecca, 2010). It is possible that analgesia effects of placebos result from activation of the descending pathway or mimicking the consequences of activation of this pathway (Zunhammer et al., 2018).

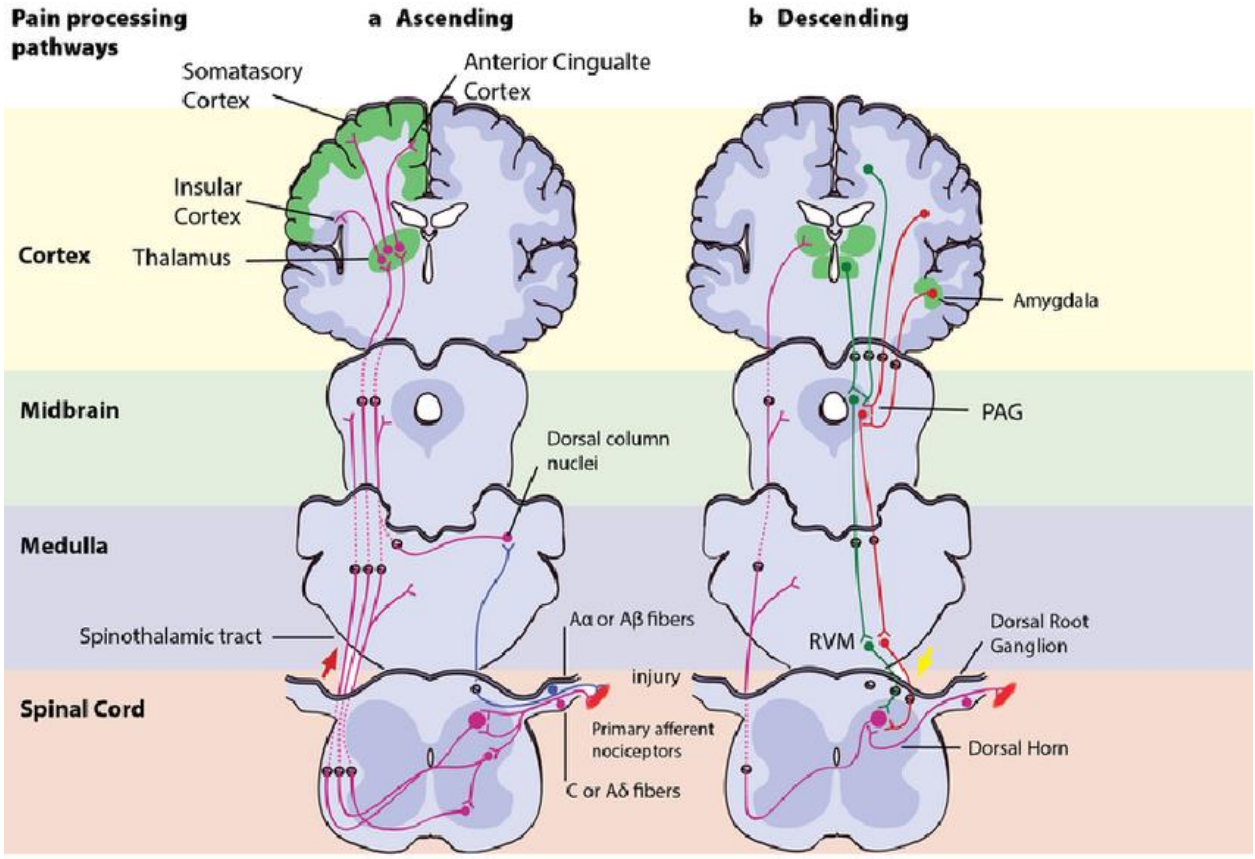

Figure 1 Pain processing pathways. A: Ascending pain pathway. An injury is signaled simultaneously from nociceptors and sends all the way up to the thalamus via the spinothalamic tract. The thalamus relays the signal to the somatosensory cortex and other cortical structures where the perception of pain takes place. B: descending pathway. Several structures in the limbic forebrain project to the periaqueductal grey (PAG), which modulates indirectly the ascending pain pathway through the rostral ventromedial medulla (RVM). This pathway induces analgesia via control of the nociceptive signals at the dorsal horn (Loseth, Ellingson & Leknes, 2013).

Placebo research

For many years placebos were used as controls in clinical trials in order to examine drug effects over and above placebo effects. However, possible beneficial effects of placebo were not isolated in this way. Since Bleecher (1955) described the effectiveness of placebos, there was more interest in the power of placebos. In order to account for the natural course of a disease, fluctuation in symptoms and regression to the mean, placebo treatments were compared with no treatment groups (Kirsch, 2003; Schafer et al., 2018).

To isolate the placebo effect, different paradigms have been applied; parallel group, open versus hidden drug, response conditioning and pharmacological conditioning design (figure 2) (Wager & Atlas, 2015). In addition, there are other methodological factors that vary within each paradigm. For example, differences in the way studies induce pain or investigate already existing pain and the quality of used neuroimaging techniques. Another important factor that differed between studies was the type of placebo treatment. While some used non-invasive treatments like pills or creams, others applied more invasive treatments like injections or sham surgeries (Atlas & Wager, 2014).

The effectiveness of placebo depends on the way of treatment. A study regarding high altitude headache compared two different placebo treatments to reduce headaches in a pharmacological conditioning design. In the conditioning phase one group of subjects received oxygen inhaled by a mask and another group received aspirin swallowed as a pill. In the testing phase the groups received a mask without additional oxygen or a placebo aspirin respectively. Although both treatments did not increase blood oxygen levels, they both reduced altitude headaches. The effects of placebo oxygen were superior to placebo aspirin. Interestingly, the pathway responsible for the relief of pain differed between the paradigms. The mask ritual induced a decrease in minute ventilation and blood pH, while the pill induced a decrease in prostaglandins (PG) and thromboxane. Both treatments lowered PGE2 levels and could therefore be a common factor in the pain relieving pathways. This study indicates that placebos associated with different therapeutic rituals use different mechanisms to reduce altitude headache (Benedetti et al., 2015).

Two meta-analyses also indicated that the effectiveness of different placebo treatments was not similar (Bannuru et al., 2015; Meissner et al., 2013). Meissner et al. (2013) compared several studies regarding placebo analgesia in migraine patients with different placebo treatments. The proportion of placebo responders was defined as having at least a 50% reduction of migraine attack frequency. The proportion of responders differed between treatment types; sham surgery was associated with the highest proportion responders (58%), followed by sham acupuncture (38%) and pharmacological placebos (22%). Another meta-analysis of studies concerning knee osteoarthritis pain found also differences in effectiveness between placebo treatment types. In this analysis the outcome measure of interest was change in pain after 3 months. 3 different types of placebo treatments were compared, including oral, intra-articular and topical. Oral placebo consisted of a sugar tablet, intra-articular was a saline injection and topical included a cream or gel on the knee. Effect size of intra-articular (0.29) and topical (0.20) were greater compared to oral placebos (Bannuru et al., 2015).

Combinations of several factors result in a wide-range in methodological differences between studies, which makes it hard to draw general conclusions about effectiveness of placebo analgesia. Therefore, it is important to describe the used methods and paradigms in much detail in scientific literature.

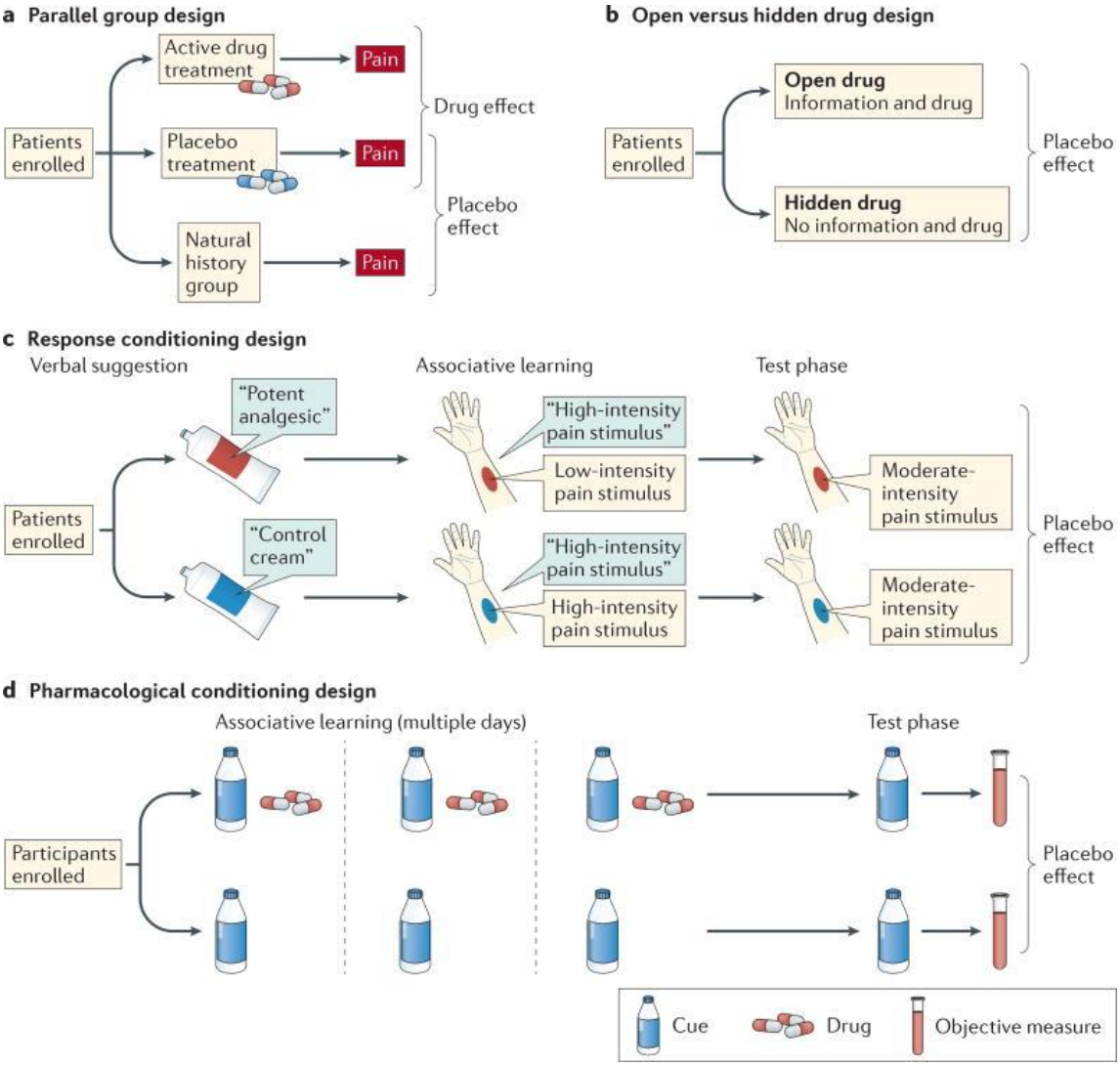

Figure 2 Four mainly used designs for assessing placebo effects. A: parallel group design. Placebo effects are measured by comparing a placebo group with a no-treatment group. B: open versus hidden design. Drugs are administrated with or without knowledge of the subject. C: response conditioning design. Verbal instructions about the placebo treatment are paired with reduced pain stimulus and control treatment with normal pain stimulus. D: pharmacological conditioning design. Verbal instructions and cues are paired with active drugs during conditioning. Placebo effects are tested by cues alone (Wager & Atlas, 2015).

Psychological factors of placebo analgesia

Placebo effects are induced via multitude psychological elements in the different paradigms. The most well-known theories have been described as expectancy and learning through classical conditioning. Both theories have been shown effective to induce placebo analgesic effects (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006; Schenk et al., 2014; Zunhammer, 2017).

Expectancies

Expectancies can be influenced by verbal suggestions of the physician and the context, like visual cues of the form or color of the pill or capsule (Rossettini et al., 2020; Schafer, Geuter & Wager, 2018). Verbal suggestions are the simplest and most direct way to induce expectations and, therefore, most often used in studies regarding expectations. This design was used by Schenk et al. (2014) to investigate the role of expectancy in pain relief during lidocaine treatment, a typical analgesic. One group received lidocaine treatment and verbal instructions to induce positive expectations about pain relief, while the other group received only lidocaine treatment. The group with verbal instructions showed additional reduction in reported pain compared with the group in which no positive instructions were given (Schenk et al., 2014). This result highlights the important role of expectancy in pain relieving effects. In addition, more precise pain reducing instructions of a placebo treatment leads to increased placebo analgesia effects compared to less precise instructions (Grahl Onat & Büchel, 2018). Helping subjects to form precise expectations about a placebo treatment could be beneficial for the analgesic effects of placebos.

The role of expectancies is not only present for placebo analgesia; it also plays an important role for analgesic medication. In an open versus hidden paradigm (figure 2B) the same analgesic was administrated under two conditions after a surgery. In the first condition the patient was aware of the time point of the analgesic; a health practitioner administered the medication. In the hidden condition, the analgesic was administered by a preprogrammed infusion machine. Subjects that received the medication in the presence of the health practitioner required much lower doses of morphine to reduce their pain with 50% than those with the preprogrammed infusion machine (Colloca et al., 2004). This study indicates that rituals could enhance the effect of real medicine.

Conditioning through learned associations

Pharmacological and response conditioning designs have provided evidence that placebo effects can depend on learned associations from prior experiences, also called classical conditioning (pavlov, 1927; Wager & Atlas, 2015) (figure 2 C and D). In the pharmacological conditioning design of Amanzio & Benedetti participants learned that a drug, morphine, was associated with reduced pain experience (1999). When the drug was replaced by a placebo, the analgesic response was still present. Another study paired placebo treatment with a decreased pain stimulus. Afterwards, painful stimuli paired to a placebo treatment resulted in less pain experiences compared to a no treatment group (Colloca & Benedetti, 2006). Both studies showed that learned associations from prior experience can induce placebo analgesia effects (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006).

Despite the positive effects described above, learned associations from prior experiences can also have negative consequences on placebo effects. In the study of Zunhammer (2017) subjects received during the conditioning phase a placebo patch with a painful stimulus. The next time subjects with the placebo patch received a decreased painful stimulus, but subjects still mentioned to experience a painful stimulus. Even when the patch was replaced by a placebo analgesic pill, subjects experienced a painful stimulus when the intensity of the stimulus was decreased. This study shows that negative experiences with placebo analgesia can influence experiences in the future, even if the type of treatment changes.

Although expectancies and learned associations are separately portrayed to explain placebo analgesia, these processes do not have to take place independent of each other. Conditioning conditions can also alter expectations, such that the placebo effects of conditioning designs are mediated by expectations (kirsch et al., 2014). Collectively, complex psychological processes are involved in placebo effects, mediated by verbal suggestions, contextual cues and prior experiences. It is important to mention and explain the psychological factors in placebo research, since they could attribute to effectiveness of the placebo treatment.

Neurological factors of placebo analgesia

The first indications that placebo effects depend on neurological processes was found in 1987. Levine et al. (1987) showed that analgesic placebo effects were abolished by the opioid antagonist Naloxone, suggesting that endogenous opioid release was involved in placebo analgesia. Later, brain imaging studies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), corroborated opioid release during placebo analgesia (Petrovic et al., 2002; Wager et al., 2004). Later studies also found evidence for the involvement of other systems, including dopaminergic and endocannabinoid systems (Zunhammer et al., 2018).

Results of individual neuroimaging studies could reflect fundamental mechanisms of placebo analgesia, but it is also possible that results are due to the unique context and designs of studies. Meta-analysis provides a good way to determine which part of the central nervous system and which neurotransmitters are consistently indicated across studies in order to differentiate fundamental effects from study specific effects. In the next section results of studies regarding the central nervous system, including the brain and spinal cord, and neurotransmitters involved in placebo analgesia will be discussed.

Central nervous system

Two large-scale meta-analyses were performed to investigate which brain areas were involved in placebo analgesia effects, including studies using PET and fMRI. All subjects were healthy and pain was induced and not chronically present. Both meta-analyses found evidence that during placebo analgesia there is reduced activation in the thalamus and insula, both known as classical pain processing areas (Amanzio et al., 2012; Atlas & Wager, 2015). Although precise location differed between meta-analysis, both showed reduced activity in the cingulate cortex. Reduced activation of ventral striatum, bilateral amygdala and bilateral lateral prefrontal cortex was indicated in one of the meta-analysis (Atlas & Wager, 2015). Differences between meta-analysis might be due to differences in analyses technique or number of included studies (11 versus 25 for Amanzio et al., 2012 and Atlas & Wager, 2015 respectively).

A more recent meta-analysis regarding neurological changes of placebo analgesia in healthy subjects with induced pain was performed by Zunhammer et al (2018). Instead of investigating separate brain areas, this study used a neurological pain signature (NPS). NPS has been shown to be a reliable measure for evoked experimental pain and includes an activation pattern of several brain areas, among others the thalamus, the posterior and anterior insula, ACC and PAG (Wager 2013). Although the meta-analyses found moderate effects on pain reports as result of placebo treatment, a very small effect on NPS was present (Zunhammer et al., 2018). These findings indicate that placebo effects depend on underlying networks that differ from those underlying primary processes of experimental evoked pain (Wager et al., 2013).

The involvement of the spinal cord in placebo analgesia is shown by Eippert et al (2009a) using fMRI. The response conditioning designs was used in this study, including a placebo pain relieving cream and a control cream (figure 2c). During conditioning the placebo cream was associated with a reduced painful stimulus and the control cream with a normal painful stimulus. In the test phase, pain stimuli on both creams were identical and fMRI measurements were done. The placebo cream resulted in significant lower pain ratings during the test phase compared to the control cream. They also found a reduction in spinal cord blood oxygen level-dependent (BOLD) response in the dorsal horn with the placebo cream, indicating inhibition of spinal cord pain processing. A more extensive research of Eippert et al (2009b) used the same setup, but subjects received either a saline injection or an opioid antagonist Naloxone injection before the test phase. Naloxone prevented placebo induced pain reduction, indicating the involvement of the opioid system in placebo analgesia. There were also neurological changes observed, naloxone modulated placebo induced activation changes in the rACC, hypothalamus, PAG and RVIM. In addition, Naloxone abolished the connection between rACC and PAG. These results suggest that placebo analgesia is possibly mediated by changes in the descending pain inhibitory circuit (Figure 1).

Neurotransmitter systems

Several neurotransmitters are indicated to play a role in aforementioned parts of the central nervous system during placebo analgesia. Neurotransmitters transfer nerve impulses across synapses and could serve as the potential mediators of placebo analgesia (Skyt et al., 2020). There is a lot of research done to specify which neurotransmitter system is involved in placebo analgesia, especially with induced pain in healthy subjects. The results are however mixed and sometimes even contradictory. It seems that the endogenous opioid system, dopaminergic system and endocannabinoid system could be involved during different circumstances under which placebo analgesia takes place.

Endogenous opioid system

The endogenous opioid system has repeatedly been found to be involved in placebo analgesia in healthy subjects. A recent review found that eight pharmacological studies showed that the placebo analgesia effect can be partly or entirely blocked by naloxone, which is a μ-opioid antagonist. In addition, the review mentioned five brain imaging studies in which increased opioid activity was observed in the rACC, amygdala and PAG (Skyt et al., 2020). Those brain areas are indicated to play a role in the descending modulatory pain system (Zunhammer et al., 2018).

Schafer et al. (2018) described in more detail the involvement of the opioid system in separate brain areas. They combined the results of several neuroimaging studies to make figure 3. Figure 3 shows that the opioid release during placebo analgesia within rACC, dorsal ACC (dACC), PAG, thalamus, hypothalamus, RVM, ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC) were all reversible by naloxone. Pain reduction after placebo administration was also abolished with naloxone in those studies. This indicates that placebo analgesia depends on opioid signaling in pain modulation areas and downstream effectors in the descending pathway (Eippert et al., 2009b; Loseth, Ellingson & Leknes, 2013; Schafer, 2018). In addition, the strength of placebo analgesia correlated with opioid activity in the AAC, vmPFC, PAG and nucleus accumbens (NAC). This indicates that the opioid system plays a regulatory role in placebo analgesia (Eippert et al., 2009b; Scott et al., 2008).

Interestingly, placebo effects were not partly or entirely blocked with naloxone under all circumstances. Subjects in aforementioned studies and review articles regarding opioid were all healthy and the pain was induced. Two studies performed in chronic pain subjects, including irritable bowel syndrome and low back pain, found that naloxone administration did not block placebo effects (Kupers et al., 2007; Vase et al., 2005). These results indicate that the opioid system is not entirely involved in placebo effects in chronic pain. It is possible that the pain perception pathway is altered by chronic pain and mechanisms underlying placebo effects differ between healthy subjects and chronic pain subjects. Since placebo is still present in chronic pain subjects, other neurotransmitter systems are probably also involved.

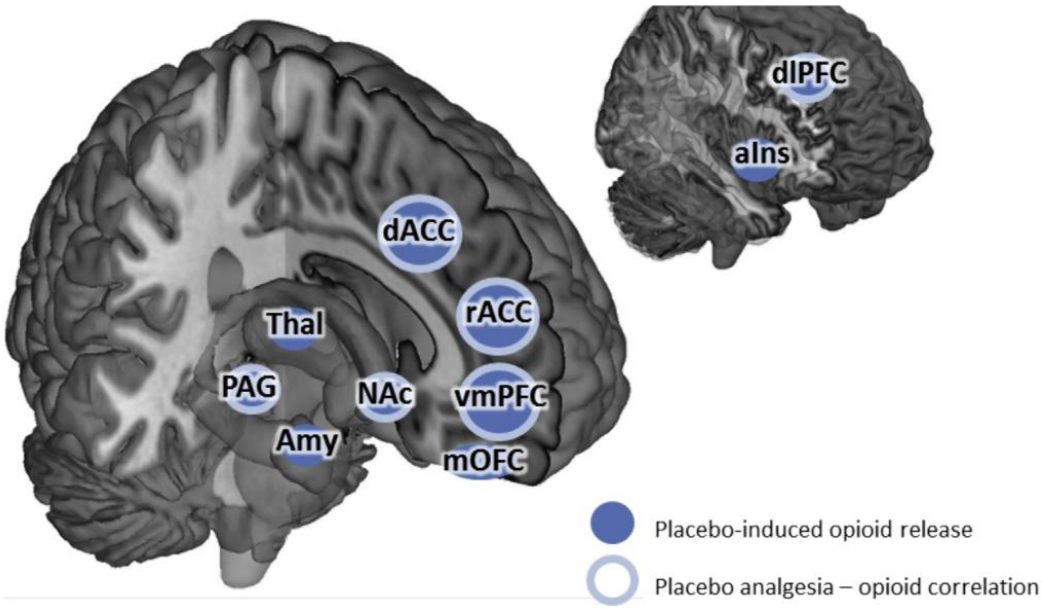

Figure 3. Placebo analgesia induced opioid release and opioid correlation in brain areas based on several neuroimaging studies. Placebo analgesia is associated with increased activity within dACC, rACC, vmPFC, medial orbitofrontal cortex (mOFC), NAc, amygdala (Amy), PAG, Thalamus (thal), aIns, dlPFC (dark blue fill). Placebo analgesia is correlated with opioid activity within dACC, rACC, cmPFC, NAC, PAG, dlPFC (Light blue outline) (Schafer, Geuter & Wager, 2018).

Dopaminergic system

The expectancies of reduced pain experience during placebo treatment can be considered as a form of reward anticipated response. Dopaminergic cells projections to the NAC are thought to be involved in the anticipated reward response (Tobler, Fiorillo and Schultz, 2005). Therefore, Scott et al. (2007) examined changes in dopamine neurotransmission during placebo analgesia. The study employed fMRI and PET scans using [C11]-labeled raclopride, which is selective for D2 receptors and also labels D3 receptors in the NAC (Seeman et al., 2006). Painful challenges were induced with 5% hypertonic saline to elicit a painful signal and took place in the presence and absence of placebo, which was introduced as a potent analgesic to the subjects. They found that placebo administration induced significant reduced binding potential of raclopride in the left and right NAC. This result implies that dopamine was already bound to the D2 and D3 receptor and is related to placebo analgesia effects. A monetary Incentive Delay (MID) task was performed to investigate NAC activation during anticipation of reward. From those results researchers concluded that greater responses in NAC during monetary reward, predicted greater pain relief induced by placebo. These results confirm the role of expectancy and the reward system in placebo analgesia. From this study it is however not clear whether NAC dopamine activation simply reflects attention to a stimulus without consequences or that dopamine activation causes placebo analgesia effects. Further research should determine if placebo analgesia effects will be present or not when dopamine receptors are blocked.

Further research of Scott et al (2008) investigated whether the opioid and dopamine systems are both involved in placebo analgesia. The same paradigm with pain challenges and placebo administration were used as in Scott et al. (2007). Raclopride was used to determine dopamine neurotransmission activation and carfentanil to determine opioid neurotransmission activation with PET scans. They detected opioids neurotransmission in several brain areas, including NAC. Dopaminergic neurotransmission was also found in NAC during placebo analgesia. Subjects in which placebo resulted in the highest pain reduction, also called high placebo responders, were associated with greater opioid and dopamine neurotransmission activation in NAC. The study suggests that both endogenous opioids and dopamine in the reward system contribute to placebo analgesia effects.

Endocannabinoid system

Although much information is available about opioid dependent placebo analgesia effects, there is also evidence for non-opioid dependent effects in healthy subjects. After repeated exposure subjects learned that administration of the non-opioid agent nonsteroidal anti-inflammatory drug (NSAID) reduced pain experience. When NSAID was replaced by placebo subjects still reported decreased pain experience. Interestingly, placebo effects were not abolished when naloxone was added to the placebo administration, suggesting that placebo analgesia effects were not mediated by opioids (Amanzia & Benedetti, 1999). Another research found that placebo analgesia effects induced by non-opioid pharmacological conditioning were blocked with rimonabant, which is a CB1 cannabinoid receptor antagonist (Benedetti et al., 2011). These results indicate that placebo analgesia effects in this case were mediated by CB1 cannabinoids. Although the site of action of CB1 cannabinoid was not established in this study, from previous research is known that CB1 receptors are present in the striatum (Wong et al., 2010). Therefore, further research should investigate the possible role of cannabinoids in the striatum during placebo analgesia.

Individual differences

A crucial point in placebo research is the understanding of why some people respond whereas others do not. It is remarkable that effect size of placebo analgesic effects varies greatly between studies (Dodd et al., 2017; Zunhammer et al, 2018). It is possible that the sufficiency to induce placebo effects differ between experimental paradigms. For instance, verbal suggestions failed to produce strong expectations in participants (Schafer, Geuter & Wager, 2018). However, variations between subjects within studies still exist; subjects are also indicated as responders and non-responders of placebo analgesia effects. Another important explanation could be found in individual differences that contribute to proneness to experience placebo analgesia. Factors that could play a role are personality traits, structure and function of brain areas, genetic influences, gender and age.

Personality traits

Personality traits have been indicated to predict the proneness to placebo effects. Optimism, suggestibility and empathy have been positively correlated to placebo analgesic effects. On the other hand, the personality trait neuroticism showed negative correlation with placebo analgesia effects (Corsi & Colloca 2017; Peciña et al., 2013). However, personality traits were not indicated to influence expectations about pain relief (Corsi & Colloca 2017).

Brain anatomy

Individual proneness to placebo could be the result of differences in brain anatomy, including structures and functioning. The results of Scott et al. (2008) indicating an association between high placebo responders and increased activity in opioid and dopamine neurotransmission corroborate this hypothesis. In addition, gray matter density in several brain areas has been linked to the magnitude of placebo analgesia effects by Schweinhardt et al. (2009). The magnitude of placebo analgesia effects was determined by the comparison of self-rated pain of a painful hypertonic saline infusion paired with a control cream and a placebo analgesic cream. Gray matter density of brain areas was investigated with MRI. Results showed that increased gray matter density in the ventral striatum was related to an increased placebo analgesic response, meaning increased pain relief with a placebo cream. Gray matter density in the insula and temporal cortex and in the medial frontal gyrus also significantly positively correlated with placebo analgesia effects.

Differences in white matter integrity could also explain individual differences in response to placebo, because efficient communication between brain areas depends on the integrity of white matter tracts. With diffusion MRI, white matter integrity was measured during placebo analgesia in healthy subjects. The response conditioning design was used in this study, consisting of a thermal stimulation paired to a control and placebo analgesic cream. The results showed a positive correlation between placebo analgesia responses and white matter integrity in rACC and DLPFC, including their pathways to the PAG (stein et al., 2012). This study provides also evidence that the modulatory pain pathway is involved in placebo analgesia.

Genetic variation

Genetic influences in several neurotransmitter pathways could determine the tendency to the formation of placebo analgesia effects. Three studies indicated a single nucleotide polymorphism (SNP) A118G in the μ-opioid receptor gene (OPRM1) as a predictor of placebo analgesia effects (Peciña et al., 2015). OPRM1 G carriers showed smaller placebo analgesic effects compared with AA homozygotes. Interestingly, G carriers presented lower activation of the μ-opioid system in the anterior insula, amygdala, thalamus and brainstem during placebo treatment (Aslaksen, Frosberg & Gjerstad, 2018; Colloca et al., 2019; Peciña et al., 2015). Higher neuroticism was also observed in G carriers, this personality trait was previously associated with lower placebo analgesia effects (Peciña

et al., 2013, 2015). Two of the aforementioned studies found an interaction effect of the SNP A118G with a SNP val158met in catechol-O-methyltransferase (COMT), which influences opioid metabolizing. The SNP in COMT SNP alone did not affect the placebo analgesia response (Aslaksen, Frosberg & Gjerstad, 2018; Colloca et al., 2019). Moreover, one study found a three-way interaction between A118G, the val158met SNP in COMT and the Pro129Thr SNP in the fatty acid amide hydrolase (FAAH) gene. FAAH is the major degrading enzyme of endocannabinoids. There was no effect of the SNP in the FAAH gene alone (Colloca et al., 2019). Those results together suggest that the endogenous system is involved in the presence and magnitude of placebo analgesia responses.

Another study did find an association between placebo analgesia and the Pro129Thr SNP in the FAAH gene. Subjects with FAAH Pro129/Pro129 showed higher placebo analgesia effects compared with thr129 carriers. In addition, administration of placebo to subjects with Pro129/Pro129 resulted in greater activation of endogenous opioid systems in several brain areas, among them the DLPC, ACC and insula (Peciña et al., 2014). These findings support the idea that endogenous opioid and cannabinoid systems act synergetic in placebo analgesia responses.

Gender

Another factor that could influence the magnitude of placebo effects is gender. Vambheim & Flaten (2017) performed a meta-analysis to compare placebo effects of sexes in 12 studies regarding administration of placebo including verbal suggestions or conditioning. They found a significant association between gender and placebo effect, in which more placebo effects were found in males compared to females. An explanation could be found in differences in psychological mechanisms involved in stress and anxiety between sexes. In addition, personal traits as discussed above could be linked to genders and subsequently affect this result.

Age

The effect of age on the magnitude of placebo analgesia was examined by several studies, which reported controversial results (Daguet et al., Ho et al., 2009; 2018; Wrobel et al., 2016). Daguet et al. (2018) showed that after placebo stimulation young individuals (21-39 years) showed 15% heat pain reduction, while older individuals (58-76 years) showed 40% heat pain reduction. These findings suggest that older subjects experience higher placebo analgesia effects than younger subjects. Ho et al. (2009) challenged this study, since they observed higher pain inhibitory effects of a placebo pill in younger migraine patients compared to older (2009). Another study found comparable capacity for placebo analgesia effects in healthy older (60-80 years) and younger (23-40 years) participants during thermal painful stimuli (Wrobel et al., 2016). These inconsistencies might be explained by methodological differences between studies, such as applied placebo treatments or differences in the way to induce pain.

Individual differences in proneness make effect size and comparison of placebo research complicated, but can also be advantageous used in the future. Aforementioned factors might be used as potential biomarkers of vulnerability for placebo analgesia effects. Physicians could for example spend more time to particular aspects for different target groups. In addition, individual differences should be taken into account during separation of drug and placebo treatment groups in scientific research to prevent uneven distribution.

Discussion

There is a wide range of study designs to investigate placebo analgesia effects, with variation in the placebo treatment, inducement of pain and analyses methods. The two main physiological processes indicated to mediate placebo effects are expectations and learning through classical conditioning (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006; Grahl Onat & Büchel, 2018; Schenk et al., 2014; Zunhammer, 2018). Factors that influence those processes are verbal suggestions, contextual cues and prior experiences.

Based on the literature it is not possible to give an unambiguously answer to the research question concerning which neurological pathways are involved in placebo analgesia. There is evidence that placebo can reduce pain and is associated with neurological changes. Those changes are often present in brain areas involved in the descending modulatory pain circuit, including the hypothalamus, PAG and RVM (Amanzio et al., 2012; Atlas & Wager, 2015). It seems that the involved neurotransmitter depends on the way placebo analgesia is induced. For example, conditioning with opioid or non-opioid determines which neurochemical mediates the placebo analgesia effects. In additions, the reward anticipated response of placebo analgesia point toward the involvement of dopamine (Scott et al., 2007, 2008).

A difficulty with the indicated brain areas and neurotransmitter associated with placebo analgesia is that those areas and neurotransmitters are involved in a range of functions. For example, they play a role in cognitive decision making, motor processes and emotion (Zunhammer et al., 2018). Such associations do not provide evidence that the brain processes that are affected by placebo are directly responsible for analgesic effects. It is also possible that during placebo analgesia brain processes reflect nonspecific processes. To determine whether brain regions and neurotransmitter reflects specific placebo analgesia processes, more sophisticated analyses are needed. One way to tackle this problem is to vary the intensity of the pain stimulus during control and placebo treatment. In this way, subject specific regions of interest involved in pain processes could be established and compared to responses during placebo effects (Atlas & Wager, 2014). In the case of chronic pain this method is not suitable to investigate placebo analgesia. Possible altered mechanisms of pain experiences during chronic pain should first be clarified in order to be able to differentiate between chronic pain and placebo analgesia effects.

Another difficulty with the neurological mechanism that mediates placebo analgesia is that several neurotransmitters are indicated by separate studies (Skyt et al., 2020). Although the exact role of each neurotransmitter is not known, it seems that endogenous opioids, dopamine and endocannabinoids could play a role in placebo analgesia under different circumstances. It is possible that methodological differences between studies cause the neurological differences. Further research should investigate several neurotransmitter systems under the same circumstances. One or more systems could be blocked by antagonist to determine exact roles. Different neurotransmitter system could have separate roles and could also enhance each other.

Since the major role of several psychological factors in placebo analgesia is repeatedly indicated, it is important to describe and explain those factors in every scientific research (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006; Grahl Onat & Büchel, 2018; Schenk et al., 2014; Zunhammer, 2018). For example, articles should include description of visual cues and the verbal instructions about the placebo treatment or the painful stimulus. In this way, comparison between studies and clarification of the role of different factors is possible. In additions, individual differences of subjects should be described, since those could affect results. Age and gender are most often mentioned, but previous experiences with pain reduction medication or personality traits could also be interesting to include. Those factors could influence and predict the proneness to placebo analgesia effects (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006; Corsi & Colloca 2017; Peciña et al., 2013). As a result, optimal conditions to increase effectiveness of placebo analgesia effects under certain circumstances could be determined and applied.

In this essay, the beneficial effects and possible underlying mechanisms of placebo analgesia are extensively described. It may be important to mention that clear-cut differences between

placebo and medicine do exist (Benedetti et al., 2016). Placebo could relief symptoms, whereas medicine also could influence underlying mechanism (Kaptchuk & Miller, 2015). The duration of effects of medicines is longer compared to that of placebos. For example, the effects of the anti-Parkinson drug apomorhine lasted on average 90 minutes, while placebo effect lasted 30 minutes. In addition, the variability in response to placebo is larger than to medicine (Benedetti et al., 2016).

The importance of placebo effects should however not be underestimated. Rather than only being used as control for medicine research, placebo effects should be deployed as enhancement of standard treatments (Schafer, Geuter & Wager, 2018). The psychological factors are wildly investigated for placebos, but could also play an important role for real medication. The open versus hidden designs to investigate analgesic indicated that awareness of treatment and expectancies are also important for real medication (Colloca et al., 2004; Bingel et al., 2011). Other factors that influence psychology could also enhance the effectiveness of medicine, such as the color or form of the medicine and the verbal explanation about the effectiveness. Interestingly, increased effects of medicine could lead to reduced doses to achieve desired effects and reduce side effects.

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