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Neuronal and Behavioural Pain Processing: A Comparison Between a Strong Brand and a Generic Medication Placebo using the Example of Aspirin vs. 1A Pharma

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Summary

In our study “Neuronal and Behavioural Pain Processing: A Comparison Between a Strong Brand and a Generic Medication Placebo using the Example of Aspirin vs. 1A Pharma”, we investigated the expectation effects associated with brands by labelling two different placebo interventions. We tested the hypothesis, whether a strong brand can influence the impact of an inert substance. We studied the potential differences between the two placebos on a behavioural and neural level inducing the stimulus with noxious heat pain using Medoc. The research objective was to unveil, whether recipients can be influenced through expectations, verbal suggestions and the brand itself.

We applied a two by two design with two identical placebo interventions that differed in their labelling. One group was told that they will receive 500 mg of “Aspirin” (original brand), while the other group was told that they will receive a popular ASA generic (“1A Pharma”). At the beginning, we established the individual pain levels of each subject with the numeric rating scale. Then we measured pain intensities before and after the intervention. The intervention was the administration of the placebo. We investigated behavioural as well as neural differences and looked for corresponding activated brain regions using functional magnetic resonance imaging (fMRI).

Those participants, who were administered the original brand in the placebo intervention, showed a decrease in pain intensity. The generic group did not show any significant pain decrease. At the neuronal level, during the native condition, we observed activations of the anterior insula in both groups. After the intervention, the participants showed activations of the dorsomedial prefrontal cortex. The direct comparison of the two placebo conditions – the branded placebo vs. the generic – showed higher activations for the bilateral dorsolateral and dorsomedial prefrontal cortex. During the anticipation phase we observed activations of hippocampal, parahippocampal and adjacent brain areas for the generic group, only.

These results suggest that only the original brand appears to evoke a behavioural response measured in terms of pain reduction. On a neuronal level, the activations were significant for the original brand only. Comparing the two placebo interventions, expectations seem to be significantly enhanced by the trusted brand, which appears to boost the placebo effect. Our results suggest that the underlying neural mechanisms of this placebo response are based on fronto-cortical neural networks.

Zusammenfassung (Übersetzung)

In unserer Studie "Neuronale und behaviorale Schmerzverarbeitung: ein Vergleich zwischen einer starken Marke und einem generischen Medikamenten-Placebo anhand der Beispiele Aspirin vs. 1A Pharma", untersuchten wir anhand von zwei Placebo-Interventionen die Erwartungseffekte, welche mit Markenpräparaten von Medikamenten verbunden sind. Wir prüften die Hypothese, ob eine starke Marke die Wirksamkeit einer inerten Substanz beeinflussen kann. Wir untersuchten die potentiellen Unterschiede beider Placebos auf neuronaler und Verhaltensebene unter Verwendung thermischer Schmerzreize. Diese wurden mittels Medoc Thermode appliziert. Das Forschungsziel war zu untersuchen, ob die Schmerzwahrnehmung der Probanden durch ihre Erwartungen, verbale Suggestionen und die Marke des Medikaments beeinflusst werden.

Als Experimentalbedingung wählten wir ein 2x2 Block-Design mit zwei identischen Placebo-Interventionen, die sich in ihrer Kennzeichnung unterschieden. Der einen Gruppe wurde mitgeteilt, dass sie 500 mg "Aspirin" (Originalpräparat) erhält. Die andere Gruppe erhielt die Information, dass sie ein beliebtes ASS Generika Präparat ("1A Pharma") verabreicht bekommt. Zunächst wurde für jeden Probanden sein individuelles Schmerzniveau anhand der numerischen Schmerzbewertungsskala bestimmt. Anschließend wurden die Schmerzintensitäten vor und nach der Intervention gemessen. Die Intervention ist hierbei die Verabreichung der jeweiligen Placebos, welche entweder als “Aspirin Original“ oder Generikum “1A Pharma“ bezeichnet wurden. Wir verglichen die Ergebnisse beider Gruppen auf behavioraler und neuronaler Ebene und ermittelten die korrespondierende Hirnareale mit erhöhter hämodynamischer Antwort mittels funktioneller Magnetresonanztomographie (fMRT).

Die Probanden der Marken-Placebo-Intervention (Originalpräparat) zeigten auf behavioraler Ebene eine Abnahme der Schmerzintensität von der Ausgangsbedingung (Nativ-Messung ohne Medikamentengabe) im Vergleich zur Interventionsbedingung (nach Placebo-Gabe). Die Generika-Gruppe zeigte keine signifikante Schmerzabnahme. Auf neuronaler Ebene fanden wir in der Nativ-Messung Aktivierungen der anterioren Insula in beiden Probanden-Gruppen. Nach

der Placebo-Gabe wurden diese durch Aktivierungen des dorsomedialen präfrontalen Kortex ergänzt. Ein direkter Vergleich beider Gruppen ergab in der Placebo-Intervention des Markenprodukts höhere bilaterale Aktivierungswerte im dorsolateralen und dorsomedialen präfrontalen Kortex. Während der Antizipationsphase zeigten sich nur in der Generika-Placebo-Gruppe Aktivierungen der hippocampalen und deren angrenzenden Hirnareale.

Diese Ergebnisse sprechen dafür, dass nur das Originalpräparat auf behavorialer Ebene zu einer Schmerzreduktion führt. Konform hiermit sind die neuronalen Ergebnisse, die ausschließlich in dieser Placebo-Gruppe signifikante Aktivierungen zeigten. Der Vergleich beider Interventionen spricht dafür, dass durch die vertrauenswürdige Marke die Erwartungen der Probanden signifikant verstärkt werden und der Placebo-Effekt gesteigert wird. Die Ergebnisse unserer Studie legen nahe, dass die zugrundeliegenden neuronalen Mechanismen dieses Placebo-Effekts auf fronto-kortikalen neuronalen Netzwerken basieren.

Die Ergebnisse dieser Dissertation wurden veröffentlicht:

Fehse, K., Maikowski, L., Simmank, F., Gutyrchik, E., & Meissner, K. (2015). Placebo Responses to Original vs. Generic ASA Brands During Exposure to Noxious Heat: A Pilot fMRI Study of Neurofunctional Correlates. Pain Medicine, 16(10), 1967-1974.

Diese Arbeit stellt eine Weiterentwicklung und Vertiefung der oben genannten Veröffentlichung dar. Es wurden auf neuronaler Ebene zusätzlich die Aktivierungen während der Antizipation analysiert.

Es wurden zudem ergänzend die folgenden behavioralen Daten ausgewertet:

- Maximale Schmerzbewertung
- Schmerzerwartung

Im Rahmen dieser Dissertation wurden die folgenden Fragebögen ausgewertet:

- POMS profile of mood states: Momentanes Befinden – aktuelle Stimmungsskala, Dalbert (1994)
- STAI-G X1 State and Trait Anxiety Inventory, Spielberger (1989)
- BMQ Beliefs about Medicines Questionnaire, Horne (1999)
- FPQ-III Fear of Pain, McNeil (1998)
- PVAQ Pain Vigilance and Awareness Questionnaire, McCracken (1997)
- SES-17 Social Desirability Scale, Stöber (2001)
- LOT-R Revision of Life-Orientation Test, Scheier, Carver and Bridges (1994)

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Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
AMY	Amygdala
ASS/ASA	acetylsalicylic acid
ATS	advanced thermal stimulation
BG	basal ganglia
BMQ	beliefs about medicines questionnaire
BOLD	blood-oxygen-level dependent contrast imaging
CBV	cerebral blood flow
CCKergic	cholecystokininergic
CL	centrolateral nucleus
deoxyHB	deoxygenated haemoglobin
dlPFC	dorsolateral prefontral
DLPT	dorsolateral pontine tegmentum
dmPFC	dorsomedial prefrontal cortex
EPI	echo-planar imaging
FA	flip angle
fMRI	functional magnetic resonance imaging
FOV	field of view
FPQ	fear of pain questionnaire
FEW	family wise error
FWHM	full-width at half maximum
g.	gyrus
GABA	gamma-Aminobutyric acid
HYP	hypothalamus
IASP	International Association for the Study of Pain
kE	cluster size
L.	left
L. hippocampus	left hippocampus
L. inf. Frontal g.	left inferior frontal gyrus

L. inf. occipital g	left inferior occipital gyrus
L. inf. temporal g	left inferior temporal gyrus
L. insula	left insula
L. middle frontal g.	left middle frontal gyrus
L. middle occipital g	left middle occipital gyrus
L. parahippocampal g	left parahippocampal gyrus
L. precunes	left precuneus
L. sup. frontal g. medial part	left superior frontal gyrus medal part
L. sup. motor area	left supplementary motor area
L./R. straight g	left and right straight gyrus
L./R. superior frontal g.	left and right superior frontal gyrus
LCD	liquid chrystal display
LMU	Ludwig-Maximilians University Munich
LOT-R	revision of life-orientation test
MCC	mid cingulate cortex
MDvc	ventrocaudal part of the medial dorsal nucleus
MHz	Megahertz
MNI	montreal neurologic institut
MPRAGE	magnetization-prepared rapid gradient echo
MRI	magnetic resonance imaging
ms	Milliseconds
NAC/Nacc	Nucleus accumbens
NCF	nucleus cuneiformis
NMDA	N-methyl-D-aspartate receptor
NRS	numeric rating scale
oxyHB	oxygenated haemoglobin
PAG	periaqueductal grey
PAVQ	pain vigilance and awareness questionnaire
PB	parabrachial nucleus
PCC	posterior cingulate cortex

PET	positron emission tomography
Pf	parafascicular nucleus
PFC	prefrontal cortex
POMS	profile of mood states
R.	Right
R. inf. frontal g.	right inferior frontal gyrus
R. insula	right insula
R. middle frontal g	right middle frontal gyrus
rACC	rostral anterior cingulate cortex
RVM	rostroventromedial medulla
SD	standard deviation
SES	social desirability scale
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
SPM	statistical parametric mapping
SPSS	statistical package for the social sciences
STAI	state and trait anxiety inventory
T	Tesla
TE	echo time
TR	repetition time
VMpo	ventromedial nucleus, posterior part
VP	ventral posterior nucleus
VPI	ventral posterior inferior nucleus
VPL	ventral posterior lateral nucleus
VPM	ventral posterior medial nucleus
VTA	ventral tegmental area

1. Introduction

1.1. Study Aims

The international association for the study of pain IASP adopted Merskey's definition of pain (1976) and defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Loeser and Treede 2008, Schäfer 2009). Pain is therefore multidimensional and indispensible for our body's integrity.

It is important to distinguish between the perceptions of stimuli and pain itself, which originates in the brain. Pain is highly subjective and can be influenced by several factors such as expectations, prior experience, suggestibility, conditioning and desire for relief. These conditions can significantly impact the individual processing of pain and thereby produce different perceptions of an identical stimulus (Price and Fields 1997, De Pascalis, Chiaradia et al. 2002, Atlas and Wager 2012).

One of the essential tasks for doctors is to ease and treat pain. But medical treatment of pain and positive therapeutic effects do not only involve the administration of drugs. The overall context contributes to therapeutical success. Placebo research helps us understand the underlying mechanisms following the administration of an inert substance or more generally, treatments with no direct physiological or pharmacological effect. The treatment is embedded in a psychosocial context, which can evoke these beneficial effects and positive outcomes (Benedetti, Carlino et al. 2010, Wager and Atlas 2015).

Prior PET (positron emission tomography) studies (Petrovic, Kalso et al. 2002) and the following advances in neuroimaging enabled the identification of a neural network activated during placebo analgesia including the anterior cingulate cortex (ACC), the anterior insula (AI) and the thalamus. Furthermore, the prefrontal areas have been activated during the anticipation of pain (Price, Finniss et al. 2008, Meissner, Bingel et al. 2011, Wager and Atlas 2015). Analysing the activation of these brain areas can thus at least in part help to investigate subjective placebo responses in a controlled and quantifiable manner.

Recent placebo studies focused on the psychosocial factors that shape and influence pain perception and its processing (Benedetti and Amanzio 2011). The underlying neural correlates are mostly well understood (Meissner, Bingel et al. 2011, Wager and Atlas 2015). Amongst these psychological stimuli, expectations and the previously shaped attitude, for example through experience or marketing, are critical (Shiv, Carmon et al. 2005, Benedetti and Amanzio 2011, Geuter, Eippert et al. 2012, Geuter, Eippert et al. 2013). The activated neural network is comprised of cingulate cortices, subcortical brain regions, prefrontal areas (dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC)) and the anterior insula (AI). Furthermore, during placebo analgesia the classical pain processing brain regions showed decreased activity (Meissner, Bingel et al. 2011, Wager and Atlas 2015).

Cognitive processes such as positive expectations and the belief in the effectiveness of the treatment seem to boost the placebo response (Wager and Atlas 2013). Interestingly, medications' cost may influence the placebo effect, too. A recent study showed that expensive placebos, in comparison to the cheap equivalent, significantly improved motoric functions in patients with Parkinson's disease (Espay, Norris et al. 2015). Another placebo study investigated the effects of changing a branded blood pressure medication to a generic one. The medication switch showed a reduced effectiveness of the treatment and enhanced side effects, suggesting higher expectations and therefore a higher placebo response for the branded drugs (Faasse, Cundy et al. 2013).

In order to assess the role of positive expectations elicited by a brand name, we used Aspirin as a model brand drug. For many years, acetylsalicylic acid (ASA) has been used to treat headaches and pain in general. It was invented by Bayer over a 100 years ago and successfully distributed under the Aspirin brand ever since. Although many ASA equivalences exist, Aspirin enjoys great trust and receives enormous brand awareness (Vane, Flower et al. 1990, Rinsema 1999, Reader's 2014).

The attitude towards generics is mostly ambiguous or critical (Keenum, DeVoe et al. 2012). The requirement of the interchangeability of a generic drug and the corresponding original is based on the criterion of "essential similarity" and is under

intense research and debate (Borgherini 2003, Wilner 2004, Shrank, Hoang et al. 2006, Kesselheim, Misono et al. 2008). There are certain differences in the drug response and effectiveness of the medication, as these are only identical to a certain degree focusing on the active substance. Excipients, bioavailability, pharmacokinetics and therefore therapeutic effects can differ (Borgherini 2003, De Vuono, Scicchitano et al. 2013). Regardless of putative quality differences between brand-name and generic drugs, the objective of this study was to investigate whether the brand-name itself induces a placebo effect on pain and to identify the underlying neurobiological mechanisms of these differences in branded and generic treatments. We therefore used the exact same placebo agent which was labelled either with the original brand or the generic name, thus controlling for possible effects of a different composition of generic drugs. We expected that with regards to placebo effects, the trusted brand Aspirin would reinforce the placebo response, as most patients believe in the positive effects of this treatment.

1.2. Physiology of Pain

The following chapter describes the processing of a noxious stimulus resulting in the sensation of pain.

1.2.1. Sensation of Pain

A noxious stimulus only results in the conscious experience of pain, when transmitted into the central nervous system resulting in activity in the corresponding brain areas. It plays an essential role in human survival as it fulfils a warning function for potential harm to the integrity of our body. Touching a hot stove we automatically retrieve from the painful stimulus caused by somatosensory reflexes (Schäfer 2009 page 1). How essential this feeling is to us becomes clear when looking at different disease where this system is defective. Patients with an insensibility to pain suffer in very early ages from severe injuries and burns. There exist a variety of rare congenital diseases, which come along with the resistance against pain. The loss of the protective mechanisms of pain results in lower life expectations (Handwerker 1998, Kohl, Hülsemann et al. 2007, Basbaum, Bautista et al. 2009, Schäfer 2009). However, when the sensory system of pain is intact, the process is subjective and individual (Auvray, Myin et al. 2010).

1.2.2. Dimensions of Pain

As we understand pain today, it is highly complex and multidimensional. Melzack and Casey defined already in 1968 three dimensions of pain – the sensory-discriminative, the motivational-affective, and the cognitive-evaluative dimension (Melzack R 1968) – and built the foundation for our modern understanding of pain. Today we understand pain as a multi-dimensional process (Treede, Kenshalo et al. 1999) containing sensory and affective dimensions (Price 2000).

The sensory-discriminative dimension of pain provides essential information about its origin, intensity and the quality of the stimulus (Treede, Kenshalo et al. 1999). The crucial step of this pain component are the nociceptors, which send the signal of a potential noxious stimulus from the periphery to the central nervous system and finally into consciousness (Handwerker 1998). This nociception builds the basis for the sensory discriminative dimension of pain, but does not include subjective

elements (Auvray, Myin et al. 2010) such as the individual evaluation of pain. The visual analogue scale is one method to objectivize this sensory-discriminative pain component (Duncan, Bushnell et al. 1989, Katz and Melzack 1999, Chapman, Nakamura et al. 2001).

The motivational-affective dimension emphasizes the unpleasantness and describes the negative emotions accompanying the pain like anxiety, despair, discomfort, tension and fear (Price and Harkins 1992, Rainville, Carrier et al. 1999, Price 2000, Ruiz-Aranda, Salguero et al. 2010). The degree of unpleasantness and negative emotions can be assessed on various verbal rating scales (Duncan, Bushnell et al. 1989, Katz and Melzack 1999).

Furthermore pain consists of a cognitive component. Depending on prior experiences and the actual situation, it leads to the evaluation of a stimulus from harmless to life threatening. The 'pain memory' plays a major role in this evaluation as the individual compares these experiences and memories with the current pain. Thus, besides situational variables the former handling of the painful situation contributes to the cognitive evaluation of the sensation of pain (Melzack R 1968, Niven and Brodie 1996, Katz and Melzack 1999, Atlas and Wager 2012). Cognitive processes can finally lead to mimic and gestural pain expression (Schaible 2011). Assuming that everyone has taken a painkiller as Aspirin or its generic equivalences, our participants have prior experiences, which shape their current cognitive evaluation of pain during the study.

Pain is also associated with vegetative reactions due to sympathetic nervous system activation such as a change in blood pressure, increased respiratory rates, perspiration increase and dilated pupils (Göbel 1988, Schaible 2011).

1.2.3. Nociception

Nociception is a physiological term, which describes the stimulus reception in the periphery, neural processing on a spinal cord level and finally the encoding of a noxious stimulus in the cerebral cortex (Handwerker 1998 page 250). Pain itself describes a complex, emotional experience, which is highly subjective (Merskey 1991). These two terms should not be confused as one can occur without the other.

A noxious stimulus does not necessarily lead to pain whereas pain is a conscious and subjective perception which can occur without a noxious stimulus, for example in the case of phantom pain (Loeser and Treede 2008).

1.2.3.1. Nociceptors

Nociceptors are specialized afferent free nerve endings, which are able to detect mechanical, thermal as well as chemical stimuli and lead to an action potential if the stimulus hits the threshold. These specialized sensory neurons are distributed throughout the whole body; however, their highest density is located in the skin (Serpell 2005, Gold and Caterina 2008, Schäfer 2009, Dubin and Patapoutian 2010). Transduction is the conversion of a physical stimulus, for example a noxious thermal stimulus, into electrical energy (sensor potential) by a free afferent nerve ending (Handwerker 1998). There exist numerous ion channels for this first step in pain processing. The TRPV1 receptor, a calcium channel, is activated by noxious heat over approximately 43 degree Celsius as well as by capsaicin (Caterina, Schumacher et al. 1997, Basbaum, Bautista et al. 2009). Many more receptor types play a role in producing an adequate receptor potential in the transduction of pain (Woolf and Ma 2007).

The sensitivity of these nociceptors can be increased by various chemical mediators – an 'inflammatory soup' – resulting in a higher response to the noxious stimulus (Julius and Basbaum 2001).

Nociceptors require appropriate stimuli to depolarize peripheral nerve endings to generate a sufficient impulse. This results in a so called receptor potential, which is a graded potential with varying sizes of amplitude and depolarizes the cell to eventually triggering an action potential (Dubin and Patapoutian 2010). The further conduction of the action potential occurs via two types of nerve fibers, which can be classified according to their velocity of nerve conduction and therefore their degree of myelination into Aδ and C-fibers. Due to these different pathways, one single noxious heat stimulus leads to two different sensations, 'first and second pain' as demonstrated in figure 1 (Campbell and LaMotte 1983, Julius and Basbaum 2001, Serpell 2005).

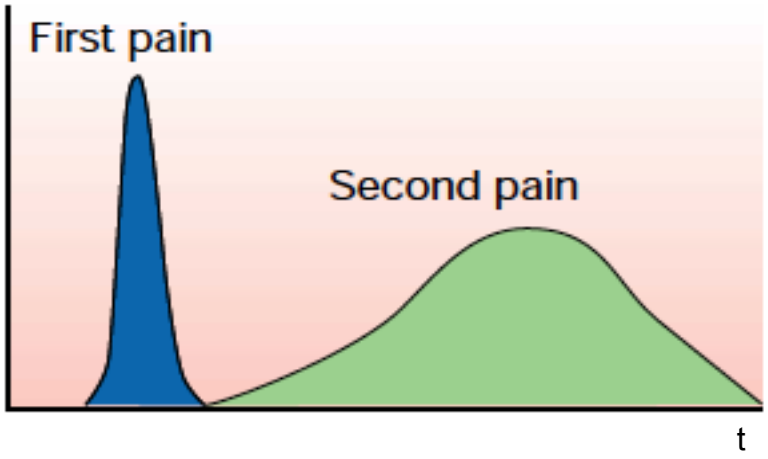


Figure 1. The Time Course of First and Second Pain.
(Julius and Basbaum 2001).

The Aδ fibers are thinly myelinated. Their activation results in the acute first sharp pain (Julius and Basbaum 2001, Basbaum, Bautista et al. 2009, Schäfer 2009). The C-fibers are unmyelinated and mediate second pain, which is long lasting, difficult to localize, burning and dull sensation. The latter play a role in inflammatory processes (protopathic sensibility) (Forss, Raij et al. 2005, Schaible 2011). The cell bodies of the neurons are located in the dorsal root ganglion. Their afferent nerve fibers enter the spinal cord via the dorsal horn. Now in the central nervous system, on the spinal cord level they synapse to second order projection neurons (Basbaum, Bautista et al. 2009, Dubin and Patapoutian 2010).

1.2.4. Spinal and Supraspinal Pain Processing

1.2.4.1. Spinal Pain Processing

As described above the A-delta and C-fibers enter the spinal cord therefore the central nervous system via the dorsal horn and terminate in the different laminae of the grey matter. There exist a variety of neurotransmitters, which shape the transmission of the noxious stimulus. Already on the spinal cord level the noxious stimulus can be modified.

As an example, inhibitory interneurons, which modulate the pain processing, can be activated by non-painful stimuli as pressure via A-beta fibers. These antinociceptive

interneurons then inhibit nociceptive neurons on the spinal cord level via the excretion of the neurotransmitter GABA (gamma-Amino butyric acid) (Sandkühler 2001).

The neurotransmitters, which shape the pain processing already on the spinal cord level can be divided into two major groups, namely the excitatory signal enhancing group and the inhibitory anti-nociceptive group (Serpell 2005). The predominant excitatory neurotransmitter glutamate is secreted by nociceptors (Julius and Basbaum 2001). A noxious stimulus as heat activates via glutamate the postsynaptic NMDA (N-methyl-D-aspartate receptor) and non-NMDA (mostly AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor)) receptors leading to a further excitatory transmission. Furthermore the painful stimulus is modified by interneurons. As described above, A-beta fibers can activate these interneurons. Also descending pain modulatory networks can activate these interneurons, which then excrete the inhibitory neurotransmitter GABA, Glycin, and other inhibitory neuropeptides as encephalin that attenuate the noxious stimulus (Julius and Basbaum 2001, Riedel and Neeck 2001, Mense 2004, Basbaum, Bautista et al. 2009, Birbaumer and Schmidt 2010). Positive emotions, expectations or attitudes can activate those descending pathways leading to the secretion of those inhibitory neurotransmitters already on the spinal cord level (see chapter 1.2.5).

After this stimulus modification and the synapse with the secondary neurons, the second order fibers then decussate via the anterior commissure and ascend contralateral as the lateral spinothalamic and the medial spinothalamic tract. The lateral tract is also referred to as neothalamic tract whereas the medial part is also labelled paleothalamic tract referring to evolutionary processes. The neothalamic tract carries the information of A-Delta fibers for cute sharp pain, whereas the paleothamalic tract transports the stimulus of C-fibers for slow pain. As the anterolateral pathway they ascend to the brain stem and the thalamus. Furthermore another ascending tract, the tractus spinoreticularis, carries via the formation reticularis vegetative impulses as the sympathetic activation accompanying the pain (Mense 2004, Basbaum, Bautista et al. 2009, Birbaumer and Schmidt 2010). Descending tracts activated by cognition and emotions are part of the pain modulation process and will be discussed in chapter 1.2.5.

1.2.4.2. Thalamus

The word thalamus is Greek and means “inner chamber”. It is often referred to as gateway to the conscious (Murray Sherman and Guillery 2001). It consists of four major regions, the nucleus anterior, medialis, ventralis and the pulvinar (nucleus posterior). Head and Holmes were the first to identify its involvement in the pain pathway (Head and Holmes 1911). The thalamus is located on the top of the brainstem. The arrangement is somatotopic, meaning a correspondence of an area of the body to a specific point in the thalamus. Besides its numerous functions as connection and information switchboard between subcortical and cortical areas, it constitutes the final relay station in the pain pathway (Hudson 2000, Riedel and Neeck 2001).

The ascending afferents terminate in the thalamus and within the general pain network a lateral and medial nociceptive system can be identified that both contribute to the sensation of pain. As shown in Figure 2, the lateral system, which is part of the sensory-discriminative component of pain, is formed by the ventral posterior nucleus (VP), consisting of the ventral posterior lateral nucleus (VPL), the ventral posterior medial nucleus (VPM) and the ventral posterior inferior nucleus (VPI). The ventromedial nucleus, posterior part (VMpo), the ventrocaudal part of the medial dorsal nucleus (MDvc), the parafascicular nucleus (Pf) and the centrolateral nucleus (CL) are part of the medial system, which is assigned to the affective-motivational component of pain (Treede, Kenshalo et al. 1999, Hudson 2000, Mense 2004, Dostrovsky and Craig 2008). The following paragraph describes in more detail the lateral and medial system and their functions. Furthermore their connections with higher brain areas, which modify the pain processing, are specified.

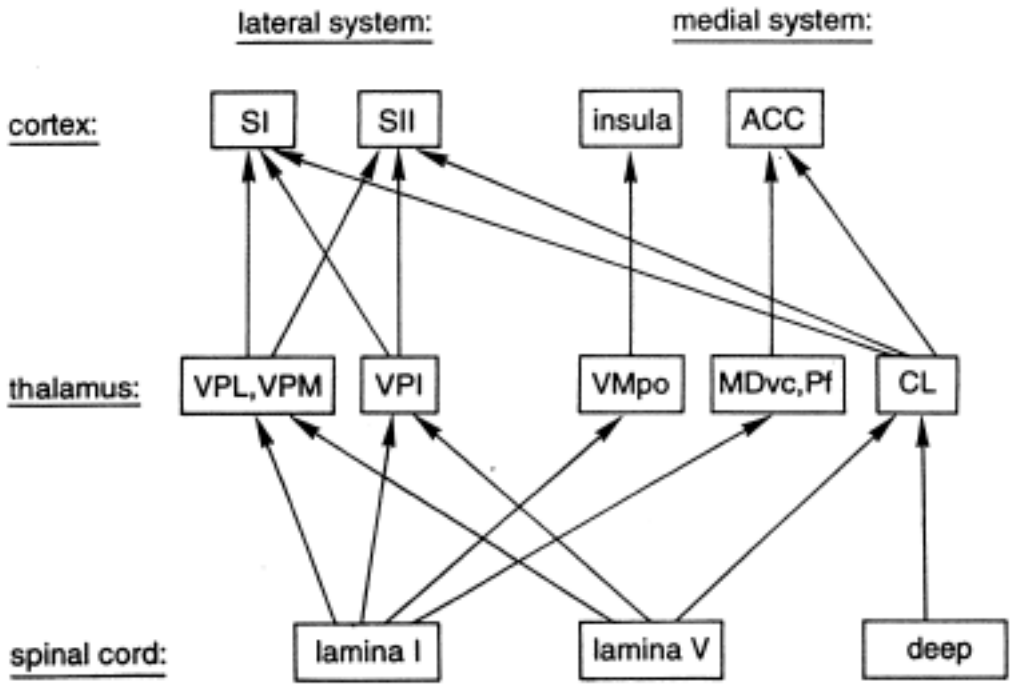


Figure 2. Medial and Lateral Nociceptive System.
(Treede, Kenshalo et al. 1999).

SI	primary somatosensory cortex
SII	secondary somatosensory cortex
ACC	anterior cingulate cortex
VPL	ventral posterior lateral nucleus
VPML	ventral posterior medial nucleus
VPI	ventral posterior inferior nucleus
VMpo	ventromedial nucleus, posterior part
MDvc	medial dorsal nucleus ventrocaudal part
Pf	parafascicular nucleus
CL	centrolateral nucleus

1.2.4.3. Lateral Nociceptive System

As shown in figure 2, the lateral nociceptive system receives information from lamina 1 and 5 of the spinal cord terminating in several nuclei of the lateral thalamus and thus projecting to the primary and secondary somatosensory cortices and to the lateral insula. It accounts for the sensory-discriminative component of pain perception and transmits information about the intensity, duration, localization and quality of the stimulus. The lateral pain system enables to differentiate the painful stimulus (Treede, Kenshalo et al. 1999, Apkarian, Bushnell et al. 2005, Schäfer 2009, Schaible 2011, Westlund 2014). Several regions, namely the thalamus, the primary and secondary somatosensory cortices and parts of the cingulate cortex, are encoding for pain intensity (Coghill, Sang et al. 1999, Westlund 2014). Furthermore the insula regions encode for stimulus intensity, however it lacks specificity for pain and is more part of the medial nociceptive system playing a role in the affective component of pain (Apkarian, Bushnell et al. 2005, Treede and Apkarian 2008, Apkarian, Hashmi et al. 2011).

The lateral system projects to the primary and secondary somatosensory cortex. The primary somatosensory cortex (S1) is located at the postcentral gyrus, which is part of the lower parietal lobe. As shown above in Figure 2, it receives its information from the ventral posterior lateral and medial nuclei (VPL, VPM) of the thalamus (Treede, Kenshalo et al. 1999). The primary somatosensory cortex is part of the tactile system enabling proprioceptive detection and encoding stimulus intensity. There exists an agreement as the S1 receives and processes the information of myelinated afferents leading to the first cortical registration of sensory modalities (Vierck, Whitsel et al. 2013).

The body representation is historically described as homunculus, displaying differently weighted body parts and displaying a somatotopic organization (Apkarian, Bushnell et al. 2005, Apkarian, Hashmi et al. 2011, Westlund 2014). This body representation in the cerebral cortex was first described by Penfield and Boldrey (Penfield and Boldrey 1937). These assumptions have been confirmed over the last decades (Nakamura, Yamada et al. 1998) and state that the somatotopic organization of the primary somatosensory cortex is consistent with Penfields homunculus even for nociceptive stimuli and allows the discrimination of the painful

stimulus (Omori, Isose et al. 2013). In an fMRI (functional magnetic resonance imaging) study, S1 was activated contralateral to the stimulation site and showed a linear correlation of brain activation in the BOLD (blood-oxygen-level dependent contrast imaging) response and the stimulus intensity (Bornhövd, Quante et al. 2002).

The role of the primary somatosensory cortex in pain processing was controversially discussed over last decades, as there were inconsistent activations of S1 during pain application across several studies (Kenshalo Jr 1996, Rainville, Duncan et al. 1997, Bushnell, Duncan et al. 1999, Vierck, Whitsel et al. 2013). In this regard, Bushnell et al. (1999) provide some profound and logic explanation for these inconsistencies, stating that the S1 activation may be shaped by cognitive factors including attention towards the stimulus and anticipation before the application of the stimulus. It receives excitatory as inhibitory inputs (Bushnell, Duncan et al. 1999, Schnitzler and Ploner 2000). Cognitive factors seem to influence the pain intensity but not the unpleasantness of the stimulus. Attention can alter activations in the primary somatosensory cortex and therefore modulate the pain response. Furthermore the precise somatotopic organization of the primary somatosensory cortex could lead to focal activations, which can be difficult to detect due to a high anatomic variability of the sulci. Bushnell et al. argue for a highly modulated role for S1 cortex in the sensory aspects of pain. In conclusion, the primary somatosensory cortex seems to be involved in stimulus perception and its modulation (Bushnell, Duncan et al. 1999, Bushnell, Čeko et al. 2013). Despite its role in the encoding of localization, duration, and intensity, the activations of the primary somatosensory cortex can be modulated by cognition (Schnitzler and Ploner 2000) and by attention and anticipation (Hauck, Lorenz et al. 2007). The primary somatosensory cortex plays a role in pain processing, but accounts more for the affective component (Auvray, Myin et al. 2010, Worthen, Hobson et al. 2011).

The secondary somatosensory (S2) cortex is part of the inferior parietal lobe located on the ceiling of the Sylvian fissure (Treede and Apkarian 2008). In 1954 its existence in humans was uncovered by Penfield and Jasper during neurosurgery (Penfield and Jasper 1954). During nociceptive stimuli, it shows mostly a bilateral activation. It receives projections mainly from the ventral posterior inferior (VPI)

thalamic nucleus as shown in Figure 2 (Treede, Kenshalo et al. 1999, Schnitzler and Ploner 2000) suggesting an involvement in the lateral nociceptive network. The secondary somatosensory cortex is one of the regions most consistently found activated (mostly bilaterally) in pain studies (Fomberstein, Qadri et al. 2013). As the primary somatosensory cortex, it plays a role in intensity coding (Timmermann, Ploner et al. 2001) and temporal coding of sensory information (Ploner, Schmitz et al. 1999, Chen, Ha et al. 2002). The thalamocortical connections and parallel activation as a direct access to the secondary somatosensory cortex support the idea of S2 major role in pain processing (Ploner, Schmitz et al. 1999, Schnitzler and Ploner 2000) and a predominant role in the sensory-discriminative dimension (Worthen, Hobson et al. 2011). Furthermore the secondary somatosensory cortex may be involved in the recognition and memory of painful experiences (Schnitzler and Ploner 2000).

1.2.4.4. Medial Pain System

The distinction between medial and lateral pain system orientates on the anatomic organization, the medial thalamic nuclei, the insula, the cingulate cortex and the prefrontal cortex (PFC) being part of the medial pain pathway. It represents more the affective-motivational component of pain. The medial pain system targets the limbic system and the frontal cortex via connections in the brainstem and the amygdala. The evaluation of the sensation as being unpleasant accounts for the affective-motivational component and are closely related to the medial pain system (Treede, Kenshalo et al. 1999, Basbaum, Bautista et al. 2009, Schäfer 2009, Westlund 2014). Positive or negative attitudes and expectations may alter this pain component.

The cingulate cortex has been considered to be a part of the limbic system and can be divided into an anterior, mid, posterior and retrosplenial part according to its anatomic segmentation. However, this model is more of theoretical nature (Vogt 2005).

The anterior cingulate cortex (ACC) has been identified to be activated by affect and shows consistent activation across several pain studies (Vogt 2005, Fomberstein, Qadri et al. 2013). It seems to be part of the pain pathway modifiable by emotions

and reactions to the painful stimulus. As affective component it puts the stimulus into context evaluating its degree of unpleasantness. It seems to be a centre of integration and can lead to autonomic reactions (Rainville, Duncan et al. 1997, Schnitzler and Ploner 2000). The anterior cingulate cortex enables the interpretation and evaluation of the emotional significance of the painful stimulus (Rainville, Duncan et al. 1997, Westlund 2014).

The mid cingulate cortex (MCC) is most likely involved in the motoric orientation and reaction following a stimulus not necessarily leading to movement, but to a cognitive processing and response influenced by the reward system. The posterior cingulate cortex (PCC) has been attributed a role in visual and spatial orientation towards or away from the stimulus assessing the self-relevance of the sensation. The role of the retrosplenial part remains unclear and suggestions are tending towards a role in memory access (Vogt 2005 page 535).

The posterior cingulate cortex has been object of intensive research and still its primary function remains unclear. It has been described as major region of the default mode network, an area which shows activations during inactivity also described as resting-state network (Fransson and Marrelec 2008). Raichle et al. (2001) describe it as a brain area that continuously gathers information around and within the human body (Raichle, MacLeod et al. 2001). Buckner et al. (2008) interpreted these activations during putative inactivity as internally directed thoughts and memory (Buckner, Andrews-Hanna et al. 2008). Furthermore, the posterior cingulate cortex seems to play a role in regulation and cognitive control (Hampson, Driesen et al. 2006, Gilbert, Dumontheil et al. 2007, Pearson, Heilbronner et al. 2011). Leech et al. (2012) describe this area as a highly complex structure and neural connecting centre suggesting a more active role in cognition (Hagmann, Cammoun et al. 2008, Hayden, Smith et al. 2009, Pearson, Heilbronner et al. 2011, Leech, Braga et al. 2012) It may play a role in the integration of different types of stimuli and information essential for controlling changes in the environment (Leech, Braga et al. 2012). The posterior cingulate cortex is likely to be a centre of information integration as suggested by Leech and therefore has a far more complex role than only the activation during inactivity.

In summary, the cingulate cortex plays a major role in the processing and integration of a variety of stimuli and multidimensional information, namely sensory, cognitive, motoric, emotional and motivational aspects. It is also part of the pain circuit receiving information from the medial thalamic nuclei and has interactions with the amygdala, the periventricular grey and the prefrontal areas suggesting an involvement in the pain processing on an affective level (Tölle, Kaufmann et al. 1999, Vogt 2005, Bushnell, Čeko et al. 2013). An early study reported of a patient, who after a cingulotomy showed a loss of the “emotional component” and response to pain (as anxiety and fear) whereas the “organic component” was unaffected (Foltz and White Jr 1962, Ballantine Jr, Bouckoms et al. 1987). These results suggest a predominant involvement of the cingulate in the affective and cognitive component of pain. However, there is further research, which could demonstrate an involvement of regions within the anterior cingulate cortex in the intensity encoding and in basic stimulus perception, thus suggesting a role of the cingulate cortex also in the sensory discriminative aspect of pain (Büchel, Bornhövd et al. 2002). Davis et al. (1997) demonstrated the involvement of the cingulate gyrus in attention-related tasks showing that there exist different spatially independent areas within the anterior cingulate gyrus for pain and attentional processes (Davis, Taylor et al. 1997).

However, several sub regions have been identified (Vogt 2005) there remains uncertainty in the exclusive involvement of these areas in pain processing. Recent studies suggest an overlapping region for negative emotions, pain and cognitive control in the mid cingulate cortex (Shackman, Salomons et al. 2011). In summary, the cingulate cortex seems to be a centre of stimulus integration processing sensory, cognitive, emotional affective, evaluative and attention-related information.

The insula cortex is part of the cerebral cortex. During embryonic formation due to the relative faster growth of the hemispheres it becomes infolded and therefore hidden in the lateral cerebral fissures (Sylvian fissure) (Tuan Diep Tran 2007, Nieuwenhuys 2012). It receives direct input from the posterior part of ventromedial nucleus of the thalamus (VMpo) and is connected with the secondary somatosensory cortex, the amygdala and other limbic regions (Treede, Kenshalo et al. 1999, Nieuwenhuys 2012).

The insula has been described as a variegated brain region involved in multiple areas such as speech, taste, vision, vestibular, auditory and olfactory processes as well as viscera-autonomic responses. The insula seems to be a motor association area and in general a sensory integration centre for a variety of stimuli (Augustine 1996, Ibañez, Gleichgerrcht et al. 2010). It has been concluded that corresponding to these assumptions the insula with its multiple connections is involved in intensity coding, in autonomic responses and in affective processing of stimuli (Coghill, Sang et al. 1999), therefore being part of the affective component of pain as well as the sensory-discriminative dimension of pain. The ventral part of the anterior insula seems to be more responsible for basic affect whereas the dorsal part seems to play a role in goal directed responses (Wager and Feldman Barrett 2004).

By looking at the variety of clinical defects after insular damage, Ibanez et al. (2010) suggest “that the insula, as a multimodal area, has a major role as a convergence zone implicated in the coordination between internal and external information through emotional subjective awareness” (Ibañez, Gleichgerrcht et al. 2010 page 397). The insula processes affective and emotional information linking subjective feelings, motivation and cognition. The insula integrates the received information and is putting the potential risks and threats into context eventually leading to an adequate response (Treede, Kenshalo et al. 1999, Price 2000, Wager and Feldman Barrett 2004). It is thus not exclusively pain related, but by this means is an essential part of the pain sensation.

The described brain areas playing a role in the affective component of pain as the cingulate cortices and the insula are displayed in figure 3 below.

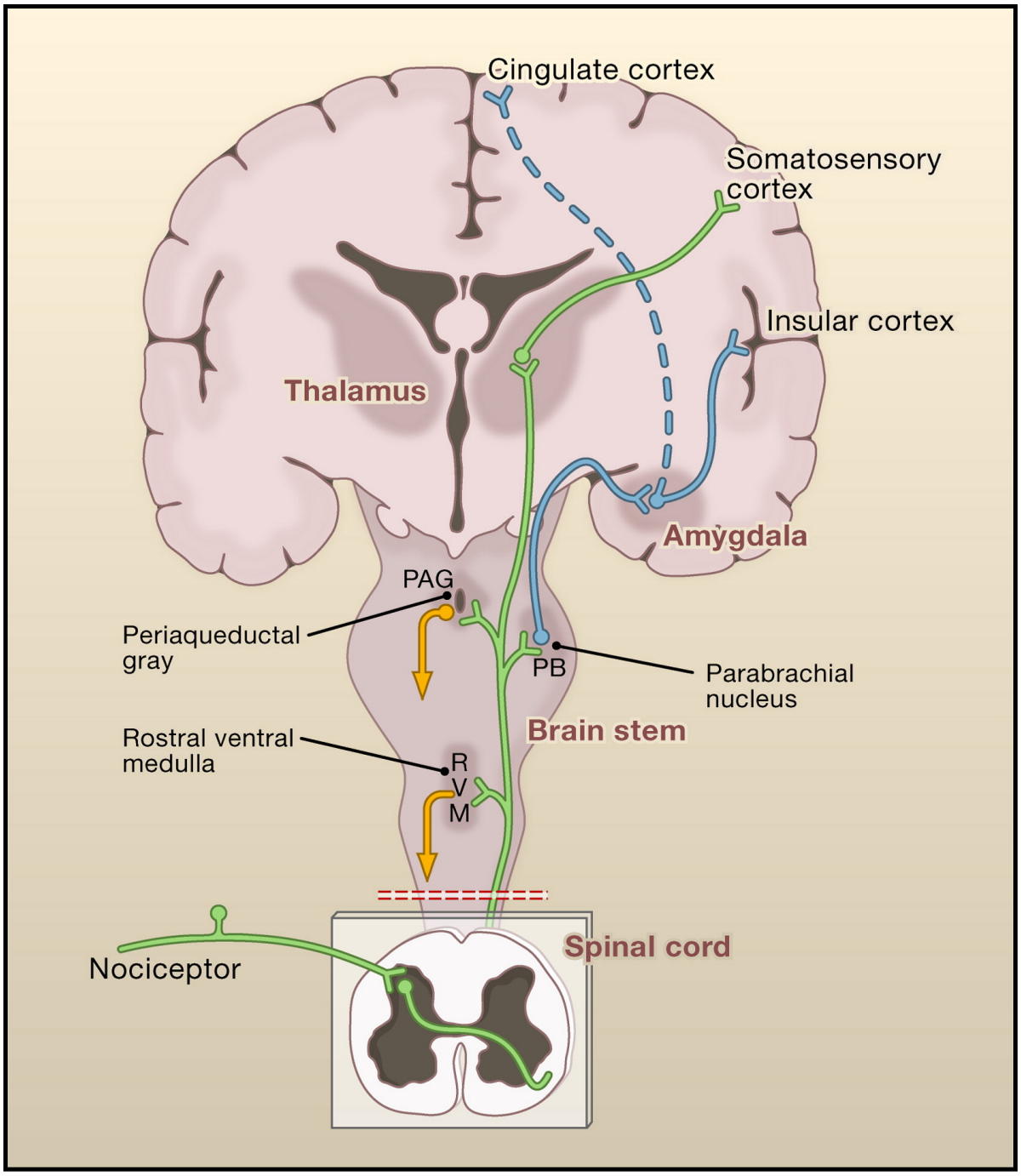


Figure 3. Anatomy of the Pain Pathway - the Neural Processing of the Affective Component of the Pain Experience.
(Basbaum, Bautista et al. 2009).

The prefrontal cortex (PFC), namely the posterior parietal and the dorsolateral prefrontal cortex (dlPFC), contributes to the cognitive dimension of pain, specifically the attentional processing of the stimulus. It could be involved in responses to that stimulus driving the attention towards or away from the unpleasant experience. As the anterior cingulate cortex the prefrontal cortex is activated during the anticipation

phase prior to the painful stimulus (Peyron, Laurent et al. 2000, Benedetti, Carlino et al. 2011). It receives information from the visual, auditory and somatosensory cortices maintaining connections to the sensory cortices, the thalamus, the basal ganglia and limbic regions. The authors Miller and Cohen argue for a general role of the prefrontal cortex in cognitive control of stimuli as it gathers multiple inputs, evaluating and integrating the received information eventually leading to a "goal directed" response (Miller and Cohen 2001). The dorsolateral prefrontal cortex could be involved in shaping the painful stimulus influencing the perception of pain by modulating corticosubcortical and corticocortical pathways. As activations of the prefrontal cortex showed a negative correlation with intensity and unpleasantness, they seem to be accompanied with decreased aversion. Its activations may be modulated by motivation and emotions, thus it seems to be part of the affective dimension of pain (Lorenz, Minoshima et al. 2003). Furthermore the prefrontal cortex showed activation during working memory processes (Peyron, Laurent et al. 2000, Miller and Cohen 2001, Murray and Ranganath 2007). The dorsomedial prefrontal (dmPFC) cortex is involved in negative affect suppression (Phan, Fitzgerald et al. 2005) and emotional appraisal (Kalisch, Wiech et al. 2006).

Furthermore, studies have shown the involvement of the dorsolateral prefrontal cortex in expectation-related pain relief (Wager, Rilling et al. 2004, Zubieta, Bueller et al. 2005, Krummenacher, Candia et al. 2010). Lorenz et al. (2003) assume a role of the opioid-transmitter-rich dlPFC in the inhibition of pain in form of a top down effect (Lorenz, Minoshima et al. 2003). Despite its specific involvement in the placebo response and the modulation of pain, the dlPFC is generally activated in processes of reasoning and decision-making (Kable 2010, Kahnt, Heinzle et al. 2011). The prefrontal cortex plays furthermore a role in placebo analgesia in terms of controlling pain and in coping mechanisms (Wiech, Kalisch et al. 2006).

In summary, the prefrontal cortices seem to be a centre of higher stimulus integration coordinating the other brain areas involved in the emotional regulation of pain (Wiech, Ploner et al. 2008). The involved brain areas and the afferent pain pathways with their projections to the prefrontal cortex are displayed in figure 4 below. The prefrontal cortex is likely to be responsible for emotional and cognitive evaluation, putting the sensation of pain into context.

Pain also involves an action component activating motoric regions as the basal ganglia and cerebellum controlling voluntary action and probably leading to a faster motoric reaction (Perini, Bergstrand et al. 2013).

The afferent pain pathways entering the central nervous system are also displayed in figure 4 below.

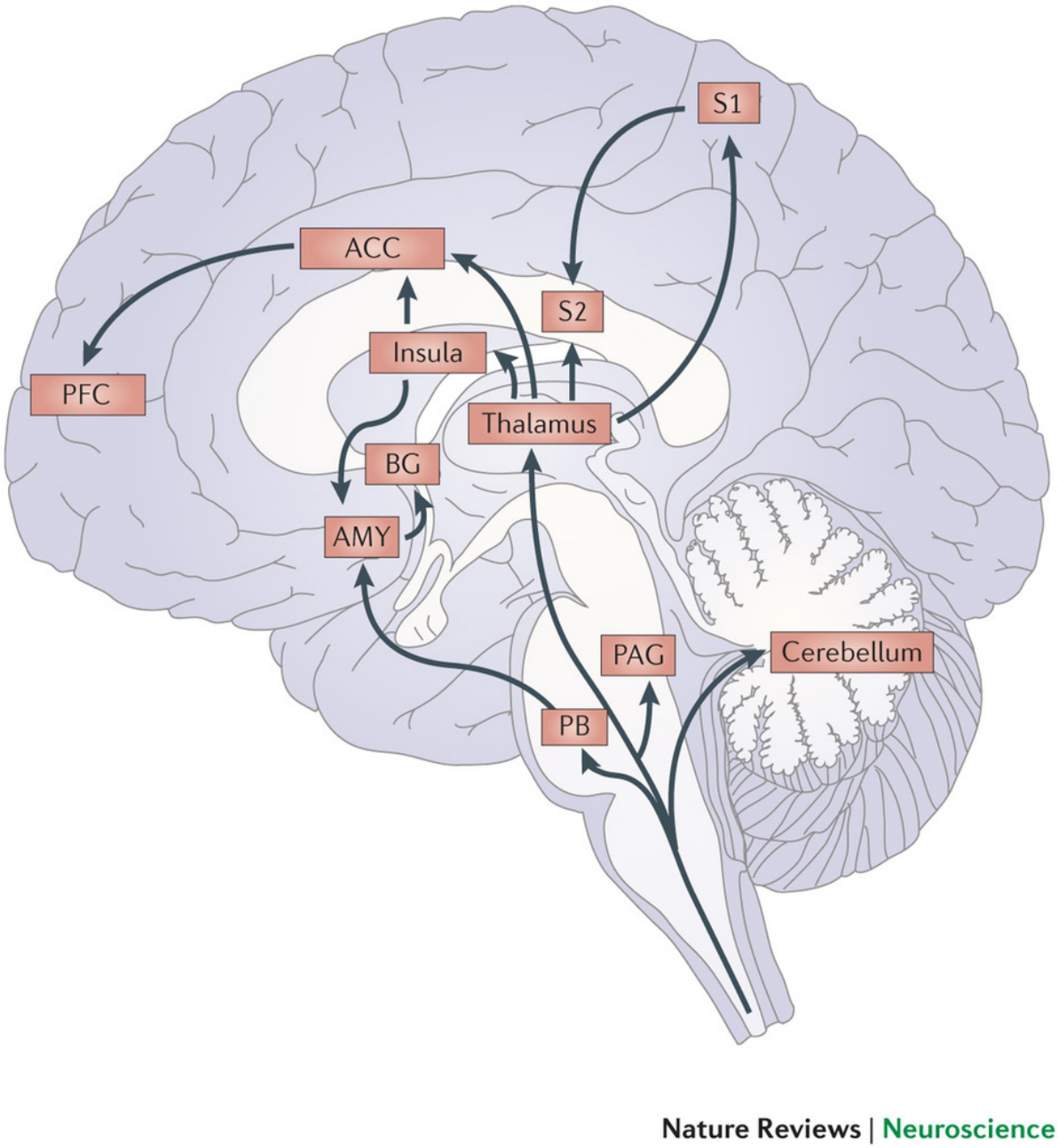


Figure 4. Afferent Pain Pathways.
Descending nociceptive information enters the central nervous system and projects to the Thalamus, the primary somatosensory cortex (S1) and secondary somatosensory cortex (S2). After the information enters the anterior cingulate cortex (ACC) it projects to the prefrontal cortex (PFC). AMY, Amygdala; BG, basal ganglia; PAG, periaqueductal grey; PB, parabrachial nucleus; PFC, prefrontal cortex (Bushnell, Čeko et al. 2013).

1.2.4.5. Summarizing Evaluation

Even though there was inconsistency in the literature regarding the activation and deactivation of certain areas involved in pain processing, there is now a consensus about several regions. S1, S2, ACC, and insula are the four regions with consistent activation (Fomberstein, Qadri et al. 2013). These regions are also activated by non-painful stimuli, indicating that nociception is part of the somatosensory modalities.

Based on the pain definition of the International Association for the Study of Pain (IASP), the emotional as well as the sensory components are essential parts of the pain sensation (Loeser and Treede 2008). Intensity ratings represent the sensory component. The degree of unpleasantness accounts more for the emotional component. Both qualities influence each other and often there are interferences. For instance, pain intensity and aversion are closely related. The higher the unpleasant stimulus, the more resentment arises and the desire to terminate the painful stimulus increases. Both factors are thus highly correlated. The segregation of the neural correlates of these two dimensions is not clear.

The different roles and overlaps of these brain regions (S1, S2, the ACC and the insula) and their involvement in the sensory and affective components of pain as well as in the anticipation of pain should be kept in mind. Some authors suggest an alternative approach, namely to use motivation to distinguish between the pain components, which enables a distinction independent of sensory encoding (Fields 2006). This field is yet to be investigated.

1.2.5. Endogenous Pain Modulation

Identical physical noxious stimuli can evoke very different pain experiences. In extreme examples of life-threatening situations some individuals show no or very little pain although injured. Activated stress hormone axis (cortisol and catecholamine) enable adequate responses potentially increasing the chance of human survival (Melzack, Wall et al. 1982, Melzack 1999). But also endogenous opioids shape the sensation of pain via ascending and descending pathways

(Serpell 2005, Pan 2012). The descending pain modulatory network is displayed in figure 5 below.

Pain is a highly shapeable, individual and context dependent sensation. The psychological state of the patient has a major impact on the sensation of pain and particularly negative emotions can increase the unpleasant experience (Tracey and Mantyh 2007, Wiech and Tracey 2009). Furthermore, attention and distraction from the noxious stimulus influence pain and can be used in pain management (Bushnell, Duncan et al. 1985, Good, Stanton-Hicks et al. 1999, Hauck, Lorenz et al. 2007). How does this modulation take place? Several mechanisms have been identified which could account for these different sensations explaining different outcomes and pain ratings of an identical stimulus.

The understanding of pain modulation along the nociceptive pathway was first described by Melzack et al. (1968) as the “gate control theory”, stating that mechanisms in the dorsal horns of the spinal cord act like a gate that inhibits or facilitates transmission of pain signals from the body to the brain (Melzack and Wall 1968, Melzack 1996). Later studies confirmed this basic idea showing that inhibitory interneurons receive inputs from A-Delta and C-Fibres modulating the stimulus via different neurotransmitter such as GABA, endogenous opioids, cannabinoids, glycin, and leucin. Furthermore these inhibitory interneurons can be activated via higher brain areas (Giordano 2005). These mechanisms have been described in the chapter above. Descending modulatory pathways are ending mostly at interneurons which can then inhibit the further transmission of the painful stimulus eventually leading to a decreased pain sensation (Schaible 2011). Eippert et al. (2009) confirmed the modulation of the painful stimulus via top down processes during a fMRI placebo study on opioid descending pain control systems. The study could show the involvement of the endogenous opioid system in placebo analgesia via descending pain modulation by using naloxone – an opioid antagonist – which lead to a decrease in placebo analgesia on a behavioural and neuronal level. By using fmri the study could display the activation of descending pain control regions displaying the top down pain modulation (Eippert, Bingel et al. 2009).

These descending pathways can highly modulate the pain experience. Several brain regions are involved in the descending modulation of pain. Figure 5

demonstrates the most prominent brain regions namely the anterior cingulate cortex, the hypothalamus, the insula, the amygdala, the prefrontal cortex, which all project to the periaqueductal grey (PAG), a nucleus in the brainstem (Tracey and Mantyh 2007).

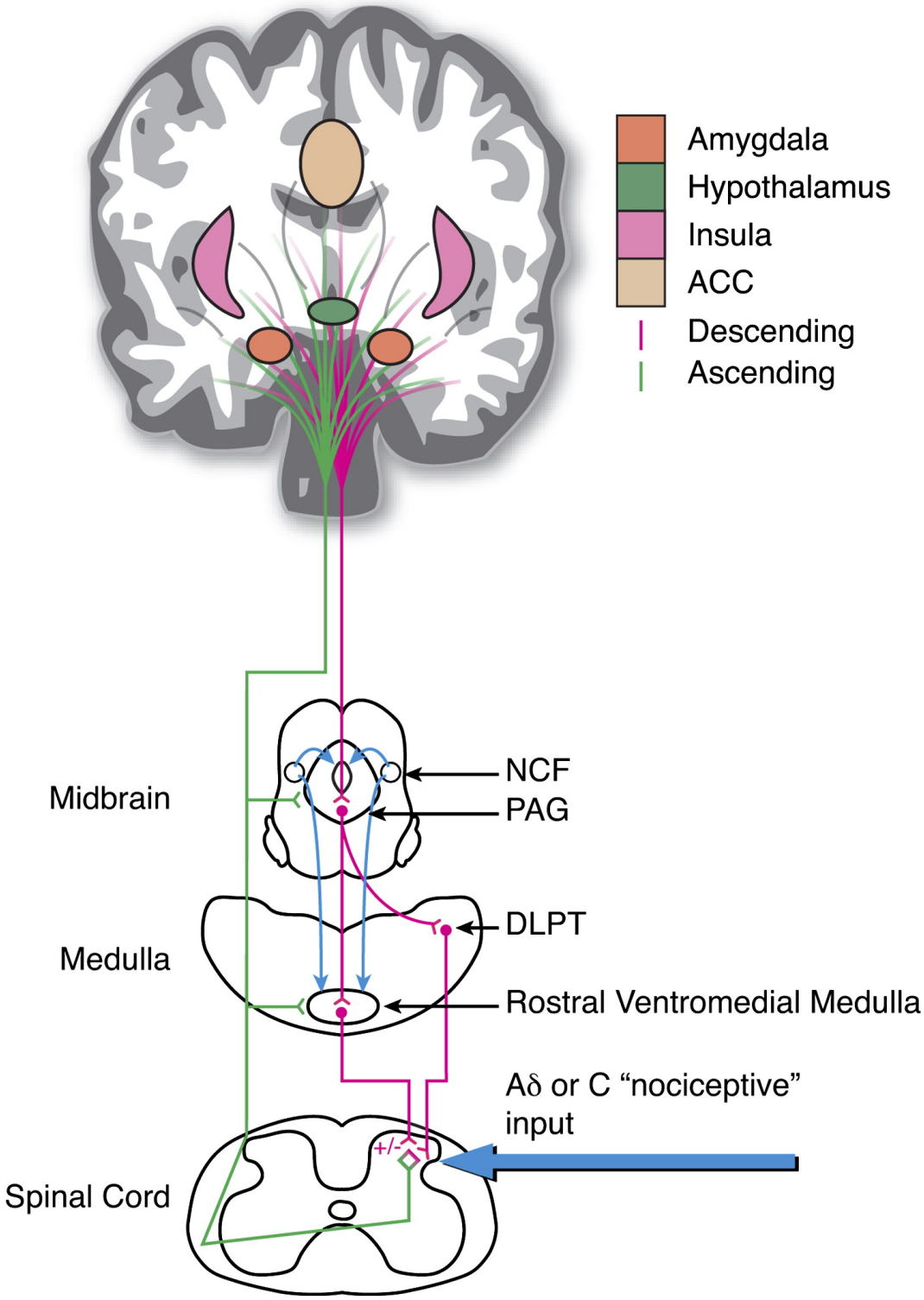


Figure 5. The Descending Pain Modulatory System.
NCF (nucleus cuneiformis); PAG (periaqueductal grey); DLPT (dorsolateral pontine tegmentum); ACC (anterior cingulated cortex); +/− indicates both inhibiting and facilitating nociceptive modulation (Tracey and Mantyh 2007).

The periaqueductal grey (PAG), a region in the midbrain, has a key role in the processing of antinociception as it is a central relay station of the projections of the descending modulatory pain pathways. In 1968, Reynolds demonstrated the major involvement of the PAG in the descending pain control system by electrical stimulation in rats resulting in analgesia without any prior anaesthesia (Reynolds 1969). Its role in antinociception has been confirmed by following animal studies (in anaesetized rats) showing that projections from the amygdala to the PAG mediated by μ-opioid receptors can result in analgesia (Tershner and Helmstetter 2000). The PAG receives inputs from the amygdala, the hypothalamus and limbic regions. It projects via the rostral ventromedial medulla (RVM) and the dorsolateral pontine tegmentum (DLPT) to the dorsal horn of the spinal cord being a key region in the descending modulatory pain pathway (Fields 2004). The projections of the PAG are not exclusively antinociceptory, they can be either inhibitory or excitatory. The facilitatory qualities in nociceptive processes have been attributed a role in secondary hyperalgesia. It thus could play a role in the development of chronic pain (Porreca, Ossipov et al. 2002, Gebhart 2004). Enhanced activity of the PAG via up regulation due to emotional stress, arousal or anxiety results in higher pain intensity. This is attributed to the cholecystokinin System (CCK). It has been argued that the interaction of the CCK and the opioid system takes place at the level of the PAG (Scott, Stohler et al. 2008, Wiech and Tracey 2009). The periaqueductal grey shows a high density of μ-opioid receptors speaking for an involvement in the endogenous opioid system. In the investigation of descending pain modulation, placebo studies revealed a higher opioid activity in the PAG and an increased activity in the rACC-PAG pathway combined with a reduced pain intensity (Wager, Scott et al. 2007). The coupling between the rACC and the PAG is positively correlated with placebo analgesia and opioidergic analgesia, whereas activity in S2 diminishes with enhanced rACC-PAG connectivity (Wager, Scott et al. 2007, Eippert, Bingel et al. 2009).

The rostroventral medulla (RVM) is located in the brainstem receiving information from the PAG and as a relay station is transmitting it further to the dorsal horn of the spinal cord. It is part of the descending pain modulatory network, however, these connections are bidirectional. The RVM can both either excite or inhibit nociceptive processing and therefore is containing inhibitory as well as enhancing qualities

(Fields 2004, Gebhart 2004, Pan 2012). It therefore also contributes to the subjective nature of pain and thus to the different perceptions of an identical painful stimulus.

The opposite inhibitory and facilitatory qualities are enabled by specific cells in the RVM, the on-cells, off-cells and neutral cells, which are defined by their response to nociceptive stimuli. Neutral cells are not activated by nociceptive stimuli, whereas on-cells respond with increased firing rates to nociceptive stimuli and off-cells with a decrease (Ossipov, Dussor et al. 2010). Both, on and off cells project to the dorsal horn of the spinal cord explaining the excitatory and inhibitory role of the RVM in pain modulation. Opioids increase activity in off-cells and seem to directly inhibit on-cells. A destruction of these on-cells may result in further analgesia. On-cells are also activated by cholecystokinin and an increased on-cell activity facilitates nociceptive responses (Fields 2004, Ossipov, Dussor et al. 2010, Wagner, Roeder et al. 2013). There exist further serotonergic neurons in the RVM projecting to the dorsal horn with excitatory and inhibitory qualities, leading to a bidirectional state-dependent nociceptive response. Nociceptive transmission in the RVM is therefore influenced by its serotonergic and opioid neurons, contributing to analgesia via different parallel and distinct pathways. The exact mechanisms and interactions are yet to be determined (Porreca, Ossipov et al. 2002, Fields 2004, Ossipov, Morimura et al. 2014). Its involvement in the individual pain relief however is clear.

The Amygdala is part of the limbic system and is attributed a role in fear, anxiety and emotional as well as cognitive evaluation of potentially harmful situations. It guides us during risk management and encodes for reward playing a role in negative and positive affect (Murray 2007). After processing the stimulus and evaluating it as a potential danger, the amygdala can lead to a rise of sympathetic reactions. The amygdala contributes to the emotional negative aspects of pain namely the affective dimension of pain maintaining connections to the prefrontal cortex and the PAG. It can aggravate or alleviate the painful stimulus putting it into context. The amygdala seems to be part of the pain network and a centre of integration of the painful stimulus (Neugebauer, Li et al. 2004, Wiech and Tracey 2009, Ji, Sun et al. 2010, Ossipov, Dussor et al. 2010, Butler, Nilsson-Todd et al. 2011). Negative emotions as fear, pessimism, dysthymia and depression can lead

to negative expectations concerning the noxious stimulus. Anticipation and anxiety may increase the perception of pain. The amygdala seems to account for these aversive aspects of pain. They activate the pain part of the amygdala exciting the facilitatory pathways and increasing pain. As these mechanisms are bidirectional positive attitudes, optimism and positive emotional states make us more resistant against pain (Neugebauer, Li et al. 2004, Tracey and Mantyh 2007). These bidirectional mechanisms caused by emotional states and traits can further account for the fact that an identical stimulus may evoke differing behavioural pain ratings and brain activations. The different contributions of emotions to the sensation of pain with the involvement of the amygdala are displayed in figure 6.

In summary, the amygdala accounts for the emotional-affective and cognitive-evaluative aspects of pain and is part of the modulatory pain network (Neugebauer, Li et al. 2004, Wiech and Tracey 2009, Ji, Sun et al. 2010, Ossipov, Dussor et al. 2010).

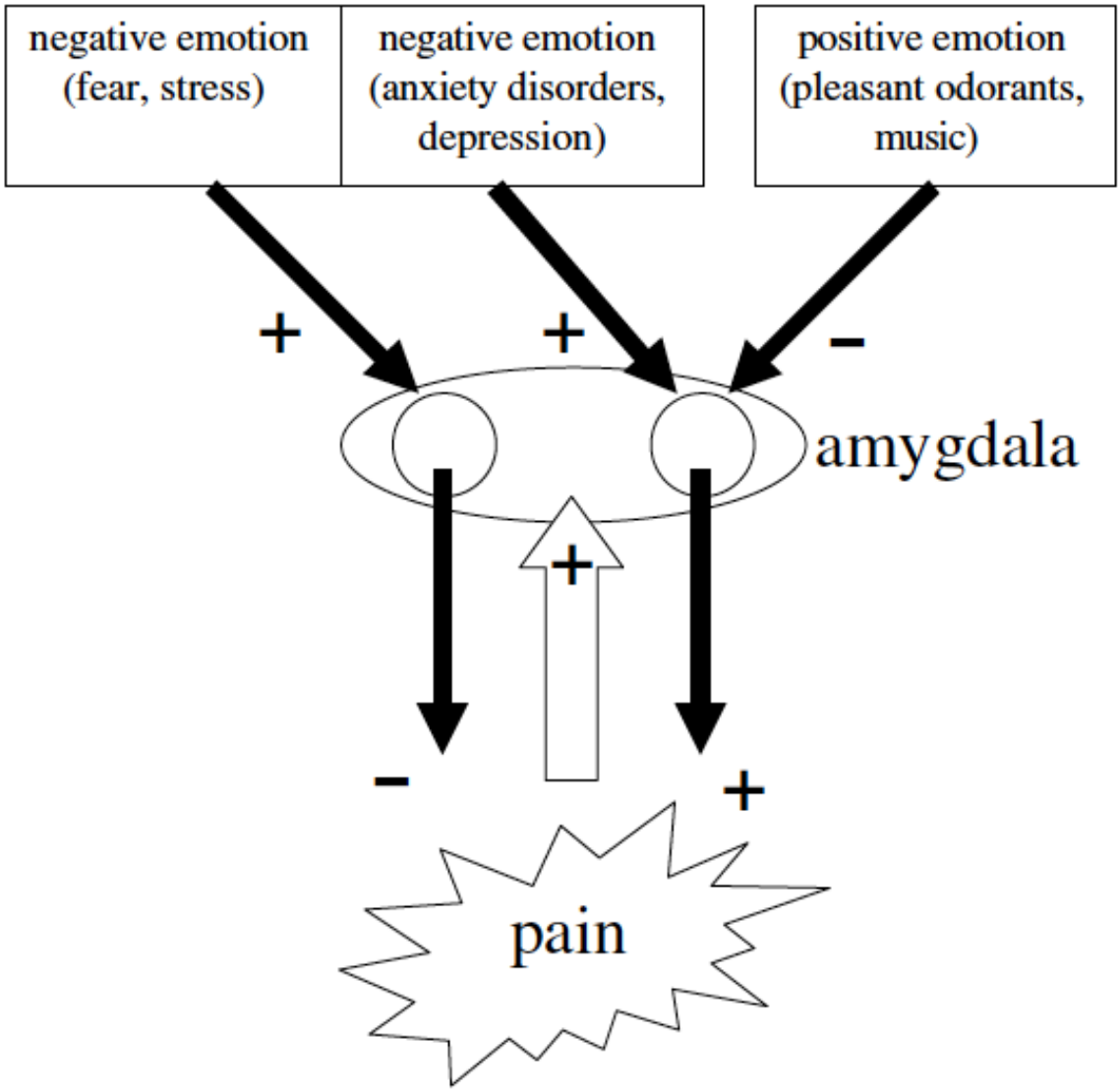


Figure 6. Pain, Emotions and the Amygdala: a Hypothetical Model.
As displayed in this figure negative emotions (including character state and traits) showed increased activations in the amygdala. Positive emotions seem to result in decreased activity in the amygdala. The amygdala plays therefore a role in facilitating or inhibiting pain. These connections are reciprocal and can be explained with the connection of the amygdala to pain facilitating and inhibiting systems (Neugebauer, Li et al. 2004).

1.3. Placebo-Analgesia

The word placebo is Latin origin meaning “I shall please” (Benedetti 2009). The modern definition of placebo was given by Shapiro in 1964, defining it as an inert treatment with no known specific effect on the disease it is supposed to cure or on the symptom it should treat (Shapiro 1964). Prior medical treatments in human

history involved the use of placebos. Benedetti described the history of medicine as the history of placebos (Benedetti 2013). Inert treatments have been carried out since human existence in every culture. However, its role in medicine from an inert treatment to a useful tool in medical research has changed. In modern medicine with advanced scientific knowledge and enormous medical and technical progress, placebos are still being used and indispensible in medical research. Placebos are used in different settings, for example in double blind clinical trials to test the pharmacological effectiveness of a certain drug or procedure. They help to control for confounders, such as the natural history of disease, biases as well as for the placebo response. Placebos applied in basic research settings also help us to better understand mind body interactions and basic brain functions. They enable the exploration of different treatment outcomes in individuals, who seem to have received identical interventions. Placebo interventions thus help us to disentangle and better understand the different factors that contribute to a treatment's success and positive outcome.

There has been some discussion and confusion among placebo researchers about the definition of placebo effect and placebo response. Benedetti uses both terms synonymously stating that the placebo effect or response is the outcome following the placebo treatment (Benedetti, Mayberg et al. 2005, Benedetti 2009, Benedetti 2013). Wager differentiates between effect and response, stating that the placebo effect is the difference in mean outcome, which occurs in the placebo group compared to a no-treatment group, while the placebo response is the active neurobiological process, in our case pain relief following the administration of the placebo treatment in one individual (Wager and Fields 2013).

The nocebo effect is the inverse placebo effect, that is, symptom impairment following sham treatment. The improvement following placebo administration can be attributed to various factors such as prior experiences, expectation, conditioning, desire for relief, the individual trait and state etc. (Benedetti 2009 pages 63-98). In this work we use the following definitions. The placebo response is used as the improvement that follows the administration of a sham treatment including the effects caused by confounders. Whereas the placebo effect is the benefit, which

can be attributed to the placebo treatment (Benedetti 2007, Benedetti, Carlino et al. 2011).

The following chapters focus on the placebo effect in pain, as it is the field of investigation of this work. The various factors contributing to the placebo effects in pain, such as expectations, conditioning, and other factors of the psychosocial context as well as the brain areas involved in placebo analgesia will be discussed.

1.3.1. Improvements after Placebo Interventions

Despite the real benefit of the placebo treatment and therefore the placebo effect, there exist several confounders, which can lead to an improvement independent of the placebo administrated such as the natural history of disease, regression to the mean as a statistical problem, reporting biases, etc. (Benedetti, Carlino et al. 2011).

By combining reported pain (e.g. via analogue rating scales) with objective markers, such as neural processing as analysed by neuroimaging techniques, a placebo effect can be correlated with the actual reported pain, thereby controlling for reporting bias (Hróbjartsson, Kaptchuk et al. 2011).

An overview of all mechanisms, which could lead to an improvement and have to be separated from the actual placebo effect as a psychobiological phenomenon gives figure 7.

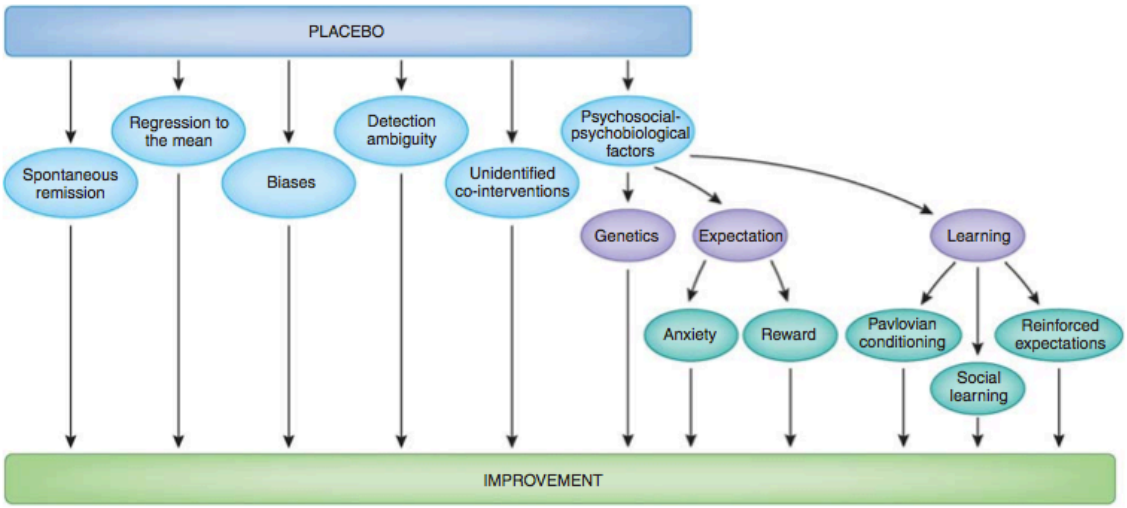


Figure 7. Factors Contributing to Improvement after Placebo Administration. (Benedetti, Carlino et al. 2011).

1.3.2. Expectations and Conditioning

Expectations towards a positive outcome can be evoked by multiple means comprising prior experiences, verbal suggestions and the overall context in which the treatment is embedded including cues for analgesia. Previous positive experiences can result in a conditioning process, also leading to a placebo response. This overlap can be seen as synergetic effect potentiating the positive response, the pain relief. Verbal suggestions alone can elicit a placebo response, which is usually lower than the one induced by conditioning processes (Colloca and Benedetti 2009, Atlas and Wager 2012, Bingel, Tracey et al. 2012, Schenk, Sprenger et al. 2014)

Pawlow developed a classical conditioning model in dogs. Before conditioning a neutral stimulus, namely ringing a bell, lead to an unspecific response. The unconditioned stimulus, namely food, leads to a natural unconditioned response, in this experiment salivation. In the following training phase, the neutral stimulus was repeatedly combined with the unconditioned stimulus, finally leading to a conditioned response, where the dogs reacted to the ringing bell with salivation. The neutral stimulus became a conditioned stimulus, which elicited a conditioned response (Schneider and Fink 2013 page 410). Even though this model cannot be completely transferred to humans, elements of this learning model are transferrable to the administration of drugs. Conditioning processes are assumed to take place whenever a patient repeatedly takes a pill (neutral stimulus) with its active substance (unconditioned stimulus), which then leads to pain relief (unconditioned response). Via conditioning this neutral stimulus becomes a conditioned stimulus, which will then evoke the conditioned response (pain relief) by itself (Price, Finniss et al. 2008). The overall context, in particular the environment, medical setting, the doctor and the pill itself, in which the administration of the agent is embedded, can be associated with pain relief and can become a conditioned stimuli. When receiving an inert substance, this conditioning process can eventually lead to pain relief (Wickramasekera 1980). It can be argued, that conditioning itself can shape and reinforce expectations (Montgomery and Kirsch 1997) and on the other hand conditioning might be mediated by expectations (De Pascalis, Chiaradia et al. 2002). Also other kinds of learning, such as observations of others – social learning

– have been shown to contribute to the magnitude of the placebo effect (Benedetti, Carlino et al. 2011, Benedetti 2013).

Furthermore, verbal suggestions of pain relief can induce a placebo effect. Verbal suggestions of pain relief may even increase the analgesic effect of a placebo treatment to the extent of an active agent (Vase, Robinson et al. 2003).

In summary, external factors such as conditioning and verbal suggestions make separate contributions to placebo analgesia. As the patient has most likely been exposed to the drug before, both aspects as a combination putatively contribute to the placebo effect in pain (Price, Milling et al. 1999, Price, Chung et al. 2005).

These external factors lead to internal individual expectations of the effectiveness of the treatment. The magnitude of the resulting expectation highly shapes the perception of the following pain. The desire for relief accounts for the motivational aspect of pain and is related to hope and trust in the treatment (Vase, Robinson et al. 2003). Price defines the desire as an avoidance goal or approach goal either to avoid an unpleasant feeling or to obtain a pleasant feeling. Desire is closely related to expectancy and both dimensions influence each other. As expectations the desire for pain relief may lead to a higher analgesic placebo effect (Price, Finniss et al. 2008). However, the desire for pain relief does not necessarily correlate with the degree of pain relief. A clinical setting or an experimental paradigm could detangle the contributions of expectancy and desire for relief to the magnitude of the placebo response (Price, Milling et al. 1999, De Pascalis, Chiaradia et al. 2002, Price, Chung et al. 2005).

Expectations further influence and modulate the emotional state of the subject, in particular anxiety. The state of mind contributes significantly to the magnitude of pain perception. These influences are bidirectional. Positive emotional states can reduce pain whereas negative ones might reinforce the unpleasant feeling (Wiech and Tracey 2009). Several studies registered a decrease of anxiety as reported by participants (behavioural results) as well as decreased activation in anxiety-related brain areas (neural correlates) following placebo administration (Petrovic, Dietrich et al. 2005, Vase, Robinson et al. 2005, Wiech and Tracey 2009). Interestingly, verbal suggestions may influence and reinforce particularly the nocebo response on pain

(Petrovic 2008). Negative expectations concerning pain intensity have been shown to increase neural activity of pain network structures (Benedetti, Carlino et al. 2011).

Expectations also influence biological reward mechanisms, particularly the dopaminergic circuit including the nucleus accumbens and the ventral basal ganglia in general. High placebo responses showed parallel high dopaminergic and opioid activity in the nucleus accumbens, nocebo effects on the other hand a decreased dopaminergic and opioid activity. Therefore, expectations appear to modulate not only anxiety, but also reward mechanisms (Scott, Stohler et al. 2007, Scott, Stohler et al. 2008, Wiech and Tracey 2009, Benedetti, Carlino et al. 2011).

1.3.3. Prefrontal Cortex and Placebo Responsiveness

Prefrontal activity is crucial for placebo responsiveness. Patients with prefrontal impairments as Alzheimer's or participants in an experimental setting with blockade of the prefrontal activity presented a loss of placebo effects (Benedetti, Arduino et al. 2006). The very same brain areas are active during placebo induced positive expectations of pain relief (Petrovic, Kalso et al. 2002, Wager, Rilling et al. 2004, Benedetti, Carlino et al. 2011). The prefrontal control can thus be considered as an essential component of expectancy-related placebo analgesia (Benedetti 2010, Krummenacher, Candia et al. 2010). These findings furthermore support the crucial role of expectations in placebo analgesia.

The importance of expectations for treatment outcome becomes also apparent, when comparing open and hidden treatments. The overt condition has a greater analgesic effect as the hidden condition. Amanzio et al. (1999) compared open and covert injections of a non-steroidal anti-inflammatory drug, ketorolac and could show that the therapy was much less effective when administered covertly. In a next step, naloxone was administered in the open condition and induced a similar effect as the hidden therapy, suggesting that the additional analgesic effect of the overt drug administration was mediated by the endogenous opioid system (Amanzio and Benedetti 1999, Scott, Stohler et al. 2008). Conditioning, however, might also activate subsystems and mechanisms other than the opioidergic system (Amanzio and Benedetti 1999).

Figure 8 demonstrates the involved brain regions in the modulation of pain via cognitive factors as expectations.

It also has been shown that expectations and conditioning seem to be not exclusive alternatives. They are often combined to maximize placebo responses (Atlas and Wager 2012).

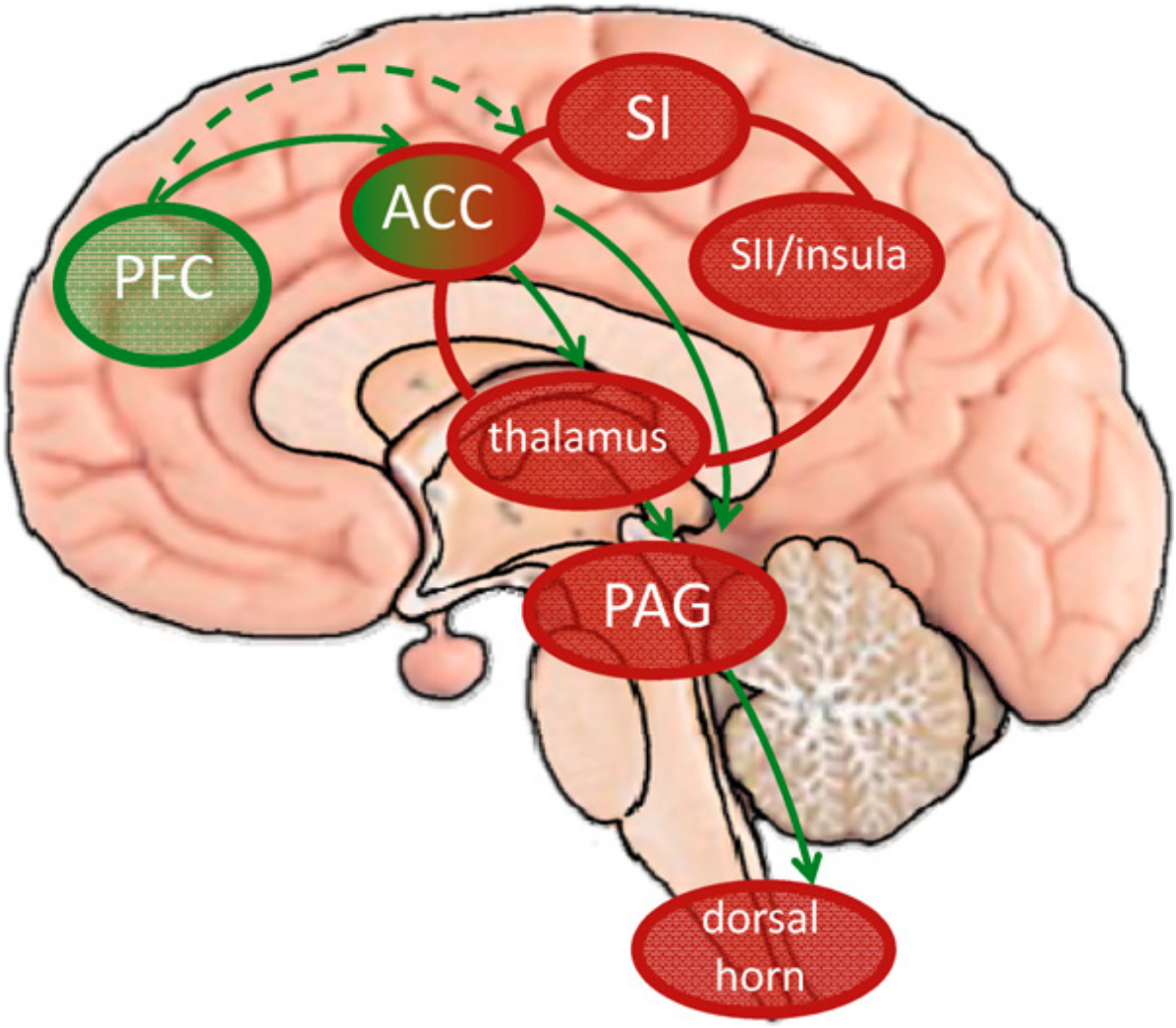


Figure 8. Top-down Modulation of Pain via Prefrontal Activity.
This figure displays the descending pain modulation circuits. Cognition may influence the perception of pain via the prefrontal cortex (PFC) that modulates the activity in pain-related brain areas (displayed in red). ACC, anterior cingulate cortex; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; PAG, periaqueductal grey" (Bingel, Tracey et al. 2012).

1.3.4. Placebo Effect is a Component of the Active Treatment

Every active treatment is embedded in a psychosocial context, and the placebo effect can be seen as an additional component complementing and enforcing the treatment. The overall context, setting, personal memories, beliefs and expectations, the person administering the drug and finally the medication itself influence the outcome of the treatment. As mentioned above the comparison of hidden and open medication support the idea that hidden medication is less effective - probably due to the lack of a synergetic effect of these various factors (Colloca, Lopiano et al. 2004, Benedetti 2013, Wager and Fields 2013). Figure 9 summarizes the factors that contribute to the placebo effect.

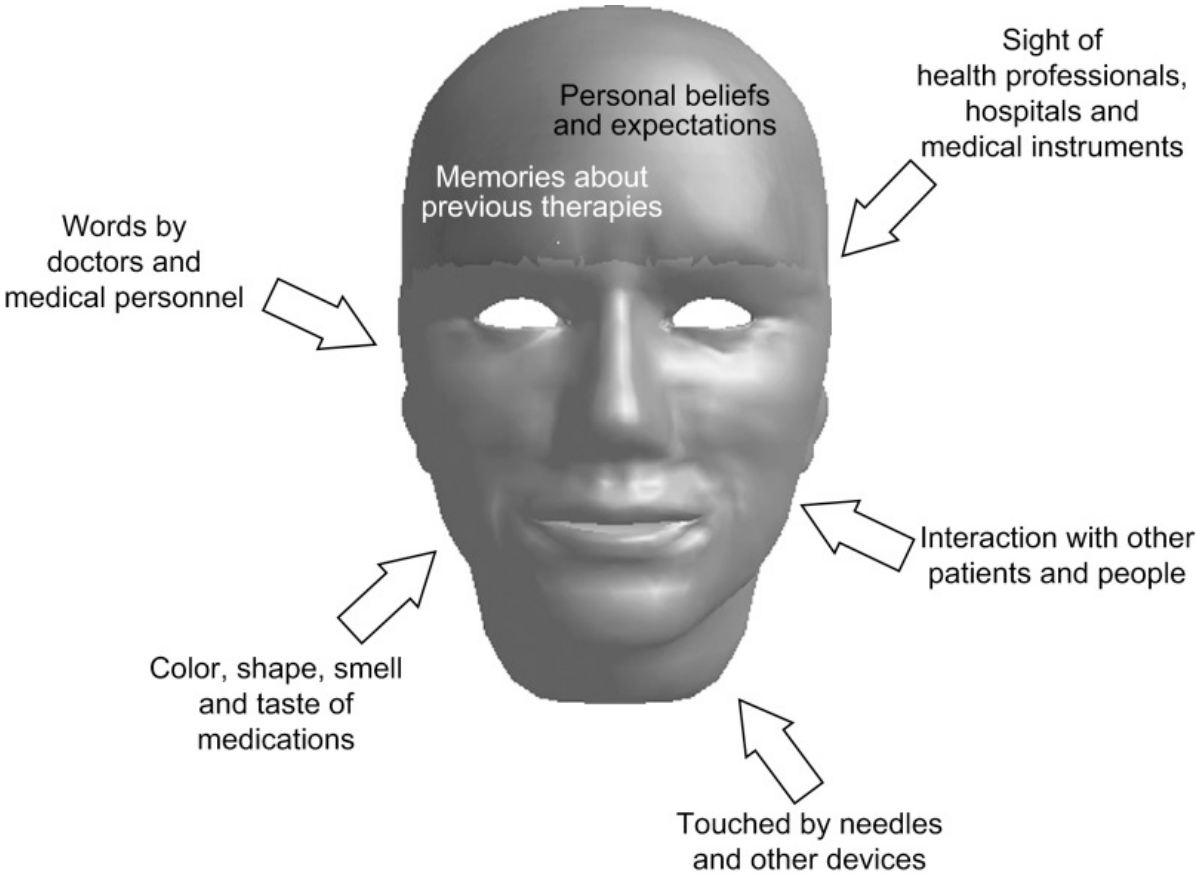


Figure 9. The Psychosocial Context around the Patient and the Therapy.
A patient receives various inputs and stimuli when receiving a medical treatment. Character traits and state, sensory and social stimuli influence the context in which the therapy is embedded. This overall context as displayed in this figure is the foundation for placebo and nocebo effects (Benedetti, Mayberg et al. 2005, Benedetti 2007, Benedetti 2013).

1.3.5. Responders and Non-responders

There has been reported a huge variance between different placebo studies concerning the magnitude of the placebo effect and the placebo response rate (Levine, Gordon et al. 1978, Benedetti 1996, Leuchter, Morgan et al. 2004, Benedetti and Amanzio 2011). There is still an uncertainty if there exist non-responders by trait or by state. It is not yet clear, if a person is by character a responder or dependent on the setting, prior experiences and expectations responds to the sham treatment. Convincing arguments speak for a combination of both components. There exists however doubt that reliable placebo responsiveness is a stable trait (Kaptchuk, Kelley et al. 2008).

Inter-individual differences such as the suggestibility, resilience, reward responsiveness, optimism and pessimism can influence and modulate the placebo response, but whether a particular person is a responder or non-responder to a specific therapy depends on the clinical setting, personal memories and experiences, her beliefs and trust in the treatment. This could explain the huge variance in the number of placebo responders across studies (Atlas and Wager 2012). The magnitude of the placebo effect is shaped by an individual's prior experiences, the clinical context, verbal suggestions and the degree of manipulation resulting in different amounts of treatment expectations (Benedetti 2009 pages 65ff.).

1.3.6. Factors, which Contribute to the Magnitude of the Placebo Effect

Prior positive experiences with the active substance resulting in a conditioning process and verbal suggestions leading to an expectation of pain relief can contribute to the placebo response (Price, Chung et al. 2005). This effect can also occur in the opposite direction, leading to a nocebo effect, in our case pain increase, when negative expectations are predominant (Petrovic 2008).

The overall context and setting, in which the placebo is administered, namely how and by whom, further shapes the placebo response (Benedetti, Carlino et al. 2011). Placebos administered by a doctor with a white coat in a clinical setting result in a higher magnitude of the placebo response. The context being it experimental or

clinical determines further the magnitude of the placebo effect. Patients tend to have higher pain relief after placebo administration in a clinical setting than participants in an experimental setting. This can be attributed to the differences in expectations and desire for pain relief between patients and participants in clinical trials (Benedetti 2009 pages 65ff.).

Finally a placebo response does not necessarily require a conscious expectation. After conditioning and learning processes placebo effects occur without conscious expectancies regarding the placebo. This has been particularly reported for hormonal responses (Benedetti, Pollo et al. 2003, Price, Finniss et al. 2008). As for pain, different results have been reported.

1.3.7. Neural and Physiological Mechanisms of Placebo Analgesia

The placebo analgesia leads to a reduction in pain related brain areas and an increased activity in pain modulatory circuits combined with an activation of the endogenous opioid and dopaminergic systems (Benedetti, Carlino et al. 2011, Wager and Fields 2013 page 12). The descending pain modulatory network described above is involved in placebo analgesia. Naloxone antagonizes placebo analgesia, implicating an activation of the endogenous opioid system via the placebo (Levine, Gordon et al. 1978, Benedetti 1996, Benedetti, Mayberg et al. 2005, Eippert, Bingel et al. 2009). These findings were supported by positron emission tomography (PET) studies, which investigated the neurotransmitter binding character during placebo analgesia. Placebo analgesia is attended by a higher binding of μ-opioid receptors in limbic brain regions (Zubieta, Bueller et al. 2005, Atlas and Wager 2012). Furthermore, the prefrontal cortex as initiating centre and activity in μ-opioid receptor rich brain regions as the rACC and the PAG influence the processing of pain (Bingel, Lorenz et al. 2006, Bingel, Tracey et al. 2012).

A recent study investigated placebo responses conditioned by non-steroidal anti-inflammatory drugs, which then were antagonized by CB1 cannabinoid receptors (Benedetti, Amanzio et al. 2011). These findings suggest an involvement of the endogenous cannabinoid system in addition to the opioidergic system and support the idea of a response, which is specifically shaped by prior conditioning processes.

Placebo analgesia can therefore be mediated by both, opioid and non-opioid pathways, depending on the type of drugs used for conditioning (Benedetti, Amanzio et al. 2011, Benedetti, Thoen et al. 2013).

Furthermore, cholecystokinin can antagonize placebo analgesia, but only when administered openly suggesting an involvement already on the expectancy level through activation of the endogenous opioid system. The cholecystokinin antagonist proglumide accordingly reinforces placebo analgesia. The investigation of the cholecystokinin system was useful in exploring the neurochemistry of nocebo hyperalgesia and lead to the conclusion that cholecystokinin inhibits not only placebo responses but also increases nocebo-induced hyperalgesia (Benedetti 1996, Benedetti, Amanzio et al. 1997, Benedetti, Amanzio et al. 2006, Wagner, Roeder et al. 2013). As cholecystokinin is closely associated with anxiety, it has been concluded that nocebo responses are associated with increased anxiety and as a result with higher pain (Lydiard 1994, Atlas and Wager 2012).

As pointed out above the dopaminergic reward system also contributes to placebo analgesia. The higher the activation in the nucleus accumbens – a central structure of the dopaminergic reward system – the greater the responsiveness to the placebo administration. The placebo responsiveness seems to be closely related to the functioning of the reward system and dopamine-related traits (Scott, Stohler et al. 2007, Schweinhardt, Seminowicz et al. 2009). Nocebo responses lead to a decrease in dopaminergic activity, leading to the conclusion that placebo and nocebo responses are associated with opposite opioid and dopaminergic activity (Scott, Stohler et al. 2008). Figure 10 displays the dopaminergic and opioid systems involved in placebo analgesia.

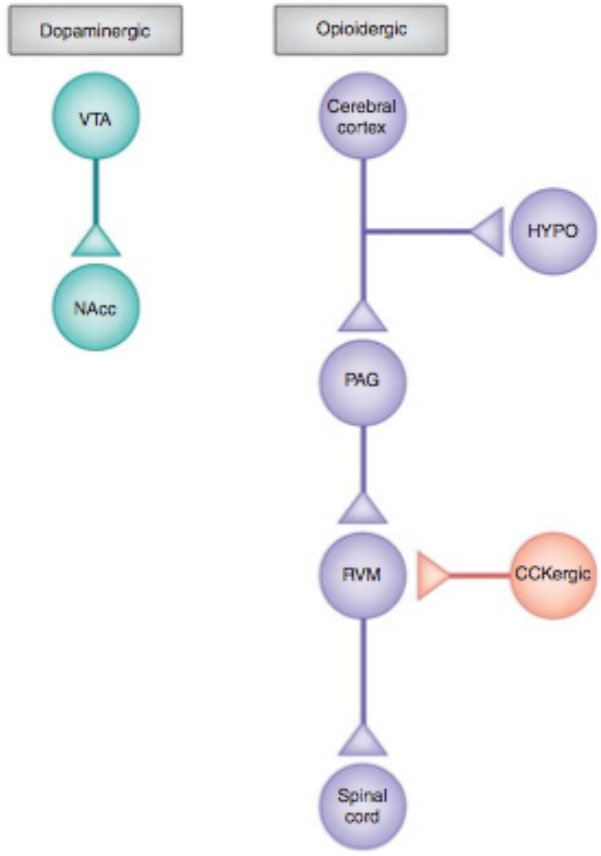


Figure 10. Neural Correlates of Placebo and Nocebo Responses to Pain.
A inhibitory top down effect is mediated by the opioid system starting at the cerebral cortex projecting to the hypothalamus (HYP), the periaqueductal grey (PAG), rostroventromedial medulla (RVM), and the spinal cord. The dopaminergic system starts at the ventral tegmental area (VTA). It then projects to the nucleus accumbens (NAcc). The cholecystokininergic (CCKergic) system antagonizes the opioid induced analgesia (Benedetti, Carlino et al. 2011).

In summary, it can be stated that placebo analgesia is modulated by conditioning, suggestions and expectations. The positive outcome of the placebo treatment further depends on the psychosocial context in which the treatment is embedded. Brain regions, which are responsible for emotional, attentional and cognitive modulation of pain, are also activated during placebo analgesia, suggesting a common pain modulatory network as basis (Wiech, Ploner et al. 2008, Bingel, Tracey et al. 2012, Bushnell, Čeko et al. 2013).

1.4. fMRI

1.4.1. MRI Mechanisms

Magnetic resonance imaging (MRI) is used in clinical practice and scientific research as a non-invasive diagnostic method generating anatomic and functional images. This technique uses the spin of hydrogen atoms to generate its images. Most of the body tissue consists of water, which is made up of two hydrogen and one oxygen atom. Hydrogen therefore produces the strongest signal as it presents the bulk of the body's tissue (Horsfield 2005, Reiser, Kuhn et al. 2011 page 80).

A hydrogen atom consists of atomic nuclei with one proton of positive elementary charge and one negative electron in its shell. Due to the oddness of its atomic nuclei, the hydrogen proton has a spin, which is a general trait of elementary particles. This spin angular momentum around its own axis generates a magnetic dipole and thus creates a magnetic field. When placed in an external magnetic field B0, the spin as a vector aligns in the direction of the field. As the atom consists of protons, neutrons and electrons of which all contribute to the angular momentum, the vector does not align completely in the magnetic field, but rotates around it. This rotation in the direction of the external magnetic field comparable to a gyroscope is called precession (Balter 1987, Weishaupt, Köchli et al. 2006, Schneider and Fink 2007, Reiser, Kuhn et al. 2011 pages 79ff.). For simplification purposes, this work further concentrates on the movement of the proton of hydrogen.

The precession's frequency is also called Lamor frequency and can be determined by the Lamor equation. This frequency is proportional to the strength of the external magnetic field, which is crucial for magnetic resonance imaging (Horsfield 2005, Schneider and Fink 2013 pages 62ff.). Figure 11 demonstrates the rotation around the dipole vector.

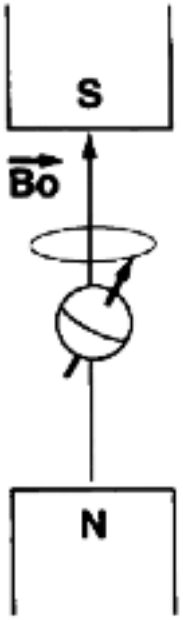


Figure 11. **The Dipole Vector in the Magnetic Field.**
The dipole vector demonstrates the rotation around the vector in the direction of the external magnetic field B0 (Balter 1987).

Precessing protons align in the magnetic field in two different stages, parallel and antiparallel. The protons, which align parallel to the external magnetic field, are in a stable low energy state whereas the antiparallel alignment represents the unstable high-energy condition (Balter 1987, Reiser, Kuhn et al. 2011 pages 79ff., Schneider and Fink 2013 pages 62ff.). Figure 12 describes the different stages of the protons being parallel or antiparallel to the magnetic field.

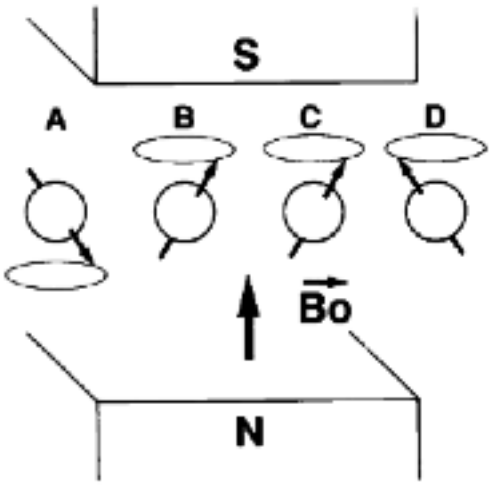


Figure 12. Phase Relations Between Protons.
Proton A is antiparallel, protons B C D are parallel to the magnetic field B0 (Balter 1987).

When adding together the magnetism of the spin of each proton, we receive the net magnetization, which points in the direction of the applied field. As this net magnetization is proportional to the magnetic field applied, a strong MRI magnet is necessary to generate a signal. However, as it is still too small and difficult to measure, the net magnetization has to be reinforced (Horsfield 2005, Weishaupt, Köchli et al. 2006).

This can be accomplished by exposing the patient to a high-energy radiofrequency impulse perpendicular to the magnetic field B0. If this energy matches the spin speed of the proton, then the proton absorbs the energy and deflects it out of alignment. Protons, which were aligned in the direction of the net magnetic field B0, will flip around for 90° and will initially precess synchronously (Weishaupt, Köchli et al. 2006, Schneider and Fink 2013 pages 62ff.).

1.4.2. T1 Relaxation Time

The protons precess in transversal direction of the magnetic field (z vector), they flip back to their original state in longitudinal alignment in z-direction. This longitudinal relaxation is affiliated with transmission of energy, which can be detected by the scanner. This effect is also called spin-lattice time as energy is transferred to the

lattice, which causes the lattice molecules to vibrate and in a next step convert this energy into heat. The spin-lattice relaxation measures the time until the protons reach the equilibrium state in longitudinal direction. It depends on the tissue type and the strength of the magnetic field applied. The time constant for this decay is called T1 (Suetens 2009, Schneider and Fink 2013).

1.4.3. T2 Spin-Spin Relaxation

After the high-energy radio frequency impulse the protons rotate in phase and are therefore synchronized. However, each proton has a slightly different magnetic field. Due to these spin-spin interactions protons precess at different angular frequencies and start to dephase. The spin-spin relaxation is transverse and highly dependent on the tissue type as different tissues relax in different ways. The time constant for this decay is called T2. The inhomogeneity created by the scanner and the corps itself leads to an even more rapid dephasing (T2* weighted time constant) (Weishaupt, Köchli et al. 2006). Figure 13 displays the different mechanisms of relaxation times T1 and T2.

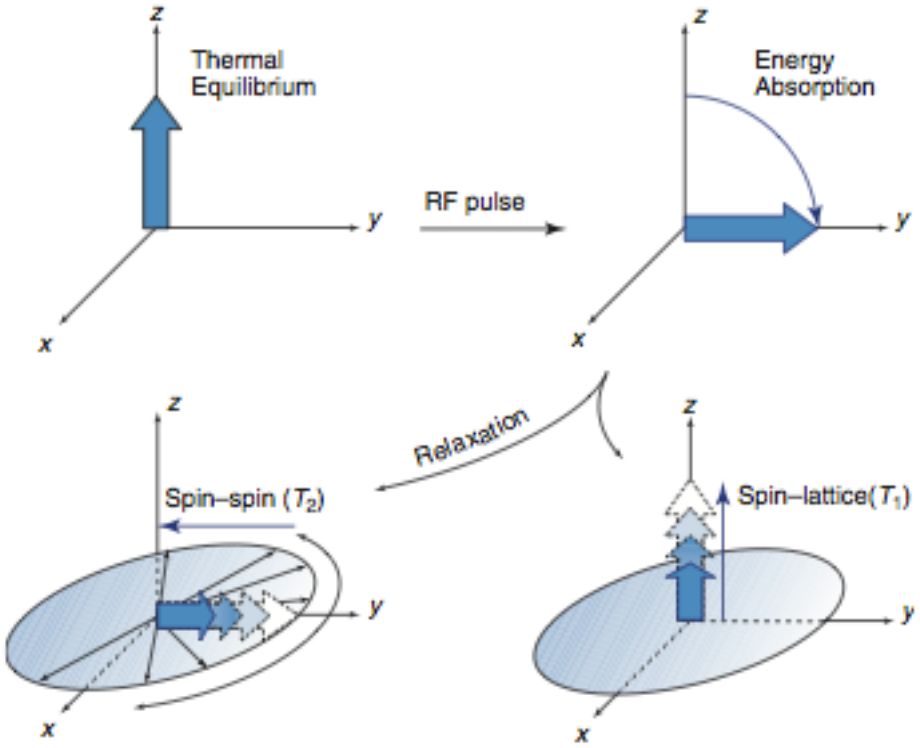


Figure 13. Relaxation Times.
The different mechanisms of Relaxation behind T1 and T2 relaxation, which occur simultaneously (Suetens 2009).

1.4.4. BOLD Response – Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is an imaging method, which enables the display of dynamic processes of brain activation. The underlying effect is the change in cerebral blood flow assuming that a haemodynamic response – an increase in blood flow after brain activity – can be correlated with increase in neural activity (Poldrack, Mumford et al. 2011).

Essential for this imaging technique is that oxygenated haemoglobin has different magnetic characteristics than deoxygenated haemoglobin, deoxy-haemoglobin being paramagnetic to the brain tissue whereas oxygenated haemoglobin is isomagnetic (Matthews and Jezzard 2004, Poldrack, Mumford et al. 2011). When neurons become active also the blood flow in the particular brain region increases (Poldrack, Mumford et al. 2011) this correlation is referred to as hemodynamic response. Interestingly, more oxygenated haemoglobin is supplied than needed, so

in total the oxygenated haemoglobin increases in the activated areas (Fox and Raichle 1986, Matthews and Jezzard 2004, Poldrack, Mumford et al. 2011). The blood flow increase is significantly higher than the oxygen metabolic rate resulting in a reduction of the oxygen extraction fraction (Buxton 2009 page 7). Already early PET studies demonstrated a correlation between increased blood flow and increased metabolic rates (Fox and Raichle 1986). Ogawa was the first to demonstrate in rats that metabolic activity of the brain tissues correlates with the oxygen supply in that area and thus its blood flow (Ogawa, Lee et al. 1990). These findings, the blood oxygen level dependent (BOLD) contrast, were later replicated in human brains (Ogawa, Tank et al. 1992). The increase in oxygenated haemoglobin results in an increased MR signal in T2* weighted images. The increase in oxygenated haemoglobin (oxyHB) after neuronal activity is delayed in time (Matthews and Jezzard 2004, Schneider and Fink 2013). Figure 14 shows the underlying mechanisms of the hemodynamic response responsible for a normal or increased signal.

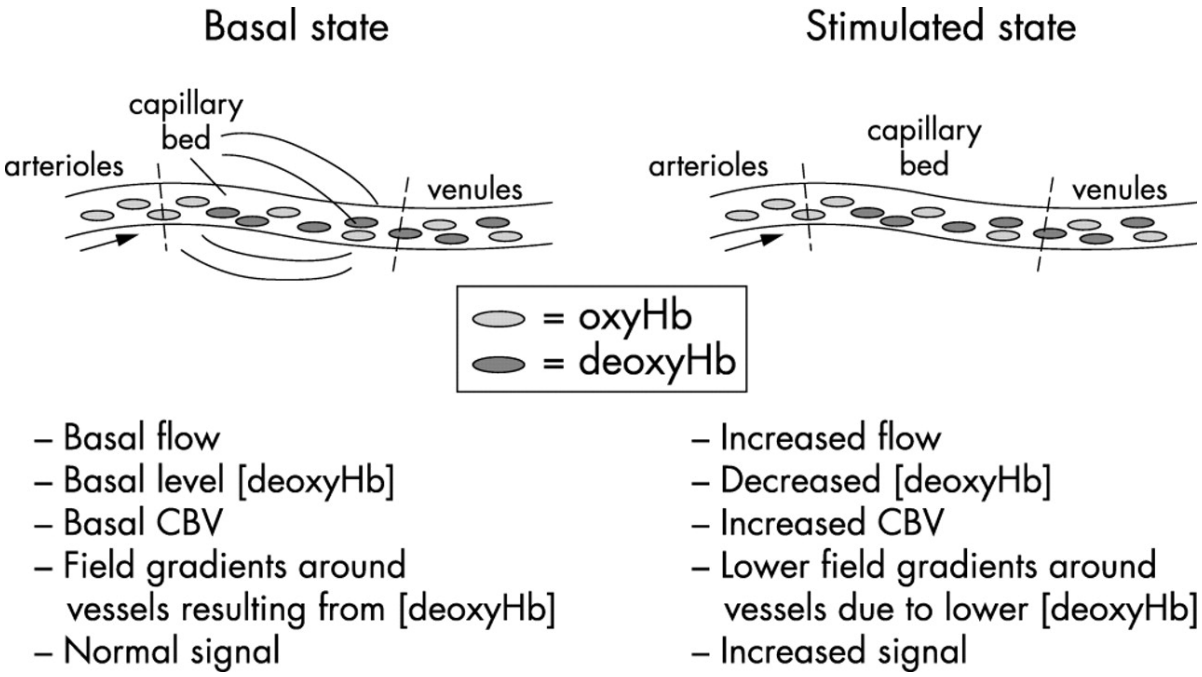


Figure 14. **The Hemodynamic Response.**
The BOLD effect and its underlying hemodynamic mechanisms during basal state and neural activity. Oxygenated haemoglobin (oxyHb); deoxygenated haemoglobin (deoxyHb); cerebral blood flow (CBV) (Matthews and Jezzard 2004).

The BOLD effect varies from 0,5% to 5% oft he MRI signal at 1,5 Tesla. In order to clearly distinguish it from the noise, larger voxel sizes and thus a lower spatial resolution of the epi (echo-planar imaging) sequence has to be selected (Schneider and Fink 2013 page 77). Furthermore the pre-processing of the fMRI data and the following statistical analysis enhance the real signal (see chapter below). In comparing the neural activity to baseline condition (no stimulus presented), the amplitude of the BOLD signal during stimulus presentation can be detected. It is important to keep in mind that fMRI is an indirect method to determine neural activity. Logothesis et al. (2001) demonstrated a direct correlation of the BOLD signal and neural activity by coupling electrophysical methods (microelectrodes) and fMRI techniques in monkeys (Logothetis, Pauls et al. 2001). It thus reflects neural activity. However, the exact physiological mechanisms of the BOLD signal have not been clearly identified yet.

1.5. Research Question

In the present study we compared the analgesic placebo effect of a placebo pill labelled with a trusted brand as compared to a placebo pill labelled with a generic brand. A trusted brand may elicit and reinforce positive expectations towards the effectiveness of a treatment. Underlying mechanisms can be advertisement, prior positive experiences, and memories. Humans tend to find a strong brand and expensive products more appealing than a weak brand and cheaper products. Several fMRI studies have investigated the underlying neurofunctional mechanisms (McClure, Li et al. 2004, Schaefer and Rotte 2007, Plassmann, O'Doherty et al. 2008) suggesting that a trusted brand itself can act as a placebo (Berns 2005, Borsook and Becerra 2005, Irmak, Block et al. 2005, Shiv, Carmon et al. 2005).

Geuter et al. (2013) investigated the behavioural and neural responses to weak and strong placebo interventions. They established these interventions with a preconditioning phase combined with verbal instructions of price levels. The weak placebo condition was implemented by a preconditioning phase with lower pain relief and verbal instructions of a cheap price. Participants in the strong placebo group experienced higher pain reduction during the preconditioning phase combined with the verbal information of a high price. The weak placebo elicited a lower behavioural placebo response and neural activations, whereas the strong placebo resulted in higher placebo analgesia and activated brain areas (Geuter, Eippert et al. 2013).

The study by Geuter et al. thus investigated the behavioural responses and neural correlates of expectations created by a weak and a strong placebo. The two types of conditioning combined with according verbal instructions lead to the corresponding high or low expectations of pain relief. Our aim was to solely focus on the brand effect of the placebo treatment. We aimed to investigate how a brand and its associated marketing cues might change the analgesic behavioural and neural response to a placebo pill. By introducing a branded and a generic ‘drug’, we provoked cognitive cues and expectations associated with the one or the other and focused on behavioural and neural placebo responses to original versus generic brands.

A recent review published by Plassmann et al. (2015) summarized findings for marketing-based expectations on a behavioural and neural level. The authors could identify individual properties and character traits as somatosensory awareness, reward responsiveness and the need for cognition, which shape and influence the "marketing placebo effects". The authors first reviewed pain placebo studies to identify determinants of expectancy effects and concluded that dopaminergic functioning influences the expectations and therefore the placebo effect. A positive cue may increase the motivational aspect of reward seeking, and therefore the character trait of reward responsiveness may increase the analgesic response. In our study, we tested for individual character trait differences in order to rule out significant differences in personality traits and to concentrate on the brand effect only. Furthermore, Plassmann et al. identified the individuals' somatosensory processing as another variable in their model of marketing placebo effects. Finally they argue that prefrontal activity with its involvement in emotional and cognitive regulation and assessments further shapes the placebo effect (Plassmann and Weber 2015). In our study, we studied expectancy effects reinforced by a strong brand possibly to be influenced by factors as cognitive control, emotional appraisal and attention. We used a paradigm, which focused on the comparison of brand and generics ruling out different character state and traits with questionnaires. Plassmann et al., however, were investigating personality traits and anatomical brain conditions to predict the outcome of marketing placebo effects. Differences of grey matter in the striatum, somatosensory cortex and prefrontal area were linked to personality traits as reward seeking, cognitive evaluation and emotional appraisal, which determined the responsiveness toward marketing placebo effects (Plassmann and Weber 2015). The authors concentrated on the identification of individual differences to predict the marketing placebo effects. In our case, we aimed to investigate how a brand and its associated marketing cues might change the analgesic behavioural and neural response despite any individual differences. By introducing a branded and a generic drug, we provoked cognitive cues and expectations associated with the one or the other and focused on behavioural and neural placebo responses to original versus generic brands.

In this study, we tested the hypothesis that placebo-induced expectations reinforced by a strong brand can enhance the neuronal impact of an inert substance described

as a painkiller. For this research aim we tested two identical placebos against each other, one labelled as ‘Aspirin’, the other one as ‘1A Pharma’ as a generic brand of Aspirin. We expected a higher pain relief in the Aspirin placebo group as compared to the 1A Pharma placebo group. Furthermore we investigated the neural correlates of the different placebo responses.

This line of research is clinically important, since it could demonstrate to what extent brand labelled drugs evoke a placebo effect in patients, and therefore which consequences it may have if doctors switch a known and proven medication to its generic equivalent. Moreover, it could show how psychosocial stimuli, such as verbal and nonverbal cues, can influence both pain perception and pain processing to the good or to the bad. The higher cost of original versus generic drugs is a further reason for exploring the underlying neural processes. The placebo study of Geuter et al. (2013), which investigated the differences in efficacies between weak and strong placebos induced by experience, verbal information and value manipulation (Geuter, Eippert et al. 2013), inspired us to investigate the effect of a trusted brand in comparison to a generic brand. The research aims of our pilot study were (1) to test, whether a placebo pill described as Aspirin elicits a larger analgesic response than a placebo pill labelled as the generic drug 1A Pharma, and (2) to identify the underlying neural correlates of this putatively differential placebo effect.

2. Materials and Methods

2.1. Participants

Thirty male right-handed subjects between the age of 27 and 45 with no history of psychiatric, internal, neurologic disease or drug abuse were selected. The recruitment was based on an existing database of the lab as well as on a university database of potential participants for medical studies. We used a specific selection questionnaire to choose potential candidates (as shown in appendix 6.1).

The questionnaire enabled the selection of participants with occasionally use of painkillers and enabled the exclusion of participants with psychological, neuronal and major systemic disease, left handiness and metal implants.

The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of the Ludwig-Maximilians-University Munich (LMU). Written informed consent was provided, and subjects received financial compensation of 150 Euros.

2.2. Medoc

The thermal stimuli were conducted via a 30x30 mm^2 Medoc Pathway thermode of the model ATS (Advanced Thermal Stimulation, Medoc Advanced Medical Systems Ltd, Ramat Yishay, Israel). The thermode was placed on the left volar forearm corresponding to dermatome 6 (Ruscheweyh, Verneuer et al. 2012, Geuter, Eippert et al. 2013). The Medoc system enables accurate programmable temperature applications between -10ºC and 55ºC with a temperature increase of 6º C per second.

It was used as a somatosensory stimulator to induce temperatures between 42-47 ° corresponding to 60/100 on the numeric rating scale.

2.3. The Placebo Agent

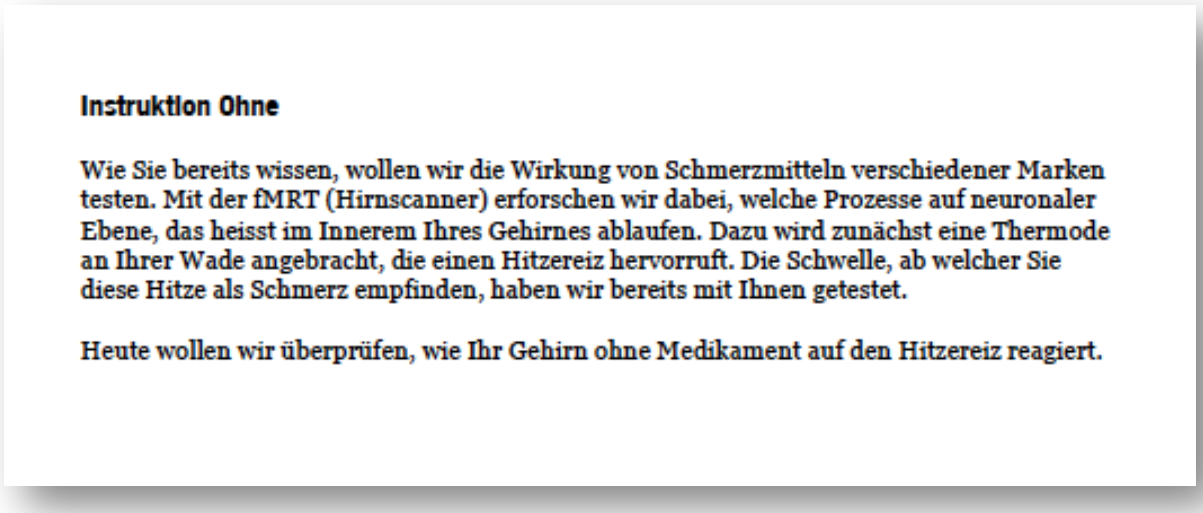
Each participant received a dose of the placebo dissolved in water. Fabian Simmank and Lea Maikowski were responsible for developing the placebo agent using a formula derived from Aspirin. The placebo agent was inspired by Aspirin plus c in look and taste. It was based on the composition and ingredients of Aspirin excluding the active agent to produce a similar taste. The ingredients of placebo were the following:

- ascorbic acid
- sodium hydrocarbonate
- saccharose
- cellulose
- maize starch

It was dissolved in 80 ml water in front of the eyes of each participant and then administered.

2.4. The Instructions

During the native condition before the scanner session all participants received the following information:



Instruktion Ohne

Wie Sie bereits wissen, wollen wir die Wirkung von Schmerzmitteln verschiedener Marken testen. Mit der fMRT (Hirnscanner) erforschen wir dabei, welche Prozesse auf neuronaler Ebene, das heisst im Innerem Ihres Gehirnes ablaufen. Dazu wird zunächst eine Thermode an Ihrer Wade angebracht, die einen Hitzereiz hervorruft. Die Schwelle, ab welcher Sie diese Hitze als Schmerz empfinden, haben wir bereits mit Ihnen getestet.

Heute wollen wir überprüfen, wie Ihr Gehirn ohne Medikament auf den Hitzereiz reagiert.

Figure 15. Instructions Native Condition.

After the randomization into the two placebo groups, the participants of the branded placebo group (Aspirin group) received the following information:

Instruktion Aspirin

Wie Sie bereits wissen, wollen wir die Wirkung von Schmerzmitteln verschiedener Marken testen. Mit der fMRT (Hirnscanner) erforschen wir dabei, welche Prozesse auf neuronaler Ebene, das heisst im Innerem Ihres Gehirnes ablaufen. Dazu wird zunächst eine Thermode an Ihrer Wade angebracht, die einen Hitzereiz hervorruft. Die Schwelle, ab welcher Sie diese Hitze als Schmerz empfinden, haben wir bereits mit Ihnen getestet.

Heute wollen wir überprüfen, wie Sie auf das Medikament mit der Marke

ASPIRIN

reagieren und in wie weit dessen Einnahme Ihre Schmerzempfindung beeinflusst.

Der Wirkstoff ist 500mg Acetylsalicylsäure (ASS).

Wir werden jetzt eine Tablette ASPIRIN wegen des leicht bitter-säuerlichen Geschmackes in einem Glas Apfelschorle auflösen, das Sie bitte austrinken. Danach warten wir 30 Minuten, bevor Sie zur Messung in den Scanner gebracht werden.

ASPIRIN wird von der Bayer AG hergestellt, einem der erfolgreichsten Pharmakonzerne der Welt mit über 100.000 Mitarbeitern. ASPIRIN wurde als eines der ersten Produkte von Bayer im Jahre 1866 auf den Markt gebracht. Seine zunächst einzigartige Rezeptur wurde später von zahllosen anderen Herstellern kopiert.

ASPIRIN ist auch heute noch das mit weitem Abstand meistverkaufte ASS-Präperat. Erst kürzlich wurde es wieder aus einer Liste von 135 Medikamenten zum vertrauenswürdigsten Schmerzmittel gewählt. Bayer steckt auch heute noch ihre Ideen und Erfahrungen als forschendes Pharmaunternehmen in ihr bekanntestes Produkt.

ASPIRIN ein sehr teures Medikament ist.

Mit € 16,95 kosten 100 Tabletten mehr als drei Mal soviel wie das vergleichbare ASS 500 von 1a PHARMA (€ 5,25).

Figure 16. Instructions Aspirin.

The generic placebo group received the following hand-out:

Instruktion 1a Pharma

Wie Sie bereits wissen, wollen wir die Wirkung von Schmerzmitteln verschiedener Marken testen. Mit der fMRT (Hirnscanner) erforschen wir dabei, welche Prozesse auf neuronaler Ebene, das heisst im Innerem Ihres Gehirnes ablaufen. Dazu wird zunächst eine Thermode an Ihrer Wade angebracht, die einen Hitzereiz hervorruft. Die Schwelle, ab welcher Sie diese Hitze als Schmerz empfinden, haben wir bereits mit Ihnen getestet.

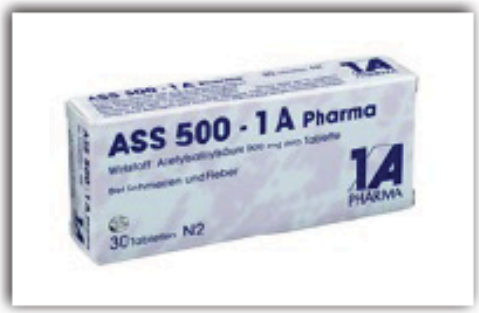
Heute wollen wir überprüfen, wie Sie auf das Medikament mit der Marke

1a Pharma

reagieren und in wie weit dessen Einnahme Ihre Schmerzempfindung beeinflusst.

Der Wirkstoff ist 500mg Acetylsalicylsäure (ASS).

Wir werden jetzt eine Tablette 1a Pharma wegen des leicht bitter-säuerlichen Geschmackes in einem Glas Apfelschorle auflösen, das Sie bitte austrinken. Danach warten wir 30 Minuten, bevor Sie zur Messung in den Scanner gebracht werden.



1a Pharma, der Hersteller der Tabletten, wurde erst 1997 in Oberhaching von Ludwig Grasmüller gegründet. Die Firma stellt ausschliesslich sogenannte Generika her. Das sind Medikamente, die chemische Kopien von erfolgreichen Produkten sind, deren Patentschutz abgelaufen ist.

1a Pharma kann sich als Hersteller von Generika die Kosten für Forschung und Entwicklung sparen und deshalb sehr günstig anbieten. Für ASS gibt es viele Dutzend Hersteller allein in Deutschland. Laut einer kürzlichen Untersuchung von 149 Präparaten bietet 1a Pharma keine besonders gute Qualität aber einen besonders guten Preis.

1aPharma ist ein sehr billiges Medikament.

Mit € 5,25 kosten 100 Tabletten weniger als ein Drittel soviel wie das vergleichbare ASPIRIN (€ 16,95).

Figure 17. Instructions 1A Pharma.

2.5. Procedure and Materials

This chapter describes the procedure of the experiments (Fehse, Maikowski et al. 2015). A 2x2 prospective block design was used in our study. We conducted a within-subjects design comparing the native with the intervention condition (before and after placebo administration) and a between subjects design comparing the two placebo interventions (Aspirin and 1A Pharma). The study design was single blinded. Thirty male right-handed subjects participated. After the native measurement, the subjects were randomly assigned to either the “Aspirin” group or the “1A Pharma” group. Lea Maikowski (L.M.) and Dr. Evgeny Gutyrchik conducted randomization by lot drawing. For this, the names of all participants were separately written on paper and L.M. drew the names alternately for assigning the participants to the two groups. Dr. Gutyrchik supervised the randomization. Then both groups received group-specific, standardized and written information on the respective brand as displayed in the chapter above.

Thereafter, all participants received the same placebo solution in the form of an inert substance based on the formula of Aspirin as described above excluding the active agent. The placebo application was always conducted by the same person (L.M.) wearing a white coat and being introduced as medical student.

Before participants went into the native round, they rated the average and maximum expected pain. After the native condition, they rated the mean and maximum perceived pain. After receiving the group-specific information, participants had to rate again their mean and maximum expected pain. Finally after the intervention round, the subjects rated the mean and maximum pain they experienced.

Figure 18 describes the study design with the native condition and the intervention condition.

Condition	Native	Intervention
Placebo-Group: original brand	Pain	Pain + „Aspirin“
Placebo-Group: generic brand	Pain	Pain + „1a Pharma“

Figure 18. **Study Design: 2x2 Block Design.**
The participants first underwent the native condition. After that, they were randomly assigned to either the original brand placebo group or the generic brand placebo group and received according information before they underwent the intervention condition.

Before the actual experiment, we started with a calibration trial. To determine the individual pain threshold a calibration was conducted with Medoc Model Pathway ATS. The calibration process took place at the day of the testings' prior to the first paradigm. The participants were instructed to rate the pain intensity on a numeric rating scale (NRS) between 0 and 100, 100 being the worst unbearable pain and 0 no pain. The aim was to determine the individual temperature that corresponds to the value of 60 at the scale. The Medoc thermode was placed on the right forearm corresponding to dermatome 6. Between 1 and 3 runs were conducted starting with a temperature of 42 degrees to a maximum of 47 degrees. Each temperature impulse lasted for 20 seconds and was followed by a pause and the rating. As soon as the value of 60 on the NRS was determined the calibration process was finished.

The 2x2 prospective parallel group block design was used, consisting of 2 blocks with duration of 4000ms per condition. For the native round 30 subjects participated. Then as described above, the participants were randomly equally assigned to the two different intervention groups, so at the beginning of the intervention condition, 15 participants were assigned to the placebo condition Aspirin and 15 to the generic placebo condition.

Subjects viewed the screen via a mirror attached to the head-coil on a liquid-chrystal display (LCD) screen behind the scanner. Prior to the first paradigm, the participant was presented a short introduction and instruction in the following sequence for 2000 milliseconds (ms).

Then the actual first paradigm - the native test - started with a 1000 ms prime (a pixelated picture). In the pain phase a red dot over a black screen was displayed for 2000 ms whilst the temperature stimulus corresponding to the individual rating was applied. Consecutively a pause for 1000 ms followed. This paradigm was repeated 6 times and afterwards the subjects evaluated the maximum and average/mean pain. The paradigm was then repeated, and ended after 12 trials in total. Figure 19 displays the time course of the study design. The behavioural pain questionnaire, which the participants filled out after the native and after the intervention round is shown in appendix 6.2 below.

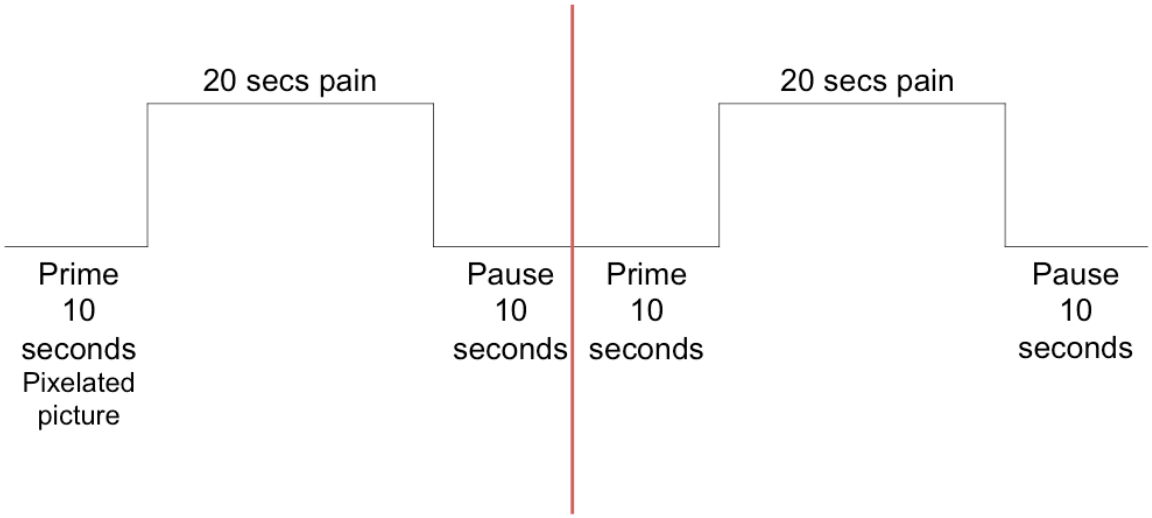


Figure 19. Time Course of the Study.
A block design was used consisting of 12 native runs followed by 12 intervention rounds.

After the first run, the native run, the participant was placed in a room outside the scanner. The subject received the placebo labelled as Aspirin or 1A Pharma together with information about the brand (see chapter above). Between 25 and 45 minutes were granted for the administered medication to take effect. During that waiting period, the participants had to fill out the following questionnaires:

- POMS profile of mood states: Momentanes Befinden – aktuelle Stimmungsskala, Dalbert (1994)
- STAI-G X1 State and Trait Anxiety Inventory, Spielberger (1989)
- BMQ Beliefs about Medicines Questionnaire, Horne (1999)
- FPQ-III Fear of Pain, McNeil (1998)
- PVAQ Pain Vigilance and Awareness Questionnaire, McCracken (1997)
- SES-17 Social Desirability Scale, Stöber (2001)
- LOT-R Revision of Life-Orientation Test, Scheier, Carver and Bridges (1994)

The POMS profile of mood states: ASTS Momentanes Befinden – aktuelle Stimmungsskala, Dalbert (1994) and the STAI-G X1 State and Trait Anxiety Inventory, Spielberger (1989) were carried out three times; before the native baseline condition, during the waiting period (see paragraph above) and after the intervention condition. In the following text these different points of data collection

are labelled with numbers 1-3 (STAI-1, STAI-2, STAI-3, POMS-1, POMS-2, POMS-3).

The Beliefs about Medicines Questionnaire evaluates the attitude towards medication use, if the person considers them as necessary and if he has apprehensions about the medication use. Fear of Pain Questionnaire (FPQ-III) assesses anxiety about pain in relation to different pain-causing stimuli (Antony and Stein 2009) . The Pain Vigilance and Awareness Questionnaire (PVAQ) measures pain related attention. The Social Desirability Scale rules out response, the person thinks are socially adequate, as disruptive factor. The Life Orientation Test serves as self-assessment instrument for individual differences of generalized optimism vs. pessimism. The questionnaires were raised before the native round.

The Profile of Mood State assesses the momentary affective mood. The State and Trait Anxiety Scores assess the actual and character based fear to diagnose anxiety and depressive syndromes. The participants had to complete the questionnaires before the native round, in-between the native and the intervention condition after receiving the group-specific information, and finally after the intervention round.

In the second condition, the time setup was identical to paradigm 1, the instruction consisted either of information about 1A Pharma or Aspirin and the prime picture was the package of the corresponding brand. A total of 12 trials and two ratings as in the paradigm 1 were compiled. Figure 20 shows the experimental design for the branded placebo condition.

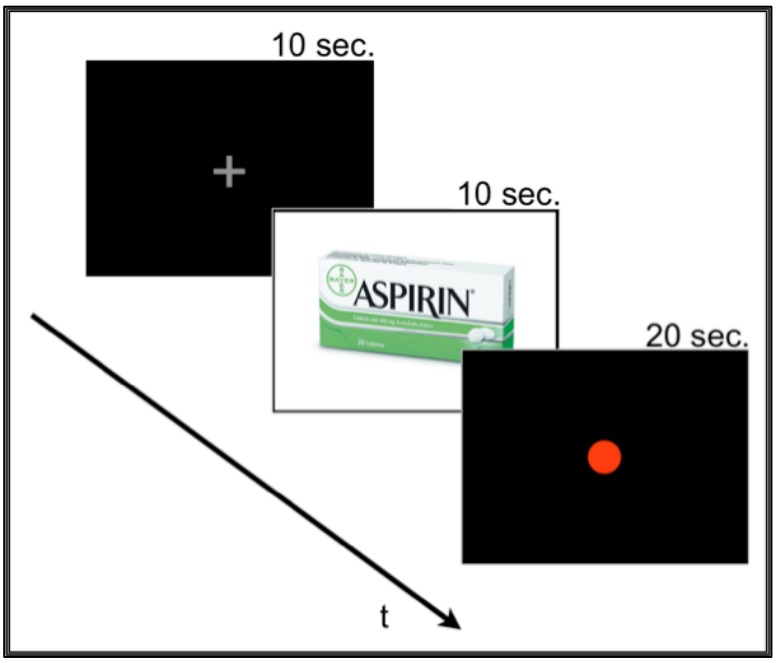


Figure 20. Experimental Design.
A fixation cross was used during the baseline condition. The acetylsalicylic acid (ASA) packaging either of Aspirin or 1A Pharma was used for anticipation. The heat application via thermode was indicated by a red dot (Fehse, Maikowski et al. 2015).

2.6. Data Processing and Analysis

A 3T whole body system (Magnetom VERIO, Siemens, Germany) at the University Hospital Großhadern of the Ludwig-Maximilians-University Munich (LMU) equipped with a standard A TIME head coil was used for fMRI scanning. The participants' heads were held in comfortable foam cushions in order to minimize head movements.

A T1-weighted, magnetization-prepared rapid gradient echo (MPRAGE) sequence was generated as anatomic reference with the following parameters: repetition time (TR) = 2400 ms, echo time (TE) = 3.06 ms, flip angle (FA) = 9°, number of slices = 160, field of view (FOV) = 240x256 mm, matrix = 224x256 and rect. FOV = 7/8. The structural images were acquired in the sagittal orientation. For the blood-oxygen-level-dependent (BOLD) functional imaging, a T2*-weighted echo-planar imaging (EPI) sequence was used with the following parameters: TR = 2500 ms, TE = 30 ms, FA = 80°, number of slices = 38, slice thickness = 3 mm, inter-slice gap = 0.4 mm, interleaved acquisition, spatial resolution 1 mm 3, FOV = 192x192 mm, matrix = 64x64, and in-plane resolution = 3x3 mm. The functional images were acquired in

axial orientation (parallel to the anterior commissure–posterior commissure [AC-PC] line) covering the whole brain.

2.6.1. Pre-processing of fMRI Data

During pre-processing, we made the data suitable for further analysis. We conducted the following steps: slice-timing, realignment, co-registration and smoothing. In the following paragraphs these steps are described in detail.

2.6.2. Slice-timing

High spatial resolution requires acquisition of many thin slices. Depending on the repetition time/interscan interval (TR) the acquisition of volumes can take up to several seconds. So not every slice is generated at the same time, whereas SPM analysis assumes the generation at one point in time (Henson, Buechel et al. 1999, Poldrack, Mumford et al. 2011, Sladky, Friston et al. 2011). A correction of the time differences in the acquisition of slices is essential for further analysis. The positive effect of this correction is especially crucial for event related designs (Sladky, Friston et al. 2011), but block designs have to account as well for the differences in acquisition time. Slice-timing corrects this temporal offset making the data processable for statistical analysis (Poldrack, Mumford et al. 2011). As a result, all slices of an image are represented at one point in time for the following analysis.

2.6.3. Motion Correction: Realignment

To compare different brain activations voxels (= volume element in a three dimensional space) have to correspond to the same brain regions. Head motions lead to distortions and a mismatch of these corresponding brain areas. Motion correction accounts for this in adjusting all volumes to a reference picture. Usually the first picture generated (Schneider and Fink 2007) or an image in the middle of the sequence is chosen as a reference (Poldrack, Mumford et al. 2011). The images are then realigned to this reference image by calculating conformities along the volumes.

2.6.4. Co-registration

The co-registration process is essential to localize the activated brain regions. As functional fMRI images have a low spatial resolution, co-registration merges these images with anatomic images to facilitate a more precise localization of the activated brain area (Schneider and Fink 2007).

2.6.5. Normalization

Normalization is essential for a comparison between the participants, as there exist differences in size and shape of their brains. The fMRI images are fitted to a standardized Echo-Planar-Imaging (EPI) template. Thus every individual brain will be displayed on a standard brain enabling further second level analysis. The Montreal Neurological Institute's Brain is usually used as the reference brain (Schneider and Fink 2007 page 156). As a common template, a standard MNI-space was developed on the basis of 305 brains of healthy participants (Poldrack, Mumford et al. 2011).

2.6.6. Smoothing

The last step of pre-processing is called smoothing. The fMRI data show spatial correlations due to functional similarities of adjacent brain regions. Smoothing uses a three-dimensional gauss distribution (full width at half maximum) as filter, thus eliminating random fluctuations and enhancing the real signal by improving the signal-to-noise ratio (Turner, Howseman et al. 1998, Schneider and Fink 2007 page 157). Furthermore the comparability between subjects is improved by spatial smoothing thereby reducing a mismatch across individuals (Poldrack, Mumford et al. 2011). The following figure 21 of Van Horton, Grafton et al. (2004) summarizes the steps in the pre-processing process of fMRI data.

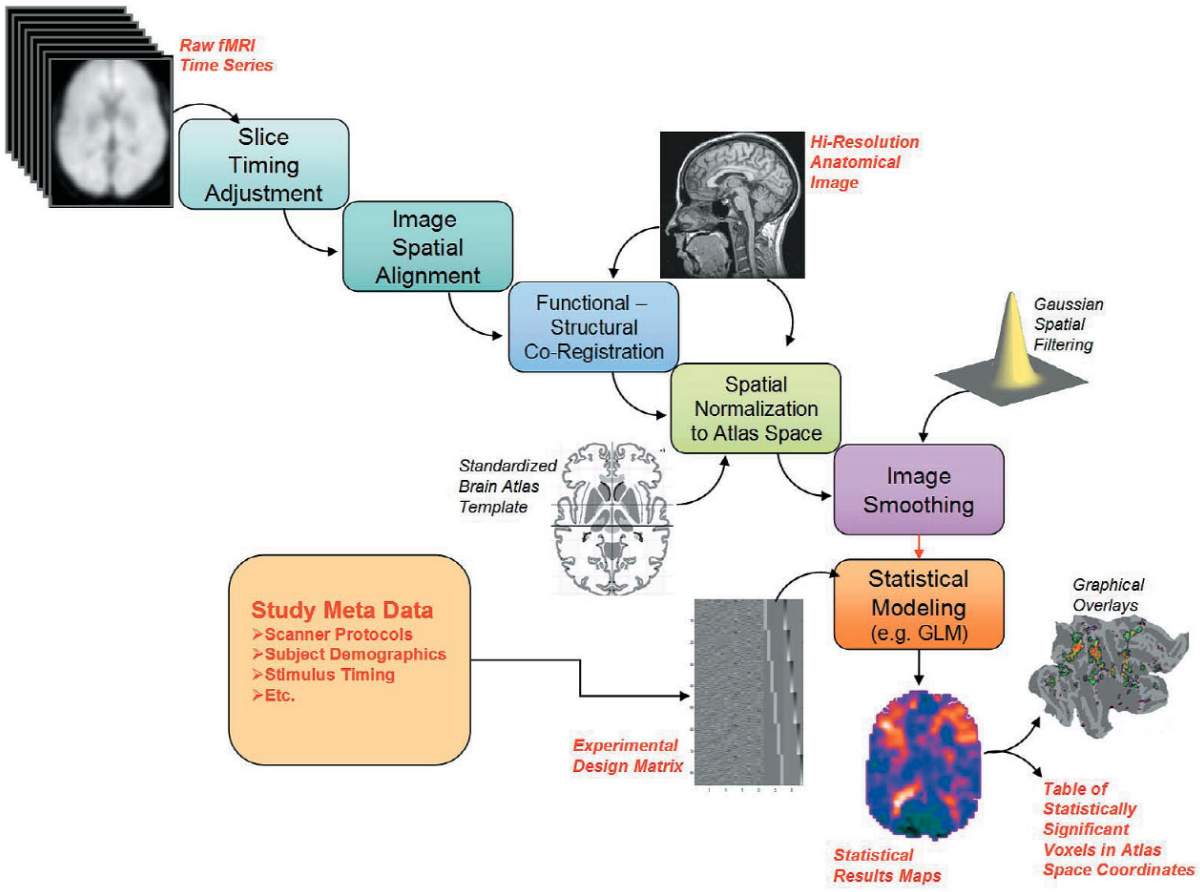


Figure 21. **FMRI Data Processing Pipelines.**
(Van Horn, Grafton et al. 2004)

2.7. Statistical Methods

FMRI data were analysed with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). The first six volumes were discarded to account for T1 saturation effects. All functional images were realigned, co-registered to the EPI template (Montreal Neurologic Institute, MNI), spatially normalized into standard stereotaxic space using standard SPM8 parameters, re-sliced to 2 × 2 × 2 mm voxels, and smoothed with an [8 8 8] mm full-width at half maximum (FWHM) Gaussian kernel. Each condition (picture, pain) was modelled by a boxcar function convolved with the canonical hemodynamic response function. This statistical method is the common procedure in our Lab (Park, Gutyrchik et al. 2014). At the first level, t-tests were computed for each subject and for each condition. The individual contrast images for each subject were used for the random-effects second level analysis. A 2 x 2 model was computed for the pain condition with one

between-subjects factor (Aspirin/1A Pharma group) and one within-subjects factor (before/after intervention). The statistical parametric maps were cluster-level thresholded at p (FWE) < .05 (starting from p uncorrected < .01). Anatomical descriptions were based on the AAL atlas (Automated Anatomical Labelling of Activations; Tzourio-Mazoyer & Landeau, 2002).

Behavioural data were analysed by using SPSS Version 21.0 (IBM Corp., Amornk, NY). All data were tested for normal distribution and were analysed accordingly by either parametric or nonparametric statistical tests. P-values < 0.05 were regarded significant.

3. Results

3.1. Participant Characteristics

As described above, thirty male right-handed subjects between the age of 27 and 45 (mean age = 31.86 years, SD = 6.39) with no history of psychiatric, internal, neurologic disease or drug abuse were recruited. Three participants were excluded during the experiment: One participant had to be excluded due to hyperalgesia during the native round (baseline) in the scanner, the second participant because of a skin reaction after the native round. The third participant cancelled study participation on the study day.

The two placebo groups were comparable in particular as regards to the psychosocial variables, pain expectancies, and pain evaluations in the native round. Concerning their age, the two groups differed significantly (see Table 1).

Table 1. Comparison of Groups at Baseline (means ± standard deviations).

	Placebo Brand	Placebo Generic	p-value
Gender	m	m	---
Age	35.25 ± 8.87	29.00 ± 2.59	0.035[a]
Temperature	46.00 ± 0.95	45.73 ± 1.28	0.702[a]
Pain Ratings NRS			
Mean Pain native	54.58 ± 16.16	56.63 ± 11.76	0.706[b]
Maximum Pain native	70.00 ± 10.87	69.90 ± 13.34	0.983[b]
STAI-G X1			
STAI-1	49.04 ± 2.10	47.38 ± 2.47	0.094[b]
POMS			
POMS-Trauer-1	3.27 ± 0.47	3.75 ± 0.29	0.594[a]
POMS-Hoffnungslosigkeit-1	3.27 ± 0.65	3.08 ± 2.89	0.462[a]
POMS-Müdigkeit-1	8.73 ± 3.93	9.50 ± 4.81	0.950[a]
POMS-positive Stimmung-1	27.64 ± 5.33	27.08 ± 7.60	0.804[a]
POMS-Zorn-1	3.09 ± 0.30	3.83 ± 1.59	0.147[a]
BMQ			
BMQ General Overuse	10.00 ± 2.26	10.20 ± 2.68	0.980[a]
BMQ General Harm	15.25 ± 1.29	14.80 ± 1.86	0.502[a]
BMQ General Benefit	7.33 ± 2.19	8.60 ± 2.03	0.096[a]

FPQ-III			
Pain minor	21.50 ± 7.78	18.87 ± 6.00	0.338[a]
Pain severe	36.83 ± 5.70	34.53 ± 6.65	0.492[a]
Pain medical	28.42 ± 7.61	23.93 ± 5.89	0.149[a]
Pain total	86.75 ± 19.72	77.33 ± 16.75	0.222[a]

LOTR			
LOTR Pessimism	11.08 ± 1.68	10.60 ± 2.41	0.423[a]
LOTR Optimism	4.92 ± 1.16	6.47 ± 2.47	0.065[a]
LOTR Optimism 1-dimensional	6.00 ± 2.09	8.20 ± 3.57	0.080[a]

PVAQ			
PVAQ	40.92 ± 12.57	32.53 ± 8.85	0.053[b]

SES			
SES	10.92 ± 3.42	9.40 ± 2.50	0.195[b]

Abbreviations: NRS, Numeric rating scale; STAI-G X1, State Anxiety Inventory; POMS, Profile of mood states; BMQ, Beliefs about Medicines Questionnaire; FPQ-III, Fear of Pain; LOT-R, Revision of Life-Orientation Test; PVAQ, Pain Vigilance and Awareness Questionnaire; SES-17, Social Desirability Scale.

[a] Mann-Whitney-U-Test

[b] ANOVA

3.2. Behavioural Results

3.2.1. Mean Pain Ratings

Mean pain ratings decreased significantly from the native to the intervention condition ($F_{time}(1,25) = 7.725$, $p = 0.010$). The decrease in mean pain ratings from the native condition to the intervention condition differed non-significantly between the two placebo groups, as shown by the time-by-condition interaction ($F_{int}(1,25) = 3.231$, $p = 0.084$). Given the trend for significance and the small sample size, we performed post-hoc tests and observed a significant decrease in mean pain ratings for the branded placebo (Aspirin) only. Mean pain ratings decreased significantly for the branded placebo group from 54.6 ± 16.2 (SD) during the native condition to 45.4 ± 15.8 (SD) after the administration of the placebo labelled as “Aspirin” ($p = 0.032$). In the generic group (1A Pharma), mean pain ratings decreased non-significantly from 56.6 ± 11.8 in the native condition to 54.7 ± 15.0 in the intervention condition; $p = 0.344$). Figure 22 displays the mean behavioural pain ratings before and after the intervention.

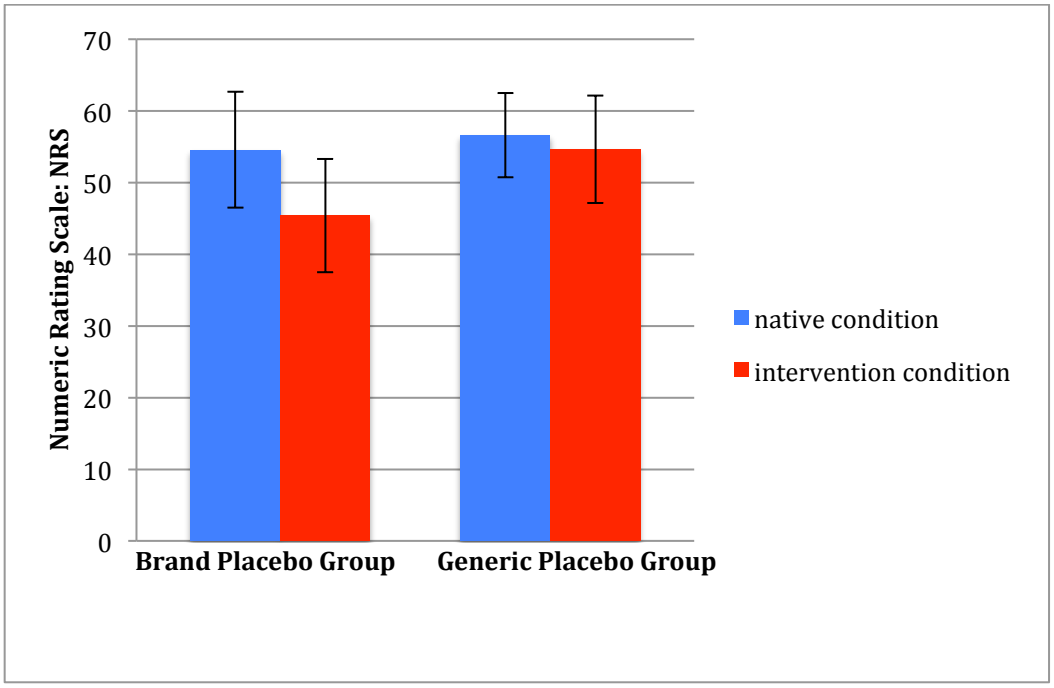


Figure 22. Mean Behavioural Pain Ratings before and after Placebo Administration.

3.2.2. Maximum Pain Ratings

Maximum pain ratings decreased significantly from the native to the intervention condition (F_{time} (1,25) = 8,602, p = 0,007). The decrease in maximum pain ratings from the native condition to the intervention condition did not differ significantly between the two placebo groups (F_{int} (1,25) = 2.783, p=0.108).

3.2.3. Pain Expectancies

Regarding pain expectancies after the administration of the two different placebos, the expected mean pain intensities differed significantly between the two placebo groups (p = 0.022). Participants in the „Aspirin“ group expected an average pain of 36.67±13.37 (SD), whereas in the „1A Pharma“ group mean pain intensities of 49.64±13.51 (SD) were expected (figure 23).

The maximum expected pain did not differ significantly between the two placebo groups (p = 0.242). In the branded group “Aspirin” maximum pain ratings were 57.08±14.05 (SD), whereas participants in the generic group expected maximum pain intensities of 64.64±17.48 (SD).

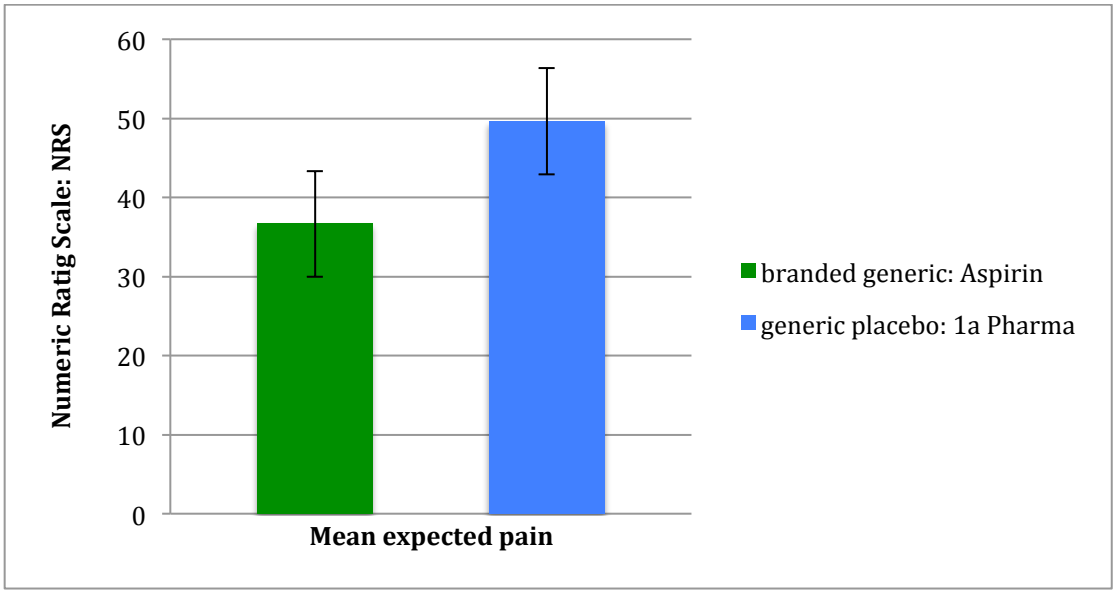


Figure 23. Expected Mean Pain Intensities before the Intervention Round after Receiving Group Specific Information.

3.2.4. State Anxiety

State anxiety increased significantly from the native condition STAI-1 to the intervention condition STAI 2, 3 with a general linear model ($F_{time}(2,44) = 3.446$, $p = 0,041$). We compared the state anxiety prior to the grouping (STAI-1) to the intervention (STAI-2 and STAI-3). The increase in state anxiety from the native condition (STAI-1) to the intervention condition (STAI-2, STAI-3) differed non-significantly between the two placebo groups ($F_{int}(2,44) = 3.104$, $p = 0.055$). Given the trend for significance and the small sample size, we performed post-hoc tests and observed a significant increase in state anxiety for the generic placebo group only. Results are displayed in table 2.

Table 2. Comparison of Groups at Intervention Condition.

	Placebo Brand	Placebo Generic	p-value
Pain ratings NRS			
Pain intervention - mean	45.42 ± 15.84	54.67 ± 15.02	0.133[b]
Pain intervention - maximum	61.87 ± 09.48	67.67 ± 15.47	0.267[b]
Pain native – intervention - mean	p = 0.032[b]	p = 0.344[b]	
Pain native – intervention - max	p = 0.027[b]	p = 0.254[b]	
3.2.4.1.1. Pain native – intervention - mean			0.084[d]
Expected Pain – mean	36.67 ± 13.37	49.64 ± 13.51	0.022[b]
Expected Pain – max	57.08 ± 14.05	64.64 ± 17.48	0.242[b]
STAI-G X1			
STAI-2	48.37 ± 1.97	48.53 ± 2.17	0.839[c]
STAI-3	49.44 ± 2.06	49.58 ± 2.22	0.872[c]
STAI-1,2,3 (prepost*placebo)	p = 0.615[d]	p = 0.022[d]	0.083[d]
POMS			
POMS-Trauer-2	3.75 ± 1.06	3.53 ± 0.92	0.591[a]
POMS-Trauer-3	3.42 ± 0.90	3.27 ± 0.59	0.737[a]
POMS-Hoffnungslosigkeit-2	3.42 ± 1.16	3.00 ± 0.00	0.107[a]
POMS-Hoffnungslosigkeit-3	3.25 ± 0.87	3.33 ± 1.29	0.914[a]
POMS-Müdigkeit-2	8.92 ± 3.92	10.01 ± 4.20	0.462[a]
POMS-Müdigkeit-3	9.20 ± 3.79	9.67 ± 4.61	0.961[a]
POMS-positive Stimmung-2	27.83 ± 5.31	27.73 ± 7.45	0.419[a]
POMS-positive Stimmmung-3	27.25 ± 5.55	24.13 ± 7.65	0.378[a]
POMS-Zorn-2	3.17 ± 0.58	3.27 ± 0.59	0.453[a]
POMS-Zorn-3	3.00 ± 0.00	3.27 ± 0.70	0.197[a]

Abbreviations: NRS: numeric rating scale, STAI: state anxiety inventory; POMS: profile of mood states. STAI-1: state anxiety inventory before the experiment, STAI-2: state anxiety inventory after the native scanner session, STAI-3: state anxiety inventory after the intervention session in the scanner.

[a] Mann-Whitney-U-test asymp. Sig. 2-seitig T-Test

[b]T-Test

[c]ANOVA

[d]Allgemeines Linerares Modell, Mixed Design

3.3. Neurofunctional Results

3.3.1. Pain Condition: Native vs Post-Intervention

We found the following results during the pain condition (Fehse, Maikowski et al. 2015). Before the placebo administration during the native condition (pain versus baseline) the participants showed activations of the right and left insulae, right inferior frontal gyrus and right putamen, left rolandic operculum and the left inferior frontal gyrus. These neurofunctional activations are shown in figure 24. Coordinates and clusters are displayed in table 3 below.

After placebo administration we observed bilateral activation of the insula, the inferior frontal gyrus, left rolandic operculum, superior temporal gyrus and the right putamen. Additional activations were observed in the bilateral supplementary motor area, bilateral medial part of the superior frontal gyrus (dorsomedial prefrontal cortex) and the bilateral cingulate cortex. Neurofunctional activations are displayed in figure 25. Coordinates and clusters are shown in table 4 below.

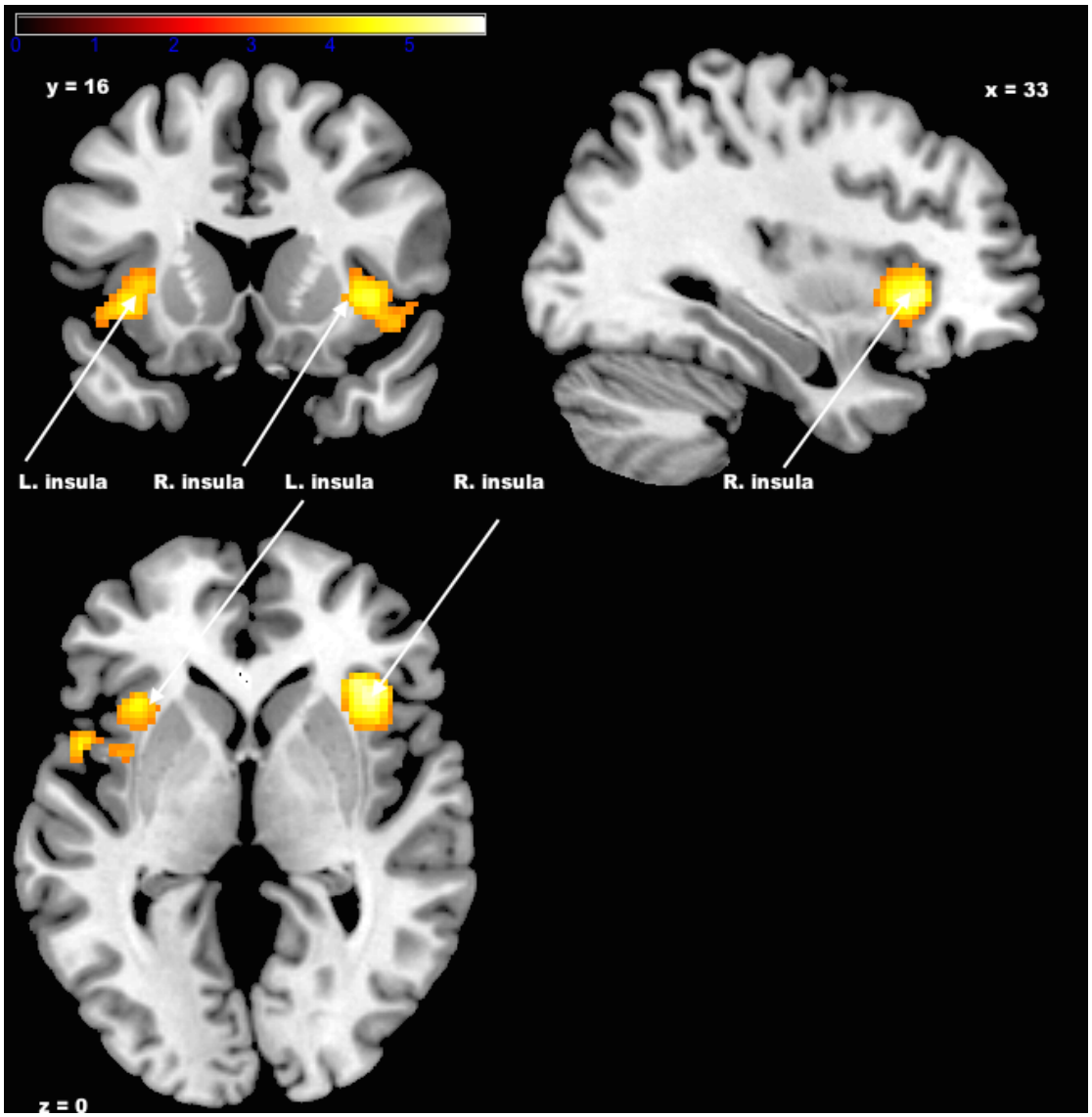


Figure 24. Neurofunctional Correlates: Pain before Placebo Administration.
Pain versus no-pain measurement in both placebo groups (Native): Pain condition versus no-pain measurement in both placebo groups. L. insula: left insula; R. insula: right insula. x, y and z coordinates are in the MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

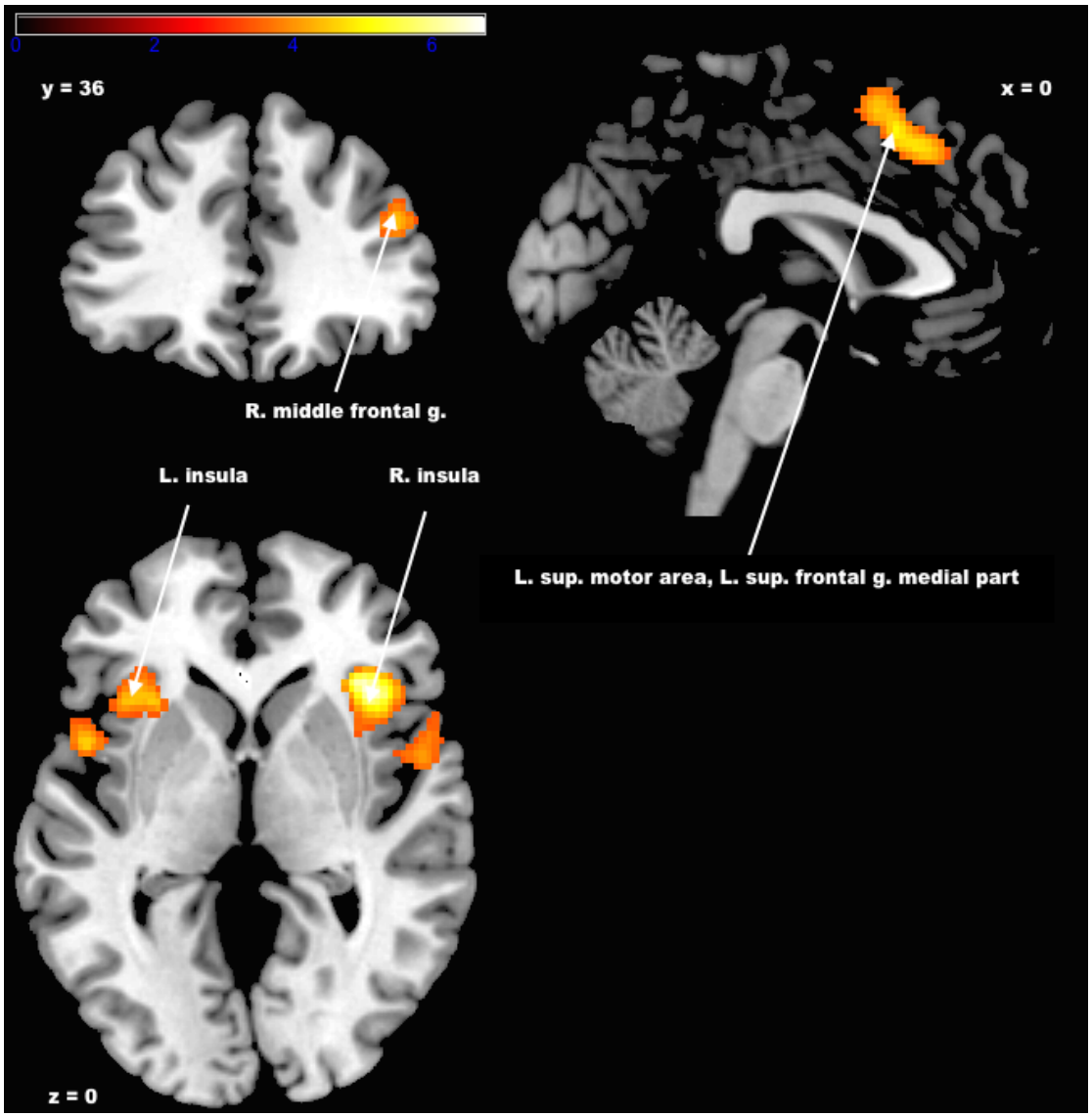


Figure 25. Neurofunctional Correlates: Pain after Placebo Administration.
Pain condition versus no-pain measurement in both placebo groups (Intervention). L. insula: left insula; R. insula: right insula; R. middle frontal g.: right middle frontal gyrus; L. sup. motor area: left supplementary motor area; L. sup. frontal g. medial part: left superior frontal gyrus medal part. x, y and z coordinates are in the MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

Table 3. Neurofunctional Correlates: Pain before Placebo Administration (versus Baseline) (Fehse, Maikowski et al. 2015).

			Coordinates			
Brain region	cluster	kE	x	y	z	*Z*-value
R. insula, R. inferior frontal g., R. putamen	1	440	38	22	–2	5.12
L. insula, L. rolandic operculum, L. superior temporal g., L. inferior frontal g.	2	366	–34	20	2	4.11

Note. kE = size in voxels (2 x 2 x 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

Table 4. Neurofunctional Correlates: Pain after Placebo Administration (versus Baseline) (Fehse, Maikowski et al. 2015).

			Coordinates			
Brain region	cluster	kE	x	y	z	*Z*-value
R. insula, R. inferior frontal g.	1	688	36	24	2	5.63
L. insula, L. inferior frontal g.	2	405	–34	20	4	4.54
L./R. supplementary motor area, L./R. superior frontal g., medial part (dmPFC), L./R. cingulate g.	3	652	–2	20	48	4.47
L. inferior frontal g., L. rolandic operculum, L. superior temporal g.	4	237	–50	8	2	4.31
R. middle frontal g. (dlPFC), R. inferior frontal g.	5	229	46	38	22	4.13
R. inferior frontal g., R. rolandic operculum, R. superior temporal g., R. insula	6	230	58	14	8	4.00

Note. kE = size in voxels (2 x 2 x 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

3.3.2. Pain Condition: Direct Comparison Between the two Placebo Conditions after the Intervention

A direct comparison of the two placebo conditions (contrast “Aspirin” – “1A Pharma”) after the placebo administrations showed higher activations of the medial part of the superior frontal gyrus (dorsomedial prefrontal cortex) and the bilateral superior frontal and right middle frontal gyri including adjacent regions (bilateral precentral gyrus, bilateral cingulate gyrus and bilateral supplementary motor areas) in the brand group (“Aspirin”) compared to the generic group (“1A Pharma”). The reversed contrast – generic intervention (“1A Pharma”) compared to the brand intervention (“Aspirin”) – showed no significant activations. Neural correlates are shown in figure 26 below. Coordinates and clusters are displayed in table 5.

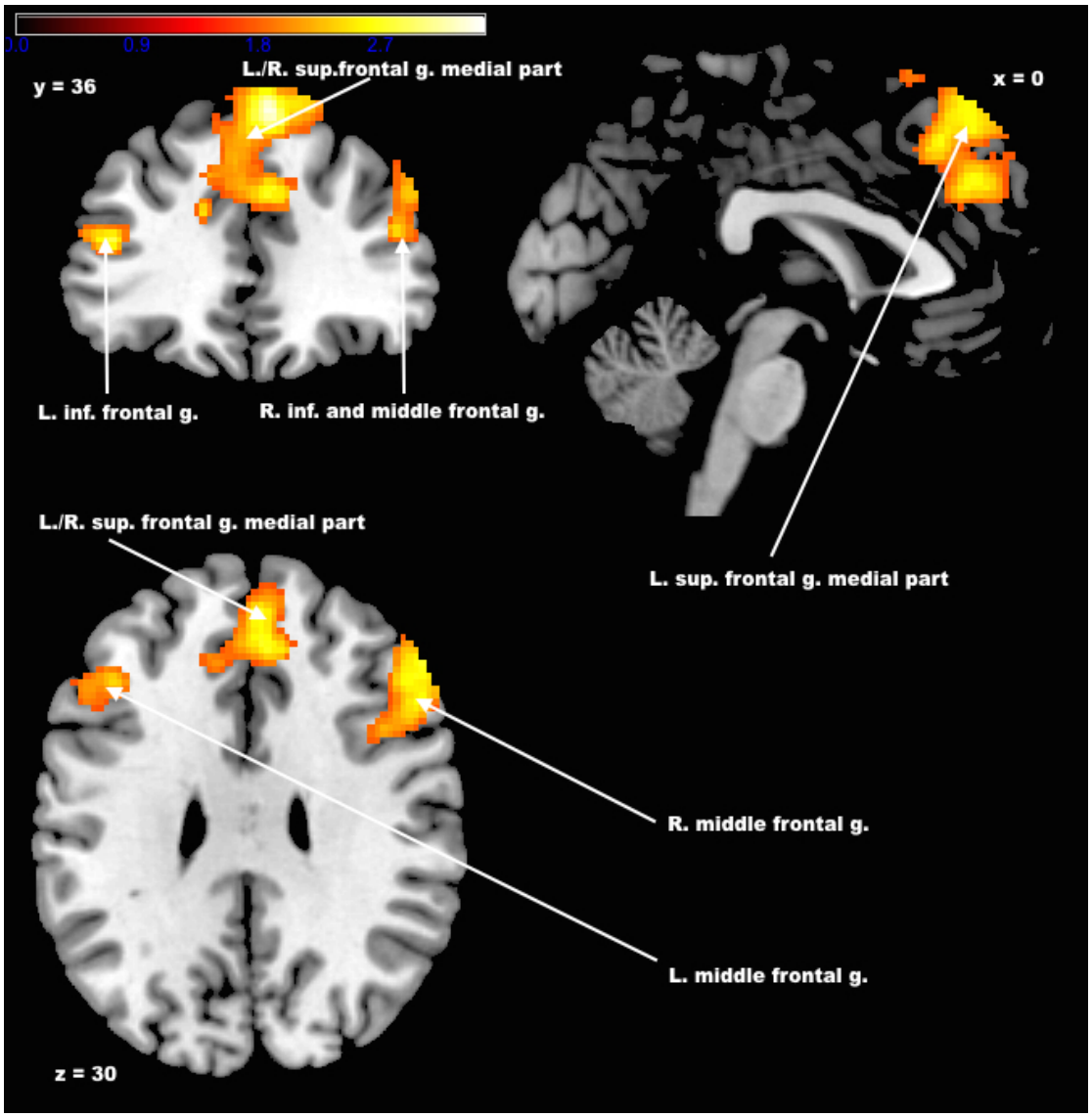


Figure 26. **After Placebo Administration: Original versus Generic Analgesic During Pain Condition.**
L. inf. frontal g.: left inferior frontal gyrus; R. inf. and middle frontal g.: right inferior and middle frontal gyrus; L./R. sup. frontal g. medial part: left/right superior frontal gyrus medial part; R. middle frontal g.: right middle frontal gyrus; L. middle frontal g.: left middle frontal gyrus. x and y coordinates are in the MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

Table 5. Neurofunctional Correlates: Pain after Placebo Administration: Original vs. Generic (Fehse, Maikowski et al. 2015).

			Coordinates			
Brain region	cluster	kE	x	y	z	*Z*-value
R. middle frontal g. (dlPFC), L./R. superior frontal g., medial part (dmPFC), R. inferior frontal g., L./R. superior frontal g. (dlPFC), R. precentral g., L/R. cingulate g., L/R. supplementary motor areas	1	3945	8	40	58	3.25

Note. kE = size in voxels (2 x 2 x 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

3.3.3. Anticipation

We furthermore analysed the anticipation phase 10 seconds prior to the heat administration. We observed bilateral activations of the inferior occipital gyrus and the inferior temporal gyrus, the left middle and occipitotemporal gyrus as well as the right angular gyrus in the branded group in the contrast after the intervention compared to the native condition. Neurofunctional results are displayed in figure 27, the coordinates and clusters are shown in table 6 below. In the generic placebo group in the same contrast (anticipation intervention > native condition) activations in the bilateral posterior cingulate gyrus, bilateral precuneus, left middle and inferior temporal gyrus, bilateral straight gyrus and left hippocampus and parahippocampal gyrus were detected. Neurofunctional results are displayed in figures 28A and 28B, the coordinates and clusters are shown in table 7 below. Only these group specific analyses did show significant results. The combined comparison between the native and intervention condition as well as a direct comparison between the two placebo groups did not show any significant results.

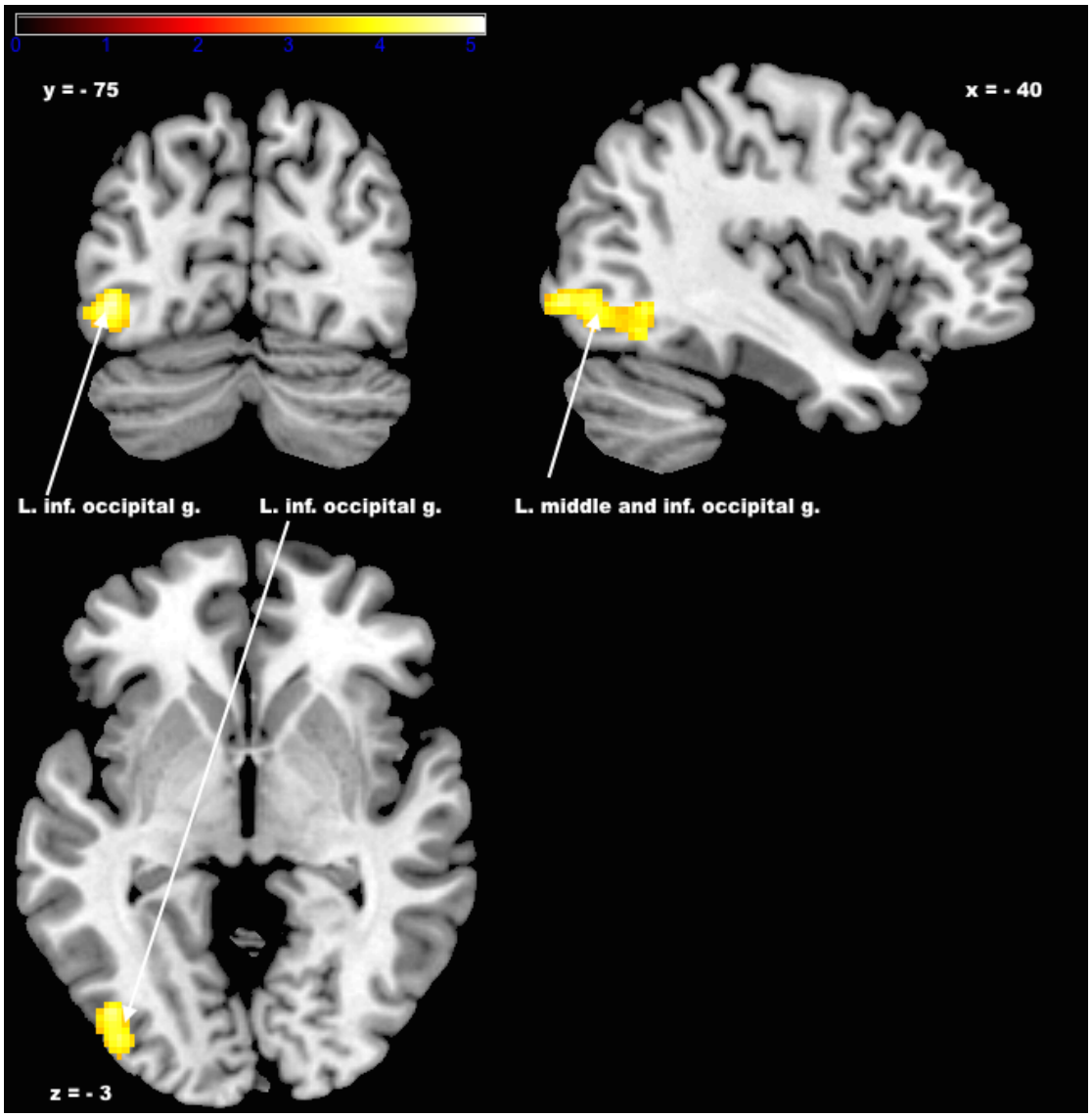


Figure 27. Neurofunctional Correlates: Anticipation Branded Group, Contrast after > before the Administration of the Placebo.
L. inf. occipital g.: left inferior occipital gyrus; L. middle occipital g.: left middle occipital gyrus. x, y and z are in the MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

Table 6. Neurofunctional Correlates: Anticipation Original Brand after > before Placebo Administration.

			Coordinates			
Brain region	cluster	kE	x	y	z	*Z*-value
L.inferior occipital gyrus, L. middle occipital gyrus, L. inferior temporal gyrus, L. fusiform gyrus (L. occipitotemporal gyrus)	1	331	-46	-80	–6	4.55

Note. kE = size in voxels (2 x 2 x 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

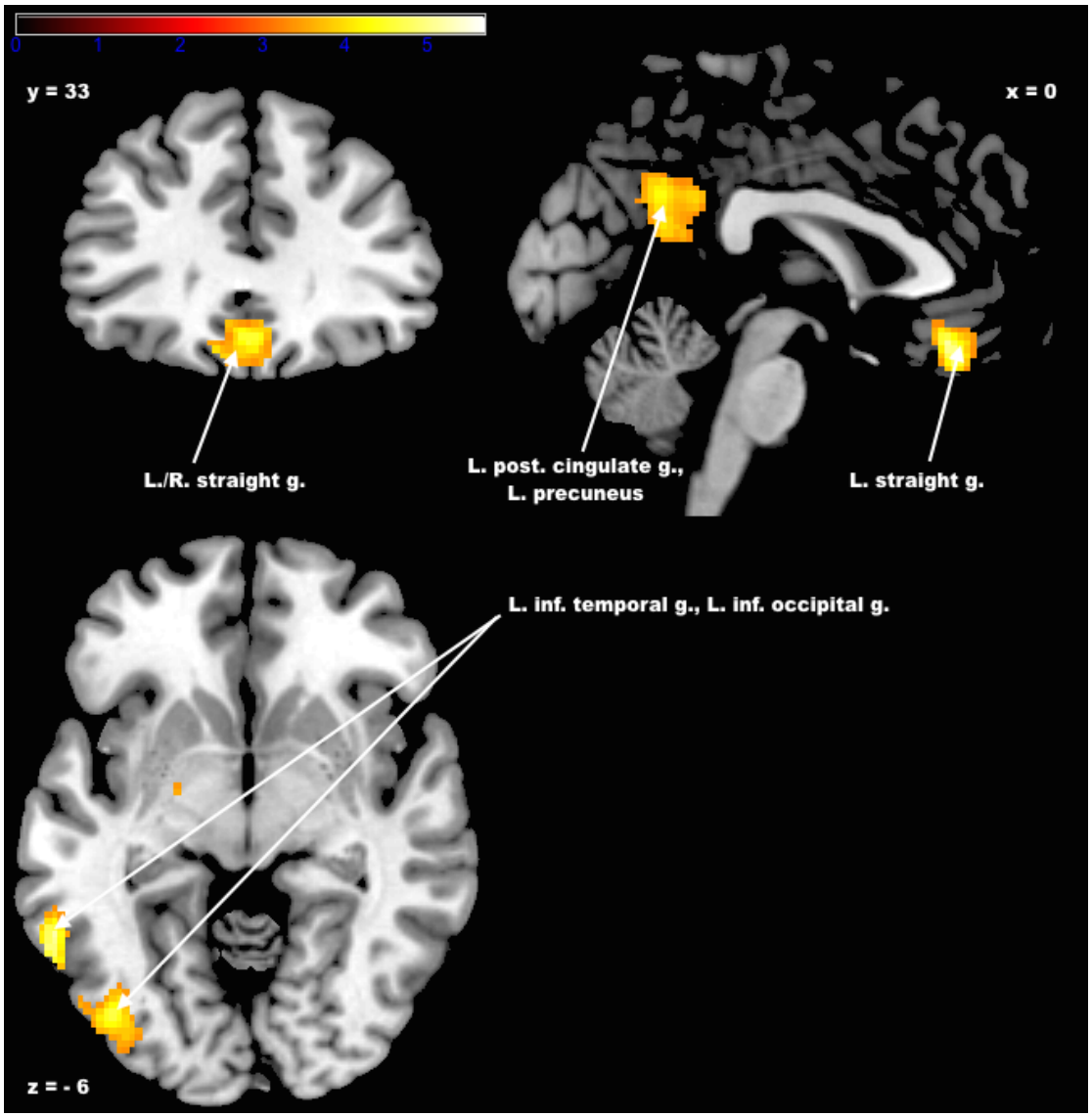


Figure 28A. Neurofunctional Correlates: Anticipation Generic Group, Contrast after > before Administration of the Placebo.
L. inf. temporal g.: left inferior temporal gyrus; L. inf. occipital g.: left inferior occipital gyrus; L. post. cingulate g.: left posterior cingulate gyrus; L. precunes: left precuneus; L./R. straight g.: left and right straight gyrus (rectus gyrus). x, y and z coordinates are in MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

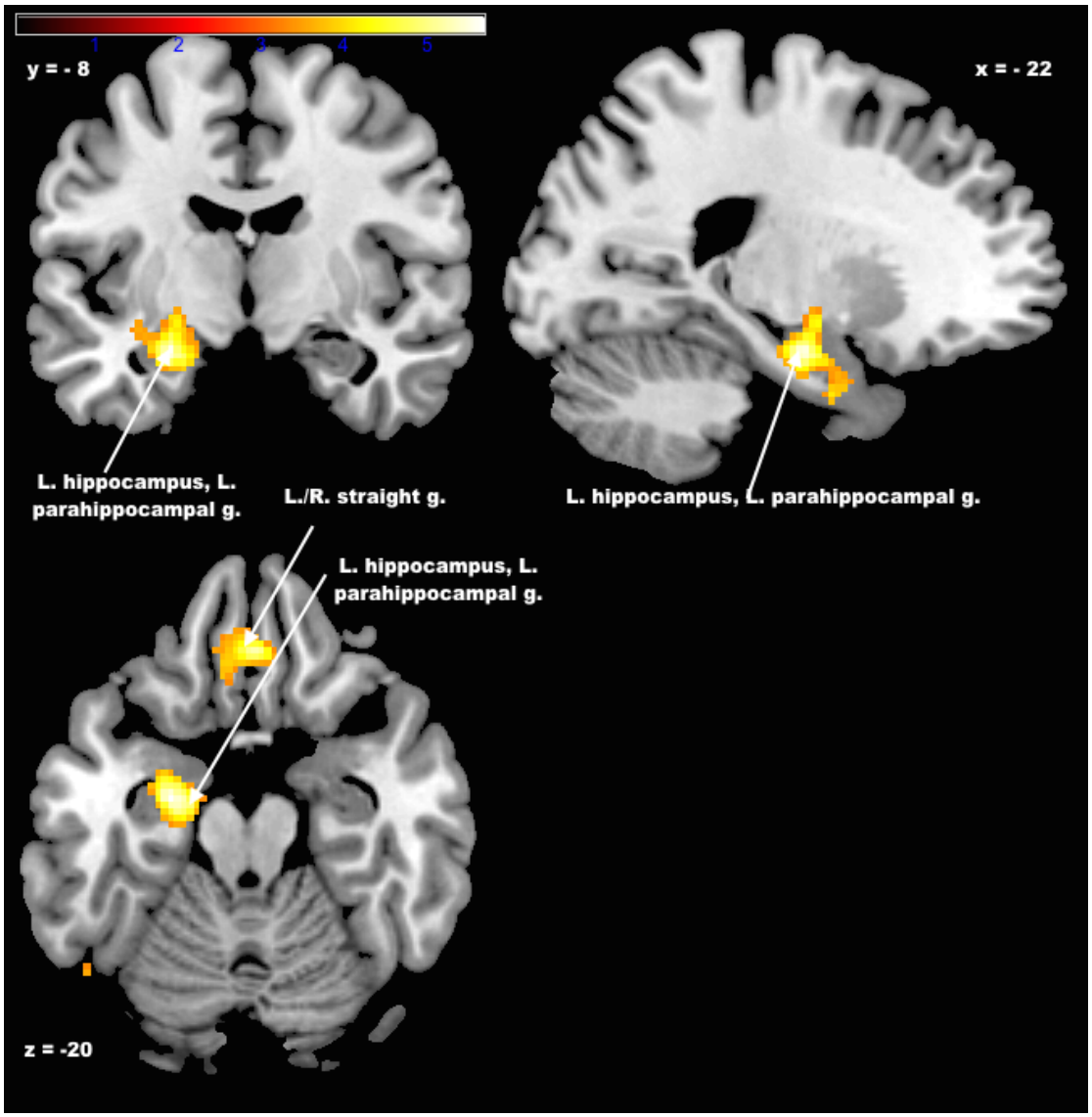


Figure 28B. Neurofunctional Correlates: Anticipation Generic Group, Contrast after > before Administration of the Placebo.
L. hippocampus: left hippocampus; L. parahippocampal g.: left parahippocampal gyrus; L.R. straight g.: left and right straight gyrus (rectus gyrus). x, y and z coordinates are in MNI stereotactic space; cluster-level thresholded at p (FWE) < .05; neurologic convention: left is left.

Table 7. Neurofunctional Correlates: Anticipation Generic after > before Placebo Administration.

			Coordinates			
Brain region	cluster	kE	x	y	z	*Z*-value
L. middle and inferior temporal gyrus, L. inferior occipital gyrus	1	484	–52	–66	–16	4.60
L./R. posterior cingulate cortex/gyrus, L./R. Precuneus	2	394	2	–54	30	4.21
L. Hippocampus, L. Parahippocampal gyrus	3	365	–24	–10	–20	4.94
L./R. straight gyrus (rectus)	4	302	2	34	–16	4.60

Note. kE = size in voxels (2 x 2 x 2 mm). R. = right, L. = left, g. = gyrus. The x, y and z coordinates are in the MNI stereotactic space.

4. Discussion

We compared the analgesic effects of two different placebo interventions. The interventions differed in their labelling and corresponding brand information. Our results displayed consistent and significant differences between the two placebo groups, on both the behavioural and the neural response levels. Only the participants in the branded placebo group showed a decrease in pain intensity, whereas no similar behavioural response was found for the generic group. However as we only observed a trend for significance in the decrease of mean pain ratings between the two placebo groups these results should be interpreted cautiously. The small sample size could be an explanation and speaks for a follow up trial with a larger population.

Concerning neural correlates, we found activations of the anterior insulae under baseline conditions. After the intervention, we observed supplementary activations of the dorsomedial prefrontal cortex. The direct comparison of the two placebo conditions showed higher activations of the bilateral dorsolateral and dorsomedial prefrontal cortex for the original brand compared to the generic condition (Fehse, Maikowski et al. 2015). Furthermore during the anticipation phase (contrast after > before placebo administration), we observed only for the generic group activations of hippocampal, parahippocampal and adjacent brain areas.

All in all, the chosen methods fulfilled the desired requirements well. The experimental design and study protocol was conducted according to plan.

We chose a 2x2 block design, which is commonly used in fMRI studies. This study design enabled us to analyse and compare brain activations of baseline conditions, anticipation and pain conditions within and between subjects in a temporal accurate manner. The use of Medoc, which precisely applies an individually calibrated noxious heat stimulus, furthermore supported the exact conduction and the success of the experiment. We used a sample size of 30 participants. Follow-up trials with a larger sample size could produce transferable findings, confirming the results of this pilot study.

Our study was carried out without prior preconditioning of the participants. In a preconditioning trial, participants experience real pain relief after placebo treatment, as for example, the intensity is turned down after the placebo intervention, while during the real experiment, intensities remain unchanged. These preconditioning trials can be carried out in pain placebo experiments to boost the placebo response (Geuter, Eippert et al. 2012, Schenk, Sprenger et al. 2014). We were able to generate significant results even without the enhancement effect of preconditioning. This supports the finding of a strong placebo response under the branded placebo condition. In the future, an investigation of the same differences with the addition of a preconditioning phase would be interesting to carry out.

Although we can summarize the evaluation of our applied methods overall positively, the limitations of our study suggest a follow-up trial with a larger sample. A prior preconditioning trial could reinforce the placebo response and the underlying neural correlates. Another interesting question is the investigation in how a double blind design, would affect the results, in order to disentangle the influence of the medical personnel, which administers the agent.

As regards to the observed results, our data demonstrate that only the original brand elicits a significant behavioural placebo response. The observed differences could be attributed to a variety of factors. First of all, original brands generally enjoy greater credibility and trust. The price itself might be a factor that leads to higher expectations (Plassmann, O'Doherty et al. 2008, Plassmann and Weber 2015). Due to years of marketing, a trusted brand is associated with a higher price and better quality. The stronger placebo response in our study appears to be enhanced by the brand, which probably serves as an external cue, creating and reinforcing positive expectations towards the treatment.

The active agent acetylsalicylic acid in Aspirin and its generics is generally used for treatment of headache pain. As pain trigger, we used heat induced pain applied with the Medoc System model ATS. Although this use is far from the regular use of ASA, we observed significant results on neuronal and behavioural levels. This observation emphasizes the expectations evoked by the branded placebo treatment.

During the native condition, before the administration of the placebo agent (comparison pain and no pain native), we observed higher activations of the anterior insula in the pain period compared to the baseline condition (no pain). The anterior insula is an essential brain structure for the sensation of pain and one of the classical pain processing areas (Brooks, Nurmikko et al. 2002). After the administration of the respective placebo (comparison before and after the intervention) we observed in both groups additional activations of the prefrontal cortex and of the cingulate gyrus, as well as higher activations of the bilateral insulae. These three areas are part of a brain network which is known to play a role in placebo analgesia (Elsenbruch, Kotsis et al. 2012). The activation of the opioid rich mPFC during the intervention condition may suggest an increased activity of the opioid system by the placebo treatment (Benedetti, Mayberg et al. 2005, Wager, Scott et al. 2007, Scott, Stohler et al. 2008, Wager and Fields 2013).

During the anticipation phase only the generic group showed activations of the hippocampal areas. The hippocampus and its adjacent brain regions are involved in memory processes (Scoville and Milner 1957, Squire 1992). Patients with damages limited to the hippocampal areas showed memory impairment, particularly anterograde amnesia (Zola-Morgan, Squire et al. 1986). Due to its enormous neural connections, the hippocampus seems to have a very complex role in information processing, suggesting it to be an information integration unit consisting of several circuits and subunits (Moser and Moser 1998). The hippocampal areas are playing an essential role in memory formation, transforming newly gained memories into long-term memory (Huijgen and Samson 2015). Despite its role in memory processes, the hippocampus maintains close connections to the amygdala (Pitkänen, Pikkarainen et al. 2000) and seems to be involved in emotional evaluation and processing of emotional experiences. Increased pain reinforced by anxiety and therefore expectations of a negative outcome have been reportedly accompanied with activations in hippocampal areas suggesting a role in pain modulation processes (Ploghaus, Narain et al. 2001, Benedetti, Carlino et al. 2011). The nocebo response of hyperalgesia seems to be related to increased anxiety. In our study only participants in the generic group showed activations in the hippocampal areas during anticipation, suggesting anxiety and aversive emotions towards the treatment and therefore attributing negative expectations towards the

generic drug. These results are in line with higher anxiety levels in the generic group and also confirm results of Bingel et al. (2011), who investigated how different expectations influence the effectiveness of a potent pharmacological treatment with the μ-opioid receptor agonist remifentanil. The experiment consisted of three conditions: no expectations (hidden medication), positive expectations and negative expectations. Expectations of hyperalgesia (negative expectations) abolished the analgesic effect of remifentanil on a behavioural level. Furthermore, these negative expectations of treatment outcome were accompanied with additional increased activity in hippocampal areas, the mPFC and the cerebellum (Bingel, Wanigasekera et al. 2011). In accordance with our results, these findings support the idea that the hippocampal brain regions are involved in nocebo effects during opioid analgesia.

The direct comparison between the two placebos during the intervention condition provided highly interesting results showing a significantly greater activation of the bilateral dmPFC and the bilateral dlPFC for the branded placebo condition. The opposite contrast (of the generic placebo compared to the branded placebo) did not show any significant activation. Several studies report the activation of the dmPFC in the context of negative affect suppression (Phan, Fitzgerald et al. 2005) as well as high level emotional appraisal and evaluation (Kalisch, Wiech et al. 2006). As pointed out in Chapter 1.2.4.4 the dlPFC has been repeatedly shown to be involved in expectation-related analgesia (Wager, Rilling et al. 2004, Zubieta, Bueller et al. 2005, Krummenacher, Candia et al. 2010), suggesting that the branded placebo enhanced the participants' expectations towards the effectiveness of the treatment, thus boosting the placebo response. The underlying mechanisms are not completely resolved, however, some authors assume a top-down effect of pain inhibition from the dlPFC (Lorenz, Minoshima et al. 2003). In a more general context, the dlPFC has been reportedly activated in processes of reasoning and decision making (Kable 2010, Kahnt, Heinzle et al. 2011).

Positive expectations are an essential part of medical treatment and may enhance the analgesic placebo response. If a person attributes negative expectations to a treatment, the positive effect may be reversed resulting in hyperalgesia. In our study, we focused on the comparison between the treatment with an original and a generic brand. On the testing day, the participants were informed in writing that the

generic drug contained the same active substance as Aspirin. Comparing the behavioural and neural results, the participants developed different expectations towards the treatment. The branded placebo triggered a stronger analgesic effect, possibly due to higher expectations and trust towards its effectiveness and reduced anxiety.

In conclusion, our study enabled us to identify brain areas involved in the branded placebo response. The behavioural responses were consistent with these findings, showing a significant decrease in pain intensity for the branded group only.

In addition to the behavioural level, results of the fMRI analysis revealed that the branded placebo elicited a significant analgesic response. The pattern of activated brain regions suggested that on a neuronal level, the processing of pain had been significantly modified. Thus, not only did the participants report increased pain reduction in the branded condition, but the modified analgesic response could also be displayed on a neuronal level. These results can demonstrate the potential consequences when changing a trusted medication to its generic equivalent. The trust and expectation towards a treatment, reinforced by a strong brand can have a major additional effect on the pain relief itself, which should not be underestimated.

The participants received written information about the brand and the generic. Therefore, it has to be taken into consideration that information about painkillers can influence the sensation of pain. As demonstrated in our study, expectations can form an essential part of medical treatment and can have an impact on the clinical effectiveness even if no active agent is administered. The expectation towards a treatment is shaped by the brand. These expectations and attitudes are individually shaped by various factors such as a person’s emotional state and perspective. However, medical professionals can influence and control these psychological contexts to a certain degree to optimize expectations and thereby the total effect of treatment. It is evident, how significantly the passed-on information can influence drugs’ treatment efficacy as part of the patient communication.

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6. Appendices

6.1. Selection Questionnaire

1) Wie häufig verwenden Sie persönlich Schmerzmittel? Wir meinen hierbei frei verkäufliche Schmerzmittel, die man ohne Rezept in Apotheken erhält.

- ☐ Seltener als 2 mal pro Monat
- ☐ Mehr als 2 mal pro Monat
- ☐ 1-2x pro Monat

2) Welches frei verkäufliche Schmerzmittel haben Sie in den letzten 12 Monaten hauptsächlich verwendet?
   - ☐ Aspirin
   - ☐ Paracetamol
   - ☐ Ibuprofen
   - ☐ Andere

3) Und welches frei verkäufliche Schmerzmittel haben Sie in den letzten 12 Monaten hin und wieder auch verwendet?
   - ☐ Aspirin
   - ☐ Paracetamol
   - ☐ Ibuprofen
   - ☐ Andere

4) Gegen Schmerzen werden häufig Tabletten auf Basis des Wirkstoffes Acetylsalicylsäure (ASS) genommen. Die bekannteste Marke darunter ist ASPIRIN von Bayer, dem Entdecker dieses Wirkstoffes. Es gibt heute aber auch andere Anbieter, die den Wirkstoff ASS verarbeiten, und sogenannte Generika anbieten (z.B. Hexal, Ratiopharm, 1A Pharma). Wie ist das bei Ihnen, welche Marke verwenden Sie?

5) Viele Menschen vertrauen beim Einkauf bekannten Marken, die für Qualität stehen. Andere Menschen versuchen möglichst, ein günstiges markenfreies Produkt zu kaufen. Wie ist das bei Ihnen?
   - ☐ Ich kaufe meistens bekannte Marken

- ☐ Ich kaufe mal Markenprodukte, mal markenfreie Produkte
- ☐ Ich kaufe fast nur markenfreie Produkte

6) Ihr Geschlecht?
   - ☐ m
   - ☐ w

7) Welche ist Ihre Muttersprache?

8) In welchem Jahr sind Sie geboren?

9) Welchen höchsten Bildungsabschluss haben Sie?
   - ☐ abgeschlossenes Studium
   - ☐ akademischer Titel
   - ☐ Haupt-/Volksschulabschluss
   - ☐ Realschulabschluss (mittlere Reife) oder gleichwertiger Abschluss
   - ☐ Schulreife

10) Haben Sie eine Berufsausbildung im klinischen, pharmazeutischen oder medizinischen Kontext?
   - ☐ ja
   - ☐ nein

11) Welcher Tätigkeitsstatus haben Sie derzeit inne?
   - ☐ teilweise berufstätig (halbtags oder stundenweise)
   - ☐ in Berufsausbildung (Schüler, Lehrling, Student)
   - ☐ voll berufstätig
   - ☐ vorübergehend arbeitslos

12) Schlaganfall: Leiden Sie an folgenden Symptomen/Problemen?
   - ☐ ja
   - ☐ nein

13) Epilepsie oder Anfälle: Leiden Sie an folgenden Symptomen/Problemen?
   - ☐ ja
   - ☐ nein

14) Drogensucht: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

15) Alkoholismus: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

16) psychische Erkrankungen: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

17) Panikattaken: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

18) Phobien: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

19) Zwangsstörungen: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

20) Platzangst: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

21) neurologische/psychiatrische Vorerkrankungen: Leiden Sie an folgenden Symptomen/Problemen?

- ☐ ja
- ☐ nein

22) Haben Sie einen Herzschrittmacher?

- ☐ ja
- ☐ nein

23) Haben Sie Metallimplantate (außer im Zahnbereich)?

- ☐ ja
- ☐ nein

24) Haben Sie Sehhilfen (Brille oder Kontaktlinsen?

- ☐ ja
- ☐ nein

25) Haben Sie Tätowierungen?

- ☐ ja
- ☐ nein

26) Wenn Sie eine Tätowierung haben, bitte beschreiben Sie deren Größe und Position

27) Nehmen Sie regelmäßig Medikamente?

- ☐ ja
- ☐ nein

28) Wenn Sie regelmäßig Medikamente nehmen, welche sind dies?

Welche Seite verwenden Sie überwiegend für die unten aufgeführten Tätigkeiten: Links/Rechts: Bitte versuchen Sie alle Fragen zu beantworten, und lassen sie eine Zeile nur dann leer, wenn sie überhaupt keine Erfahrung mit dem Objekt oder Aufgabe haben.

29) Schreiben

- ☐ links
- ☐ rechts

30) Malen

- ☐ links
- ☐ rechts

31) Werfen

- ☐ links

- ☐ rechts

32) Schere
- ☐ links
- ☐ rechts

33) Zahnbürste
- ☐ links
- ☐ rechts

34) Messer
- ☐ links
- ☐ rechts

35) Löffel
- ☐ links
- ☐ rechts

36) Besen
- ☐ links
- ☐ rechts

37) Streichholz zünden
- ☐ links
- ☐ rechts

38) Schachtel öffnen
- ☐ links
- ☐ rechts

39) Mit welchem Fuß treten Sie bevorzugt einen Gegenstand
- ☐ links
- ☐ rechts

40) Welches Auge benutzen Sie, wenn Sie nur eines benutzen
- ☐ links
- ☐ rechts

6.2. Behavioral Questions Pain

1) Nativ-Bedingung 1A
   a) Schmerzbewertung Durchgang 1A durchschnittlich:
      Wie bewerten Sie den Schmerzreiz auf einer Skala von 0-100 durchschnittlich?
   b) Schmerzbewertung Durchgang 1A maximal:
      Wie bewerten Sie den maximalen Schmerzreiz auf einer Skala von 0-100?

2) Nativ-Bedingung 1B
   a) Schmerzbewertung Durchgang 1B durchschnittlich:
      Wie bewerten Sie den Schmerzreiz auf einer Skala von 0-100 durchschnittlich?
   b) Schmerzbewertung Durchgang 1B maximal:
      Wie bewerten Sie den maximalen Schmerzreiz auf einer Skala von 0-100?

3) INTERVENTION
   a) Schmerzerwartung Durschnitt
      Welche Schmerzstärke erwarten Sie nach der Medikamentengabe im Durchschnitt
   b) Schmerzerwartung Durschnitt
      Welche Schmerzstärke erwarten Sie nach der Medikamentengabe Maximal

4) Interventionsbedingung 2A
   a) Schmerzbewertung Durchgang 2A durchschnittlich:
      Wie bewerten Sie den Schmerzreiz auf einer Skala von 0-100 durchschnittlich?
   b) Schmerzbewertung Durchgang 2A maximal:
      Wie bewerten Sie den maximalen Schmerzreiz auf einer Skala von 0-100?

5) Interventionsbedingung 2B
   a) Schmerzbewertung Durchgang 2B durchschnittlich:
      Wie bewerten Sie den Schmerzreiz auf einer Skala von 0-100 durchschnittlich?
   b) Schmerzbewertung Durchgang 2B maximal:
      Wie bewerten Sie den maximalen Schmerzreiz auf einer Skala von 0-100?

6.4. Eidesstattliche Versicherung / Affirmation in Lieu of Oath

Eidesstattliche Versicherung

Maikowski, Lea Friederike

Name, Vorname

Ich erkläre hiermit an Eides statt,

dass ich die vorliegende Dissertation mit dem Thema

Neuronal and Behavioural Pain Processing: A Comparison Between a Strong Brand and a Generic Medication Placebo using the Example of Aspirin vs. 1A Pharma

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Neustadt, 12.01.2017

Ort, Datum

Unterschrift Doktorandin/Doktorand

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