universität wien

DIPLOMARBEIT

Titel der Diplomarbeit

„The extended placebo effect – an fMRI study“

verfasst von

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Angestrebter akademischer Grad

Magistra der Naturwissenschaften (Mag. rer. nat.)

Wien, 2014

Studienkennzahl lt. Studienblatt:	A 298
Studienrichtung lt. Studienblatt:	Diplomstudium Psychologie
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Acknowledgements

I would like to thank Mag. Dr. Eva-Maria Seidel, my supervisor, for her invaluable advice, guidance and encouragement throughout the entire project, Mag. Markus Rütgen for interesting and diverting days at the MR center, Prof. Claus Lamm and the team of the SCAN-Unit for the opportunity to be part of their research team.

My gratitude further goes to my proof-readers Mag. Mira Seitzer, Dr. Karlheinz Tovar, Brandon Guzman and Adam Westhorpe, B.Sc. for their time and effort to make this work better, to Martin Tik for sharing his expertise, and most importantly to my friend Julia Hebestreit for being a great colleague and thesis partner.

Finally, I would like to thank Moritz Tovar for contributing to my emotional well-being by taking my mind off the thesis every once in a while and my parents Klaus & Bruni, my brother Maurice and my friends for their love, trust and support.

Abstract

Introduction. Placebo research has generated important knowledge about the mechanism of placebo effects, in particular regarding their effectivity. However, learning about the specificity of placebo responses is crucial in order to be able to use the benefits of placebos to their full extent. The aim of the present study was to investigate whether the placebo effect extends to domains it has not specifically been administered for.

Methods. 120 participants (60 placebos, 60 controls) were included in the present functional magnetic resonance imaging (fMRI) experiment. Responses to unpleasant, neutral and pleasant visuotactile stimulation following pain-specific placebo induction were compared on a neural and behavioral level.

Results. Subjective rating data showed that unpleasant stimuli were perceived as less unpleasant when participants had received a placebo, whereas ratings of neutral and pleasant stimuli were not affected. This was also reflected in the fMRI data. Placebo administration led to BOLD signal chances in the unpleasant condition only. In the placebo group compared to the control group, neural activation was increased in the dorsolateral prefrontal cortex (DLPFC) and decreased in the primary (SI) and secondary (SII) somatosensory cortex and the frontoinsular cortex.

Conclusion. The results imply an extended placebo effect that transferred from pain to unpleasant touch. The involvement of the DLPFC and restriction to unpleasant somatosensory experiences suggest that top-down evaluation processes underlying the placebo response allow its extension to domains with similar valences.

Keywords. Placebo, top-down processing, analgesia, unpleasant, fMRI, visuotactile, touch, dorsolateral prefrontal cortex (DLPFC), insula, primary somatosensory cortex (SI), secondary somatosensory cortex (SII).

Zusammenfassung

Einführung. Die Placebo-Forschung hat wichtiges Wissen über die Mechanismen des Placeboeffekts generiert, besonders in Bezug auf dessen Effektivität. Darüber hinaus jedoch ist die weitere Erforschung der Spezifität des Effekts entscheidend, um die Vorteile des Placeboeffekts im vollen Ausmaß nutzen zu können. Das Ziel der vorliegenden Studie bestand darin, zu untersuchen, ob sich der Placeboeffekt auf Bereiche ausbreiten kann, für die er ursprünglich nicht spezifisch induziert war.

Methoden. 120 Probanden (60 in der Placebobedingung, 60 in der Kontrollbedingung) nahmen an der vorliegenden Studie Teil. Nach schmerzspezifischer Placeboinduktion wurden unangenehme, neutrale und angenehme visuell-taktile Reize vorgegeben und hinsichtlich ihrer Placeboantwort verglichen. Mittels funktioneller Magnetresonanztomographie konnten neuronale Korrelate untersucht werden.

Ergebnisse. Subjektive Ratings zeigten, dass unangenehme Reize als weniger unangenehm empfunden wurden, wenn die Probanden ein Placebo erhalten hatten. Die Ratings der neutralen und angenehmen Reize wurden vom Placebo nicht beeinflusst. Das Verabreichen eines Schmerzplacebos führte außerdem zu neuronalen Aktivierungsänderungen in der unangenehmen Berührungsbedingung. Der Vergleich von Placebo- und Kontrollgruppe zeigte eine Zunahme der Gehirnaktivität im dorsolateralen präfrontalen Kortex sowie eine Abnahme der Aktivität im primären und sekundären somatosensorischen Kortex und im frontoinsulären Kortex.

Conclusio. Es ließ sich eine bereichsspezifische Erweiterung des Placeboeffekts von Schmerz auf unangenehme Berührung beobachten. Die Involvierung des DLPFC und Beschränkung auf lediglich unangenehme somatosensorische Reize lassen vermuten, dass dem Placeboeffekt top-down Evaluierungsprozesse unterliegen, die eine Erweiterung auf Bereiche möglich macht, deren Bewertung eine ähnliche Valenz trägt.

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1. Introduction

The placebo effect has been a phenomenon of interest and discussion in various disciplines. It has been extensively studied from a psychological and neurological perspective over the past decades, leading to considerably advanced knowledge about its mechanisms. Price, Finniss and Benedetti (2008) define the placebo effect as the change in a symptom or condition that occurs as a result of a sham treatment.

Placebo treatments have proven effective for a variety of medical conditions such as Parkinson's Disease (Benedetti et al., 2004; de la Fuente-Fernandez et al., 2001; Strafella, Ko & Monchi, 2006), depression (Leuchter, Cook, Witte, Morgan & Abrams, 2002; Mayberg et al., 2002) or the irritable bowel syndrome (Kelley et al., 2009; Vase, Robinson, Verne & Price, 2003).

Yet, most scientific focus has been put on the investigation of placebo induced analgesia and the factors contributing to its effectivity. Analgesia is defined as a reduction in the magnitude of pain on the sensory or affective dimension or both (Price et al., 2008). The effectiveness of placebo induced changes in experienced pain has been demonstrated in a variety of settings and across diverse paradigms (Brown, Seymour, Boyle, El-Deredy & Jones, 2008; Meissner et al., 2011).

The experience of pain is highly subjective and has been known to be modifiable by numerous psychological factors. These include attention (Bantick et al., 2002; Legrain et al., 2009), emotional arousal (de Wied & Verbaten, 2001; Rhudy & Meagher, 2001) and even personality traits, such as high Ego-Resiliency (Pecina et al., 2013). Various studies identified expectancy as a mediator in placebo effects and a crucial factor in its effectivity (Atlas & Wager, 2012). In essence, the induction of a placebo is the induction of expectations regarding its outcome. Consequentially, a patient or subject needs to expect a placebo treatment to cause pain relief in order for it to take effect. A number of factors have been identified that contribute to raising these expectations, such as previous experience, the verbal instruction framing the placebo administration, the interaction with healthcare providers/experimenters, or environmental clues like white coats or the color, taste and shape of a pill (Benedetti & Amanzio, 2011). The magnitude of effect sizes varies greatly across different settings. The efficiency of active drugs, for instance, is significantly higher when administered openly as compared to hidden administration (Benedetti, Carlino & Pollo, 2011). According to Vase, Riley & Price (2002) effects are smaller when placebos are used as control condition in pharmaceutical studies than in experiments investigating the placebo

effect itself. Thus, the effectivity of placebo treatments depends decisively on the experimental manipulation and psychosocial context, in which they are embedded.

In recent years there have been great advances in understanding the neurobiological mechanisms underlying the placebo analgesic response. Several neuroimaging studies found placebo-related changes in neural activity within brain areas known to process somatic and affective components of pain, such as the primary and secondary somatosensory cortex (SI and SII), the insular cortex as well as brain areas involved in emotion regulation, for example the anterior cingulate cortex (ACC) (Amanzio, Benedetti, Porro, Palermo & Cauda, 2013; Lu et al., 2010; Watson et al., 2009).

Wager et al. (2004) conducted an fMRI study, in which placebo administration was not only related to decreased signal in the neural pain network, but also to increased activation in the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) during anticipation of pain. The DLPFC has been repeatedly associated with expectation, cognitive control and emotion regulation and thus contributes considerably to the effectivity of placebo effects (Kong et al., 2009; Krummenacher, Candia, Folkers, Schedlowski & Schönbächler, 2010). In addition, Wager et al. (2004) found that increases in DLPFC activation levels correlate with decreases in pain related midbrain activity. The magnitude of decrease in these areas was correlated with subjective ratings of pain reduction, supporting their view, that expectations encoded in the DLPFC modulate experienced pain and its neural underpinnings. The OFC serves as part of the neural reward circuitry and represents the value of received rewards (Kahnt, Heinzle, Park & Haynes, 2010; Klein-Flügge, Barron, Bordersen, Dolan & Behrens, 2013). Based on their results Wager and colleagues (2004) concluded that the OFC also plays a role in processes that occur during anticipation of painful stimulation including affective and motivational responses to pain.

Elsenbruch and colleagues (2012) investigated the impact of expectancy modulations on the experience of pain. Expectations were manipulated by inducing either certainty or uncertainty of receiving an analgesic drug. They found variations in the magnitude of experienced pain complying with the level of induced certainty as well as corresponding reductions in activity in the neural pain network. Another important aspect of their study was the comparison of placebo responders and non-responders within the group that had certainty they would not receive an analgesic. Unexpectedly, results showed that responders had increased pain ratings. The researchers argued that even though their instructions did not contain elements to induce negative treatment expectation, a nocebo side effect occurred. This raises the question on how specific placebo effects really are.

Due to growing understanding about their mechanisms, placebos are now widely recognized as a valid treatment. However, as any other treatment, placebos might produce unwanted side effects. Current research focuses mainly on the factors contributing to the effectivity of placebo and nocebo inductions. Yet, as Elsenbruch et al.'s (2012) study shows, learning about the specificity of the responses is essential in order to be able to use the benefits of placebos to their full extent. It is still unclear whether the placebo effect is limited to the domain it has been administered for or whether it extends to other areas.

One could assume that placebo induced reductions in experienced pain are caused by a down-regulation of somatosensory processing in general, leading to decreased sensibility to all somatosensory experiences, thus giving rise to potentially unwanted side effects such as general numbness. Petrovic et al. (2005), however, proposed an emotion processing approach underlying placebo analgesia due to similar processing mechanisms observed for unpleasant emotions (Phillips, Drevets, Rauch & Lane, 2003). They suggested that placebo effects result from top-down emotion processing mediated by reward expectancy. The study investigated which effect placebo administration had on the perception of emotional visual stimuli. Therefore, participants rated neutral and unpleasant pictures in three sessions on three subsequent days. First, the pictures were presented and rated without any treatment. Second, expectations of anxiety relief were induced by administering an anxiolytic drug. After rating the pictures, the participants were treated with an anxiolytic blocker. In the third session they were told they would receive the same drug as the day before. Instead, they received saline solution as a placebo before rating the pictures. Results show that placebo treatment significantly reduced unpleasantness ratings for the unpleasant pictures, while ratings for the neutral pictures did not differ significantly. FMRI imaging revealed decreased activations in the ACC and OFC regarding the unpleasant stimuli in the placebo condition. Petrovic and colleagues (2005) concluded that stimuli were categorized into being unpleasant or neutral before top-down emotion processing is initiated. They assumed that the placebo effect is a general process of emotion modulation induced by expectations.

If placebo effects are not restricted to one domain and underlie the emotion processing approach, placebo analgesic responses may not only affect pain modulation, but the general modulation of unpleasant emotions. Consequently, inducing analgesia through placebo treatment may extend to other aversive somatosensory experiences.

The aim of the present fMRI study was to investigate whether placebo analgesia is specific for pain, or whether an extended placebo effect could be observed. Responses to unpleasant, neutral and pleasant visuotactile stimulation were compared following pain-

specific placebo induction. Behavioral data were collected as well as blood oxygen level dependent (BOLD) signal changes.

The paradigm used to generate these distinct tactile experiences had been previously introduced by Silani et al. (2013). In the present study, disgust was chosen as a measure for unpleasantness, since disgust and pain have proven to be well distinguishable (Benuzzi, Lui, Duzzi, Nichelli & Porro, 2008). Additionally, the experience of disgust has been known to be responsive to placebo treatment (Schienle, Übel, Schöngaßner, Ille & Scharmüller, 2013). Neural representations of disgust have been located in the insula, the cingulate cortex and the medial orbitofrontal cortex (MOFC) (Klucken et al., 2012; Schienle et al., 2013; Wicker et al., 2003).

In line with previous findings concerning neural representations of touch, increases in brain activity following tactile stimulation were anticipated in particular areas. We hypothesized, that the actual tactile stimulation would be associated with neural activation in the primary (SI) and secondary (SII) somatosensory cortex while affective components for painful and pleasant touch would be associated with the anterior (ACC) and midcingulate cortex (MCC) and the insula. Furthermore, we expected pleasant touch to activate the reward center in the MOFC (McCabe, Rolls, Bilderbeck & McGlone, 2008; Rolls et al., 2003). Derived from the emotion processing approach to placebo analgesia (Petrovic et al., 2005), it was further hypothesized that pain specific placebo administration would cause an extended placebo effect to unpleasant visuotactile stimulation. Due to its role in expectation in placebo induction (Wager et al., 2004), increased neural activations in the DLPFC were expected. Moreover, increases in activity were expected in areas representing unpleasant touch, such as the SI and SII, insula and cingulate cortex, as well as reductions in subjective unpleasantness ratings.

2. Methods

2.1. Participants

One hundred and twenty healthy, right-handed Caucasian participants (60 placebos, 60 controls) aged between 20 and 40 years were included in the study. The placebo group consisted of 43 women and 17 men (mean age = 25.8, SD = 3.4). The control group included 37 women and 23 men (mean age = 27.6, SD = 4.5). All participants had normal or corrected-to-normal vision. They were recruited via two separate online advertisements for control and placebo group offering incentives (30 and 90 Euros, respectively). Psychology students were excluded from the experiment as well as people who did not meet the usual criteria for MR-compatibility (see Appendix). The study had been previously approved by the ethics committee of the Medical University of Vienna and was conducted in conformance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants after full explanation of the procedure of the study.

2.2. Experimental Procedure

The issue presented in this paper was embedded in a large-scale pain research project which included several paradigms and research aims. Figure 1 outlines the full procedure. In the following, only those operations will be described in detail which contribute to the understanding of this thesis.

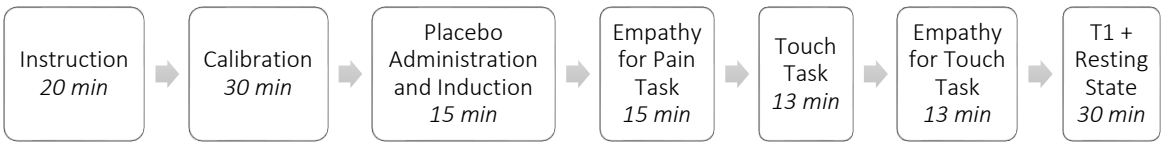

Figure 1. Overview of the full procedure including each operation's duration time.

At arrival to the laboratory, participants were welcomed by one of the female experimenters introducing herself as a medical doctor. Participants were then elaborately instructed about the procedure and signed the consent form.

In preparation for the pain task (for further information see Hebestreit, 2014) that preceded the touch paradigm participants underwent a standardized pain calibration, adapted from Singer et al. (2004). Stimuli were electric impulses delivered by a constant current stimulator (DS5, Digitimer Ltd., Herfordshire, UK). Two platinum surface electrodes with 7 mm diameter transmitted the impulses to the dorsum of the left palm with a duration of 500 ms. First, each participant's individual tactile (lowest perceptible stimulation) and pain

(highest tolerable stimulation) thresholds were assessed. Therefore stimuli were delivered in ascending, then descending sequence (increments of .05 mA) starting on a non-perceptible level (.05 mA) until tactile and pain sensation were induced. Participants rated the stimuli on a scale from "1" (perceptible) to "8" (worst pain imaginable), yet no impulses were delivered that were rated higher than "6" (extremely painful) (see Appendix). In order to achieve a stable value for the pain threshold this was repeated once more.

The experimenter then administered a placebo pill to the participants of the placebo group and provided information about its alleged pain-reducing effect and possible side effects. After a waiting period of 15 minutes the placebo response was induced according to the following procedure: Participants anew received electrical impulses - allegedly to determine whether the analgesic's effect had already set in. The experimenter delivered impulses the participants previously had rated as "4". If participants reported that the stimulation was experienced as „4" or lower, they were informed that before, the same stimulation had been rated „6" and thus the pill acted very well and very quickly. If the stimulation was experienced as "5" or "6", there was another waiting period of 10 minutes before the induction was repeated. Repetitions were performed a maximum of two times. Participants then proceeded with the MR session. The control group did not receive a placebo pill and started the MR session right after the calibration. Following the pain paradigm a touch paradigm was conducted, the results of which will be presented and discussed in this thesis.

The touch paradigm, adapted from Silani et al. (2013), consisted of 15 pleasant, 15 neutral and 15 unpleasant visuotactile stimuli (full list see Appendix). Pictures of objects were visually presented on a screen in randomized order. Each picture was displayed for 2 s and accompanied by simultaneous stroking of the left palm at ~1 Hz for 2 s with materials resembling the objects (see Figure 2).

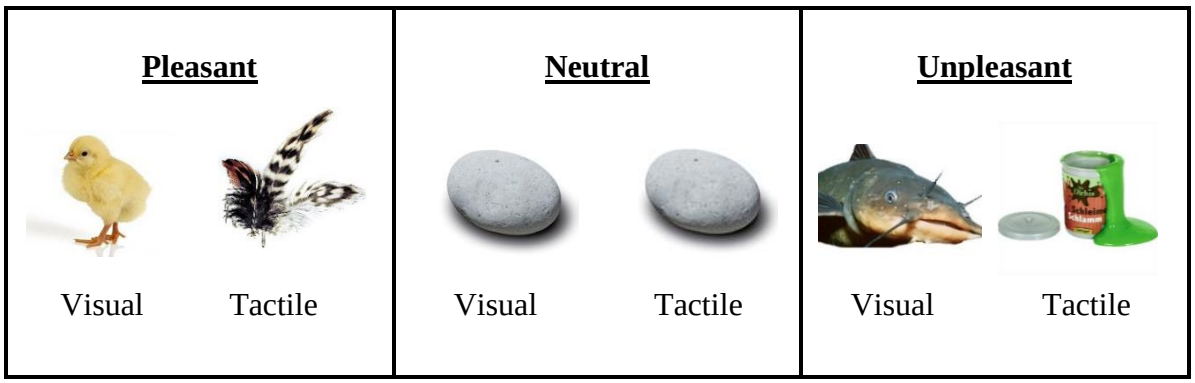

Figure 2. Examples for pleasant, neutral and unpleasant stimuli used in touch paradigm. Visually presented objects were accompanied by tactile stimulation of the left palm.

Throughout the task, participants occasionally rated on a 7-point rating scale how unpleasant or pleasant they experienced the previous stimulation. The scale ranged from -3 (very unpleasant) through 0 (neutral) to +3 (very pleasant). For each valence, participants gave eight ratings in total. (see Figure 3).

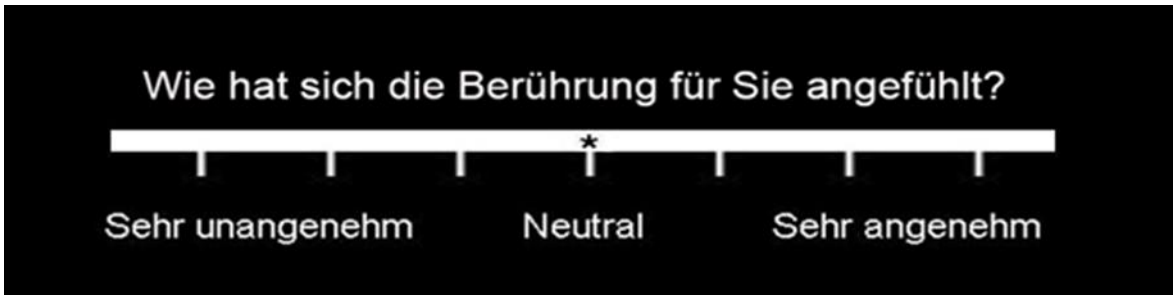

Figure 3. Rating scale used to determine experienced pleasantness of tactile stimulation.

The touch paradigm was followed by a paradigm tapping empathy for touch, which is outside the scope of this thesis. Before releasing the participants, anatomical measurements (T1) and resting state data were collected. The whole experiment lasted for about 125 minutes per participant.

2.3. fMRI Data Acquisition

All data were collected on a 3 Tesla Tim Trio whole-body scanner (Siemens, Erlangen, Germany) located at the MR Centre of Excellence of the Medical University of Vienna using a 32-channel head coil. Ear plugs were used to reduce scanner noise for the participants and foam pillows were applied to minimize head motion. Stimuli were projected onto a screen which the participants viewed over a mirror mounted on the head coil. The functional imaging data were acquired using a multiband echo-planar imaging (EPI) sequence sensitive to blood oxygenation level-dependent (BOLD) contrast imaging (54 sliced, voxel size 1.5 x 1.5 x 2 mm, TR 1800ms). Structural images were acquired using an MPRAGE sequence (1 x 1 x 1 mm voxel size, TE/TR = 4/2300 ms). Overall scan time was 65 minutes including T1 and resting state measures.

2.4. Analysis

2.4.1. Behavioral Data

Subject-wise mean scores for each valence were calculated and used for group data analysis. A 2×3 repeated measures ANOVA was performed with *group* (control, placebo) as between-subjects factor and *valence* (unpleasant, neutral, pleasant) as within-subject factor. All analyses were carried out using SPSS (Statistical Packages for the Social Sciences, Version 21.0, SPSS Inc., USA). The significance level was set at $p < .05$.

2.4.2. fMRI Data

Functional data were analyzed using the Statistical Parametric Mapping software package SPM8 (Welcome Trust Centre for Neuroimaging, UCL, London, UK), implemented in MATLAB 7 (Mathworks, Sherborn, MA). Pre-processing included slice-timing and motion correction, normalization to standard anatomical space (MNI, Montreal Neurological Institute template) and spatial smoothing with a Gaussian kernel of 8 mm full width at half maximum (FWHM). Pre-processed data were then analyzed using a general linear model (GLM). Each valence (unpleasant, neutral, pleasant) was modeled with a separate regressor convolved with the canonical hemodynamic response function. For each subject, main effects were computed by applying appropriate baseline contrasts for each valence. These first-level individual contrasts were then fed into a second-level group analysis (Placebo: 60, Controls: 60) using a flexible factorial ANOVA (factors: subject, group, valence). Statistical contrasts (t tests) were performed to examine cortical activation associated with pleasant and unpleasant touch relative to neutral touch (*pleasant* > *neutral* and *unpleasant* > *neutral*). For the purpose of investigating whether there was a statistically significant effect of placebo administration on cortical activation, the contrasts *placebo* > *control* and *control* > *placebo* were computed. Results are reported family-wise error (FWE) corrected at $p < .05$ with a voxel extent threshold of k=20. Anatomical interpretation of the functional imaging results was performed using the SPM Anatomy toolbox (Eickhoff et al., 2005).

3. Results

3.1. Behavioral Data

The repeated measurement ANOVA revealed a significant main effect of the factor "valence" ($F_{(1,108)} = 695.50$, $p < .001$, $\eta_p^2 = .87$). All three valences differed significantly with $p < .001$. Unpleasant stimuli (mean = -2.58, SD = 1.33) were rated less pleasant compared to neutral stimuli (mean = .21, SD = .93). Pleasant stimuli (mean = 2.82, SD = 1.09) were rated more pleasant than neutral stimuli. Moreover, we observed a significant "valence × group" interaction ($F_{(1,108)} = 4.36$, $p = .014$, $\eta_p^2 = .039$). Follow-up comparison showed a significant effect for "group" in the unpleasant condition ($p = .008$) but not in the neutral ($p = .891$) and pleasant ($p = .57$) conditions, indicating that pleasantness ratings in placebo and control group differed significantly only regarding unpleasant stimuli (see Figure 4).

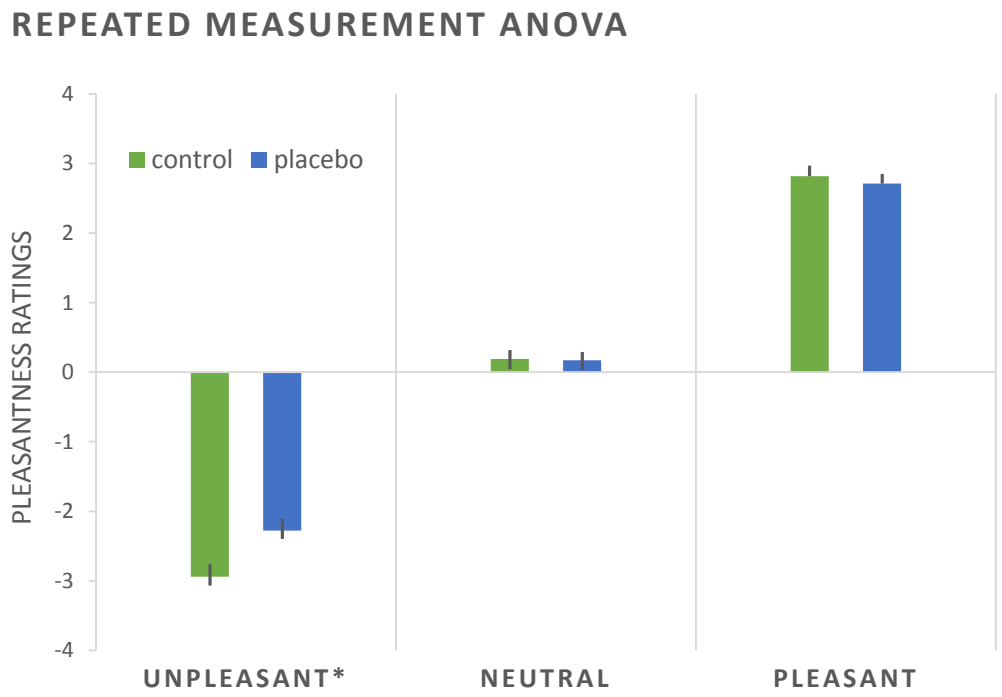

Figure 4. Behavioral ratings (mean ± SE) regarding unpleasant, neutral and pleasant visuotactile stimulation for placebo and control group, revealing a significant placebo effect for unpleasant touch. *$p < .01$

3.2. fMRI Data

3.2.1. Neural representation of unpleasant and pleasant touch

To identify the activation patterns involved in pleasant and unpleasant touch, the contrasts *unpleasant > neutral* and *pleasant > neutral* were computed, with neutral touch serving as a baseline.

Unpleasant condition. Neural activations associated with unpleasant stimulation were observed in the left insula, the left ACC and the bilateral MCC (see Figure 5A). Further regions of increased activity included the right precentral gyrus, the right cerebellum, the left SI, the bilateral fusiform gyrus and bilateral rolandic operculum.

Pleasant condition. Pleasant compared to neutral stimulation showed significant neural responses in the bilateral MCC, bilateral insula and MOFC (see Figure 5B), as well as the bilateral precentral gyrus, right cerebellum and various occipital and temporal regions.

Full details on brain regions, cluster size, coordinates and statistical values are provided in Table 1.

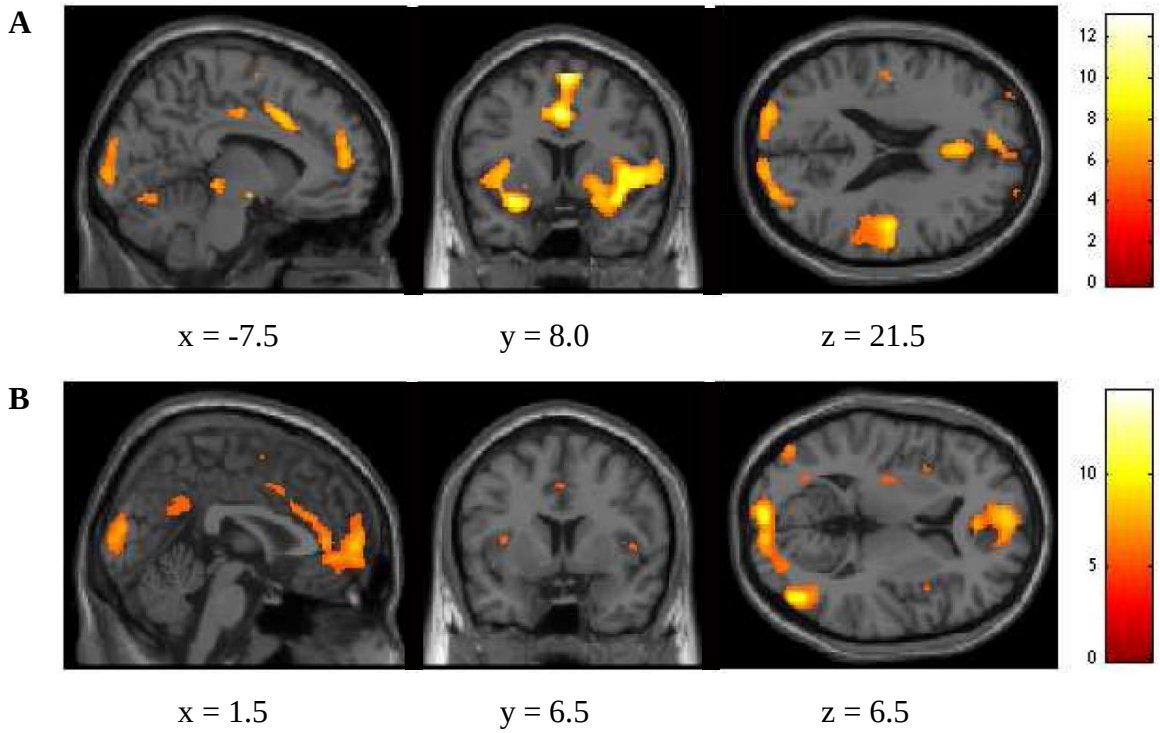

Figure 5. Significant brain activations for unpleasant and pleasant touch. The contrast *unpleasant > neutral* (A) revealed increased activity of insula, ACC and MCC, the contrast *pleasant > neutral* (B) heightened activity in MCC, insula and MOFC. $p < .05$, FWE corrected.

Table 1.

Brain regions showing significant activations in response to unpleasant and pleasant touch compared to neutral touch, including cluster-size (k), MNI coordinates, t-values of peaks and p-value.

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
Contrast: UP > N							
fusiform gyrus	L	9021	-24	-66	-16	9.48	.000
fusiform gyrus	R	7436	27	-85	-13	10.25	.000
MCC	R	4757	2	12	40	13.01	.001
insular lobe	L	2295	-22	4	-14	10.96	.000
precentral gyrus	R	2234	46	-16	42	10.97	.000
rolandic operculum	R	1992	50	-16	18	10.46	.000
ACC	L	1514	-8	52	14	7.62	.000
SI	L	1284	-45	-18	44	9.66	.000
precuneus	R	588	3	-46	58	7.25	.000
middle frontal gyrus	L	285	-27	50	32	7.11	.000
rolandic operculum	L	266	-48	-16	17	6.50	.000
MCC	L	89	-14	-38	48	6.57	.000
cerebellum	R	42	14	-55	-22	6.19	.000
inferior frontal gyrus	R	27	44	26	4	5.62	.003
Contrast: P > N							
inferior occipital gyrus	R	11672	45	-74	-2	14.54	.000
MOFC	L	3799	-4	56	-2	9.05	.000
precentral gyrus	L	2034	-40	-25	60	10.66	.000
middle occipital gyrus	L	1402	-44	-80	2	8.67	.000
posterior cingulate cortex	L	1130	-8	-49	24	8.95	.000
precentral gyrus	R	816	46	-10	54	9.16	.000
MCC	L	362	-6	-4	50	6.46	.000
MCC	L	44	-2	-16	44	5.83	.001
putamen	L	138	-28	-16	2	6.81	.000
middle frontal gyrus	L	82	-30	42	32	6.48	.000
lingual gyrus	R	47	6	-70	-4	6.21	.000
MCC	R	43	4	2	64	5.85	.001
middle temporal gyrus	L	35	-62	-10	-16	5.90	.001
cerebellum	R	34	15	-50	-20	6.55	.000
insula lobe	R	33	46	5	4	5.67	.003
insula lobe	L	24	-34	8	8	6.27	.000

Notes. $p < .05$, FWE corrected, voxel threshold k > 20, L=left, R=right.

3.2.2. Increased neural activation associated with placebo administration

In order to assess increases in neural activation in the placebo compared to the control group the contrast *placebo > control* was conducted for each valence.

Unpleasant condition. The placebo compared to the control group showed significantly stronger activation in the right dorsolateral and dorsomedial prefrontal cortex (Figure 6) for unpleasant touch. Further regions of increased activity included the bilateral occipital and bilateral temporal gyrus, the left calcarine gyrus and the left inferior parietal lobe.

Neutral condition. Activations that were significantly heightened in the placebo compared to the control group were found in the left DLPFC (see Figure 6), the bilateral middle occipital gyrus, left cuneus and right calcarine gyrus when responding to neutral touch.

Pleasant condition. Regions that showed significant group differences in neural activity included following pleasant stimulation included the bilateral middle and right superior occipital gyrus, as well as the right calcarine gyrus and right superior temporal gyrus.

Full details on brain regions, cluster size, coordinates and statistical valued are provided in Table 2.

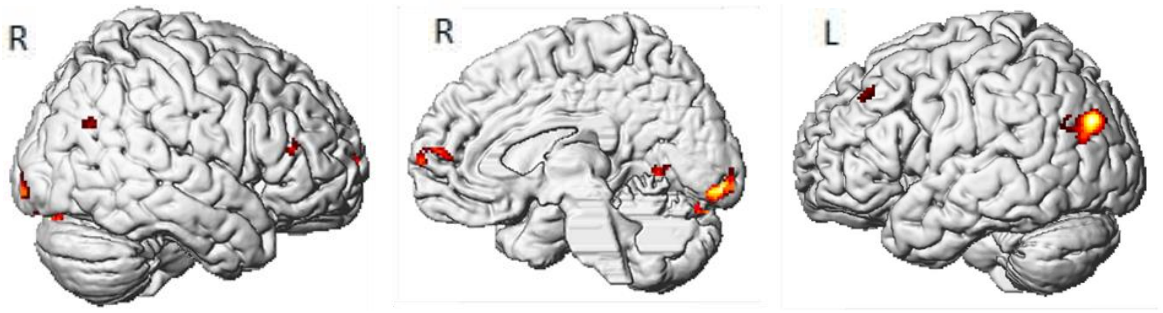

Figure 6. Significant placebo-related increases in brain activation. Visualization of DLPFC and DMPFC activations in the right hemisphere for unpleasant touch, as well as DLPFC activations in the left hemisphere for neutral touch in the contrast *placebo > control*. $p < .05$, FWE corrected.

Table 2.

Regions of significant activation differences in the contrast placebo > control for each valence, including cluster-size (k), MNI coordinates, t-values of peaks and p-value.

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
Contrast: PG > KG UP							
calcarine gyrus	L	432	6	-96	-4	7.73	.000
middle occipital gyrus	L	408	-33	-86	30	10.90	.000
middle occipital gyrus	R	182	39	-58	34	6.80	.000
middle occipital gyrus	R	32	48	-80	2	5.61	.004
DLPFC	R	140	60	24	10	6.77	.000
DMPFC	R	122	6	60	11	6.26	.000
calcarine gyrus	R	82	27	-66	5	7.36	.000

Table 2. (continued)

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
superior temporal gyrus	R	60	68	-46	20	6.10	.000
superior temporal gyrus	R	29	70	-18	11	5.81	.001
white matter	L	59	-12	-97	30	6.37	.000
white mater	L	24	-28	-66	2	5.96	.001
superior occipital gyrus	R	41	26	-88	41	7.06	.000
superior occipital gyrus	R	26	20	-96	29	6.82	.000
inferior parietal lobe	L	31	-9	-32	18	6.29	.000
Contrast: PG > KG N							
middle occipital gyrus	L	549	-33	-85	30	10.91	.000
calcarine gyrus	R	162	27	-64	5	8.76	.000
white matter	L	161	-26	-70	2	6.89	.000
DLPFC	L	83	-22	26	46	5.90	.001
angular cortex	R	73	52	-68	29	6.35	.000
lingual gyrus	R	66	14	-85	-13	6.40	.000
middle occipital gyrus	R	45	44	-80	32	5.76	.002
cuneus	L	44	-2	-92	17	6.74	.000
cuneus	L	38	-10	-85	17	6.48	.000
superior temporal gyrus	R	39	68	-43	14	5.88	.001
Contrast: PG > KG P							
middle occipital gyrus	L	291	-33	-85	30	10.02	.000
middle occipital gyrus	L	30	-40	-91	0	5.43	.009
white matter	L	171	-28	-66	4	7.31	.000
white matter	L	25	-8	-104	14	5.57	.004
calcarine gyrus	R	147	27	-66	5	8.81	.000
middle occipital gyrus	R	82	12	-97	30	6.99	.000
middle occipital gyrus	R	72	48	-80	4	6.21	.000
white matter	R	82	38	-86	32	6.26	.000
superior occipital gyrus	R	44	28	-88	41	6.57	.000
superior occipital gyrus	R	34	18	-96	29	6.97	.000
superior temporal gyrus	R	31	68	-43	12	5.88	.001
angular gyrus	R	30	5	-70	29	5.55	.005

Notes. $p < .05$, FWE corrected, voxel threshold k > 20, L=left, R=right. Clusters of the same anatomical region are listed below the largest one.

3.2.3. Decreased neural activation induced by placebo administration

In order to detect decreased neural activation in the placebo group compared to the control group, the contrast *control > placebo* was conducted for each valence.

Unpleasant condition. Activations that were significantly heightened in the control compared to the placebo group were found in the bilateral SI and SII (see Figure 7), the

bilateral frontoinsular cortex, the left cerebellum, the right precentral gyrus and various occipital regions.

Neutral condition. The control compared to the placebo group showed increased neural activation in the right SI (see Figure 7), bilateral superior parietal lobe, right inferior frontal gyrus and several occipital regions.

Pleasant condition. Regions that showed significant group differences in neural activity included the right middle occipital gyrus, the right SI (see Figure 7) and the right cerebellum.

Full details on brain regions, cluster size, coordinates and statistical valued are provided in Table 3.

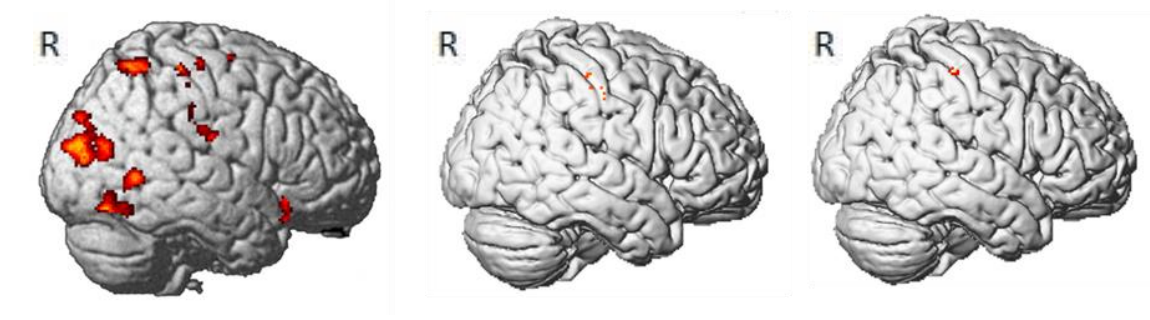

Figure 7. Significant placebo-related decreases in brain activation. Visualization of SI activation in the right hemisphere for each valence in the contrast *control* > *placebo* and SII in the unpleasant condition. For reasons of clarity a SI mask was used for the neutral and pleasant images for visualization purposes only. $p < .05$, FWE corrected.

Table 3.

Regions of significant activation differences in the contrast control > placebo for each valence, including cluster-size (k), MNI coordinates, t-values of peaks and p-value.

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
Contrast: KG > PG UP							
fusiform gyrus	R	2012	34	-60	-18	10.13	.000
middle occipital gyrus	R	1350	27	-85	17	11.96	.000
superior occipital gyrus	L	489	-26	-90	22	9.23	.000
superior occipital gyrus	L	52	-14	-74	-16	7.22	.000
SI	R	417	26	-58	56	8.40	.000
SI	R	211	32	-34	53	7.48	.000
SI	R	68	9	-38	59	6.84	.000
cuneus	L	351	-14	-86	34	7.96	.000
fusiform gyrus	L	345	-30	-66	-18	10.06	.000
fusiform gyrus	L	24	-42	-36	-19	5.91	.001
cerebellum	L	253	-48	-60	-22	6.94	.000

Table 3. (continued)

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
cerebellum	L	52	-21	-76	38	6.51	.000
cerebellum	L	44	-40	-74	-20	6.80	.000
white matter	R	218	46	-55	0	8.04	.000
middle temporal gyrus	L	196	-52	-58	2	7.56	.000
frontoinsular complex	L	104	-58	14	2	6.25	.000
SII	R	92	60	-20	26	6.08	.000
SII	R	28	51	-26	35	5.78	.002
lingual gyrus	R	72	32	-24	59	6.84	.000
precentral gyrus	R	68	48	23	-14	7.72	.000
calcarine gyrus	R	64	10	-86	12	6.56	.000
superior frontal gyrus	R	61	20	-8	64	7.49	.000
SI	L	58	-28	-48	52	6.21	.000
lingual gyrus	L	43	-9	-88	-13	6.03	.000
frontoinsular cortex	R	38	34	23	-22	6.86	.000
SII	L	28	-48	-20	28	6.36	.000
Contrast: KG > PG N							
middle occipital gyrus	R	595	27	-85	17	10.78	.000
lingual gyrus	R	238	6	-60	0	7.25	.000
superior parietal lobe	R	201	27	-58	56	7.47	.000
superior occipital gyrus	L	197	-26	-90	22	7.37	.000
superior occipital gyrus	L	44	-21	-76	38	7.01	.000
fusiform gyrus	R	185	34	-60	-18	7.84	.000
superior parietal lobe	L	117	-20	-66	50	7.25	.000
fusiform gyrus	L	104	-30	-64	-18	7.86	.000
fusiform gyrus	L	86	-40	-43	-24	6.12	.000
cerebellum	R	79	22	-73	-16	7.59	.000
inferior occipital gyrus	R	76	36	-70	-10	6.70	.000
middle temporal gyrus	L	74	-56	-56	0	6.55	.000
inferior frontal gyrus	R	61	34	24	-22	8.03	.000
calcarine gyrus	L	52	-9	-62	8	5.94	.001
white matter	L	49	-26	-73	18	6.58	.000
white matter	R	35	46	-55	0	6.14	.000
SI	R	31	45	-22	48	5.63	.003
SI	R	29	39	-30	48	6.40	.000
Contrast: KG > PG P							
middle occipital gyrus	R	862	27	-85	17	11.64	.000
middle occipital gyrus	R	71	39	-73	11	5.94	.001
fusiform gyrus	R	277	28	-60	-14	8.64	.000
lingual gyrus	R	265	8	-58	-1	7.33	.000
superior occipital gyrus	L	213	-26	-90	22	7.51	.000
SI	R	183	26	-56	58	8.02	.000

Table 3. (continued)

Brain Region	L/R	k	MNI (x,y,z)			t-value	p-value
inferior occipital gyrus	R	141	-30	-66	-18	8.09	.000
fusiform gyrus	R	141	36	-70	-10	6.91	.000
superior parietal lobe	L	103	-21	-64	50	6.46	.000
calcarine gyrus	R	86	12	-85	12	7.05	.000
calcarine gyrus	R	30	18	-50	4	5.97	.001
calcarine gyrus	L	84	-8	-61	6	6.83	.000
cuneus	L	73	-15	-86	34	6.52	.000
cerebellum	R	52	22	-74	-16	6.95	.000
inferior frontal lobe	R	51	36	24	-22	6.81	.000
middle temporal gyrus	R	49	54	-61	-2	5.84	.001
middle temporal gyrus	L	40	-51	-60	4	5.68	.003
white matter	L	36	-27	-73	17	6.07	.000

Notes. $p < .05$, FWE corrected, voxel threshold $k > 20$, L=left, R=right. Clusters of the same anatomical region are listed below the largest one.

4. Discussion

The aim of the present fMRI study was to investigate the specificity of the placebo effect for somatosensory experiences. Hence, neural and behavioral responses to unpleasant, pleasant and neutral visuotactile stimulation were compared between a placebo and a control group following pain-specific placebo induction (in the placebo group). The data revealed three principal findings:

First, as expected the paradigm was effective in generating pleasant and unpleasant touch experiences, similar to prior studies (Klucken et al., 2012; Rolls et al., 2003; Silani et al., 2013). Neural as well as behavioral data confirm the induction of pleasantness regarding the different qualities of touch. As predicted, stimulation led to neural activations in insula and MCC in the unpleasant and pleasant conditions. Moreover, heightened activations were detected in the ACC for unpleasant touch and in the MOFC for pleasant touch. Consequentially, as intended, participants perceived unpleasant stimulation as more unpleasant and pleasant stimulation as more pleasant than neutral stimulation. Our results demonstrate that unpleasant somatosensory experiences can be generated by exposure to visuotactile stimuli that evoke feelings of disgust.

Second, the results suggest that placebo induction was successful and expectations regarding the drug's effect were built up. The placebo group showed heightened activations in the DLPFC and DMPFC for unpleasant visuotactile stimulation. These results agree with studies associating prefrontal areas with top-down processing in placebo effects, such as context monitoring and expectancy of pain relief (Krummenacher et al., 2010; Wager et al., 2004; Watson et al., 2009). Limitations of Wager et al.'s (2004) study were overcome in which DLPFC activation was only measured during the anticipation and rating phase of painful stimulation, while in this study DLPFC activations were noted over the course of the paradigm in the unpleasant condition. Smaller group differences in BOLD signal in the DLPFC were also observed in the neutral condition. For pleasant touch, however, placebo administration had no impact on activations in prefrontal areas. Concluding, top-down emotion processing involved in placebo responses seems to depend on prior evaluation of the stimulation regarding its valence, as suggested by Petrovic et al. (2005).

Third, an extended placebo effect from analgesia to unpleasant touch was observed. Accordingly, pain specific placebo induction reduced the perceived unpleasantness of visuotactile stimulation with disgusting objects. Large neural decreases in SI and SII and smaller decreases in the frontoinsular complex were observed in the unpleasant condition. Further the placebo group showed significant reductions in reported unpleasantness. Thus,

participants experienced the unpleasant stimulation as less unpleasant on a behavioral level and showed reduced activity in the somatosensory system when they had received a sham analgesic - however, there were no activation differences in the cingulate cortex, an area associated with emotion regulation (Etkin, Egner & Kalisch, 2011). Since activation differences mainly appeared in prefrontal and somatosensory areas, the placebo effect seems to manifest itself more on cognitive and somatic levels. The experience of neutral and pleasant touch however appeared to be unaffected by placebo administration. This supports the idea that placebo induction is established by top-down evaluative processes (Colloca & Grillon, 2014). Ultimately, an extension seems to occur when the evaluation of the placebo-induction stimulus has a similar valence as the stimulus it extends to.

This new insight in the mechanism of placebo brings along important implications for the health care system. In the present study, the placebo effect induced for pain extended to another negative domain, while neutral and positive experiences remained unaffected. The obtained results imply that even though the placebo effect extended to a domain it had not specifically been induced for, no unwanted effects occurred and it only affected domains of similar valences. Benedetti et al.'s (2011) study on open and hidden administration of medicine indicates that even the effectiveness of pharmaceuticals can partly be ascribed to placebo responses induced by expectancy of the drug's effect. As research demonstrates, placebo treatment is an effective instrument to reduce the experience of pain. If more is learned about the specificity of placebos, their allocation in clinical contexts could be augmented.

Since this was the first study to investigate the specificity of the placebo effect, the results raise many new research questions that need to be addressed in future studies. It is still unclear why and under what circumstances an extension of the placebo effect is possible. Manipulations regarding the experimental context and instructions would provide more information about the coherencies resulting in an extension. Further, the reach of efficacy of the extension needs investigation. So far, the transferal of the placebo effect was only observed from one quality of somatosensation to another. Lui et al. (2008) showed that the neural processes underlying touch and pain are similar and related. Exploring the possibility of placebo extension to less correlated processes should be an issue in future research. Another topic of interest should be the investigation of placebo extension in terms of adverse effects. Elsenbruch et al. (2012) found a nocebo response that had not specifically been targeted by their instructions. Participants in their study experienced heightened pain when they were told they would receive a placebo instead of an analgesic. The researchers assumed

that the expectation of a treatment's effect may integrate both therapeutic and adverse effects.

The obtained findings need to be considered as preliminary and need further affirmation. In terms of limitations, the fMRI data revealed a multitude of movement artifacts, even after computed motor correction. Physical reactions to touch, especially to unpleasant stimulation, are an instinctive function and thus involuntary movement, such as twitching, was not controllable by the participants. This may also be reflected in neural activations in the precentral gyrus and cerebellum, where movement is represented (Manto et al., 2012). Further fMRI studies could use optimized motion correction algorithms when working with touch. In addition, several pictures in the paradigm were resembled with identical tactile materials. The picture of a snail, for instance, was accompanied by stroking with the same slimy object as the picture of mushroom or fish. In total, eight of the fifteen unpleasant pictures were represented by the same tactile stimulus. Hence, participants may have recognized the repeated tactile stimuli and rated the stimulus in the repetitions the same as the first time it appeared instead of fully considering each visuotactile stimulus as a whole.

Taken together, this work suggests that top-down evaluation processes underlying the placebo response allow its extension to domains with similar valences. These results complement previous findings on placebo effects, and show the relevance of learning about the specificity of placebo treatments.

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6. Appendix

6.1. MR-Checkliste

ProbandInnen-Name

Um ein bei Ihnen möglicherweise bestehendes höheres Risiko besser abschätzen zu können, bitten wir Sie, **folgende Fragen durch Ankreuzen zu beantworten:**

1. **Haben oder hatten Sie einen Herzschrittmacher?** □ ja □ nein □ weiß nicht
2. **Wurde bei Ihnen eine Operation am Herzen, am Kopf oder an einem Gelenk durchgeführt?** □ ja □ nein □ weiß nicht

   Wenn ja: Haben Sie Implantate? z.B. Defibrillator, Herzklappe**,** Ohrimplantat, Aneurysmaclip, Insulinpumpe, Schmerzpumpe, Gelenksprothese, Shunt, Port-a-Cath, Stent

   □ ja □ nein □ weiß nicht

   Welche:……..
3. **Haben Sie Metallteile o. –splitter (Marknagel,…) im Körper?**

   □ ja □ nein □ weiß nicht

   Wenn ja, welche:…….
4. **Haben Sie schon einmal eine MR-Untersuchung gehabt?** □ ja □ nein

   Wenn ja: hat es dabei Probleme gegeben? □ ja □ nein

   Welche:……
5. **Leiden Sie unter Platzangst?** □ ja □ nein
6. **Leiden Sie an einer Nierenerkrankung oder sind Sie schon an der Niere operiert worden?**

   □ ja □ nein □ weiß nicht
7. **Leiden Sie an Zuckerkrankheit (Diabetes)?** □ ja □ nein
8. **Leiden Sie an Bluthochdruck (Hypertonie)?** □ ja □ nein
9. **Leiden Sie an Gicht?** □ ja □ nein
10. **Haben Sie Allergien, Asthma oder Medikamentenunverträglichkeiten?**

    □ ja □ nein □ weiß nicht

    Wenn ja, welche:……..

    Allergische Reaktionen auf MR-Kontrastmittel sind extrem selten.

    Jodallergien spielen bei dieser Untersuchung keine Rolle.
11. **Sind Sie tätowiert, tragen Sie Körperschmuck (Piercing)?** □ ja □ nein
12. **Körpergewicht …….. kg Körpergröße …… cm**

Für Probandinnen:

14. **Könnten Sie schwanger sein?** □ ja □ nein □ weiß nicht

15. **Verhüten Sie mit Spirale?** □ ja □ nein

Ich bestätige, dass ich den Text gelesen, verstanden und die mich betreffenden Fragen nach bestem Wissen beantwortet habe. Ich bestätige, dass die von mir am _____ unterzeichnete Einwilligungserklärung zum jetzigen Zeitpunkt noch immer gültig ist. Ich stimme der Durchführung der MRT-Untersuchung im Rahmen des Forschungsprojekts „Striatale Funktionen bei Prodynorphin-Genvarianten“ zu. In einem persönlichen Gespräch sind meine Fragen ausreichend beantwortet worden.

……	**……**
Unterschrift der/des Probandin/en und oder des gesetzlichen Vertreters	Name und Unterschrift der Testleiterin/des Testleiters
……	**……**
Datum/Uhrzeit	Name und Unterschrift der/des MTD

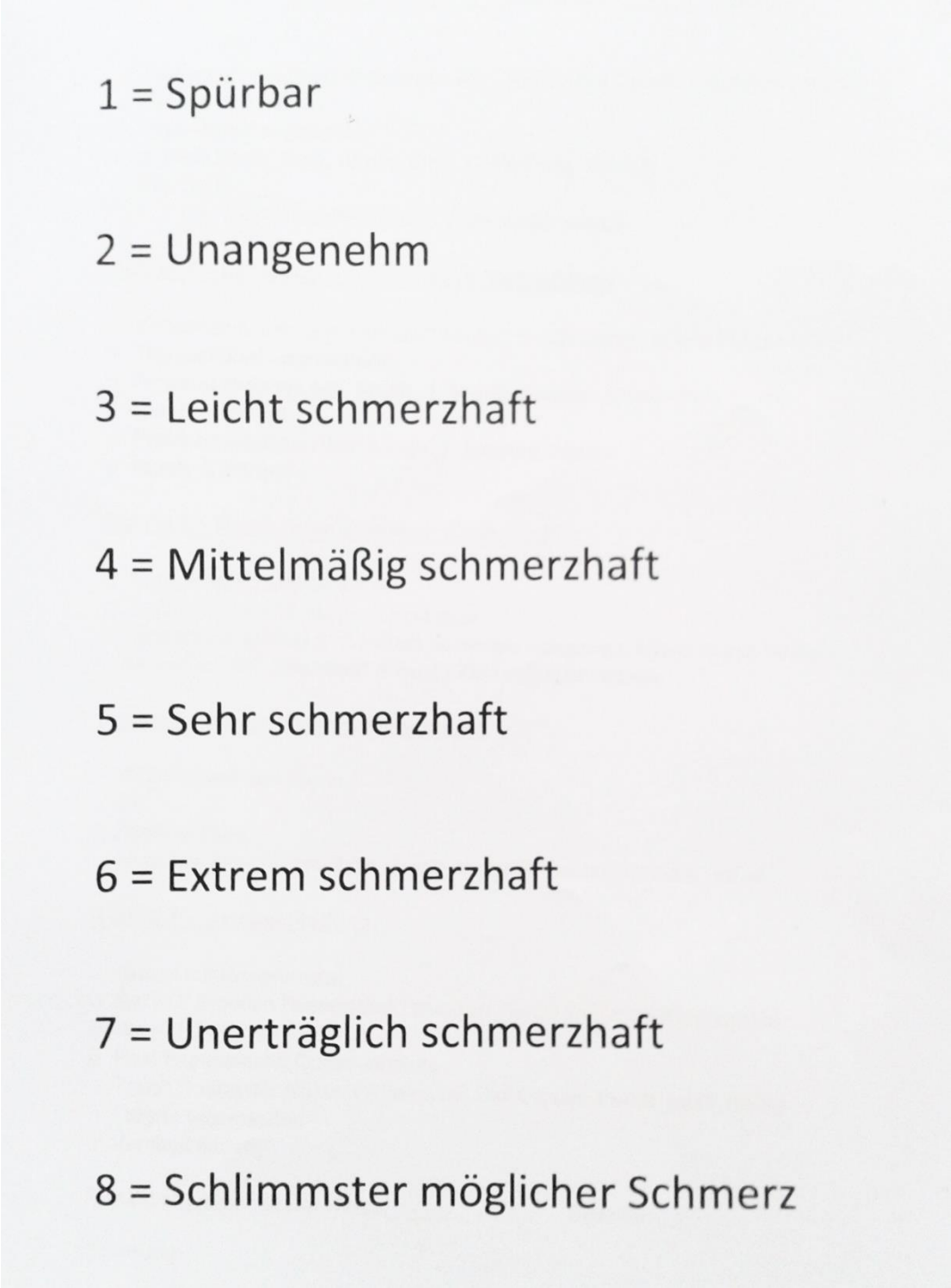
Anmerkung der Testleiterin/des Testleiters zum Aufklärungsgespräch:

……

……

Der Proband stimmt der Untersuchung nicht zu. □

6.2. Calibration Scale



6.3. Full List of Visuotactile Stimuli

Chronological Order	*Pictures*	*Materials*	*Valence*
1	Babyhund	Braunes Fell	**Pleasant**
2	Bürste	Bürste	**Neutral**
3	Rose	Satinband	**Pleasant**
4	Pilze	Slimey	**Unpleasant**
5	Stinkwanze	Plastikinsekt	**Unpleasant**
6	Hase	Schwarzes Fell	**Pleasant**
7	Walnuss	Walnuss	**Neutral**
8	Schachtel	Karton	**Neutral**
9	Rasierpinsel	Rasierpinsel	**Pleasant**
10	Schnecke 1	Slimey	**Unpleasant**
11	Stift	Stift	**Neutral**
12	Tausendfüßler	Gummifüßler	**Unpleasant**
13	Leber	Slimey	**Unpleasant**
14	Küken	Federn	**Pleasant**
15	Walnuss 2	Walnuss	**Neutral**
16	Schaf	Watte	**Pleasant**
17	Hase 2	Schwarzes Fell	**Pleasant**
18	Wels	Slimey	**Unpleasant**
19	Küken 2	Federn	**Pleasant**
20	Hund	Bürste	**Neutral**
21	Rentier	Ast	**Neutral**
22	Maden	Gummiwürmer	**Unpleasant**
23	Stein	Stein	**Neutral**
24	Käfer	Plastikinsekt	**Unpleasant**
25	Wels 2	Slimey	**Unpleasant**
26	Wattebausch	Watte	**Pleasant**
27	Rasierpinsel 2	Rasierpinsel	**Pleasant**
28	Ast	Ast	**Neutral**
29	Erdnuss	Erdnuss	**Neutral**
30	Aal	Slimey	**Unpleasant**
31	Schildkröte	Walnuss	**Neutral**

32	Tausendfüßler 2	Gummifüßler	**Unpleasant**
33	Schwan	Federn	**Pleasant**
34	Wattebausch 2	Watte	**Pleasant**
35	Schnecke 2	Slimey	**Unpleasant**
36	Stift 2	Stift	**Neutral**
37	Schnecke 3	Slimey	**Unpleasant**
38	Babyhund 2	Braunes Fell	**Pleasant**
39	Käfer 2	Plastikinsekt	**Unpleasant**
40	Wollknäuel	Wollknäuel	**Pleasant**
41	Bürste	Bürste	**Neutral**
42	Kätzchen	Schwarzes Fell	**Pleasant**
43	Maden 2	Gummiwürmer	**Unpleasant**
44	Stein 2	Stein	**Neutral**
45	Ast 2	Ast	**Neutral**

6.4. List of figures

6.5. List of Tables

6.6. Curriculum Vitae

PERSONAL INFORMATION

Name:	Bernadette Hippmann
E-mail:	bernadette.hippmann@gmail.com

EDUCATION

Oct 08 – present	Diploma program (equivalent to M. Sc.) in psychology at the University of Vienna, Austria
Aug 11 – Dec 11	Exchange semester at the University of Helsinki, Finland
Oct 05 – Jun 08	Diploma program in nanotechnology at the University of Würzburg, Germany
Oct 96 – May 05	Secondary school Johannes Gutenberg Gymnasium with focus on natural science, Waldkirchen, Germany
Sep 02 – Jul 03	Exchange year at the Scuola Germanica, Rome, Italy

PROFESSIONAL EXPERIENCE

Jul 14 – present	JOB Bowl Personalberatung, Vienna *Position:* Market research assistant
Feb 13 – Jan 14	Project work at the Faculty of Psychology, Vienna, Social, Cognitive and Affective Neuroscience Unit *Position:* Research assistant
Jul 09 – Sep 09	Bildung & Beruf, Grafenau, Germany *Position:* Job coach
Jul 08 – Aug 08	Ananke, clinic for psychosomatic, Freyung, Germany *Position:* Intern
Oct 08 – Dec 10	Advocado, direct sales & market communication agency, Vienna *Position:* Human ressources manager

SKILLS

Languages	German, English, Italian, Spanish, French
Technical skills	SPSS, Matlab, SPM