

Threat Prompts Defensive Brain Responses Independently of Attentional Control

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Negative emotional signals are known to influence task performance, but so far, investigations have focused on how emotion interacts with perceptual processes by mobilizing attentional resources. The attention-independent effects of negative emotional signals are less well understood. Here, we show that threat signals trigger defensive responses independently of what observers pay attention to. Participants were scanned using functional magnetic resonance imaging while watching short video clips of threatening actions and performed either color or emotion judgments. Seeing threatening actions interfered with performance in both tasks. Amygdala activation reflected both stimulus and task conditions. In contrast, threat stimuli prompted a constant activity in a network underlying reflexive defensive behavior (periaqueductal gray, hypothalamus, and premotor cortex). Threat stimuli also disrupted ongoing behavior and provoked motor conflict in prefrontal regions during both tasks. The present results are consistent with the view that emotions trigger adaptive action tendencies independently of task settings.

Keywords: attention, defense, emotion, fMRI, threat

Introduction

Adaptive behavior entails attending to the task at hand while remaining able to promptly detect and react to relevant or unpredictable threat signals in the environment. How does the brain achieve a balance between these 2? There is now clear evidence that salient stimuli influence the course of perceptual processes. Emotional signal processing, notably that of threatening facial and bodily expressions, is prioritized (Hansen and Hansen 1988; Ohman et al. 2001; Fox and Damjanovic 2006; Tamietto et al. 2007; Becker 2009; Zeelenberg and Bocanegra 2010). Animal and human studies support the view that the amygdala increases vigilance and facilitates perceptual processing (Whalen 1998; Davis and Whalen 2001; Vuilleumier et al. 2004) and is particularly sensitive to threatening stimuli (LeDoux 1995; Morris et al. 1996; Whalen 1998; Phelps and LeDoux 2005; Hoffman et al. 2007). In line with this, several researchers have argued that the amygdala operates relatively independently of whether or not the stimulus is attended to (Vuilleumier et al. 2001; Ohman 2002; Dolan and Vuilleumier 2003). This does not exclude top-down influences as high task demands have been shown to reduce amygdala responses (Pessoa et al. 2002; Bishop et al. 2007; Mitchell et al. 2007; Silvert et al. 2007; Lim et al. 2008; Pessoa 2008).

In addition to facilitating perceptual processing, threat signals also trigger physiological reflexes and influence ongoing behavior (Davis et al. 1993; Ohman et al. 1995; Hamm et al.

1997; Lang et al. 1998; Panksepp 1998; Williams et al. 2005; Pessoa 2009). The underlying rationale seems to be that threatening stimuli enhance responsiveness in regions related to defensive behavior. In monkeys, premotor neurons of the region polysensory zone (PZ) respond to looming stimuli and the electrical stimulation of the same neurons produces defensive movements (Cooke and Graziano 2004; Graziano and Cooke 2006). In humans, observing threatening actions (as compared with neutral or joyful actions) increases activity in regions involved in action preparation: premotor cortex (PM), pre-supplementary motor area (pre-SMA), and inferior frontal gyrus (IFG) (de Gelder et al. 2004; Grosbras and Paus 2006; Grèzes et al. 2007; Pichon et al. 2008, 2009). Also, exposure to anger signals increases activity in the amygdala and the hypothalamus (Pichon et al. 2008, 2009), 2 nuclei that are part of subcortical networks that interface with motor and autonomic systems important for the emotional experience of fear and rage (Bard 1928; Brown et al. 1969; Siegel and Edinger 1983; LeDoux 1995; Panksepp 1998; Canteras 2002; Barbas et al. 2003; Sowards and Sowards 2003; Adams 2006).

But while the effects of threatening stimuli on the attentional demands in perception have already been explored, it remains largely unknown whether attention influences activity in action and defense-related brain areas. Amygdala response to threat can be altered by a high task load, but other brain regions may react relatively independently and continue to support adaptive behavior and action preparation whatever the task at hand. If so, motor-related regions may react differently to task conditions and attentional demands than will the amygdala. Here, we tested this hypothesis using functional magnetic resonance imaging (fMRI). Participants watched movies of threatening and of neutral bodily actions. In one condition, they were requested to name the color of a dot that appeared very briefly on the actor's upper body (color-naming task) while in the other condition they named the emotional expression of the actor (emotion-naming task). The motivation to use a demanding color-naming task was to isolate threat-responsive regions independently of the task requirements. As stimuli, we used dynamic actions expressing fear and anger that were previously shown to elicit strong activations in subcortical and cortical regions important for preparation of defensive behavior (de Gelder et al. 2004; de Gelder 2006; Grèzes et al. 2006; Grosbras and Paus 2006; Pichon et al. 2008, 2009).

Materials and Methods

Participants

Sixteen right-handed volunteers (8 females; mean age = 25.6 years \pm SD = 8; and 8 males; mean age = 23.5 years \pm 2.6) with no neurological or

psychiatric history participated in the imaging study. All provided written informed consent according to institutional guidelines of the local research ethics committee and were paid for their participation.

Stimuli

Seventy-one full-light 3-s videos (23 fear, 24 anger, and 24 neutral) were used for the present experiment. Videos were selected from a larger set of stimuli based on the recognition performance obtained in a pilot study and were previously used (Grezes et al. 2007; Pichon et al. 2008; Pichon et al. 2009). One fear movie was dropped because of frequent misclassification. A group of 12 semiprofessional actors (6 males), all graduates from a professional acting school, were hired in order to account for variability in acting style. They were paid for their services. Under professional direction, they enacted different scenarios corresponding to fearful, angry, and neutral situations. The fear script instructed the actors to open the door and face a threat (human or nonhuman, such as a snake). The anger version of this scenario also consisted of opening the door but at the same time reacting to someone or something that made them angry. We used these 2 emotions because, for the observer, perceiving a fearful expression or an angry expression directed at oneself signals a potential threat (Dimberg 1986; Schupp et al. 2004; Strauss et al. 2005). Therefore, in order to create the impression for the observer to be involved in the scene, the recordings were made with the camera positioned directly facing the door viewed from the outside. For the neutral scenario, the actors were required to open the same door in a neutral way. The actors' performance was repeated until deemed satisfactory by the director. Importantly, faces were blurred such that only information from the body was available. All video clips were further computer edited to insert a small color dot (red, green, or blue, visual angle = 0.3°) that was briefly flashed during 50 ms at random times in the second half of the movie. To minimize shifts in spatial attention between tasks, the location of the color dot was carefully chosen so that it always fell on the actor's upper body. Colors were randomized across emotional expressions.

Design and fMRI Procedure

We aimed at comparing the neural responses induced by attended or unattended threatening and neutral actions. To manipulate attention, we used 2 tasks (see Fig. 1). During the emotion-naming task, subjects attended video clips of body expressions and were asked to judge whether the action was neutral, signaled fear, or signaled anger. In the color-naming task, subjects were requested to detect a color dot appearing briefly (50 ms) during the video clip and to report whether it

was red, green, or blue. Importantly, the video materials including the color dots were the same in both conditions such that actions were to be ignored in the color-naming task and colors were to be ignored in the emotion-naming task.

The experiment was divided into 2 successive scanning runs of 21 min each. Within each run, stimuli were blocked by task and blocks alternated between series of attention to emotion or attention to color tasks. At the beginning of each block, subjects were instructed by a text on the screen lasting 2 s whether they had to recognize emotions or detect colors. Stimuli and null events (5 s) were randomly mixed within blocks. Each task block contained 6 events (including nulls). After each stimulus presentation, subjects were instructed by a response screen (fear/anger/neutral or red/green/blue) to push the corresponding button using a response pad placed in their right hand. Subjects had a delay of 2 s to give their answer. The order of responses was randomized between trials to avoid motor anticipation-related effects. A total of 36 blocks per task was presented (142 video clips + 74 null events per task). Stimuli were back projected onto a screen positioned behind the subject's head and viewed through a mirror attached to the head coil. The stimulus was centered on the display screen and subtended 10.8° of visual angle vertically and 7.3° horizontally.

fMRI Data Acquisition

Gradient-echo T_2^* -weighted transverse echo-planar images (EPI) with blood oxygenation level-dependent (BOLD) contrast were acquired with a 3-T Siemens Magnetom Trio scanner (Siemens, Erlangen, Germany). Participants used earplugs to attenuate scanner noise, and padding was used to reduce head movements. Each volume contained 32 axial slices (repetition time [TR] = 2000 ms, echo time [TE] = 30 ms, 3.5 mm thickness without gap yielding isotropic voxels of 3.5 mm³, flip angle = 90°, field of view [FOV] = 224 mm, resolution = 64 × 64) acquired in an interleaved manner. An automatic shimming procedure was performed to minimize inhomogeneities of the static magnetic field. We collected a total of 1270 functional volumes for each subject as well as high-resolution T_1 -weighted anatomical images (TR = 2250 ms, TE = 2.6 ms, slice thickness = 1 mm, 192 sagittal slices, flip angle = 9°, FOV = 256 mm, resolution = 256 × 256). We administered the behavioral protocol using Presentation software (www.neurobs.com).

fMRI Image Processing

Image processing was carried out using SPM2 (Wellcome Department of Imaging Neuroscience; see www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks Inc., Sherborn, MA). The first 5 volumes of each scanning run were discarded to avoid T_1 saturation effects. The remaining 1260 functional images were reoriented to the AC-PC line, corrected for differences in slice acquisition time using the middle slice in time as reference, spatially realigned to the first volume by rigid body transformation, spatially normalized to the standard Montreal Neurological Institute (MNI) EPI template to allow group analysis, resampled to an isotropic voxel size of 2 mm, and spatially smoothed with an isotropic 8-mm full width at half-maximum Gaussian kernel (Friston et al. 1995).

Behavioral Analysis

Reaction times (RTs) and accuracy were analyzed by means of repeated measures analyses of variance (ANOVAs) with task (emotion and color) and expression (threat and neutral) as within-subject factors. Two-tailed paired *t*-tests were used for comparisons between experimental conditions. We considered 3 significance levels: 0.05, 0.01, and 0.001.

fMRI Image Analysis

A 2-stage general linear model (GLM) was used to examine the effect sizes of each condition and compare them to the group level. The statistical analyses were also carried out using SPM2.

At the subject level, we performed standard GLM analyses where task-related signal changes were modeled separately for each subject. Fear and anger expressions were collapsed into a single regressor to estimate threat-specific effects. Beforehand, we used the behavioral data to ensure that the recognition of fear and anger did neither differ

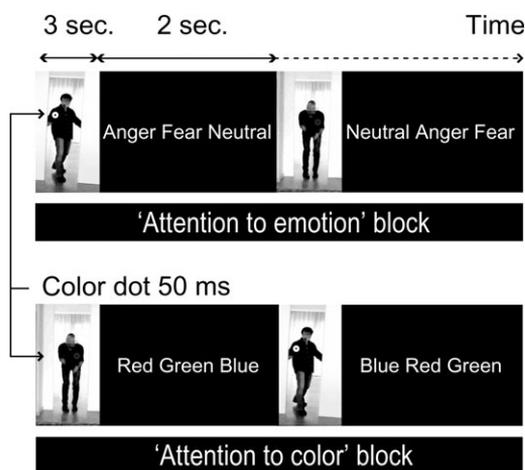


Figure 1. Experimental design and stimulus examples. Subjects viewed a video sequence showing an actor expressing a threatening or neutral action and a color dot appearing briefly for 50 ms onto the actor's upper body. Depending on the task, subjects categorized the emotion or the color of the dot.

in terms of main effects of task or expression (repeated measures ANOVA, $P > 0.4$ and $P > 0.08$) nor was there an interaction between both factors although the P value was close to significance ($P = 0.056$). Additional paired t -tests showed that the recognition rates between anger and fear did differ neither in the color task ($T_{1,15} = -0.68$, $P = 0.503$) nor in the emotion task ($T_{1,15} = 1.8$, $P = 0.084$). For RTs, neither main effects of task or expression nor their interaction reached significance (all P values > 0.35). We modeled 5 conditions for each session: 4 conditions modeled the occurrence of threat and neutral stimuli within each task (emotion and color). The fifth condition was used to model the instruction screen preceding each block. For each condition, a covariate was calculated by convolving the onset of each event with a canonical hemodynamic response function over a duration that encompassed the stimulation (3 s) and the response (2 s) periods. Six additional covariates were modeled per session, corresponding to the temporal derivatives of the realignment parameters (the difference between scans in the estimation of the 3 rigid body translations and the 3 rotations determined from initial spatial registration) in order to capture residual movement-related artifacts. A last constant covariate represented the session-specific mean over scans. The model included a high-pass filter with a standard cutoff period of 128 s to account for low-frequency noise of the scanner. Effects at each brain voxel were estimated using a least squares algorithm to produce condition-specific images of parameter estimates for each experimental condition.

At the group level, we performed 2-way repeated measures ANOVA with the factors task (emotion and color) and expression (threat and neutral). In this way, the variance estimates at the group level incorporated appropriately weighted within-subject and between-subject variance effects. A nonsphericity correction was applied for variance differences across conditions. After model estimation, we calculated the following contrasts:

1. To isolate threat-driven responses independently of task, we performed a conjunction analysis (null hypothesis) between the 2 following contrasts: emotion-naming task (threat vs. neutral) and color-naming task (threat vs. neutral).
2. Within threat-responsive regions revealed in 1, we performed correlation analyses with the slowing in response times observed when subjects processed threat stimuli in both tasks. We used the magnitude of the contrast of threat versus neutral stimuli (estimated for each subject at the first level) and the difference in response time between threat and neutral conditions. These correlations were calculated separately for emotion- and color-naming tasks (see Supplementary Table S3).
3. We then estimated brain regions showing a task-by-expression interaction, that is, regions that showed a greater differential response between threat and neutral stimuli in the emotion-naming task as compared with the color-naming task (see Fig. 4 and Table 2, inclusive masking procedure using the simple effect of naming threatening vs. neutral actions).
4. To isolate responses showing an additive effect of threat and task, we estimated a conjunction (see Table 3) between the following contrasts: emotion-naming task (threat vs. neutral), color-naming task (threat vs. neutral), threat stimuli (emotion-naming vs. color-naming task), and neutral stimuli (emotion-naming vs. color-naming task).
5. We calculated the main effects specific to each task to ensure they were associated with consistent BOLD responses within brain regions engaged in emotion- and color-naming tasks (see Fig. 5, Supplementary Figs S1 and S2 and Supplementary Tables S1 and S2).

For all statistical maps, we report activations that survived the threshold of $T > 3.28$ ($P < 0.001$, uncorrected) and indicate peaks that survived false discovery rate correction (Genovese et al. 2002). We also inspected all contrasts with a liberal threshold of $P = 0.005$ in a priori regions of interest (amygdala, hypothalamus, and periaqueductal gray [PAG]) and reported these brain areas when they survived small volume correction (SVC) (familywise error [FWE], $P < 0.05$) (peaks from the meta-analysis of Kober et al. 2008, [± 2 -30 -6] for PAG and [± 10 -6 -6] for hypothalamus, SVC 5 mm). Illustrations of maps were overlaid on the ICBM-152 brain template. Anatomical labeling was performed with reference to the atlas of Duvernoy (1999) and the anatomy toolbox

(Eickhoff et al. 2005). Surface rendering of statistical maps and estimation of Brodmann areas (BAs) were carried out using Caret (Van Essen et al. 2001) and the PALS-B12 atlas (Van Essen 2005), an average brain atlas derived from structural MRI volumes of 12 normal young adults that were adjusted to the ICBM-152 space. Finally, to ensure that threat-related responses were not led by fear or anger only, we estimated a new GLM where fear and anger responses were modeled separately and compared using post hoc t -tests fear and anger responses in the above regions of interest (see Figs 3 and 4).

Results

Quantitative and Qualitative Analyses of Video Clips

In order to control for quantitative differences in movement between the anger, fear, and neutral movies, we estimated the amount of movement per video clip by quantifying the variation of light intensity (luminance) between pairs of frames for each pixel. For each frame, these absolute differences were averaged across pixels that scored higher than 10 (on a scale reaching a maximum of 255), a value which corresponds to the noise level of the camera. These estimations were then averaged for each movie, and the resulting scores were used to test the hypothesis of a difference in movement between expressions. Mean quantification of movement for threat and neutral movies (see Fig. 2C) were, respectively, 40.69 ± 6.18 and 40.03 ± 4.82 (40.88 ± 7.56 for fear and 41.12 ± 6.72 for anger). No significant differences were detected between threat and neutral movies or between fear, anger, and neutral movies (all P values > 0.4).

To assess potential differences in emotional intensity between fear and anger movies, each movie was also rated by a different group of 39 subjects using a graded Likert scale with extremities labeled "low" and "high" (27 females, mean age = 22.63 ± 2.47 years; and 12 males, mean age = 21.45 ± 2.07 years). Subjects could slide a mouse cursor along this scale and the scores collected ranged from 0 to 100. Mean estimations of intensity for threat and neutral movies (see Fig. 2E) were, respectively, 47.1 ± 12.9 and 12.3 ± 19 (48.1 ± 13.2 for fear and 46.2 ± 13.6 for anger). A repeated measure ANOVA revealed a significant difference between fear, anger, and neutral expressions ($F_{2,74} = 99.18$, $P < 0.001$, Greenhouse-Geisser sphericity correction). Post hoc paired t -tests corrected for multiple comparisons showed that whereas fear and anger movies were rated similarly ($T_{1,37} = 1.59$, $P = 0.36$), they were perceived as more intense than neutral movies (respectively, $T_{1,37} = 10.51$, $P < 0.001$, and $T_{1,37} = 10$, $P < 0.001$).

Behavioral Results

RTs and accuracy were analyzed by means of repeated measures ANOVAs with task (emotion and color) and expression (threat and neutral) as within-subject factors. RTs showed that threatening stimuli influenced performance in both emotion- and color-naming tasks. Subjects' responses were slower for threatening stimuli compared with neutral ones (main effect: $P < 0.05$; simple effect in the emotion-naming task: $P = 0.11$; simple effect in the color task: $P < 0.05$; Fig. 2A). We also observed a cumulative effect across trials since response time also increased when the preceding trial was a threatening stimulus as compared with a neutral one ($P < 0.05$; Fig. 2B). This effect is comparable to the interference observed in emotional variants of the Stroop task, which show that naming a word, a color, or performing a lexical decision is

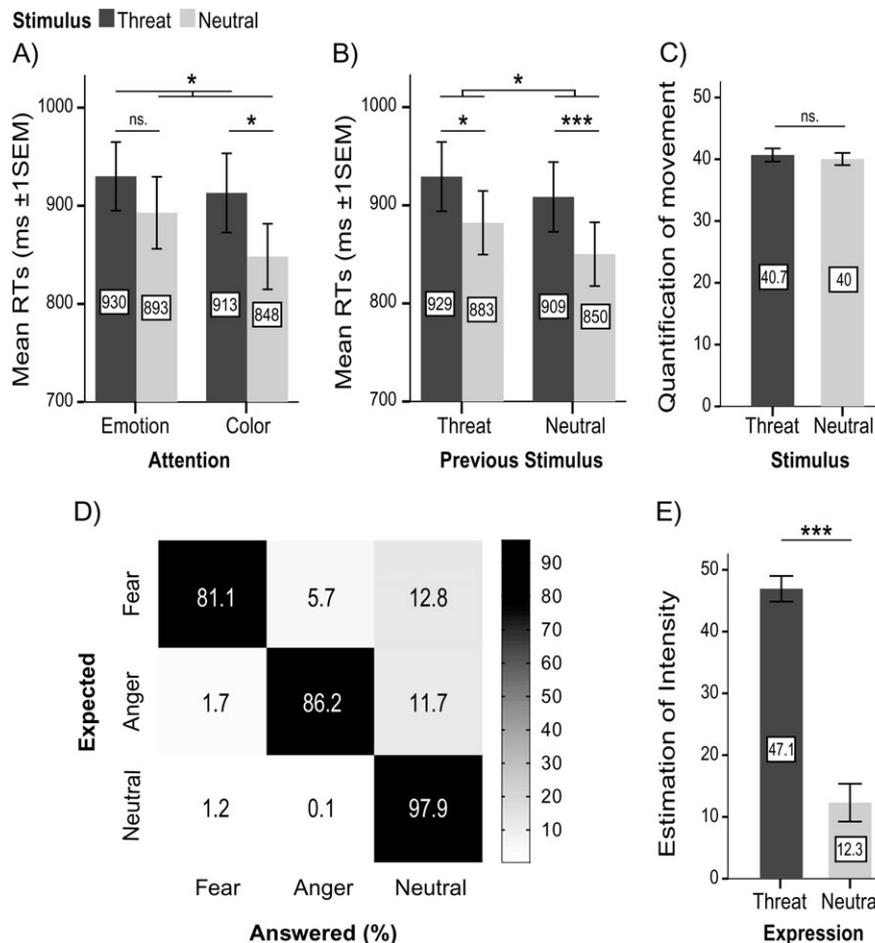


Figure 2. Behavioral results. (A) RTs plotted as a function of attention and stimuli expressions showed that threatening stimuli were recognized more slowly than neutral ones. (B) This effect was cumulative in time since RTs were increased when the previous trial contained a threatening stimulus. (C) Mean quantification of movement across expressions was estimated by quantifying, for each video clip, the variation of light luminance between pairs of frames for each pixel. According to this quantification, threat and neutral movies did not differ significantly. (D) Confusion matrix showing that all expressions were clearly recognized above chance during the emotion-naming task (percentages displayed take into account omitted responses that are not displayed here). (E) Mean emotional intensity scores across expressions. Subjects rated threat movies as subjectively more emotionally intense than neutral ones. Error bars represent standard error of the mean. The asterisks denote levels of statistical significance (* $P < 0.05$, *** $P < 0.001$).

slower when the underlying stimulus is emotional (Mathews 1990; Fox 1993; Algom et al. 2004). This increase in response latency provides an index of the extent to which the task-irrelevant emotional stimulus was processed (Okon-Singer et al. 2007). Accuracy showed that participants performed well in both emotion- (88.5 ± 4.7%) and color-naming tasks (77.3 ± 20.2%), although the color-naming task was more difficult ($P < 0.05$). Additional paired t -tests showed that the recognition rates between anger and fear did differ neither in the color task ($T_{1,15} = -0.68$, $P = 0.503$) nor in the emotion task ($T_{1,15} = 1.8$, $P = 0.084$), although this almost significant result may suggest that anger movies tend to be slightly better identified than fearful movies (86.2% vs. 81.1%). For RTs, there were no significant differences between fear and anger in both tasks (all P values > 0.22).

Brain Regions Responsive to Threat

To identify brain regions responsive to threat, we searched for all voxels that responded to the presentation of threatening versus neutral actions both in the emotion-naming and the color-naming tasks. Independent of task requirements, exposure to threatening body signals produced increased activity in the PAG and the posterior medial hypothalamus, subcortical structures that play a considerable role in autonomic reflexes

and integrated defensive behaviors (Carrive 1993; Panksepp 1998; McNaughton and Corr 2004; Mobbs et al. 2007). Coordinates of the present PAG activation were similar to those reported previously for imminent danger ($x y z$: [3 -25 -7] in Mobbs et al. 2007; $x y z$: [2 -26 -4] here). Activity also increased in cortical regions including right lateral PM, bilateral anterior insula, pre-SMA, and left IFG BA44 (see Fig. 3, the full list of activations is provided in Table 1). The same network was revealed at $P < 0.005$ uncorrected when modeling correct trials only. We also tested whether activity in these regions was modulated by the task using ANOVA with beta values associated with each maximum peak. Only the right anterior insula ($F_{1,15} = 15.881$, $P = 0.001$) and the hypothalamus ($F_{1,15} = 13.761$, $P = 0.002$) showed a main effect of task, with higher activity during the emotion-naming task for the right anterior insula and higher activity during the color-naming task for the posterior hypothalamus. We could not detect any main effect of task or any task-by-threat interaction in IFG BA44 (all P values > 0.65), pre-SMA (P values > 0.18), left anterior insula (P values > 0.36), right PM (P values > 0.63), and PAG (P values > 0.59). Finally, to ensure that these responses were not led by fear or anger only, we estimated a new GLM where fear and anger responses were modeled separately and compared using

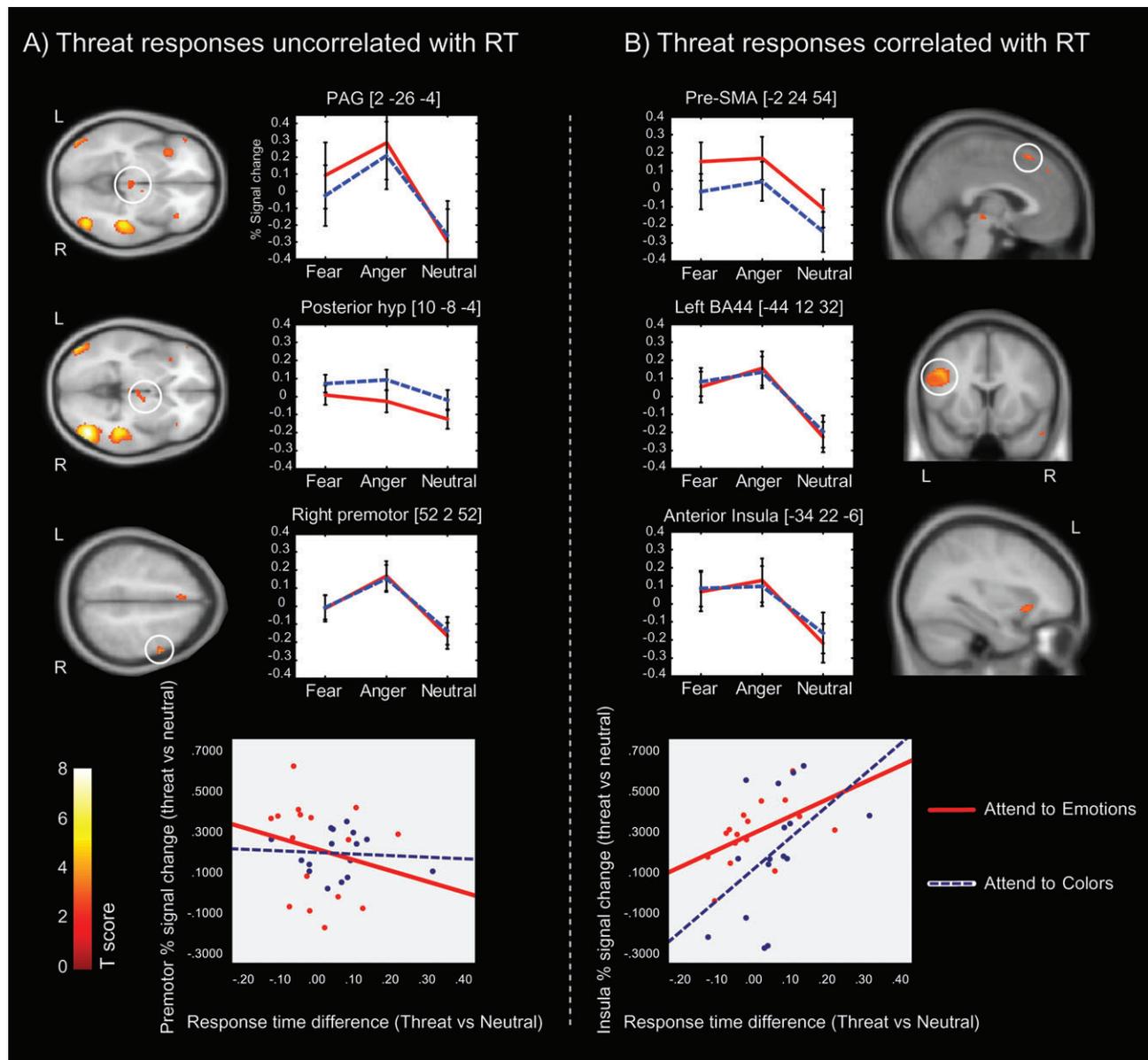


Figure 3. Statistical map representing threat-responsive regions, irrespective of the task performed by subjects. (A) On the left, group ($n = 16$) average activations and percent signal change at local maxima in the PAG extending to posterior medial hypothalamus (HYP) and right lateral PM. (B) On the right, group average activations and percent signal change at local maxima in pre-SMA, left IFG BA44, and anterior insula for the same contrast across tasks. The lower scatterplots show that during exposure to threat, anterior insula (right scatterplot) was significantly correlated with slowing in response times in both tasks, whereas activity in lateral PM, PAG, or HYP was not (left scatterplot). This correlation was also true in the demanding color-naming task for the pre-SMA and left BA44 (see Supplementary Table S3). Activations were rendered on sections of the ICBM-152 average T_1 -weighted brain (SPM(t), thresholded at $P < 0.005$ uncorrected for illustrative purpose only, error bars represent 95% confidence interval, and emotion- and color-naming tasks represented, respectively, by the red solid line and blue dotted line).

post hoc t -tests fear and anger responses in the above regions of interest. We observed no difference between fear and anger. P values were, respectively for the emotion- and color-naming tasks, $P = 0.21$ and $P = 0.22$ in PAG, $P = 0.58$ and $P = 0.57$ in right hypothalamus, $P = 0.77$ and $P = 0.66$ in right pre-SMA, and $P = 0.07$ and $P = 0.51$ in left BA44. Only right PM response was stronger for anger as compared with fearful stimuli in both tasks ($P < 0.001$ and $P = 0.015$).

Within the above brain areas, we then searched for a neural signature of the behavioral response pattern. We performed correlation analyses between magnitude of activity within above threat-responsive regions independent of task demands

and response time slowing observed during exposure to threat stimuli as compared with neutral ones (Fig. 3A,B). Trials where subjects made an error were not taken into account for the calculation of this RT index. Correlations were performed separately for each task using the contrast (threat vs. neutral) specific to emotion- or color-naming tasks. Mean contrast values were extracted for each subject using a 5-mm sphere centered onto the group mean coordinates of the above regions (pre-SMA, bilateral anterior insula, left BA44, PAG, hypothalamus, and right lateral PM, see Table 1). We observed significant positive Spearman rho correlations during the color-naming task in left BA44 ($r = 0.494$, $P = 0.026$), pre-SMA ($r =$

0.694, $P = 0.001$), left ($r = 0.667$, $P = 0.002$), and right anterior insula ($r = 0.794$, $P < 0.001$) and during the emotion-naming task in left anterior insula only ($r = 0.579$, $P = 0.009$), with a trend toward significance in pre-SMA ($r = 0.374$, $P = 0.1$). The same results were found when modeling correct trials only. In contrast, PAG, hypothalamus, and right lateral PM were not correlated with behavioral interference effects (see Supplementary Table S3 for full correlation results).

Table 1
Conjunction analysis of brain regions showing an effect of threat (vs. neutral) in both tasks

R/L	Anatomical region	MNI coordinates			Z value	Size in voxels
		x	y	z		
L	pre-SMA	-2	24	54	3.21 ^a	3
L	Inferior frontal sulcus (BA44)	-44	12	32	3.92 ^a	227
L and R	Anterior insula	±38	30	-6	3.17/3.3 ^a	6/2
R	PM	52	2	52	3.28 ^a	11
R	Thalamus	8	-10	0	3.1 ^a	1
R	Hypothalamus dorsal	10	-8	-4	3.03 ^b	88
R	PAG	2	-26	-4	2.63 ^b	↓ 88
L	Fusiform gyrus	-40	-44	-22	4 ^a	96
R	Fusiform gyrus	44	-48	-20	3.65 ^a	29
R	STS, posterior part	46	-36	-2	5.17 ^a	↓ 1912
L and R	STS, posterior part	±50	-50	8	4.76/4.85 ^a	↓ 1067/↓ 1912
L and R	Middle temporal gyrus (MTV5/EBA)	±48	-66	4	5.28/7.16 ^a	1067/1912
L	Occipital pole	-16	-104	8	3.37 ^b	20

^aIndicates activation peaks that survive false discovery rate correction ($P < 0.05$) with a height threshold of $P < 0.001$ (uncorrected). MTV5, middle temporal V5 complex; EBA, extrastriate body area.

^bIndicates peaks in a priori regions (amygdala, hypothalamus, and PAG) that survive SVC (FWE $P < 0.05$) at $P < 0.005$ uncorrected. Subpeaks in clusters marked with ↓

Brain Regions Responsive to Threat during the Emotion-Naming Task

As expected from the literature (Winston et al. 2003), amygdala activity increased when subjects perceived threatening stimuli (vs. neutral) and were requested to name the emotion (Fig. 4B). This effect was not observed in the color-naming task (Fig. 4C). Therefore, we identified voxels that showed a task-by-threat interaction (Fig. 4A), that is to say which responded more to threatening stimuli than neutral ones, in the emotion-naming task as compared with the color-naming task (inclusive masking procedure of the interaction with the simple effect emotion-naming threat vs. emotion-naming neutral and a threshold of $P < 0.001$ uncorrected). This interaction revealed increased bilateral anterior hippocampus response to threat during the emotion-naming task only (left: [-16 -14 -16], $Z = 5.44$, and right: [32 -8 -22], $Z = 3.9$). Careful examination using the anatomy toolbox (Eickhoff et al. 2005) established that a portion of each cluster extended to the posterior part of the amygdala. This illustrated the tendency toward interaction in the parameter estimates of the amygdala, that is, a difference between threatening and neutral stimuli only detected in the emotion-naming task (see Fig. 4 and Table 2 for full results). Moreover, we identified brain areas that showed additive effects of threat and emotion-naming task, such that responses to threat stimuli were elevated relative to neutral actions and were increased in the emotion-naming task relative to the color-naming task (see Table 3 for full results). We detected, among other areas, the superior temporal sulcus (STS), the fusiform gyrus, and the IFG. Again, we performed post hoc t -tests to ensure that responses to threat observed in amygdala and hippocampus during the emotion-naming task

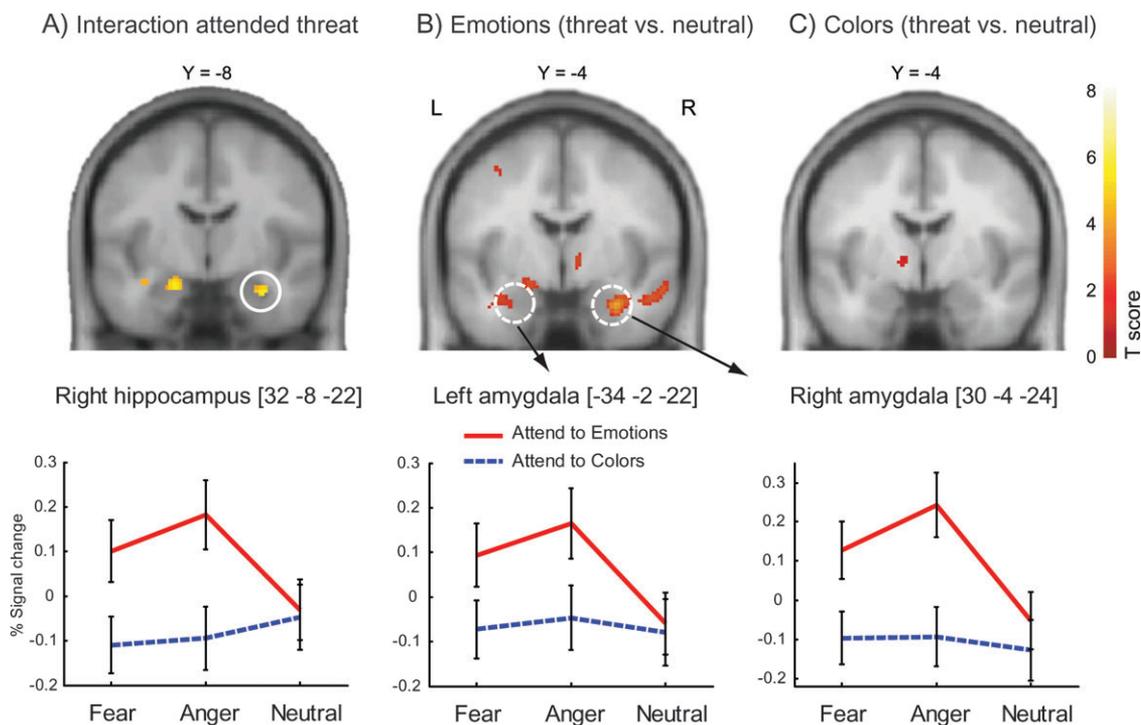


Figure 4. Attentional modulation in hippocampus and amygdala. Group average activation and percent signal change showing (A) the interaction for attended threat in the right anterior hippocampus/posterior amygdala and (B) the bilateral amygdala response to threat in the emotion-naming task. (C) Contrasting threat to neutral stimuli in the color-naming task yielded no significant response in bilateral hippocampus or amygdala, even using a liberal threshold of $P = 0.005$ uncorrected as shown in the present contrast. Plots were computed on local activation peaks and use the same conventions as in Figure 3; SPM(t) thresholded at $P < 0.001$ uncorrected (< 0.005 for C).

were not led either by fear or anger. No significant difference between fear and anger was observed in right hippocampus ($P = 0.27$ and $P = 0.77$) and left ($P = 0.14$ and $P = 0.77$) or right amygdala ($P = 0.16$ and $P = 0.95$).

Effectiveness of Task Manipulations

To further assess the validity of our experimental manipulation, we established that both tasks effectively influenced the activity of the specific brain areas, which play a key role in body and color perception, respectively (see Supplementary Figs S1 and S2). On the one hand, the contrast between emotion- versus color-naming tasks revealed increased activity in the fusiform body area (see Fig. 5A, and Supplementary Table S1 for full results), which is indeed known to selectively respond to perception of whole bodies, body parts, and schematic depictions of body shapes (Peelen and Downing 2005; Schwarzlose et al. 2005; Peelen et al. 2006). On the other hand, the contrast between situations where subjects attended to colors versus emotions also revealed significant responses in the fusiform gyrus but in a more posterior area than the peak observed in the emotion-naming task (see Fig. 5B, and Supplementary Table S2 for full results). This location

corresponds to the location of the human visual area V4 ($x y z_{\text{TAL}}$: [20 -66 -4] and [-26 -68 -8], corresponding to MNI coordinates [20 -68 -9] and [-26 -70 -14], from Zeki et al. 1991) important for color perception (Lueck et al. 1989; McKeefry and Zeki 1997; Gallant et al. 2000). Thus, both tasks met our experimental requirements as they induced task-specific modulations in regions involved in body or color perception.

Discussion

The present study explored the neural bases of the ability to carry out a task while still being able to react to threatening signals in the environment. We compared behavioral performance and brain activation in a color-naming and an emotion-naming condition. We identified 2 subcortical networks. The first, which includes the PM, the hypothalamus, and the PAG, is impervious to attentional influence from task demands. Its reactivity to threatening stimuli is the same whether or not the subjects attend to the affective content of actions and this irrespective of the changes in amygdala's activity that were modulated by the task. We suggest that this network plays a role in reflexive defensive actions. In addition, threatening stimuli impact subject's behavioral responses in both tasks and provoke motor conflict in the first network's prefrontal areas. This is reflected by a correlation between the magnitude of activity within these regions and response time slowing between threatening and neutral signals. The second network, which includes the amygdala and regions of the temporal cortex such as the fusiform gyrus and the STS, is susceptible to influence from task demands and emotional factors as it primarily responds when subjects attend to actions and their affective content.

Threat-Related Subcortical Network Independent of Tasks

The set of brain areas responsive to threatening expressions but unaffected by the type of attention (either the emotion- or color-naming task) consists of the subcortical structures PAG, hypothalamus, and thalamus and of a cortical premotor area at the border between ventral and dorsal PM (PMv/PMd). The observed subcortical areas are well known for their role in emotional reactivity (Bard 1928; Hess and Akert 1955; Brown et al. 1969; Siegel and Edinger 1983; Blanchard and Blanchard 1988; Carrive 1993; Panksepp 1998; Canteras 2002; Swards

Table 2

Brain regions showing a significant interaction for attended threat

R/L	Anatomical region	MNI coordinates			Z value	Size in voxels
		x	y	z		
L	Medial superior frontal gyrus (dmPFC BA9)	-6	64	28	4.2 ^a	249
L	Posterior orbital gyrus	-28	22	-20	3.91	49
R	IFG (BA45)	50	32	-2	3.2	7
L	Anterior hippocampus (extending to amygdala)	-16	-14	-16	5.44 ^a	118
R	Anterior hippocampus (80%/amygdala (50%))	32	-8	-22	3.9	38
R	Pulvinar	14	-30	0	3.7	27
L	Thalamus	-4	-16	6	3.23	2
L	Parahippocampal gyrus	-12	-34	-4	3.35	16
L	Temporoparietal junction, supramarginal gyrus	-56	-40	24	3.31	7
R	Fusiform gyrus	38	-56	-12	3.31	2
R	Fusiform gyrus	40	-58	-10	3.14	1
R	STS	50	-16	-10	3.22	6
R	STS	46	-28	2	3.17	1
R	STS	62	-32	2	3.18	5

^aIndicates activation peaks that survive false discovery rate correction ($P < 0.05$) with a height threshold of $P < 0.001$ (uncorrected). dmPFC, dorsomedial prefrontal cortex.

Table 3

Brain regions showing an additive effect of threat and the emotion recognition task

R/L	Anatomical region	MNI coordinates			Z value	Size in voxels
		x	y	z		
R	Lateral orbitofrontal cortex (BA47)	38	30	-6	3	1
L	IFG (dorsal BA45)	-54	22	24	3.39	19
R	Temporoparietal junction, supramarginal gyrus	54	-34	24	3.91 ^a	↓ 1352
L and R	Fusiform gyrus (fusiform body area)	±40	-42	-24	3.98/3.65 ^a	33/27
R	STS, posterior part	48	-32	-4	4.98 ^a	↓ 1352
L	STS, posterior part	-58	-62	8	4.12 ^a	270
L and R	STS, posterior part	±50	-50	8	3.86/4.85 ^a	↓ 270/↓ 1352
R	STS, horizontal segment	52	-60	8	5.43 ^a	1352
R	Middle temporal gyrus (MTV5/EBA)	52	-74	2	3.32 ^a	↓ 1352
L	Inferior occipital gyrus	-44	-86	-6	4.24 ^a	28

^aIndicates activation peaks that survive false discovery rate correction ($P < 0.05$) with a height threshold of $P < 0.001$ (uncorrected). Subpeaks in clusters marked with ↓. MTV5, middle temporal V5 complex; EBA, extrastriate body area.

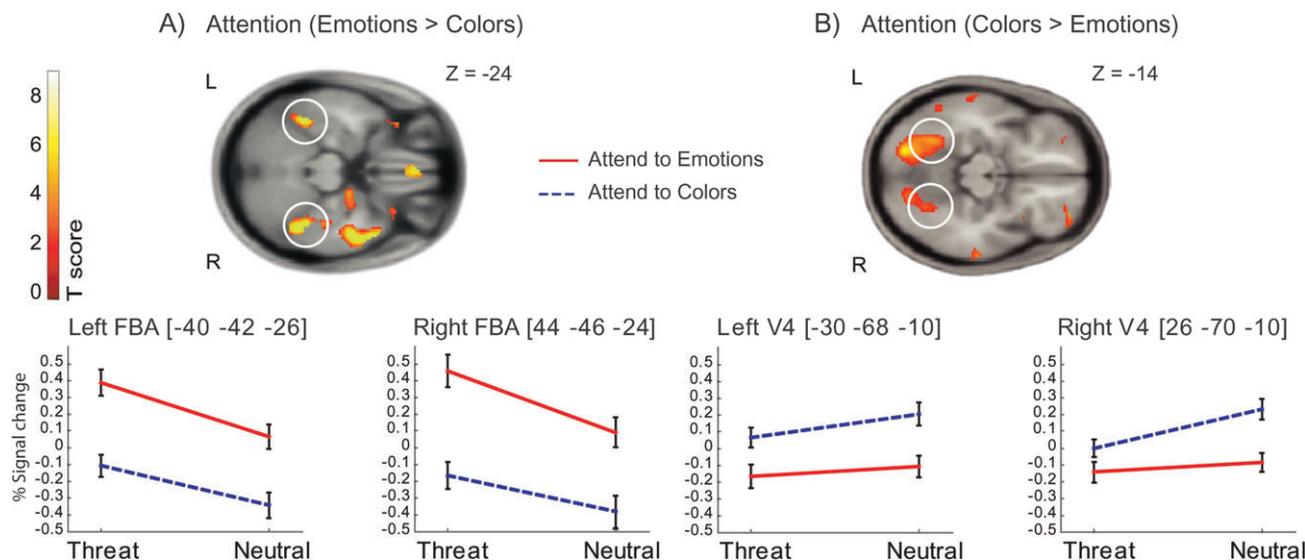


Figure 5. Effect of attention in the fusiform gyrus. Although visual stimulation was kept identical between tasks, activations in the fusiform gyrus, as shown here, reflected the attentional and perceptual requirements of each task. (A) During the body emotion-naming task, we observed bilateral activation in fusiform body area (Peelen and Downing 2005). The parameter estimates confirmed that activity in fusiform body area was higher during emotion- (red solid line) than color-naming task (blue dotted line). (B) During color-naming task, bilateral activations were detected in the human homologue of V4, known to play a crucial role in color perception and visual attention, especially during demanding tasks (Zeki et al. 1991; Gallant et al. 2000). The parameter estimates confirmed that activity in this regions was higher during color-naming than body emotion-naming task (both SPMs superimposed on axial sections of the ICBM-152 average T_1 -weighted brain; SPM(t) thresholded at $P < 0.001$ (uncorrected), plots of percent signal change used the same conventions as in Fig. 3).

and Swards 2003; Adams 2006) and are part of the defensive fear system described in mammals and humans (Panksepp 1998; McNaughton and Corr 2004). In animals, electrical and chemical stimulation of the hypothalamus and PAG elicit vegetative responses as well as typical defensive reactions ranging from stereotypical flight to attack (Brown et al. 1969; Bandler and Shipley 1994; Swards and Swards 2003). Consistent with this, lesion of these structures severely reduces defensive behavior (Blanchard et al. 1981; Canteras et al. 1997). In humans, stimulation of the posterior medial hypothalamus, with a location corresponding to the present peak of activity, results in aggressive behavior (Bejjani et al. 2002). Moreover, 2 neuroimaging studies have shown that, as the distance between observer and source of threat decreases and threat becomes more imminent, activity in the PAG increases (Mobbs et al. 2007; Mobbs et al. 2009). Taken together, the recruitment of these subcortical areas during attended as well as unattended threat suggests that salient threat signals autonomously trigger neural structures involved in reflexive defensive responses (de Gelder et al. 2004; de Gelder 2006; Grèzes et al. 2007; Pichon et al. 2008, 2009; Bannerman et al. 2010).

Also of interest is the activity observed in cortical areas, notably at the PMv/PMd border. The PM is known to be implicated in external stimulus-driven actions (Passingham 1993; Hoshi and Tanji 2004) and motor preparation (Hoshi and Tanji 2004). Electrophysiological studies in monkeys report that the PZ of F4, at the PMv/PMd border, hosts neurons that respond to the perception of tactile and approaching visual stimuli, and electrical stimulation of this area triggers characteristic defensive movements (Cooke and Graziano 2004; Graziano and Cooke 2006). Interestingly, a recent fMRI study in humans has identified a polysensory region in the PM responding to both visual and tactile stimuli near the peak observed here (Nakashita et al. 2008). Our coordinates ($z_{MNI} = 52$) correspond to the PMv/PMd border (range, $z = 40$ –56, see

Tomassini et al. 2007) and are similar to those reported in previous research using threatening faces or actions ($z = 46$ in Whalen et al. 2001; $z = 40$ in Grèzes et al. 2007; $z = 52$ in Pichon et al. 2008; $z = 52$ in Pichon et al. 2009). As suggested earlier, perceiving threat in others automatically triggers action preparation (de Gelder et al. 2004; de Gelder 2006; Grèzes et al. 2007; Pichon et al. 2008, 2009). We now demonstrate that this motor preparation mechanism is resistant to attentional control and remains functional when one is engaged in an unrelated task.

Conflict between Reflexive and Intentional Actions

Completing a challenging task requires one to disregard potentially distracting information including emotional signals (Pochon et al. 2002) as illustrated by the present color-naming task. Yet, when danger looms, the brain must remain able to detect it and disengage from the ongoing task in order to allocate resources to cope with the new situation (Corbetta et al. 2008). Automatically triggered defensive actions may thus potentially conflict with the subject's intentional response to the current task. If a threatening stimulus acts as a distracter and interferes with both emotion- and color-naming tasks, one expects this to be reflected in participants' performances. This is indeed the case. Response times were slower for threatening action stimuli as compared with neutral ones even during the color-naming task. This indicates that the emotional content of the stimuli is sufficiently threatening to divert resources toward their processing and therefore to provoke an interference with ongoing tasks (Lang et al. 1998; Panksepp 1998; Pessoa 2009).

To find the neural signature of interference between reflexive and task-related actions, we searched for threat-responsive regions in the brain network unaffected by attentional control, where activity correlated with the increase

in response latency measured for threatening actions. As described before, this behavioral measure provides an index of the extent to which the task-irrelevant emotional stimulus is processed. Slower response time was correlated with the magnitude of activity in the pre-SMA, left IFG BA44, and bilateral anterior insula during the demanding color-naming task and with the magnitude of activity in left anterior insula only during the emotion-naming task.

The pre-SMA has been implicated in voluntary actions that are “self-initiated” or driven by “internal goals” and participates in complex cognitive control, such as alternation of motor plans, and motor selection and preparation (e.g., Passingham 1993; Picard and Strick 1996; Deiber et al. 1999; Lau et al. 2004; Nachev et al. 2008). Importantly, it also plays a critical role in situations of response conflict by exerting control over voluntary actions and suppression of competing prepotent actions (Isoda and Hikosaka 2007; Nachev et al. 2007; Chen et al. 2009). In monkeys, electrical microstimulation in the pre-SMA induces a switch between automatic incorrect responses to slower correct responses (Isoda and Hikosaka 2007). Importantly the present context, Lee et al. (2008) found more activity in the pre-SMA when participants produced facial expressions discordant with observed emotions (e.g., smiling in response to angry expressions). The pre-SMA may therefore play a role in overcoming the primary emotional motor response induced by perceived emotions.

The anterior part of the insula/frontal operculum was also shown to be implicated in interference resolution and task control (Badre and Wagner 2005; Wager et al. 2005; Nee et al. 2007; Higo et al. 2011), particularly when the conflicting information is emotion laden (Levens and Phelps 2010). Finally, according to Brass and von Cramon (2004), activity in the posterior inferior frontal sulcus (which corresponds to IFG BA44 here) allows one to selectively attend to specific information while ignoring irrelevant information ($x, y, z_{\text{MNI}} [-41, 18, 26]$ in Brass and von Cramon 2004; present coordinates $[-44, 12, 32]$). Similarly, Koechlin et al. (2003) and Koechlin and Hyafil (2007) propose that BA44 is involved in action selection as a function of the immediate context ($[-44, 8, 20]$ in Koechlin et al. 2003; $[-45, 15, 30]$ in Kounieher et al. 2009), while Rushworth et al. (2005) suggest that it underlies the selection of appropriate stimulus-response association among alternative possibilities. In the present context, we suggest that the activations of pre-SMA, anterior insula/frontal operculum, and IFG BA44 may underlie interference resolution between automatic and task-instructed actions (Chen et al. 2009; Nelson et al. 2009).

Emotional Signals and the Amygdala

Activity in amygdala was triggered during visual presentation of threatening stimuli specifically during the emotion-naming task. However, the level of activity was lower when the subject’s attention was not directed to the emotional content but to the color of visually presented dots. The anterior hippocampus, which sends contextual input to the amygdala (Phelps and LeDoux 2005), also displayed a similar pattern of interaction. Several experiments have shown that the amygdala can respond independently of selective attention (Vuilleumier et al. 2001; Anderson et al. 2003; Winston et al. 2003), while others have shown that task demands and degree of covert attention influence the extent to which emotionally salient stimuli such as fearful faces are processed (Pessoa et al. 2002;

Bishop et al. 2007; Mitchell et al. 2007; Silvert et al. 2007; Lim et al. 2008). It has been suggested that the discrepancy between studies is related to the fact that high-load tasks as compared with low-load tasks (e.g., gender discrimination) compromise amygdala responses to unattended threat signals (Pessoa 2005). The present results are in line with the proposition by Lavie (2005) proposition that tasks involving high but not low perceptual load (Sinke et al. 2010) weaken the perceptual processing of potentially interfering distracters, here the emotional stimuli.

The finding that the subcortical network described above is independent of amygdala activation raises the question how emotional information reaches that network. First, anatomical studies in macaque monkeys have shown that the PAG receives cortical projections from the STS and the PM (An et al. 1998). Monkey data also suggest that different sites of the prefrontal cortex, including ventral insula and orbital area 12o and caudal 12l (area 47/12 in humans, see Monchi et al. 2001), have direct connections with the PAG (An et al. 1998). These latter prefrontal areas also project to the hypothalamus (Ongur et al. 1998; Barbas et al. 2003). In addition, the STS is connected to the PM (Luppino et al. 2001). All these brain areas show an increased response during the perception of threatening signals and may therefore be critical for sustaining emotional processing independently of the amygdala.

Second, it is proposed that fear-induced defensive behavior relies on a hierarchically organized subcortical circuit consisting of the amygdala, hypothalamus, and PAG. Indeed, while defensive behavior triggered by amygdala stimulation requires the integrity of both the hypothalamus and the PAG, defensive behavior triggered by hypothalamus or PAG stimulation does not depend on the integrity of the amygdala (Fernandez de Molina and Hunsperger 1962). Amygdala lesions performed in adult monkeys indicate that this structure is important for the normal acquisition of a fear-potentiated startle reflex, but not for its retention and expression (Antoniadis et al. 2007). Also, PAG inactivation impairs acquisition of unconditioned freezing indicating that PAG participates in relaying aversive information to the amygdala (Johansen et al. 2010). The hierarchical organization of the subcortical defensive system could explain why monkeys with neonatal amygdala lesions display non-adaptive fearful behaviors during dyadic social interactions (Prather et al. 2001). This suggests that if the amygdala is not essential for the expression of defensive behavior, it may nevertheless serve to refine reflexive actions elaborated in hierarchically lower regions such as the PAG and the hypothalamus (Panksepp 1998) and relate these to learned behavioral contexts (Prather et al. 2001).

Conclusion

The present study shows that threat signals interfere with ongoing behavior and trigger responses independently of attention in a subcortical network related to defensive behavior (PAG, hypothalamus, and PM) and in a network underlying interference resolution (pre-SMA, IFG BA44, and anterior insula/frontal operculum). In contrast to the amygdala, where activity can be modulated by task demands, response to threat in this network is independent from attentional control. We suggest that the identified brain network sustains motor vigilance and supports reflexive defensive behaviors that evolved to cope with threat. In this sense, the present results are consistent with the view that, at their core, emotions are

essentially action tendencies that represent “efficient modes of adaptation to changing environmental demands” (Frijda 1986; Davidson 1993; Levenson 2003; Low et al. 2008).

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Supplementary Material

Supplementary material can be found at <http://www.cercor.oxfordjournals.org/>.

Notes

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