

## A direct brainstem–amygdala–cortical ‘alarm’ system for subliminal signals of fear

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We examined whether consciously undetected fear signals engage a collateral brainstem pathway to the amygdala and prefrontal cortex in the intact human brain, using functional neuroimaging. ‘Blindsight’ lesion patients can respond to visual fear signals independently from conscious experience, suggesting that these signals reach the amygdala via a direct pathway that bypasses the primary visual cortex. Electrophysiological evidence points to concomitant involvement of prefrontal regions in automatic orienting to subliminal signals of fear, which may reflect innervation arising from brainstem arousal systems. To approximate blindsight in 22 healthy subjects, facial signals of fear were presented briefly (16.7 ms) and masked such that conscious detection was prevented. Results revealed that subliminal fear signals elicited activity in the brainstem region encompassing the superior colliculus and locus coeruleus, pulvinar and amygdala, and in fronto-temporal regions associated with orienting. These findings suggest that crude sensory input from the superior colliculo-pulvinar visual pathway to the amygdala may allow for sufficient appraisal of fear signals to innervate the locus coeruleus. The engagement of the locus coeruleus could explain the observation of diffuse fronto-temporal cortical activity, given its role in evoking collateral ascending noradrenergic efferents to the subcortical amygdala and prefrontal cortex. This network may represent an evolutionary adaptive neural ‘alarm’ system for rapid alerting to sources of threat, without the need for conscious appraisal.

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### Introduction

With increasing fears about global-scale dangers, there is a noticeable rise in the vigilance and alertness of individual humans (IPSOS News Centre, 2003). The amygdala is critically involved in an organism’s response to sources of danger, as evidenced by a large number of neurobiological and neuroimaging studies (Davis and Whalen, 2001; Halgren, 1992; LeDoux, 1998; Phan et al., 2002; Zald, 2003). This structure allows us to rapidly orient to sources of potential threat in the environment, which may occur without conscious awareness as an evolutionary adaptive mechanism. Following threatening and traumatic events, amygdala responsiveness and associated vigilance may be abnormally enhanced, as observed in disorders such as post-traumatic stress disorder (Rauch et al., 2000; Williams et al., under review).

In response to consciously attended visual signals of fear, the amygdala is engaged together with the primary visual cortices for processing sensory input (Adolphs, 2002; LeDoux, 1998). To be able to respond to danger rapidly and reflexively, both human and nonhuman animals may also have evolved a direct pathway to the amygdala that bypasses the primary sensory cortices and relies on only crude sensory input in the visual domain. Key evidence for such a pathway comes from ‘blindsight’ patients with striate cortex lesions, who are unable to consciously experience a visual stimulus presented to their blind visual field. In response to fear-related stimuli, blindsight patients nonetheless show amygdala modulation as well as activity in the superior colliculo and pulvinar regions (Morris et al., 2001). Converging electrophysiological evidence involving the same blindsight subject, G.Y., suggests that undetected emotion stimuli can access extrastriate cortical regions by recruiting subcortical visual routes and bypassing the striate cortex itself (De Gelder et al., 1999). Studies of parietal lesion patients, in which visual stimuli are ‘extinguished’, provide convergent evidence that the amygdala, with frontal and intact extrastriate cortical regions, are recruited to process unseen fear

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faces (Vuilleumier et al., 2002). These observations from lesion patients suggest that the superior colliculus–pulvinar projections may subserve the direct relay of crude sensory information to the amygdala. Indeed, neuroimaging studies of healthy humans point to the engagement of a subcortical pathway for fear processing with sensory input via this network (Morris et al., 1999; Vuilleumier et al., 2003).

Previously, electrophysiological studies have approximated blindsight in the intact human brain by using backward masking with extremely brief stimulus durations. Based on signal detection criteria, masking has ensured that subjects cannot consciously detect the presence (versus absence) of face stimuli presented for less than 20 ms (Williams et al., 2004; see Materials and methods for further details). Undetected fear faces have been found to elicit an enhanced ‘automatic’ event-related potential (ERP) complex, which is greater than that elicited to both undetected neutral faces and consciously perceived fear and neutral faces. This ERP complex is defined by the negatively polar N2 (which is greater with nonconscious fear) and the subsequent positive-polar early P3 (faster with nonconscious fear) components, which occur approximately 200–300 ms post-stimulus onset (Liddell et al., 2004). The N2 component has been directly linked to amygdala activity in depth-recording studies (Halgren, 1992; Halgren and Marinkovic, 1995; Krolak-Salmon et al., 2004), and the generation of the early P3 (P3a) component has been localized to prefrontal networks, including the anterior cingulate and inferior frontal gyri (Halgren and Marinkovic, 1995). Notably, the early P3 is distinguished both functionally and anatomically from the later P3b, which has a posterior topography and is associated with controlled contextual processing (Halgren, 1992). The N2/early P3 complex has been associated with automatic orienting to stimuli of biological import (such as fear faces) and novelty processing, consistent with the role of the amygdala (Glascher and Adolphs, 2003) and the anterior cingulate cortex (Halgren and Marinkovic, 1995). Indeed, the P3a is consistently regarded as an index of novelty processes (Friedman et al., 2001), and may reflect anterior cingulate involvement in the “rapid encoding of significant and discrepant signals” (Phan and Tucker, 2003, pp. 216). While emotion processing has also been found to elicit physiologically detectable changes earlier than the 200 ms post-stimulus period (Holmes et al., 2003; Pizzagalli et al., 2002; Williams et al., 2004), early ERP effects specific to fear have been less robust than those for the N2 (Williams et al., 2004), suggesting that these earlier effects may reflect more generalized (rather than valence-specific) sensory processes.

To date, neuroimaging has not been used to explore consciously undetected fear signals in healthy subjects. However, fMRI studies have used backward masking to study the very early stages (approximately 30 ms post-stimulus) of threat-related face processing (Morris et al., 1999; Phillips et al., 2004; Whalen et al., 1998). These studies have prevented subjects from discriminating the valence of facial expressions, but nonetheless allowed face detection to occur (Williams et al., 2004). Under these conditions, amygdala involvement has been equivocal and may depend on the inclusion of stimulus conditioning in the experimental paradigm. The N2 component of the “orienting” complex is also relatively attenuated when masked fear signals are presented for 30 ms, suggesting there may be a different amygdala mechanism involved for consciously *undetected* (versus *undiscriminated*) fear signals (Williams et al., 2004). Previous studies have also not explicitly examined whether

cortical regions are modulated by subliminal fear, although whole-brain analyses provide evidence for prefrontal and temporal modulation to ‘covert’ (30 ms and masked) signals of fear and disgust (Phillips et al., 2004). Electrophysiological recordings indicate that the frontal regions, particularly the anterior cingulate, may be engaged as part of an initial and automatic orienting response to salient signals, such as fear (Halgren and Marinkovic, 1995). The automaticity of this response suggests that these processes may also be engaged by subliminal presentations of fear. Using fMRI, we tested the hypothesis that undetected signals (below the threshold of conscious detection) of fear will engage an automatic alerting network, subserved by brainstem (pulvinar and superior colliculus), thalamus and amygdala, consistent with a direct sensory route to the amygdala, and cortically by the anterior cingulate.

## Materials and methods

### Subjects

Participants were 22 healthy volunteers (mean age = 32 years, SD = 13; 11 males and 11 age-matched females), with normal vision and right-handed predominance. Exclusion criteria were history of head trauma, DSM-IV Axis I diagnosis for self and immediate family, and drug/alcohol abuse. The presence of a depressive, somatic, or anxiety disorder was also assessed via the application of SPHERE-12 (Hickie et al., 2001), and participants were excluded accordingly. Informed written consent was provided in accordance with approved National Health and Research Council ethical guidelines.

### Signal detection analysis

The *discrimination* threshold (or point at which subjects cannot discriminate emotion from neutral with above-chance accuracy) has been the criterion for nonconscious perception used in previous neuroimaging studies of masked stimuli (Esteves and Öhman, 1993; Morris et al., 1998; Öhman and Soares, 1998; Rauch et al., 2000; Whalen et al., 1998). In this study, we focused on the *detection* threshold (the point at which subjects cannot detect whether a face stimulus or blank screen has been presented with above-chance accuracy), to provide a stringent test of below-awareness perception. We drew on data from the threshold-setting experiment of Williams et al. (2004), which determined the point at which subjects could not detect the presence of a ‘face’ versus a ‘blank screen’ stimulus. In this experiment, fear and neutral face stimuli were presented for 10, 20, 30, 40, and 50 ms, with backward masking by neutral faces for 100 ms. The neutral mask was superimposed but spatially offset by 1° in one of the four diagonals from the target mask, to control for perceptual differences in the transition between target and mask faces (i.e., apparent motion). Using signal detection theory (Macmillan, 1986), the objective criterion for lack of conscious detection was  $d' = 0$  (i.e., the duration at which performance accuracy did not differ significantly from chance performance or 50%). Performance in the detection task was found to be above ( $P < 0.001$ ) chance level for 30, 40, and 50 ms, marginally different ( $P = 0.05$ ) for 20 ms, and no different from chance for 10 ms, suggesting a threshold of less than 20 ms is necessary for establishing nonconscious detection.

### Design and procedure

Fear and neutral stimuli (depicting eight different individuals) were selected from a standardized series (Gur et al., 2002). Based on the Williams et al. (2004) data, target stimuli (fear and neutral faces) were presented for 16.7 ms, followed immediately by slightly spatially offset (by 1° in the four diagonals) neutral face mask for 163.3 ms. Stimuli were presented in 30 blocks of eight target-mask pairs per block, with a jittered ISI of 1088 ms on average between stimulus pairs. A total of 30 pseudo-randomized blocks (50% fear and 50% neutral blocks) were presented. Stimulus presentations were synchronized with the refresh rate (60 Hz), displayed via an external projector (Sanyo ProX, Multiverse Projector), and viewed via a mirror system. Participants were asked to actively attend to the face stimuli: Instructions were to actively concentrate on the first face of each pair even though it may be difficult to see, in preparation for post-scan briefings.

### Data acquisition and analysis

A total of 90 T2\*-weighted volumes (3 per stimulus block) were acquired with a Siemens VISION Plus 1.5-T scanner, using a gradient echo echoplanar sequence, with 15 axial slices of 6 mm (0.6-mm gap) thickness, parallel to the AC–PC line, TR 3.3 s, TE 40 ms, and matrix 128 × 128. Three initial ‘dummy’ volumes were acquired to ensure blood-oxygen-level-dependent (BOLD) saturation, and later discarded upon analysis. Adequate coverage of the anterior section of the brainstem was ensured for individual subjects.

Preprocessing (realignment and unwarping, normalization to standardized MNI space, smoothing using 8-mm full width at half maximum isotropic Gaussian kernel) and statistical analysis were performed using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/spm2.html>) with Matlab v.6.5.1.

To test our a priori hypothesis, we undertook region of interest (ROI) analyses for brainstem, thalamic pulvinar, amygdala, and anterior cingulate regions. Regional masks were based on standardized neuroanatomical divisions (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). The anterior cingulate was defined rostrally by the paracingulate sulcus and caudally by the white matter of the corpus callosum, and was 21,704 voxels in total volume across both hemispheres. Central coordinates were left anterior cingulate [−4.36, 34.2, 12.5] and right anterior cingulate [8.12, 35.7, 14.4]. The amygdala mask employed extended to the rostral hippocampus and to the caudal limits of the uncus. Left amygdala volume was 220 voxels (central coordinate: −23.5, −1.95, −18.5) and right amygdala volume the right was 248 (central coordinate: 27.1, −0.57, −18.8). The pulvinar ROI was explored using a thalamus mask, which was defined anatomically by the extent of gray matter in the thalamic region and the left thalamus was 8800 voxels (central coordinate: −11.2, −18.8, 6.61) and the right thalamus was 8456 voxels (central coordinate: 12.7, −18.8, 6.73). The superior colliculus was investigated using a whole brainstem mask, which allowed for elucidation of other brainstem activity. The brain stem mask was defined dorsally by the thalamus ( $z = 0$ ) and ventrally by the medulla ( $z = -52$ ) and incorporated a volume of 2856 voxels.

Table 1

Results of ROI ( $P < 0.05$  small volume corrected) and whole brain analysis ( $P < 0.001$  uncorrected) in which there was a significant response for the contrast of masked fear versus masked neutral faces

Region	Hemisphere (left/right)	Coordinates (mm)*			Voxels	Brodmann area	Z score
		x	y	z			
<i>Region of interest analysis</i>							
Amygdala	L	−18	2	−20	4	n/a	1.80
	R	28	−4	−12	8	n/a	2.04
Pulvinar	L	−16	−24	10	23	n/a	2.80
Superior colliculus	L	−0.5	−24	−8	306	n/a	2.66
Locus coeruleus	L	−2	−36	−23	306	n/a	2.66
Anterior cingulate	L	−6	20	−8	12	25	3.01
	R	8	36	−2	5	24	1.80
<i>Whole brain analysis</i>							
<b>Frontal regions</b>							
Anterior cingulate	L	−2	16	−6	10	25	3.2
Inferior frontal (subgyral)	L	−38	26	−4	13	47	3.4
Middle frontal gyrus (premotor)	R	46	6	38	46	9	3.58
Cingulate gyrus	L	−10	−14	44	10	24	3.34
Medial frontal	L	−8	28	36	7	9	2.96
Superior/middle frontal gyri	L	−34	18	54	47	6/8	4.25
<b>Basal ganglia</b>							
Caudate (head)	L	−12	16	−4	12	n/a	3.25
<b>Somatosensory regions</b>							
Insula	L	−38	6	−2	4	n/a	3.21
Postcentral gyrus	L	−32	−38	50	11	3/4	3.48
<b>Temporal cortex</b>							
Superior temporal gyrus (extends to inferior frontal)	L	−52	10	−2	185	22/47	4.25
Middle temporal gyrus	L	−50	−36	−16	10	21	3.48
Temporal complex (inferior and middle temporal gyri)	L	−52	−66	−6	9	19/37	3.18

Activity was examined for the contrast of masked fear faces relative to ‘baseline’ masked neutral faces, with an alpha level of  $P < 0.05$  (small volume corrected) and clusters defined by at least 3 contiguous voxels, using the WFU PickAtlas (Maldjian et al., 2003). To examine activity in these ROI’s relative to the distribution of whole-brain activity, we also conducted a random-effects group analysis of the equivalent contrast using one-sample  $t$  tests, with an alpha level of  $P < 0.001$  uncorrected (Morris et al., 1999), and with clusters defined by at least three contiguous voxels of significant response.

## Results

### Region of interest analyses

Consistent with our predictions, there was a significant increase in response to subliminal fear for each ROI: left superior colliculus ( $P = 0.004$ ), left pulvinar ( $P = 0.003$ ), bilateral amygdalae (left;  $P = 0.036$ , right;  $P = 0.02$ ), and bilateral anterior cingulate (left:  $P = 0.001$ ; right:  $P = 0.036$ ) (Table 1; Figs. 1 and 2). The right

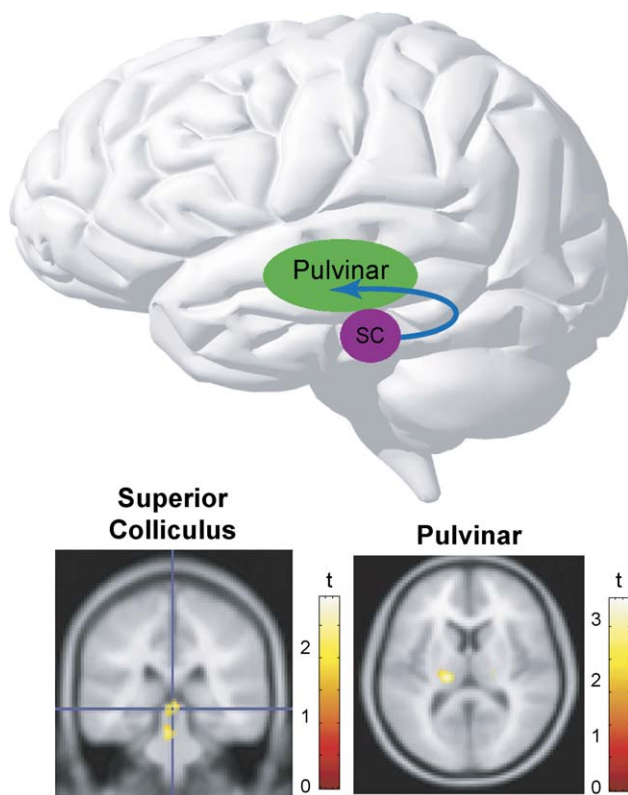


Fig. 1. Colliculo-pulvinar secondary visual pathway. Activation maps show significant BOLD signal in the left superior colliculus (SC) and left pulvinar as a result of the ROI analysis ( $P < 0.05$  small volume corrected). Colored  $t$ -bars are provided to indicate the level of significance of observed BOLD activation. The observed activity in these regions to undetected fear signals suggest a crude relay of stimulus information from the retina to the superior colliculus, which conveys stimulus information to the pulvinar in the posterior thalamus. Such information is of a lower spatial resolution than the dominant visual processing stream involving the lateral geniculate nucleus in the thalamus and the striate cortex, but may facilitate some degree of processing when this primary pathway is unavailable, such as in subliminal processing or blindsight.

amygdala was defined by a larger cluster of activation than the left amygdala. The point of maximal superior colliculus activity was part of a large cluster that extended ventrally into the brainstem, and encompassed a cluster in the region of the locus coeruleus (Fig. 2).

### Whole brain analysis

Whole brain analysis revealed significant responses to subliminal fear in the fronto-temporal and somatosensory-related cortices, which have been associated with face and facial emotion perception (Adolphs, 2002) (Table 1; Fig. 3). Consistent with the ROI analysis, significant activity was observed in the ventral portion of the left anterior cingulate, which has been called the ‘affective’ division, attuned to the emotional aspects of sensory stimuli (Bush et al., 2000). This cluster was proximal to observed activity in the head of caudate. No other ROI findings were confirmed in the whole brain analysis. Additional clusters of significant frontal response to subliminal fear were revealed in the highly interconnected medial prefrontal cortex, as well as the left inferior and superior frontal, cingulate, and right premotor cortices. Together with the anterior cingulate, these regions have been implicated in a frontal mechanism for alerting to significant and novel stimuli (Berns et al., 1997; Halgren and Marinkovic, 1995). Concomitant activity observed in the temporal cortex (encompassing superior, middle and inferior temporal gyri), and somatosensory-related insula and postcentral gyrus, have also been involved in the processing of biologically salient stimuli (Table 1; Fig. 3).

## Discussion

Our findings suggest that evaluation of the significance of biologically salient signals does not rely on conscious appraisal of these signals. Rather, direct sensory input from the brainstem may provide a neural mechanism for automatic alerting to danger signals, such as fear faces, which may occur without conscious stimulus detection. Neuroimaging studies have not previously examined the networks engaged by consciously undetected signals of fear. Rather, they have focused on neural responses to undiscriminated signals (Morris et al., 1999; Phillips et al., 2004; Whalen et al., 1998). A lack of conscious discrimination may not provide an exhaustive behavioral test of subliminal perception, because while the valence of the face (e.g., fear versus disgust) cannot be consciously determined, the presence of the face stimulus can nonetheless be detected above chance (Williams et al., 2004). The results of this study indicate that responses to subliminal signals of fear may be distinguished from subliminal neutral signals by direct engagement of cortical orienting networks, in addition to the amygdala, without the usual overarching involvement of the primary visual cortex. Activation observed in brainstem structures, superior colliculus, and locus coeruleus, as well as the thalamic pulvinar, suggest that brainstem tracts may provide an alternative pathway for crude sensory information concerning fear signals, to reach the amygdala and the cortex without conscious awareness. Our findings suggest that brainstem–amygdala and cortical regions provide a rapid and automatic alerting mechanism for responding to subliminal signals of fear (Fig. 4).

While the primary pathway for sensory input involves a relay of information via the thalamus to the striate sensory cortices,



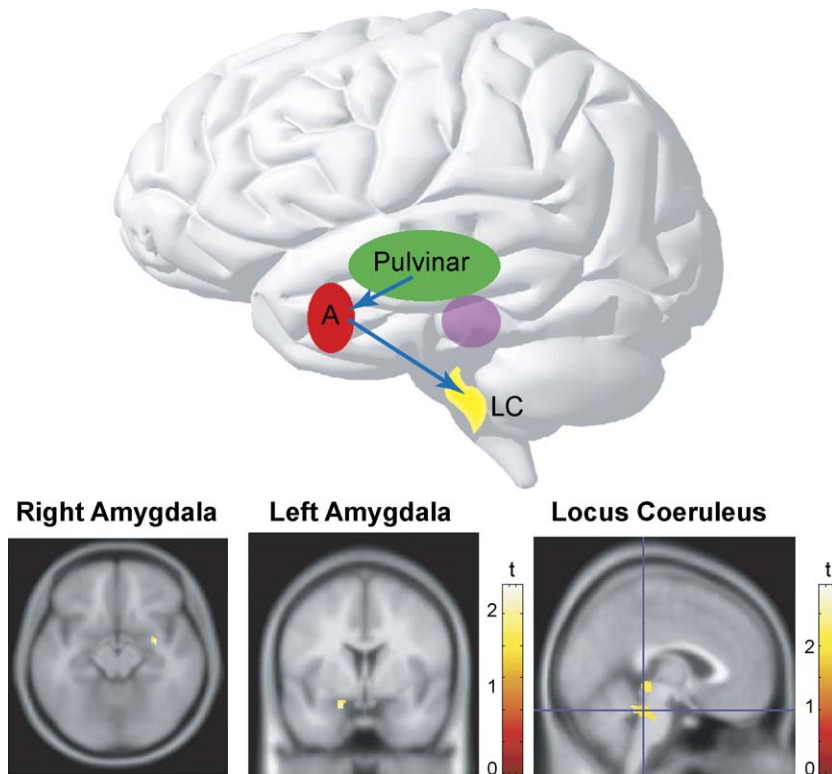


Fig. 2. Brainstem (locus coeruleus) and amygdalae. Activation maps show significant BOLD activity in the bilateral amygdalae (A) and the left brainstem, encompassing the locus coeruleus (LC). This was a result of the ROI analysis ( $P < 0.05$  small volume corrected). Amygdala activations are presented at a  $P = 0.1$  threshold for illustration purposes only. Colored t-bars are provided to indicate level of significance of observed BOLD activation. Evidence suggests that the pulvinar is functionally connected with the amygdala (A), which may facilitate rapid processing to the amygdala in response to threat-related signals (Morris et al., 1998). Such signals may initiate the fight/flight mechanisms of the brainstem, including the involvement of the locus coeruleus (LC) from which the ascending noradrenergic pathways are triggered in times of stress or in response to significant stimuli (Aston-Jones et al., 1996).

brainstem networks are capable of processing low level sensory features (Morris et al., 2001). The superior colliculus, and its projections to the thalamic pulvinar, is a key brainstem structure involved in responding to crude visual stimulation, and receives direct retinal input (Morris et al., 1999; Vuilleumier et al., 2003) (Fig. 1). This colliculo-pulvinar pathway may form the neural basis of the phenomena of 'blindsight' (Weiskrantz, 1996). In the intact brain, the primary purpose of these alternative visual pathways is to support the act of saccadic eye movements, but may also play a role in orienting to novel stimuli and stimulus detection (as reviewed by Morris and Dolan, 2001). This subcortical pathway may underlie the ability to rapidly respond to alterations in the visual environment in an initial response to significant stimuli (Vuilleumier et al., 2003).

The brainstem activation observed to undetected fear signals encompassed a region representing the locus coeruleus (Fig. 2). While neuroimaging studies have not explicitly implicated the locus coeruleus in emotion processing, there is substantial evidence from animal neuroscience to suggest that it plays an important role in facilitating the rapid neural responses required for responses to fear-related signals (Aston-Jones et al., 1996). The locus coeruleus directs noradrenergic neural stimulation in response to salient sensory input (Berntson et al., 2003). Locus coeruleus projections also provide a volley of collateral excitatory noradrenergic efferents to diffuse regions of the cortex (Jones, 2003), particularly frontal and temporal structures, as well as to the subcortical amygdala, pulvinar, and superior colliculi (Aston-Jones et al.,

1996; Berntson et al., 2003; Jones, 2003) (Fig. 3). These proposals accord with our finding that regions of the anterior brainstem, incorporating the superior colliculus and locus coeruleus, were enhanced for fear relative to neural subliminal face stimuli in healthy human subjects (Figs. 1 and 2). It has also been suggested that the locus coeruleus noradrenergic system may be directly activated by initial emotional evaluative processes in the amygdala and pulvinar, to facilitate the physiological mechanisms of emotional behavioral responses (Aston-Jones et al., 1996). In this regard, we propose that the locus coeruleus may drive the automatic capturing of attention and orienting of behavior, vital to rapid reactions to signals of potential danger and import (Öhman et al., 2000). However, given the difficulty inherent in localizing small structures (Griffiths, 2001), replication of the present findings in an independent sample, and with additional subliminal fear stimuli, is warranted.

Our observation of amygdala activity to consciously undetected signals of fear provides the first demonstration that this structure may modulate vigilance in the absence of conscious *detection* of these signals (Fig. 2). Extensive animal, human, and theoretical models of emotion advocate the importance of the amygdala in the cascade of emotion processing (Davis and Whalen, 2001; Gray, 1987; Halgren, 1992; LeDoux, 1998). Many argue the amygdala may be the lynch-pin of an organism's ability to rapidly respond to sources of threat without explicit knowledge of the presence of the stimulus, i.e., before conscious detection (Zald, 2003). The evidence presented here suggests that the amygdala is certainly

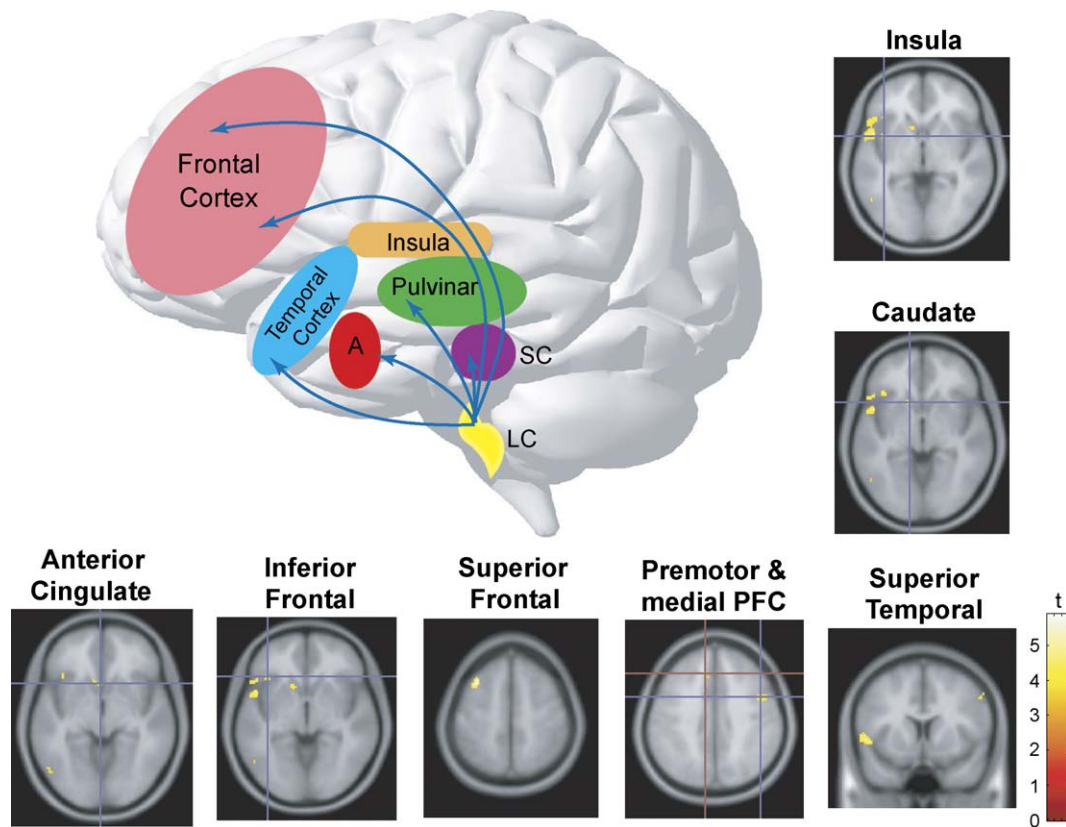


Fig. 3. Frontal and temporal regions. Activation maps shown here are as a result of the whole brain analysis ( $P < 0.001$  uncorrected). Only the key regions are displayed. Colored t-bars are provided to indicate level of significance of observed BOLD activation. The brainstem (primarily the locus coeruleus) can innervate diffuse regions of the cortex and subcortical structures, including amygdala (A), via ascending collateral noradrenergic pathways. Such a broad innervation of the cortex, including frontal (anterior cingulate, inferior, superior frontal gyri, premotor, cingulate and medial prefrontal cortex), temporal (superior, middle, and inferior temporal gyri), and somatosensory [insula (presented at  $P = 0.01$  for illustration purposes only), post central gyrus] regions, was observed to undetected fear signals in this study. This may resemble a neural alarm system, incorporating aspects of alerting and orienting, to most efficiently process threat-related stimuli.

enhanced in response to consciously undetected fear signals, but that it is part of an automatic alerting system, and as previous work suggests (Aston-Jones et al., 1996; Berntson et al., 2003), both projects to and is modulated by regions of the brainstem. Our findings provide support for the notion that the amygdala acts as the brain's 'lighthouse', which constantly monitors the environment for stimuli which signal a threat or danger to the organism (Davis and Whalen, 2001).

The pattern of amygdala and prefrontal activity observed in this study is consistent with electrophysiological evidence that these same subliminal signals of fear elicit an enhanced N2/early P3 orienting complex (Halgren and Marinkovic, 1995; Liddell et al., 2004; Williams et al., 2004). The generators of the ERP components of this complex have been localized directly to these same structures observed active in this study (Halgren, 1992) and is convergent with recent depth electrode recordings in response to emotional faces (Krolak-Salmon et al., 2004). The conceptualization of the orienting complex in this context refers to an automatic and reflexive response, vital for the orienting of attention toward the stimulus and to highlight the stimulus for further cognitive evaluation, (Halgren, 1992). Halgren and Marinkovic (1995) suggest that the automatic orienting complex could represent an electrophysiological index of a "preparation-to-process" alerting function to significant stimuli. The co-activation of brainstem, amygdala, and cortex in response to

undetected fear signals in this fMRI study may also reflect the neural correlates of this "preparation-to-process" aspect of the orienting reflex (Fig. 4).

The activation of specific regions of the frontal cortex supports the proposal that an alerting mechanism is triggered by unseen threat-related signals. Given the concomitant involvement of the brainstem, the cortex may be activated via ascending collateral pathways originating in the brainstem (Fig. 3). These frontal regions, including the inferior frontal gyrus (Yamasaki et al., 2002) and the ventral anterior cingulate (Bush et al., 2000), have been linked to novelty processing (Ranganath and Rainer, 2003) and the assessment of the emotional significance of incoming signals. The left anterior cingulate in particular, may be engaged specifically in the redirecting of attention because of exposure to nonconscious emotional (happy and sad) signals (Killgore and Yurgelun-Todd, 2004). We suggest that the directing of attention occurs as part of an automatic alerting mechanism. The involvement of the head of the caudate in subliminal fear processing in this study is consistent with evidence that caudate neurons have a role in detecting salient features, such as novelty, and may also contribute to unconscious alerting to novel stimuli (Berns et al., 1997; Gray, 1987). The observation of concomitant subcortical and cortical regions accords with models of attention that propose parallel mechanisms for automatic 'orienting' (involving superior colliculus and

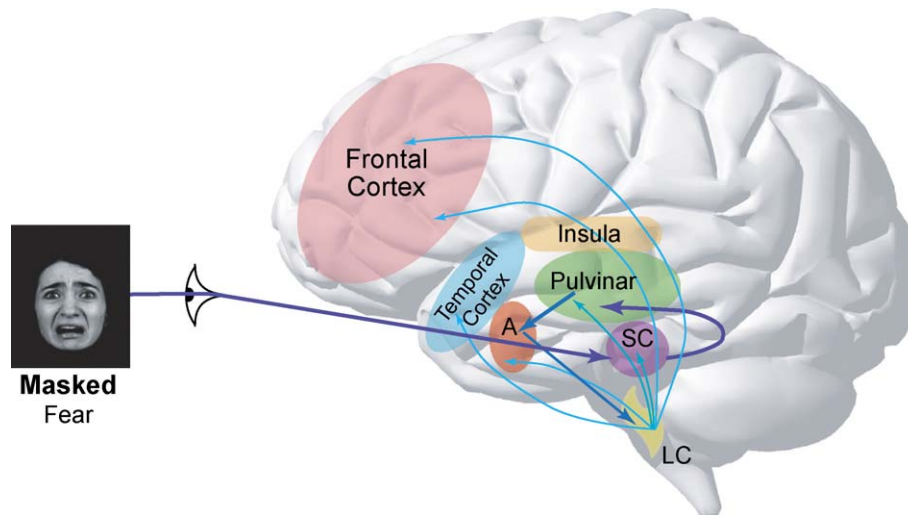


Fig. 4. Brainstem–amygdala–cortical ‘alarm’ system for subliminal signals of fear: a heuristic model. Figs. 1–3 demonstrate possible interconnections between activated brain regions in response to undetected signals of fear, as observed in this study, based on substantial neuroscientific evidence (as outlined in the discussion). We propose that these systems are integrated to form the neural basis of an initial alarm mechanism, offset to provide an evolutionary adaptive mechanism to respond optimally, with heightened vigilance, to threat-related stimuli in the environment. The fear faces in this study are presented briefly, followed immediately by a superimposed but spatially offset neutral face mask, in a backward masking procedure. The fear face is thus consciously undetected. Crude sensory information most likely reaches the amygdala (A) via a colliculo (SC)–pulvinar pathway, bypassing the primary visual cortex. Activation observed within the anterior midbrain region of the brainstem, which encompasses the locus coeruleus (LC), suggests that these regions may play an important role in initiating basic fight/flight responses. The brainstem can provide broad excitatory collateral innervation of the cortex, including anterior cingulate and other frontal–temporal structures, to facilitate an increase in the alert state.

pulvinar) and ‘alerting’ (involving efferent noradrenergic pathways from brainstem to diffuse cortical regions) (Posner et al., 1997).

Other neural regions activated to unseen fear signals in the whole brain analysis may also contribute to effective alerting and orienting us to sources of threat (Fig. 3). Temporal regions have been associated with the visual perception of biologically significant signals (Allison et al., 2000) and their recruitment by unseen fear signals suggests their biological import does not rely solely on conscious attention. The insula may also contribute to alerting without awareness, given that like the brainstem, it receives direct signals from the internal milieu to monitor homeostasis (Damasio, 1996).

While the findings in this study are consistent with our a priori predictions, the focus on relatively small subcortical and brainstem regions requires replication with convergent methods, including manual tracing of ROIs, the use of different scanning parameters, and the inclusion of different subliminal fear stimuli. Moreover, future research might seek to include concurrent measures of autonomic responsiveness (such as skin conductance recording), which may provide an independent means to examine modulation of responses to fear via brainstem systems.

## Conclusion

This study provides new evidence to suggest that subliminal signals of fear trigger the activation of brainstem, amygdala, and cortical regions involved in fast tracking a central nervous system response to a potentially threatening encounter (Fig. 4). We propose that this network reflects a direct brainstem sensory pathway for processing crude stimulus information, involving the superior colliculus and pulvinar, to the amygdala, thought to be engaged to crude representations of threat-related

signals. The observation of concurrent locus coeruleus activity suggests that this norepinephrine center may be engaged in response to undetected fear signals to provide rapid and diffuse noradrenergic excitatory innervation of regions of the cortex and subcortical structures, including the amygdala. In essence, locus coeruleus involvement may represent activation of arousal mechanisms involved in accessing the cortex to further the evaluation of significant stimuli and to facilitate automatic orienting and the eventual experience of emotion within awareness. Cortical activation in response to undetected fear faces, particularly prefrontal, may reflect the neural correlates of a frontally driven automatic orienting response to the novel aspects of fear signals in a type of alerting process. This innate ‘alarm’ system could provide an evolutionary adaptive mechanism for the most efficient neural processing of threat-related and other highly salient signals in humans. A neural alarm system (Fig. 4) that can be triggered automatically to potential signals of threat without the need for conscious experience is essential for facilitating accelerated and efficient responses, to avoid danger and threats to security.

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