

Brief report

Investigating visual effects of a disgust nocebo with fMRI

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Abstract

There is growing evidence that placebos are able to influence visual perception. A previous functional magnetic resonance imaging study on the processing of disgust images demonstrated that a “disgust placebo” (inert pill administered with the verbal suggestion of an anti-nausea medication) reduced visual cortex activity and connectivity. In the present functional magnetic resonance imaging investigation, visual effects corresponding to a “disgust nocebo” (an odorless substance introduced as an aversive smell that enhances disgust feelings) were examined. Data from 29 females were reanalyzed. They viewed disgusting, fear-eliciting, and neutral images once with and once without the nocebo. In the nocebo condition with disgusting images disgust experienced that significantly increased fusiform gyrus activation, which also showed enhanced coupling with the amygdala and several (extra)striate cortex regions. The nocebo changed the affective value and motivational relevance of the stimuli as well the perception of basic visual features. These findings demonstrate that nocebo-related expectations can have a strong influence on the experience of sensory input.

Keywords

Placebo; nocebo; disgust; visual cortex; functional magnetic resonance imaging; psychophysiological interaction analysis

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1. Introduction

When people look at affective pictures, compared to neutral ones, this not only leads to activation in limbic brain areas, but also involves numerous visual regions located along the ventral and dorsal processing stream [1–4]. The emotional significance of images correlates with enhanced visual system recruitment. Especially scenes related to primary motive states (e.g., viewer-directed threat, food, erotica) are associated with extensive activation of the visual cortex. This reflects ‘motivated attention’, a neuronal mechanism that facilitates fast stimulus detection, which is a prerequisite for adequate action [1, 3, 5].

Previous studies have demonstrated that placebo-induced expectations are able to modulate visual processing [6, 7]. A placebo is a substance or treatment with no active therapeutic effect [8]. In a study by Sterzer et al. [6], subjects viewed an ambiguous visual motion stimulus (random-dot kinematogram perceived as a cylinder rotating in depth despite absence of depth cues). The administration of ‘placebo glasses’ induced a perception to rotate towards the suggested direction. Thus, the placebo influenced motion perception. In another study [7], subjects performed a visual search task in conjunction with olfactory stimulation. Odour administration was combined with either a positive or a negative verbal suggestion regarding performance change. Those subjects given positive information suggesting increased performance demonstrated faster reaction times without reduced detection accuracy. Consequently, the placebo modulated visual attention and exploration. This was also shown in an eye-tracking study by Schienle et al. [9]. The authors demonstrated, that an emotion-specific placebo expectation altered exploratory visual

behavior. Subjects viewed disgusting pictures once with, and once without a ‘disgust placebo’ (an inert pill administered with the suggestion that it would reduce disgust symptoms). Disgust-relevant placebo expectations modulated eye movements. The number of fixations on the disgust pictures significantly increased in the placebo condition. This change might reflect a greater willingness of subjects to view these stimuli after a placebo. In a functional magnetic resonance imaging (fMRI) study, Schienle et al. [4, 10] investigated the underlying neuronal processes of placebo-associated gaze changes. The authors again administered a ‘disgust placebo’ during the presentation of disgusting images. The placebo reduced activation in the insula and several visual cortex regions. Moreover, functional coupling between the striate cortex, the amygdala, and insula decreased. These results imply that a suggestive emotion-specific placebo can evoke substantial change in the visual perception of affective information.

The present study examined whether the opposite phenomenon exists and if a nocebo is able to modulate perceptual processing of affective information. Nocebos generally lead to harmful effects or worsening of symptoms due to negative expectations coupled with an inert substance or a sham treatment [8, 11]. Neuroimaging research has identified a crucial role for the insula, orbitofrontal cortex (OFC), and hippocampus in nocebo responses [8]. These findings were primarily derived from the study of pain processing (i.e. nocebo-related hyperalgesia).

To test nocebo effects in the context of affective processing, Schienle et al. [12] conducted a ‘smell study’ during which subjects were presented with an odorless stimulus (distilled water) together with the verbal suggestion that this fluid had an aversive odor that enhanced feelings of disgust. The nocebo was presented while subjects

viewed disgusting, fear-inducing, and neutral images. This nocebo procedure intensified experienced disgust during the viewing of disgusting images and increased orbitofrontal cortex (OFC) activation. In addition, the OFC showed increased functional connectivity with areas involved in interoception (insula), autobiographical memories (hippocampus), and odor imagery (piriform cortex) during nocebo administration. Since visual cortex regions had not been selected as regions of interest, in the present reanalysis all visual masks provided by the SPM anatomy toolbox [13] were chosen and analyzed regarding increased nocebo-related activation. Moreover, it was investigated whether the ‘disgust nocebo’ would enhance connectivity of the selected visual cortex regions with brain areas involved in affective value assignment (i.e. amygdala, OFC).

2. Methods

2.1. Data set

Data from 29 right-handed, non-smoking, healthy females was reanalysed (mean age: 22.31 years, SD = 2.95). Only females were studied because of significant sex differences in disgust proneness [14]. Subjects had originally been presented with an odorless fluid (distilled water) together with the verbal suggestion that it smelled disgusting (‘like sour milk, rancid butter, vomit’). The original experiment had a repeated-measures design with two conditions: a nocebo condition and a control condition (without nocebo). During both conditions subjects viewed images from the categories Disgust (e.g., rotten food, worms), Fear (e.g., pointed gun, knife attack), and Neutral (pixelated disgust and fear pictures). Each category consisted of 30 pictures. Images were selected from the International Affective Picture System [15] and a validated set of the authors [16]. The study had an event-related design; each picture was presented for four seconds in a pseudorandomized order to avoid the successive presentation of more than two pictures from the same category. Inter-presentation interval varied between 3.5 and 8 seconds. Subjects were instructed to look at the images and to allow all affective responses. Each image was rated according to the level of disgust, fear, and arousal experienced according to a nine-point-Likert scale (9 = very intense). In the control condition, experienced disgust (mean, standard error) was significantly higher for Disgust images (6.72, 0.28) than Fear images (2.55, 0.27) and Neutral images (1.52, 0.26; $p < 0.001$). Fear scenes elicited more fear (5.62, 0.36) than Disgust scenes (2.69, 0.31) and Neutral scenes (1.17, 0.09; $p < 0.001$). The categories Disgust (4.93, 0.33) and Fear (4.52, 0.34) did not differ in terms of experienced arousal ($p = 0.24$) but both received higher arousal ratings than Neutral images (2.00, 0.26; $p < 0.001$).

The nocebo provoked a significant increase in disgust ratings for the Disgust pictures (Nocebo: 7.38, 0.25; $t(28) = 3.77$, $p = 0.001$), but not for the images of the other two categories (both $p > 0.53$). For more details see Schienle et al. [12].

2.2. fMRI recording and analysis

Functional runs were acquired with a 3T scanner (Skyra, Siemens, Erlangen, Germany) using an echoplanar imaging protocol (35 slices, descending, flip angle 90°, slice thickness: 3 mm; matrix: 64 × 64 mm; TE = 30 ms; TR = 2290 ms; FoV: 192 mm; in-plane resolution 3 × 3 × 3 mm). All analyses were conducted using SPM12 (Wellcome Department of Cognitive Neurology, London). Three volumes from the beginning of the time series were discarded to account for saturation effects.

First, acquisition timing was accounted for in a slice timing step followed by motion-correction in the realign and dewarp step. Afterwards individual T1 images were coregistered to their functional data and were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid. To increase intersubject alignment, individual images of GM and WM were registered by a ‘Fast Diffeomorphic Registration Algorithm’ (DARTEL) to an IXI550 template (MNI-space) implemented by an VBM 8 toolbox. Resulting individual DARTEL flow fields were used to normalize slice-timed, realigned, and dewarped functional images to MNI-space (3 mm isotropic voxel). Finally, for smoothing, a Gaussian kernel of 6 mm was applied. Vectors were compiled for each event of interest (picture onset) and were entered into a design matrix to model event-related responses with a canonical hemodynamic response function. Data were high pass filtered (128 s). As the realign and dewarp step already models the B0**motion* interaction, the motion parameters were not included as regressors in the first level of analysis. Temporal sphericity was controlled by an AR(1) process with consecutive data prewhitening.

For the fMRI data, planned t-contrasts were computed (Disgust > Neutral; Fear > Neutral) to compare the two conditions (Nocebo, Control). Region of interest (ROI) analyses were conducted for the visual masks provided by the SPM anatomy toolbox [13]. These were the dorsal/ventral extrastriate cortex (V3/V4), the fusiform gyrus, the lateral occipital cortex (V3/V4), the pre/striate cortex (V1/V2), and the middle temporal visual area (V5).

Psychophysiological interaction (PPI) analyses [17] were also conducted to investigate nocebo-related connectivity (Nocebo > Control) for the emotion contrasts (Disgust > Neutral; Fear > Neutral). Those visual brain regions that showed significant nocebo-related activation were defined as seeds. Amygdala, insula, and the OFC were chosen as ROIs because of their involvement in affect processing and nocebo responsivity [4, 8, 10]. For the fMRI and PPI analysis, a height threshold of $p < 0.005$ (uncorrected) and an extent threshold of 10 voxels were applied. Reported results are based on

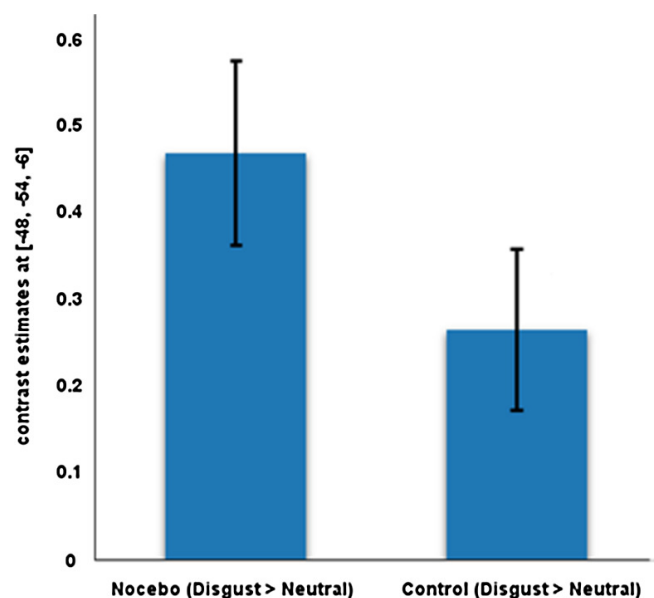


Fig. 1. Contrast estimates for the fusiform gyrus.

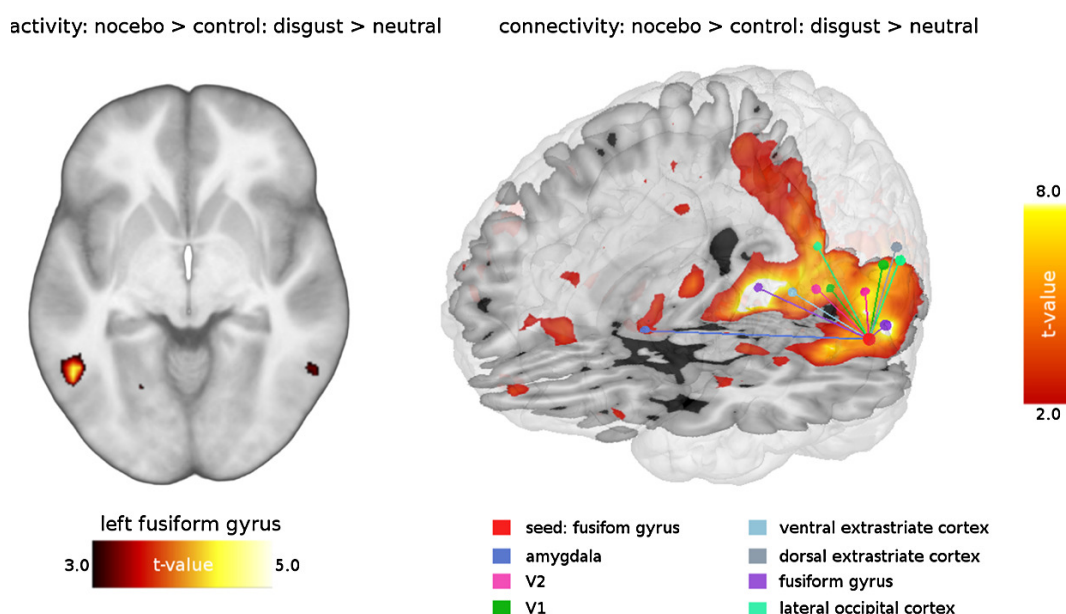


Fig. 2. Nocebo-related activity and connectivity of fusiform gyrus during disgust elicitation.

family-wise error (FWE) correction for voxel intensity tests (FWE $p < 0.05$; small volume correction).

3. Results

Two experimental conditions (Nocebo, Control) were associated with activation in the predefined visual ROIs for both contrasts (Disgust > Neutral, Fear > Neutral; see Table 1).

Relative to the control condition, the nocebo administration was associated with activation in the fusiform gyrus (contrast: Disgust > Neutral; MNI coordinates: $-48, -54, -6$; $t = 4.20$, $p(\text{FWE}) = 0.039$, cluster size = 181). Contrast estimates for the fusiform gyrus are given in Fig. 1.

PPI analysis for the contrast Disgust > Neutral revealed enhanced coupling of the fusiform gyrus with the amygdala and several visual areas (V1, V2, V3, V4; see Table 2 and Fig. 2). For the Fear condition (Fear > Neutral) the activity/connectivity analyses showed no statistically significant results.

4. Discussion

A “disgust nocebo” (distilled water administered with the verbal suggestion that this fluid has an aversive odor which enhances disgust feelings) was able to change visual cortex activity and connectivity. During the viewing of disgust images, the nocebo enhanced experienced disgust and fusiform gyrus activation. The fusiform gyrus is the largest macro-anatomical structure within the ventral temporal cortex; its subregions are involved in higher-order visual processes and contribute to the identification of faces, objects, words and colors, as well as their categorization and differentiation [18]. The categorization function of the fusiform gyrus extends to the affective domain. For example, images related to primary motive states such as visual food cues consistently provoke fusiform gyrus activation relative to non-food items with comparable visual features [19]. Moreover, in a previous fMRI investigation using the same disgust picture set as in the current study, the contrast Disgust > Neutral was

associated with fusiform gyrus activation, which had been significant even in the whole-brain analysis [10]. These findings suggest that categorization based on the motivational value of stimuli might be another function of the fusiform gyrus. Following this interpretation, the nocebo might have enhanced motivated attention for the disgust images [1].

The PPI approach demonstrated that the nocebo provoked enhanced coupling between the fusiform gyrus (seed region) and the primary visual cortex (V1). As the striate cortex is involved in the decoding of basic stimulus features, these data imply that subjects perceived Disgust images differently in the nocebo relative to the control condition. Other recent discoveries concerning V1 activation refer to attentional modulation effects [20]. Attended stimuli trigger increased response magnitudes in V1. Thus, the PPI findings also point to an attentional amplification of Disgust perception via the nocebo.

The fusiform gyrus also showed enhanced interactions with parts of the visual associative cortex (V2, V3, V4). All of the mentioned regions have higher-order visual functions, such as visual discrimination, object recognition memory, or perceptual organization [21]. Consequently, the nocebo influenced visual integration processes.

Finally, the nocebo also increased the coupling between the fusiform gyrus and the amygdala. There are strong reciprocal projections between these two brain areas, and fMRI studies have provided evidence for the modulation of fusiform activity by the amygdala [5, 22]. This modulation reflects increased attention to emotional relative to non-emotional events. The amygdala plays a central role in the processing of the motivational relevance of information and affective attention [5]. Therefore, the present finding suggests that the nocebo changed the affective meaning of the pictures, which was also reflected by the enhanced disgust ratings. Interestingly, in a previous fMRI study on a disgust placebo, the opposite pattern was observed [4]. A pill administered with the suggestion of an anti-disgust medication while viewing disgusting scenes reduced visual cortex activity and connectivity with the amygdala.

Table 1. Results of the planned *t*-contrasts for the control and the placebo condition

Region	H	<i>x</i>	<i>y</i>	<i>z</i>	<i>t</i>	<i>p</i> (FWE)	Cluster size
<i>Control: Disgust > Neutral</i>							
Striate cortex	L	-18	-84	15	6.16	<0.001	12
Striate cortex	R	18	-90	15	6.50	<0.001	230
Prestriate cortex	R	12	-60	9	4.86	0.010	125
Middle temporal	L	-45	-81	0	13.86	<0.001	56
Middle temporal	R	48	-75	3	12.08	<0.001	43
Dorsal extrastriate	L	-24	-93	21	11.22	<0.001	98
Dorsal extrastriate	R	21	-90	21	5.90	<0.001	56
Fusiform gyrus	L	-33	-48	-18	16.01	<0.001	631
Fusiform gyrus	R	36	-60	-12	18.17	<0.001	502
Lateral occipital	L	-42	-81	-6	19.53	<0.001	340
Lateral occipital	R	45	-72	-6	15.05	<0.001	246
Ventral extrastriate	L	-24	-69	-9	13.78	<0.001	256
Ventral extrastriate	R	30	-72	-6	13.39	<0.001	264
<i>Nocebo: Disgust > Neutral</i>							
Striate cortex	L	-18	-84	15	8.06	<0.001	221
Striate cortex	R	21	-84	15	5.90	0.001	273
Prestriate cortex	L	-21	-63	6	5.40	0.002	143
Prestriate cortex	R	21	-54	3	5.32	0.003	164
Middle temporal	L	-42	-81	0	13.37	<0.001	56
Middle temporal	R	48	-72	0	13.16	<0.001	43
Dorsal extrastriate	L	-27	-93	15	9.96	<0.001	103
Dorsal extrastriate	R	21	-90	21	5.60	0.001	43
Fusiform gyrus	L	-33	-48	-15	18.06	<0.001	644
Fusiform gyrus	R	36	-57	-12	15.10	<0.001	505
Lateral occipital	L	-42	-84	-3	16.98	<0.001	336
Lateral occipital	R	51	-69	-6	14.62	<0.001	244
Ventral extrastriate	L	-33	-84	0	15.70	<0.001	308
Ventral extrastriate	R	39	-75	-9	10.38	<0.001	272
<i>Control: Disgust > Neutral</i>							
Striate cortex	L	-18	-84	15	6.91	<0.001	37
Striate cortex	R	15	-90	18	7.16	<0.001	272
Prestriate cortex	L	-12	-57	3	5.54	0.001	78
Prestriate cortex	R	21	-57	12	7.25	<0.001	238
Middle temporal	L	-48	-75	6	19.45	<0.001	56
Middle temporal	R	48	-72	0	16.64	<0.001	43
Dorsal extrastriate	L	-21	-93	21	10.88	<0.001	138
Dorsal extrastriate	R	21	-90	21	7.96	<0.001	121
Fusiform gyrus	L	-42	-69	-18	17.66	<0.001	620
Fusiform gyrus	R	48	-72	-3	16.64	<0.001	496
Lateral occipital	L	-48	-75	6	19.45	<0.001	319
Lateral occipital	R	48	-72	-3	16.64	<0.001	238
Ventral extrastriate	L	-33	-84	0	12.70	<0.001	184
Ventral extrastriate	R	42	-78	-9	12.20	<0.001	222
<i>Nocebo: Fear > Neutral</i>							
Striate cortex	L	-18	-84	15	7.64	<0.001	25
Striate cortex	R	24	-57	9	5.99	0.001	262
Prestriate cortex	L	-18	-54	3	5.02	0.004	97
Prestriate cortex	R	21	-57	12	6.68	<0.001	211
Middle temporal	L	-45	-75	9	17.78	<0.001	56
Middle temporal	R	48	-69	12	17.83	<0.001	43
Dorsal extrastriate	L	-21	-90	18	8.90	<0.001	122
Dorsal extrastriate	R	21	-90	24	5.90	<0.001	104
Fusiform gyrus	L	-39	-60	-15	14.54	<0.001	629
Fusiform gyrus	R	48	-72	0	17.49	<0.001	500
Lateral occipital	L	-45	-75	9	17.78	<0.001	311
Lateral occipital	R	51	-72	0	17.55	<0.001	232
Ventral extrastriate	L	-33	-81	-3	11.40	<0.001	182
Ventral extrastriate	R	39	-78	-6	11.12	<0.001	212

H: hemisphere (L: left; R: right); *x*, *y*, *z*: MNI coordinates; *p*(FWE): *p*-value (corrected for family-wise error); *t*: *t*-value; cluster size: number of voxels in associated cluster.

Table 2. Connectivity between the left fusiform gyrus (seed) and regions of interest for the contrast Nocebo > Control: Disgust > Neutral

Region of interest	H	x	y	z	t	p(FWE)	Cluster size
Amygdala	R	24	-3	-18	3.32	0.046	18
Striate cortex (V1)	L	-12	-96	6	8.18	< 0.001	402
Striate cortex (V1)	R	9	-87	-9	7.02	< 0.001	593
Prestriate cortex (V2)	L	-9	-90	-6	7.71	<0.001	247
Prestriate cortex (V2)	R	12	-81	-9	8.17	<0.001	428
Dorsal extrastriate cortex (V3/V4)	L	-18	-96	15	5.87	<0.001	138
Fusiform gyrus	L	-30	-81	-12	9.64	<0.001	350
Fusiform gyrus	R	27	-60	-9	10.52	<0.001	378
Lateral occipital cortex (V4)	L	-18	-99	9	5.61	0.001	182
Lateral occipital cortex (V4)	R	27	-93	6	6.24	<0.001	95
Ventral extrastriate cortex (V3/V4)	R	21	-75	-12	9.46	<0.001	399

H: hemisphere (L: left; R: right); x, y, z: MNI coordinates; p(FWE): *p*-value (corrected for family-wise error); *t*: *t*-value; cluster size: number of voxels in a cluster. Bold: significant on the whole brain level.

The following limitations of investigation have to be mentioned. Only females were investigated, due to their greater disgust reactivity [14]. This reduced inter-gender variance but consequently, findings cannot be generalized to males. Moreover, the PPI findings indicated enhanced fusiform gyrus coupling in the nocebo condition with several other regions of interest. To determine the direction of influence (inhibitory vs. excitatory) other methods, such as direct causal modeling are required.

In summary, the current analysis demonstrated that nocebo-related expectations can have a strong influence on the experience of sensory input. It was shown for the first time that disgust-related nocebo suggestions modulated visual cortex activity and connectivity during visual disgust elicitation. The brain regions affected by the nocebo included secondary but also primary visual areas. This implies that not only the affective value and motivational relevance of the stimuli were altered but also the perception of basic visual features. For future studies it would be of interest to follow-up on the idea that ‘believing is seeing’ [6] and to test whether a placebo or nocebo might be able to change V1 functions such as perception of visual orientations, spatial frequencies, or colors.

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Conflict of Interest

All authors declare no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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