From Threat to Fear: The Neural Organization of Defensive Fear Systems in Humans

Dean Mobbs,1,2 Jennifer L. Marchant,1 Demis Hassabis,1 Ben Seymour,1 Geoffrey Tan,1 Marcus Gray,1–5 Predrag Petrovic,1,3 Raymond J. Dolan,1 and Christopher D. Frith1,4

Postencounter and circa-strike defensive contexts represent two adaptive responses to potential and imminent danger. In the context of a predator, the postencounter reflects the initial detection of the potential threat, whereas the circa-strike is associated with direct predatory attack. We used functional magnetic resonance imaging to investigate the neural organization of anticipation and avoidance of artificial predators with high or low probability of capturing the subject across analogous postencounter and circa-strike contexts of threat. Consistent with defense systems models, postencounter threat elicited activity in forebrain areas, including subgenual anterior cingulate cortex (sgACC), hippocampus, and amygdala. Conversely, active avoidance during circa-strike threat increased activity in mid-dorsal ACC and midbrain areas. During the circa-strike condition, subjects showed increased coupling between the midbrain and mid-dorsal ACC and decreased coupling with the sgACC, amygdala, and hippocampus. Greater activity was observed in the right pregenual ACC for high compared with low probability of capture during circa-strike threat. This region showed decreased coupling with the amygdala, insula, and ventromedial prefrontal cortex. Finally, we found that locomotor errors correlated with subjective reports of panic for the high compared with low probability of capture during the circa-strike threat, and these panic-related locomotor errors were correlated with midbrain activity. These findings support models suggesting that higher forebrain areas are involved in early-threat responses, including the assignment and control of fear, whereas imminent danger results in fast, likely “hard-wired,” defensive reactions mediated by the midbrain.

Introduction

Evolution has endowed all living organisms with a repertoire of adaptive responses to circumvent a wide range of ecological dangers (Bolles and Fanselow, 1980). One influential model posits that distinct types of threat are compartmentalized into several core contexts along a “threat imminence continuum” (Fanselow and Lester, 1988; Bouton et al., 2001). In the context of a predator, the postencounter reflects the initial detection of the potential threat, whereas the circa-strike is associated with direct interaction with the predator (i.e., when the predator attacks). The postencounter is linked with “passive freezing” and elevated anticipatory anxiety when an aversive stimulus is remote in time (Bouton et al., 2001). The “circa-strike” is exemplified by fear, “active escape and avoidance,” and panic surges associated with imminent threat (Craske, 1999; Gray and McNaughton, 2000; Bouton et al., 2001; Phelps and LeDoux, 2005; Rau and Fanselow, 2007). Although these biologically potent defense reactions to postencounter and circa-strike threat are well-characterized in rodents, no studies have explicitly explored these fear contexts in humans.

It has been theorized that the inhibitory interactions between the brain systems supporting the postencounter and circa-strike threat allow the organism to rapidly switch between evolutionary conserved defense reactions (Fanselow and Lester, 1988). Postencounter and circa-strike defensive states are thought to be topographically organized along a medial prefrontal cortical (mPFC) network (Blanchard et al., 1990a; Fanselow, 1994; Price, 2005), an hierarchical continuum supported by brain defense system models (Deakin and Graeff, 1991; McNaughton and Corr, 2004; Burghardt et al., 2007; Lowry et al., 2008). In essence, these models posit that when a remote threat is confronted, specialized higher corticolimbic regions including the ventral mPFC (vmPFC) and hippocampus gather contingency and contextual information and, via the amygdala instigate survival actions by controlling midbrain systems [e.g., ventrolateral periaqueductal gray (PAG) evoked freezing] (Fanselow, 1994; LeDoux, 1996; Amat et al., 2005, 2006; Quirk and Beer, 2006; Schiller et al., 2008; Jhou et al., 2009). Conversely, imminent threat in the form of circa-strike corresponds with the inhibition of forebrain circuits, with midbrain regions such as the dorsolateral PAG becoming dominant, which, in turn, enable active defense reactions [e.g., fight or flight (Fanselow and Lester 1988; Blanchard and Blanchard, 1990b; Bandler et al. 2000; Dayan and Huys, 2009; Robbins and Crockett, 2009)].
In the current study, we build on previous observations (Mobbs et al., 2007) that have showed simple proximity effects during active avoidance of a predator, in which brain activity switches from prefrontal cortical areas to midbrain areas as a predator comes closer. Here, we explicitly examine distinct contextual fear states along a threat continuum (i.e., postencounter vs circa-strike context; see Fig. 1A–I). Furthermore, we also manipulate probability of capture (i.e., shock), which has been previously hypothesized to relate to distance along the threat imminence continuum (Bolles and Fanselow, 1980; Fanselow and Lester, 1988). Therefore, to gain a clearer picture of these ecologically defined contexts, we combined capture probability with early danger (i.e., postencounter) versus imminent danger (i.e., circa-strike) detection.

Consistent with previous findings (Mobbs et al., 2007), we predict that the midbrain is associated with immediate circa-strike, whereas postencounter threat recruits the vmPFC, hippocampus, and amygdala regions implicated in coding fear contingency, context, vigilance, and behavioral control (LeDoux, 1996; Davis and Whalen, 2001; Amat et al., 2005; Schiller et al., 2008). We also aimed to assess a simple putative analog of panic: we reasoned that a high probability of capture during the circa-strike would result in increased locomotor errors, psychophysiological arousal (i.e., skin conductance), and recruitment of midbrain structures implicated in panic. Last, to further characterize these fear states, we examined functional coupling between these regions to characterize the hypothesized inhibitory relationship between midbrain and forebrain areas as determined by threat context.

**Materials and Methods**

**Subjects**

Twenty-four healthy subjects (12 males; mean age and SD 27.0 ± 4.7) were scanned. All were right-handed, had normal or corrected vision, and were screened for a history of psychiatric or neurological problems. All subjects gave informed consent, and the study was approved by the joint Ethics Committee of the National Hospital for Neurology and Neurosurgery (University College London Hospital National Health Service Trust) and the Institute of Neurology.

**Pain calibration**

A cutaneous electrical pain stimulation was applied to the dorsum of the left hand for 1 or 3 ms via an in-house built functional magnetic resonance imaging (fMRI) compatible electrical stimulator. Each subject was allowed to calibrate the shocks to their own tolerance level. The intensity of the shock was tested before the experiment and set to the maximum tolerable painful stimulation (~20 mA). The average shock intensity was 10.3 ± 2.6 mA.

**Artificial intelligence predator model**

The computerized predator was programmed using a standard algorithm in artificial intelligence. More specifically, we implemented a recursive breadth-first search algorithm (Russell and Norvig, 2003) to control the behavior of the artificially intelligent predator. This works by computing the distance to the target prey for each of the valid adjacent positions (i.e., not wall blocks) to the current predator position and selecting the one with the shortest distance as the predator’s next movement. Distances are computed by a recursive search algorithm that maintains a queue of current search positions. On each pass of the algorithm, each position in the queue is removed, and in its place, all the valid adjacent positions (excluding its “parent” position in the search tree) are added. When one of the search paths reaches the target prey position, all other searches are terminated, and the path and its distance are returned (i.e., a breadth-first search). For mazes with no dead ends, as used in this study, this algorithm yields the optimal strategy for the high probability of capturing the subject (CSHI) or CSLO. For both CSHI and CSLO, the speed linearly increased after 15 s in the maze until the subject was caught by the CSHI (87.5% of the time) and 12.5% of the CSLO trials. Probability of capture in the circa-strike conditions was achieved by making the artificial predator disappear when within one-to-three squares away from the subjects’ blue triangle.

**Paradigm**

Subjects were presented with a two-dimensional maze containing a 9 × 13 rectangle grid of walls (●) and paths (●) (see Fig. 1). The paradigm consisted of three core contexts. All experimental contexts commenced with a pre-encounter context (PrE) in which a maze appeared surrounded by a gray box. During this context, the subject was asked to navigate a triangle toward flashing yellow squares presented for 100 ms and appearing at different locations every 5 s. Next, subjects either moved to the “postencounter” context, which was separated into two contexts, each determined by the color of the box surrounding the maze. An orange box (postencounter high probability of capture; PEH) indicated to the subject that there was a probability (16 blocks = 69.6%) of moving on to the circa-strike contexts with the circa-strike predator with CSHI. Likewise, a purple box (PELO) signaled that there was a probability (16 blocks = 69.6%) that the subject would move on to encounter the circa-strike predator with CSLO. A green box (safe context; SC) indicated to the subjects that they would avoid any interaction with the artificial predator (14 blocks). The final context was the circa-strike in which the artificial predator began to chase and attempt to capture the subject. The subject’s goal was to try and avoid the artificial predator for as long as possible. The orange CSHI predator caught the subject on 87.5% of the trials. Conversely, the purple CSLO predator was nonoptimal with CSLO (i.e., capture on 12.5% of the trials). The difficulty of each game was set on a person-by-person basis, using performance in the training session. Capture was manipulated by making the artificial predator disappear from three to one squares from the subject’s blue triangle. When the subjects were caught, a 2 s wait was given before one shock (50% of the time) or three shocks (50% of the time) were administered. A 2 s rest was given before the subject moved back to the next “pre-encounter” context. The exact instructions can be found in supplemental materials (available at www.jneurosci.org).

**Questionnaires**

After scanning, subjects completed a questionnaire that asked them to indicate on a 10-point analog scale (1) how much anxiety they felt in the preferred, pre-encounter, postencounter, and circa-strike contexts and (2) how much panic they felt in the postencounter and circa-strike contexts. An example of a question is, “Did you panic when the orange circle got close to you in the chase condition?” See supplemental material (available at www.jneurosci.org) for more examples.

**fMRI acquisition**

A 3T Allegra head scanner (Siemens Medical Systems) with standard transmit-receive head coil was used to acquire functional data using echoplanar imaging (EPI) sequences (matrix size, 64 × 64; Fov, 192 × 192 mm; in-plane resolution, 2 × 2 mm; 40 slices with interleaved acquisition; slice thickness, 2 mm with a 1 mm gap between slices; repetition time, 2.6 ms). To maximize statistical power, we used only 40 slices that were optimized to cover the brainstem and angled at ≈30° to cover the whole brain. The slice tilt, z-shim gradient compensation reduced signal loss in the vmPFC (Weiskopf et al., 2006). In addition, field maps were acquired for reduction of geometric distortions of the EPI images (Hutton et al., 2002). A high-resolution T1-weighted structural scan was obtained for each subject [1 mm isotropic resolution three-dimensional modified driven equilibrium Fourier transform (Deichmann et al. 2004)] and coregistered to the subject’s mean EPI. The average of all structural images permitted the anatomical localization of the functional activations at the group level.

**fMRI analysis**

Statistical parametric mapping (SPM; Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk) was used to preprocess all fMRI data and included spatial realignment, coregistration, normalization, and smoothing. To control for motion, all functional volumes were realigned to the mean volume. Using the FieldMap toolbox, field maps were estimated from the phase difference between the images acquired at the short and long echo time and unbinned (Hutton et al., 2002). Voxel displac-
ments in the EPI were determined from the field map and EPI parameters. Distortions were corrected by applying the inverse displacement to the EPIs. Images were spatially normalized (Ashburner and Friston, 1999) to standard space Montreal Neurological Institute template with a voxel size of 2 × 2 × 2 mm and smoothed using a Gaussian kernel with an isotropic full width at half maximum of 8 mm. In addition, high-pass temporal filtering with a cutoff of 128 s was applied to remove low-frequency drifts in signal, and global changes were removed by proportional scaling.

After preprocessing, statistical analysis was conducted using the general linear model. Analysis was performed to determine each subject’s voxelwise activation during artificial predator and yoked contexts. Activated voxels in each experimental context were identified using a statistical model containing boxcar waveforms representing each of the four experimental contexts, convolved with a canonical hemodynamic response function, and mean-corrected (Turner et al., 1991). The cardiac noise correction was implemented at the level of modeling the measured signal and not at the level of image reconstruction, i.e., image data were not modified. The underlying model assumed that cardiac effects on a voxel’s signal depend on the phase of the image slice acquisition within the cardiac cycle. Sine and cosine series (third order) were used to describe the phase effect on a single reference slice (passing through PAG), creating six regressors (Josephs et al., 1997).

Connectivity analyses Psychophysiological interaction. In our study, the connectivity arising from different fear context is modulated by the following contrast: [(CSH – PEHI) – (CSLO – PELO)]. We sought to identify “target areas,” which had differential connectivity with the source region in the midbrain. This was achieved using a moderator variable, derived from the product of source and context. Hence, for the subsequent functional connectivity analyses, the midbrain was chosen as the source region for each participant, we computed the above contrasts to determine the local activation and context. Hence, for the subsequent functional connectivity analyses, the midbrain was chosen as the source region. For each participant, we computed the above contrasts to determine the local maximum that was the nearest voxel to the activation peak in the midbrain defined by the whole-group cluster (supplemental Tables 1 and 3, available at www.jneurosci.org as supplemental material). Analysis used a standardized 6 mm sphere across all participants for midbrain: seed (x = 20, y = 26, and z = −8), which was the maximal voxel. Using these same procedures, we also examined the connectivity for the CSH – CSLO contrast using a right pregennal anterior cingulate cortex (pgACC) seed (x = 20, y = 44, and z = 6).

Skin conductance response analysis. In parallel to the acquisition of the fMRI data, we continuously monitored skin conductance level (SCL), from electrodes placed on the middle and index fingers of the left hand. However, as a result of technical problems, one subject was dismissed from the analysis. Thus, we recorded skin conductance data in 23 subjects out of 24. Skin conductance data were segmented into single epochs containing pre-encounter, postencounter, and circa-strike phases, and where necessary, individual epochs were rotated to correct for drift. Mean SCLs were then calculated for each phase within an epoch, and each subject normalized by setting the maximum and minimum of all means to 100 and 0, respectively. Finally, to allow for meaningful comparison, we adjusted the CSH and CSLO conditions so that group means (PrEs) began at 0.

Results Subjective ratings of panic and anxiety

We first examined subjective reports of anxiety and fear using postexperimental questionnaires. Both PEHI and PELO predator interactions were rated as causing significantly more anxiety than the safe (mean ± SD, 1.8 ± 1.2) and pre-encounter (1.8 ± 1.9) contexts (Wilcoxon signed rank test, p < 0.001, one-tailed) (Fig. 1 I). Greater anxiety was observed when encountering the CSH predator (CSH, 4.5 ± 2.2; CSLO, 3.5 ± 2.1; Z = −2.844; p = 0.004). No significant differences were found between safe (SC) and the PrE (Z = −0.333; p = 0.739). For subjective ratings of panic, a significant difference was evident between the CSH (5.5 ± 2.2) and CSLO predator (4.7 ± 1.8; Z = −2.473; p = 0.013). Panic was also rated as being significantly higher for the CSH conditions compared with the PEHI conditions (2.9 ± 1.9; Z = −3.8; p = 0.0005). A similar pattern was observed for the CSLO conditions compared with the PELO conditions (2.3 ± 1.58; Z = −4.1; p = 0.0005).

Panic-related locomotor errors

We also used an indirect measure of panic. Specifically, we tested if locomotor errors quantified by calculating the amount of button presses directed into the walls of the maze, during the circa-strike, were indicative of disorganized behavior typically
observed during panic (Fanselow, 1988) and conditions where there is a high probability of capture (McNaughton, 1993). Because we expected more panic-like locomotor errors when subjects encountered the CSHI predator, we first tested if subjects made more errors for the CSHI compared with the CSLO (Wilcoxon signed ranks test, $Z = 0.44; p = 0.032$). No significant differences were found for the PEHI and PELO conditions ($Z = 0.815; p = 0.415$). We next subtracted the number of errors for the CSLO from the CSHI predator and correlated the residual locomotor errors (divided by time to account for time differences between the CSHI and CSLO condition) with subjective ratings of panic. We found a positive correlation between amount of panic-like errors and self-reported panic for the CSHI condition (Spearman, $r = 0.35; p = 0.048$) (Fig. 1J).

Skin conductance levels
Concomitant recordings of SCLs were taken during the whole experiment. We ran a repeated-measures ANOVA on probability of capture and postencounter and circa-strike conditions. In addition to significant main effects for conditions [$F_{(22)} = 66.275; p = 0.0005$] and capture probability [$F_{(22)} = 28.868; p = 0.0005$], we found an interaction [$F_{(22)} = 32.129; p = 0.0005$], indicating that SCL increases from postencounter to circa-strike were considerably larger for the encounter with the CSHI predator (Fig. 2B).

fMRI results
Postencounter versus circa-strike contexts
For the fMRI analysis, we first examined the interaction highlighting postencounter contexts [i.e. $(PE_{HI} - CS_{HI}) - (PE_{LO} - CS_{LO})$].

Figure 2. Theoretical model of defense avoidance, SCLs, and fMRI results. A, McNaughton and Corr’s defense avoidance model (McNaughton and Corr, 2004). B, Mean-normalized SCLs for the pre-encounter and postencounter contexts. C, BOLD signal for the interaction between circa-strike (shown in orange) and postencounter contexts (shown in purple); parameter estimates for activity in the sgACC (0, 26, −12; $p < 0.0005$) (D), right amygdala (24, −8, −24; $p < 0.0005$) (E), hypothalamus (−2, 2, −12; $p < 0.0005$) (F), and midbrain (8, −26, −8; $p < 0.0005$) (G); family wise error corrected for whole brain (FWEcorr).

Figure 3. PPIs from the midbrain seed. A, Positive connectivity with the dACC and lateral midbrain. B, Midbrain seed (seed location, 8, −26, −8). C, Negative PPIs with the sgACC, pgACC, PCC, insula, amygdala, ventral striatum (VS), and hippocampus. Blue arrow indicates negative connectivity. Red arrow indicates positive coupling.

A, Defensive Avoidance
B, Ventral Prefrontal cortex
C, ACC
D, Amygdala (Avoid)
E, Amygdala (Arousal)
F, Hypothalamus (Escape)
G, PAG (Panic)
In this analysis, we observed increased posterior cingulate cortex (PCC), bilateral hippocampus, hypothalamus, amygdala, vmPFC, and subgenual ACC (sgACC) activity (Fig. 2C–G; supplemental Table S1, available at www.jneurosci.org as supplemental material).

Circa-strike versus postencounter contexts

For the interaction highlighting circa-strike context [i.e. (CSHI/H11002PEHI) – (CSLO/H11002PELO)] increased activity was observed in the midbrain, mediodorsal thalamus, right striatum, right insula, and dorsal ACC (dACC) (Fig. 2C–G, supplemental Table S1, available at www.jneurosci.org as supplemental material). To investigate activity in these regions further, we examined the psychophysiological interaction (PPI) (i.e., functional coupling) with the PAG for the contrast [(CSHI – PEHI) – (CSLO – PELO)]. A midbrain seed region revealed positive connectivity with the dACC, ventral striatum, medial dorsal thalamus, anterior insula, and lateral midbrain (Fig. 3A) and negative connectivity with the right amygdala, hippocampus, insula, vmPFC, PCC, and sgACC (Fig. 3B, supplemental Table S2, available at www.jneurosci.org as supplemental material).

CSHI versus CSLO conditions

To examine the neural systems associated with probability of capture, we next directly compared CSHI and CSLO conditions. The main effect of CSHI > CSLO revealed increased vmPFC activity, namely the pgACC. Another cluster was observed in the dorsal mPFC (Fig. 4A, supplemental Table S3, available at www.jneurosci.org as supplemental material). Using the right pgACC peak coordinate as a seed, we also conducted a PPI analysis showing this region to have decreased connectivity with the amygdala, insula, and vmPFC (Fig. 4B, supplemental Table S4, available at www.jneurosci.org as supplemental material). To further interrogate this activity, we examined the covariation between State Anxiety Inventory trait anxiety scores and blood oxygenation level-dependent (BOLD) signal for the main effect of CSHI > CSLO showing increased correlation with the bilateral amygdala and sgACC (supplemental Table S5, available at www.jneurosci.org as supplemental material). Supporting the putative role of the pgACC in high shock probability, we also observed activity in this region for the interaction between CSHI and PEHI conditions (pgACC, 20, 44, 6; p < 0.001).

CSHI versus CSLO: panic-related locomotor errors

To probe the relationship between panic and shock probability more directly, we next subtracted the CSLO condition locomotor errors from the CSHI and correlated the residual errors with the BOLD signal for the CSHI – CSLO comparison. This analysis showed the left PAG, dACC, and right insula activity correlated...
with panic-related locomotor errors (supplemental Fig. S6, available at www.jneurosci.org as supplemental material). Decreased panic-like errors elicited activity in the ventrolateral prefrontal cortex and pgACC, albeit somewhat weaker (p < 0.005).

Discussion

We set out to characterize the neural systems associated with ethologically defined postcounter and circa-strike threat contexts, as well as how these systems are influenced by capture probability. Our key neurobiological findings show that an early anticipation of a possible nociceptive event (i.e., the postcounter) increased activity in a set of forebrain structures, most prominently the vmPFC, hippocampus, hypothalamus, and amygdala. Imminent threat in the form of circa-strike elicited activity in midbrain regions, including the PAG and cortical regions, known to be involved in analgesia and panic (i.e., dACC) (Petrovic et al., 2002; Tamburin et al., 2008). Encountering the CS TH elicited pgACC activity consistent with the notion that this region is involved in behavioral control and analgesia (Petrovic et al., 2002; Amat et al., 2005; Schiller et al., 2008). Finally, we show for the first time a neurobehavioral index of panic in which elevated locomotor errors were associated with increased with midbrain activity. Our observations have strong resonance to theoretical models of threat imminence and demonstrate that threat context evokes distinct parts of the fear system the human brain (Fanselow and Lester, 1988; Deakin and Graeff, 1991; Gray and McNaughton, 2000; McNaughton and Corr, 2004).

The so-called postcounter, which involves the detection but not interaction with a threat, is characterized in the rodent by passive defenses such as freezing, although flight is sometimes observed when escape is possible (Rau and Fanselow, 2007). Our results indicate that a postcounter threat preferentially engages the vmPFC, sgACC, pgACC, hippocampus, amygdala, and hypothalamus. Although other structures (e.g., ventrolateral PAG) are also engaged during a real “life-endangering” postcounter threat, the forebrain regions we describe are known to play a critical role in a postcounter threat by influencing visceral functions (Crittchley et al., 2001), prediction, and prefiguring analgesic and strategic responses (Fanselow and Lester, 1988; Petrovic et al., 2002). These forebrain areas also have dense connections to the basolateral amygdala as well as the hypothalamus, hippocampus, and PAG, forming a critical component of a mPFC network that is known to exert control over these emotion systems (Price, 2005). The amygdala receives contextual input from the hippocampus (Phillips and LeDoux, 1992; LeDoux, 1996; Phelps and LeDoux, 2005) and is an integral component of the postcounter instigating behavioral reactions (e.g., ventrolateral PAG evoked freezing), vigilance (Whalen, 1998), as well as encoding information about the threat stimulus (Fanselow, 1994). The precise role of these forebrain structures is likely to encompass complex reactions to ecological dangers (Price, 2005), including the assignment and control of fear (Schiller et al., 2008).

The circa-strike is characterized by direct predator attack, which results in reactive defensive strategies. Self-report panic was significantly higher for the circa-strike than postcounter conditions as were SCLs, presumably reflecting increased autonomic sympathetic arousal (Crittchley, 2002). Moreover, increased midbrain activity was observed, again supporting previous theory (Deakin and Graeff, 1991; Gorman et al., 2000; McNaughton and Corr, 2004). A previous study from our group showed that the midbrain is more active when a threat is spatially close during circa-strike attack (Mobbs et al., 2007). Nonetheless, the exact role of this region still remains unresolved. It is known that overactivity of the midbrain PAG results in maladaptive responses such as panic, which manifest as uncoordinated behavior and loss of control (Graeff, 2004). Panic is defined as an overwhelming surge in behavior with robust flight (or fight) reactions (Bouton and Grahm, 2001). Supporting the notion that panic is associated with uncoordinated behavior during inescapable threat (McNaughton, 1993), we found that midbrain activity increased with the amount of panic-related locomotor errors for the CS TH → CS LO threat (Fig. 4).

Indeed, chemical stimulation of the rodent dorsolateral PAG elicits uncoordinated panic-like behaviors such as uncontrolled activity bursts (e.g., vigorous running and jumping) (Deakin and Graeff, 1991; Bandler et al., 2000; Vianna et al., 2001), whereas lesions to the same region eradicate such activity bursts to threat (Fanselow, 1991). We also observed increased activity in the midACC, a region with strong connectivity to the midbrain and implicated in panic (Asami et al., 2008). Indeed, damage to this region can cause panic attacks (Tamburin et al., 2008). Although future studies need to probe the role of these regions with different aversive stimuli, our observations suggest that the midbrain may reflect uncoordinated flight or panic-like behaviors.

The high-level processes instantiated in forebrain regions involving predictive coding, monitoring, and encoding of contingencies and uncertainty means that the time course of their response is likely to be slow, and contrast with an obligatory response profile of midbrain regions evoked during circa-strike (Fanselow and Lester, 1988; Mobbs et al., 2007; Ochsner et al., 2009). It follows that when circa-strike is initiated, it is optimal if these forebrain regions are inhibited (Fanselow and Lester, 1988; Butler et al., 2007; Martel et al., 2008). In support of this, we found decreased forebrain activity for the interaction between circa-strike contexts. Moreover, the amygdala and hippocampus, along with other regions of the forebrain, showed negative connectivity with the midbrain. However, the amygdala also showed negative connectivity with pgACC during the CS TH condition. These two findings are important in light of studies showing, on one hand, that the midbrain PAG results in inhibition of the amygdala during conditioned fear (Fanselow et al., 1995), whereas stimulation of the pgACC results in similar inhibition of the amygdala (Quirk et al., 2003). Our findings are in line with the notion that distinct divisions of the fear system are evoked during postcounter versus circa-strike contexts (Fanselow, 1994).

It has previously been suggested that shock probability fundamentally models distance on the predatory imminence continuum (Bolles and Fanselow, 1980; Fanselow and Lester, 1988). Compared with low probability, high probability of capture resulted in increased right vmPFC (i.e., pgACC) activity. We also found that the pgACC was primarily linked with decreased panic-related locomotor errors during the CS TH → CS LO threat. Thus, when the subjects thought there was a low probability of shock, they had more controlled locomotor behaviors, yet the knowledge they were likely to be caught increased locomotor errors. The mPFC also regulates the amygdala and expression of fear (Phelps and LeDoux, 2005; Schiller et al., 2008) and extinction (Phelps et al., 2004) and augments hypothalamic stress hormones (Figueiredo et al., 2003). Stimulation of the mPFC homolog decreases activity in the rodent central nucleus of the amygdala (CeA) (Quirk et al., 2003). The CeA projects to the midbrain PAG and hypothalamus and acts as a control hub for fear responses (LeDoux, 1996). It is proposed that via GABAergic-intercalated cells, mPFC mediates the expression of fear by gating transmission from the basolateral amygdala to the CeA (Quirk et al., 2003; Bermpohl et al., 2006). Indeed, these regions have been shown to control stress reactions (Salomons et al., 2004; Amat et al., 2005; Salomons et al., 2007).
and to be abnormal in patients with posttraumatic stress disorder and panic disorder (Zubieta et al., 1999; Asami et al., 2008; Uchida et al., 2008). Although one might argue that this activity reflects cognitive predictive process, which function independently from the emotional system, our findings support the notion that the vmPFC regulates the fear systems possibly via the amygdala (Reiman et al., 1989; Schiller et al., 2008). Similarly, it could be suggested that prefrontal cortex exerts inhibitory control on the fear system in the midbrain.

Although the current results only present contexts analogous to real defensive states, they are strongly consistent with brain antipredator defensive systems models developed in rodents (Deakin and Graeff, 1991; Gorman et al., 2000; McNaughton and Corr, 2004) and human psychiatric models of panic (Gorman et al., 2000). It is conceivable that distinct parts of the fear system are modulated by contextual factors expounded by the threatimmunence continuum (Fanselow, 1995). For example, when a threat is spotlighted, slow, but accurate, higher parts of the fear system organize fear and preparatory responses. This higher threat system, however, is seemingly inhibited when the organism shifts to a circa-strike level of threat, which evokes responses associated with fast hard-wired defenses in the midbrain. Although our conclusions remain tentative and need further empirical verification, these evolutionary conserved systems are critical to the rapid switch in adaptive behavior, and we speculate that different symptoms associated with anxiety and panic are modulated by disruption to differential components of the fear circuitry.

References