

Modulation of anticipatory emotion and perception processing by cognitive control

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Strategies of cognitive control are helpful in reducing anxiety experienced during anticipation of unpleasant or potentially unpleasant events. We investigated the associated cerebral information processing underlying the use of a specific cognitive control strategy during the anticipation of affect-laden events. Using functional magnetic resonance imaging, we examined differential brain activity during anticipation of events of unknown and negative emotional valence in a group of eighteen healthy subjects that used a cognitive control strategy, similar to “reality checking” as used in psychotherapy, compared with a group of sixteen subjects that did not exert cognitive control. While expecting unpleasant stimuli, the “cognitive control” group showed higher activity in left medial and dorsolateral prefrontal cortex areas but reduced activity in the left extended amygdala, pulvinar/lateral geniculate nucleus and fusiform gyrus. Cognitive control during the “unknown” expectation was associated with reduced amygdalar activity as well and further with reduced insular and thalamic activity. The amygdala activations associated with cognitive control correlated negatively with the reappraisal scores of an emotion regulation questionnaire. The results indicate that cognitive control of particularly unpleasant emotions is associated with elevated prefrontal cortex activity that may serve to attenuate emotion processing in for instance amygdala, and, notably, in perception related brain areas.

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Introduction

In everyday life we are often faced with approaching events that we know to be unpleasant or expect to be potentially unpleasant. Prior to their actual occurrence we may experience and have to cope with the uneasy feeling or even anxiety associated with the anti-

icipation of such events. In coping effectively, we may apply cognitive strategies to control the concomitant emotions. An efficient method for cognitive emotion regulation is the strategy of “reappraisal” (Gross and John, 2003). Cognitive reappraisal is defined as a form of an active cognitive process that involves construing an emotion-eliciting situation in a way that changes its emotional impact (Lazarus and Alfert, 1964). It is considered an antecedent strategy apt to successfully reduce the behavioral and experiential component of negative future emotions. A specific kind of reappraisal that is used as a psychotherapeutic anxiety management strategy is the “reality checking”. Performing a “reality check” entails a cognitive shift from the awareness of the unpleasant emotional impact of a situation to a realistic cognitive evaluation of the objective context of the actual situation during exposure, but not to anticipate future and possibly unrealistic scenarios. Thus, as the reappraisal technique used for instance by Ochsner et al. (2002) consisted of directly reappraising a presented visual stimulus, “reality checking” consists of reappraising the meaning of an actual situation for instance while expecting an emotional event. This technique of self-regulation or cognitive control helps patients to learn that they can successfully cope with feared situations. It is therefore commonly used in cognitive-behavioral therapies in the treatment of for example phobic anxiety disorders with exposure-response prevention in order to reduce avoidance behaviors (e.g., Hand, 2000; Otto et al., 2004).

Concerning the associated neural correlates, models of top-down cognitive control of emotion processing areas have been proposed (Mathews and MacLeod, 2005). These models draw attention to the involvement of prefrontal areas in modulating for example amygdala activity (Ochsner et al., 2002; Ochsner, 2001; Ochsner et al., 2004; Roffman et al., 2005; Harenski and Hamann, 2006; Kalisch et al., 2006; Ohira et al., 2006; Urry et al., 2006). They are supported by animal studies that demonstrate the inhibiting influence of medial prefrontal projections on centromedial amygdala efferents to basolateral amygdala, which in turn modulates output to

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brainstem areas (Quirk et al., 2003). In human neuroimaging studies, reappraisal of negative emotion was found to activate dorsal prefrontal cortex (PFC) and anterior cingulate cortex (ACC) systems that support the selection and application of reappraisal strategies. Further, reappraisal (Ochsner et al., 2002, 2004; Phan et al., 2005; Ochsner and Gross, 2005) or other emotion regulation strategies (Beauregard et al., 2001; Schaefer et al., 2002; Levesque et al., 2003) were found to modulate activity in emotion processing systems such as the amygdala or insula. These studies investigated the effect of cognitive control upon concomitant *perception* of unpleasant stimuli. However, in depression and anxiety disorders, a major feature is the *anticipation* of the future to become negative as expressed for instance by the cognitive triad of Beck (Beck, 1967). To a certain extent one may therefore argue that central nervous information processing during anticipation of known negative or potentially negative events may show similarities with negative attitudes towards the future in anxiety and depression. Generally, the involvement of distinct brain areas as PFC regions, ACC, insula, amygdala and others during the expectation of unpleasant stimuli is well documented (e.g., Nitschke et al., 2006; Phelps et al., 2001; Ploghaus et al., 1999; Simmons et al., 2004; Ueda et al., 2003; Wager et al., 2004). In a previous study (Herwig et al., 2007), we investigated brain activity during the expectation of emotional events with known positive, negative and neutral valence, and of events with unknown valence that were either negative or positive. However, in the light of the treatment of anxiety disorders or depression, not only the regions involved but also their responses to interventions like psychotherapeutic techniques are of particular interest. In order to investigate the issue of brain activation associated with the cognitive technique of “reality checking”, we tested with the same task a group of subjects while they exerted a corresponding cognitive control strategy during anticipation of negative and “unknown” stimuli. The results were compared with the data of the first group. According to the abovementioned literature (Ochsner et al., 2002; Ochsner, 2001; Roffman et al., 2005; Beauregard et al., 2001; Levesque et al., 2003; Phan et al., 2005; Schaefer et al., 2002; Mathews and MacLeod, 2005; Harenski and Hamann, 2006; Kalisch et al., 2006; Ohira et al., 2006; Urry et al., 2006), we hypothesized an elevated activity in prefrontal cortex areas and decreased activity in emotion processing areas as the amygdala in the group exerting cognitive control compared to the basic group.

Materials and methods

Subjects

Thirty-four healthy subjects (ages 23–36, all right-handed, 18 female) without any history of neurological or psychiatric illness and without medication participated in this study. All participants gave written informed consent. The local ethics committee approved the study. Sixteen subjects participated in the trial without cognitive control (“basic group”), an analysis of which has been reported recently (Herwig et al., 2007). Eighteen other subjects were included in the group studied with performing cognitive control (“cognitive control group”).

Experimental design

While being scanned with fMRI, the subjects performed a task comprising 56 trials in which they expected and were presented

emotional pictures (Fig. 1). The trials comprised two main conditions: “known” or “unknown”. For each trial under the “known” condition a small cue was presented that depicted either a smiling “U” (“pleasant”), a non-smiling “∩” (“negative” or “unpleasant”) or a neutral symbol “–” and indicated the emotional valence of the pictures presented after a delay period. In the “unknown condition”, “|”, either pleasant or unpleasant pictures appeared randomly. The cues were of 1/40 of screen height and the subsequent pictures filled the screen. The highly abstract and graphically comparable cues were intuitively understandable, and no prominent working memory component had to be used to establish their meaning. Further, no motor reaction was required, the preparation and exertion of which may have interfered with the emotional anticipation. The cues were presented for 1000 ms followed by an anticipation period of a further 6920 ms (cue and anticipation: 4 TRs), during which a blank screen with a small fixation point was shown. Subsequently, pictures of the International Affective Picture System (IAPS, Peter Lang, Miami, USA; Lang, 1995) of either pleasant, unpleasant or neutral content

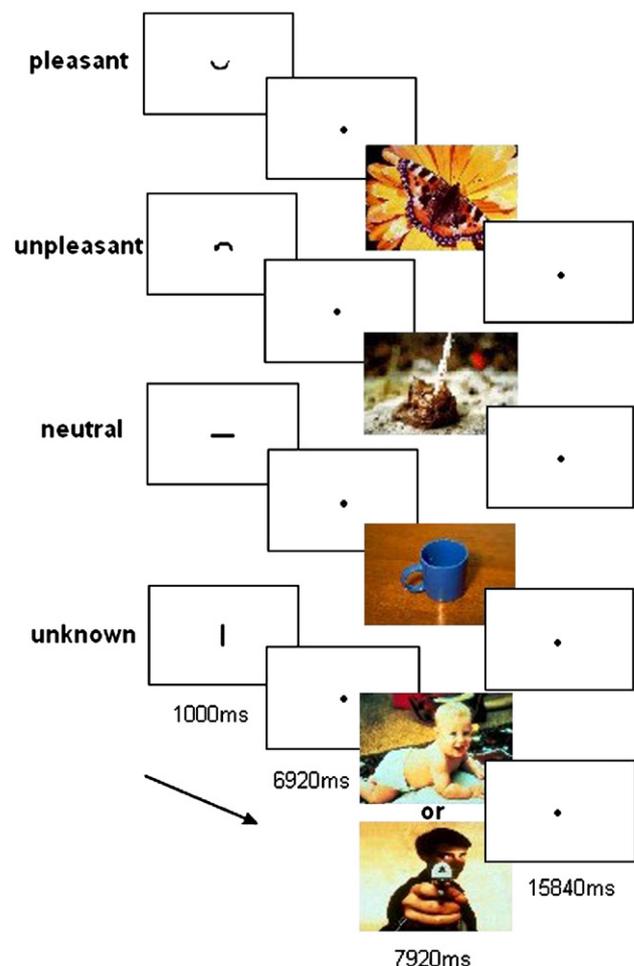


Fig. 1. Experimental task. The four conditions with the respective cues and the durations are presented. The cues, presented for 1000 ms, indicated the valence of the ensuing picture which appeared after a delay of further 6920 ms: “U” prior to a “pleasant” picture, “∩” prior to an “unpleasant” picture, “–” prior to a “neutral” picture, “|” prior to a picture of “unknown” valence, that is, of either pleasant or unpleasant content. In the figure, the cues are relatively enlarged for presentation reasons. In the experiment they were of about 1/40 of screen height.

were presented for 7920 ms (4 TRs), followed by a baseline of 15840 ms (8 TRs) to allow the BOLD signal to level off before a new trial started. Altogether, 56 pre-cued pictures were shown, 14 for each of the conditions known positive (ps), negative (ng) and neutral (nt) valence and unknown (uk, comprising 7 ps and 7 ng) valence. The trials and correspondingly the different conditions appeared in a randomized order. The stimuli were matched for equal difference in the valence rating from neutral (IAPS picture rating; Lang, 1995; mean ps 2.53, mean ng 2.20, *t*-tests for continuous variables: $p=0.14$), for complexity (two or more categories as faces and scenery; ps $n=19$ of 21 ps pictures in total, ng $n=17/21$; Chi square tests for categorical variables: $p=0.22$) and contents (sums more than the total of each 21 ps and ng pictures because of complexity) of faces (ps $n=11$, ng $n=11$; $p=1.0$), scenery (ps $n=13$, ng $n=14$; $p=0.61$) and food and nature (ps $n=8$, ng $n=6$; $p=0.74$). With priority to the matching of valence, content and complexity, arousal was matched by selecting positive and negative pictures with descriptively comparable IAPS arousal ratings (IAPS picture rating: ng mean 5.71, mean IAPS standard deviation 2.22; ps mean 4.86, mean IAPS standard deviation 2.36). However, the samples differ statistically concerning this measure ($p<0.01$). This resulted as a consequence from the effort on a good matching of valence, content and complexity on the one hand, and facing the fact that negative pictures are commonly more arousing than positive ones, despite comparable differences of valence values from neutral. This hard-to-avoid issue was not considered a problem because we analyzed the *expectation* period, and because the fMRI contrast analyses were based on the “negative” and the “unknown” condition versus neutral, not on the “positive” condition. After the scanning, the presented pictures were rated for valence by the subjects of the “basic group” after the scanning on a 9-step visual analogue scale with 1 being most negative, 5 being neutral and 9 being most positive. Both positive and negative valence ratings were equally different from the neutral ratings: The mean ratings (and standard deviations) for the negative pictures over all subjects were 2.96 (1.35), for the neutral pictures 5.10 (0.67) and for the positive pictures 7.20 (1.25). The valence differences of the negative and the positive pictures from neutral were similar ($p=0.87$). The task was programmed with Presentation™ (Neurobehavioral Systems, USA).

In the “basic group”, subjects were simply instructed to expect the emotional stimuli after the cue and to be aware of the emotional valence indicated and to subsequently look at the following picture. The subjects of the “cognitive control group” were instructed to perform “reality checking” derived as a standard intervention from cognitive-behavioral therapy (Hand, 2000; Otto et al., 2004) during the unpleasant and unknown expectation conditions, not during the pleasant and neutral expectation conditions, in order to reduce anticipatory emotional arousal after cue presentation: They were instructed to repeatedly evaluate the realistic context of their actual situation by, e.g., thinking: “I am lying in a scanner”, “They will show me a picture, this is part of the study”, while waiting during the anticipation period for the emotional picture. Both groups performed training sessions with examples of their respective tasks prior to the experiment in the scanner. After scanning, both groups were asked in an unstructured non-quantitative interview about their experience with the task and how they were able to perform the task. The “cognitive control group” was further asked explicitly about the subjective ability to perform the reality checking.

fMRI acquisition

Imaging was performed with a 1.5-T Siemens Sonata whole-body scanner (Erlangen, Germany) equipped with a head coil. Initially, for each subject three-dimensional T1*-weighted anatomical volumes were acquired (TR/TE 1880/3.22 ms; matrix size 256×256 ; slice thickness 1 mm) for later coregistration with the fMRI. T2*-weighted functional MR images were obtained using echoplanar imaging in an axial orientation. Image size was 64×64 pixels, with a field of view of 220 mm, flip angle was 90° . One volume covering the whole brain consisted of 22 slices. Slice thickness was 4 mm with 1 mm gap resulting in a voxel size of $3.4 \times 3.4 \times 5$ mm. Volumes were obtained every 1980 ms (TE 40 ms), 16 volumes per scanning session and altogether 908 volumes. The subjects watched the stimuli in a mirror attached to the head coil and directed to a screen onto which the stimuli were projected with a video beamer.

fMRI data analysis and statistics

fMRI data were analyzed using BrainVoyager™ QX 1.8 (Brain Innovation, Maastricht, The Netherlands). The first four images of each functional scan were discarded to allow for T2* equilibration effects. Preprocessing of the functional scans included motion correction, slice scan time correction, high frequency temporal filtering and removal of linear trends. Functional images were superimposed on the 2D anatomical images and incorporated into 3D data sets. The individual 3D data sets were then transformed into Talairach and Tournoux space (Talairach and Tournoux, 1988) resulting in a voxel size of $3 \times 3 \times 3$ mm and then spatially smoothed with an 8-mm Gaussian kernel for subsequent group analysis. Eight predictors, defined to represent the anticipation conditions (negative, pleasant, neutral, unknown) and the presentation conditions (negative, pleasant, neutral, ex ante unknown—either pleasant or unpleasant) were used to build the design matrix of the experiment. Expectation period and picture presentation periods were modeled as epochs using the standard two-gamma hemodynamic response function (HRF; peak after 5 s, undershoot peak 15 s) provided by BrainVoyager.

The fMRI data analysis based on the general linear model comprised the following steps: First, fixed effects analyses were calculated separately for each subject for the three contrasts comparing the emotion expectation conditions “negative versus neutral”, “positive versus neutral” and “unknown versus neutral” and resulting in summary images. We focused on the contrasts of the emotion expectation conditions versus the “neutral” condition in order to reveal areas selectively involved in emotion processing and not just in expectation of a visual stimulus. These summary images were subjected to second level random effects analyses (rfx), separately for both groups, with and without cognitive control. For these random effects analyses we set a threshold of $p<0.005$ and used a cluster threshold of 135 voxels of $1 \times 1 \times 1$ mm as provided by BrainVoyager corresponding to 5 voxels \hat{a} $3 \times 3 \times 3$ mm. These thresholds were chosen because most studies in this field of affective neuroscience have used statistical thresholds of similar sizes in order to avoid type-2 errors (e.g., Phelps et al., 2001; Phan et al., 2005; Wittmann et al., 2005). The application of more lenient thresholds in this research field is justified because the hemodynamic responses in the emotional network are weaker than in perception and motor studies due to methodological constraints.

The next step addressed our main question and consisted of random effects group comparisons of the “basic” and the “cognitive

Table 1
Demographic and psychometric data of the subjects included in the analysis

	Basic	Cognitive control	
Age, mean/range	27.8/23–36	28.9/21–37	n.s.
Gender, <i>n</i> f/m	8/6	9/5	n.s.
SDS, mean/SD	35.4/6.4	33.1/5.1	n.s.
STAI, mean/SD	30.1/4.2	27.2/6.3	n.s.
EPI neur, mean/SD	13.6/3.4	11.7/3.4	n.s.
EPI extra, mean/SD	4.9/2.7	5.1/2.9	n.s.

Abbreviations: SDS, Self-Rating Depression Scale; STAI, State–Trait Anxiety Inventory; EPI, Eysenck Personality Inventory; SD, standard deviation, n.s., difference not significant.

control” group of brain activity related to the expectation period. This comparison was performed in order to evaluate which regions exert different activity in both groups with respect to the cognitive control related contrasts “negative versus neutral” and “unknown versus neutral”. Analyzing the contrasts emotion condition versus neutral within each group and comparing these between the groups made results just due to different general activation levels between the groups unlikely. Further, we tested the group comparison “expectation pleasant versus neutral” with the hypothesis that no relevant differences should be prominent. The statistical threshold for reporting results was also set to the level $p < 0.005$ uncorrected and a cluster threshold of 135 mm³ voxel. The results were cross-validated by considering that regions that complied with the regions derived from the prior single group contrast analysis within both groups (also consider Herwig et al., 2007). Results due to a substantial deactivation (more than 4 volumes with a negative signal change of more than -0.05% in the expectation and presentation periods) during the analyzed emotion conditions were not reported because in those cases the difference between the conditions could not be attributed clearly to a positive signal change of one condition but alternatively to the observed negative signal change of the other condition. Thereby, we avoided interpretational problems and reporting misleading results (Wade, 2002; Shmuel et al., 2002). The identification of the anatomical regions was based on the Talairach atlas (Talairach and Tournoux, 1988).

An analysis of the presentation period was out of the scope of this study and was therefore performed on an explorative basis only, not presented here.

Questionnaires and correlation statistics

The subjects completed handedness questionnaires (Annett, 1967; Bryden, 1977; German versions), self-ratings of depressive-ness (Self-Rating Depression Scale, SDS; Zung, 1965; German version) and anxiety (State–Trait Anxiety Inventory, STAI-G; Kendall et al., 1976; German version) and completed personality questionnaires measuring neuroticism and extraversion (Eysenck Personality Inventory, EPI; Eysenck and Eysenck, 1964; Eysenck and Eysenck, 1971). To evaluate emotion regulation strategies, the group exerting cognitive control completed the Emotion Regulation Questionnaire (ERQ; Gross and John, 2003; German translation).

Considering the finding of a negative correlation between prefrontal and amygdala activation beta weights during reappraisal of negative stimuli (Ochsner et al., 2002), we performed Pearson’s correlations (one-tailed) of the amygdala activity beta weights with the prefrontal activations (hypothesis: negative correlation). Further, we analyzed correlations between the amygdala activity and the

other activated subcortical areas for the “negative” and the “unknown” condition in order to address connectivity (hypothesis: positive correlations).

In order to investigate whether activation differences between the basic group and the cognitive control group could be brought into association with the use of “reappraisal” as a strategy of emotion regulation as has been shown for depressed patients (Abler et al., 2007), we calculated Pearson’s correlations (one-tailed, hypotheses: prefrontal areas positive correlation with ERQ, subcortical areas negative correlation with ERQ) between the individual ERQ “reappraisal” score results and the individual beta weights (mean from all voxels of the respective activated cluster of the random effects analysis) in those regions showing a difference between the groups.

Results

Demographic data

Data were obtained from altogether 34 healthy subjects. 16 subjects participated in the basic fMRI experiment, 14 were included in the analysis (8 female, ages 23–36 years; Herwig et al.,

Table 2
fMRI-Analysis of emotion expectation contrasts

Anatomic regions	Brodmann area	Voxel mm ³	Talairach coordinates			<i>t</i> -max
			<i>x</i>	<i>y</i>	<i>z</i>	
<i>(a) Expectation negative > neutral, rfx p < 0.005</i>						
Ant. insula/inf. frontal gyrus R	13/45	3420	39	20	2	7.3
Ant. insula/inf. frontal gyrus L	13/45	3299	−34	−9	0	5.7
Medial frontal cortex L	8	7097	2	8	51	7.5
Ant./medial cingulate gyrus blt.	24/32	1782	−4	18	29	5.4
DLPFC L	9/46	1299	−41	8	30	5.7
Ant.thal./BedNST./ncl. caud. R		1869	13	1	10	7.0
Ant.thal./BedNST./ncl. caud. L		1796	−8	−3	10	6.0
Med. thalamus L > R		950	−5	−17	9	4.9
Upper brainstem/ncl. ruber R		730	8	−22	−9	6.9
Occipital cortex L	19	533	−53	−55	21	5.5
			−48	−53	−3	
<i>(b) Expectation unknown > neutral, rfx p < 0.005</i>						
Ant. insula/inf. frontal gyrus R	13/45	523	42	20	1	4.6
Ant. insula/inf. frontal gyrus L	13/45	243	−39	16	4	4.4
Medial frontal cortex R	8/9	387	3	9	57	4.5
Upper brainstem/coll. sup.		935	−3	−27	−1	8.1
<i>(c) Expectation positive > neutral, rfx p < 0.005</i>						
Anterior cingulate gyrus	24	297	−4	46	10	4.2
Ant./medial cingulate gyrus R.	24/32	1423	3	4	58	5.7
Ant.thal./BedNST./ncl. caud. R		544	9	4	14	5.3
Septum/ant. thalamus		368	−1	−10	14	6.2
Occipital cortex R > L	19/37	1024	42	−64	1	5.2

fMRI analysis of emotion expectation in the cognitive control group. Activated regions according to the random effects analyses (rfx) of the contrasts: (a) expectation negative versus neutral, (b) expectation positive versus neutral, (c) expectation unknown versus neutral. Indicated are the amount of voxels in mm³, the Talairach coordinates (*x*, *y*, *z*) of the centre of mass of the activation and the maximal *t*-value of the voxels within each region. Abbreviations: R, right; L, left; ant., anterior; inf., inferior; blt., bilateral; DLPFC, dorsolateral prefrontal cortex; ncl., nucleus; caud., caudatus; thal., thalamus; BedNST, bed nucleus of stria terminalis; coll. sup., colliculus superior.

2007). Eighteen subjects participated in the “cognitive control” experiment; the data of 14 could be included in the group analysis. Four subjects had to be excluded due to fMRI signal artifacts caused by head movements (sudden head movements of more than 3 mm in translation or rotation or more than three movements of more than one mm) or by the beamer lamp. All subjects were right-handed and were healthy with subthreshold ratings of depressiveness (self-rating depression scale, SDS, range 27.5–47.5), anxiety (STAI-G, range 20–43), “neuroticism” (EPI, range 0–10) and “extraversion” (EPI, range 1–18). The two groups did not differ concerning these factors (Table 1). In the interview after the scanning, all included subjects stated that they were able to perform the task, and the subjects of the “cognitive control group” explicitly stated that they were able to perform the reality check as instructed. None of the subjects of the basic group reported anything comparable to an applied cognitive control strategy when asked about their experiences during the task.

Brain activation during the expectation of emotional stimuli

In a first step, we compared the emotion expectation conditions negative (ng), unknown (uk) and positive (ps) with the neutral (nt) expectation condition. The results of the basic group are described in detail in the previous report (Herwig et al., 2007). In the following, the results of the “cognitive control” group and the comparisons with the basic group are presented.

The analysis of the single contrast *expectation negative versus neutral* under condition of cognitive control (exp-c ng>nt, Table 2a) revealed activity within bilateral inferior frontal gyrus (IFG) and insula, anterior and medial cingulate cortex (ACC), medial prefrontal cortex (MPFC), dorsolateral prefrontal cortex (DLPFC), anterior thalamus and bed nucleus of stria terminalis (BedNST), medial thalamus, midbrain nuclei (nucleus ruber) and left lateral occipital cortex.

The analysis of *expectation unknown versus expectation neutral* under condition of cognitive control (exp-c uk>nt, Table 2b)

pointed to activity within right medial prefrontal cortex, bilateral IFG and insula and bilateral upper brainstem areas/midbrain.

The analysis of *expectation pleasant versus expectation neutral* (exp ps>nt, Table 2c) showed activity within septum, anterior and medial cingulate gyrus, anterior and posterior thalamus, right bed nucleus of stria terminalis (BedNST)/caput of caudate nucleus and bilateral occipital cortex.

Group comparison cognitive control versus no-control

In order to address our main question concerning the influence of cognitive control on brain activation, we compared the activity related to the period of the conditions “expectation negative versus neutral” and “expectation unknown versus neutral” in the “cognitive control group” with the “basic group” (Table 3). During the expectation of negative events, comparing the “cognitive control group” with the “basic group”, we found increased activity within the medial prefrontal cortex (group analysis Fig. 2, single subject data of a trained psychotherapist Fig. 3) and in the left DLPFC. Upon cognitive control, we further found decreased activity in the regions of the left extended sublenticular centromedial amygdala/parahippocampal gyrus (Heimer, 2003), in the region of the left pulvinar/lateral geniculate nucleus (LGN) and in the left fusiform gyrus (Fig. 2). Comparing the “unknown expectation” in both groups did show increased activity in the MPFC associated with cognitive control, which however was not different to the basic group that also exerted increased activity compared to the “negative” and the “neutral” condition (Fig. 4). Further, upon cognitive control, we revealed relatively decreased activity in the right extended amygdala/parahippocampal gyrus, in bilateral insula and in bilateral dorsomedial and posterior thalamus regions (Fig. 5). Comparing “expectation positive versus neutral” revealed relatively diminished activity in the “cognitive control” group in the left extended amygdala and in the left fusiform gyrus.

We found no correlation between medial and dorsolateral prefrontal and amygdala activation beta weights during reappraisal of

Table 3
Group comparisons of the emotion expectation contrasts

Anatomic regions	Brodmann area	Voxel mm ³	Talairach coordinates			t-max	Figure
			x	y	z		
Group comparison							
(a) Control>no-control/expectation negative>neutral rfx p<0.005							
Medial prefrontal cortex L	6/8	1316	-9	15	60	+5.8	2a/4
DLPFC L	9	694	-40	14	37	+4.0	-
Ext. amygdala/parahipp. gyrus L		374	-16	-7	-13	-4.8	2b
Pulvinar/lat. genic. ncl. L		775	-25	-25	0	-4.7	2c
Fusiform gyrus L	37	621	-38	-49	-7	-4.6	2d
(b) Control>no-control/expectation unknown>neutral rfx p<0.005							
Ext. amygdala/parahipp. gyr. R		1200	25	-2	-9	-4.5	5a
Insula L	13	167	-44	2	-7	-3.8	-
Post. insula R	13	188	36	-16	1	-3.6	5b
Dorsomedial thal./pulvinar R		637	10	-21	6	-4.4	5c
Pulvinar L		404	-16	-26	0	-4.4	-
(c) Control>no-control/expectation positive>neutral rfx p<0.005							
Ext. amygdala/parahipp. gyr. L		577	-15	-5	-9	-3.9	-
Fusiform gyrus L	13	541	-35	-48	-9	-5.1	-

Group comparison cognitive control versus no control. (a) Negative versus neutral, (b) unknown versus neutral, (c) positive versus neutral. Abbreviations: consider legends Table 2; ext., extended; parahipp. gyr., parahippocampal gyrus; lat. genic. ncl., lateral geniculate nucleus.

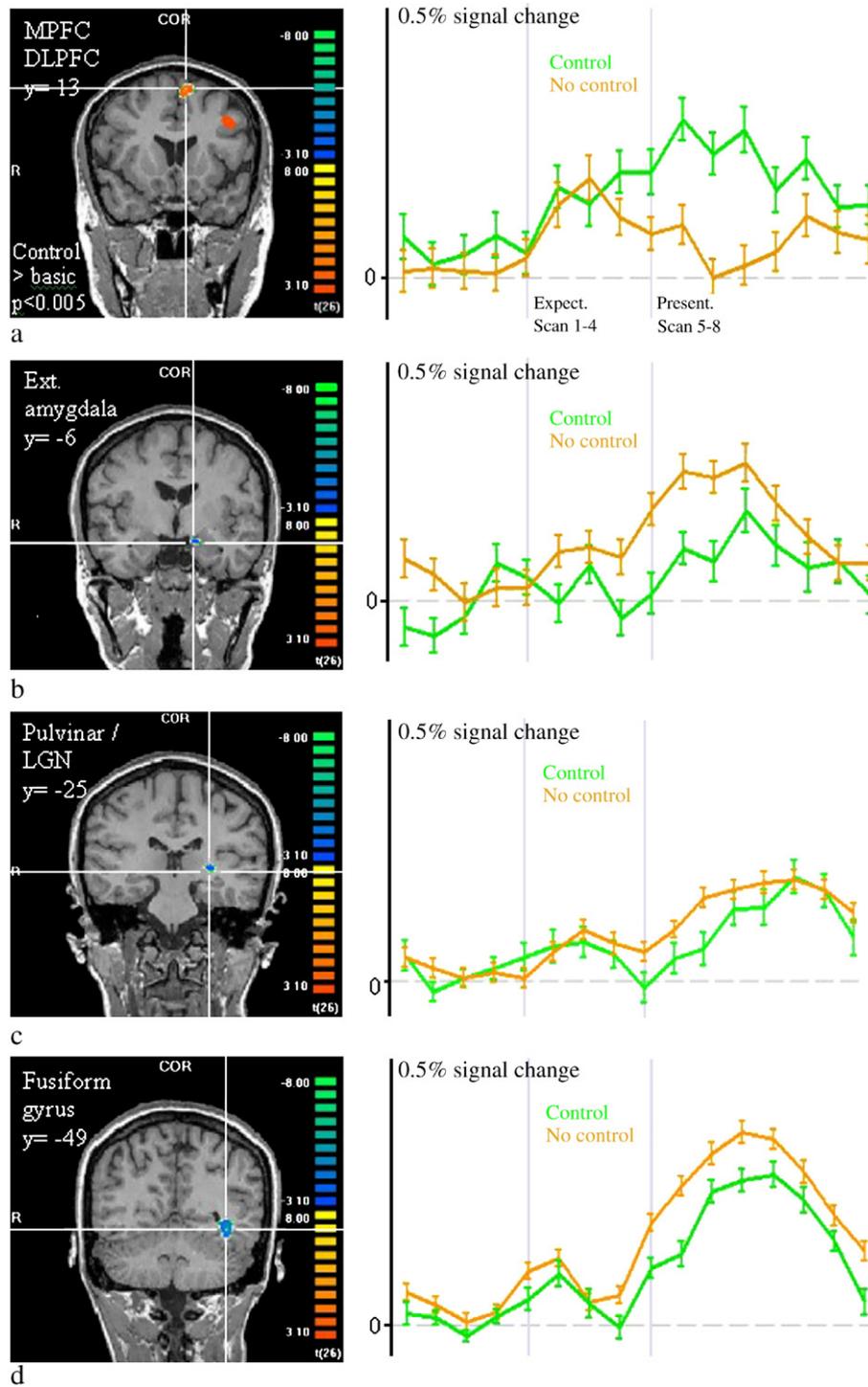


Fig. 2. Results of the group comparison based on a random effects analysis of the cognitive control group ($n=14$) and the basic task group ($n=14$). Presented are activated voxels and time courses in percent BOLD signal change. The vertical grey bars represent the beginning of the expectation and presentation periods. When interpreting the time courses, the delayed hemodynamic response function (HRF) has to be considered. Here, the results of the contrast “negative” expectation versus “neutral” expectation are shown, whenever for presentation reasons only the time courses of the “negative” expectation conditions are plotted. The “cognitive control group” shows (a) higher activity in medial prefrontal cortex and left dorsolateral prefrontal cortex than the “basic group”, (b) reduced amygdalar activity, (c) reduced pulvinar/lateral geniculate nucleus (LGN) activity and (d) reduced fusiform gyrus activity.

negative stimuli. The activations of medial and dorsolateral prefrontal areas in the “negative” condition were correlated with each other (Pearson, one-tailed, $r=0.75$, $p=0.001$). Correlations were also found between amygdala activity and left insular ($r=0.62$,

$p=0.01$), right insula ($r=0.86$, $p<0.001$), dorsomedial thalamus ($r=0.61$, $p=0.01$) and pulvinar/LGN activation ($r=0.77$, $p=0.001$) in the “unknown” condition and for amygdala activity and pulvinar/LGN activation ($r=0.49$, $p=0.04$) for the “negative” condition.

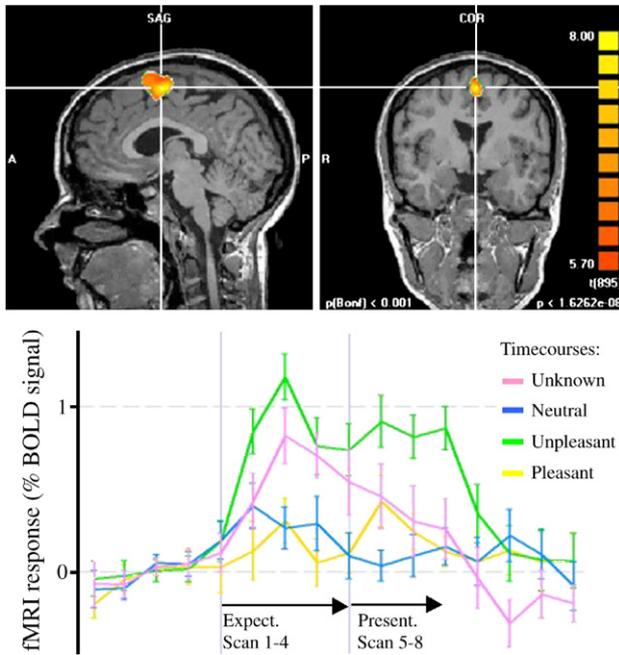


Fig. 3. Activation in the medial prefrontal cortex (MPFC) due to cognitive control of negative expectation in a single subject (trained psychotherapist).

All areas that were relatively decreased in the cognitive control group compared to the basic group were significantly activated in the corresponding conditions in basic group (Herwig et al., 2007).

Correlation with psychometric questionnaires

In the “cognitive control group”, we correlated the individual beta weights of the activity within the regions showing a difference between both groups with the individual scores of the emotion regulation questionnaire (ERQ; Table 4, Fig. 6; three subjects missed to complete the questionnaire). Negative correlations were found between the reappraisal scores and the beta weights of the activations in left extended amygdala ($p < 0.01$) and, with a trend, in pulvinar/LGN ($p = 0.06$) for the “negative” expectation condition. For the “unknown” expectation we found correlations between reappraisal scores and the activity in the left and the right insula (both $p = 0.01$), in the amygdala/PHG ($p = 0.03$) and with a slight trend in the dorsomedial thalamus ($p = 0.09$).

Discussion

The aim of our study was to investigate the effects of a cognitive control strategy on brain activity while anticipating potentially or definitely unpleasant events. Our main findings were that during anticipation of unpleasant events the exertion of cognitive control compared to no control resulted in an increase in activation of medial and left dorsolateral prefrontal cortex and a decrease in the left extended amygdala and in perception-related areas such as the regions of the left pulvinar/LGN and the fusiform cortex. The activity in the extended amygdala and the pulvinar/LGN further correlated with the degree to which “reappraisal” strategies were applied as a trait marker. This can be interpreted as a more successful downregulation in subjects with more frequent use of reappraisal strategies in everyday life. Further, we found relatively decreased

activity during cognitive control while expecting “unknown” events in the right amygdala/parahippocampal gyrus and in bilateral insula and dorsomedial/posterior thalamus. The amygdalar and bilateral insular activations were negatively correlated with the reappraisal scores in this contrast as well. Additionally and unexpectedly, we revealed relatively diminished activity for the “cognitive control” group in the left amygdala and fusiform cortex also in the “positive expectation” condition, despite no explicit control had to be exerted in this condition.

Disturbed control of emotions and of emotion-driven behavior is a key feature of psychiatric disorders such as anxiety, resulting for instance in panic and associated behavior, and depression (Beauregard et al., 2006). Effective strategy training is an important aspect of psychotherapy, especially training designed to promote control of emotional arousal, for instance by “reality checking” during exposure to fear-inducing situations (e.g., Hand, 2000; Otto et al., 2004). Several previous attempts have been made to uncover the underlying neurobiology of cognitive interventions during presentation of fear-inducing stimuli. Reappraisal of presented negative stimuli was found to be associated with increased activity in dorsolateral and dorsomedial PFC and in the anterior cingulate gyrus, as well as with decreased activity in amygdala and orbitofrontal cortex (Ochsner et al., 2002; Phan et al., 2005). These results were in line also with studies investigating the influence of other emotion regulation strategies on brain activity during the presentation of unpleasant or positive emotional stimuli (Beauregard et al., 2001; Levesque et al., 2003; Schaefer et al., 2002).

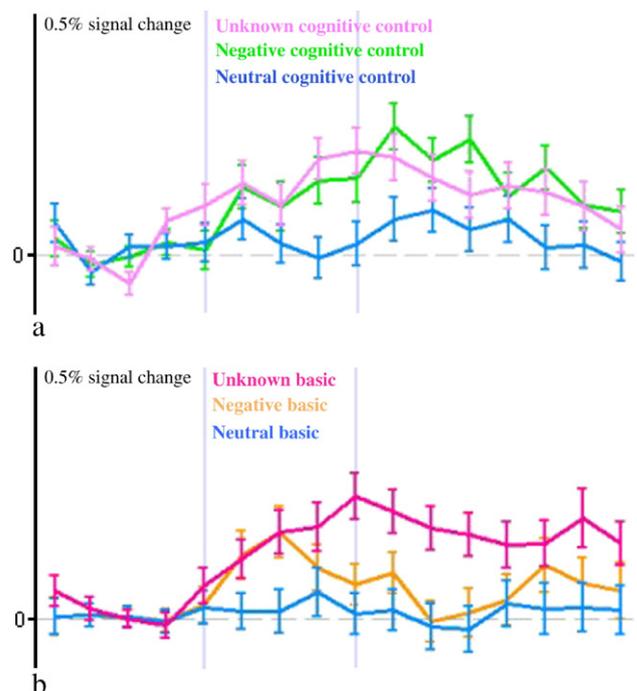


Fig. 4. Time courses of the peak activated voxels (here presented for $p < 0.0001$) during “negative” expectation within the MPFC (a) with and (b) without cognitive control (consider Fig. 2a for anatomical location). During the “cognitive control” condition, both, the “unknown” and the “negative” expectation were associated with increased and sustaining activity. However, the “unknown” expectation already was associated with increasing and then sustaining activity in the basic condition, unlike the “negative” expectation, thus that there was no further difference to the “cognitive control” condition.

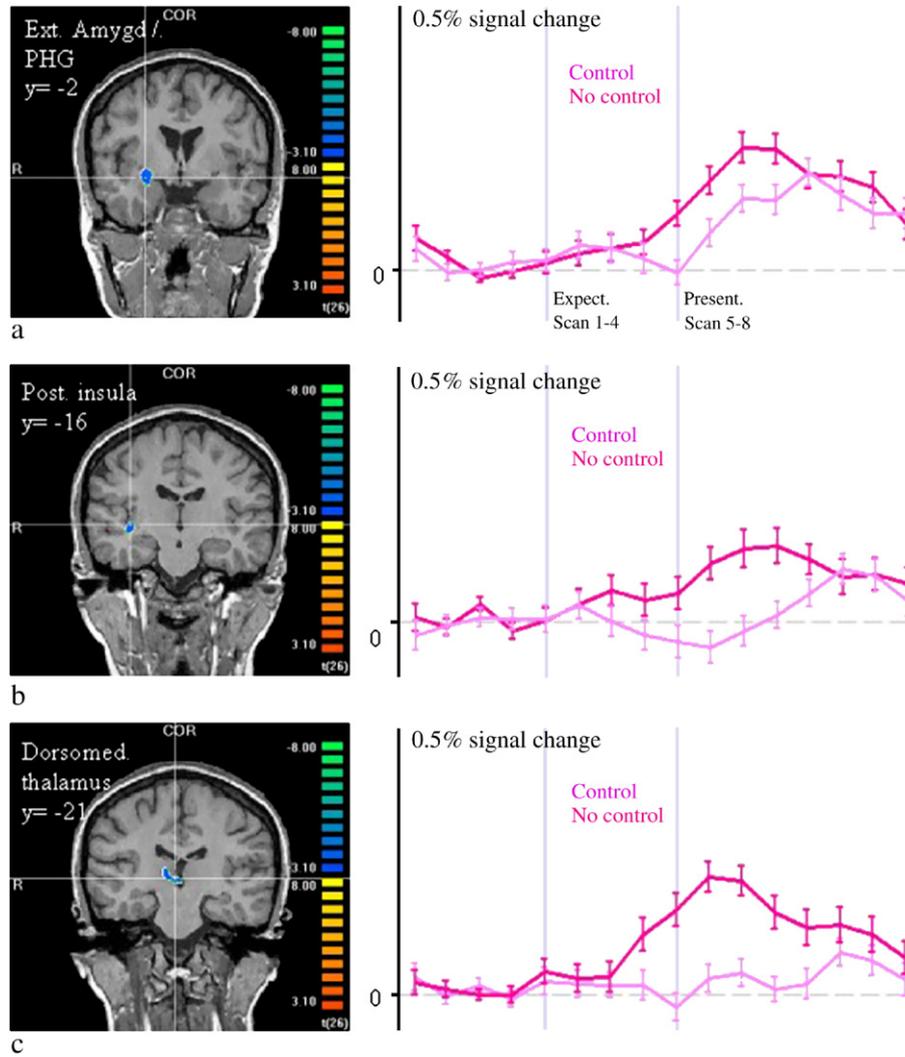


Fig. 5. Results of the group comparison of the contrast “unknown” expectation versus neutral expectation. The cognitive control group shows reduced activity in (a) right extended amygdala and parahippocampal gyrus (PHG), (b) right posterior insula and (c) dorsomedial thalamus.

We provide evidence that the use of cognitive control strategies in the period during which an emotional stimulus is *expected*, that is, in its absence, is already associated with brain activity in areas known to be involved in emotion regulation. This is of importance because the expectation of unpleasant events is encountered on an everyday basis, and because psychotherapeutic interventions seek

also to alter affect-laden preparatory responses concomitant to the anticipation of stimuli such as anxiety-triggering stimuli. The effect of cognitive control exerted by a trained psychotherapist on MPFC activity at the single subject level is presented in Fig. 3. There, a prominent activation occurred in the “negative” and the “unknown” condition throughout the expectation period. Considering, that our

Table 4
Correlation of beta weights of negative and unknown expectation with reappraisal rating scores (Pearson’s *r*)

Negative exp.	MPFC L	DLPFC L	Amg/PHG L	Pulv./LGN L	Fus. gyr. L
<i>r</i>	0.14	-0.08	-0.71	-0.50	0.04
<i>p</i>	0.345	0.412	0.007	0.060	0.453
Unknown exp.	Ins. L	Post. ins. R	Amg/PHG R	Dm. thal.	Pulv. L
<i>r</i>	-0.70	-0.74	-0.59	-0.41	-0.38
<i>p</i>	0.012	0.008	0.028	0.094	0.144

Correlation of beta weights of the activated regions of the cognitive control group during negative and unknown expectation versus neutral with the individual reappraisal rating scores. Pearson’s correlation coefficients (*r*) and *p*-values (one-tailed) are indicated. Significant correlations and trends are indicated in bold. Abbreviations: exp, expectation; L, left; R, right; MPFC, medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; Amg, amygdala; PHG, parahippocampal gyrus; Pulv., pulvinar; LGN, lateral geniculate nucleus; Fus. gyr., fusiform gyrus; Ins., insula; post., posterior; Dm. thal., dorsomedial thalamus.

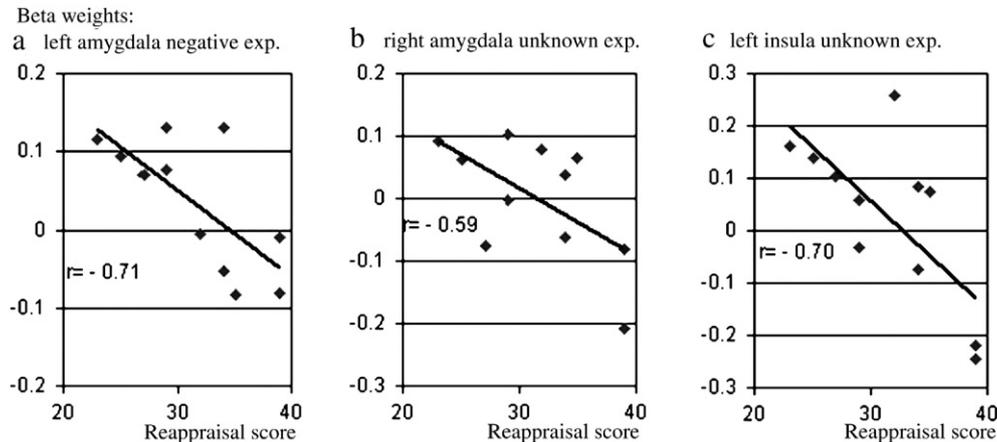


Fig. 6. Correlation between “reappraisal” scores and beta weights within the cognitive control group of (a) left extended amygdala during negative expectation (exp.; $p < 0.01$), (b) right extended amygdala ($p = 0.03$) during unknown expectation and (c) left insular activity ($p = 0.01$) also during unknown expectation.

subjects were largely naive to psychotherapeutic cognitive control strategies, it may be suggested that with an intensive training the increased prefrontal activations would even be more prominent. Our results support the view of a top-down inhibition mediated by medial prefrontal areas (Ochsner et al., 2002). We also found relatively increased left dorsolateral prefrontal cortex (DLPFC) activity. The DLPFC is known to be involved in executive control when for example withholding a reaction is required (e.g., Fuster, 2000; MacDonald et al., 2000). The DLPFC may therefore be associated with the control of external behavioral reactions to emotional events. The MPFC on the other hand may be associated with controlling the internal state associated with emotional events.

Our results provide evidence that reappraising an actually presented stimulus, as in the technique used for instance by Ochsner et al. (2002), involves comparable cognitive processes as the reality checking, consisting of a reappraisal of the meaning of an actual situation. This had to be expected because the principal issue of reappraising something unpleasant remains the same in both conditions.

When regarding the time courses of the “unknown” condition during cognitive control in the MPFC, the activation was comparable with the “negative” expectation (Fig. 4a) suggesting a cognitive control-associated activation also during “unknown” expectation. However, this increased activation in prefrontal areas in the “cognitive control” group was not different compared to the basic group during “unknown” expectation. At the first look, this appeared to be a confounding finding regarding our hypothesis. But in fact, in the basic group there already was an increased and sustaining activity in the MPFC during “unknown expectation” unlike in the “negative” condition (Fig. 4). Thus, the activation during “unknown expectation” in the context of cognitive control may not have led to a difference compared to the basic group despite a “cognitive control” associated activation was prominent. This can be interpreted in the sense that “unknown” expectation generally is associated with a certain cognitive component for instance due to developing different strategies for the occurrence of the negative or the pleasant event.

The activity of the left extended amygdala was relatively decreased during cognitive control while expecting negative stimuli. Amygdala activation has been reported to be associated with fear processing (Compton, 2003; Hamann and Mao, 2002; LeDoux, 2000; Morris et al., 1998; Phelps et al., 2001), but also with pleasant emotional stimuli (Canli et al., 2002; Garavan et al., 2001; Hamann

and Mao, 2002; McClure et al., 2004), reward-related processing (Breiter and Rosen, 1999; Gottfried et al., 2003), encoding of emotionally salient information (Canli et al., 2000), risk processing (Ernst et al., 2002) and appetitive or aversive olfactory learning (Gottfried et al., 2002). Taken together, these studies lend support to the view that attributes to amygdalar function a more general role in emotion processing such as emotional arousal or intensity without valence specificity (Anderson et al., 2003; Baxter and Murray, 2002; McClure et al., 2004), a role that may be attenuated by cognitive control (Ochsner et al., 2002; Phan et al., 2005; Urry et al., 2006). During “unknown” expectation decreased activity was observed in the right extended amygdala/parahippocampal gyrus and left pulvinar, and also in insular regions and dorsomedial thalamus that are known to be involved in emotion regulation and visceroperception (for a more detailed discussion, consider Herwig et al., 2007). The amygdala and insular activations were correlated negatively with the reappraisal scores which lends further support to the hypothesis of a cognitively mediated inhibition. Finally, the beta weights of these activations were correlated with each other suggesting an associated activation in the network with respective connectivity.

Unlike the report of Ochsner et al. (2002), our data did not reveal a negative correlation between prefrontal and amygdala activity. Although such correlations seemed expectable in our task, this may be explained by the different task designs. Ochsner and colleagues used a direct reappraisal of a presented stimulus, whereas our subjects performed a regulation strategy concerning the actual situation while expecting an emotional stimulus.

Notably, we provide new evidence for the influence of cognitive control on perception-related brain regions such as the pulvinar/LGN and the fusiform gyrus. This is of particular interest, as it may be interpreted as a top-down influence on a very early hierarchical perception level of emotional information processing. It is conceivable that due to this “priming” the perception (and the evaluation) of an upcoming emotional event may be influenced before one is aware of it. The effect on these areas may be due to a reduced arousal supposedly mediated by the amygdala: The pulvinar which includes the LGN has reciprocal connections with the amygdala (Doron and Ledoux, 2000) and stimulation of the central part of the amygdala influences activity in LGN neurons (Cain et al., 2002). The fusiform cortex is involved in processing of visual information particularly in face processing, including detection of the emotional valence of face expression (e.g., Ishai et al., 2005).

From a certain perspective conflicting with our hypothesis, we found diminished activity in amygdala and fusiform gyrus also with the “positive” expectation condition. Thus, one may argue that the decreases of activity observed during cognitive control may be solely due to less attention being drawn to the experiment in the sense that the subjects were non-specifically distracted by the fact of performing the cognitive control task. However, this would not explain the increase of medial and dorsolateral prefrontal activity in the “negative expectation” condition, and further supposedly should have resulted in a more general relative deactivation for instance also in the visual cortex, but this was not the case. Further, if that argument would be valid it nevertheless would be an indication that performing such a cognitive task is associated with deactivation in emotion processing areas during affect-laden events and may therefore be suitable to attenuate concomitant emotions. Importantly, we analyzed the contrasts of the emotion conditions versus “neutral” within each group and compared the differences between the groups in order to focus specifically on emotion processing areas. Thus, if general emotion unspecific or solely expectation related differences had been present between the groups, these should have been valid for the neutral condition as well and would not have led to the reported results. However, the fact of a deactivation during “positive” expectation despite no explicit cognitive control had to be exerted remains to be interpreted. This may have been caused by a generally increased awareness of the cognitive control group about the “real” experimental setting due to the reality checking, independent of the emotion conditions and independent of actively applying cognitive control. This however would not be an argument against the presented results but add the interpretation that reality checking in a certain context may lead to a general context-related awareness of the “real”, emotion-independent aspects of the situation.

Finally, our findings are supported by a negative correlation of the amygdalar activations during both, cognitive control of “negative” and “unknown” expectation, with the degree to which “reappraisal” strategies are applied, according to an emotion regulation questionnaire used as a trait marker (Gross and John, 2003). This indicates a direct influence of the applied reappraisal onto emotional arousal as processed by the amygdala.

Generally, our findings support models of cognitive control that propose the engagement of prefrontal circuitry by for instance reappraisal techniques in decreasing activity in limbic structures such as the amygdala (Ochsner, 2001; Phan et al., 2005; Roffman et al., 2005). This view is underlined by findings from animal studies as well: Electrical stimulation of medial prefrontal cortex neurons in cats inhibited output neurons from centromedial amygdala, which was suggested to implicate a cortical control of fear (Quirk et al., 2003). Sustained or repeated cognitive control in the course of behavioral therapy may unfold its impact by potentiating PFC activity and/or attenuating amygdalar activity by neuroplastic synaptic adaptations resulting in desensitization or extinction of learned dysfunctional emotional responses (Roffman et al., 2005).

Findings within this field of research may help to understand the neurobiological correlates of psychotherapeutic interventions. They further may be drawn on for the purpose of treatment response prediction and treatment effect monitoring, for instance, by monitoring MPFC activity over the course of psychotherapy. As a perspective, one may even contemplate the application of reappraisal in fMRI settings with real-time feedback of respective MPFC or amygdalar activity as a method of cognitive training in the treatment of affective disorders (Linden, 2006).

In conclusion, our findings indicate that cognitive control is exerted particularly during the anticipation of negative events by prefrontal cortical areas associated with the inhibition of regions recruited in emotion and perception processing.

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