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Fear and the Amygdala: Manipulation of Awareness Generates Differential Cerebral Responses to Phobic and Fear-Relevant (but Nonfeared) Stimuli

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Rapid response to danger holds an evolutionary advantage. In this positron emission tomography study, phobics were exposed to masked visual stimuli with timings that either allowed awareness or not of either phobic, fear-relevant (e.g., spiders to snake phobics), or neutral images. When the timing did not permit awareness, the amygdala responded to both phobic and fear-relevant stimuli. With time for more elaborate processing, phobic stimuli resulted in an addition of an affective processing network to the amygdala activity, whereas no activity was found in response to fear-relevant stimuli. Also, right prefrontal areas appeared deactivated, comparing aware phobic and fear-relevant conditions. Thus, a shift from top-down control to an affectively driven system optimized for speed was observed in phobic relative to fear-relevant aware processing.

Fear is a ubiquitous human experience in response to threat, which is rooted in defense systems of the mammalian brain (Lang, Davis, & Öhman, 2000; LeDoux, 1996; Öhman & Mineka, 2001). Its nature is captured in exaggerated form in specific phobias—intense, irrational fears of circumscribed objects or events. When confronted by their feared object, people with small animal phobias (e.g., snakes, spiders) exhibit a distinct psychophysiological response that includes increases in skin conductance and blood pressure, a rapid heart rate acceleration, and potentiated startle reflexes to acoustic probe stimuli (e.g., Globisch, Hamm, Esteves, & Öhman, 1999). The characteristics of this response, in particular the startle potentiation, suggests that it is mediated by the hub of the brain's fear network, the amygdala in the medial temporal lobe (Davis, 1992; Lang et al., 2000). Öhman and Mineka (2001) suggested that a vast literature on fears and phobias could be organized around the concept of a fear module—a behavioral, mental, and neural system that evolved to help our distant forefathers to cope with recurring life-threatening events in their ecological niches. Its behavioral characteristics include that it may be automatically (or unconsciously) activated by stimuli that derive part of their threat potential from evolutionary contingencies. The automaticity of phobic responses has been documented in studies using backward masking to preclude conscious awareness of the phobic stimulus (Öhman & Soares, 1994), but so far, this technique has not been used to examine responses of the human brain to phobic material.

Accordingly, the primary objective of the present study was to examine brain responses to phobic

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stimuli whose accessibility to awareness was controlled. Participants were presented with repeated, very short exposures of phobic, fear-relevant, and control material using a backward-masking technique in separated positron emission tomography (PET) scans (cf. Morris, Öhman, & Dolan, 1998).

Animal studies suggest that the amygdala projects to a set of nuclei controlling overt manifestations of fear (Davis, 1992) such as the periaqueductal gray (PAG) and other motor control systems in the brainstem (Davis, 1992; Fanselow, 1994). Likewise, a multitude of data associates amygdala activation with fear and other aversive emotions also in humans (Dolan, 2002). The subcortical fear circuitry has reciprocal connections with cortical areas such as the midanterior insula, the anterior cingulate cortex (ACC), and the orbitofrontal cortex (OFC) (e.g., Emery & Amaral, 2000), areas known to contribute to affective information processing. For example, the anterior insula has been implicated in affective autonomic feedback during emotional arousal (Mesulam & Mufson, 1985). Critchley, Wiens, Rothstein, Öhman, and Dolan (2004) recently reported activation of the insula when subjects performed an interoceptive awareness task in which they judged whether a series of tone pips were correlated with their heartbeats. Furthermore, interoceptive accuracy was predicted by insula activation and correlated with indices of negative emotional experience. Supporting its role in the integration of sensory-affective processes, imaging studies have shown anterior insular activations in response to exposure of disgusted and fearful faces (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Phillips et al., 1997) as well as to phobic stimuli (Rauch et al., 1995). Among other things, the ACC is involved in attentional control as well as in emotional responses and in the motivational relevance of internal and external stimuli (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995; Vogt, Finch, & Olson, 1992). The OFC has been suggested to mediate the effect of reinforcement contingencies on behavior (Rolls, 1999), and relationships have been reported between activation of this area and negatively valenced emotional events, such as pain, threat, or punishment (Blair, Morris, Frith, Perrett, & Dolan, 1999; Hsieh, Belfrage, Stone-Elander, Hansson, & Ingvar, 1995; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000), as well as phobic stimuli (Rauch et al., 1995). This area has also been attributed a role in regulating the affective processing in emotional situations in which cognitive control is possible (Drevets, 2000; Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Ochsner, Bunge, Gross, & Gabrieli, 2002; Petrovic & Ingvar, 2002).

Threatening situations (e.g., an attacking predator or conspecific) often impose time constraints that, if effectively met, yield a clear survival advantage to rapid response recruitment. Thus, affective information prioritizes speed rather than accuracy or completeness (e.g., LeDoux, 1996; Öhman, 2000). In emotionally stressful situations, therefore, higher order cognitive operations mediated by the prefrontal cortex (e.g., Smith & Jonides, 1999) might be downregulated, whereas the performance of innate, automatic, or well-rehearsed responses is facilitated (Arnsten, 1998). Several imaging studies have demonstrated a decrease in the parietal and prefrontal activity whenever the subject is continuously attentive to the surrounding rather than to the inner processing, illustrating the inhibition of such higher order processing in stressful situations (Baker et al., 1996; Cabeza & Nyberg, 2000; Ghatan et al., 1995; Shulman et al., 1997).

Öhman and coworkers (Esteves & Öhman, 1993; Öhman & Soares, 1993) have developed a backward-masking methodology that interrupts information processing of visual emotional stimuli in humans. For example, a picture of a snake is very briefly presented (less than 30 ms) and then immediately followed by a masking picture. With an effective masking interval, participants do not perform above chance in recognizing the picture, using a forced-choice recognition procedure (Öhman & Soares, 1993). Nevertheless, subjects selected to be fearful of snakes (but not spiders, and vice versa) showed elevated skin conductance responses to masked snakes as compared with masked spiders or masked neutral stimuli (Öhman & Soares, 1994).

The results of these studies (e.g., reviewed by Öhman & Mineka, 2001) are consistent with the fear module concept in suggesting that the amygdala and its associated subcortical circuit may result in nonconsciously elicited automatic response to fear-related stimuli. In line with this theory, Morris et al. (1998) demonstrated specific activation of the right amygdala to masked presentations of an angry face that had previously been associated with an aversive noise. Similarly, Whalen et al. (1998) showed specific activation of the amygdala to masked fearful faces compared with masked happy faces.

The purpose of this PET study was thus to further characterize the network of brain regions involved in the processing of consciously and nonconsciously perceived fearful stimuli. We selected participants

that were phobic of either snakes or spiders (but not of both) and exposed them to photos of the same as well as a neutral control stimulus. It is well documented that such a procedure results in robust fear responses (e.g., Globisch et al., 1999). We contrasted PET-assessed regional cerebral blood flow (rCBF) responses to phobic material with responses to fear-relevant (e.g., a spider to snake phobics) and neutral stimuli. In this way, we could contrast a stimulus likely to elicit an explicit fear response with the response to stimuli that were fear relevant but were not actually feared by the participants as well as with neutral stimuli. In addition, we used the backward-masking technique in order to control the conscious access. On the basis of previous research, we hypothesized that our experimental paradigm would engage several brain regions, including the amygdala, the PAG, the OFC, the anterior insula, and the ACC. In order to optimize the statistical sensitivity, we used a hierarchical hypothesis testing approach, focusing on the amygdala and the other regions of interest described and exploring the rest of the brain, with a corresponding increasing correction for multiple non-independent comparisons of the significance levels.

Method

Participants

Sixteen right-handed healthy female subjects (M = 26 years, SD = 5) were included in the study on the basis of an extensive selection procedure. The participants were students at the Karolinska Institute, Stockholm, Sweden, who were initially screened for animal fears by answering short versions of the specific snake and spider fear questionnaires (Klorman, Weerts, Hastings, Melamed, & Lang, 1974). Those scoring above the 90th percentile for either snake or spider fear and below the 50th percentile for the other fear met with a clinical psychologist who checked that they fulfilled the criteria of specific phobia given in the *Diagnostic and Statistic Manual of Mental Disorders,* 4th edition (*DSM–IV;* American Psychiatric Association, 1994). Eight subjects with specific fear for snakes and normal scores (i.e., below median) for spider fear were selected. Likewise, 8 subjects with specific fear for spiders and normal scores for snake fear were selected. None of the subjects fulfilled criteria for any other *DSM–IV* anxiety or mood disorder. Nor did any of the subjects use any medication or nicotine, or had a history of drug use, head trauma, neurological or psychiatric illness, or family history of neurological or psychiatric illness. The study was approved by the local Ethics and Radiation Safety committees at the Karolinska Hospital.

Apparatus

Visual stimulus presentations. For the rating procedure, an 8600 Power Macintosh, with a 19-in. (48-cm) monitor and Director 5.0 software (Macromedia, 1996), was used. The presentation of stimuli during the PET experiment was performed on a 72 Hz, 17-in. (43-cm) computer monitor. The Experimental Run Time System software (BeriSoft Cooperation, 1999, Frankfurt, Germany) was used for the visual presentation.

PET equipment and PET scan acquisition. Each subject underwent 12 measurements of rCBF with a three-dimensional (3-D) ECAT EXACT HR PET scanner (Wienhard et al., 1994) and intravenous bolus injections of [15_O] butanol. The PET scanner was used in the 3-D sampling mode, producing 60-s tracer uptake images. The stimulus presentation was initiated at the time of tracer injection, data acquisition, and the scanning was automatically started when the brain radioactivity level exceeded a predetermined threshold above background. Scatter correction was made, and a two-dimensional (2-D) transmission scan was used for attenuation correction (a second transmission scan was performed at the end of the PET experiment if the subject left the scanner during the experiment).

Procedure

Visual stimuli. Color slides of snakes, spiders, and mushrooms were selected from a stimulus material used in previous research (Öhman & Soares, 1993, 1994). The pictures were digitized (using AGFA Sprintscan 35) and then converted to adaptive 8-bit color and cropped to 450 × 300 pixels size. The pictures were 21 × 14 cm in size when presented on the monitor, with a distance of 100 cm from monitor to eye.

Rating procedure. A rating task was performed 1–2 weeks after the PET experiment (in an attempt to minimize the interference from the processing during the scanning). The subjects viewed 18 pictures of snakes, spiders, and mushrooms, respectively, and three pictures of masks presented in a randomized order on a computer screen. Each picture was exposed for 5 s, and then a Self-Assessment Mannequin scale (SAM; Lang, 1980), consisting of schematic human figures, appeared on the right side of the screen while the target picture was still present on the left side. The ratings were made for valence and arousal by adjust-

ing the position of a marker with the computer mouse on a scale on which the endpoints were those of the SAM scale. The subjects had no time limitation in making the ratings, and as soon as they had made their choices, a new target came into view.

PET paradigm. The paradigm included six conditions, each repeated twice, with at least 10 min between scans (allowing the radioactivity level of the subjects to approximately return to background). The visual stimulus consisted of a 14-ms target stimulus, followed by a 56-ms masking stimulus. The onset of the masking stimulus was either 14 ms (short) or 308 ms (long) after the target onset. This means that in the short condition, the mask appeared right after the target offset, and that there were 294 ms between the target offset and mask onset in the long condition (see Figure 1a). Scanning was preceded by a 500-ms exposure of a hair cross, followed by a 500-ms black screen. During the 1-min scan window, a mask–mask pair was shown three times, followed by nine target–mask pairs. Between the visual stimuli, a black background was shown. The intertrial interval was 4 s for the mask–mask pairs and the first five target–mask pairs and 5 s for the rest of the target–mask pairs. The rate of presentation was set to maximize the exposure of the significant stimuli during the bolus arrival (see Figure 1b).

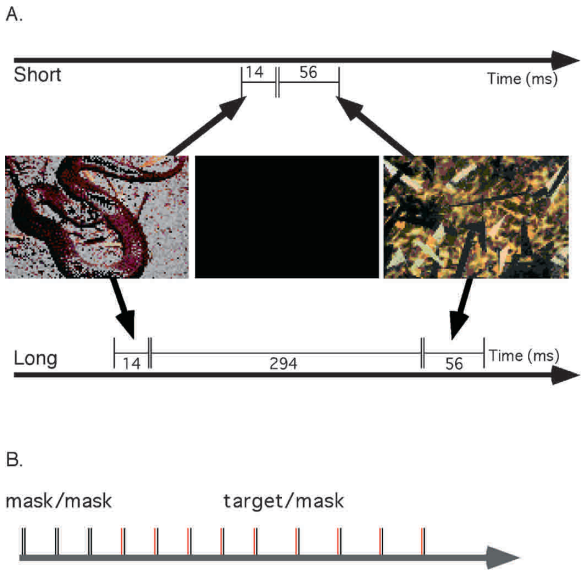

Figure 1. The stimuli (A) and 1-min scan (B). The visual stimulus consisted of a target stimulus shown for 14 ms, followed by a 56-ms masking stimulus. There were 294 ms and 0 s in between target offset and mask onset in the long and short conditions, respectively. Each scan began with three presentations of the mask only (during the prebolus arrival period), followed by five target–mask pairs presented with an interval of 4 s, additionally followed by four target–mask pairs presented with a 5-s interval.

There were three different types of targets: phobic (P); nonphobic, fear relevant (F); and neutral (N). The target and mask pictures were randomly chosen and ordered from a set of nine pictures for each type of target and three mask pictures. For subjects with specific snake fear, the phobic stimulus consisted of snake pictures and the nonphobic fear-relevant stimulus of spider pictures. For subjects with specific spider fear, the stimuli were reversed. The neutral stimulus was a picture of a mushroom, and the masking stimulus was a picture constructed by randomly reassembling pieces of the snake and spider pictures. The masking stimuli thus had similar visual characteristics compared with the target pictures but without any recognizable central object. Hence, the six conditions included in the PET experiment were P-short, F-short, N-short, P-long, F-long, and N-long. In other words, we used a 3 × 2 factorial design, with two factors, target type (three levels: P, F, and N) and time interval between target offset and mask onset (two levels: short and long).

Data Analysis

For the rating data, separate analyses of variance (ANOVAs) were conducted for each of the two measures, arousal, and negative valence (valence scores being inversed so that high scores on both measures reflect increased fear). The statistical design was a Stimulus Type (mushroom vs. snake vs. spider) × Fear Group (snake phobia vs. spider phobia) factorial design, with stimulus type as a within-group variable and fear type as a between-group variable. Tukey's honestly significant difference test was used for follow-up tests when appropriate.

The PET images were realigned, spatially normalized, and transformed into Talairch–Tournoux space (Talairach & Tournoux, 1988), as defined by the statistical parametric mapping (SPM99) PET-template, 3-D isotropic Gaussian filtered (14 mm FWHM), proportionally scaled to account for global effects and analyzed with SPM99 (Friston et al., 1995). A linear model was used to model the PET data, and a statistical parametric map (SPM) was estimated for each contrast-of-condition effect using a t statistic for each voxel. The resulting set of voxel values for each contrast, a t statistic image SPM$\{t\}$, was in a per voxel fashion, transformed into a standard normal SPM$\{Z\}$.

The activated regions were then characterized in terms of peak height of local maxima and spatial extent of suprathreshold clusters. Using a hierarchical approach in order to optimize sensitivity at a given level of specificity, the hypothesis testing was performed at three levels. Our primary region of interest was the amygdala. We chose centers at the x, y, z coordinates, equaling [±24, −8, −18] and made a small volume search within the amygdala (spherical region of interest with a 10-mm radius), and Z scores > 2.33, $p = .01$ were considered significant. Only maxima within the amygdala were included. Additional regions of interest included the OFC, the anterior insula, the ACC, the PAG of the brain stem and hypothalamus, and the SPM{Z} was thresholded at $Z = 3.09$, $p = .001$ to investigate effects in these regions. Finally, a global search for effects related to regions that were not part of the regionally specific hypotheses was performed, and the SPM{Z}s were thresholded at $Z = 4.27$, corresponding to $p = .1$, corrected for multiple non-independent comparisons on the basis of the theory of smooth 3-D random fields (Worsley et al., 1996).

Activation and *deactivation* are used as synonyms for relative increased and decreased rCBF, respectively. For reasons of portability of data, the tables of local maxima use approximate Talairach designations (Talairach & Tournoux, 1988). When a region is described to include a Brodmann area (BA), this is not meant in an inclusive sense but only implies that parts of that BA are included in the region.

Results

Behavioral Results

The analyses of arousal and negative valence ratings showed similar effects. There were main effects of stimulus type on both arousal, $F(2, 28) = 31.9$, and negative valence, $F(2, 28) = 62.6$, that were modified by significant interactions with fear group, $F(2, 28) = 32.8$ (arousal); and, $F(2, 28) = 40.8$ (negative valence). The interaction reflected a double dissociation according to which snake-fearful participants rated snakes as more arousing and more negatively valenced than spiders (ps $< .05$), whereas spider-fearful participants showed a significant difference in favor of spiders over snakes (see Figure 2). The groups did not differ in their ratings of mushrooms. Thus, the selection procedure resulted in groups that were specifically fearful of one but not the other of the fear-relevant stimuli.

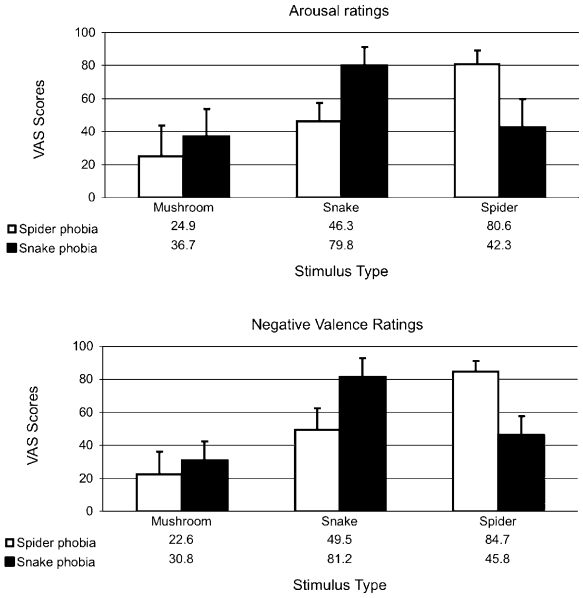

Figure 2. Bar graph depicting a double dissociation of the ratings of both valence and arousal (Mean ± 1 standard deviation) in response to the unmasked exposure of the stimuli. The ratings were made by subjects with phobia for either spiders (open squares) or snakes (solid squares) in a session separate from the positron emission tomography scanning. VAS = visual analogue scale.

PET Results

Short-exposure conditions. The left amygdala/anterior medial temporal lobe was activated in both the P-short versus N-short and the F-short versus N-short contrast as the only region that reached significance during the short-exposure conditions (see Table 1, Figure 3).

Table 1
Amygdala/Anterior Medial Temporal Lobe Activations

Contrast	Z	x, y, z coordinates
P-long vs. F-long		
R	3.66	22, 0, −16
L	2.84	−28, −16, −14
P-long vs. N-long		
R	4.53	22, 0, −16
L	3.21	−24, −8, −14
P-short vs. N-short		
L	2.47	−24, −14, −14
F-short vs. N-short		
L	3.29	−26, −16, −16

Note. The x, y, z coordinates refer to an approximate Talairach space (Talairach & Tournoux, 1988). P-long = Phobic-long; F-long = Fear-relevant long; R = Right; L = Left; N-long = Neutral-long.

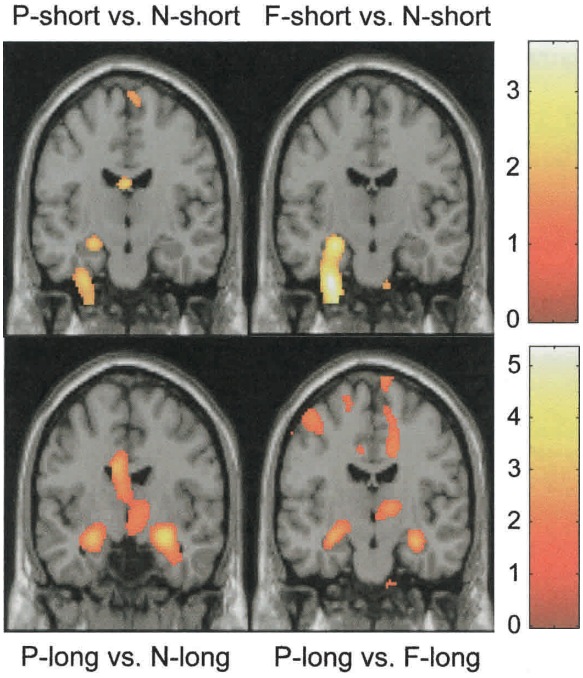

Figure 3. Axial view (in the P-long vs. N-long contrast, $y = -8$; in the rest of the figure, $y = -4$; Talaraich and Tournoux, 1988) depicting amygdala/anterior medial temporal lobe. All the scans from all 16 subjects acquired from the exposure to phobic stimuli were pooled. Hence, the activation material is balanced across the subjects, as 8 of them expressed phobia for snakes but not spiders, and vice versa. Images are displayed according to neurological convention (i.e., right = right). The images are thresholded at $Z = 1.64$, or $p = .05$, for illustrative purposes. Normalized t value maps are superimposed onto an averaged brain magnetic resonance image. P = Phobic; vs. = versus; N = Neutral; F = Fear relevant.

Long-exposure conditions. The amygdala was activated also in P-long versus N-long, both on the left and the right side, but it did not reach significance on either side of the F-long versus N-long contrast. This difference was evident in a bilateral amygdala activation when comparing P-long versus F-long (see Table 1, Figure 3). The amygdala activations were more anteriorly located in the long compared with the short conditions. Because of limitations in spatial resolution in this technique, it is difficult, however, to evaluate the significance or meaning of this difference. The mentioned maxima coordinates and the activation extentions are within or on the border of the amygdala structure. Other areas that were activated when contrasting the P-long and F-long conditions included areas known to be active during the processing of affective information: Anterior insular regions were activated bilaterally (BA 14/15), activations that extended into the orbitofrontal cortex (BA 47). The right-sided activation was located more inferiorly compared with the one on the left side and extended also into the ventral striatum. We also observed activations in the ACC (BA 32) and the PAG (see Table 2, Figures 4a and 4b). The differences between the short- and long-exposure conditions were supported by the interaction contrasts between masking interval and type of stimulus.

The pattern of activation in the reverse comparison (F-long vs. P-long) included a dorsolateral prefontal cortex (DLPFC) (BA 8/9 extending into superior parts of BA 46) and the right lateral OFC (BA 47) (see Table 2, Figure 4c).

The findings in comparing P-long and N-long were similar to the corresponding comparisons of P-long and F-long, the difference being that the ACC activation was located in BA 24 in the P-long versus N-long contrast instead of in BA 32 (see Table 2, Figure 4b).

We observed no significant activations in the F-long versus N-long contrast except for in the cerebellum.

Discussion

The pattern of changes in rCBF in response to fear stimulation revealed left amygdala activations in both the P-short and F-short condition (in relation to the neutral stimulus). The amygdala was activated bilaterally in the long-phobic condition (P-long vs. N-long) but was not significantly activated on either side in the long fear-relevant but nonfeared condition (e.g., a picture of a spider for a snake-phobic participant; F-long vs. N-long). Thus, the amygdala responded to both types of stimuli when the exposure times only allowed for very rapid incomplete visual processing. In the long-exposure conditions, which provided time for more elaborate stimulus processing, a different scenario appeared: In the phobic condition, the amygdala response was enhanced (particularly on the right side), and it was associated with an activated affective processing network, including the ACC, the anterior insula, the OFC, and the PAG, whereas neither the amygdala nor any other of the affective processing areas was significantly activated in the fear-relevant condition. Thus, when the phobic stimulus became more completely processed, a fear network that included both subcortical and cortical nodes was recruited as fear accelerated. However, with time to decide that the fear-relevant (but nonfeared) stimulus

Table 2
Local Activation Maxima

Region	BA	*Z*	x, y, z coordinates
P-long vs. F-long			
OFC/insula	25/47 R	4.9	26, 14, −14
Insula	14/15 L	3.72	−36, 20, 0
OFC/insula	14/15/47 L	5.1	−56, 10, −4
Medial frontal lobule*	6/8 R	4.76	4, 8, 72
ACC	32 L	3.46	−10, 2, 46
PAG		3.74	2, −36, −18
Cerebellum		4.17	−8, −52, −22
F-long vs. P-long			
OFC	47 R	3.86	42, 46, −12
OFC	11 R	3.32	4, 32, −22
DLPFC*	8/9 R	4.38	48, 26, 38
P-long vs. N-long			
OFC/insula	25/47 R	5.22	28, 14, −14
Insula	14/15 R	4.12	−30, 12, 2
ACC	24 R	3.75	4, 28, 16
ACC	24 R	3.33	12, 18, 26
Medial frontal lobule*	6/8 R	5.37	10, 14, 79
PAG		3.11	0, −32, −10
Precuneus*	7	4.60	−2, −88, 44
Cerebellum		4.52	44, −58, −44
N-long vs. P-long			
OFC	47 R	3.6	44, 46, −14
F-long vs. N-long			
Cerebellum*		4.29	54, −64, −50

Note. The x, y, z coordinates refer to an approximate Talairach space (Talairach & Tournoux, 1988). Reported *Z* scores correspond to $p < .001$ (uncorrected). Those regions marked with an asterisk are significant in the global search (see the Method section). BA = Brodmann area; P-long = Phobic-long; F-long = Fear-relevant long; OFC = Orbitofrontal cortex; R = right; L = left; ACC = Anterior cingulate cortex; PAG = Periaqueductal gray; DLPFC = Dorsolateral prefrontal cortex; N-long = neutral-long.

was in effect not dangerous, the initial amygdala response to the stimulus was relatively disengaged, and the cortical areas were never recruited. When contrasting the P-long and F-long conditions, this distinct difference between the two conditions was confirmed. That is, the right amygdala, the ACC, the anterior insula, and the PAG were more active in the phobic condition compared with the fear-relevant condition. Also, right prefrontal areas, the DLPFC, and the lateral OFC appeared deactivated in the P-long compared with the F-long condition (P-long < F-long). Structures in this system have been identified with preparing and applying goal-directed selection for stimuli and responses (e.g., Corbetta & Shulman, 2002). Thus, our results suggest that top-down control was exerted to fear-relevant (but nonfeared) stimuli when time was available but that this system was relatively deactivated when the stimulus elicited phobic-level fear.

The target–mask interval of the short conditions was only 14 ms; nevertheless, we observed robust amygdala activation during these conditions. These activations are consistent with the assumption that the amygdala is part of an early warning or vigilance system, detecting biologically relevant stimuli for further prioritized processing (Davis & Whalen, 2001; Whalen, 1998). There are limitations to what the brain can process at a given point in time. Top-down direction of attention is one means of compensating for such limitations, a function that allows for focused and continuous processing of what is goal relevant. This must be complemented with perceptual processes that permit detection of crucial but unpredicted events outside the focus of attention. Researchers have suggested that stimuli of survival relevance are "tagged" to automatically evoke an emotional response and thus to get priority for further processing (e.g., Öhman, 2000). The influence of emotional stimuli on perception has been examined in visual search paradigms. For example, Öhman, Flykt, and Esteves (2001) showed that fear-relevant (snakes or spiders), but not fear-irrelevant (flowers or mushrooms), targets were detected more quickly among fear-irrelevant distractors, independent of the numbers of distractors in a display. Fear-irrelevant target stimuli, however, required more time to detect in larger displays. Thus, it appears that the fear-relevant targets "popped out" to be automatically located in the display (cf. Treisman & Gelade, 1980), whereas the fear-irrelevant targets were searched for in a serial fashion. Moreover, with a design similar to the present one, which included subjects afraid of snakes but not spiders (or vice versa), Öhman et al. (2001) showed that the bias for detecting threatening stimuli faster than nonthreatening ones was enhanced in subjects specifically fearful of the target, both in comparison to nonphobic fear-relevant targets and to nonfearful control subjects.

Another line of investigation has examined brain responses presented outside the focus of attention. When altering the attention in terms of spatial location or which of two overlapping objects that was task relevant, two different effects were observed. First, attending to stimuli resulted in enhanced activity in relevant sensory processing areas. Second, the amygdala response to fearful stimuli was unaffected by the manipulation of attention. Thus, the amygdala was

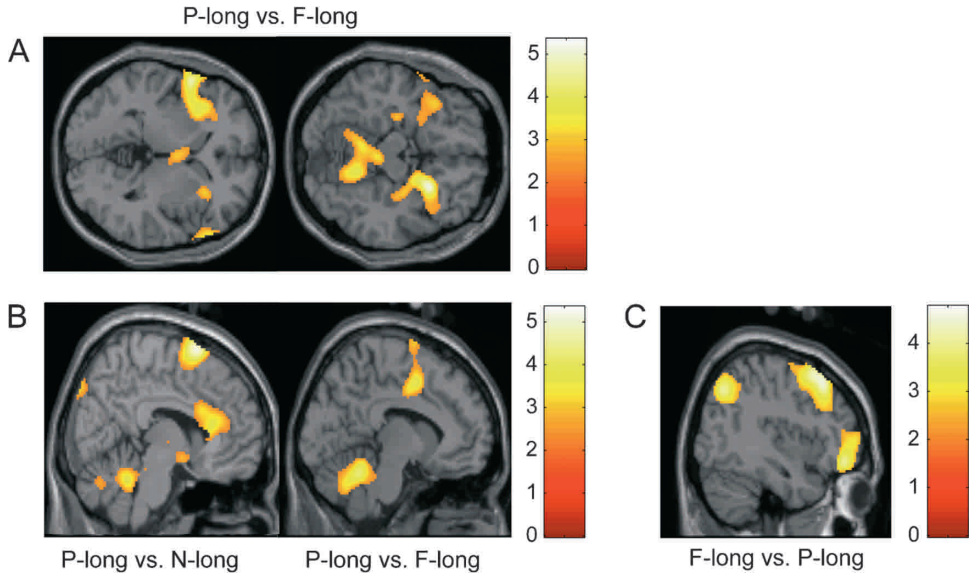

Figure 4. A: Coronal view ($z = 0$ mm, left picture; $z = -14$, right picture), illustrating the insular, orbitofrontal, and periaqueductal gray activations, thresholded at 2.33, or $p = .01$, for illustrative purposes. B: Sagittal view (x = 8 mm, left picture; x = −8 mm, right picture), illustrating the anterior cingulate cortex activations, thresholded at $Z = 2.33$, or $p = .01$. C: Sagittal view (x = 40 mm) of the deactivations of dorsolateral prefrontal cortex and the lateral orbitofrontal cortex. The parietal signal seen in this image did not reach significance, thresholded at $Z = 2.33$, or $p = .01$. P = Phobic; vs. = versus; F = Fear relevant; N = Neutral.

active in response to fearful targets irrespective of whether they were attended to or not (Vuilleumier, Armony, Driver, & Dolan, 2001). Furthermore, amygdala activity was also enhanced in response to disgust faces, but only when they were unattended and the cortical influences on perception were presumably lower (Anderson et al., 2003). In concert with our data, these results suggest that one of the functional roles of the amygdala is to monitor the outside world for emotionally relevant events relatively independent of the current focus of attention. When such events are detected, attention is redirected to them for further analysis (Öhman, 2000). As a result, there is an immediate recruitment of the autonomic nervous system in order to deal with the threat, as shown by enhanced skin conductance responses to backward-masked phobic stimuli (Öhman & Soares, 1994).

LeDoux and colleagues (Armony & LeDoux, 2000; LeDoux, 1996, 2000) have suggested that visual or auditory information may reach the amygdala via a direct "low road," incorporating midbrain and thalamic nuclei. Assuming that backward masking blocks processing of visual stimuli in the primary visual cortex (Rolls & Tovee, 1994; Rolls, Tovee, & Panzeri, 1999), the present as well as several other demonstrations of amygdala activation to masked stimuli (Morris, Buchel, & Dolan, 2001; Morris et al., 1998; Whalen, 1998) provide support for this notion. Morris, Öhman, and Dolan (1999) reported functional connectivity data in favor of the low-road concept. Their results indicated that regions of the pulvinar and superior colliculus covaried with the right amygdala during masked presentations of conditioned stimuli, thus suggesting that these structures served as way stations in the low road to the amygdala. In addition, similar patterns of connectivity were observed in a blind sight patient who showed reliable activation in the right amygdala to fearful faces presented in the cortically blind field (Morris, DeGelder, Weiskrantz, & Dolan, 2001). These effects are likely to be mediated by fast automatic perceptual pathways that are served by large rapidly conducting neurons working on low-level stimulus features (Leventhal, Rodieck, & Dreher, 1985). This is also consistent with data reported by Vuilleumier, Armony, Driver, and Dolan (2003), who filtered the spatial frequency of pictures of faces to produce facial stimuli that retained only high- or low-frequency spatial information. Their results indicate that high-spatial frequency face stimuli induced a greater fusiform activity than low-spatial frequency stimuli, regardless of emotional expression. Amygdala responses, however, were larger for low-frequency faces, provided that they showed expres-

sions of fear. Moreover, they demonstrated activation of the pulvinar and superior colliculus specifically by low-frequency fearful faces. Given the hypothesis that the amygdala is specialized for socioaffective information processing (Emery & Amaral, 2000; Öhman, 2002), it is also noteworthy that positive evidence for amygdala activation to masked stimuli exclusively has come from studies using facial stimuli. In the present study, we demonstrate in addition that the amygdala responds also to other kinds of threatening stimuli presented below the level of awareness.

With the long masking interval allowing conscious processing, phobic stimulation (P-long vs. N-long) resulted in increased activity in a cortical network known from previous studies to be active in cognitive–affective evaluation processes. However, no reliable cortical activations were observed for the fear-relevant nonphobic stimuli (F-long vs. N-long). Indeed, one of the advantages of the present design is that it allows imaging of a genuine emotional response rather than responses to stimuli of questionable emotional intensity such as fearful faces. The network activated in the long-phobic condition included areas that have direct connections to the amygdala, such as the ACC, the insula, and the OFC (Bush et al., 2000; Cavada, Compañy, Tejedor, Cruz-Rizzolo, & Reinoso-Suárez, 2000; Mesulam & Mufson, 1985).

The ACC has been subdivided into a rostral-ventral affective division and a dorsal cognitive division (Bush et al., 2000; Devinsky et al., 1995). The activity noticed in the P-long versus N-long condition is located within the "affect division" of the ACC. Similar to the insula and the OFC, the affective division of the ACC is part of a network of brain areas that interact and reciprocally modulate each other in representing the emotional and behavioral response as well as autonomic activity (Devinsky et al., 1995). Numerous imaging studies have reported activity in the rostral part of the ACC in association with affect-related tasks and situations. Accordingly, it has been implicated in the evaluation of emotional salience (e.g., Bush et al., 2000; Phan, Liberzon, Welsh, Britton, & Taylor, 2003; Whalen et al., 1998).

The insula responds to interoceptive stimulation, correlates with autonomic activity, and is activated during emotional states. Thus, visceral stimulation through inflation of a balloon in the esophagus resulted in insular activation (Aziz, Schnitzler, & Enck, 2000). In addition, insular activation has been frequently found as a response to painful stimuli (Petrovic & Ingvar, 2002) and, more specifically, in relation to subjective magnitude ratings of perceived intensity of temperature (Craig, Chen, Bandy, & Reiman, 2000) and pain (Brooks, Nurmikko, Bimson, Singh, & Roberts, 2002). Critchley, Corfield, Chandler, Mathias, and Dolan (2000) demonstrated direct correlations between insular activity, on the one hand, and blood pressure and heart rate, on the other. Examples of emotional manipulations that activate the insula include sexual arousal (Stoleru et al., 1999), self-generated sadness, happiness and anger (Damasio et al., 2000), seeing faces with emotional expressions of disgust and fear (Morris et al., 1998; Phillips et al., 1997), as well as being exposed to phobic stimuli (Dilger et al., 2003; Rauch et al., 1995). These findings are consistent with notions interpreting the anterior insula as central to the representation of the internal bodily state, which, since the seminal contribution of James (1884), has been regarded as a critical basis for felt emotion (Craig, 2002; Damasio et al., 2000; Mesulam & Mufson, 1985). Critchley, Mathias, and Dolan (2002) concluded that the right insula provides an interface between the mapping of bodily states and the representation of these states as subjective feelings because, similar to our data, activation of this area was observed in response to nonmasked but not to masked conditioned stimuli. Indeed, the fact that participants could recognize the phobic stimulus in the long-phobic condition and that the anterior insula and the ACC were active during this condition are consistent with the thesis that these areas are associated with the subjective experience of fear (Craig, 2002; Critchley et al., 2002; Damasio et al., 2000; Lane, 2000). Our results suggest that the amygdala rapidly and automatically provides a segregation of stimuli in terms of potential significance, and that this step is followed by a second one involving a cortical network, only activated by more intense, conscious threats such as a phobic stimulus. The anterior insula and the PAG (Damasio, 1999; Panksepp, 1998) contribute a map of the internal bodily changes initiated from the significance analysis in the amygdala, which is integrated with the stimulus in the felt emotion, in a process possibly mediated by the ACC (e.g., Lane, 2000).

The activations seen in the P-long condition were paralleled by corresponding deactivations in the right lateral OFC and the right DLPFC (in the N-long vs. P-long and F-long vs. P-long contrast; see Figure 4c). In addition to the amygdala, the OFC has direct connections to emotionally relevant areas, including the PAG and the striatum (Cavada et al., 2000), through which reciprocal modulation of activity may occur. Accordingly, researchers have suggested that activa-

tion of the lateral OFC during episodes of emotional stress may mediate endogenous attempts to attenuate the emotional expression by inhibiting the activity of the amygdala (Drevets, 2000; Hariri et al., 2003; Ochsner et al., 2002; Petrovic & Ingvar, 2002). If we interpret the role of the OFC in line with this reasoning, the deactivation of the right lateral OFC during the P-long condition may reflect less modulation in the phobic stimulation relative to the fear-relevant condition. The different subregions of the OFC exhibit different patterns of connectivity (Elliott, Dolan, & Frith, 2000), which implies a wide range of functions, and there is no conclusive theory of the role of the intricate OFC. The OFC has been implied in carrying representations of affective values of a stimulus (Rolls, 1999) in addition to the suggestion of it having a role in modulating and suppressing emotional processing. Neuronal firing in the OFC in response to a stimulus would hold the value associated with the stimulus as well as be part of a system underlying selection of behaviors. The diversity in the OFC functions is illustrated by the fact that the medial OFC showed a reversed activation pattern compared with the lateral OFC.

The prefrontal cortex is an area that, in concert with the right parietal region, has been suggested to exert top-down influences on lower level cognitive processing (Corbetta & Shulman, 2002). For example, short-term working memory, as instantiated in the DLFPC, uses representations held online to promote planning and the execution of higher order behavior as well as to inhibit inappropriate environmentally cued responses (Smith & Jonides, 1999). Whereas the frontal cortices are of importance for goal-oriented behavior on the basis of elaborate representations, this type of processing may not be sufficiently rapid to manage the real-time requirements of certain stressful situations. In such situations, it is functionally appropriate to relinquish control to evolutionary history, as distilled in time-proven defense systems (e.g., LeDoux, 1996). In support of this notion, behavioral and animal studies indicate that environmentally cued, automatic responses are favored under exposure to stress at the expense of more cognitively controlled ones, and that the mesolimbic dopamine system has a role in achieving this objective (for a review, see Arnsten, 1998). From this perspective, the deactivation of right prefrontal cortex in response to phobic stimuli that we observed can be interpreted as an active reallocation of processing priorities in order for the fast subcortical defense system to handle the situation in its initial phase. Thus, when responding to the phobic stimuli, participants may have down-regulated the cognitive functions operated by the frontal network in favor of a more instinctively driven network.

In addition to the deactivation of the frontal areas and the amygdala activity, we observed a dorsal ACC activation when contrasting the phobic condition to the fear-relevant condition. One difference between these two conditions is that in the F-long condition, the initial amygdala response seen in the short condition was weakened, whereas the fear reaction was enhanced in the phobic condition. This may suggest that a cognitive reframing of the emotional event was successful during the fear-relevant condition but not during the more intense fear generated in the phobic condition. The cognitive transformation of emotional experience involves both the generation of a strategy to alter the emotional event and the monitoring of the interference between top-down functions that neutralize affect and bottom-up evaluations that continue to generate an affective response (Ochsner et al., 2002). Successful cognitive transformation or the reframing of an emotional event has been attributed to working memory processes in DLPFC and the monitoring of the results to the dorsal ACC (Carter et al., 2000; Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; Ochsner et al., 2002). This suggestion fits our data well. Thus, the DLPFC deactivation during phobic stimulation may be attributed to a failure of applying a nonfearful cognitive reframing strategy to the situation. The concurrent dorsal ACC activation may then be related to the continuous monitoring of the situation in which the bottom-up-induced fear reaction was developing unconstrained by failed attempts to cope by cognitively transforming the threat to a less serious one.

Conclusion

In conclusion, our results indicate that the left amygdala was activated to a similar degree in response to both phobic and fear-relevant stimuli in the short-masked conditions. However, when the masking stimulus was delayed so that the stimuli were consciously perceived, enhanced bilateral amygdala activity was elicited by the phobic stimulus, whereas the fear-relevant but nonfeared stimulus no longer showed any significant amygdala activation. We suggest that the amygdala responds to anything that might turn out to have important consequences for safety and for survival. That is, amygdala may be prone to false positive responses (responding to an innocuous stimulus) rather than to false negative ones (missing a dan-

gerous stimulus) when the masking interval only allowed very shallow processing. When the masking interval was increased to allow for more elaborate processing, the amygdala and pertinent affective processing areas, including the anterior insula, the ACC, the OFC, and the PAG, were recruited in response to the phobic stimulus. However, the amygdala response that was evident to the fear-relevant but nonfeared stimulus with the short-masking interval was nonsignificant when there was time available for more complete processing of the stimulus. Indeed, there was evidence to suggest that the waning of this response could be attributed to inhibitory effects via the prefrontal cortex.

In optimizing the interaction with the environment, it is of importance that task-relevant processing is up-regulated, whereas task-irrelevant processing is down-regulated, attention is directed to relevant external events, and appropriate behavioral choices are made. Thus, in addition to conceptualizing the functional networks as a fear response, we suggest that the regions with altered activity complement each other in constituting a system that allows for reactions and behavioral planning at different time scales.

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