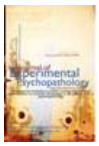
Journal of
Experimental Psychopathology
JEP Volume # (201#), Issue #, 1-30
ISSN 2043-8087 / DOI:10.5127/jep.00



The neurobiology of dispositional negativity and attentional biases to threat: Implications for understanding anxiety disorders in adults and youth

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Abstract

When extreme, anxiety can become debilitating. Anxiety disorders, which often first emerge early in development, are common and challenging to treat, yet the neurocognitive mechanisms that confer increased risk have only recently begun to come into focus. Here we review recent work highlighting the importance of neural circuits centered on the amygdala. We begin by describing dispositional negativity, a core dimension of childhood temperament and adult personality and an important risk factor for the development of anxiety disorders and other kinds of stress-sensitive psychopathology. Converging lines of epidemiological, neurophysiological, and mechanistic evidence indicate that the amygdala supports stable individual differences in dispositional negativity across the lifespan and contributes to the etiology of anxiety disorders in adults and youth. Hyper-vigilance and attentional biases to threat are prominent features of the anxious phenotype and there is growing evidence that they contribute to the development of psychopathology. Anatomical studies show that the amygdala is a hub, poised to govern attention to threat via projections to sensory cortex and ascending neuromodulatory systems. Imaging and lesion studies demonstrate that the amygdala plays a key role in selecting and prioritizing the processing of threat-related cues. Collectively, these observations provide a neurobiologically-grounded framework for understanding the development and maintenance of anxiety disorders in adults and youth and set the stage for developing improved intervention strategies.

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Keywords: affective neuroscience, amygdala, anxiety disorders, attentional biases to threat, behavioral inhibition, developmental psychopathology, fear and anxiety, fMRI, individual differences, neuroimaging, personality and temperament

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Received 29-Dec-2015; received in revised form 08-May-2016; accepted 09-Jun-2016

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Introduction

When extreme, anxiety—a sustained state of apprehension, arousal, and vigilance in the absence of immediate danger—can become debilitating (Davis, Walker, Miles, & Grillon, 2010; Grupe & Nitschke, 2013; LeDoux, 2015). Anxiety disorders, which often first emerge early in development (Kessler et al., 2005), are the most common family of psychiatric disorders and contribute to the later development of co-morbid depression and substance abuse (DiLuca & Olesen, 2014; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Collectively, these disorders impose a staggering burden on both public health—more than 100 million life-years lost to disability—and the economy, with billions of dollars devoted to healthcare costs and lost productivity (Collins et al., 2011; Whiteford et al., 2013). These data underscore the need to develop a deeper understanding of the neurocognitive mechanisms that underlie the development and maintenance of anxiety disorders. Here we review recent work highlighting the importance of the amygdala. We begin by describing dispositional negativity, an important temperamental risk factor for the development of anxiety disorders, depression, and other kinds of stress-sensitive psychopathology. Next, we review new evidence that the amygdala supports stable individual differences in dispositional negativity across the lifespan and contributes to the development of anxiety and mood disorders among individuals exposed to stress. Hyper-vigilance and attentional biases to threat-related[1] cues are key features of dispositional negativity in both

[1] The terms 'threat-related' or 'threat-relevant' encompass a broad range of stimuli, including clear and immediate dangers (e.g., cues paired with shock), novel situations or individuals, uncertain or diffuse dangers (e.g., darkness), aversive stimuli (e.g., unpleasant images or films), and angry and fearful facial expressions. Angry faces signal a direct threat to the observer and prompt the mobilization of defensive responses, as indexed by potentiation of the startle reflex (Dunning, Auriemmo, Castille, & Hajcak, 2010; Hess, Sabourin, & Kleck, 2007; Springer, Rosas, McGetrick, & Bowers, 2007), facilitation of avoidance-related movements (Marsh, Ambady, & Kleck, 2005), and increased fear ratings (Dimberg, 1988). In contrast, fearful faces signal the presence, but not the source of potential threat, and promote heightened vigilance in the absence of defensive mobilization. That is, static images of fearful faces do not amplify the startle reflex (Grillon & Charney, 2011; Springer et al., 2007) or autonomic measures (Dunsmoor, Mitroff, & LaBar, 2009). But they can increase subjective feelings of anxiety (Blairy, Herrera, & Hess, 1999) and are perceived as more threatening and arousing than neutral or happy faces (Grillon & Charney, 2011; Wieser & Keil, 2014). Among adults, they also appear to increase vigilance for potentially threat-relevant information. Fearful faces have been shown to increase contrast sensitivity (Phelps, Ling, & Carrasco, 2006) and

children and adults and there is growing evidence that they contribute to the development of psychopathology. In the next section, we highlight recent work suggesting that that these features partially reflect the influence of brain circuits centered on the amygdala. Although these observations provide important new insights, they also raise a number of other interesting questions. We conclude by outlining some of the most important avenues for future research and some strategies for addressing them.

Elevated Dispositional Negativity Confers Heightened Risk for the Development of Anxiety Disorders

Dispositional negativity or 'negative emotionality'—the propensity to experience and express more frequent, intense, or enduring anxiety and negative affect—is a fundamental dimension of childhood temperament and adult personality. Dispositional negativity is a broad dimension that subsumes a number of more specific traits, including anxious temperament, behavioral inhibition, harm avoidance, neuroticism, and trait anxiety (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2013; Caspi, Roberts, & Shiner, 2005). We conceptualize dispositional negativity as an extended family of closely related phenotypes that first emerge early in childhood, persist into adulthood, and reflect a combination of heritable and non-heritable factors (Fox & Kalin, 2014; Lake, Eaves, Maes, Heath, & Martin, 2000; Ormel et al., 2013; Power & Pluess, 2015; D. J. Smith et al., 2015; Soto & John, 2014; Turkheimer, Pettersson, & Horn, 2014; Vukasovic & Bratko, 2015). Key features of this family, including increased caution and heightened vigilance in the face of potential danger, are expressed similarly across mammalian species, enabling mechanistic studies in rodents and monkeys (Boissy, 1995; Kagan, Reznick, & Snidman, 1988; Kalin & Shelton, 2003; Mobbs & Kim, 2015; Oler, Fox, Shackman, & Kalin, 2016).

The Consequences of Elevated Dispositional Negativity for Mental Illness

Dispositional negativity is a prominent risk factor for some of the most common and burdensome mental illnesses, including anxiety disorders, depression, and co-morbid substance abuse (Clauss & Blackford, 2012; Conway, Craske, Zinbarg, & Mineka, 2016; Hakulinen et al., 2015; Kendler & Gardner, 2014; Soldz & Vaillant, 1999; Watson & Naragon-Gainey, 2014; S. Wilson, Vaidyanathan, Miller, McGue, & Iacono, 2014). The magnitude of these associations is substantial; a recent meta-analysis incorporating 175 cross-sectional studies reported that the mean Cohen's *d* across mood, anxiety, and substance use disorders was 1.65, ranging from $d \cong 2$ for anxiety disorders to $d = .77$ for alcohol use disorder (Kotov, Gamez, Schmidt, & Watson, 2010). Among children, recent work suggests that nearly half of those with stable and extreme levels of behavioral inhibition—a core facet of dispositional negativity—are diagnosed with social anxiety disorder later in life (N = 692; risk ratio = 3.4; Clauss & Blackford, 2012). Other work suggests that dispositional negativity is among the strongest prospective predictors of disorder onset in adults ($k = 46$ studies; mean Cohen's $d = .63$; Ormel et al., 2013) and adolescents (Craske et al., 2012). For example, adult data from the Zurich Cohort Study ($n = 591$) indicates that a one standard-deviation increase in dispositional negativity at the time of the baseline assessment in 1988 increased the odds of developing a major depressive episode by 41% and an anxiety disorder by 32% during the twenty year (1988-2008) follow-up period (Hengartner, Ajdacic-Gross, Wyss, Angst, & Rossler, 2016). These relations are particularly evident among individuals exposed to stress and negative life events (e.g., childhood maltreatment; Kopala-Sibley et al., *in press;* Kopala-Sibley et al., 2016; Vinkers et al., 2014), suggesting that high levels of dispositional negativity represent a diathesis for the internalizing spectrum of disorders (i.e., anxiety and depression). Among adults with a history of internalizing disorders, higher levels of dispositional negativity are associated with a greater number of co-morbid diagnoses (Hengartner, Kawohl, Haker, Rossler, & Ajdacic-Gross, 2016) and a more pessimistic prognosis (Berlanga, Heinze, Torres, Apiquian, & Cabellero, 1999; Duggan, Lee, & Murray, 1990; Faravelli, Ambonetti, Pallanti, & Pazzagli, 1986; Hirschfeld, Klerman, Andreasen, Clayton, & Keller, 1986; Kendler, Neale, Kessler, & Heath, 1993; Ormel, Oldehinkel, & Vollebergh, 2004; Quilty et al., 2008; Scott, Williams, Brittlebank, & Ferrier, 1995; Weissman, Prusoff, & Klerman, 1978). For example, Steunenberg and colleagues found that individuals with above-median levels of dispositional

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orientation sensitivity (Bocanegra & Zeelenberg, 2009); to boost the spatial and temporal resolution of visual processing (Bocanegra & Zeelenberg, 2011); and to enhance the efficiency of visual search (Becker, 2009).

negativity were 2.8-times more likely to relapse or experience a new depressive episode across a six-year follow-up period (Steunenberg, Beekman, Deeg, & Kerkhof, 2010). Importantly, dispositional negativity continues to predict self-reported anxious and depressive symptoms after eliminating overlapping item content (Uliaszek et al., 2009).

Dispositional negativity is relatively stable over time, but not immutable, and like other emotional traits continues to develop and change across development (Fraley & Roberts, 2005; Roberts & DelVecchio, 2000; Roberts & Mroczek, 2008). Indeed, mean levels of dispositional negativity show substantial fluctuations—equivalent to *T*-scores of 2 in males and 5 in females—between the ages of 10 and 65, peaking in adolescence (Soto, John, Gosling, & Potter, 2011). A range of evidence shows that dispositional negativity can be increased by exposure to stress or trauma in adolescence and adulthood (Barlow et al., 2013; Jeronimus, Riese, Sanderman, & Ormel, 2014; Jokela, Hakulinen, Singh-Manoux, & Kivimaki, 2014; Jokela, Kivimaki, Elovainio, & Keltikangas-Jarvinen, 2009; Laceulle, Nederhof, Karreman, Ormel, & Van Aken, 2011; Ludtke, Roberts, Trautwein, & Nagy, 2011; Parker, Ludtke, Trautwein, & Roberts, 2012; Roberts, Caspi, & Moffitt, 2003; Robins, Caspi, & Moffitt, 2002). For example, exposure to more frequent negative life events (e.g., death of an immediate family member or friend, academic expulsion, running away) between the ages of 11 and 16 is associated with elevated levels of dispositional negativity in Dutch adolescents (n = 1,197; Laceulle et al., 2011). Conversely, there is growing evidence that cognitive-behavioral (Barlow et al., 2013; Bennett et al., 2015; Mihalopoulos et al., 2015) and pharmacological interventions for anxiety and depression (Barlow et al., 2013; Knutson et al., 1998; Soskin, Carl, Alpert, & Fava, 2012) can produce lasting reductions in dispositional negativity. This plasticity raises the possibility of developing targeted prevention and treatment strategies (Barlow, Ellard, Sauer-Zavala, Bullis, & Carl, 2014; Barlow et al., 2013; Bennett et al., 2015; Chronis-Tuscano et al., 2015; Hudson & Fraley, 2015; Magidson, Roberts, Collado-Rodriguez, & Lejuez, 2014; Mihalopoulos et al., 2015).

Relevance of the Amygdala to Dispositional Negativity and Stress-Sensitive Psychopathology

The neural circuits that govern trait-like individual differences in dispositional negativity have only recently begun to come into focus. Work by our group and others demonstrates that humans and monkeys with a more negative disposition show heightened responses to threat-relevant cues in a number of brain regions, including the amygdala, anterior hippocampus, anterior insula, bed nucleus of the stria terminalis (BST), mid-cingulate cortex, orbitofrontal cortex, and periaqueductal gray (Avery, Clauss, & Blackford, 2016; Calder, Ewbank, & Passamonti, 2011; Cavanagh & Shackman, 2015; Fox & Kalin, 2014; Fox, Oler, Shackman, et al., 2015; Fox, Oler, Tromp, Fudge, & Kalin, 2015; Shackman et al., 2011). Here, we focus on the most intensely scrutinized of these regions, the amygdala. As shown in Figure 1, the amygdala is a heterogeneous collection of nuclei buried beneath the temporal lobe (Freese & Amaral, 2009; Swanson & Petrovich, 1998; Yilmazer-Hanke, 2012). The amygdala is poised to use information from sensory, contextual, and regulatory regions to assemble a broad spectrum of emotional reactions via projections to the downstream regions that directly mediate the behavioral (e.g., passive and active avoidance), peripheral physiological (e.g., cardiovascular and neuroendocrine activity, startle), and cognitive (e.g., vigilance) features of momentary fear and anxiety (Davis & Whalen, 2001; Freese & Amaral, 2009).

Relevance of the Amygdala to Dispositional Negativity

Brain imaging studies provide ample evidence that adults with a more negative disposition or a childhood history of extreme dispositional negativity show increased or prolonged activation in the dorsal or central (Ce) nucleus of the amygdala in response to novelty and threat-related cues (Ball et al., 2012; Blackford, Avery, Shelton, & Zald, 2009; Calder et al., 2011; Fox & Kalin, 2014; Schuyler et al., 2012; Stein, Simmons, Feinstein, & Paulus, 2007) (Figure 2**a-b**). This is particularly evident following periods of acute stress (Everaerd, Klumpers, van Wingen, Tendolkar, & Fernandez, 2015). Amygdala reactivity also tends to habituate more slowly among young adults and adolescents with a more negative disposition (Blackford, Allen, Cowan, & Avery, 2013; Blackford, Avery, Cowan, Shelton, & Zald, 2011; Hare et al., 2008).+

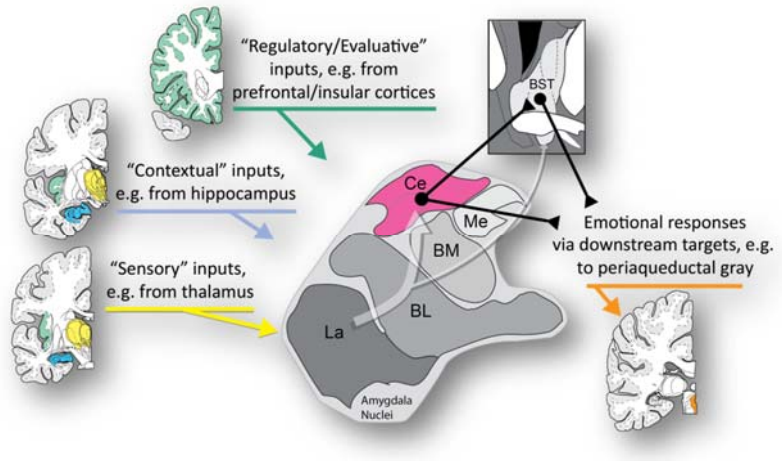

Figure 1: Simplified schematic of amygdala circuitry relevant to dispositional negativity, attentional biases, and hyper-vigilance to threat.

The amygdala is a heterogeneous collection of nuclei buried beneath the temporal lobe. It receives inputs from sensory (yellow), contextual (blue), and regulatory (green) systems and, as shown by the translucent white arrow at the center of the figure, information generally flows from the more ventral basal regions of the amygdala shown at the lower left toward the central (Ce) nucleus of the amygdala (magenta) and the neighboring bed nucleus of the stria terminalis (BST) at the upper right. The Ce and BST are, in turn, poised to orchestrate or trigger specific physiological, behavioral, and cognitive components of negative affect via their projections to downstream effector regions (orange). Prioritized processing of threat-related and other kinds of cues can occur through two mechanisms: *directly*, via projections from the basolateral (BL) nucleus to relevant areas of sensory cortex (e.g., fusiform face area) and *indirectly*, via projections from the Ce and BST to neuromodulatory systems in the basal forebrain and brainstem that, in turn, can modulate sensory cortex. Portions of this figure were adapted with permission from the atlas of Mai and colleagues (Mai, Paxinos, & Voss, 2007).

Abbreviations: Basolateral (BL), Basomedial (BM), Central (Ce), Lateral (La), and Medial (Me) nuclei of the amygdala; Bed nucleus of the stria terminalis (BST).

Like dispositional negativity, metabolic activity in the Ce (Figure 2**c**) is moderately stable over time and context (i.e., trait-like), heritable, and associated with heightened behavioral and neuroendocrine reactions to threat in juvenile monkeys (Fox & Kalin, 2014; Fox, Oler, Shackman, et al., 2015; Fox et al., 2012; Fox, Shelton, Oakes, Davidson, & Kalin, 2008; Shackman et al., 2013). For example, Fox and colleagues reported that Ce activity associated with prolonged exposure to an unfamiliar human intruder's profile showed an intra-class correlation of 0.64 across three occasions over a 1.1 year span, similar to the concurrent re-test stability of dispositional negativity in peri-adolescent monkeys (ICC = 0.72; Fox et al., 2012) and the 5-year stability of dispositional negativity in adult humans (partial R = .60; n = 56,735; Hakulinen et al., 2015).

Other work in young nonhuman primates suggests that elevated amygdala activity is a shared substrate for different presentations of dispositional negativity (Figure 3). Like humans, peri-adolescent monkeys express dispositional negativity in different ways. Some characteristically respond to threat with high levels of the stress hormone cortisol (and middling levels of behavioral inhibition), whereas others show the reverse profile. What these individuals share is heightened threat-related activity in the Ce (Shackman et al., 2013). This observation is consistent with evidence from patient studies that elevated amygdala reactivity is a transdiagnostic marker of the internalizing disorders (Etkin & Wager, 2007; Hamilton et al., 2012).

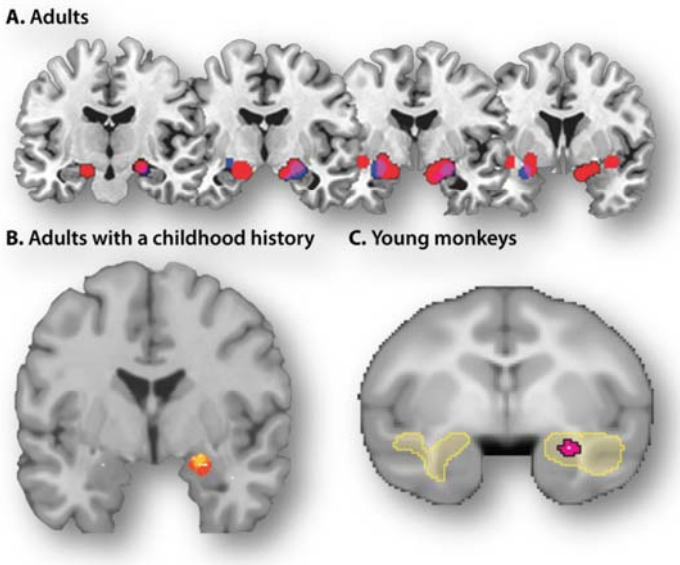

Figure 2: The dorsal amygdala is more reactive to threat-related cues in individuals with a more negative disposition.

A. *Adults with elevated dispositional negativity*. Meta-analysis of six published imaging studies reveals consistently elevated activation bilaterally in the vicinity of the dorsal amygdala (Calder et al., 2011). Significant relations with dispositional negativity (trait) are shown in blue; significant relations with momentary negative affect (state) are depicted in red; and the overlap is shown in purple.

B. *Adults with a childhood history of elevated dispositional negativity*. Meta-analysis of seven published imaging studies reveals consistently elevated activation in the right dorsal amygdala (Fox, Oler, Tromp, et al., 2015). Six of eight amygdala peaks overlapped (yellow) in the dorsal amygdala; four of the peaks extended into the region shown in red.

C. *Young monkeys*. Using high-resolution 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) acquired from 238 young rhesus monkeys, Oler, et al., (2010) showed that threat-related activity in the right Ce (i.e., dorsal amygdala) predicts differences in dispositional negativity. Figure depicts regions identified by a voxelwise regression analysis (yellow; $p < .05$, whole-brain corrected). The peak voxel and corresponding 95% spatial confidence interval are depicted in white and magenta, respectively. Portions of this figure were adapted with permission from (Calder et al., 2011; Fox & Kalin, 2014; Fox, Oler, Tromp, et al., 2015).

Commented [CE1]: Not listed in reference.

The observations reviewed in the prior section motivate the hypothesis that variation in dispositional risk (i.e., dispositional negativity) reflects stable individual differences in amygdala function. Other evidence raises the possibility that elevated amygdala reactivity contributes to the development and maintenance of internalizing disorders. In particular, amygdala activation:

1. Is elevated in children, adolescents, and adults with anxiety and mood disorders (Beesdo et al., 2009; Etkin & Wager, 2007; Hamilton et al., 2012; McClure et al., 2007; Monk et al., 2008; Thomas et al., 2001) and co-varies with the severity of anxious symptoms in adolescent patients (Thomas et al., 2001; van den Bulk et al., 2014).
2. Is amplified by exposure to the same kinds of stressors and psychological pathogens that can precipitate acute mental illness, including combat and childhood maltreatment (Dannlowski et al., 2012; Seo, Tsou, Ansell, Potenza, & Sinha, 2014; Swartz, Williamson, & Hariri, 2015; van Wingen, Geuze, Vermetten, & Fernandez, 2011).

3. Prospectively predicts heightened internalizing symptoms among adolescents and young adults exposed to stress, trauma, or negative life events (Admon et al., 2009; McLaughlin et al., 2014; Swartz, Knodt, Radtke, & Hariri, 2015). For example, McLaughlin and colleagues showed that adolescents marked by a more reactive amygdala at initial assessment experienced heightened posttraumatic symptoms 9 months later, following exposure to the terrorist attacks at the 2013 Boston Marathon (McLaughlin et al., 2014).

4. Is attenuated by clinically effective cognitive-behavioral and pharmacological (e.g., benzodiazepine) treatments for anxiety and depression in adults (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Brown et al., 2015; Felmingham et al., 2007; Furmark et al., 2002; Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Paulus, Feinstein, Castillo, Simmons, & Stein, 2005; Phan et al., 2013; Sheline et al., 2001; Strawn, Wehry, DelBello, Rynn, & Strakowski, 2012; Windischberger et al., 2010). As yet, the impact of treatment on pediatric amygdala function has received little attention and remains unclear (Maslowsky et al., 2010; Strawn et al., 2012).

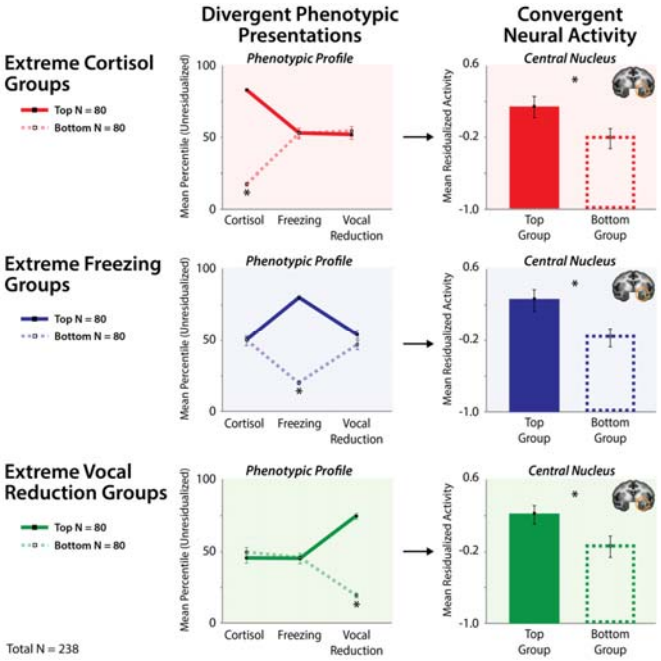

Figure 3: Elevated amygdala activity is a shared substrate for different phenotypic presentations of dispositional negativity.

Shackman, et al., (2013) used a well-established monkey model of childhood dispositional negativity and high-resolution FDG-PET to demonstrate that individuals with different presentations of the negative phenotype show increased activity in the central (Ce) nucleus of the amygdala (orange ring).

Divergent phenotypic presentations: To illustrate this, phenotypic profiles are plotted for groups (N = 80/group) selected to be extreme on a particular dimension of the phenotype (Top tercile: solid lines; Bottom tercile: broken lines). The panels on the left illustrate how this procedure sorts individuals into groups with divergent presentations of dispositional negativity.

Convergent neural activity: To illustrate the consistency of Ce activity across divergent presentations, mean neural activity for the extreme groups (± SEM) is shown on the right. Individuals with high levels of cortisol, freezing, or vocal reductions (and intermediate levels of the other two responses) were characterized by greater metabolic activity in the Ce (*p*s < .05). This figure was adapted with permission from (Shackman et al., 2013).

Mechanistic Work Indicates that the Amygdala Causally Contributes to Extreme Anxiety

Mechanistic work in monkeys and rodents demonstrates that the amygdala causally contributes to extreme anxiety. Selective lesions to the amygdala, particularly the Ce, markedly reduce the expression of fear and anxiety elicited by a broad spectrum of learned and innate (e.g., predators, intruders, snakes) threats (Choi & Kim, 2010; Davis & Whalen, 2001; Izquierdo, Suda, & Murray, 2005; Kalin et al., *in press;* Kalin, Shelton, & Davidson, 2004; LeDoux, 2012; Mason, Capitanio, Machado, Mendoza, & Amaral, 2006; Oler et al., 2016; Tovote, Fadok, & Luthi, 2015). Conversely, genetic manipulations that increase metabolic activity in the Ce are associated with heightened signs of anxiety in young monkeys exposed to intruder threat (Kalin et al., *in press*). These experimental findings in animals are consistent with observations made in humans with amygdala damage (Adolphs, *in press;* Feinstein, Adolphs, Damasio, & Tranel, 2011; Klumpers, Morgan, Terburg, Stein, & van Honk, *in press*). For example, Patient SM, who has near-complete bilateral destruction of the amygdala, shows a profound lack of fear and anxiety when exposed to frightening movies, haunted houses, tarantulas, and snakes (Feinstein et al., 2011). Over the past two decades,

> She has been held up at knife point and at gun point, she was once physically accosted by a woman twice her size, she was nearly killed in an act of domestic violence, and on more than one occasion she has been explicitly threatened with death...What stands out most is that, in many of these situations, SM's life was in danger, yet her behavior lacked any sense of desperation or urgency...Moreover…SM has great difficulty…learning to avoid dangerous situations" (Feinstein et al., 2011, p. 307).

Importantly, patients like SM also report low levels of dispositional negativity on standardized paper-and-pencil measures (Feinstein et al., 2011), consistent with informal clinician ratings of temperament (Tranel, Gullickson, Koch, & Adolphs, 2006). In sum, converging lines of epidemiological, physiological, and mechanistic evidence suggest that the dorsal amygdala supports stable individual differences in dispositional negativity and causally contributes to the development of anxiety and mood disorders.

Attentional Biases to Threat-Related Cues

Like the internalizing disorders, dispositional negativity is a complex, multidimensional phenotype that encompasses individual differences in feelings, neuroendocrine activity, peripheral physiology, attention, memory, and behavior (Barlow et al., 2014; Barlow et al., 2013; Cavanagh & Shackman, 2015; Fox & Kalin, 2014; Grupe & Nitschke, 2013; LeDoux, 2015; Okon-Singer et al., *in press;* Oler et al., 2016; Shackman et al., 2013). An important challenge is to identify the psychological and neurobiological mechanisms that underlie each of these core features and understand how they confer increased risk for psychopathology. In the remainder of this review, we focus on the role of attentional biases to threat-related cues and outline recent advances in our understanding of the underlying neurobiology.

Threat-Related Cues Grab Attention

Attention is a fundamental property of perception and cognition. "Attention is necessary because…the environment presents far more perceptual information than can be effectively processed, one's memory contains more competing traces than can be recalled, and the available choices, tasks, or motor responses are far greater than one can handle" (Chun, Golomb, & Turk-Browne, 2011, p. 75). Attentional mechanisms prioritize the most relevant sources of information while inhibiting or ignoring potential distractions and competing courses of action (Desimone & Duncan, 1995). Once a target is selected, attention determines how deeply it is processed, how quickly and accurately a response is executed, and how well it is later remembered. Thus, attention involves both stimulus selection and the intensity of processing once a stimulus has been selected.

Threat-related cues—snakes, spiders, angry faces, and conditioned fear cues, to name a few—strongly influence both feature selection and the depth of processing. Across a range of laboratory assays, they are more likely to be detected, to capture attention, and to be remembered (Carretie, 2014; Markovic, Anderson, & Todd, 2014; Sheppes, Luria, Fukuda, & Gross, 2013). Threat-related stimuli are associated with enhanced processing in sensory regions of the brain and this amplified processing is associated with faster and more accurate behavioral performance

(Carretie, 2014; Kouider, Eger, Dolan, & Henson, 2009; Lim, Padmala, & Pessoa, 2009; Pourtois, Schettino, & Vuilleumier, 2013; Vuilleumier et al., 2002).

Relevance of Attention to Dispositional Negativity and Anxiety Disorders

Heightened vigilance and exaggerated risk assessment behaviors are hallmarks of both dispositional negativity and anxiety disorders (Grupe & Nitschke, 2013), particularly generalized anxiety disorder (Salum et al., 2013; Waters, Bradley, & Mogg, 2014). Like many patients with anxiety disorders, adults, adolescents, and children with a more negative disposition are biased to allocate excess attention to threat-related cues, even when they are irrelevant to the task at hand (Aue & Okon-Singer, 2015; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Cole, Zapp, Fettig, & Perez-Edgar, 2016; Dudeney, Sharpe, & Hunt, 2015; LoBue & Perez-Edgar, 2014; Van Bockstaele et al., 2014) (for thoughtful discussions of heterogeneity, see Naim et al., 2015; Roy, Dennis, & Warner, 2015; Waters et al., 2015)[2]. In particular, recent meta-analyses indicate that children and adolescents with elevated levels of dispositional negativity or frank anxiety disorders show a significantly greater attentional bias for threat-related stimuli when compared to typical youth (k = 44 studies; mean Cohen's d = 0.21) or when compared emotionally neutral stimuli (k = 16 studies; mean Cohen's d = 0.54; Dudeney et al., 2015). The latter effect is similar in magnitude to that reported in studies of adults (k = 101 studies; mean Cohen's d = 0.45; Bar-Haim et al., 2007). On average, dispositionally negative adults are more likely to initially orient their gaze towards threat-related cues in free-viewing tasks; quicker to fixate threat-related targets in visual search tasks; and slower to disengage from threat-related distractors in spatial cueing, visual search, and dot-probe[3] tasks (Armstrong & Olatunji, 2012; Cisler & Koster, 2010; Rudaizky, Basanovic, & MacLeod, 2014). Recent work employing tasks designed to more cleanly dissociate biases in attentional engagement from disengagement (i.e., release-from-capture paradigm) suggests that adults with a more negative disposition are particularly impaired in disengaging from threat-related cues (Sheppes et al., 2013). Whether this is also evident in youth remains unknown.

A range of evidence motivates the hypothesis that attentional biases to threat-related cues contribute to the development and maintenance of extreme anxiety. From a longitudinal perspective, attentional biases to threat-related cues have been shown to moderate the impact of dispositional negativity on the development of internalizing symptoms in youth. For example, Pérez-Edgar, Fox, and colleagues have demonstrated that among youth with an early childhood history of extreme dispositional negativity, it is the subset who also show an attentional bias to threat-related cues on the dot-probe task that is most likely to exhibit social withdrawal and elevated anxiety symptoms later in development, at ages 5 and 15 (Perez-Edgar, Bar-Haim, et al., 2010; Perez-Edgar et al., 2011; White et al., in press). Likewise, there is emerging evidence that clinically effective cognitive-behavioral and pharmacological treatments for anxiety also tend to reduce attentional biases to threat-related cues (Murphy, Yiend, Lester, Cowen, & Harmer, 2009; Reinecke, Waldenmaier, Cooper, & Harmer, 2013; Van Bockstaele et al., 2014). Direct support for this hypothesis comes from studies using computer-based interventions targeting attentional biases to threat. In non-clinical samples, attention modification has been shown to reduce distress, behavioral signs of anxiety, and intrusive thoughts elicited during subsequent exposure to cognitive stressors, public speaking challenges, and worry inductions in adults and children (Bar-Haim, Morag, & Glickman, 2011; Dennis & O'Toole, 2014; MacLeod & Mathews, 2012). In adult clinical samples, medium-to-small treatment effects have been consistently observed compared to placebo training (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; MacLeod & Clarke, 2015). Results have been somewhat less consistent in pediatric clinical samples, with some studies reporting positive effects compared to placebo (Eldar et al., 2012; Riemann, Kuckertz, Rozenman, Weersing, & Amir, 2013; Waters, Pittaway,

[2] Or show more complex patterns of initial vigilance followed by avoidance (Armstrong & Olatunji, 2012; Di Simplicio et al., 2014; Onnis, Dadds, & Bryant, 2011; Weierich, Treat, & Hollingworth, 2008; Zvielli, Bernstein, & Koster, 2014).

[3] In the 'dot-probe' paradigm, subjects are presented with two lateralized cues (e.g., words, faces), one threat-related, the other emotionally neutral. A short time following the offset of the cues (e.g., 500 msec), a probe (e.g., a dot) is presented in either the same location as the threat-related ('congruent') or neutral cue ('incongruent') with equal probability. Bias scores are computed by subtracting the mean reaction time for congruent trials from the mean reaction time for incongruent trials. Positive scores indicate faster engagement or slower disengagement from the threat-related cue.

Mogg, Bradley, & Pine, 2013) and others reporting similarly positive effects for both the active and placebo training groups (Britton et al., 2013; Shechner et al., 2014). Taken together, these observations are consistent with the idea that attentional biases to threat represent an 'active ingredient' in the etiology of pediatric and adult anxiety disorders.

Relevance of the Amygdala to Hyper-Vigilance and Attentional Biases to Threat

The neural mechanisms underlying attentional biases to threat remain poorly understood, particularly in youth, but there is correlational evidence that the prioritized processing of threat-related cues reflects the influence of neural circuits encompassing the amygdala. Imaging and single unit studies performed in humans and monkeys demonstrate that the amygdala is sensitive to a broad range of emotionally salient, attention-grabbing stimuli, including faces, aversive images, erotica, and food and drug cues (Chase, Eickhoff, Laird, & Hogarth, 2011; Costafreda, Brammer, David, & Fu, 2008; Fried, MacDonald, & Wilson, 1997; Fusar-Poli et al., 2009; Gothard, Battaglia, Erickson, Spitler, & Amaral, 2007; Hoffman, Gothard, Schmid, & Logothetis, 2007; Kuhn & Gallinat, 2011; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Sabatinelli et al., 2011; Sergerie, Chochol, & Armony, 2008; Sescousse, Caldu, Segura, & Dreher, 2013; D. W. Tang, Fellows, Small, & Dagher, 2012; Wang et al., 2014). Furthermore, adults with a more negative disposition show heightened amygdala activation to threat-related cues (Calder et al., 2011), even when they are task-irrelevant (Ewbank et al., 2009), and there is evidence that this is associated with enhanced attentional capture (i.e., response slowing; Ewbank et al., 2009). Other recent work shows that adults (Boehme et al., 2015) and youth (9-14 years; Price et al., 2016) with anxiety disorders show increased amygdala activation and exaggerated behavioral interference when performing standard emotional attention tasks (e.g., emotional Stroop, dot-probe).

As shown in Figure 4**a**, anatomical tracing studies in nonhuman primates and mechanistic studies in rodents demonstrate that the amygdala is well-positioned to prioritize the processing of threat and other salient stimuli. Enhanced attention can occur via at least two mechanisms: *directly*, via projections from the basolateral (BL) nucleus of the amygdala (Figure 1) to the relevant areas of sensory cortex (e.g., fusiform face area) and *indirectly*, via projections to neuromodulatory systems in the basal forebrain and brainstem that, in turn, can modulate sensory cortex (i.e., increase the neuronal signal-to-noise ratio; Davis & Whalen, 2001; Freese & Amaral, 2009). Consistent with this perspective, adult imaging research shows that trial-by-trial fluctuations in amygdala activity predict whether degraded threat stimuli are detected and demonstrate that this association is statistically mediated by enhanced activation in the relevant areas of sensory cortex (Lim et al., 2009) (Figure 4**b**). Whether this distributed amygdalo-cortical circuitry is altered in individuals with a negative disposition or anxiety disorder remains unknown.

A growing body of research in human adults and monkeys indicates that the amygdala plays a mechanistically important role in biasing attention to threat-related cues. Manipulations that potentiate amygdala reactivity also enhance behavioral measures of the attentional bias to threat-related information (Herry et al., 2007). For example, Herry and colleagues demonstrated that exposure to an emotionally neutral, temporally unpredictable train of auditory pulses activates the lateral and BL amygdala (cf. Figure 1) and amplifies attentional biases to angry faces in the dot-probe task. Conversely, patients with amygdala damage and monkeys with selective amygdala lesions do not show enhanced processing of threat-related cues (i.e., fearful or threatening faces) in sensory cortex (Hadj-Bouziane et al., 2012; Rotshtein et al., 2010; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). In particular, amygdala insults markedly reduce 'valence' effects for facial expressions (i.e., Threat > Neutral) in the fusiform face area in humans (Vuilleumier et al., 2004) (Figure 4**c**) and inferior temporal cortex in monkeys (Hadj-Bouziane et al., 2012). In humans, amygdala damage also disrupts the prioritized processing of threat-related faces in crowded stimulus arrays (i.e., the 'Face-in-the-Crowd' task; Bach, Hurlemann, & Dolan, 2015).

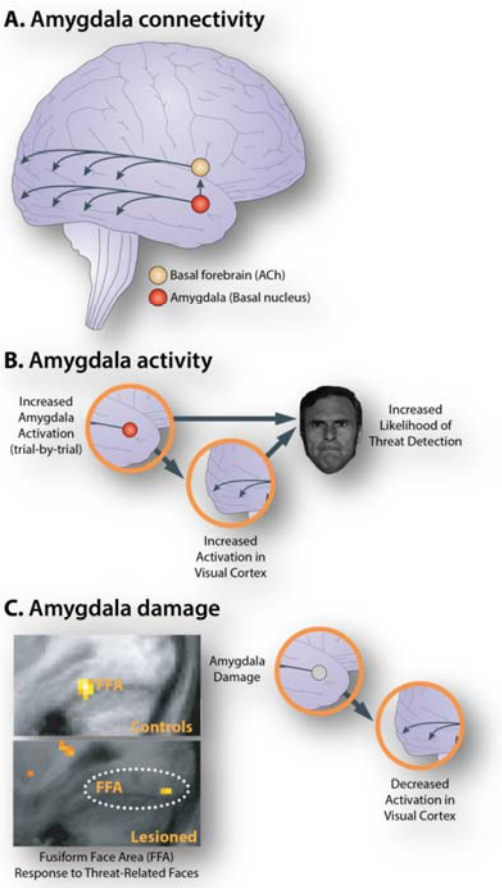

Figure 4: The amygdala plays a key role in enhancing attention to threat-relevant information.

A. Amygdala connectivity. Anatomical tracing Invasive studies in monkeys and mechanistic studies in rodents indicate that the amygdala can enhance vigilance and prioritize the processing of threat-relevant information via direct projections to sensory cortex as well as indirectly, via projections to ascending neurotransmitter systems in the basal forebrain and brain stem. In turn, these transmitter systems can enhance the signal-to-noise ratio of neuronal processing in cortical sensory regions. In this simplified illustration, select projections from the basal forebrain cholinergic (ACh) system to the visual cortex are depicted.

B. Amygdala activity. In a recent fMRI study, Lim and colleagues demonstrated that amygdala activation predicts trial-by-trial fluctuations in threat detection (Lim et al., 2009). Mediation analyses revealed that relations between the level of amygdala activation and performance were explained by increased activation in the visual cortex, consistent with work in animals.

C. Amygdala damage. In a seminal study, Vuilleumier and colleagues showed that individuals with amygdala damage do not show increased activation to threat-related facial expressions in the fusiform face area (FFA) of the visual cortex, indicating that the amygdala causally contributes to the enhanced processing of threat-related stimuli (Vuilleumier et al., 2004). This observation has since been replicated using more selective chemical lesions in monkeys (Hadj-Bouziane et al., 2012). Portions of this figure were adapted with permission from (Y. Y. Tang, Holzel, & Posner, 2015; Vuilleumier et al., 2004).

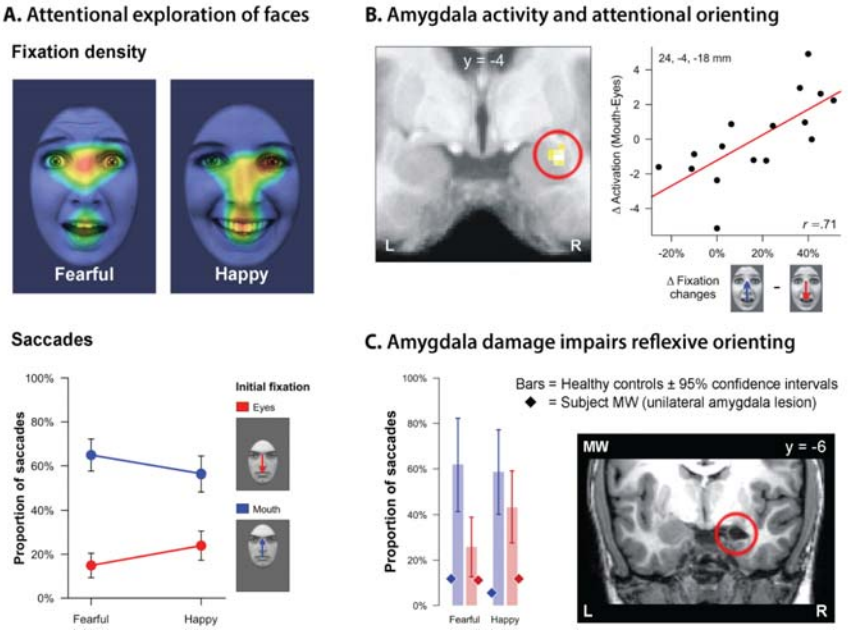

Figure 5: The amygdala plays a key role in orienting overt attention to threat-diagnostic information in the environment.

A. Attentional exploration of faces. Eye tracking data reveal a strong bias for scanning the eye and brow region, particularly for fearful faces (Scheller, Buchel, & Gamer, 2012). This bias is evident in both the density of fixations over time (top panel: warmer colors indicate higher density) and the likelihood of reflexive saccades toward the facial feature presented in the visual periphery (bottom panel).

B. Amygdala activation and attentional orienting. Individuals with increased activation in the right amygdala (indicated by the red ring) are more likely to orient their gaze to the eye and brow region of fearful faces (Gamer & Buchel, 2009).

C. Amygdala damage impairs reflexive orienting. Patient MW has selective damage to the right amygdala (indicated by the red ring) and shows a profound reduction in reflexive saccades to the eye region of the face (Gamer, Schmitz, Tittgemeyer, & Schilbach, 2013). Portions of this figure were adapted with permission from (Gamer & Buchel, 2009; Gamer et al., 2013; Scheller et al., 2012).

Other work suggests that the amygdala is not necessarily the passive recipient of threat-related information streaming in from the environment. In addition to biasing selection and increasing the depth of processing, there is compelling evidence that the amygdala plays a key role in redirecting gaze (i.e., overt attention) to those features of the face, such as the eyes and brow, that are most diagnostic of threat, trustworthiness, anger, and fear (Oosterhof & Todorov, 2008, 2009; Smith, Cottrell, Gosselin, & Schyns, 2005). Using a combination of eye tracking and brain imaging, Gamer and colleagues have demonstrated that human adults are biased to reflexively attend the eye and brow region of the face, that this bias is most pronounced for threat-related (i.e., fearful) facial expressions, and that individuals with greater amygdala activation are more likely to shift their gaze to the eyes (Gamer & Buchel, 2009; Scheller, Buchel, & Gamer, 2012) (Figure 5**a, b**). Similar effects have been obtained for complex non-social cues; subjects are biased to fixate the visual features most predictive of threat and this tendency co-varies with trial-by-trial fluctuations in amygdala activation (Eippert, Gamer, & Buchel, 2012). With regard to faces, this attentional bias is exaggerated among adults with a more negative disposition (Perlman et al., 2009) or a social anxiety disorder (Boll, Bartholomaeus, Peter, Lupke, & Gamer, 2016). Importantly, patients with circumscribed amygdala damage do not show reflexive saccades to the eyes (Gamer, et al., 2013) (Figure 5**c**). Instead, they tend to fixate the mouth, both in laboratory assessments and real-world social interactions (Adolphs et al., 2005; Spezio, Huang, Castelli, & Adolphs,

2007), and this impairs the ability to recognize facial expressions of fear (Adolphs et al., 2005). Likewise, monkeys with selective lesions of the amygdala show markedly reduced detection of threat-diagnostic facial features (i.e., enhanced capture) and spend more time visually exploring the mouth region of the face (Dal Monte, Costa, Noble, Murray, & Averbeck, 2015). These converging lines of neurophysiological and mechanistic evidence indicate that the amygdala is crucial for the rapid detection and re-allocation of attention to threat-diagnostic social cues in adults. A key challenge for the future is establishing whether the amygdala performs a similar role in youth and other clinical populations.

Persistent Hyper-vigilance for Threat May Reflect Stress-Induced Sensitization of the Amygdala

Hyper-vigilance in the absence of immediate danger is a core feature of extreme anxiety. Persistent, contextually inappropriate vigilance or attentional biases to threat-related information may reflect stress-induced sensitization of the amygdala. Recent work in adult humans shows that brief exposure to experimental stressors, such as threat-of-shock or aversive film clips, causes sustained increases in spontaneous amygdala activity (Cousijn et al., 2010) and amplifies amygdala reactivity to subsequent threat-related facial expressions (Pichon, Miendlarzewska, Eryilmaz, & Vuilleumier, 2015; van Marle, Hermans, Qin, & Fernandez, 2009). Acute stressor exposure can produce even longer-lasting changes, on the order of minutes to hours, in amygdala functional connectivity (Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernandez, 2010). Furthermore, these kinds of sensitization or 'spill-over' effects are exaggerated among individuals who are at elevated risk for developing stress-related psychopathology. For example, a recent large-scale imaging study (n = 120) showed that adults with a more negative disposition exhibit a larger increase in activation elicited by threat-related faces following acute stressor exposure (Everaerd et al., 2015). Sustained amygdala sensitization could promote pervasive anxiety and negative affect by increasing the likelihood that attention is allocated to threat-related cues in the environment (MacLeod & Mathews, 2012; Van Bockstaele et al., 2014). Understanding the relevance of these pathways to the development of anxiety disorders is an important avenue for future research.

Future Challenges

The data that we have reviewed provide new insights into the mechanisms that underlie the development and maintenance of anxiety disorders in adults and youth. Collectively, this work demonstrates that amygdala-centered circuits support trait-like individual differences in dispositional risk across the lifespan and contribute to hyper-vigilance and attentional biases to threat-related cues in monkeys and humans. Among adults, this circuitry is sensitized by acute exposure to stressors, is dampened by clinically effective treatments for anxiety and mood disorders, and prospectively predicts the emergence of internalizing symptoms among stressor-exposed individuals. In adult humans and monkeys, damage to the amygdala markedly reduces threat-elicited anxiety, blocks the prioritized processing of threat-related cues in sensory cortex, and abolishes reflexive saccades to threat-diagnostic facial features. Conversely, manipulations that enhance amygdala activity amplify anxiety and attentional biases to threat-related cues. In short, the amygdala appears to be a key substrate for extreme anxiety. Despite this progress, it is clear that a number of important questions remain unanswered. Here, we highlight several of the most crucial questions and outline some strategies for starting to address them.

1. ***Which brain circuits underlie hyper-vigilance and attentional biases to threat in anxious youth?*** Although some progress has been made at identifying the brain circuitry mediating attentional biases to threat-related cues in adults, the relevance of these circuits to early-life anxiety has received much less empirical attention and remains poorly understood. Addressing this challenge will require overcoming several key barriers, including the absence of significant attentional biases in imaging studies of anxious youth (k = 4, mean Cohen's d = 0.09; Dudeney et al., 2015), the inadequate reliability of reaction-time measures of the attentional bias (Kappenman, Farrens, Luck, & Proudfit, 2014; Kappenman, MacNamara, & Proudfit, 2015; Price et al., 2014), and heterogeneity in biases toward ('vigilance') and away ('avoidance') from different kinds of threat (Pine & Fox, 2015; Roy et al., 2015; Zvielli et al., 2014). Developing a deeper understanding of early-life attentional biases is particularly important because the roots of anxiety disorders often extend

into childhood (Kessler et al., 2005) and mental illnesses that emerge before adulthood impose a 10-fold higher economic cost than those that emerge in mid or later life (WHO, 2007).

2. ***How do different aspects of attention contribute to the development of anxiety disorders?*** In this review, we have treated hyper-vigilance and attentional biases to threat-related informationas virtually synonymous. Yet, there is a growing recognition that the amount of attention allocated to threat-related cues can fruitfully be decomposed into several key constituents: (i) the likelihood that task-relevant threat will be detected and attention will be re-oriented (i.e., heightened 'vigilance'), (ii) the likelihood that task-irrelevant threat will capture attention or bias behavior (i.e., reduced attentional control or selectivity), (iii) the rapidity of disengagement from threat, and (iv) the degree of attentional avoidance (or maintenance) during sustained, free-viewing tasks (Richards, Benson, Donnelly, & Hadwin, 2014). Although work by Gamer and colleagues demonstrates that the amygdala plays a crucial role in the initial re-orienting to threat-diagnostic features of the face (Gamer & Buchel, 2009; Gamer et al., 2013), relatively little is known about the clinical relevance or neurobiology of these other kinds of attentional biases in adults or youth. Addressing this key question will require the integration of eye tracking with brain imaging or electrophysiological assays in individuals with anxiety disorders or varying levels of familial or dispositional risk. Longitudinal studies in high-risk populations (e.g., patient offspring, individuals with a more negative disposition) would be especially valuable.

3. ***How do different components of the extended amygdala contribute to risk?*** Like attention, the amygdala can be divided into meaningful sub-components or nuclei (Fox & Kalin, 2014; Freese & Amaral, 2009; Swanson & Petrovich, 1998) (Figure 1). These nuclei are a key component of the central extended amygdala, a larger anatomical complex that runs from the dorsal amygdala (Ce), through the substantia innominata (SI), to the BST and the shell of the nucleus accumbens (Alheid & Heimer, 1988; Heimer et al., 1999; Oler et al., 2012; Yilmazer-Hanke, 2012). Recent mechanistic work in rodents demonstrates that specific nuclei, circuits, and neuronal populations within the extended amygdala make dissociable contributions to fear and anxiety. Some of these sub-components promote rapid responses to immediate danger, some promote sustained responses in the face of novelty and uncertain threat, some support both kinds of response, and still others appear to dampen fear- and anxiety-related responses (Botta et al., 2015; Daniel & Rainnie, 2016; Davis et al., 2010; Duvarci, Bauer, & Pare, 2009; Kim et al., 2013; Tovote et al., 2015; Walker & Davis, 2008).

The relevance of these sub-components for dispositional risk and hyper-vigilance for threat or potential threat in humans or other primates has only recently been explored. In particular, imaging studies in humans and monkeys highlight the importance of the Ce and BST for dispositional risk and anxiety disorders (Avery et al., 2016; Fox, Oler, Shackman, et al., 2015; Fox, Oler, Tromp, et al., 2015; Shackman, Stockbridge, LeMay, & Fox, *in press*). This work suggests that the BST may be particularly important for orchestrating persistent defensive responses and vigilance in contexts where threat is uncertain, psychologically diffuse, or temporally remote (Alvarez et al., 2015; Jahn et al., 2010; Kalin, Shelton, Fox, Oakes, & Davidson, 2005; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Somerville et al., 2013). Other work demonstrates that the BL (Figure 1), which sends heavy projections to cortical sensory areas (Freese & Amaral, 2009) and is sensitive to the valence of facial expressions (Hoffman et al., 2007), specifically contributes to the re-orienting of attention to threat-diagnostic facial features (Gamer & Buchel, 2009; Gamer, Zurowski, & Buchel, 2010).

Developing a deeper understanding of this heterogeneity and its relevance to the development of stress-sensitive psychopathology requires that we first acknowledge it. Although investigators need to be cautious when assigning specific labels (e.g., BL, BST, Ce) to activation clusters in imaging studies, we encourage them to describe the relative position of activation peaks (e.g., dorsal-posterior amygdala) and interpret their results on the basis of the most likely sub-component of the extended amygdala (e.g., 'in the region of the BST'). The use of high-field MRI or specialized analytic approaches (e.g., using spatially unsmoothed data) may also prove useful (Avery et al., 2014; Sladky et al., 2013; Torrisi et al., 2015; van der Zwaag, Da Costa, Zurcher, Adams, & Hadjikhani, 2012).

1. ***Which brain circuits are associated with individual differences in risk?*** There is widespread consensus that dispositional negativity and hyper-vigilance for threat, like other psychologically and psychiatrically

relevant processes, reflect the coordinated activity of distributed brain circuits (Okon-Singer, Hendler, Pessoa, & Shackman, 2015; Pessoa, 2013; Shackman, Fox, & Seminowicz, 2015). Yet most imaging investigators (including our team) have relied heavily on localization strategies in which function is mapped to isolated brain structures. Unfortunately, this approach tends to promote the development of models in which a single brain region, such as the amygdala, does most of the 'heavy lifting.' Overcoming this important barrier requires that we accelerate the transition from localization strategies to network-based approaches (Anticevic et al., 2013; Fornito, Zalesky, & Breakspear, 2015; McMenamin et al., 2014; Petersen & Sporns, 2015; Servaas et al., 2014; Turk-Browne, 2013). Information-based approaches, such as multivoxel pattern analysis (MVPA), provide another powerful tool for discovering functional networks associated with emotional states, traits, and disorders (Chang, Gianaros, Manuck, Krishnan, & Wager, 2015; Lewis-Peacock & Norman, 2014; Wager et al., 2013). As Janak and Tye recently noted, "neural circuit analysis is key. This way of thinking about the amygdala is different from past conceptions of it as a fear hub or as a circuit providing a readout of positive or negative affect…Instead, the emphasis is on understanding the behaviourally relevant functions of paths of information flow through these regions" (Janak & Tye, 2015, p. 290).

2. ***What is the relevance of individual differences in brain function to anxiety-related experience and behavior in the real world?*** Most psychophysiological and imaging studies of anxiety and attention rely on a limited number of well-controlled, but highly artificial manipulations (e.g., static emotional faces, threat-of-shock; Coan & Allen, 2007), collected under unnatural conditions. Although this approach has afforded a number of important insights, the real-world significance of the neural circuitry identified in the laboratory remains poorly understood. Given the limitations of ambulatory measures of brain activity—there is no 'fMRI helmet' as yet—addressing this fundamental question requires integrating assays of brain function and behavior (e.g., eye tracking) acquired in the scanner with thoughts, feelings, and behavior assessed under naturalistic conditions in the laboratory (e.g., during semi-structured interactions; Creed & Funder, 1998; Laidlaw, Foulsham, Kuhn, & Kingstone, 2011; Perez-Edgar, McDermott, et al., 2010; Pfeiffer, Vogeley, & Schilbach, 2013) or in the field.

Recent work combining fMRI with intensive experience-sampling techniques highlights the value of this approach for identifying the neural systems underlying naturalistic variation in mood and behavior in adults, adolescents, and even older children (Berkman & Falk, 2013; Forbes et al., 2009; Heller et al., *in press;* Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014; Price et al., 2016; S. J. Wilson, Smyth, & MacLean, 2014). The development of robust mobile eye trackers (e.g., Applied Science Laboratories' Mobile Eye system), the emergence of commercial software for automated facial analytics (e.g., from Affectiva, Emotient, and Noldus; Olderbak, Hildebrandt, Pinkpank, Sommer, & Wilhelm, 2014), and the widespread dissemination of smart phone technology afford additional opportunities for objectively and unobtrusively quantifying social attention, context, and daily behavior (Gosling & Mason, 2015; Sano et al., 2015; Wrzus & Mehl, 2015). Combining these measures with laboratory assays of brain function would open the door to discovering the neural systems underlying maladaptive experiences and pathology-promoting behaviors (e.g., social withdrawal, avoidance, and hyper-vigilance) in the real world, close to clinical end-point (Price et al., 2016). This approach promises a depth of understanding that cannot be achieved using animal models or isolated measures of brain function and is a key step to establishing the clinical and potential therapeutic relevance of these brain circuits.

1. ***What mechanisms underlie individual differences in risk?*** Much of the data that we have reviewed comes from brain imaging studies. Aside from unresolved questions about the origins and significance of the measured signals (Logothetis, 2008), the most important limitation of imaging studies is that they cannot address causation. A crucial challenge for future studies is to develop a mechanistic understanding of the brain circuits that confer increased risk for the development of internalizing disorders in adults and youth. Addressing this fundamental question requires coordinated research efforts in humans and nonhuman animal models. This could be achieved by combining mechanistic techniques in animals with the same whole-brain imaging strategies routinely used in humans, enabling the development of bidirectional translational models (Borsook, Becerra, & Hargreaves, 2006; Casey et al., 2013; Desai et al., 2011; Ferenczi et al., 2016; Fox et al., 2010; Kaiser & Feng, 2015). Nonhuman primate models are likely to be particularly useful for modeling and understanding the neurobiology of dispositional negativity because monkeys and

humans share similar genes and brains (Freese & Amaral, 2009; Gibbs et al., 2007; Preuss, 2007), which endow the two species with a shared repertoire of complex social, emotional, and cognitive behaviors (Belmonte et al., 2015; Kalin & Shelton, 2003; Preuss, 2007; Wise, 2008). Furthermore, well-established techniques already exist for studying both dispositional negativity and attention in nonhuman primates (Hadj-Bouziane et al., 2012; Noudoost, Albarran, & Moore, 2014; Oler et al., 2016). Human studies will be crucial for determining whether mechanisms identified in animal models are conserved across species and, hence, relevant to understanding human affect and human disorders. In human studies, imaging approaches can be applied to patients with circumscribed brain damage (Motzkin, Philippi, Oler, et al., 2015; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014, 2015). Alternatively, fMRI or EEG can be combined with noninvasive perturbation techniques (Bestmann & Feredoes, 2013; Reinhart & Woodman, 2014), neurofeedback (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015; Greer, Trujillo, Glover, & Knutson, 2014; Stoeckel et al., 2014), cognitive-behavioral interventions (Britton et al., 2015; Schnyer et al., 2015), or more passive psychological manipulations (i.e., temporally unpredictable auditory stimuli; Herry et al., 2007). 'Gameified' approaches may be particularly useful for studies of youth. Prospective longitudinal imaging studies represent another fruitful approach to identifying candidate mechanisms, especially in relation to the development of internalizing disorders (Admon, Milad, & Hendler, 2013; Burghy et al., 2012; Herringa et al., 2013; McLaughlin et al., 2014; Swartz, Williamson, et al., 2015).

Conclusions

The work that we have reviewed highlights the relevance of amygdala function to individual differences in dispositional negativity, to attentional biases to threat-related cues, and ultimately to the development of anxiety disorders and other forms of stress-sensitive psychopathology in adults and youth. This is important because existing treatments are inconsistently effective or associated with significant adverse effects (Bystritsky, 2006; Griebel & Holmes, 2013; Insel, 2012). The observations that we have reviewed provide new insights into the etiology of these debilitating disorders and set the stage for developing novel strategies for preventing or treating them.

Acknowledgements

Authors acknowledge assistance from L. Friedman, S. Haas, and J. Smith and support from the European Research Council (ERC-2013-StG-336305.), German Research Foundation (GA 1621/2-1), National Institute of Mental Health (MH107444), and University of Maryland. Authors declare no conflicts of interest.

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