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PLACEBO TREATMENT CAN ALTER PRIMARY VISUAL CORTEX ACTIVITY AND CONNECTIVITY

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Abstract—Placebo treatment can alter brain activation in regions implicated in affective processing and cognitive control of emotions. This functional magnetic resonance imaging (fMRI) study investigated whether a placebo can additionally modulate visual cortex activity and connectivity during affective picture perception. The participants underwent a retest design where they were presented with disgusting, fear-eliciting and neutral pictures both with, and without a placebo (inert pill presented with the suggestion that it can reduce disgust symptoms). The placebo provoked a strong decrease in experienced disgust. This was accompanied by a reduced activation of the primary visual cortex, which showed reduced interaction with the amygdala and the insula. Accordingly, placebos are able to affect basic perceptive processes.

Key words: fMRI, placebo, disgust, affective pictures, functional connectivity.

INTRODUCTION

Brain imaging investigations have shown that the viewing of affective, relative to neutral, pictures provokes increased activation of visual cortex areas (e.g., Britton et al., 2006; Sabatinelli et al., 2007). For example, when participants look at disgusting scenes compared to neutral scenes, this not only activates limbic regions, such as the insula, and the amygdala, but several visual areas located in the occipital, parietal and inferior temporal cortex (e.g., Schienle et al., 2002).

Models of visual emotional perception suggest that the amygdala is central for the initiation of increased extrastriate cortex recruitment. Sabatinelli et al. (2007) demonstrated that during affective picture processing, increases of hemodynamic responses in the occipital cortex were preceded by activation changes in the amygdala. This sequence supports the view that information on the emotional significance of stimuli is first identified in the amygdala and then transferred to the visual association cortex. This process serves motivated attention which allows enhanced perceptual processing of salient and survival-relevant visual information in the environment (Bradley et al., 2003).

Besides this bottom-up-regulation, top-down modulations of visual and affective processing systems have been described. For example, amygdala as well as visual cortex activity during affective picture processing can be altered via cognitive control strategies (e.g., Banks et al., 2007; Goldin et al., 2008). Reappraisal (the conscious attempt to view emotional scenes in a detached way) decreased amygdala activation and increased activation in lingual and angular gyri (e.g. Goldin et al., 2008). Also, reappraisal was able to change functional connectivity between prefrontal cognitive control areas, the amygdala and areas involved in visual attention, such as the inferior parietal cortex (Banks et al., 2007).

Whether automatic emotion regulation strategies are also able to modify amygdalar-occipital activity and connectivity has not been studied thus far, and therefore was the goal of the present study. As a method to initiate unconscious emotion regulation, we chose placebo treatment. The most widely studied placebo phenomenon in neuroimaging research is placebo analgesia, where an inert substance (i.e., a pill filled with sugar) is administered with the verbal suggestion that it is a pain medication. According to Wager (2005), a placebo primarily affects expectancy and appraisal, two related processes crucial in determining the subjective pain experience. In the present investigation, we studied if a 'disgust placebo' (an inert pill which was presented to the recipient with the instruction that the substance efficiently reduces disgust symptoms) is able to alter (extra)striate cortex activation during visual emotion elicitation. Moreover, we conducted psychophysiological interaction (PPI) analyses in order to explore functional connectivity between visual cortex areas and brain regions involved in disgust processing (amygdala, insula). We reanalyzed data from a previously published study (Schienle et al., in press), where the administration of the mentioned disgust placebo had provoked a marked decrease in experienced disgust and insula activation during the presentation of disgusting pictures. Interestingly, this placebo had not evoked neural changes during the presentation of fear-relevant pictures, which constituted a second affective condition in the experiment. Thus,

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Abbreviations: DMPFC, dorsomedial prefrontal cortex; fMRI, functional magnetic resonance imaging; FWE, family-wise error; PPI, psychophysiological interaction.

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the explicit verbal suggestion of disgust reduction had induced an emotion-specific change of brain activation.

We now tested the hypothesis that the disgust placebo (a positive expectation concerning disgust relief) is not only able to specifically change activation and connectivity in brain regions implicated in affective processing, but also in primary and secondary visual areas.

EXPERIMENTAL PROCEDURES

Participants

Thirty-four right-handed, healthy women (mean age = 23.9 years, SD = 4.0) participated in this study. All participants had a high school diploma and 91% were students. The sample had been restricted to females as there are significant sex differences in disgust proneness (Schienle et al., 2002). All participants were free from mental disorders, medication, and somatic problems as assured by the Brief Symptom Inventory (Derogatis, 1993). Written informed consent was obtained from all subjects. The study was conducted in accordance with the Declaration of Helsinki and was reviewed by the ethics committee of the Medical University of Graz. None of the women had previously participated in a drug study.

Material

The participants were shown a total of 45 affective pictures from two picture sets (Lang et al., 2008; Schienle et al., 2002) representing the three categories DISGUST (e.g. dirty toilet, rotten corpse, maggots), FEAR (e.g. shark, a man attacking a woman with a knife) and NEUTRAL (e.g. household objects, geometric figures). The stimuli had been matched in image complexity, and color composition. Each scene was presented for 4 s, followed by a variable interstimulus interval (range: 3.5–8 s). The presentation sequence of the stimuli was randomly chosen and repeated once (30 events per condition).

Procedure

All 34 subjects underwent two functional magnetic resonance imaging (fMRI) sessions where they passively viewed the picture set with disgusting, fear-eliciting and neutral scenes. The sessions were separated by 1 week.

In one session (the placebo condition), the participants received a placebo pill (a 1-cm-long silica-filled capsule) prior to the presentation of the pictures. They were told that the pill contains the pulverized bark of the angostura tree (galipea officinalis) which can be found in South America. The native Indians have used this herbal medicine for a long time to treat digestion problems (nausea, diarrhea) and fever. Further, they were informed that a previous investigation using this dietary supplement (without fMRI) had already demonstrated that angostura effectively reduces disgust symptoms, and that the positive effect occurs approximately 15 min after the application. Thus, the cover story suggested a clinical trial of a dietary supplement. The study was conducted at the Medical University of Graz (department of neuroradiology). The experimenter as well as the fMRI staff wore white coats during the conduction of the study in order to enhance the credibility of the cover story.

Subsequent to the fMRI recording, the subjects were presented with three sheets of paper depicting the 15 pictures representing an affective category (DISGUST, FEAR, NEUTRAL). They were asked to rate the intensity of elicited fear and disgust for each category by means of 9-point Likert scales (1 = little; 9 = very intense). Mean judgments were obtained for each of the three picture categories.

In the other session (no-placebo condition), the participants received no capsule and viewed the same pictures. The sequence of the pictures within one session as well as the sequence of the two sessions (placebo, no-placebo) was random. At the end of the investigation, the participants were asked whether they were convinced that they had received angostura or a placebo (yes/no).

fMRI

Data were collected using a 3-T scanner (Siemens Trio, Erlangen, Germany). A total of 385 volumes were acquired using a modified EPI sequence (number of slices: 35, descending, tilted $-25°$ from the AC-PC line; flip angle = 90°, slice thickness: 3 mm, 1 mm gap; matrix: 64 × 64; TE = 30 ms; TR = 2300 ms; FoV: 192; in-plane resolution = 3 × 3 mm). All analyses were conducted using SPM8 (Wellcome Center for Neuroimaging, University College London, UK). Data were slice-time corrected, realigned including unwarping and coregistration, normalized to Montreal Neurological Institute (MNI) space (2-mm isotropic voxel), and smoothed with an 8-mm isotropic Gaussian kernel. Individual conditions were modeled using the canonical hemodynamic response function. Each condition (Disgust/Fear/Neutral) was modeled with a duration of 4 s including the six movement parameters from the realignment step. T-contrasts were created (e.g., Disgust > Neutral) and compared between the placebo and no-placebo condition (random effects analyses for voxel intensities; paired *t*-tests).

We defined the following regions of interest (ROIs) which were taken from the Harvard-Oxford cortical and subcortical structural atlas (Center for Morphometric Analysis, MGH-East, Boston/MA, USA): calcarine fissure, lingual, fusiform, medial, superior, inferior occipital gyrus, and cuneus. These regions had been activated in the no-placebo condition during emotion elicitation (Schienle et al., in press). Statistical maps were thresholded with an uncorrected p of .05 and at least five contiguous voxels. Results were considered significant with a family-wise error (FWE) corrected p-value < .05.

To investigate placebo-specific connectivity, we conducted PPI analyses (Friston et al., 1997) for each participant. PPIs assess the extent to which an experimental factor modulates the connectivity of one