On the unconscious subcortical origin of human fear

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Abstract

Consistent with the hypothesis that the amygdala is central to fear activation, brain imaging studies show that fear stimuli activate the amygdala, even when conscious recognition is prevented by backward masking. The bulk of the data suggest that the amygdala can be activated from potentially accessible but unattended fear stimuli. Activation of the amygdala facilitates low level visual processing. Several lines of evidence suggest that activation of the amygdala is mediated by a subcortical pathway. Thus, according to data from patients with lesions in the primary visual cortex, the amygdala can be activated in the absence of cortical processing. There is considerable support for the hypothesis that visual stimuli can access the amygdala via a pathway that includes the superior colliculus and the pulvinar nucleus of the thalamus. These data are consistent with an evolutionary argument, focusing of the role of snakes as a predator on primates.

1. Introduction

Fear denotes an emotion that has been primarily shaped in evolutionary arms races between predators and prey. Improved predator hunting skills have prompted more efficient defense manoeuvres by preys, which have put a pressure on further skill development in the predator, and so on. Thus, the function of fear is to motivate organisms to cope with threats that have jeopardized survival throughout evolution [e.g., [1]]. The coping attempts are more or less clearly focused on metabolically taxing defense behaviors such as escape and attack. However, they also include immobility (freezing), which is a behaviorally quiescent state that involves active scanning of the environment in order to assess risks and opportunities [2]. In primates, the fear system has been imported into the social domain as the submissive pole of social dominance [3]. While there is still a role for active defenses like escape and attack in the social context, the emphasis is less on automatic, fast defense recruitment than on sophisticated threat assessment with a considerable role for strategic considerations [e.g., [3,4]].

A substantial literature documents that the amygdala, a collection of nuclei in the medial temporal lobe, is a central neural node for fear both in predatory and social dominance contexts [e.g., [5-7]]. Amygdala has downstream connections to hypothalamic, midbrain, and brainstem nuclei that control psychophysiological (e.g., cardiovascular changes) and behavioral responses (e.g., escape) that are commonly taken to be symptoms of fear and anxiety [6]. Upstream, it receives information from all sensory modalities. More controversially, it has been suggested that it also receives crudely processed information from thalamic nuclei that define rapid “low roads” to the amygdala, independently of the cortex [8]. This argument was bolstered by neuroanatomical data suggesting a direct pathway from the auditory thalamus to the amygdala [7], and by evolutionary arguments on the critical functional edge provided by early threat detection and defense mobilization [e.g., [9]].

The ground plan for the current understanding of the amygdala was laid by animal researchers [see reviews in Ref. [5]], but the last decade has seen a rapidly expanding body of knowledge of the amygdala based on human neuropsychological and brain imaging data. The purpose of the present article is to provide a concise overview of the role of the amygdala in human fear activation. The review is organized around six central predictions from the LeDoux [7] model: (a) fear stimuli should activate the amygdala; (b) the amygdala activation should be rapid and not
require conscious recognition of the eliciting stimulus; (c) activation of the amygdala should be independent of focal attention to the eliciting stimulus; (d) activation of the amygdala should not require cortical activation; (e) amygdala activation should enhance perceptual sensitivity; and (f) the amygdala should be directly activated by visual stimuli via a subcortical route that includes the superior colliculus of the midbrain and the pulvinar nucleus of the dorsal thalamus.

2. Fear stimuli activates the amygdala

Several studies have demonstrated that effective fear stimuli, such as pictures of snakes or spiders for human research participants selected on the basis of phobic level fear of these animals, provoke a distinct fear response that includes pronounced autonomic activation and rapid potentiation of the startle reflex [e.g., [10]]. Furthermore, studies that present relatively short-lasting pictorial representations of phobic stimuli to selected phobics show reliable activation of the human amygdala as assessed by functional Magnetic Resonance Imaging (fMRI) or Positron Emission Tomography (PET) [11-14]. However, studies that involve relatively prolonged presentations of symptomatically relevant phobic stimuli often fail to observe amygdala activation [e.g., [15-18]], which should not be surprising given that the most important function of the amygdala appears to be the initial appraisal of the threat value of stimuli [11].

3. The amygdala can be activated by stimuli that are not consciously perceived

Öhman and co-workers [19,20] developed a backward masking technique to examine autonomic responses to very briefly (15–30 ms) presented pictorial stimuli that were prevented from reaching awareness by an immediately following masking stimulus. In support of the notion of a direct, very fast route to fear activation, Öhman and Soares [21] demonstrated that participants selected to be highly afraid of snakes (but not of spiders) or of spiders (but not of snakes) showed elevated autonomic responses to effectively masked presentations to their feared (but not to their non-feared) animal.

Morris et al. [22] used the masking technique to examine regional cerebral blood flow responses assessed by PET to masked facial stimuli whose emotional impact had been enhanced by Pavlovian fear conditioning before scanning. Confirming previous data on nonconscious activation of autonomic responses to feared stimuli, Morris et al. [22] reported specific activation of the right amygdala to masked conditioned angry faces as compared to masked nonconditioned angry faces. Similar data on masked activation of the amygdala to facial stimuli were obtained by Whalen et al. [23], who reported larger responses of masked fearful than masked neutral faces.

To further elucidate the dynamics of fear activation in the human brain, Carlsson et al. [11] recruited participants who were fearful of snakes or spiders (but not of both) for a PET study with masked stimuli. During different scans, participants were exposed to repeated brief presentation of pictures of snakes, spiders or mushrooms that were effectively or ineffectively masked following the procedure of Öhman and Soares [20]. Compared to the effectively masked mushroom control condition, the left amygdala was activated both to the feared (e.g., snakes) and the fear-relevant but non-feared (e.g., spiders) condition with no difference between the two types of fear-relevant stimuli. This implies that the amygdala initially responded to the threat potential of stimuli rather than to a specifically defined fear stimulus. However, as the processing time was extended to allow conscious perception of the stimuli by increasing the masking interval, there was strong bilateral amygdala activation to the actually feared stimulus (e.g., snakes), but no significant amygdala activation on either side in the fear-relevant but non-feared condition (e.g., spiders for a snake fearful participant). These data are illustrated in Fig. 1.

Binocular rivalry is an alternative method of backward masking for presenting stimuli outside of awareness. If two different stimuli are separately projected on corresponding retinal locations of the two eyes, rather than appearing as a mixture, they will compete to determine the percept. Given that the two stimuli are roughly matched in salience, the percept will spontaneously shift between them. However, if one stimulus is in some sense more salient than the other, it will suppress the other, which implies that the suppressed stimulus is presented outside of the

![Fig. 1. Axial view (in the two upper panels y=-8; in the two lower y=-14) depicting amygdala responses to masked phobic (P-short, e.g., pictures of snake for phobic individual) and fear-relevant but non-feared (F-short, e.g., pictures of a spider) stimuli as contrasts to a neutral picture (N; a mushroom; the two upper and lower left panels) or between phobic and fear-relevant pictures (lower right panel). The masking interval was 15 ms and the mask was scrambled pictures. 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<0.05 for illustrative purposes. Normalized t-value maps are superimposed onto an averaged brain MRI (data from Ref. [11] reprinted by permission).](image-url)
4. Amygdala can be activated by non-attended stimuli

Fear stimuli have privileged access to attention. For example, Öhman et al. [26] instructed their participants to look for discrepant stimuli in arrays of pictures. They reported that fear-relevant stimuli (snakes and spiders) were more quickly detected among neutral distracter stimuli (flowers and mushrooms), than were neutral stimuli among fear-relevant ones, and that these effects were specifically enhanced in fearful participants. Furthermore, their data suggested that snakes and spiders could be preattentively located and brought to focal attention. Given the sensitivity of the amygdala to fear-relevant stimuli, these data are likely to reflect involvement of this structure. Indeed, from a functional perspective one could argue that bringing fear stimuli into the focus of attention is a central task for the neural fear network [7,27].

The role of attention in activating the amygdala was directly examined by Vuilleumier et al. [28]. They exposed their participants to pairs of faces and houses that were either horizontally or vertically arranged as a cross around a fixation point. Attention was manipulated by asking the participants to judge whether the pairs of faces or houses showed identical pictures. In contrast to the cortical fusiform gyr facial recognition area, whose response to fearful faces was enhanced by attention, amygdala activation was larger to fearful than to neutral faces both when faces and houses were the targets of attention. Thus, these data support the hypothesis that the amygdala can be activated by non-attended stimuli.

This conclusion was further supported by Anderson et al. [29] in a similar paradigm in which participants attended to either faces (showing fear, disgust or a neutral expression) or houses in different colors that were superimposed on each other. In support of the hypothesis that the amygdala activation is independent of attention to the eliciting stimulus, they reported that the amygdala response to fearful faces did not differ as a function of whether the faces were attended or not.

In a similar study, Straube et al. [14] required their spider phobic participants either to identify whether pictures showed a spider or a mushroom, or perform a perceptual judgment task on a circle superimposed on spiders or mushrooms. Amygdala responses to spiders (relative to mushrooms) were larger in phobic than in non-phobic participants. Furthermore, in contrast to the responses in other structures (e.g., insula, anterior cingulate, dorsomedial prefrontal cortex) in which the responses to spiders were smaller during the perceptual task, the amygdala response was as large during this task as when participants focused on spiders and mushrooms in a picture identification task, again supporting independence of the amygdala to attentional conditions.

However, the data remain somewhat contentious because Pessoa et al. [30] reported strong effects of attention on the amygdala in a task where participants either attended to focularly presented fearful, happy and neutral faces by judging their gender, or to eccentrically presented bars in the upper left and right quadrants of the display by deciding whether their orientations were the same. Contrary to the other findings, Pessoa et al. [30] reported that none of the emotional faces differed from the neutral ones with regard to amygdala activation in the unattended condition. The basis for this discrepant finding remains unclear. In contrast to the studies reporting the amygdala to be independent of attention [14,28,29], which used superimposed stimuli for the two attention conditions, Pessoa et al. [30] used spatially separated stimuli. This stimulus arrangement may have facilitated rejection of non-attended stimuli.

Another possibility was suggested by Bishop et al. [31], who showed that the amygdala response to fearful faces was unaffected by attention only in highly anxious participants. Low anxious participants, on the other hand, showed larger amygdala responses to attended than to unattended fear faces. Therefore, they argued that anxiety could modulate the effect of attention on amygdala activation and suggested that Pessoa et al. [30] inadvertently may have recruited low-anxious subjects for their study.

5. Amygdala influences perception

The amygdala is richly connected with neocortex. However, these connections are biased in the sense that the amygdala has many more efferent than afferent cortical projections [7,32]. With regard to the visual system, it receives input from the primary visual cortex (V1) and the inferotemporal cortex (IT), but it has efferent projections to several levels of the ventral visual processing stream [32]. This anatomical organization suggests that the rapid amygdala activation occasioned by a fearful encounter may tune subsequent visual processing of the stimulus situation. This notion was tested by Vuilleumier et al. [33] in patients with focal amygdala and hippocampal lesions. These investigators replicated previously demonstrated emotional enhancement by a cortical area involved in vision, the fusiform cortex, to fearful faces [e.g., [28]] in normal controls and patients with focal hippocampal lesions only. However, such emotional enhancement was not observed in the patients with amygdala lesions (with or without hippocampal lesions). Thus, these findings imply that the amygdala is rapidly activated in order to prime early visual processing of emotional stimuli as suggested by LeDoux [7].

In an ingenious study, de Gelder et al. [34] examined a blind-sight male patient, who reported no visual sensation for objects presented to the damaged cortical areas. Nevertheless, when exposed to stimuli in the blind field, the patient could indicate their location and discriminate between two stimuli better than by chance even though he denied seeing anything. De Gelder et al. [34] presented emotional faces to the patient’s blind right hemi field simultaneously with visual stimuli presented to the intact left visual field or with emotional voices. In this way, they were able to study the interaction between unconscious and conscious emotion in one brain. The results showed that fearful faces unconsiously presented in the blind field biased conscious perception of emotional faces and affective pictures as well as emotional voices, and that these effects were mediated by the amygdala.

Phelps et al. [35] reported an experiment in which they briefly cued a perceptual task (judging line orientations as a function of
contrast) by fearful or neutral faces. Confirming that emotion facilitates perception of low level visual features, their data showed improved contrast sensitivity after fearful as opposed to neutral faces. This effect, however, was not obtained with inverted faces, which provides support for the emotional origin of the effect. Furthermore, in a second experiment, Phelps et al. [35] showed that this enhanced contrast sensitivity was stronger for emotional than for neutral upright (but not inverted) faces both during focused and divided attention conditions, suggesting that it did not depend on attention. However, the emotion effect was larger with focused than divided attention, which implies that emotion potentiated the effect of attention.

In concert, these lesion and behavioral data suggest that amygdala activation (consciously or unconsciously) results in improved perceptual performance.

6. Amygdala can be activated in the absence of relevant sensory cortex

A central point in the LeDoux [7] model of fear activation is that the amygdala can be rapidly activated by a “low road”, via the thalamus, that does not require the cortex. This notion implies that it should be possible to activate the amygdala even if cortical processing of the fear stimulus is impossible because of lesions in the relevant sensory cortices. To examine this prediction, Morris et al. [36] examined a patient with lesions in the primary visual cortex, which resulted in blind-sight. Nevertheless, when exposed to faces in the blind field the patient showed reliable activation of the right amygdala to fearful as compared to neutral faces. Furthermore, similar results were obtained in a patient whose extensive occipital lesion was associated with total blindness without any signs of residual vision [37].

In a further analysis of the role of cortex in amygdala activation, Vuilleumier et al. [38] examined a patient with right inferior parietal lobe damage, which resulted in visual extinction to stimuli presented in the anatomically intact left visual field when another stimulus was simultaneously presented in the right visual field. For example, the patient failed to notice a picture of a face in the left visual field when a picture of a house was concurrently presented in the right visual field (even though the patient did perceive the face when it was presented alone in the left visual field). Nevertheless, brain imaging data showed amygdala activation to extinguished faces particularly when they were fearful. Thus, this study showed the amygdala was activated by fear faces that remained non-perceived because they were presented in spatial locations corresponding to damaged areas in higher order visual brain areas. Hence, spatial neglect and visual extinction caused by the neural damage prevented awareness [38]. These data are consistent with the notion that the human amygdala can be activated by fear stimuli in the absence of cortical processing and visual awareness.

7. A subcortical pathway to the amygdala?

To examine the route to nonconscious amygdala activation, Morris et al. [39] used their previously reported data [20] to examine the neural connectivity between the amygdala and other brain regions when the amygdala was activated by masked stimuli. In support of the low road hypothesis [7], Morris et al. [39] found that activation of the right amygdala by masked stimuli could be reliably predicted from activation of subcortical way-stations of the visual pathways such as the superior colliculus and the right pulvinar nucleus of the thalamus, but not from cortical regions.

Lidell et al. [40] examined the effect of masked fearful versus masked neutral faces on anatomically defined regions of interest. Confirming the connectivity data reported by Morris et al. [39], they found reliable activation to masked fearful faces in the left superior colliculus, the left pulvinar, and bilateral amygdalae. In addition, they found activation in the locus coeruleus and the anterior cingulate.

In an ingenious elaboration of the low road concept, Vuilleumier et al. [41] suggested that neural processing of faces and emotional expressions operates primarily on gross, low-frequency information. Accordingly, they filtered the spatial frequency of pictures of faces to produce facial stimuli that retained only high- or low-frequency spatial information. Their results showed that amygdala responses were larger for low-frequency information form faces provided that they showed expressions of fear. Moreover, they demonstrated activation of the pulvinar and superior colliculus by low-frequency, but not high-frequency, information from fearful faces. Thus, these results suggest that there is a distinct superior colliculus–pulvinar pathway to the amygdala that operates primarily on low-frequency information.

The low road hypothesis has been controversial, and it has been met with articulated challenges [42-45]. A recurrent theme has been that input from the IT is necessary for discrimination of facial emotion by the amygdala. However, Pasley et al. [24], who reported amygdala activation to fearful faces suppressed from awareness by binocular rivalry, demonstrated that areas of the IT that responded to faces under normal viewing did not discriminate faces from objects under conditions of binocular rivalry. Assuming that rivalry suppressed the V1, these data strongly suggest a subcortical origin of the visual input that allowed the amygdala to discriminate suppressed fearful from suppressed neutral faces in the absence of cortical processing.

8. An evolutionary basis for the low road concept

In an elaborated argument that provides an evolutionary basis for the low road concept, Isbell [46] has suggested that fear (related to predation) has played a major role in shaping the visual system of primates. Specifically, she proposed that snakes, because they provided the major predatory threat, played an important role in shaping the brains of early primates as well as that of anthropoids (i.e., monkeys and apes). First, primitive constrictor snakes were the main threat to the primitive primates that emerged roughly 100 million years ago. Second, the appearance of venomous snakes provided a decisive predatory advance during the Eocene (roughly 55–35 million years ago), which accelerated evolution of the primate visual system in old world (as opposed to new world) monkeys, and its integration with the fear circuit centered on the amygdala. Because venomous snakes are deadly but hard to detect, there was development of greater orbital convergence
allowing better short-range stereopsis, particularly in the lower visual field. The koniocellular pathway from the retina was further developed to connect the superior colliculus with the dorsal pulvinar nucleus of the thalamus in assisting visual attention, and particularly the pretettive detection of snakes and other fear-relevant stimuli. Furthermore, it assisted the parvocellular pathways to the lateral geniculate nucleus in allowing trichromacy and superb foveal vision, which may have served to facilitate detection and awareness of snakes on the ground or hidden in foliage. Higher order visual areas such as parietal cortex and superior temporal sulcus, as well as the dorso-lateral prefrontal cortex, also expanded for similar reasons.

The brain that emerged from these evolutionary contingencies had much more cortex than that of non-primate mammals, most of it devoted to vision. Furthermore, the refined visual system was integrated with the amygdala and its associated defense circuitry to the extent that cortical processing of visual input was tuned by the amygdala. Whereas snakes served as the most important evolutionary vehicle, the resulting changes were useful for discovering and defending against more diverse threats. Effective attention deployment and astute perceptual mechanisms partly relying on rapid subcortical mechanisms played key roles in quick identification of threats, which permitted early defense mobilization providing adaptive edges in many situations.

9. Concluding remarks

Research on the neural basis of fear has made important headways during the last few decades. We have gained important knowledge about the factors that activate fear, including the role of nonconsicous processes and the role of fear in guiding attention. Furthermore, we are beginning to come to grips with the neural mechanisms behind these behavioral effects. Fear stimuli engage a subcortical network of structures that is centered on the amygdala and that can activate fear responses via an automatic, subcortical, route. A plausible evolutionary scenario supports this conceptualization. Further psychological and neuroscientific elucidation of these systems will offer new insights into fear and fear-related disorders.

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