

Modulation of emotion by cognition and cognition by emotion

K.S. Blair,^{a,*} B.W. Smith,^b D.G.V. Mitchell,^a J. Morton,^c M. Vythilingam,^a
L. Pessoa,^d D. Fridberg,^a A. Zametkin,^a D. Sturman,^e E.E. Nelson,^a
W.C. Drevets,^a D.S. Pine,^a A. Martin,^e and R.J.R. Blair^a

^aMood and Anxiety Disorders Program, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-2670, USA

^bDepartment of Psychology, University of New Mexico, Albuquerque, NM 87505, USA

^cInstitute of Cognitive Neuroscience, University College London, London, England

^dDepartment of Psychological and Brain Sciences, Indiana University, Bloomington, Indiana 47405-7000, USA

^eLaboratory of Brain and Cognition, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892-2670, USA

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In this study, we examined the impact of goal-directed processing on the response to emotional pictures and the impact of emotional pictures on goal-directed processing. Subjects ($N=22$) viewed neutral or emotional pictures in the presence or absence of a demanding cognitive task. Goal-directed processing disrupted the BOLD response to emotional pictures. In particular, the BOLD response within bilateral amygdala and inferior frontal gyrus decreased during concurrent task performance. Moreover, the presence of both positive and negative distractors disrupted task performance, with reaction times increasing for emotional relative to neutral distractors. Moreover, in line with the suggestion of the importance of lateral frontal regions in emotional regulation [Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D., et al. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*, 23(2), 483–499], connectivity analysis revealed *positive* connectivity between lateral superior frontal cortex and regions of middle frontal cortex previously implicated in emotional suppression [Beauregard, M., Levesque, J., and Bourgouin, P. (2001). Neural correlates of conscious self-regulation of emotion. *J. Neurosci.*, 21 (18), RC165.; Levesque, J., Eugene, F., Joanette, Y., Paquette, V., Mensour, B., Beaudoin, G., et al. (2003). Neural circuitry underlying voluntary suppression of sadness. *Biol. Psychiatry*, 53 (6), 502–510.; Ohira, H., Nomura, M., Ichikawa, N., Isowa, T., Iidaka, T., Sato, A., et al. (2006). Association of neural and physiological responses during voluntary emotion suppression. *NeuroImage*, 29 (3), 721–733] and *negative* connectivity with bilateral amygdala. These data suggest that processes involved in emotional regulation are recruited during task performance in the context of emotional distractors.

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* Corresponding author.

E-mail address: peschark@mail.nih.gov (K.S. Blair).

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Introduction

Emotional responses to affective stimuli can reduce our ability to perform goal-directed tasks. This form of interference is a major feature of mood and anxiety disorders such as Major Depressive Disorder and Post Traumatic Stress Disorder (Drevets, 2001; Rauch et al., 2003). However, the impact of emotional responding upon goal-directed processing is not yet well understood. Moreover, the impact of goal-directed processing upon emotional responding also remains unclear.

Some studies have indicated that emotional distractors disrupt goal-directed processing in healthy individuals (Simpson et al., 2000; Vuilleumier et al., 2001). However, frequently disruption in behavioral performance on emotional interference paradigms is only found in clinical groups (Williams et al., 1996), making the extent to which emotional stimuli can disrupt goal-directed processing in healthy individuals unclear. Moreover, if behavioral performance is not affected by the presence of emotional distractors, it becomes difficult to associate regions with the compensation for emotional distractors as the behavioral data indicate that compensation is unnecessary. Recently, though, paradigms have been developed where emotion can be reliably shown to alter task performance in healthy adults. These paradigms have involved the rapid, serial presentation of stimuli (Anderson and Phelps, 2001). One such task is the Affective Stroop.

The Affective Stroop involves an adaptation of the Number Stroop task of Pansky and Algom (2002). In this task, subjects are presented sequentially with two numerical displays and asked to determine which numerical display contained the greater numerosity; see Fig. 1. The Number Stroop is modified in one crucial aspect. A positive, negative, or neutral image from the International Affective Picture System (IAPS) (Lang and Greenwald, 1988) temporally bracketed the numerical displays such that a trial now consisted of four consecutive displays (e.g., four 5s → picture

of snake → five 4s → picture of snake); see Fig. 1. Previous work with a very similar task (Mitchell et al., 2006) and pilot work with the current task, have shown that task performance is significantly and detrimentally affected by emotional distractors relative to neutral ones.

We wanted to examine two main issues using this task. The first concerned the impact of emotional distractors on goal-directed processing. Specifically, would regions involved in goal-directed processing show increased activity during trials involving emotional relative to neutral distractors; i.e., would the regions involved in task performance compensate for the emotional distractors themselves? Alternatively, would additional regions be recruited to potentially down-regulate the response to the emotional distractors? Previous work has suggested that middle frontal cortex may be particularly implicated in the down-regulation of the emotional response (Bishop et al., 2004; Shin et al., 2001; Simpson et al., 2000; Vuilleumier et al., 2001; Whalen et al., 1998). We wished to determine whether we might see middle frontal cortex potentially play such a role in the context of the current task.

The second issue concerned the impact of goal-directed processing on the neural response to emotional stimuli. Some studies have reported that concurrent goal-directed processing does not disrupt the emotional response to emotional visual stimuli. Thus, Vuilleumier and colleagues reported comparable amygdala activation by fearful expressions whether these faces were the foci of task-related attention or the distractors to the stimuli (Vuilleumier et al., 2001). Similar results were reported by Williams et al. (2004). However, other studies have indicated that goal-directed processing does disrupt the neural response to emotional stimuli. Thus, Pessoa and colleagues found that the amygdala response to fearful faces was modulated by the degree of attention directed towards them (Pessoa et al., 2002, 2005). Similarly, Liberzon et al. (2000) and Hariri et al. (2002) showed that the amygdala response to emotional stimuli were modulated by attentional manipulations (Hariri et al., 2000; Liberzon et al., 2000). Moreover, studies examining the neural basis of emotional

regulation have reported decreases in several regions associated with emotional responding (e.g., the amygdala, insula, hypothalamus and inferior frontal gyrus) when subjects are instructed to, for example, “distance themselves” from the stimuli (Beauregard et al., 2001; Levesque et al., 2003; Ochsner, 2004).

The studies of emotional regulation are of particular interest with respect to the question regarding how concurrent goal-directed processing impacts upon the neural response to emotional stimuli. These studies have implicated several frontal regions in emotional regulation, including lateral (typically lateral regions of 46, 9, 6/8) orbital (BA 10 and 11) and dorsomedial (BA 32 and medial BA 8) frontal cortex, with activity in these regions increasing as a function of the reappraisal process (Beauregard et al., 2001; Levesque et al., 2003; Ochsner, 2004). However, the process of emotional regulation remains poorly understood. One possibility is that prefrontal cortex directly suppresses negative emotion “via an inhibitory connection from regions of the prefrontal cortex, probably the OFC, to the amygdala;” p. 592 (Davidson et al., 2000). Middle frontal cortex has reciprocal connections with both lateral frontal cortex and the amygdala (Cavada et al., 2000). It is possible that lateral frontal cortex could blunt processing in the amygdala indirectly via medial orbital frontal cortex by “directly modulating representations of the affective significance of a stimulus in the medial OFC” (Ochsner, 2004).

We examined three predictions with the Affective Stroop task. First, we predicted that the presence of emotional distractors would lead to middle frontal cortex activity associated with the regulation of emotional responding. Second, we predicted that task performance would disrupt the response of the amygdala response to the emotional stimuli. Third, we predicted that if Ochsner is correct about the role of lateral frontal cortex in emotional regulation then connectivity analysis would reveal that activity in lateral frontal cortex was positively associated with activity in regions of middle frontal cortex associated with emotional regulation and negatively associated with responding in the amygdala.

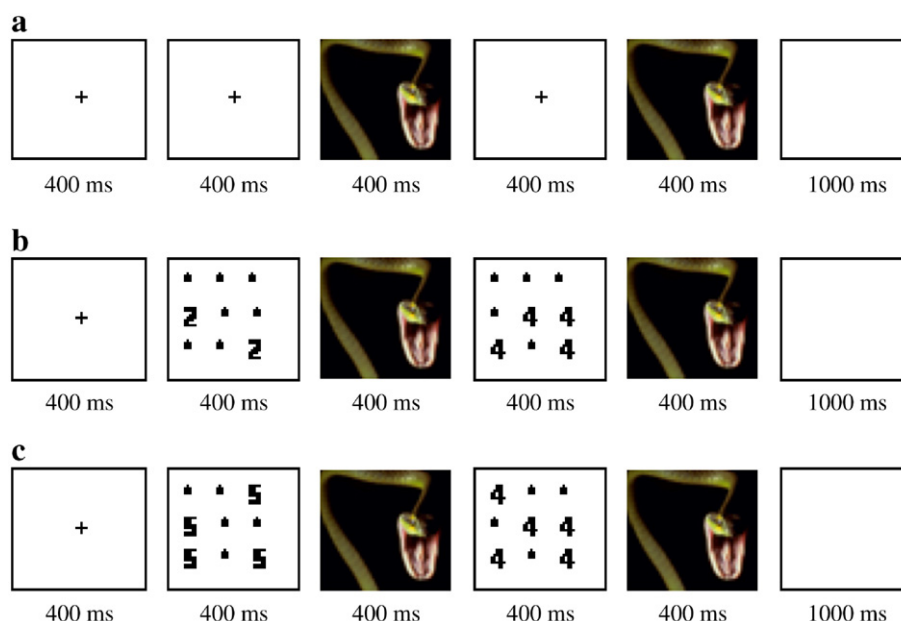


Fig. 1. Example trial sequences. (a) Negative view trial; (b) negative congruent trial; (c) negative incongruent trial.

Materials and methods

Subjects

Twenty-two right-handed subjects (ten males, twelve females; aged 21–42, mean age=27.95) from the Washington, DC, metropolitan area volunteered for the study and were paid for their participation. All subjects gave written informed consent to participate in the study, which was approved by the National Institute of Mental Health Institutional Review Board. Subjects were in good health, with no history of psychiatric or neurological disease.

Task

The individual numerical stimuli consisted of two, three, four, or five 1s, 2s, 3s, 4s, 5s, or 6s randomly presented within a 9-point grid of * symbols (see Fig. 1 for example stimuli). The emotional stimuli consisted of 40 positive, 40 negative, and 40 neutral pictures selected from the IAPS (Lang and Greenwald, 1988). The normative mean (\pm S.E.) valence and arousal values on a 9-point scale were respectively 2.71 ± 0.11 and 5.85 ± 0.11 for negative pictures, 7.30 ± 0.11 and 5.01 ± 0.10 for positive pictures, and 4.96 ± 0.07 and 2.78 ± 0.08 for neutral pictures.

Each trial began with a fixation point (+) presented for 400 ms in the middle of the screen. For the numerical trials, the fixation point was then replaced by the first numerical display presented for 400 ms, followed by the first picture stimuli presented for 400 ms, followed by the second numerical display presented for 400 ms, followed by the second picture display presented for 400 ms, followed by a blank stimulus for 1000 ms (see Fig. 1). The subject had to determine which numerical display contained the greater numerosity. If there were more numbers in the first numerical display, they responded by pressing a button with their left hand (50% of task trials). If there were more numbers in the second numerical display, they responded by pressing a button with their right hand (50% of task trials). Subjects did not receive feedback on their performance. On congruent trials, the Arabic numeral distractor information was consistent with the numerosity information; i.e., the second (greater numerosity) display also contained Arabic numerals of larger value than the first display (e.g., two 2s and four 4s) (see Fig. 1b). On incongruent trials, the Arabic numeral distractor information was inconsistent with the numerosity information; i.e., the second (greater numerosity) display contained numerals of smaller value than the first display (e.g., two 4s and four 2s) (see Fig. 1c). For the view trials, there were no numerical displays only the picture stimuli; the numerical displays were replaced by fixation points (see Fig. 1a). Before beginning the task, the subjects were informed to pay attention to the pictures presented as they might be questioned about them later.

There were four runs, each consisting of ten presentations of each emotion by task condition randomized throughout the run. In addition, ten fixation points (staying on the screen for the duration of a condition trial 2500 ms) were randomly presented throughout each run, six fixation points were presented in the beginning of each run, and six fixation points were presented at the end of each run. Thus, overall each subject was presented with 40 positive view trials, 40 negative view trials, 40 neutral view, 40 positive congruent trials, 40 negative congruent trials, 40 neutral congruent trials, 40 positive incongruent trials, 40 negative incongruent trials, 40 neutral incongruent trials, and 88 fixation trials. The

presentation of the four runs was counterbalanced between subjects.

Image acquisition and analysis

Whole-brain blood oxygen level-dependent (BOLD) fMRI data were acquired using a 1.5-T Siemens MRI scanner. Following sagittal localization, functional T2*-weighted images were acquired using an echo-planar single-shot gradient echo pulse sequence with a matrix of 64×64 mm, repetition time (TR) of 3000 ms, echo time (TE) of 30 ms, field of view (FOV) of 240 mm, and voxels of $3.75 \times 3.75 \times 4$ mm. Images were acquired in 30 contiguous 4 mm axial slices per brain volume across four runs. The duration of each run was 4 min 39 s. In the same session, a high-resolution T1-weighted anatomical image was acquired to aid with spatial normalization (three-dimensional Spoiled GRASS; TR=8.1 ms; TE=3.2 ms, flip angle=20°; field of view=240 mm, 128 axial slices, thickness=1.0 mm; 256×256 acquisition matrix).

fMRI analysis

Data were analyzed within the framework of a random effects general linear model using Analysis of Functional Neuroimages (AFNI) (Cox, 1996). Both individual and group-level analyses were conducted. The first 4 volumes in each scan series, collected before equilibrium magnetization was reached, were discarded. Motion correction was performed by registering all volumes in the EPI dataset to a volume that was collected shortly before acquisition of the high-resolution anatomical dataset.

The EPI datasets for each subject were spatially smoothed (using an isotropic 6 mm Gaussian kernel) to reduce the influence of anatomical variability among the individual maps in generating group maps. Next, the time series data were normalized by dividing the signal intensity of a voxel at each time point by the mean signal intensity of that voxel for each run and multiplying the result by 100. Resultant regression coefficients represented a percent signal change from the mean. Following this, regressors depicting each of the response types were created by convolving the train of stimulus events with a gamma-variate hemodynamic response function to account for the slow hemodynamic response. This involved 10 regressors (positive view, negative view, neutral view, positive congruent, negative congruent, neutral congruent, positive incongruent, negative incongruent, neutral incongruent, error/missed responses). Each trial was modeled as a single regressor using an event-related model. Linear regression modeling was performed fitting the BOLD signal to the 10 regressors. A baseline plus linear drift and quadratic trend were modeled in each voxel's time series to control for voxel-wise correlated drifting. This produced for each voxel and each regressor, a beta coefficient and its associated *t*-statistic.

Voxel-wise group analyses involved transforming single subject beta coefficients into the standard coordinate space of Talairach and Tournoux (1988). Subsequently, 2 ANOVAs were performed to produce statistical parametrical maps of the main effect of emotion, task and interaction of emotion and task. The first ANOVA involved a 2 (emotion: negative, neutral) by 3 (task: view, congruent, incongruent) design and examined the interactions of negative emotion and task. The second ANOVA involved a 2 (emotion: positive, neutral) by 3 (task: view, congruent, incongruent) design and examined the interaction of positive emotion and task. Separate analyses were conducted for negative and

positive distractors because there have been suggestions that only negative, and in particular frightening, stimuli can interfere with on-line processing (Hariri et al., 2000; Ohman et al., 2001; Vuilleumier et al., 2001). We wished to determine whether positive stimuli can also interfere with on-line processing. Given the differential pattern of activation often reported for the processing of negative and positive stimuli (Dolcos et al., 2004; Liberzon et al., 2003; O’Doherty et al., 2001), we examined the issue through separate analyses.

The result was six whole brain group maps of areas of differential activation ($p < 0.005$) with each ANOVA allowing the identification of clusters of activity that showed a significant main effect of task, a significant main effect of emotion, and a significant task by emotion interaction. For both task main effects, a large area of activation including extended cingulate, insula, and premotor regions was identified (see Tables 2 and 3). In order to consider these regions individually, anatomically defined ROIs were used to identify separate cingulate cortex (BA 24/32), insula, and premotor (BA 6) regions within this one area of activation. In addition, and in accordance with our hypotheses, we applied an anatomically defined amygdala mask to the six group maps of areas of differential activation (at $p < 0.05$). A functional ROI of voxels significantly activated by this ROI approach was identified for the main effect of task in the 2 (emotion: negative, neutral) by 3 (task: view, congruent, incongruent) ANOVA. Prior to anatomical ROI separation a spatial clustering operation was performed to correct for multiple comparisons using AlphaSim with 1000 Monte Carlo simulations taking into account the entire EPI matrix ($p < 0.005$), with a map-wise false-positive probability of $p < 0.05$. The labeling of anatomical locations was determined by the Talairach–Tournoux Daemon. Even though the purpose of the study was to test our *a priori* hypotheses, whole brain analyses were conducted in order to ensure identification of the most statistically significant regions involved in task performance.

For each significantly active cluster yielded by the two ANOVAs, we conducted follow-up analyses to determine the nature of the main effect of emotion and task by using pair-wise comparisons, and paired *t*-tests to delineate the nature of the interactions. For the main effect of emotion, we compared the percent signal change of negative trials (or positive trials in the case of the ANOVA involving positive/neutral stimuli) and neutral trials collapsed across task (view, congruent, and incongruent). For the main effect of task, we compared the percent signal change of view, congruent, and incongruent trials collapsed across emotion (i.e., negative/neutral trials were collapsed for the analysis involving negative stimuli, and positive/neutral trials were collapsed for the analysis involving positive stimuli). Similarly, a series of paired *t*-tests were used to delineate the nature of the task by emotion interaction.

Functional connectivity was measured by examining covariation across the whole brain with the activation within functionally defined ROIs. Each individual subject’s time series was converted to common Talairach space according to their structural data set. Ochsner et al. (2002) reported a left lateral frontal region involved in reappraisal (BA 46: –54, 52, 12). We found no activation peaks associated with task performance in BA 46 (see Tables 2 and 3). However, we did find bilateral activation of relatively lateral regions of superior frontal cortex (BA 9: –31, 48, 27 and 40, 38, 33). These activations were proximal to regions of BA 9 implicated in reappraisal by both Levesque et al.

(2001) and Ochsner et al. (2004) (right BA 9, Levesque et al. (2001): 36, 25, 26; bilateral BA 9, Ochsner et al. (2004): 42, 30, 38/–16, 46, 42). We thus used for our connectivity analysis, the voxel with the peak signal change for the main effect of processing load within right superior frontal cortex (BA 9). This voxel with peak signal change became our “seed” voxel, and the time series within it was extracted for each subject. Baseline plus linear and quadratic trend were removed from each voxel’s time series to control for voxel-wise correlated drifting. To control for global drifting, the average signal across the whole brain (global signal collapsed across all type trials), was used as a covariate in the correlation analysis. The average of the resulting time series inside the brain was treated as a global signal and used as a covariate in the correlation analysis. A voxel-wise correlation analysis was conducted between each individual voxel’s time series and that of the identified seed. The proportion of the variation in the signal that could be explained by the correlation with the seed was determined by squaring the resulting correlation coefficient. Correlation coefficients were converted to a Gaussian variable using a Fisher transformation formula in order to reduce the skew and normalize the sampling distribution. To identify regions significantly positively or negatively correlated with the target voxel at group level, a one-sample *t*-test was performed on the transformed correlation coefficients. As with the previous analysis, a spatial clustering operation was performed to correct for multiple comparisons using AlphaSim with 1000 Monte Carlo simulations taking into account the entire EPI matrix ($p < 0.005$), with a map-wise false-positive probability of $p < 0.05$.

Results

Behavioral data

Mean RTs for each trial were computed for each subject. We first examined the effect of negative emotion and task on RTs (see Table 1). This involved a 2 (emotion: negative, neutral) by 2 (task: congruent, incongruent) repeated measures ANOVA. There was a significant main effect of emotion ($F(1,21)=13.12$; $p < 0.005$); subjects were significantly slower to respond to trials involving negative, relative to neutral pictures ($M(\text{negative})=745.81$, S.E.=23.63; $M(\text{neutral})=719.53$, S.E.=24.30). There was also a significant main effect for task ($F(1,21)=13.83$; $p < 0.005$); subjects were significantly slower to respond to incongruent, relative to congruent trials ($M(\text{incongruent})=746.54$, S.E.=25.18; $M(\text{congruent})=718.80$, S.E.=22.73). There was a trend toward a significant emotion by task interaction, however, this result did not reach significance ($F=2.25$, $p=0.149$).

We next examined the effect of positive emotion and task on RTs (see Table 1). This involved a 2 (emotion: positive, neutral) by

Table 1
Subject RTs; S.E. in brackets

Emotion	Task	RT
Negative	Congruent	738.27 (24.54)
	Incongruent	753.35 (24.61)
Neutral	Congruent	699.32 (22.07)
	Incongruent	739.74 (27.42)
Positive	Congruent	714.63 (23.49)
	Incongruent	752.88 (25.24)

2 (task: congruent, incongruent) repeated measures ANOVA. There was a significant main effect of emotion ($F(1,21)=4.57$; $p<0.05$); subjects were significantly slower to respond to trials involving positive, relative to neutral trials ($M(\text{positive})=733.75$, S.E.=23.85; $M(\text{neutral})=719.53$, S.E.=24.30). There was also a significant main effect for task ($F(1,21)=25.75$; $p<0.001$); subjects were significantly slower to respond to incongruent, relative to congruent trials ($M(\text{incongruent})=746.31$, S.E.=25.83; $M(\text{congruent})=706.98$, S.E.=25.83). The emotion by task interaction did not reach significance ($F<1$).

Functional MRI data

We first examined the effects of task and emotion involving negative stimuli using a 2 (emotion: negative, neutral) by 3 (task: view, congruent, incongruent) ANOVA. This revealed significant main effects for both emotion and task, as well as a significant interaction of emotion and task.

Main effect of emotion: negative stimuli

The first main effect identified regions which showed a differential BOLD response for emotion. These included left inferior frontal cortex and bilateral fusiform cortex (see Table 2). In addition, there was a main effect of emotion in bilateral amygdala ($p<0.05$; uncorrected). All regions showed significantly greater activation to negative relative to neutral stimuli (see Table 2).

Main effect of task: negative stimuli

The second main effect identified regions which showed a differential BOLD response for task. These included superior, middle and inferior frontal cortex as well as anterior cingulate gyrus (see Table 2). In addition, there was bilateral amygdala activation ($p<0.05$; uncorrected). Superior and middle frontal cortex, as well as anterior cingulate, showed increased activation during incongruent/congruent trials relative to view trials; see Fig. 2 and Table 2. In contrast, inferior frontal cortex as well as bilateral amygdala showed decreased activation during view trials relative to incongruent/congruent trials. Indeed, the degree of activation in the left and right amygdala showed a linear function with the BOLD response greater to view trials than congruent trials, and greater to congruent than incongruent trials (see Fig. 3).

Task by emotion interaction: negative stimuli

The analysis identified one region where there was a significant task by emotion interaction, middle frontal cortex BA 10 (significant at $p<0.005$ uncorrected for multiple comparisons); see Table 2. The BOLD response within this region was significantly greater in the context of negative stimuli during incongruent relative to view trials ($F(1,21)=4.58$; $p<0.05$) but significantly less in the context of neutral stimuli during incongruent relative to view trials ($F(1,21)=4.69$; $p<0.05$); see Fig. 4. The BOLD response was significantly greater in this region in the context of negative rather than neutral stimuli only during incongruent trials ($F(1,21)=8.18$, $p<0.01$; 3.38, n.s.; and 2.95 for incongruent, congruent and view trials respectively).

We next examined the effects of task and emotion involving positive stimuli using a 2 (emotion: positive, neutral) by 3 (task: view, congruent, incongruent) ANOVA. This revealed significant main effects for both emotion and task, as well as a significant interaction of emotion and task.

Table 2

Significant areas of activation for analysis involving negative stimuli

Region	BA	mm ³	X	Y	Z	F-value
<i>Main effect emotion</i>						
L inferior frontal gyrus	47	450	-34	21	-7	15.81
R medial frontal gyrus	8	432	4	45	39	13.41
L amygdala**		118	-19	-6	-14	6.54
R amygdala**		153	27	-5	-21	6.94
L fusiform gyrus	19	14,801	-39	-75	-5	38.51
R fusiform gyrus	19	14,020	45	-71	-2	43.41
<i>Main effect task</i>						
Incongruent > congruent > view						
L superior frontal gyrus	9	4218	-31	48	27	11.84
R superior frontal gyrus	9	3576	40	38	33	12.94
R middle frontal gyrus	11	185	19	50	-9	13.06
L middle frontal gyrus	11	357	-20	47	-9	8.76
R middle frontal gyrus	10	932	33	52	9	9.36
L anterior cingulate gyrus	24	4833	-8	16	28	7.93
L insula	13	438	-39	-2	10	9.21
R insula	13	1017	37	21	0	9.89
L precentral gyrus	6	7266	-55	3	29	10.19
R precentral gyrus	6	6444	7	17	43	10.49
R inferior parietal lobule	40	268,887	50	-42	58	38.33
R substantia nigra		476	10	-19	-7	8.88
R middle frontal gyrus	10	932	33	52	9	9.38
View > congruent = incongruent						
L inferior frontal gyrus	47	242	-37	19	-4	8.04
L superior frontal gyrus	6	1067	-17	28	53	9.34
L precuneus	39	4649	-45	-76	36	14.14
R precuneus	31	1046	3	-50	32	13.98
View > congruent > incongruent						
R amygdala**		168	20	-8	-15	5.14
L amygdala**		34	-26	1	-18	4.03
<i>Interaction emotion × task</i>						
R middle frontal gyrus	10	52*	37	55	7	6.93

All activations are effects observed in whole brain analyses significant at $P<0.005$ corrected for multiple comparisons (significant at $P<0.05$) except * significant at $P<0.005$ and ** significant at $P<0.05$ uncorrected for multiple comparisons.

Main effect of emotion: positive stimuli

The first main effect identified regions which showed a differential BOLD response for emotion. This identified inferior temporal cortex which showed significantly greater activation to positive relative to neutral stimuli (see Table 3).

Main effect of task: positive stimuli

The second main effect identified regions which showed a differential BOLD response for task. These included superior and middle frontal cortex as well as anterior cingulate gyrus (see Table 3). Superior and middle frontal cortex, as well as anterior cingulate cortex, showed increased activation during incongruent/congruent trials relative to view trials; see Fig. 5 and Table 3. In contrast, superior frontal cortex (BA 6) as well as left and right precuneus showed decreased activation during view trials relative to incongruent/congruent trials; Table 3.

Task by emotion interaction: positive stimuli

The analysis identified one region where there was a significant task by emotion interaction, middle frontal cortex BA 10 (significant

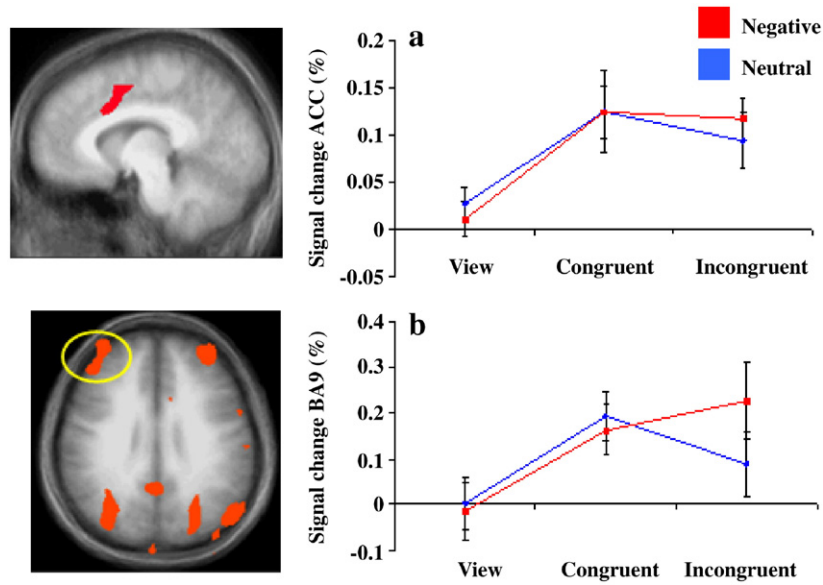


Fig. 2. The response to task involving negative stimuli for (a) left ACC (−8, 16, 28); and (b) right superior frontal gyrus (40, 38, 33).

at $p < 0.005$ uncorrected for multiple comparisons); Table 3. This activation was very proximal to the region identified by the task by emotion interaction for negative stimuli (see Table 2). The BOLD response within this region was significantly greater in

the context of positive stimuli during incongruent relative to view trials ($F(1,21)=5.37$; $p < 0.05$) but not significantly different in the context of neutral stimuli during incongruent relative to view trials ($F(1,21)=1.59$; n.s.); see Fig. 4. The BOLD response

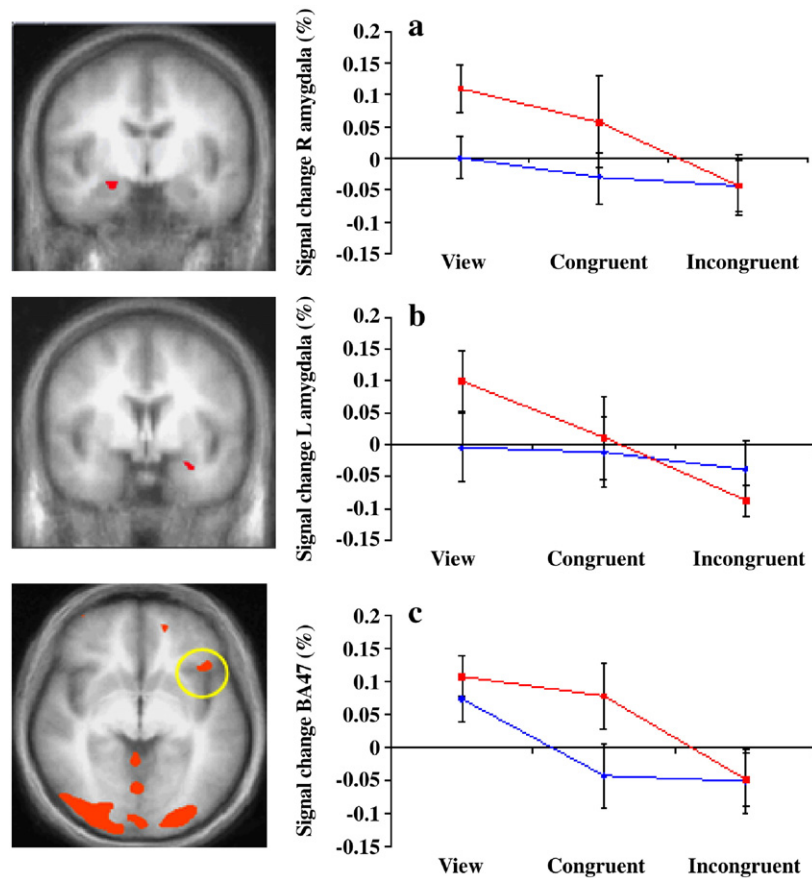


Fig. 3. The response to task involving negative stimuli for (a) right amygdala (20, −8, −15); (b) left amygdala (−26, 1, −18); and (c) left inferior frontal gyrus BA 47 (−37, 19, −4).

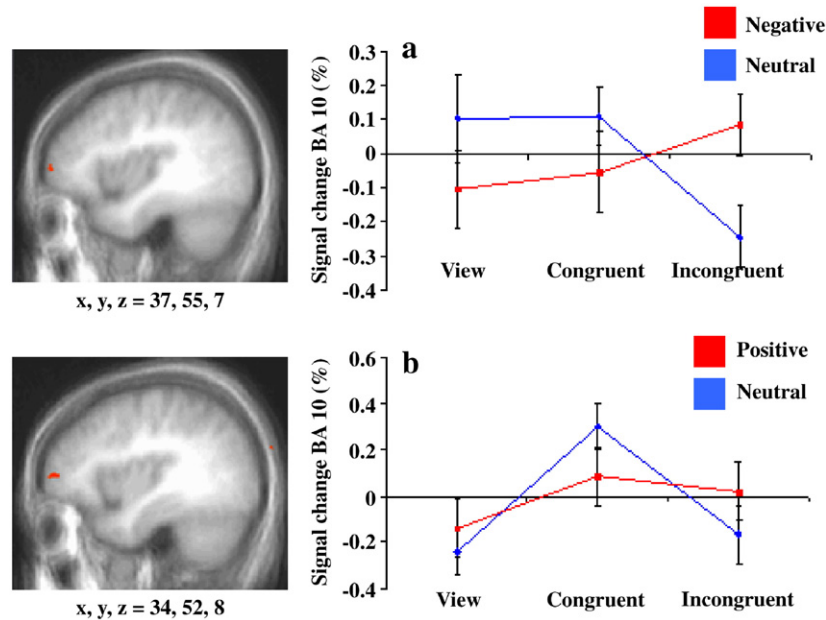


Fig. 4. The response to interaction of emotion and task load involving negative and positive stimuli for (a) right middle frontal gyrus (37, 55, 7); and (b) right middle frontal gyrus (34, 52, 8).

was significantly greater in this region in the context of positive rather than neutral stimuli during incongruent trials but not view trials ($F(1,21)=9.93$, $p<0.005$; 1.69, n.s.; for incongruent and view trials respectively). However, during congruent trials, the BOLD response was greater for neutral relative to view trials ($F(1,21)=6.79$, $p<0.05$).

Table 3
Significant areas of activation for analysis involving positive stimuli

Region	BA	mm ³	X	Y	Z	F-value
<i>Main effect emotion</i>						
R inferior temporal gyrus*	19	144	48	-81	-5	14.65
<i>Main effect task</i>						
Incongruent > congruent > view						
R superior frontal gyrus	9	3766	39	34	31	19.35
L middle frontal gyrus	10	5941	-28	49	27	15.73
R middle frontal gyrus	10	989	31	51	7	10.51
L middle frontal gyrus	11	288	-21	45	-10	9.94
L anterior cingulate gyrus	32	15,523	-15	29	18	9.46
L insula	13	2702	-28	22	3	16.57
R insula	13	4092	35	22	0	16.57
L precentral gyrus	6	9732	-56	5	13	11.49
R precentral gyrus	6	9712	37	4	26	13.99
R inferior parietal lobule	40	2250	61	-26	19	13.97
R declive		423,006	30	-60	-19	47.57
View > congruent = incongruent						
L superior frontal gyrus	6	3727	-16	27	53	16.94
R precuneus	31	1068	0	-49	32	10.47
View > congruent > incongruent						
L precuneus	39	3217	-47	-75	37	14.57
<i>Interaction emotion × task</i>						
R middle frontal gyrus	10	93*	34	52	8	8.11

All activations are effects observed in whole brain analyses significant at $P<0.005$ corrected for multiple comparisons (significant at $P<0.05$) except * Significant at $P<0.005$ uncorrected for multiple comparisons.

Connectivity analysis

If, as Ochsner has suggested, lateral frontal cortex plays a role in emotional regulation, activity in lateral frontal cortex should be positively associated with activity in regions of middle frontal cortex associated with emotional regulation and negatively associated with activity in amygdala. We found task-related activity in superior frontal cortex through the ANOVAs described above (BA 9: -31, 48, 27 and 40, 38, 33). These activations were proximal to regions of BA 9 implicated in reappraisal by both Levesque et al. (2003) and Ochsner et al. (2004) (right BA 9, Levesque et al., 2003: 36, 25, 26; bilateral BA 9, Ochsner et al., 2004: 42, 30, 38/-16, 46, 42). We therefore measured the functional connectivity between the voxel with the peak signal change for the main effect of task within right superior frontal cortex (BA 9) and other regions using functional connectivity analysis. Functional connectivity is a measure of correlated activity, derived from BOLD fMRI data, between a reference region and other neural regions.

There was a positive connectivity with a large area encompassing middle frontal cortex (see Table 4). Critically, this area covered the entire regions of activation potentially implicated in the suppression of emotional responding as indicated by the task by emotional interactions for both ANOVAs (37, 55, 7 and 34, 52, 8 respectively); see Fig. 6. In addition, there was a positive connectivity with ACC (BA 32). In contrast, there was a negative connectivity with inferior frontal gyrus (BA 47) and bilateral amygdala; Fig. 6 and Table 4.

Discussion

In this study we examined the impact of goal-directed processing on the response to emotional pictures and the impact of the response to emotional pictures on goal-directed processing. There were three principle findings: (1) emotional distractors disrupted goal-directed processing; subjects had slower RTs in the

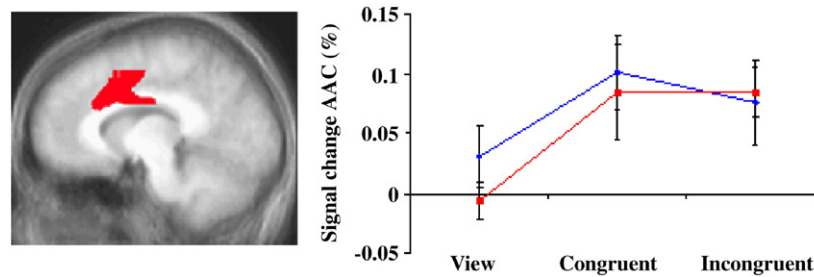


Fig. 5. The response to task involving positive stimuli for left ACC (−15, 29, 18).

presence of emotional relative to neutral distractors. This was seen for both negative and positive emotional distractors; (2) goal-directed processing disrupted the BOLD response to emotional pictures. In particular, the BOLD response within inferior frontal cortex (also referred to as ventrolateral prefrontal cortex; BA 47) and bilateral amygdala decreased as the goal-directed load increased; (3) in line with the suggestion of the importance of lateral frontal regions in emotional regulation (Ochsner, 2004), connectivity analysis revealed *positive* connectivity between lateral superior frontal cortex and regions of middle frontal cortex previously implicated in emotional suppression (Beauregard et al., 2001; Levesque et al., 2003; Ohira et al., 2006) and *negative* connectivity with bilateral amygdala. In addition, we observed significant task by emotion interactions in the BOLD responses within middle frontal cortex while performing the task ($p < 0.005$ though these did not survive correction for multiple comparisons). These interactions were seen for both negative and positive emotional distractors.

Behavioral data

In line with previous work, we observed a Stroop effect; subjects took longer to respond to incongruent than congruent trials.

Table 4
Significant areas of connectivity for analysis involving BA 9

Region	BA	mm ³	X	Y	Z	F-value
<i>Positive connectivity</i>						
R superior frontal gyrus	9	31,672	39	37	32	24.54
L superior frontal gyrus	9	1784	−31	35	32	6.83
L superior frontal gyrus	6	392	−45	1	40	5.15
R cingulate gyrus	32	5616	7	17	36	6.05
R middle temporal gyrus	20	408	55	−47	−10	4.94
L precuneus	7	2104	−27	−55	40	5.74
L middle occipital gyrus	37	504	−59	−65	−8	4.23
L middle occipital gyrus	19	696	−49	−77	−10	4.14
<i>Negative connectivity</i>						
L inferior frontal gyrus	47	4768	−39	25	−10	7.14
L inferior frontal gyrus	45	496	−47	23	18	4.83
L amygdala*		208	−27	−3	−16	3.43
R amygdala/parahippocampal gyrus		2736	27	−15	−14	4.93
L posterior cingulate gyrus	23	2104	−1	−53	14	6.13
L superior temporal gyrus	22	3088	−53	−9	4	5.60
R superior temporal gyrus	22	2232	59	−59	16	5.02

All activations are effects observed in whole brain analyses significant at $P < 0.001$ corrected for multiple comparisons (significant at $P < 0.05$) except for * significant at 0.005 uncorrected for multiple comparisons.

Moreover, and in line with earlier work (Mitchell et al., 2006), subjects were significantly slower to perform the task when stimuli were temporally bracketed by emotional rather than neutral stimuli. In addition, and again in line with our earlier work (e.g., Mitchell et al., 2006), both positive and negative emotional stimuli interfered with performance. There have been previous suggestions that only negative, and in particular frightening, stimuli can interfere with on-line processing (Hariri et al., 2000; Ohman et al., 2001; Vuilleumier et al., 2001). Our results suggest that positive stimuli can have a similar disruptive effect; the detection of food may be as important for survival as the detection of threat.

It is interesting to note that the impact of emotional distractors on behavioral performance was equivalent for the two levels of “cognitive load” of the task (congruent and incongruent trials). This suggests that the emotional distractors did not differentially disrupt the executive systems implicated in task performance. Data suggest that while disruption of the executive systems involved in the performance of Stroop tasks does impact on the performance of congruent trials, the impact is considerably greater for incongruent trials rather than congruent trials (Cohen et al., 1990, 1992). In other words, if emotional distractors were disrupting the executive systems implicated in task performance, they should have had a differentially greater impact upon incongruent rather than congruent trials. This suggestion is supported by the fMRI data. Regions identified as being implicated in task performance (e.g., ACC; precentral regions) were not significantly influenced by the presence of emotional relative to neutral distractors (see Fig. 2a; Fig. 5).

fMRI data

We observed amygdala activity in response to the negative emotional stimuli during view trials. However, this activity was significantly reduced during task trials, particularly when subjects were performing incongruent trials (see Figs. 3a/b). Theories of automaticity suggest that the amygdala responds to emotional

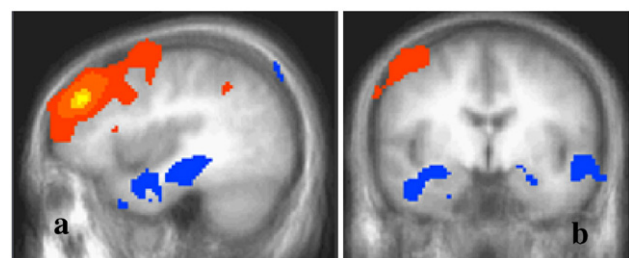


Fig. 6. The functional connectivity with DLPFC for (a) right superior frontal gyrus (39, 37, 32); and (b) left amygdala (−27, −15, −14).

stimuli regardless of attentional resources available, perhaps through a sub-cortical route (Dolan and Vuilleumier, 2003; Morris et al., 1998, 2001). It remains possible that the amygdala does receive information through a sub-cortical route independent of attention. However, the current data, together with that of Pessoa and colleagues (Pessoa et al., 2002, 2005), suggest that the amygdala also receives information through a cortical route and that this information is subject to the effects of attention. Within the framework of Desimone's model of visual attention (Desimone and Duncan, 1995) it might be suggested that in the current study, as in other studies involving the presentation of serial stimuli (Anderson and Phelps, 2001; Mitchell et al., 2006), the representation of the stimuli necessary for goal-directed processing competes with the representation of the emotional distractors, reducing their activity, so that there is less information to, and corresponding activity within, the amygdala (Blair et al., 2005).

The BOLD response within inferior frontal cortex to emotional distractors was also significantly reduced during task trials, particularly incongruent trials, relative to view trials (see Fig. 3c). Previous considerable data have reported responses in inferior frontal gyrus to emotional stimuli (Hariri et al., 2002; Heinz et al., 2005). The current data suggest that responding to emotional stimuli in this region, as well as the amygdala, is subject to top-down control related to attentional selection.

Previous work has implicated several frontal regions in emotional regulation, including lateral (typically lateral regions of 46, 9, 6/8) orbital (BA 10 and 11) and dorsomedial (BA 32 and medial BA 8) frontal cortex (Beauregard et al., 2001; Levesque et al., 2003; Ochsner, 2004; Ohira et al., 2006; Phan et al., 2005; Urry et al., 2006). Emotional regulation through reappraisal (i.e., the reinterpretation of the stimulus so that it no longer elicits a negative response) has often been associated with dorsomedial (BA 32, medial BA 8) frontal cortex and lateral regions of superior (e.g., BA 9 and 6/8) and inferior (BA 44, 46 and 47) frontal cortex (Ochsner et al., 2002, 2004; Phan et al., 2005). Emotional regulation through suppression (i.e., the distancing of the self from the stimulus/the inhibition of any emotional reaction to the stimulus) has often been associated with activation within superior frontal cortex (BA 9; Levesque et al., 2003) and middle frontal cortex/orbital (BA 10/11) frontal cortex (Beauregard et al., 2001; Levesque et al., 2003; Ohira et al., 2006); see also Hariri et al., 2002.

In the current study, both negative and positive emotional distractors caused greater interference on task performance than neutral distractors (see Table 1). However, there was no increase in BOLD responses in regions such as ACC involved in mediating task performance. Instead, there were significant ($p < 0.005$) task by emotion interactions for both the positive and negative distractors in the BOLD responses with very similar regions of middle frontal cortex (BA 10: 37, 55, 7 and 34, 52, 8 for negative and positive distractors respectively); though these activations did *not* survive correction for multiple comparisons and thus their interpretation must be treated with caution see Fig. 4. Interestingly, the literature considering emotional regulation through suppression has implicated this region/a closely proximal region in the suppression of emotional responses in healthy adults; i.e., BA 10/11 with reported peaks of 24, 46, -17 (Levesque et al., 2003), 22, 46, 13 (Beauregard et al., 2001), -30, 52, -2 (Ohira et al., 2006), 40, 28, 0 (Hariri et al., 2002); see also Urry et al. (2006). Animal data suggest that this region has at least some interconnectivity with the amygdala (Ongur and Price, 2000). In short, the suggestion can be made that this region was recruited as a consequence of the

presence of the emotional distractors to reduce emotional responding within the amygdala to these distractors.

Ochsner has argued that lateral frontal cortex may blunt processing in the amygdala indirectly via medial orbital frontal cortex by "directly modulating representations of the affective significance of a stimulus in the medial OFC" (Ochsner, 2004). We examined this suggestion through a connectivity analysis with a lateral region of superior frontal cortex seed shown to be involved in task performance. This connectivity analysis revealed significant positive connectivity between this seed region and the region of middle frontal cortex identified by the task by emotion ANOVA interactions and negative connectivity with the amygdala and inferior frontal cortex. This may indicate that lateral frontal cortex does reduce responding within the amygdala, and possibly inferior frontal cortex, by activating this region of middle frontal cortex revealed in this study, and the emotional regulation through suppression studies (Beauregard et al., 2001; Levesque et al., 2003; Ohira et al., 2006), as being important in the regulation of emotion. Moreover, the presence of this activity in the current study suggests that not only can emotional regulation via this route occur following the active process of reappraisal, where participants were asked to inhibit their emotional response, but also "automatically" as a response to emotional distractors interfering with goal-directed processing.

It is also notable that the connectivity analysis also revealed significant connectivity between the region of lateral frontal cortex involved in task performance and temporal and occipital cortex (see Table 4). It is possible that emotional regulation is not only achieved by the activation of regions of middle frontal cortex associated with the down-regulation of the amygdala but also by modulation, by the frontal cortex, of perceptual and semantic representations activated by the stimulus array; i.e., through attentional control (Blair et al., 2005; Mitchell et al., *in press*; Ochsner et al., 2002). Indeed, emotional regulation through reappraisal (i.e., the reinterpretation of the stimulus so that it no longer elicits a negative response) might be conceptualized in this way. Studies of emotional regulation through reappraisal have observed considerable modulation of activity in temporal cortex as a function of reappraisal (Ochsner et al., 2002, 2004). If non-emotional perceptual and semantic features are primed by top-down mechanisms, it can be predicted, following Desimone and Duncan (1995), that emotional features will be inhibited via representational competition (Desimone and Duncan, 1995). This in turn should lead to a reduction in the emotional response to these emotional features. It is possible that the significant connectivity between the region of lateral frontal cortex involved in task performance and temporal and occipital cortex reflects this process.

One potential caveat should be mentioned. It could be suggested that an arousal response to the emotional stimuli was affecting the deployment of cognitive resources. However, it should be noted that increased arousal has been associated with increased activity within anterior cingulate cortex (Critchley et al., 2000, 2005). While anterior cingulate cortex activity was seen in the current study, it was seen in response to task performance (congruent and incongruent trials as opposed to view trials) rather than in response to the emotional distractors.

Clinically, we would suggest that these data imply that if patients with mood and anxiety disorders are impaired in the ability to suppress the impact of emotional material on goal-directed behavior, this might reflect a decreased ability, at least in some patients, of lateral/middle frontal cortex to suppress a pathological

increased amygdala response to emotional stimuli. Current work using the current and related tasks is exploring these possibilities with patients with Generalized Anxiety Disorder and patients with Post Traumatic Stress Disorder.

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