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When opposites lead to the same: a direct comparison of explicit and implicit disgust regulation via fMRI

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Abstract

Cognitive reappraisal and placebo administration constitute two different approaches for modulating one's own emotional state. Whereas reappraisal is an explicit (effortful) type of self-regulation, placebo treatment initiates implicit processes of affective control. The brain mechanisms underlying these processes have not been directly compared with each other up until now; doing this enables the identification of distinct and shared neuronal features. We conducted a functional magnetic resonance imaging study with 45 women, who were presented with disgusting and neutral images in a block design, at three experimental sessions, over 3 consecutive days. They were asked to passively view the images in one session, engage in reappraisal in another, and in another session they received a placebo pill: a disgust-reducing 'anti-nausea drug'. Relative to passive viewing, both reappraisal and placebo treatment effectively reduced the experienced disgust intensity. In the placebo condition, this reduction was associated with decreased activation of the insula and the dorsolateral prefrontal cortex (DLPFC). In contrast, reappraisal induced increased activation in both regions. Furthermore, both regulation strategies were associated with opposite patterns of connectivity in a network encompassing the amygdala, the insula and the DLPFC. Only placebo administration led to a reduced coupling in this network.

Key words: placebo; reappraisal; disgust; fMRI

Introduction

Placebos elicit their effects by altering expectancies and beliefs (Benedetti *et al.*, 2005). For example, in placebo analgesia—one of the most studied placebo phenomena—the mere belief that one is receiving an effective analgesic treatment can ease experienced pain (Wager and Atlas, 2015). On the neuronal level, this change is accompanied by altered activity in the 'pain matrix', including somatosensory, insular and prefrontal cognitive control regions (e.g. dorsolateral prefrontal cortex; DLPFC). The altered activity in this matrix reflects changes in the perceived intensity, and unpleasantness of the noxious stimulation (Wager and Atlas, 2015). Because the placebo recipients are not aware of the fact that they change their attitude toward the noxious stimulation, but nevertheless 'mentally re-describe its meaning', this process can be conceptualized as automatic or implicit emotion regulation (Ochsner and Gross, 2007). Emotion regulation strategies are considered implicit when they are performed without making a conscious decision to do so, without paying attention to the regulation process, and without engaging in deliberate control (Mauss *et al.*, 2007). Neuroimaging studies showed that mainly (sub)cortical regions associated with bodily arousal, implicit memory, and conflict monitoring (e.g. amygdala, insula, anterior cingulate cortex (ACC)) are recruited when affective processing occurs outside of conscious awareness (see meta-analyses on subliminal stimulus exposure by Brooks *et al.*, 2012 and Meneguzzo *et al.*, 2014).

Cognitive reappraisal is another emotion regulation strategy; however, it involves a voluntary change of the affective meaning of a stimulus. This change is carried out according to one's own goals and beliefs. Individuals who engage in reappraisal

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when confronted with an unpleasant situation make a conscious decision to do so, they choose a specific tactic to implement this strategy (e.g. reinterpretation, distancing), and they monitor the regulation process (Ochsner and Gross, 2007). Reappraisal and its affective and neuronal correlates have been extensively studied in neuroimaging research. Converging evidence suggests prefrontal cognitive control areas (e.g. dorsolateral/ventrolateral prefrontal cortex (DLPFC/VLPFC) has a central role in this context. These prefrontal areas are crucial for attention (re)direction, as well as for the maintenance or update of internal goal representations (see the meta-analysis by Buhle *et al*., 2013). Cognitive control areas, such as the DLPFC, modulate the activation of brain regions involved in detecting and encoding affectively salient stimuli; in particular, the amygdala. The observed increased fronto-amygdala connectivity is thought to reflect top-down modulatory effects during reappraisal (Buhle *et al*., 2013). This modulation is not straightforward as the DLPFC lacks direct projections to the amygdala and first transmits information to ventral and medial prefrontal areas (McDonald *et al*., 1996).

Although reappraisal and placebo effects can be conceptualized as opposite phenomena of explicit (conscious) *vs* implicit (unconscious) emotion regulation, it needs to be mentioned that placebo effects are based on expectations acquired through verbal instructions. This implies conscious cognitive processes and points to 'cognitive framing' as a shared feature of both regulation strategies.

The goal of the present functional magnetic resonance imaging (fMRI) investigation, with three separate experimental sessions, was to directly compare the neuronal networks involved in implicit and explicit disgust regulation. All participants received placebo treatment, engaged in reappraisal, and used no specific emotion regulation strategy (passive viewing) during the presentation of repulsive images. We focused on the emotion disgust because of its relevance for psychopathology. Many patients, who are diagnosed with obsessive-compulsive disorder (washing/cleaning), blood phobia, or borderline personality disorder experience excessive and difficult-to-control disgust feelings as a core feature of their disorder. Therefore, an understanding of (dys)functional disgust regulation has important clinical implications.

Placebo effects on affective picture processing in general and specifically on disgust processing have been investigated previously via fMRI (Petrovic *et al*., 2005; Zhang *et al*., 2013; Schienle *et al*., 2014a,b). Petrovic *et al*. (2005) demonstrated that a 'placebo anxiolytic' decreased negative affect and modulated activation in prefrontal brain regions (e.g. orbitofrontal/ventrolateral prefrontal cortex) during the viewing of unpleasant pictures. Schienle *et al*. (2014a,b) presented their participants with disgust-inducing images and administered a placebo pill, paired with the verbal suggestion that it was an effective anti-nausea medication. This treatment reduced both the intensity of experienced disgust as well as the activation of the insula. Zhang *et al*. (2013) compared conditioned placebo effects and cognition-based reappraisal effects in an experiment, during which the participants were presented with negative pictures and painful heat stimuli. They showed that both strategies reduced the unpleasantness of the images as well as the activity in the amygdala and insula. In addition, the DLPFC was demonstrated to be involved in reappraisal. However, the two strategies differed with regard to previous learning experiences; this influences neuronal responses, and makes interpretation of these findings problematic. Since it is also possible to induce placebo effects without preceding conditioning phases, a placebo manipulation based only on verbal suggestions seems better suited for a direct comparison with reappraisal. This was done in the present investigation.

Based on previous research, we predicted that both placebo administration and cognitive reappraisal would decrease self-reported disgust and insula activation during emotion elicitation by visual stimuli. Given that reappraisal is a conscious, effortful type of emotion regulation, we expected that this strategy would lead to greater activation of cognitive control areas (e.g. DLPFC), and greater functional connectivity of these frontal areas with the amygdala/insula, relative to placebo administration.

Materials and methods

Participants

Forty-five right-handed women completed the study (M_{age} = 22.91 years, SD = 3.21). The majority of participants were students (82%), the rest white-collar workers. All participants provided written informed consent. The study had been approved by the ethics committee of the University of Graz (Austria). Preliminary eligibility was assessed with a general health questionnaire (Brief Symptom Inventory; Derogatis, 1993) and an fMRI safety screening form. Participants reported no history of mental and neurological disorders. We only recruited women because they report higher disgust proneness (temporally stable tendency of a person to experience disgust across different situations) than men (Schienle *et al*., 2002a).

Stimuli and design

We administered a total of 90 disgusting and 90 neutral images. The affective images depicted core disgust elicitors (disgusting animals such as snails and worms, rotten food and body secretions). The neutral images consisted of scrambled versions of the disgust images (with a mosaic-like appearance). The stimuli were taken from the International Affective Picture System (Lang *et al*., 2008), from our own validated picture set (Schienle *et al*., 2002b) or had newly been developed for the experiment. In a pilot study, the affective pictures were rated by four independent raters with respect to elicited disgust intensity. The disgust sets were comparable in rated disgust intensity as well as content (e.g. each set contained a comparable number of the above mentioned core elicitors). The pictures were divided into three parallel sets (30 disgusting, 30 neutral stimuli) for the three experimental conditions Passive Viewing (PV) Placebo Administration (PA) and Cognitive Reappraisal (CR).

The instructions were as follows:

PV: The participants were asked to look at the pictures and to allow all affective responses.

PA: Fifteen minutes prior to the fMRI experiment the participants received a white 1 cm long silica-filled capsule for oral intake together with the verbal suggestion that this was a homoeopathic medication ('anamirta cocculus'), which is able to reduce disgust-related symptoms. They were told that a previous study without brain imaging had already demonstrated that this treatment was very effective in reducing experienced disgust. They were also told that effects would be noticeable in ~15 min after intake.

CR: The participants were asked to imagine that the stimuli shown in the pictures were not real, but created by a Hollywood style special effects makeup artist.

The participants were told that the experimental instructions only referred to the disgust pictures.

The experimental conditions were conducted at three separate sessions over 3 consecutive days. The study had a repeated-measures design. All participants underwent all three conditions. The sequence of the conditions was counterbalanced across all participants. Within a session, the pictures were presented for 5 s each, in blocks of three pictures of the same type (Disgust or Neutral). Then, a fixation cross was shown (variable interval: 2–4 s), which was followed by ratings for the intensity of experienced disgust on a 9-point scale (1 = no disgust; 9 = intense disgust). Participants gave their ratings via a scanner-suitable track ball. There was no time restriction for the rating. The paradigm only continued when participants completed their ratings. After each rating the trial ended with a 15 s resting period during which a fixation cross was shown. Each condition consisted of 10 disgust blocks (30 images) and 10 neutral blocks (30 images). The sequence of the blocks was random.

At the end of the complete study the participants were fully debriefed concerning the goals of the study and that the received an inert pill in the placebo condition.

fMRI measures and analysis

Recording. Functional volumes were acquired using an echo-planar imaging protocol (number of slices: 35, descending, flip angle = 90°, slice thickness: 3 mm, 1 mm gap; matrix: 64 × 64; TE = 30 ms; TR = 2290 ms; FoV: 192; voxel size = 3 × 3 × 3 mm) with a 3T scanner (Skyra, Siemens, Erlangen, Germany).

Analysis. All analyses were conducted with SPM12 (Wellcome Department of Cognitive Neurology, London). Three volumes from the beginning of the time series were discarded to account for saturation effects. First functional data were slice-timed and motion-corrected via realignment. Individuals T1-weighted mean images calculated from all three sessions were coregistered to their mean functional data. Afterwards coregistered T1-weighted mean images were segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid. To increase inter-subject alignment individual images of GM and WM were registered in a 'Fast Diffeomorphic Registration Algorithm' (DARTEL) to the IXI550 template implemented in the VBM 8 toolbox. Resulting individual DARTEL flow fields were used to normalize slice-timed and realigned functional images to MNI-space (3 mm isotropic voxel). Finally, for smoothing a Gaussian kernel of 6 mm was applied. In the first level stage, across each session each event of interest (e.g. Placebo_Disgust, Reappraisal_Disgust) were modelled together in one design matrix. Additionally, re-align parameters for each session were entered as regressors of no interest. Responses were modelled by the canonical hemodynamic response function. Data were high pass filtered (128 seconds). Temporal sphericity was controlled by an AR(1) process with consecutive pre-whitening of the data.

Statistical analysis. We computed an analysis of variance (flexible factorial) with the factors 'Condition' (PV, PA, CR), and 'Emotion' (Disgust, Neutral). Statistically significant main effects and interaction effects were followed up by 1D t-contrasts. We conducted exploratory whole-brain voxel intensity tests as well as region of interest (ROI) analyses for the amygdala, the insula, the DLPFC and the OFC. These regions had been selected based on previous findings on placebo effects (Wager and Atlas, 2015). The uncorrected height threshold for the analyses was set to $P < 0.001$ with a minimum extent threshold of five voxels. The used ROI masks were taken from the Harvard-Oxford cortical structural atlas (Center for Morphometric Analysis, MGH-East, Boston/MA, USA) and from the Automatic Anatomy Labeling Atlas (Tzourio-Mazoyer *et al.*, 2002), these ROIs were created with the WFU PickAtlas (WFU Pickatlas v2.4; Wake Forest University School of Medicine). Results were considered significant when p corrected for family-wise error (FWE) was < 0.05 (small volume correction).

Psychophysiological interaction analysis (PPI)

We conducted PPI analyses (Friston *et al.*, 1997) to investigate emotion-specific connectivity in the three conditions (PV, PA, CR). PPI assesses the extent to which an experimental factor modulates the connectivity of one brain region with others, in terms of condition-specific covariation in residuals. Given specific seed regions (e.g. left insula) PPI identifies voxels that covary differentially with the seed region as a function of an experimental factor. For each participant, a PPI analysis was performed by setting up a design matrix containing three columns of variables: the first regressor, the physiological variable, represented the time series of activity taken from the seed region by taking the first eigenvariate of the corresponding mask. The second regressor, the psychological variable, represented the condition type (e.g. the contrast Placebo_Disgust > Placebo_Neutral). The PPI variable (PPI term) represented the third regressor, which was computed as the element by element product of the deconvolved extracted time series of the selected seed region and a vector coding for the effect of task. Subject-specific contrast images were then entered into a paired *t*-test analysis (cluster-building threshold at $P < 0.001$ and thresholded at $P < 0.05$, corrected for multiple comparisons (FWE) on the voxel level; small volume correction) in order to explore connectivity (Disgust > Neutral) for the contrasts PV *vs* PA, PV *vs* CR and PA *vs* CR. As seed regions we defined those regions which showed significant activation in the fMRI analysis (insula, amygdala, OFC, DLPFC). The ROIs were the same as in the fMRI analysis.

Results

Self-report

We first compared the disgust intensity ratings between the three experimental conditions by means of an ANOVA [$F(2,88) = 153.33$, $P < 0.001$]. *Post-hoc t*-tests indicated that experienced disgust was more intense for passive viewing (M = 6.58, SD = 1.28) than for placebo (M = 3.62, SD =1.58) and reappraisal (M = 2.81, SD = 1.19) (both P's < 0.001). All participants had reported decreases in the intensity of experienced disgust due to placebo (range: −0.6 … −7.1) and reappraisal (range: −1.3 … −7.0). The disgust ratings for the neutral pictures were always '1'.

Brain imaging

The analysis of variance revealed significant effects (on the whole brain level) for the factors Emotion and Condition as well as for the interaction Emotion × Condition (all P's < 0.001, FWE-corrected). The large activation clusters for the main and interaction effects encompassed all selected ROIs. Therefore, we looked at specific contrasts of interest [passive viewing (Disgust > Neutral) *vs* Placebo (Disgust > Neutral); passive viewing (D > N) *vs* Reappraisal (D > N), and Reappraisal (D > N) *vs* Placebo (D > N)]. Prior, we had also assured that the disgusting pictures (contrast D > N) had elicited the expected ROI activation

Table 1. Comparison of brain activation (Disgust > Neutral) between passive viewing placebo treatment and reappraisal

Region	H	X	Y	Z	T	P(FWE)	Cluster size
Passive Viewing >Placebo							
Insula	L	−33	9	−12	4.348	0.003	21
DLPFC	L	−27	30	45	3.964	0.046	56
Reappraisal > Passive Viewing							
Insula	R	33	18	3	3.388	0.038	17
DLPFC	L	−48	6	45	4.168	0.007	49
OFC	L	−39	45	−6	3.911	0.034	37
OFC	R	39	39	−3	3.945	0.032	37
Reappraisal > Placebo							
Insula	L	−33	27	3	5.117	<0.001	169
Insula	R	36	21	3	4.104	0.007	70
DLPFC	L	−48	15	36	5.801	<0.001	653
DLPFC	R	30	6	63	4.788	0.002	92
OFC	L	−51	24	−3	5.708	<0.001	197

DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex.

(especially insula, amygdala) during passive viewing as a manipulation check (Supplementary Table S1).

The placebo reduced activation of the insula, and the DLPFC relative to passive viewing (Table 1). Reappraisal was associated with activation increases in the insula, the DLPFC and the OFC. The direct comparison of the two regulation conditions showed increased ROI activation in the insula, the OFC, and the DLPFC for reappraisal.

PPI

Relative to passive viewing, the placebo led to reduced connectivity between the left insula (seed) and the right amygdala as well as the right insula (Table 2). Also, connectivity between the right DLPFC (seed) and the right amygdala decreased. Placebo-related increases in functional connectivity were identified between the bilateral amygdala (seeds) and the left OFC.

Relative to passive viewing, reappraisal was associated with increased coupling between the right amygdala (seed) and the right OFC, as well as the right DLPFC (seed) and the right OFC (Figure 1). The reversed contrast (Passive Viewing > Reappraisal) showed enhanced insula-amygdala connectivity.

The direct comparison of the two regulation strategies showed increased connectivity between DLPFC (seed)—amygdala, amygdala (seed)—insula and OFC (seed)—insula for reappraisal.

Discussion

This fMRI study directly compared two disgust regulation strategies, placebo administration and cognitive reappraisal. The placebo, a presumed homeopathic anti-nausea medication, effectively reduced the intensity of experienced disgust during emotion elicitation by visual stimuli. This was accompanied by reduced insula activation. This finding is in line with a previous fMRI experiment, which demonstrated that a placebo pill suggested to have disgust-reducing properties was able to decrease insula activation (Schienle *et al.*, 2014a). Placebo-related effects on insular function have also been observed very consistently with other placebo designs (Wager and Atlas, 2015) and designs for the study of unconscious affective processing (Brooks *et al.*, 2012; Meneguzzo *et al.*, 2014).

Table 2. Comparison of functional connectivity (Disgust > Neutral) between passive viewing placebo treatment and reappraisal

Region	H	X	Y	Z	T	P(FWE)	Cluster size
Seeds							
Passive Viewing > Placebo							
insula left							
Amygdala	R	30	0	−15	3.12	0.047	50
Insula	R	33	−15	18	3.86	0.046	47
DLPFC right							
Amygdala	R	24	−3	−12	3.31	0.028	23
Placebo > Passive Viewing							
amygdala left							
OFC	L	−48	27	−9	3.54	0.045	60
amygdala right							
OFC	L	−42	24	−18	3.76	0.045	79
Reappraisal > Passive Viewing							
amygdala right							
OFC	R	30	15	−21	3.62	0.049	43
DLPFC right							
OFC	R	9	24	−21	4.20	0.036	158
Passive Viewing > Reappraisal							
insula right							
Amygdala	L	−21	−3	−12	3.39	0.019	11
Reappraisal > Placebo							
DLPFC right							
Amygdala	R	21	−3	−15	3.03	0.043	37
amygdala right							
Insula	R	42	12	−15	3.80	0.045	28
OFC left							
Insula	R	45	3	−3	3.68	0.032	52

DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex.

Cognitive reappraisal also significantly reduced experienced disgust, but it increased insula activation. The direct comparison of the two regulation strategies showed stronger bilateral insular recruitment for reappraisal. This is a striking finding. In the traditional approach for interpreting fMRI findings, the direction of localized change in activation is connected to changes in specific cognitive/affective states. Relating this to the insula, it is known that this region is involved in interoceptive awareness and integration of sensory and affective information; more specifically, the anterior part has been linked with the processing of specific emotions, such as disgust (e.g. Phillips *et al.*, 1997). Consequently, reduced insula activation should be associated with reduced disgust. Our data clearly indicate that this is not always the case. It seems that reappraisal enabled the participants to fully participate in the feeling of disgust, in terms of interoceptive awareness—much more than during passive viewing and placebo administration. The applied reappraisal strategy obviously elicited interoceptive activations, which were then reframed. Thus, cognitive reappraisal might not be associated with dampening of disgust activations at all, but rather to fully experience the affective stimulation with a different, deliberative cognitive label.

This interpretation also fits nicely with another observed opposite activation change elicited by the two regulation strategies. Whereas the placebo decreased activation within the DLPFC, we observed an increase here during reappraisal. This has been described previously by others (e.g. Ochsner and Gross, 2007). The DLPFC is involved in selective attention and working memory, and assists in holding reappraisals in mind. In the reappraisal condition of this study, participants were

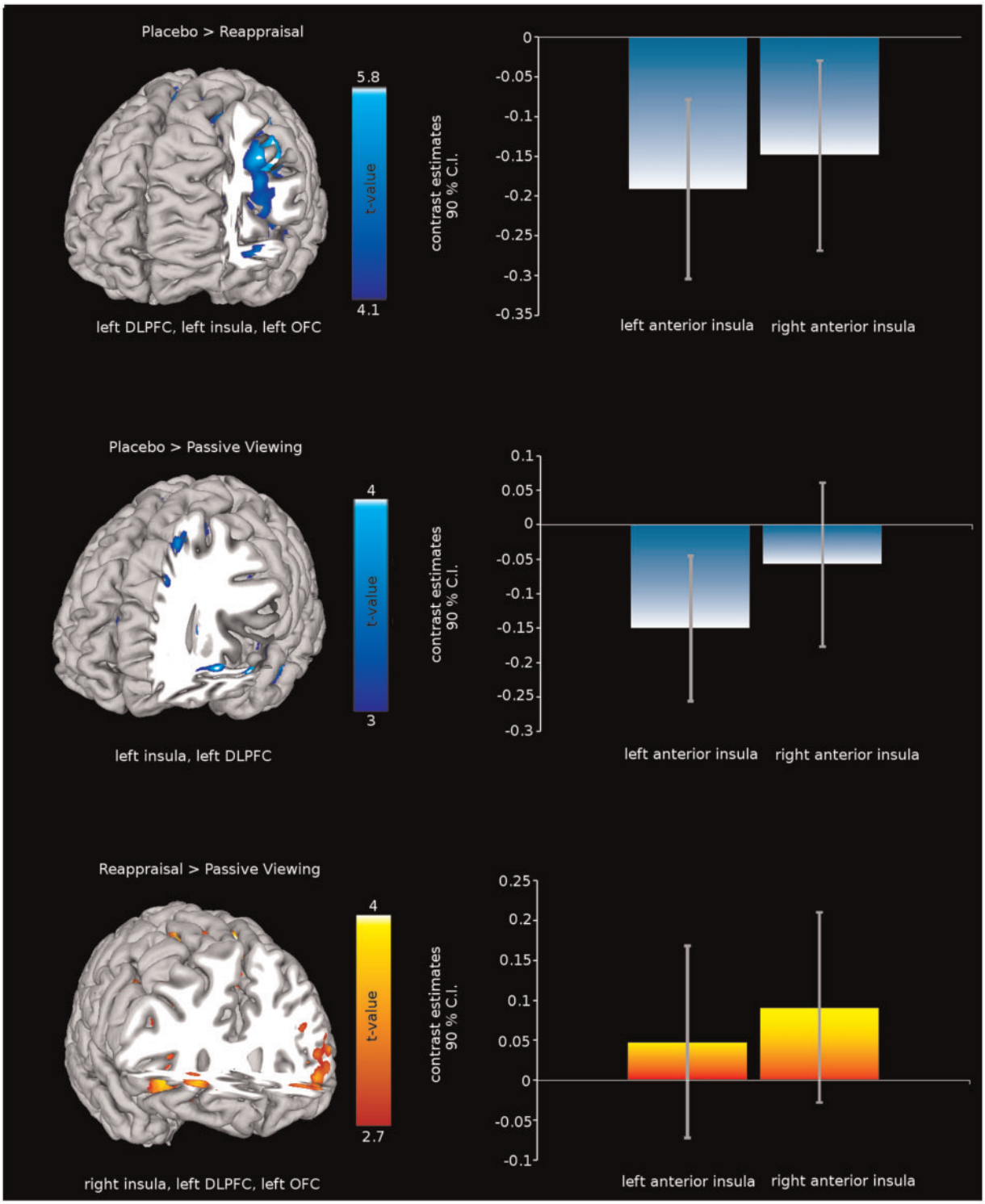

Fig. 1. Comparison of brain activation (Disgust > Neutral) between passive viewing, placebo treatment and reappraisal with corresponding contrast estimates.

asked to instruct themselves that the depicted disgust items were not real. Such repeated self-instruction was not necessary in the placebo condition.

We then conducted a connectivity analysis. The placebo, relative to passive viewing, reduced the coupling between the DLPFC and the amygdala. In contrast, reappraisal was characterized by greater DLPFC-amygdala connectivity than the placebo treatment. In their meta-analysis, incorporating data from 48 studies, Buhle *et al.* (2013) found strong evidence that reappraisal modulates activity in the bilateral amygdala, via the DLPFC. The use of cognitive control strategies changes semantic representations of emotional stimuli (DLPFC). In turn, these altered representations attenuate activity in the amygdala. The amygdala is implicated in the detection, encoding, and

organization of responses to stimuli with motivational relevance (LeDoux, 2014).

Another interesting differential pattern of functional connectivity involved the amygdala and the insula. Placebo administration was associated with reduced amygdala-insula coupling, relative to both passive viewing and reappraisal. This might imply a placebo-induced decoupling between the internal representation of one's own body state (insula) and the assignment of negative affective value (amygdala).

We also detected connectivity patterns which were similar in both regulation strategies. Relative to passive viewing both placebo and reappraisal increased the coupling between the OFC and the amygdala. The OFC is involved in cue–outcome learning. For example, this region will be activated during reversal learning, when a previously negative cue now signals a reward outcome (or the omission/absence of a negative outcome). Reward/punishment expectations were changed by both the placebo and reappraisal instructions. During passive viewing the participants associated the disgusting images with punishment (a feeling of repulsion). In contrast, both regulation strategies reduced this punishment value by means of two different types of positive suggestions. This effect can also be understood as reinterpretation of emotional meaning (reappraisal). It has repeatedly been demonstrated the cognitive reappraisal recruits the OFC (Ochsner and Gross, 2007), but it is important to note that placebo effects are based on some form of cognitive reframing as well. The participants believed that they took an arousal-reducing pill, which might have influenced the present results.

In conclusion, in this study we investigated neuronal correlates of explicit/implicit emotion regulation. A comparable regulation effect (reduced disgust experience) was observed in both the placebo and reappraisal condition; however, this effect was associated with opposite activation changes in the DLPFC and the insula for each strategy. The conducted connectivity analyses proposed that reappraisal very likely inhibited negative valence assignment (amygdala) to the repulsive images with the help of altered semantic representations (DLPFC). The placebo, on the other hand, reduced the information exchange between the insula and amygdala. This may have made it more difficult to associate the affective experience elicited by the repulsive images with a negative label. The amygdala is responsible for threat detection and for the initiation of protective responses (LeDoux, 2014). The disgusting images signaled a threat (possible disease transmission). However, the placebo suggested: the threat has been conquered; avoidance or defense is not necessary anymore. In line with this interpretation are findings by an eye-tracking study on the effects of a disgust-reducing placebo (Schienle *et al.*, 2016). Participants in this study reduced their visual avoidance of repulsive scenes, if they were convinced they had received an effective disgust-reducing medication; under placebo, the participants increased their number of fixations for disgusting images.

We have to mention the following limitations of our study. We chose abstract neutral images (scrambled disgust images) as control stimuli. Consequently, the neutral condition was qualitatively different from the affective condition. We decided to use this type of control condition, because prior studies had revealed pronounced context effects of disgust. Scenic stimuli (e.g. household articles) which are usually administered as neutral images are rated as highly pleasant when all other pictures are disgusting. Further, we only studied female participants. Therefore, our findings cannot be generalized to men. Finally, for the PPI analysis we specified only those regions as seeds that showed significant activations in the fMRI analysis (e.g. DLPFC). However, the DLPFC lacks direct projections to the amygdala. Future studies should therefore perform a more detailed connectivity analysis which additionally includes causal models.

In summary, our findings underline the importance of viewing psychological functions (disgust experiences) as products of connectivity systems rather than of specific brain areas. Only if such systems are sufficiently understood, they can be altered. This might be of special importance for some mental disorders, which are characterized by excessive and difficult to control disgust feelings (e.g. washing compulsions, blood phobia). The patients might profit from different psychotherapeutic options, such as explicit and implicit regulation of disorder-relevant affective states. Clinical experience shows that many patients have problems to effectively engage in cognitive reappraisal—at least during the early phases of psychotherapy. Placebo treatment might be one way to overcome these initial difficulties. This should be the focus of future studies in the clinical context.

Supplementary data

Supplementary data are available at *SCAN* online.

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Conflict of interest. None declared.

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