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**Neural correlates of fear: Insights from neuroimaging**

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## 1.0 Abstract

Fear anticipates a challenge to one's wellbeing and is a reaction to the risk of harm. The expression of fear in the individual is a constellation of physiological, behavioral, cognitive and experiential responses. Fear indicates risk, and will guide adaptive behavior, yet fear is also fundamental to the symptomatology of most psychiatric disorders. Neuroimaging studies of normal and abnormal fear in humans extend knowledge gained from animal experiments. Neuroimaging permits the empirical evaluation of theory (emotions as response tendencies, mental states and valence and arousal dimensions) and improves our understanding of mechanisms of how fear is controlled by both cognitive processes and bodily states. Within the human brain, fear engages a set of regions that include insula and anterior cingulate cortices, amygdala and dorsal brainstem centres such as periaqueductal gray matter. This same fear matrix is also implicated in attentional orienting, mental planning, interoceptive mapping, bodily feelings, novelty and motivational learning, behavioral prioritization and the control of autonomic arousal. The stereotyped expression of fear can thus be viewed as a special construction from combinations of these processes. An important motivator for understanding neural fear mechanisms is the debilitating clinical expression of anxiety. Neuroimaging studies of anxiety patients highlight the role of learning and memory in pathological fear. Post-traumatic stress disorder is further distinguished by impairment in cognitive control and contextual memory. These processes ultimately need to be targeted for symptomatic recovery. Neuroscientific knowledge of fear has broader relevance to understanding human and societal behavior. As yet only some of the insights into fear, anxiety and avoidance at the individual level extrapolate to groups and populations, and can be meaningfully applied to economics, prejudice and politics. Fear is ultimately a contagious social emotion.

Key words            Amygdala, anxiety, arousal, autonomic, emotion, phobia

## 2.0 Emotions and fear

Emotions can be viewed as transient stereotyped reactions to motivationally-salient events or stimuli. These reactions reprioritise perceptual, cognitive and behavioral states. Emotions have psychological (cognitive, perceptual and experiential), physiological (bodily arousal), and behavioral (expressions and action tendencies) dimensions. Most formulations of emotion also emphasize a social role, where motivational states such as hunger and thirst are conceptualized at a lower level. Distinctions based on temporal duration are made between emotions and other affective states, eg moods. Some researchers define emotions as the (bodily) responses, as distinct from feeling states that arise as the perceptual/experiential consequences of the emotion.<sup>1</sup> Many authorities<sup>2-4</sup> propose the notion of basic emotions: Each emotion type (eg happiness, disgust, anger, and fear) is envisaged as distinct, with separate links to evolutionary imperatives. Thus, fear is proposed as a distinct emotion characterised by an orientation of resources towards physical self-preservation and protection. It carries the anticipation of a potential catastrophic outcome that challenges the integrity and viability of an individual. Fear encompasses characteristic negative psychological feelings and states of mental and physiological arousal. Fear responses can be engendered rapidly and preconsciously to impact on behavior, attention and memory processes. There are a plethora of close and distant fear signals across senses for the rapid communication of fear to others, notably facial expression (wide eyes<sup>5</sup>), vocalisations (gasps towards screams), posture (retracted) and skin (pallor, pilo-erection) are potent cues for conveying the presence of danger. These signals even communicate across species.<sup>6</sup> Nevertheless, the view of fear as a primary emotion can break down with detailed analysis. Perhaps more accurately, fear can be conceptualised as an overarching emotion category that embraces different, but related, instances and functions.<sup>7-9</sup>

## 2.1 Outline

In this review, we will take an integrative perspective on what we can learn from neuroimaging studies of fear, and how such studies, examining mechanisms at the level of the individual, implicitly inform our understanding of social affective processes and potential have broader relevance for society. Specifically, this review will address the expression and measurement of fear, and the different ways to induce and assess fear, including fear induction paradigms, fear conditioning (focusing on fear acquisition, extinction learning), and threat anticipation to cues and contexts. The impact of fear on cognitive functioning will be considered in sections pertaining to attention and memory. The contextual modulation of fear processing will also be highlighted, since the magnitude and expression of responses to threat are sensitive to both the internal (psychological and physiological) state of the individual and/or external factors (environment, social context and proximity of threat). A section examines pharmacological and genetic imaging describing neurochemical modulation and individual differences (genetic or otherwise) in anxiety and fear processing. This leads to the clinical expressions of fear, notably in PTSD and phobia, where neuroimaging reveals neural substrates underling fear psychopathology and potential strategies for intervention. We focus on fear mechanisms within the individual and how fear signals are exchanged between individuals. These processes underpin and are expressions of genetic and societal processes that transcend the individual. The topic of human fear, while a focus of much interest a decade ago has not been comprehensively reviewed within the recent literature, despite important new empirical findings. This review paper provides a much-needed updated perspective on human fear for which improved understanding has broader implications across and beyond basic, clinical and social psychology.

### 3.0 Expression and measurement of fear

The feeling states associated with fear and anxiety have a substantial physiological / interoceptive component. This is often cited as the basis of the peripheral theories of emotion, illustrated by the suggestion of William James that we feel afraid because we run from a bear.<sup>10</sup> Emotional feeling states are proposed to originate from sensory feedback representation of changes induced within the body by emotional reaction. Such feelings are typically viewed as valenced, but poorly localizable, mental phenomena. However, fear feelings are physiological responses and are often clear and localizable: These include a tightness in throat, tension in chest, dry mouth, sweating, gastrointestinal sensations and heart pounding. Such sensations are instilled with a feeling of danger, imminent collapse or catastrophe. While the mental experience of fear is tied to future uncertainties, it is intensified by physiological sensations and their perceived negative meaning.

The pattern of autonomic bodily response elicited by fear induction is characterised by heightened sympathetic activation, reflected in increased heart rate, myocardial contractility, peripheral vasoconstriction and increased electrodermal activity.<sup>11</sup> In contrast to anger, systemic vascular resistance is often reduced.<sup>12,13</sup> Parasympathetic vagal influences on the heart are also usually diminished, decreasing heart rate variability.<sup>14</sup> In some fear contexts however, bradycardia appears as a dominant and amplified early orienting response that enhances cardiac filling for the next heartbeat. Sudden display of threat cues can elicit this initial bradycardia,<sup>15</sup> frequently accompanied by motoric freezing. Both bradycardia and freezing are proposed to enhance information intake and the appraisal of the source of threat. Tachycardia

follows shortly after; yet increasing vagal tone in anticipation of imminent threat outcome may lead to complex triphasic cardiac fear responses. Here the proximity of threat is an important determinant of pattern of heart rate response.<sup>16</sup> Fear states are also accompanied by increased respiratory rate as a result of reduced duration of expiration and more variable inspiratory flow, which can decrease blood carbon dioxide (CO<sub>2</sub>) levels.<sup>12,14,17</sup> Fear also elicits humoral (adrenal) stress responses, with adrenaline and cortisol release into the blood stream.<sup>18</sup> Within neuroimaging contexts, the objective autonomic measurement of fear responses is mostly confined to unitary autonomic measures of arousal, notably electrodermal responses, particularly in the context of conditioned learning.<sup>19-22</sup> The coupling of amygdala responses to evoked autonomic changes appears a useful signature of fear.<sup>23,24</sup> Other brain regions may be more important to sympathetic (electrodermal or cardiac) arousal in non-threat contexts.<sup>25</sup> Cortisol responses are more often used in stress induction studies (often including social threat challenges).<sup>18</sup>

### 3.1 Fear reactions

Fear reactions include visible changes in bodily and facial expression, some of which relate directly to sympathetic autonomic reactions. Widening of eyes, gaping of mouth and related changes in facial expression constitute automatic motor responses that can be measured even covertly using electromyography.<sup>26</sup> These cues rapidly perceived by others, along with more explicit signals of threat and distress (eg screams) are potent drivers for the rapid spread of fear between individuals. Whole body retraction is a component of early freezing and alarm response, linked to the 'play dead' responses of animals (which may have a further human homologue in simple emotional fainting). Human correlates of freezing can be induced by external threat stimuli, yet can also be

elicited by direct physiological induction of the fear states, for example using 20% CO<sub>2</sub> inhalation.<sup>27</sup> Immobility is thus one basic early response to threat which is also expressed as impairments in behavioral measures, eg slowed reaction time. In neuroimaging and other experimental contexts, delayed reaction times may be a useful objective index of fear, but again this is contextual: Fear-evoked enhancement of motor response (to flee or fight) also occurs associated with more rapid reaction times. These potentially conflicting inhibitory and facilitatory motor responses to threat are important since they may show task dependence, change over the course of an experimental task, and show inter-individual differences in their expression. The startle reflex is a simple defensive reflex, typically to loud unexpected sounds. While animal studies typically measure whole body startle responses, the focus in humans is on the blink component.<sup>28</sup> The presence of a threat, often in the form of a fear-conditioned stimulus, results in an amplification of the startle response. The fear-potentiated startle response in animals is a reliable measure of central fear processing and used to test the likely efficacy of anxiolytic drugs. Fear-potentiated startle has been used in human neuroimaging experiments,<sup>29</sup> yet its use in fMRI is constrained by logistical considerations.

Fear thus engages the individual systemically, changing bodily state in a coordinated way that facilitates rapid adaptive responses to threat. These responses in the body are automatic and can act as objective measures of threat processing that can then be related to self-reported fear and behavioral response. However, the dichotomy between fight and flight tendencies is mirrored in bodily response, where bradycardia or tachycardia and immobilization or mobilization may represent context and experience-dependent expressions of fear.

#### 4.0 Induction of fear in an individual

We can understand more about the expression and neural mechanisms of fear by directly evoking fear in individuals undergoing brain imaging experiments. Ways by which fear can be induced directly within an individual include physiological challenge, pharmacological manipulation, direct exposure to intrinsically threatening stimuli (phobic stimuli, snakes etc), threat learning, and psychological induction techniques (recollection / visualization). Perhaps more striking though is the contagion of fear responses between individuals, where fear signals (see below) in another's voice, facial expression, and even smell<sup>30</sup> can rapidly activate one's own fear circuitry.

A raised concentration of CO<sub>2</sub> in inhaled air, or within the blood stream, is a potent physiological stimulus for inducing anxiety, fear and panic. Such hypercapnia evokes a sensation of breathlessness, labelled 'air hunger'. Widespread activation of cortical and subcortical regions is observed when CO<sub>2</sub> levels are raised.<sup>31-33</sup> There is enhanced engagement of brainstem (pons), midbrain (including periaqueductal gray), hypothalamus, thalamus, amygdala and periamygdalar regions, cingulate, anterior insula, caudate nuclei and fusiform gyrus. Importantly for interpretation, such effects can be dissociated from generalized global effects of CO<sub>2</sub> level on brain blood flow. Correspondingly, deactivations are observed within regions including posterior cingulate and prefrontal cortex.<sup>31</sup> Air hunger, even when CO<sub>2</sub> levels are kept constant, elicits a similar pattern of neural activity responses, particularly involving anterior insula cortex.<sup>33</sup> Interestingly, CO<sub>2</sub> inhalation can induce panic and fear sensations even in people with no functional amygdalae, challenging the view that the amygdala is necessary or sufficient for the experience of fear at the individual level, yet consistent

with core contributions of brainstem and insula regions in the generation of fear sensations.<sup>34</sup> The novelty of this observation, to the patients concerned as well as to the scientific community, also highlights the fact that fear is almost always perceived in social contexts that likely necessitate amygdala involvement.

Among pharmacological agents associated with the induction of fear and panic, cholecystinin tetrapeptide (CCK-4) is a useful tool that has been employed in neuroimaging settings.<sup>35,36</sup> CCK-4 infusion can induce a reliable physiological and psychological replication of panic, which can be reversed with anxiolytic drugs such as benzodiazepines. When administered in an fMRI experimental context, CCK4 activates insula and cingulate cortices, temporal poles, thalamus and cerebellar vermis.<sup>36</sup> CCK4 induced panic also engages the ventral anterior cingulate cortex, lateral prefrontal regions and precuneus, with around half of participants also showing amygdala activity changes.<sup>35</sup> Interestingly, CCK4 panic and its association with cingulate and insula activation may be relatively resistant to the pharmacological suppression by potent anxiolytic benzodiazepines.<sup>37</sup>

Exposure to fear-inducing stimuli, threat of pain (see fear learning section 5 below), and recollection of previous threat, have all been used in neuroimaging contexts for the experimental provocation of fear and anxiety symptoms at the individual level. In humans, tasks that tap into social fears, including the threat of evaluation by others and anxiety about performing poorly in front of one's peers, are often more potent stressors. Social evaluative threat with the anticipation of public scrutiny and related performance challenges, as evoked by the Trier social stress test,<sup>21,38-40</sup> provide useful experimental models of everyday fears and anxiety for which the neural processing overlaps with

core features of 'basic' fear. Across these different methods of fear induction, there is a reliable enhancement of activity within dorsal anterior cingulate cortex, bilateral insula cortex and, perhaps less consistently, subcortical activation within centres including amygdala and head of caudate, and brainstem (typically dorsal pons). Brain regions including ventromedial orbital and subgenual cingulate cortices are typically deactivated. Interestingly, this same pattern of brain activity can be elicited by physical challenges; including exercise stress,<sup>41</sup> cold pressor tests,<sup>42</sup> inflammatory challenges,<sup>43</sup> experienced pain,<sup>44</sup> by psychological challenges including mental stress<sup>41,45</sup> and by 'social' challenges that include rejection by others,<sup>46</sup> or perceiving another person to be in pain.<sup>47</sup> While there may be modality-specific differences in the patterns of brain activity produced by these different stressors, the commonalities described above seem to represent a signature of physiological and often psychological arousal challenging the individual<sup>48,49</sup> and is subsumable under the concept of emotional or behavioral salience.<sup>50</sup> Fear is thus only one example of the engagement of this system. Amygdala activation is often assumed as a definitive signature of fear processing, yet is observed in only a proportion of fear studies<sup>51</sup> and as a component of the proposed salience network can occur with non-fear demanding tasks and arousing stimuli.<sup>52,53</sup>

## 5.0 Fear learning and extinction

Fear is learned rapidly through a basic associative mechanism. Pavlovian fear conditioning describes the pairing of a stimulus (CS) with an aversive unconditioned stimulus (US), to induce a fear reaction known in this context as the conditioned response (CR). The CS becomes predictive of the occurrence of the US and therefore gains emotional salience as a conditioned threat cue (CS+), able on its own to induce a fear reaction / CR. Repeated presentations of the CS+ in the absence of the aversive

US can lead to 'extinction' of the capacity of the CS to induce the CR. Extinction learning does not erase the fear memory, but rather creates a new inhibitory safety memory<sup>54</sup> which may be confined to a particular context. Delayed testing can explore extinction retention, indicating whether, with the passage of time, extinction memory still prevails, or whether the initial fear memory is now expressed.

Human neuroimaging experiments emphasize the role of the amygdala in the establishment of conditioned fear. This is in keeping with fear learning mechanisms defined in non-human animals.<sup>55</sup> Such research has progressed to understanding neural processing and temporal dynamics involved in assigning, reassigning and predicting value to stimuli, often within established learning theory models.<sup>19,21-23</sup>

Reviews and meta-analyses of human neuroimaging studies of classic Pavlovian fear conditioning highlight the engagement of amygdala along with insula and cingulate cortices.<sup>56,57</sup> Additional engagement of the hippocampus occurs when there is a delay between the threat and predicted aversive outcome (trace conditioning). In conditioning experiments the amplitude of amygdala (and hippocampal) responses to conditioned threat stimuli appears to decrease over time with repeated presentations.<sup>23,56</sup> This is consistent with a consolidation of initial associative processing within medial temporal lobe into representations elsewhere in the brain (striatal and cortical regions).<sup>56,57</sup> A number of neuroimaging studies that do not show strong amygdala involvement in fear conditioning also do not test for time dependent effects.<sup>57</sup> It should be noted, however, that the habituation of amygdala responses is not limited to conditioned stimuli but appears more generalizable and occurs to other classes of emotional stimuli, including emotional faces.<sup>58</sup> The amygdala is sensitive to salience and novelty<sup>59</sup>, and here the notion of neophobia is important. With repeated stimulus presentations (and better perceptual and affective characterisation) amygdala activation is dampened over time.

Regional brain activity during conditioned fear also maps changes in physiological arousal: Activation of regions including amygdala and insula are sensitive to feedback of autonomic response.<sup>60</sup> The response within right mid and anterior insula furthermore reflects the conjunction of autonomic response and conscious awareness of the threat, consistent with some 'constructionist' models of emotion.<sup>9,61</sup>

Fear extinction is a form of new learning that results in the inhibition of conditioned fear, where trait deficits in fear extinction are a risk factor for anxiety disorders. It is important for a fear system to adaptively learn that something that was once feared is no longer a threat. The prefrontal cortex has a key role in the process of extinction: Animal studies specifically implicate infra-limbic cortex.<sup>54,62</sup> In humans, neuroimaging suggests a human homologue within subgenual anterior cingulate and adjacent ventromedial prefrontal cortex. This region interacts with amygdala reactivity to suppress fear response across a number of contexts.<sup>19,63</sup> Interestingly activity within this area correlates inversely with the tonic state of sympathetic arousal.<sup>64</sup> The hippocampus also contributes to fear extinction, influencing the strength of safety memory and its recollections, thereby extending the suppression of fear reactions beyond the immediate situation.<sup>63,65</sup> Contextual information is critical for interpreting ambiguous cues, modulating expression of stimulus-response contingencies when cue meanings depend on specific environments.<sup>65</sup> When fear acquisition and extinction occur in different contexts, fear returns when a CS+ is re-introduced in the acquisition context, a phenomenon known as *fear renewal*.<sup>66</sup> In contrast, when the extinguished CS is re-introduced in the extinction context, it does not elicit fear, demonstrating *extinction recall*. The acquisition environment thus represents a "danger" context and the extinction environment a "safety" context.

## 6.0 Fear and anticipation

Fear conditioning exemplifies a more general principle of fear as an anticipatory emotion; Beyond delay-conditioning studies (in which there is immediate learning that a specific cue signals an aversive event), fear and anxiety can be robustly elicited using 'anticipation of shock' paradigms in which a context for example a coloured screen probabilistically signal the likelihood of a receiving a 'random' shock. These types of study are better experimental models of anxiety, encapsulating how a generalised expectation of something aversive underpins the expression of anxiety disorders, including panic. Speculatively, the fact that one is intrinsically unable to identify a specific object cue ramps up the arousal and sensory attentional processes to fuel the fear state and enhance the salience of interoceptive cues (e.g. sensations of autonomic arousal) and memory of prior aversive (shock) stimuli, as might occur in fear potentiated startle in anxious individuals.<sup>67</sup> Trace (unlike delay) conditioning protocols embody an anticipatory interval before an aversive outcome: here the bodily (electrodermal) and subjective expression of anxiety ramps up with the proximity and signalled intensity of shock, mirroring the linear ramping of activity within insula, anterior cingulate cortex and inferior frontal gyrus.<sup>68</sup> These findings highlight the tuning of psychophysiological arousal and subjective emotional responses during fear anticipation to the activity within a tight network of affective and regulatory paralimbic and prefrontal cortices, without obligatory amygdala engagement.<sup>69</sup>

## 7.0 Communication of fear signals

The majority of neuroimaging studies of emotion (including fear) use face stimuli depicting emotional expressions to activate fear centres in the scanned observer.<sup>70</sup> Implicit to this approach is the notion of emotion contagion, social cognition and

empathy that were explored, where the reactivity of amygdala to fear faces predicts social cognitive functioning in healthy individuals and clinical populations (eg autism).<sup>71,72</sup> Across studies, it is found that fear faces relative to other emotional facial expressions are associated with enhanced amygdala responses.<sup>49,63</sup> This observation remains largely true, even for parts of faces (fear eyes) and subliminal processing of such fear signals.<sup>73,74</sup> However, it is important to acknowledge, as illustrated empirically, that the amygdala will respond more generally to face stimuli, to emotional information, and to the meaning, salience and arousal contained within the faces.<sup>53</sup> Fear faces (and vocalizations) are often more emotive, salient and arousing than other emotional expressions. Thus the specificity of the fear circuitry and amygdala responses to fear faces may be, in part, confounded by generic qualities of these stimuli. Consistent with this view is the observation that amygdala responses correlate with ratings of emotional arousal in face stimuli irrespective of the type and valence of the depicted emotion.<sup>51,53</sup> The incidental and predicted physiological arousal state of the individual may also contribute to such responses.<sup>75,76</sup>

## 7.1 Body and posture

Bodily expressions are also important to the communication of fear, yet are often overlooked relative to facial signals of emotion. Observed posture can communicate the emotional state (and implied risk to others), from a much greater distance than facial expression. Neuroimaging studies of the perception of fear signals from static or dynamic bodily postures show the engagement of amygdala and insula to fear and anger bodily signals, along with visuomotor and somatosensory regions encoding movements and their motivational meanings.<sup>77,78</sup>

## 7.2 Music and fear

Fear is typically considered a low-level basic emotion, transmittable between individuals involuntarily through fast perceptual contagion. Yet as with other emotions, through music fear can also reach a level of cognitive, interpersonal and cultural sophistication. Music can be a powerful means to evoke fear, and will amplify the processing of cues of threat and menace from other modalities (much used by the film industry). Fearful music may attenuate the extent and amplitude of auditory activity (most activated by joyful music). This effect is associated with decreased activity within regions of (superficial) amygdala associated with motivation and action through dense anatomical connections to ventral striatum. However, when viewing fearful visual object cues, the activity within basolateral amygdala is augmented by congruent fear evoking music.<sup>78</sup> On its own, fear evoking music increases functional connectivity between auditory cortex, insula and anterior cingulate,<sup>79</sup> where the processing of musical cues of fear overlap with responses to fear vocalizations.<sup>80</sup> Thus through music fear may be conveyed both as a context and cue. However, the ability to recognize fear within music appears to be universal.<sup>81</sup>

## 8.0 Fear, awareness and attention

Fear stimuli grab attention, and perhaps none more so than fear signals from other people. People orientate to potential threat, even if the threat signal is degraded or ambiguous, leading to shifts in spatial attention and the size of the attentional window. Stimuli presented at the limits of perceptual detection (for example, in an attentional blink or partial masking paradigm) are more likely to break through to conscious awareness if they convey a fearful facial expression, or are threat related. Memory is enhanced for threatening items, and for items processed in a threatening context.

Human functional brain imaging has enabled identification of the neural substrates through which sensory processing and attention are modulated by threat stimuli. Again, the amygdala is implicated in both direct and indirect top-down enhancement of earlier sensory processing, to influence the representation of threat.<sup>83</sup>

### 8.1 Subliminal detection of fear

Importantly for survival value, the detection of fear signals can occur subliminally, evoking covert motoric and autonomic responses and often behavioral response tendencies in the absence of evidence for conscious processing. Neuroimaging has helped understand the underlying neurobiological processes. The amygdala responds to masked ('unseen') emotional stimuli.<sup>21,24,74</sup> Based on animal experiments, a subcortical route to the amygdala for rapid preconscious processing of threat is supported by neuroimaging findings, including studies of patients with 'blindsight'. These individuals are blind in sectors of their visual field following damage to primary visual cortex. Nevertheless, it can be shown that they can process information from fear faces presented within the visual blind area.<sup>83</sup> When fear faces are presented subliminally, there is increased functional connectivity between right amygdala, pulvinar, and superior colliculus.<sup>21,24</sup> This subcortical pathway provides a fast subcortical route to amygdala for the rough and ready, but evolutionarily advantageous rapid detection of threat triggering automatic defensive reactions.<sup>55</sup>

### 8.2 Conscious detection of threat

It is clearly advantageous for conscious attention to be drawn to threat. The capturing of attention by fear stimuli is evident in findings that show increased detection of threat-

related stimuli presented at the limits of conscious perception. The emotional attentional blink task is a useful illustration of this: If two target stimuli are embedded within a series of rapidly presented distractor stimuli, the detection of the second target is impaired by presentation of the first target in the region of 200-350ms earlier. This is known as the attentional blink, describing a time-window within which attentional resources are relatively impoverished. Emotional stimuli, notably fear faces, when presented as this second target can 'break through' to be detected more than non-emotional stimuli. This effect is referred to as the emotional attentional blink. Functional neuroimaging demonstrates enhanced activity within fusiform cortex for stimuli that break through. Also enhanced activity within rostral anterior cingulate cortex<sup>84</sup> and amygdala<sup>85</sup> can account for the particular benefit in detection of fearful stimuli. Functional connectivity between amygdala and visual cortex is also enhanced with fear stimuli, as demonstrated using fear evoking music<sup>80</sup>, providing a potential additional mechanism through which fear can induce increase visual alertness and orientating of attention.

### 8.3 Spatial attention and threat

Spatial attention is also drawn to potential threats: The combination of a fear-conditioning protocol and a target detection task has been used to test how threat signals that capture an individual's spatial attention can lead to more efficient detection of, and faster responses to, events occurring in that part of the environment. While conditioned fear stimuli enhance activity within amygdala and extrastriate visual cortex, the modulation of spatial attention by fear is mediated by lateral fronto-parietal cortices (implicated in spatial attention) and changes in the activity of lateral orbitofrontal cortex.<sup>86</sup> Within early visual cortices, the facilitation by fear of the detection of targets

in particular spatial locations is demonstrated using electroencephalography (EEG) in which covert orientating due to fear stimuli selectively increases an early positive (P1) potential from a lateral occipital/ extrastriate source.<sup>87</sup> The very earliest EEG of visual processing in (C1 from striate cortex) is amplified in fearful individuals in response to both fear eliciting (e.g. spider) and non-fearful stimuli (e.g. flowers).<sup>88</sup> Moreover, using fear faces in a task requiring detection of spatial targets, there is a selective modulation of intraparietal and orbitofrontal cortex when fear stimuli distract attention away from the spatial location of the target, yet for the same location, there is enhanced occipital cortex activity is enhanced.<sup>89</sup> These observations suggest two partially dissociable mechanisms through which fear signals influence spatial attention by 1) disengaging parietal spatial attention to alternative locations and, 2) increasing sensory processing within visual cortical representation of the fear location.

Figure 1 about here

## 9.0 Contextual influences on fear

The magnitude and expression of responses to threat is highly dependent on context, which may be internal to the individual (psychological and physiological state, prior experience)<sup>90</sup> or it may be external, ie related to the environment (proximity and setting of the threat and the social context) or the conjunction of a threat with other moderating cues: We feel less fear when we feel stronger, protected and reassured (eg by the knowledge that the nearby snake is in a cage). This dependence of fear responses on context is important, not least because it qualifies the notion of fear as an automatic, universal, defensive emotion. Recognition of context effects also enriches our

understanding of the genesis and potential management of psychological disorders such as phobia, fear and panic.

Fear reactions, as defensive behaviors, are attuned to the context of threat. The expression of fear changes in proportion to the proximity of threat. In predated animals, there is gradated behavioral switching along a continuum of proximity from 'pre-encounter' (no immediate danger), via encounter (imminent danger) to 'circa strike' where danger is unavoidable. This 'predatory imminence continuum' is proposed to modulate consequent fight, flight or freeze behaviors.<sup>91</sup> One elegant neuroimaging study used a maze-based video game that required players to avoid 'predators' where capture was associated with electrocutaneous shocks.<sup>92</sup> The study found that the shift toward imminent danger was instantiated within the brain by a shift in activity from rostral and ventromedial prefrontal cortex and basolateral amygdala (arguably engaged in evaluative processing) toward the central amygdala nucleus and midbrain periaqueductal gray matter (more closely coupled to bodily response). Interestingly, periaqueductal gray matter activity correlated with the dread elicited by increasing proximity of threat. This set of findings reconciles a number of discrepancies within the fear literature (including for example distinct cardiac responses to threat at different physical proximities), and bridges human and animal literature.<sup>93</sup>

### 9.1 Body posture and fear

As noted above, distant fear signals are conveyed by the posture and bodily actions (facial expressions are more proximate signals) and are rapidly processed and lead to contagion of similar postures that ready an individual for rapid escape. The signals

from bodily posture can override or reframe the interpretation of signals from facial expressions, such that up to a 30% shift in the rating of 'basic' emotional facial expressions can occur if, for example, a fearful face is placed on an angry body or vice versa.<sup>94,95</sup> An individual's own posture and physiological state also influences sensitivity to emotive cues and shapes the emotional response: Holding a facial expression of emotion influences the judgment of emotional facial expressions of others<sup>96</sup> and this effect is associated with differences in the engagement of brain including amygdala, STS, and insula. Bodily posture, eg leaning forward or reclining, has similar impact on one's responses to, and appraisal of, emotive material.<sup>97</sup> This may be an important consideration when generalizing inferences from neuroimaging experiments, given the constraint upon participant posture and action within scanning environments.

Posture and action also influence dynamically the physiological state of the body. Internal states of arousal exert a major influence on fear processing. A state of exaggerated physiological arousal is associated with increased fear reactivity, particularly in clinical conditions such as anxiety disorders. The neural mechanisms through which this interoceptive context influences fear processing can be explored in a number of ways using neuroimaging, for example increasing heart rate and blood pressure using drugs or incidental tasks. One neat approach is to exploit the cardiac cycle.<sup>98</sup> The strength and timing of individual heart beats is conveyed to the brain by baroreceptor activity: Each time the heart ejects blood a signal from arterial baroreceptors in the great vessels is transmitted centrally. Brief experimental stimuli can be presented during this baroreceptor signal (on the heart beat) or between heart beats when baroreceptors are quiet. The baroreceptor signal is used in the reflex control of blood pressure (eg with posture) and was previously thought to have a general inhibitory effect on sensory attentional processes, including pain. Recently,

Garfinkel and colleagues<sup>75</sup> overturned this generalized view to show that fear processing is enhanced by baroreceptor activation. There is better detection of per-  
liminal fear faces (in an emotional attentional blink task), and augmentation of fear  
ratings of overt fear faces, when these stimuli are presented on the heartbeat (at  
systole). The neural responsivity of regions including the amygdala, mediates this  
dependence of fear-processing on heartbeat timing (see Figure 2). These findings  
highlight the contribution of physiological signals from the body to the processing of  
fear stimuli, effects previously noted in fear conditioning studies of patients with  
autonomic failure (see Figure 3).<sup>60</sup>

Figure 2 and 3 about here

#### 10.0 Insights from pharmacological and genetic neuroimaging

Neuroimaging studies of the pharmacological /neurochemical modulation of fear  
responses and of individual differences (genetic or otherwise) in fear processing  
typically link changes in the experience of fear to measured differences in amygdala  
reactivity. As noted earlier (section 5), amygdala responses to threat stimuli change  
with time over the course of an experiment. Hence reports of 'enhanced' amygdala  
reactivity may reflect more complex expression of time-dependent effects. Classic  
anxiolytic medication such as the benzodiazepine *Diazepam* attenuates amygdala  
responses to angry and fear faces. This is associated with reduced anxiety and also  
accompanied by reduced orbitofrontal cortex activation. Interestingly, effects on  
anterior cingulate function are more complex, with different effects on responses to  
angry and fear faces.<sup>99</sup> Some other pharmacological agents show gender-specific

effects: For example, in men, oxytocin decreases amygdala reactivity to aversive, threat-related scenes and fearful, threat-related faces,<sup>100,101</sup> but in women elicits increases in amygdala reactivity to similar stimuli.<sup>102,103</sup> The effect, at least in men, may be potentially useful in mitigating or attenuating the expression of post-traumatic stress disorder.<sup>104</sup>

The efficacy of particular pharmaceutical agents in the treatment of clinical anxiety has directed exploration of candidate genes and common variants in receptors and transporter molecules linked to affective vulnerability. Examples include the relationship between post-traumatic stress disorder and 5-hydroxytryptamine (5-HT, serotonin) transporter *SERT*. Common *SERT* genetic polymorphisms within the promoter region (such that there is a long *L* allele and a short *S* allele) influence inter-individual differences in expression of response to traumatic events.<sup>105</sup> *SERT* expression at the pre-synaptic membrane and 5-HT uptake activity are significantly greater in carriers of the long compared to the short allele.<sup>106</sup> The specificity to fear and anxiety related responses is weak however, yet interactions between 5-HT polymorphism with early stressful life events influence vulnerability factor to depressive illnesses<sup>105</sup> and anxiety sensitivity. Similar common polymorphisms are present in the Catechol-O-methyltransferase (COMT) gene. COMT is an enzyme responsible for removal of monoamine neuromodulators including dopamine and noradrenaline. Met (methionine), compared to val (valine) variants of COMT leads to slower monoamine degradation and is associated with improved functioning on some cognitive domains, differences in vulnerability to affective and anxiety disorders and enhanced amygdala responses to negative visual stimuli. Amygdala reactivity to fear stimuli is proposed as a heritable trait, linked to both the expression of anxiety and depression.<sup>107</sup> Both the *SERT*(long) and the *COMT*(met) polymorphisms enhance this reactivity, likely increasing sensitivity

to detect biologically and socially relevant information.<sup>108</sup> Other polymorphisms over represented in anxiety and panic populations and linked to enhanced amygdala responsiveness to threat stimuli include neuropeptide-S<sup>109</sup> and pituitary adenylate cyclase-activating polypeptide receptor genes.<sup>110</sup> There is also interest in polymorphisms of brain derived neurotrophic factor (BDNF),<sup>111,112</sup> which appear to exert a constrained effect on extinction learning and could therefore represent a further target for personalized treatment of anxiety symptoms. Anxiety disorders vary in the degree to which there is familial loading and genetic vulnerability. Heritability is commonly observed in obsessive compulsive disorder, for select 'vulnerability' subgroups eg people with blood phobia syncope including systemic conditions (eg joint hypermobility syndrome).<sup>113</sup> Anxiety is however a pervasive symptom across different psychiatric disorders, including persecutory ideation in people with psychosis and social fears expressed in autism spectrum conditions. Nevertheless, the genetics of 'pure' anxiety disorder is illustrated by twin studies, analyses of specific phenotypes and at the population level, facilitated now by access to genome wide scanning.<sup>114</sup>

Anterior and posterior hippocampal formation show different cytoarchitectonic properties and distinct patterns for gene expression.<sup>115</sup> Neuroimaging studies also reveal a contrast between posterior hippocampus, as a substrate for predominantly spatial and cognitive (memory) processes, and anterior hippocampus which is implicated in emotional processes, particularly in regard to negative affect, fear and stress<sup>115,116</sup>

## 11.0 Clinical expressions: Phobia and post-traumatic stress disorder

### 11.1 Specific Phobia

In patients with specific phobia, neuroimaging has been applied to understand the neural substrates underlying the psychopathology and reveal potential novel pathways for intervention. Different types of phobia are important to consider here, notably a distinction between blood phobia (including needle and body boundary violation phobia) and other specific phobias, eg spiders or other animals. Social phobia is more related to general anxiety disorder and other less specific anxiety conditions. Blood and needle phobia is closely coupled to emotional 'simple' fainting (neurocardiogenic syncope). Structural anatomical differences in brainstem are associated with a vulnerability to simple faints too, while local volume of neighboring sectors of caudate nucleus correlate with parasympathetic tone and trait anxiety and, where these regions overlap, predict fainting frequency.<sup>117</sup> Across specific phobias, functional imaging studies report enhanced activation of amygdala (and/or adjacent globus pallidus), insula, thalamus and cerebellum to phobic stimuli.<sup>118,119</sup> These findings are in keeping with an exaggerated sensitivity to particular stimuli as salient threat, rather than pointing to a core neurobiological abnormality.

## 11.2 Posttraumatic Stress Disorder

Similar conclusions come from a meta-analysis searching for functional neurobiological signatures of anxiety disorders that made direct comparison to brain correlates of anticipatory anxiety induced using fear conditioning relative to healthy individuals.<sup>120</sup> Patients with posttraumatic stress disorder (PTSD), social anxiety disorder or specific phobia share the enhanced activation of amygdala and insula, in a similar pattern to the response of healthy individuals during conditioned fear. However, the pattern of exaggerated fear appears different in people with PTSD: In these patients, amygdala and insula responses are relatively attenuated compared to patients with phobia and

social anxiety. Hypoactivation of dorsal and rostral anterior cingulate and ventromedial prefrontal cortex are also observed in PTSD. Thus while there are common brain mechanisms in anxiety disorders and 'normal' fear processing, there are unique additional features to the expression of PTSD that distinguish it from exaggerated fear.<sup>120</sup>

PTSD is associated with abnormalities in fear associated learning, including greater acquisition of conditioned fear, overgeneralization of conditioning, impaired inhibitory learning, and impaired extinction<sup>121-123</sup> It is suggested that deficits in fear associated learning play a role in the development and maintenance of PTSD.<sup>121,123</sup> Abnormalities in the extinction and retention of conditioned fear are important to the persistence of fear memories in PTSD (see figure 4) .<sup>124,125</sup> In PTSD a pervasive sense of impending danger, fearfulness and heightened arousal persists when no actual threat is present. This is thought to reflect an inability to modulate fear expression using contextual information<sup>126</sup>. Amygdala, ventromedial prefrontal cortex and hippocampus are all involved in fear-associated learning and contextual processing.<sup>65</sup> Not only do PTSD patients manifest raised amygdala activity,<sup>127</sup> suggesting enhanced fear signal processing, they also show decreases in ventromedial prefrontal responsivity.<sup>128</sup> This pattern is a basis to problems in emotion regulation and fear inhibition,<sup>129,130</sup> contributing both to enhanced fear state and deficits in extinction (ie safety) recall.<sup>124</sup> Hippocampal function is also abnormal in PTSD<sup>131</sup> and there is also evidence of structural hippocampal deficits with reduced volume and neuronal integrity.<sup>132,133</sup> Given the role of amygdala, hippocampus and ventromedial prefrontal cortex in context-dependent fear,<sup>134</sup> this evidence supports more extensive examination of context processing in PTSD. It is suggested that PTSD patients fail to utilize safety signals.<sup>135</sup>

Fear memories that are not modulated by context can contribute to a persistent state of

perceived threat and imminent danger, driving hyperarousal and avoidant behaviors. The flip side is that there may be a failure to respond appropriately to novel threats. This provides a neurobiological explanation for the seemingly counterintuitive observation that often PTSD patients are exposed to repeated traumas, potentially indicating a failure to recognize danger.<sup>136,137</sup>

Figure 4 about here

Abnormal processing of trauma-related threat stimuli in PTSD patients is demonstrated by over-attention to trauma-related cues,<sup>138</sup> exaggerated physiological responses such as heart rate (HR), skin conductance, EMG and blood pressure to trauma-cue exposure<sup>122,139</sup> and altered brain activation patterns in symptom provocation studies.<sup>140</sup> Yet PTSD patients display more general information processing deficits. There is evidence that PTSD brains are attuned to preferentially detect and process threat material,<sup>141,142</sup> show heightened orientating responses to novel stimuli<sup>143</sup> and may fail to filter out irrelevant sensory information.<sup>144</sup> These deficits underlie the difficulty PTSD patients have in learning safety cues<sup>145</sup> and facilitate re-emergence of conditioned fear responses after extinction.

## 12.0 Conclusions

What we are learning about fear at the neural and behavioral level in humans may be generalized to understanding the processes that shape our engagement with others, our willingness to pursue novel and potentially risky situations. While fear is a negative emotion, it shapes adaptive behaviour, prudent decision-making and self-fulfilment

through brave deeds and selfless actions. Human neuroimaging studies are largely constrained by their focus on the individual, underplaying the more social aspects of fear, for example the way in which panic can spread through a crowd (or financial market). The processing of risk and threat appears stereotyped in automaticity and response repertoires, yet proves to be context-dependent and potentially either inhibit or facilitate on action. There is redundancy within the fear system. Potential threats are inferred from partial information as the cost of missing a real threat may be catastrophic. Neuroimaging teaches us how fear and risk closely interacts with learning and memory to set emotional tone and response style at the individual level. The same themes play out at a societal level where fear, prejudice can control populations and catastrophic outcomes are repeated in different contexts with each generation.

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## 12 Figures

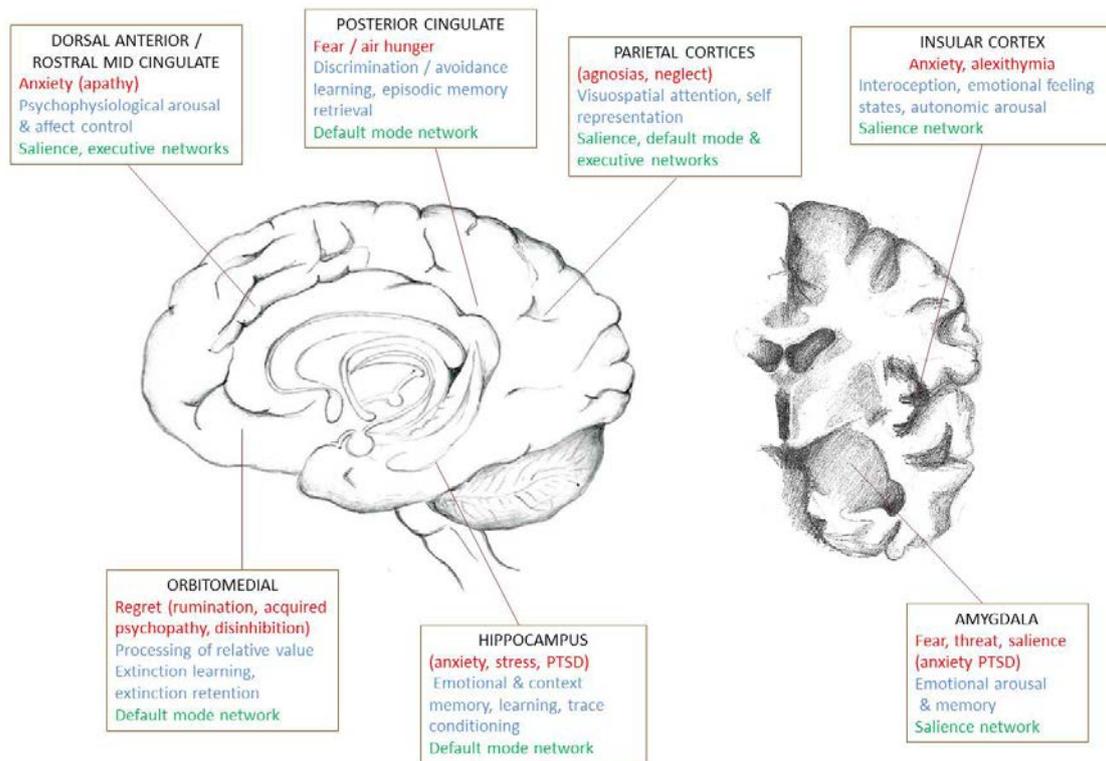
Figure 1: A schematic diagram depicting different brain regions and their involvement in specific fear processes (red), and more general role in cognitive / affective processing (blue). The brain is organized into functional networks, with the salience network thought to regulate dynamic changes in other networks, principally the default mode network, which represents the brain at rest (networks are specified in green).

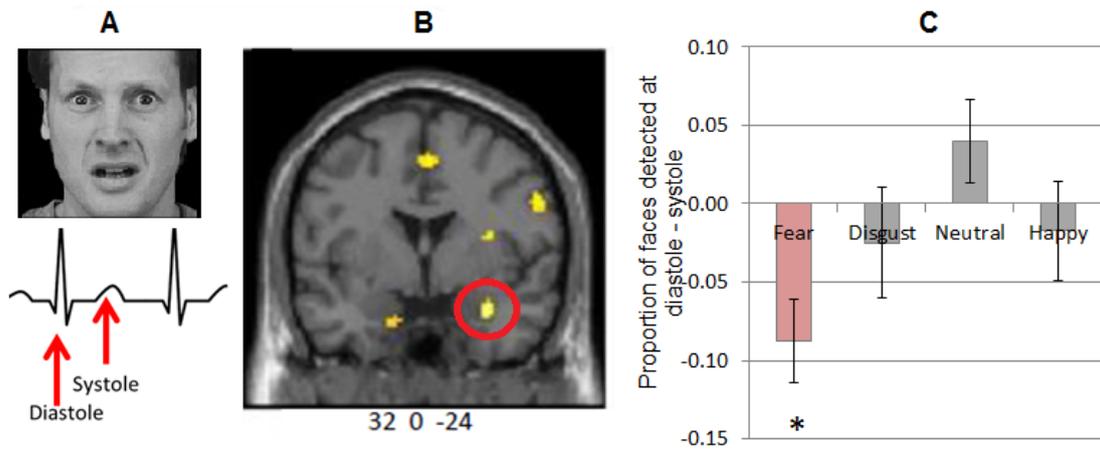
Figure 2. Brain and body interact to affect the perception and expression of fear. Physiological signals from the body can alter fear signal in the brain: Patients with pure autonomic failure (PAF) had a reduced neural expression of fear in amygdala and insula during a fear conditioning task.

Figure 3: A: Fear faces time-locked to distinct parts of the cardiac cycle were judged as more intense at systole (on the heart beat) relative to diastole (between heart beats). B: Observing these fear faces induced a fear reaction in the brain which was also modulated by cardiac cycle (eg enhanced amygdala activation at systole) indicating that the contagion of fear responses are altered by bodily context. C: Attentional capture of fear faces was exaggerated at systole, as demonstrated using the attentional blink paradigm to present fear faces at the cusp of conscious awareness.

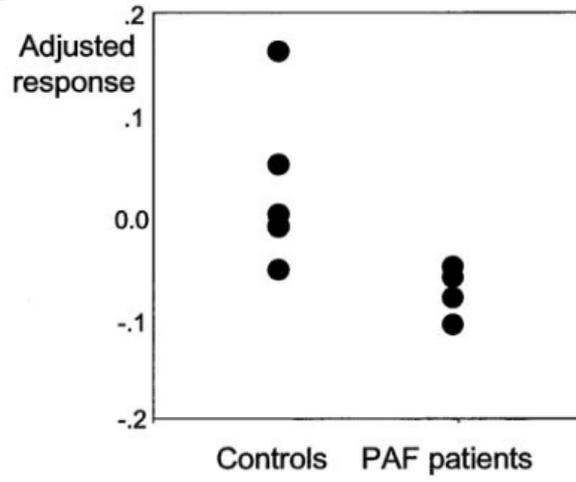
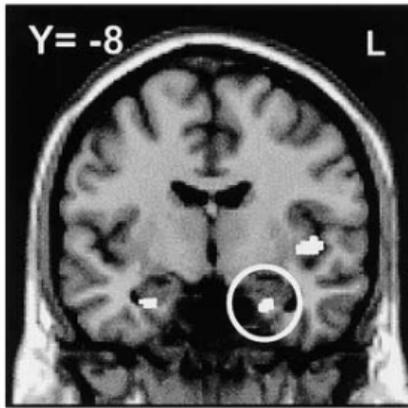
Figure 4. Fear conditioning and extinction procedures can be used to demonstrate deficits in the retention of safety information over time in patients with PTSD relative to combat control participants. Using a fear conditioning procedure in the scanner, a light is paired with a shock to form a CS+. Compared to a CS- (different colored light never

followed by shock), the CS+ elicits a fear signal in the brain with activation of amygdala and insula, as demonstrated in both PTSD patients and combat control participants (A). Extinction (repeated presentation of the CS+ in the absence of shock) leads to a reduction in this fear signal. However, the next day when both PTSD patients and combat control participants return to the lab, combat control participants are able to retain this safety information, while PTSD patients display an enhanced fear signal in the amygdala to the CS+ relative to control participants (B) demonstrating that this safety information is not retained over time in this patient population.





### Amygdala/anterior hippocampus



### Insula

