CHAPTER

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Dispositional negativity, cognition, and anxiety disorders: An integrative translational neuroscience framework

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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 underlying mechanisms have only recently begun to come into focus. Here, we review new insights into the nature and biological bases of dispositional negativity, a fundamental dimension of childhood temperament and adult personality and a prominent risk factor for the development of pediatric and adult anxiety disorders. Converging lines of epidemiological, neurobiological, and mechanistic evidence suggest that dispositional negativity increases the likelihood of psychopathology via specific neurocognitive mechanisms, including attentional biases to threat and deficits in executive control. Collectively, these observations provide an integrative translational framework for understanding the development and maintenance of anxiety disorders in adults and youth and set the stage for developing improved intervention strategies.

Keywords

Affective neuroscience, Amygdala, Attentional biases, Developmental psychopathology, Emotion, Fear and anxiety, Individual differences, Neuroimaging

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1 Introduction

Anxiety is a sustained state of elevated apprehension, arousal, and vigilance that occurs in the absence of clear and immediate danger (Davis et al., 2010; Grupe and Nitschke, 2013; LeDoux, 2015; Shackman and Fox, 2016). Anxiety lies on a continuum and, when expressed in extreme ways or in inappropriate contexts, can become debilitating (Conway et al., n.d.; Craske et al., 2017; Salomon et al., 2015; Shackman et al., 2016b). Anxiety disorders are the most prevalent family of mental illnesses (Global Burden of Disease Collaborators, 2016; U.S. Burden of Disease Collaborators, 2018; Wang et al., 2017). They typically emerge early in life, enabling greater cumulative damage, and can contribute to the development of depression, substance abuse, and other adverse outcomes (Bitsko et al., 2018; Fox and Kalin, 2014; Kessler et al., 2007, 2012; Lee et al., 2014; McGorry et al., 2011; Pratt et al., 2016; Shackman et al., 2016b; Torvik et al., in press). Existing treatments are underutilized, inconsistently effective, and, in the case of pharmaceuticals, associated with significant adverse effects (Craske et al., 2017; Gordon and Redish, 2016; Griebel and Holmes, 2013). In short, anxiety disorders impose a staggering burden on public health and the global economy, underscoring the urgency of developing a more complete understanding of the underlying mechanisms (DiLuca and Olesen, 2014; Global Burden of Disease Collaborators, 2016; Roehrig, 2016; U.S. Burden of Disease Collaborators, 2018).

We begin by describing new insights into the nature and the biological bases of *dispositional negativity*, a central dimension of mammalian temperament that confers elevated risk for the development of anxiety disorders and other stress-sensitive psychiatric diseases. Like anxiety disorders, dispositional negativity is a complex, multidimensional phenotype that encompasses variation in behavior, peripheral physiology, feelings, and cognition (Cavanagh and Shackman, 2015; Grupe and Nitschke, 2013; LeDoux, 2015; Shackman et al., 2016a,b). A key challenge is to identify the mechanisms underlying these features and discover how they contribute to the etiology of psychiatric disease in adults and youth. Here, we focus on recent advances in our understanding of threat-related[a] attentional biases and deficits in

[a]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 et al., 2010; Hess et al., 2007; Springer et al., 2007), facilitation of avoidance-related movements (Marsh et al., 2005), and increased fear ratings (Dimberg, 1988). In contrast, fearful faces signal the presence, but not the source of potential threat, and can promote heightened vigilance in the absence of defensive mobilization (Whalen, 1998). Static images of fearful faces typically do not amplify the startle reflex (Grillon & Charney, 2011b; Springer et al., 2007) or autonomic measures (Dunsmoor et al., 2009). But they can increase subjective feelings of anxiety (Blairy et al., 1999) and are perceived as more threatening and arousing than neutral or happy faces (Grillon & Charney, 2011b; Wieser and Keil, 2014). Fearful faces elicit a more cautious, inhibited behavioral response style (Tipples, 2018). They also increase vigilance for potentially threat-relevant cues, particularly for low spatial-frequency (LSF) information. Indeed, the mere presentation of fearful faces has been shown to enhance subsequent contrast sensitivity (Phelps et al., 2006), LSF orientation sensitivity (Bocanegra and Zeelenberg, 2009; Nicol et al., 2013), and context memory (Davis et al., 2011); boost the temporal resolution of subsequent visual processing (Bocanegra and Zeelenberg, 2011a, 2011b); and increase the efficiency of visual search (Becker, 2009).

executive control. These intermediate cognitive phenotypes are key features of dispositional negativity and there is compelling evidence that each can contribute to the development and course of anxiety disorders. While important strides have been made at delineating the neural underpinnings of attentional biases to threat, much less scientific attention has been devoted to executive deficits. In the final section, we highlight emerging evidence that these intermediate phenotypes can interact when threat-related cues are present but unrelated to on-going goals. While these new observations provide important insights, they also raise a number of interesting questions. We conclude by outlining some of the most important avenues for future research and some strategies for addressing them.

2 The nature, consequences, and neurobiology of dispositional negativity

2.1 The nature of dispositional negativity

Dispositional negativity or "negative emotionality"—the propensity to experience and express more frequent, intense, or persistent fear, anxiety, and other negative emotions—is a fundamental dimension of childhood temperament and adult personality (Shackman et al., 2016b, 2018a). We conceptualize dispositional negativity as an extended family of closely related phenotypes that first emerge early in development, persist into adulthood, and reflect a combination of heritable and non-heritable factors (Gustavson et al., in press; Kandler et al., n.d.; e.g., Kendler et al., 2018; Roysamb et al., 2018; Savage et al., 2017; Soto and John, 2014; Vukasovic and Bratko, 2015). The psychometric structure of dispositional negativity is relatively invariant across cultures, languages, and ages, at least from elementary school onward (De Pauw, 2017; Kajonius and Giolla, 2017; McCrae et al., 2005; Schmitt et al., 2007; Shiner, 2018; Soto and John, 2014; van Hemert et al., 2002). Individual differences in dispositional negativity are highly reliable, show substantial agreement across instruments and informants, and predict objective behavioral and psychophysiological indices of anxiety in the laboratory, indicating that dispositional negativity is more than just a negative response bias (Back et al., 2009; Borkenau et al., 2001; Brunson et al., 2016; Buss, 1991; Connelly and Ones, 2010; Connolly et al., 2007; Costa Jr. and McCrae, 1988; Fetvadjiev et al., 2018; Holland and Roisman, 2008; Kurtz et al., 2012; McCrae and Costa Jr., 1987; Mõttus et al., 2014; Nuzum et al., in press; Pace and Brannick, 2010; Shackman et al., 2016b; Smith et al., 2016; Soto et al., 2011; Thielmann and Hilbig, 2018; Vazire, 2010; Vazire and Carlson, 2010; Watson et al., 2019). Indeed, core features of this phenotypic family—including increased behavioral inhibition, heightened vigilance, and other signs of fear and anxiety—are expressed similarly across mammalian species, enabling "mechanistic" (i.e., focal perturbation) studies to be performed in rodents and monkeys (Boissy, 1995; Capitanio, 2018; Fox and Kalin, 2014; Mobbs and Kim, 2015; Oler et al., 2016; Qi et al., 2010). Although the molecular pathways underlying dispositional negativity remain poorly understood, some promising candidates have been identified in humans and animals (Alisch et al., 2014, 2017; Fox et al., 2012; Grotzinger et al., 2018; Hill et al., 2018; Kalin et al., 2016; Lo et al., 2017; Luciano et al., 2018; Nagel et al., 2018a, b; Okbay et al., 2016; Oler et al., 2009; Rogers et al., 2013; Roseboom et al., 2014).

2.2 Dispositional negativity confers risk for anxiety disorders and other psychiatric diseases

Dispositional negativity is robustly associated with some of the most common and burdensome mental illnesses, including anxiety disorders, depression, and co-morbid substance abuse (e.g., Castellanos-Ryan et al., 2016; Davis et al., 2018; Hayes et al., 2017; Hengartner et al., 2018; Kendler et al., 2018; Navrady et al., 2017; Paulus et al., 2015; Seeboth and Mottus, 2018; Shackman et al., 2016b). Likewise, dimensional approaches to psychopathology indicate that dispositional negativity is associated with the *p*-factor, a superordinate dimension that encompasses both internalizing and externalizing symptoms (Brandes et al., in press; Caspi and Moffitt, 2018; but cf. Markon, in press; Watts et al., 2019). Longitudinal work shows that individuals with elevated levels of dispositional negativity are more likely to develop internalizing (i.e., anxiety and mood) disorders or experience more severe internalizing symptoms in the future (e.g., Buzzell et al., 2017; Clark et al., 2017a; Goldstein et al., 2018; Klein and Mumper, 2018; Luan et al., 2018; Mu et al., 2016; Struijs et al., 2018; Wichstrom et al., 2018; Zinbarg et al., 2016). The magnitude of these prospective associations is substantial. A recent meta-analysis indicates that nearly half of children who show consistently elevated levels of shyness and behavioral inhibition—a core facet of dispositional negativity—were diagnosed with social anxiety disorder later in life ($N = 692$; risk ratio = 3.4; Clauss and Blackford, 2012). Among adults, data from the Zurich cohort study ($N = 591$) shows that a one standard deviation increase in dispositional negativity at the time of the baseline assessment in 1988 increased the odds of developing an anxiety disorder by 32% and a major depressive episode by 41% during the 20-year follow-up period (Hengartner et al., 2016a). Likewise, a recent meta-analysis of prospective longitudinal studies revealed medium-to-large relations between measures of dispositional negativity and future anxiety symptoms (Cohen's $d = 0.68$), anxiety disorders ($d = 0.48$), depressive symptoms ($d = 0.74$), and major depressive disorder (MDD; $d = 0.50$) ($N = 7748$–$39{,}161$; Jeronimus et al., 2016). Relations between dispositional negativity and internalizing symptoms remain evident after eliminating overlapping item content or adjusting for baseline symptoms and they are magnified by social isolation, social exclusion, and stressor exposure (Frenkel et al., 2015; Gazelle and Rudolph, 2004; Hartley et al., in press; Hengartner et al., 2018; Jeronimus et al., 2016; Kendler et al., 2004; Kopala-Sibley et al., 2016a, b; Lahey et al., 2017; Markovic and Bowker, 2017; Uliaszek et al., 2009; Vinkers et al., 2014). Taken together, these observations suggest that high levels of dispositional negativity represent a diathesis for the internalizing spectrum of disorders (*disposition* × *stressor* → *psychopathology*). Other work suggests that dispositional negativity can promote mental illness by increasing the likelihood of experiences (e.g., loneliness, low self-esteem, difficulty adjusting to university) and events (e.g., conflict, divorce, sickness) that, themselves, confer risk for internalizing illness in vulnerable individuals (*disposition* → *stressor* × *disposition* → *psychopathology*) (Abdellaoui et al., 2018; Clarke et al., 2018; Credé and Niehorster, 2012; Hengartner et al., 2018; Howland et al., 2017; Jocklin et al., 1996; Klimstra et al., 2018; Matthews et al., 2019; Mu et al., 2019; Overstreet et al., 2017; Serrat et al., 2018; Shackman et al., 2016b; Soto, 2019; Tackett and Lahey, 2017).

Among individuals with a history of internalizing illness, higher levels of dispositional negativity are associated with a greater number of diagnoses and a more pessimistic prognosis (e.g., Buckman et al., 2018; Bufferd et al., 2016; Hengartner et al., 2016b; Shackman et al., 2016b; Spinhoven et al., 2016; Struijs et al., 2018).

Consistent with these phenotypic associations, family, twin, and genome-wide association studies (GWAS) show that dispositional negativity is genetically correlated with internalizing symptoms and disorders (Adams et al., 2019; Glahn et al., 2012; Gottschalk and Domschke, 2017; Hettema, 2008; Hill et al., 2018; Howard et al., 2018; Kendler and Myers, 2010; Lee et al., 2019; Levey et al., 2019; Li et al., 2018; Lo et al., 2017; Luciano et al., 2018; Meier et al., 2018; Nagel et al., 2018b; Navrady et al., 2018; Purves et al., 2017; Taylor et al., 2018; Wray et al., 2018). For example, dispositional negativity is genetically associated with anxiety disorders ($r_G = 0.82$, $N = 17{,}310$), depressive symptoms ($r_G = 0.79$, $N = 688{,}809$), and MDD ($r_G = 0.68$, $N = 18{,}759$) (Nagel et al., 2018a). These observations show that dispositional negativity, anxiety disorders, and depression are marked by similar patterns of intergenerational transmission: they "pass down the family tree" in tandem. The sizable magnitude of these genetic correlations indicates strongly overlapping molecular genetic roots, dovetailing with psychometric and clinical evidence of continuity across the internalizing disorders and between normal phenotypic variation in personality in the population and psychopathology (Barlow et al., 2013; Conway et al., n.d.; Sullivan et al., 2018; Waszczuk et al., 2018). Interestingly, "mendelian randomization" analyses (Burgess et al., 2012, 2015; Davey Smith, 2010; Davey Smith and Ebrahim, 2005; Davey Smith et al., 2005; Holmes et al., 2017; Lawlor et al., 2016)—a family of genetic approaches that mitigate some of the most serious limitations of cross-sectional observational studies (e.g., confounding, reverse causation, reporting biases)—suggest that the causal pathways underlying these genetic correlations are similar, with a unidirectional pattern evident for both anxiety disorders and MDD (*disposition → psychopathology*) (Howard et al., 2019; Nagel et al., 2018a; Speed et al., 2018). In the case of depression, molecular genetic and longitudinal studies suggest that the experience of MDD can, over the course of a lifetime, enhance dispositional negativity (*psychopathology → disposition*), although this "scar" effect appears to be substantially weaker than the reverse association (Howard et al., 2019; Nagel et al., 2018a; Ormel et al., 2013).

2.3 Dispositional negativity causally contributes to psychopathology

Dispositional negativity is stable, but not immutable, and can change in response to experience. Like anxiety disorders and depression, dispositional negativity is amplified by exposure to stressors, trauma, and negative life events (Allen and Walter, 2018; Barlow et al., 2017; Bateson et al., 2011; Bentley et al., 2018; Kandler and Ostendorf, 2016; Kornadt et al., 2018; Milojev et al., 2014; Mueller et al., 2018; Roy, 2002; Shackman et al., 2016b; Wilson et al., 2006; Woods et al., 2019), particularly when negative events occur prior to adulthood (Newton-Howes et al., 2015; Ogle et al., 2014; Shiner et al., 2017). On the other hand, there is evidence that dispositional negativity can be attenuated by positive experiences, such as job promotions and marriage (Denissen et al., n.d.; Klimstra et al., 2018; Schalet et al., 2016;

Shackman et al., 2016b). Likewise, genetic analyses of data gleaned from the UK Biobank ($N = 328{,}917$) suggest that increased educational attainment tends to reduce dispositional negativity (Nagel et al., 2018a). Other work demonstrates that dispositional negativity is sensitive to clinical interventions targeting anxiety and depression, including pharmacological interventions (Schalet et al., 2016; Widiger et al., 2019). In a comprehensive meta-analysis of clinical intervention studies ($k = 199$ studies), Roberts and colleagues showed robust reductions in dispositional negativity following psychosocial or pharmacological treatment for internalizing disorders (Cohen's $d = 0.59$ for pre vs post; $d = 0.69$ for treatment vs controls; Roberts et al., 2017). Likewise, childhood interventions targeting heightened dispositional negativity reduce the likelihood of future internalizing problems (Rapee and Bayer, 2018). Taken together, these more mechanistic observations suggest that elevated levels of dispositional negativity causally contribute to the development and maintenance of internalizing disorders.

2.4 Relevance of the amygdala to dispositional negativity

The neural circuits governing trait-like individual differences in dispositional negativity have only recently started 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), midcingulate cortex, orbitofrontal cortex, and periaqueductal gray (Avery et al., 2016; Cavanagh and Shackman, 2015; Fox and Kalin, 2014; Fox and Shackman, 2019; Kalin, 2017; Kirlic et al., 2019; Lowery-Gionta et al., 2018; Shackman and Fox, 2016; Shackman et al., 2011b, 2016b). While all of these regions are important, here we focus on the most intensely scrutinized component of this system, the amygdala, a heterogeneous collection of nuclei buried beneath the temporal lobe (Freese and Amaral, 2009; Yilmazer-Hanke, 2012) (Fig. 1). Anatomically, the amygdala is poised to use information from sensory, contextual, and regulatory regions to assemble a range of reactions via dense mono- and polysynaptic 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 and Whalen, 2001; Fox et al., 2015b; Freese and Amaral, 2009; Fudge et al., 2017; Lapate and Shackman, 2018) (Fig. 1). Functional neuroimaging studies in monkeys and humans demonstrate that many of these downstream regions show robust connectivity with the amygdala, reinforcing the possibility that they represent coherent functional circuits that are relevant to human experience and disease (Birn et al., 2014; Fox et al., 2018b; Gorka et al., 2018; Tillman et al., 2018; Torrisi et al., 2015, 2018).

Human imaging research demonstrates that the amygdala is engaged by a broad range of unpleasant and potentially threat-relevant stimuli (Costafreda et al., 2008; Fox and Shackman, 2019; Fusar-Poli et al., 2009; Lindquist et al., 2016; Naaz et al., 2019; Price et al., 2018; Sabatinelli et al., 2011; Sergerie et al., 2008). Recent high-resolution fMRI research indicates that the dorsal-posterior amygdala—in the approximate location of the central nucleus (Ce) (cf. Fig. 1)—is particularly sensitive

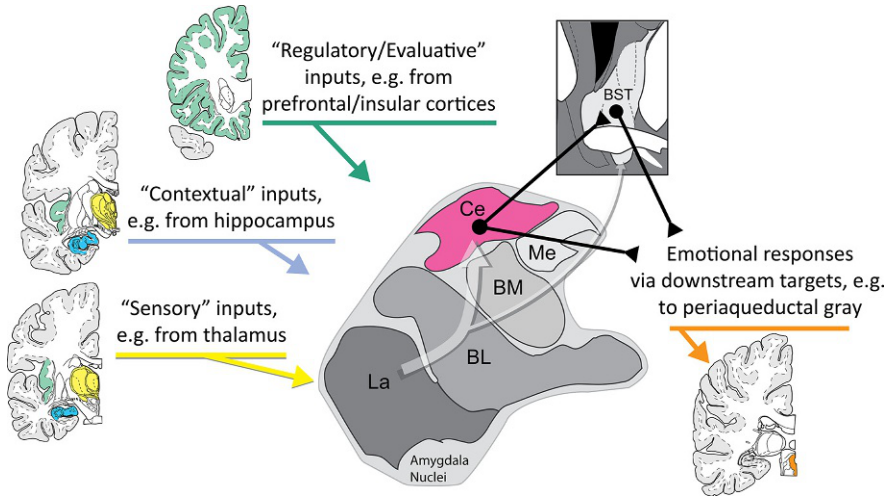

FIG. 1

Simplified schematic of amygdala circuitry relevant to dispositional negativity, attentional biases, and hypervigilance 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. Abbreviations: BL, basolateral; BM, basomedial; Ce, central; La, lateral; Me, medial nuclei of the amygdala; BST, bed nucleus of the stria terminalis. BM is often termed the "accessory basal" (AB) nucleus. The term "basolateral amygdala" (BLA) is often used to refer to the basal and lateral nuclei.

Figure adapted with permission from Tillman, R.M., Stockbridge, M.D., Nacewicz, B.M., Torrisi, S., Fox, A.S., Smith, J.F., Shackman, A.J., 2018. Intrinsic functional connectivity of the central extended amygdala. Hum. Brain Mapp. 39, 1291–1312.

to aversive visual stimuli (Hrybouski et al., 2016). Increased activation in this region has, in turn, been associated with elevated signs and symptoms of arousal in response to threat (Fox and Shackman, 2019; Sjouwerman et al., 2017). More recent work has leveraged machine-learning approaches to show that the dorsal-posterior amygdala (in the region of the Ce) is a key component of circuits that underlie negative affect elicited by aversive photographs (Chang et al., 2015) and that distinguish conditioned threat (CS+) from safety (CS−) (Reddan et al., 2018) (see also Taschereau-Dumouchel et al., 2019).

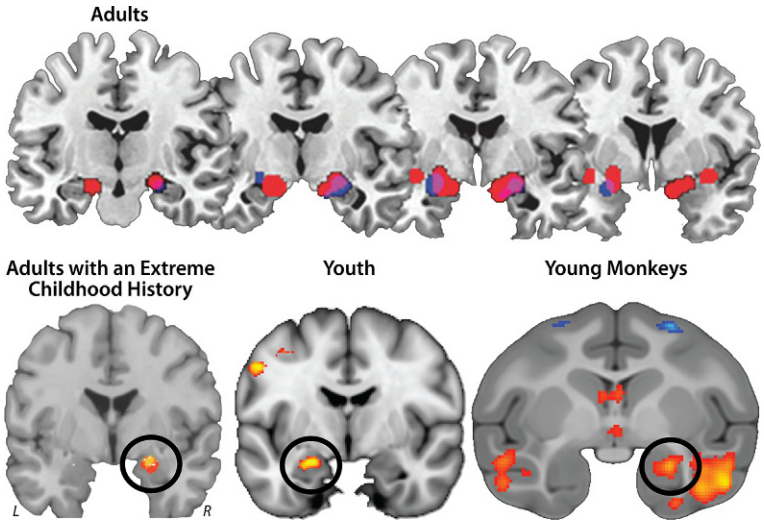

FIG. 2

Elevated dispositional negativity is associated with increased activity in the dorsal amygdala in the region of the Ce. *Adults*. Meta-analysis of six published imaging studies reveals consistently elevated activation bilaterally in the dorsal amygdala among adults with a more negative disposition (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*. *Adults with an extreme childhood history*. Meta-analysis of seven published imaging studies reveals consistently elevated activation in the dorsal amygdala (*black ring*) in adults with a childhood history of elevated dispositional negativity (Fox and Kalin, 2014). Six of eight amygdala peaks overlapped (*yellow*) in the dorsal amygdala; four of the peaks extended into the region shown in *red*. *Youth*. Using arterial spin labeled (ASL) functional MRI acquired in the absence of an explicit task (at rest) from 878 youth ($M = 16.5$ years, range = 12–23 years), Kaczkurkin and colleagues (2016) demonstrated that individuals with a more negative disposition show elevated perfusion in the dorsal amygdala (*black ring*). Panel depicts the results of a voxelwise regression analysis. *Young monkeys*. Using high-resolution 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) acquired from 592 young rhesus monkeys, Fox and colleagues (2015a, b) showed that threat-related metabolic activity in the dorsal amygdala (*black ring*) is increased among individuals with a more negative disposition. Abbreviations: *L*, left hemisphere; *R*, right hemisphere. Panel depicts the results of a voxelwise regression analysis.

Portions of this figure were adapted with permission from Calder, A.J., Ewbank, M.P., Passamonti, L., 2011. Personality influences the neural responses to viewing facial expressions of emotion. Philos. Trans. R. Soc. B 366, 1684–1701; Fox, A.S., Kalin, N.H., 2014. A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. Am. J. Psychiatr. 171, 1162–1173; Fox, A.S., Oler, J.A., Shackman, A.J., Shelton, S.E., Raveendran, M., McKay, D.R., et al., 2015a. Intergenerational neural mediators of early-life anxious temperament. Proc. Natl. Acad. Sci. U. S. A. 112, 9118–9122; Kaczkurkin, A.N., Moore, T.M., Ruparel, K., Ciric, R., Calkins, M.E., Shinohara, R.T., et al., 2016. Elevated amygdala perfusion mediates developmental sex differences in trait anxiety. Biol. Psychiatry 80, 775–785.

Brain imaging studies provide compelling evidence that adults and youth with a more negative disposition are prone to increased or prolonged activity in the dorsal-posterior amygdala (Fig. 2). This has been observed both at "rest" (i.e., in the absence of an explicit task) and in response to novelty, negative emotional faces, unpleasant images, and conditioned threat cues (CS+) (e.g., Coombs 3rd et al., 2014; Gaffrey et al., 2016; Kann et al., 2017; Shackman et al., 2016b; Sjouwerman et al., 2017; Stout et al., 2017). For example, Kaczkurkin and colleagues used a large peri-adolescent youth dataset ($N = 875$) to show that adolescent women are marked by a more negative disposition, on average, compared to adolescent men (consistent with other large-scales studies; Shackman et al., 2016b) and that this sex difference reflects elevated "resting" perfusion in the dorsal amygdala (*female*-vs-*male* → *resting amygdala activity* → *disposition*) (Kaczkurkin et al., 2016). The association between dispositional negativity and task-related amygdala reactivity appears to be amplified among individuals with lower levels of perceived social support (Hyde et al., 2011), an important risk factor for the development of internalizing disorders (Kendler and Gardner, 2014; Shackman et al., 2018b).

Studies of nonhuman primates afford an important opportunity to obtain concurrent measures of brain metabolism and naturalistic defensive responses to ethologically relevant threats—something that would be difficult to accomplish in humans, given the sensitivity of functional MRI to even modest amounts of motion artifact (Ciric et al., 2018), and the challenges of eliciting robust fear and anxiety in the laboratory (Shackman and Wager, 2019). Using fluorodeoxyglucose-positron emission tomography (FDG-PET) in samples encompassing as many as 592 individuals, we have demonstrated that metabolic activity in the Ce (Fig. 2) is associated with heightened behavioral and neuroendocrine reactions to naturalistic threat (Fox and Kalin, 2014; Fox et al., 2015a). Ce metabolism is moderately stable over time and context and, as such, represents a trait-like feature of brain function (Fox et al., 2008). For example, Fox and colleagues showed that metabolic activity in the Ce during exposure to an unfamiliar human intruder's profile showed an intra-class correlation (ICC) of 0.64 across three occasions over a 1.1-year span, similar to the concurrent re-test stability of dispositional negativity in young monkeys (ICC = 0.72; Fox et al., 2012; see also Shackman et al., 2013, 2017) and the 5-year stability of dispositional negativity in humans (partial $R = 0.60$; $N = 56{,}735$; Hakulinen et al., 2015). Other work in nonhuman primates suggests that elevated activity in the Ce is a core substrate for different presentations of dispositional negativity (Fig. 3). Like humans, individual monkeys have different ways of expressing their extreme disposition. Some characteristically respond to threat with high levels of the stress-sensitive hormone cortisol (and average levels of behavioral inhibition), whereas others show the reverse profile. Yet across these different phenotypes, we have observed a remarkably consistent pattern of elevated metabolism in the Ce (Shackman et al., 2013). This observation is broadly consistent with evidence suggesting that elevated amygdala reactivity to threat-related cues is a transdiagnostic marker of the internalizing disorders in humans (Etkin and Wager, 2007; Hamilton et al., 2012).

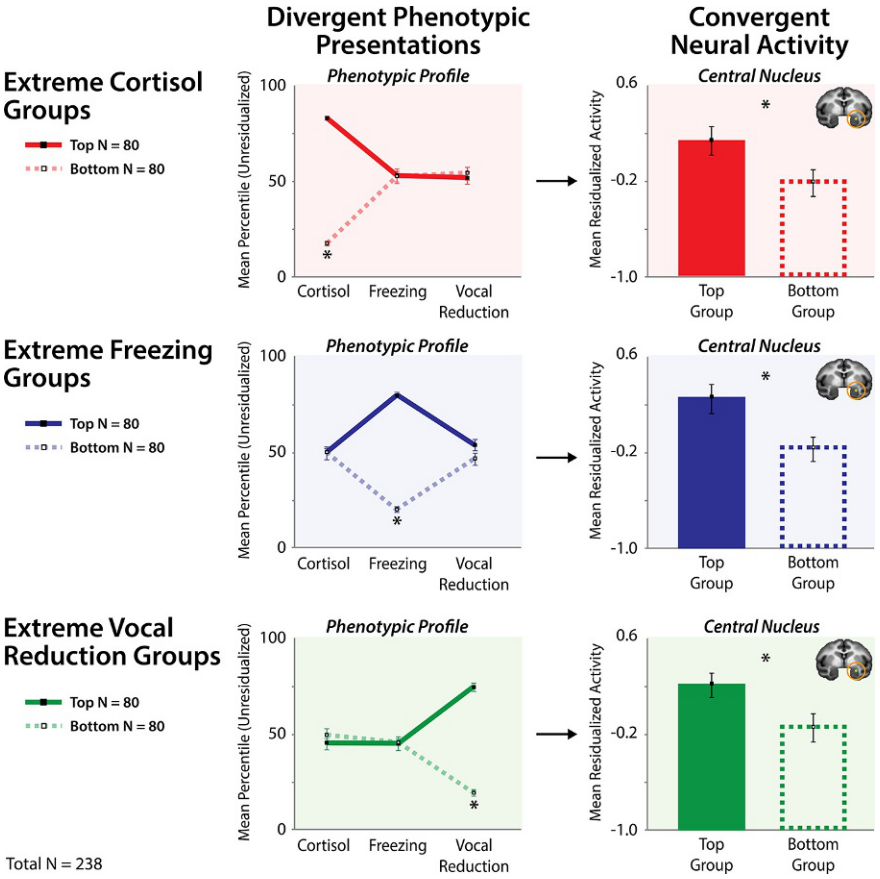

FIG. 3

Elevated amygdala activity is a shared substrate for different phenotypic presentations of dispositional negativity. Shackman et al. (2013) used a well-established young nonhuman primate model of childhood dispositional negativity and high-resolution FDG-PET to demonstrate that individuals with divergent phenotypic presentations of their extreme disposition show increased activity in the Ce (*orange rings*). *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 phenotypic 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.

Figure adapted with permission from Shackman, A.J., Fox, A.S., Oler, J.A., Shelton, S.E., Davidson, R.J., Kalin, N.H., 2013. Neural mechanisms underlying heterogeneity in the presentation of anxious temperament. Proc. Natl. Acad. Sci. U. S. A. 110, 6145–6150.

Like the internalizing disorders, dispositional negativity is moderately heritable in humans and monkeys (Fox et al., 2015a; Shackman et al., 2016b). Recent work in nonhuman primates demonstrates that the neural circuitry underlying trait-like individual differences in dispositional negativity can be genetically fractionated. Metabolic activity in the Ce, while heritable, appears to be more relevant to understanding variation in dispositional negativity attributable to experience, such as stressor exposure ($h^2 = 0.26$, r_G = n.s., $N = 592$) (Fox et al., 2015a) (Fig. 2). In contrast, functional connectivity between the Ce and BST (Fig. 4A) appears to be more relevant to understanding heritable variation in dispositional negativity and, hence, to the intergenerational transmission of risk from parents to their offspring ($h^2 = 0.45$, $r_G = 0.87$, $N = 378$) (Fox et al., 2018b). Whether this pattern translates to humans remains unknown, making it a key challenge for future research.

Recent work has begun to move beyond the amygdala and clarifies the architecture of the distributed neural circuitry underlying dispositional negativity (Fox and Shackman, 2019; Shackman et al., 2016b). For example, using a combination of chronic electrophysiological recordings, experience sampling, and machine learning, Kirkby and colleagues showed that momentary fluctuations in negative mood are reliably associated with the functional connectivity of a circuit linking the posterior-dorsal amygdala to the hippocampus, and that this association was only evident among individuals with a more negative disposition (Kirkby et al., 2018) (Fig. 4B). Work using more conventional fMRI techniques demonstrates that young monkeys with elevated levels of dispositional negativity and children with anxiety disorders show reduced functional connectivity between the Ce and dorsolateral prefrontal cortex (dlPFC) at "rest" (Fig. 4C). Monkeys with a more negative disposition also showed reduced functional connectivity between the Ce and mesial prefrontal cortex (mPFC)—including regions of the pregenual anterior cingulate (pgACC)—broadly consistent with work in human adults (Kim et al., 2011; Pezawas et al., 2005).[b] Taken together, this suggests that alterations in these evolutionarily conserved functional circuits may confer risk for the development of pathological anxiety (Birn et al., 2014; Oler et al., 2016). More broadly, these observations show that core features of personality and temperament—features that confer increased risk for mental illness—are embodied in the spontaneous activity of the brain, in the absence of overt trait-relevant challenges. An important avenue for future research will be to use focal perturbations, pharmacological interventions, or other mechanistic approaches to clarify the causal contribution of this circuitry to dispositional negativity and psychopathology (Dubois et al., n.d.; Grayson et al., 2016; Kalin et al., 2016). Prospective longitudinal studies will be required to understand the relevance of this circuitry to the emergence of psychopathology.

[b]Although other studies in youth have identified relations between amygdala-mPFC functional connectivity and anxiety, the sign of the association (i.e., *hyper*- vs *hypo*-connectivity) has proven inconsistent, potentially reflecting differences in sample age, analytic approach, or the specific amygdala nuclei examined (Gee et al., 2013; Jalbrzikowski et al., 2017; Qin et al., 2014).

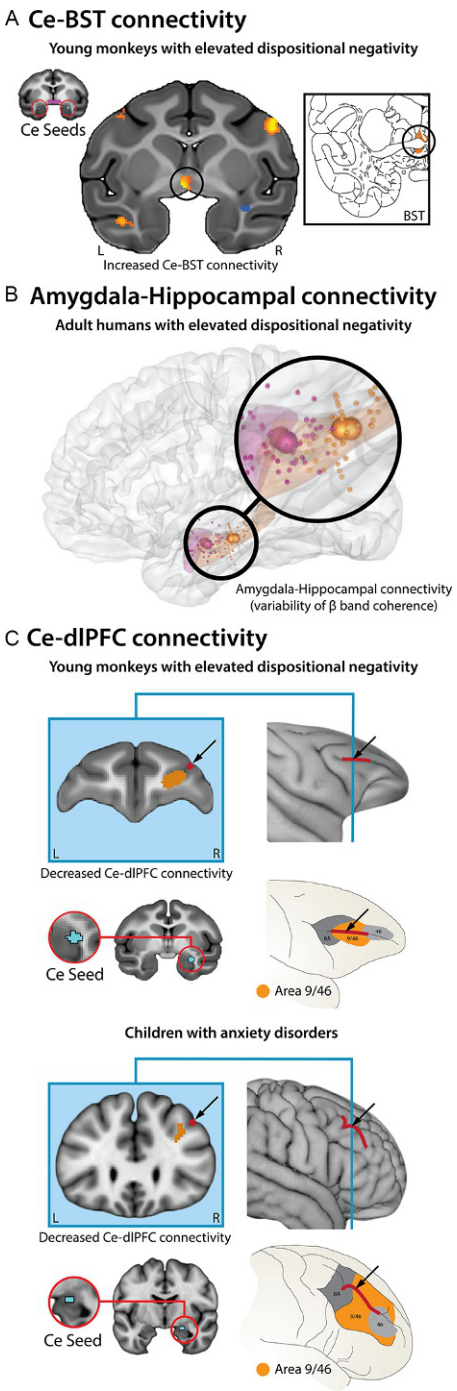

FIG. 4

See legend on opposite page.

2.5 The amygdala causally contributes to extreme fear and anxiety

Mechanistic work in rodent models demonstrates that neuronal microcircuits encompassing the Ce are critical for orchestrating defensive responses to a wide variety of threats (Choi and Kim, 2010; Fox and Shackman, 2019; Gungor and Paré, 2016; Pliota et al., 2018; Pomrenze et al., 2019; Tovote et al., 2015). Other work indicates a role in dispositional negativity (Fadok et al., 2018). For example, Ahrens and colleagues showed that anxious, behaviorally inhibited mice are characterized by tonically elevated activity in a specific type of Ce neurons—cells within the lateral division that expresses somatostatin and project to the BST (Ahrens et al., 2018)—consistent with the much coarser results revealed by FDG-PET and arterial spin labeling (ASL) perfusion fMRI studies of humans and monkeys (Abercrombie et al., 1998; Canli et al., 2006; Fox et al., 2008; Kaczkurkin et al., 2016). In an elegant series of experiments, Ahrens and colleagues demonstrated that these neurons are

FIG. 4

Elevated dispositional negativity is associated with alterations in Ce functional connectivity. (A) Ce-BST connectivity. Fox and colleagues (2018a, b) used fMRI to demonstrate that functional connectivity between the Ce (*red rings*) and BST (*black rings*) is associated with elevated dispositional negativity in a sample of 378 young monkeys drawn from an extended 8-generation pedigree ($N = 1928$). They also showed that Ce-BST functional connectivity is genetically correlated with individual differences in dispositional negativity, indicating an overlapping pattern of intergenerational transmission. *Inset* depicts the corresponding plane of the rhesus brain atlas. (B) Amygdala-Hippocampal connectivity. Kirkby et al. (2018) used a combination of intracranial electrophysiological recordings, experience sampling, and machine-learning techniques to identify an amygdala-hippocampal functional network (i.e., temporal variability of coherence in the β-band; 13–30 Hz) that reliably predicted momentary fluctuations in negative mood among treatment resistant, adult epilepsy patients with elevated levels of dispositional negativity. Figure depicts the spatially normalized centroid locations of amygdala (*magenta*) and hippocampal (*orange*) recording electrodes. (C) Ce-dlPFC connectivity. Birn et al. (2014) demonstrated that young monkeys with elevated levels of dispositional negativity (*top*) and children with anxiety disorders (*bottom*) show a similar pattern of reduced functional connectivity between the Ce (*red rings*) and dorsolateral PFC (dlPFC; *black arrows*). Pediatric imaging data were collected while patients were quietly resting. Nonhuman primate data were collected under anesthesia, eliminating potential individual differences in scanner-elicited apprehension or neuroendocrine activation (cf. Shackman et al., 2016b). Abbreviations: *L*, left hemisphere; *R*, right hemisphere.

Portions of this figure were adapted with permission from Birn, R.M., Shackman, A.J., Oler, J.A., Williams, L.E., McFarlin, D.R., Rogers, G.M., et al., 2014. Evolutionarily conserved dysfunction of prefrontal-amygdalar connectivity in early-life anxiety. Mol. Psychiatry 19, 915–922; Fox, A.S., Oler, J.A., Birn, R.M., Shackman, A.J., Alexander, A.L., Kalin, N.H., 2018c. Functional connectivity within the primate extended amygdala is heritable and predicts early-life anxious temperament. J. Neurosci. 38, 7611–7621; Kirkby, L.A., Luongo, F.J., Lee, M.B., Nahum, M., Van Vleet, T.M., Rao, V.R., et al., 2018. An amygdala-hippocampus subnetwork that encodes variation in human mood. Cell 175, 1688–1700.

sensitive to uncertain danger (i.e., unpredictable shock) and that they are both necessary and sufficient for heightened defensive responses (e.g., freezing) to novelty and diffuse threat (e.g., a brightly lit open field). This and other recent studies that have exploited the cellular precision afforded by opto- and chemogenetic techniques make it abundantly clear that the Ce, like many other brain regions, harbors a variety of intermingled cell "types"—populations of neurons that can be distinguished based on their protein expression, firing characteristics, connectivity, and other features—and that different cell types within the Ce perform distinct, even opposing functional roles (Fox and Shackman, 2019; Pignatelli and Beyeler, 2018). The upshot is that research that relies on traditional lesion techniques, pharmacological interventions, or in vivo imaging techniques will necessarily reflect a mixture of cells and signals. Making sense of this complexity and identifying the circuit components most relevant to human experience and psychiatric disease represent important avenues for future research.

While our understanding of the primate amygdala lags behind that of rodents, work in monkeys and humans suggests that this region is crucial for extreme anxiety. In monkeys, fiber-sparing (excitotoxic) lesions of the amygdala—of the Ce in particular—have been shown to attenuate defensive behaviors and endocrine responses to a range of learned and innate threats (Davis et al., 2008; Kalin et al., 2016; Oler et al., 2016). These observations are consistent with studies of humans with disease-related amygdala damage (Bechara et al., 1995; Feinstein et al., 2011, 2016; Klumpers et al., 2015; Korn et al., 2017). Patient SM, for example, is marked by near-complete bilateral destruction of the amygdala and shows a profound lack of fear and anxiety—whether measured objectively or subjectively—to both diffusely threatening contexts (e.g., a haunted house) and acute threat cues (e.g., spiders, snakes, clips of horror films, conditioned threat cues, "jump-scares" in the haunted house, and even real-world assault) (Feinstein et al., 2011). Moreover, SM reports abnormally low levels of dispositional negativity when assessed using standard psychometric measures (Feinstein et al., 2011), consistent with clinical assessments of her temperament (Tranel et al., 2006). An important caveat is that SM's deficits may reflect damage to fibers of passage or more subtle functional disconnections (Davis and Whalen, 2001; Fox and Shackman, 2019; R. Adolphs, Personal communication, 24 July 2017). It also merits comment that SM and other patients with substantial amygdala damage can experience fear, even panic attacks, in the laboratory in response to breathing air enriched with CO_2 (Feinstein et al., 2013; Khalsa et al., 2016). On balance, this body of work teaches us that the amygdala is not a fear or anxiety center, per se, but instead plays a critical role in assembling responses to threats encountered in the external environment.

Other research has examined the consequences of amplifying amygdala activity. Work in monkeys shows that genetic manipulations that increase metabolic activity in the Ce potentiate signs of anxiety (Kalin et al., 2016), in broad accord with rodent studies (Ahrens et al., 2018). Electrical stimulation studies in humans have revealed a more complex pattern of results (Inman et al., 2018). Subjective responses to amygdala stimulation are infrequent, likely due to heterogeneity in electrode placement

(C. Inman, Personal communication, 24 March 2018). Nevertheless, when feelings are reported, they are typically described as a heightened state of negative affect and can be quite robust (Inman et al., 2018). Inman and colleagues recently described an individual (subject 8) who experienced intense fear and anxiety in response to 6 V stimulation in the region of the right Ce: "It was, um, it was terrifying, it was just…it was like I was about to get attacked by a dog…like someone unleashes a dog on you, and it's just like it's so close, and you feel like you're going to s*** your pants. It's terrifying." At 8 V, he asked to terminate the stimulation, saying "that was so scary it was nauseating. It's like, um, I went zip-lining a few weeks ago…and this was worse" (Inman et al., 2018).[c] Such feelings were never reported during intermixed sham trials. Taken together, the results of lesion and stimulation studies suggest that a circuit centered on the Ce is necessary and sufficient for many of the core signs and symptoms of anxiety.

2.6 Relevance of the amygdala to psychopathology

Four lines of evidence motivate the hypothesis that elevated amygdala reactivity contributes to the development and maintenance of mental illness. Amygdala activation:

1. Is elevated in children, adolescents, and adults with internalizing disorders and individuals with a positive family history (Shackman et al., 2016a). Heightened "resting" activity has also been found in psychotic patients marked by elevated levels of paranoia and negative affect (Pinkham et al., 2015; Stegmayer et al., 2017). Amygdala activation has also been shown to co-vary with the severity of anxious symptoms, albeit less consistently (Thomas et al., 2001; van den Bulk et al., 2014).
2. Is amplified by exposure to the same kinds of stressors and psychological pathogens (e.g., combat, childhood maltreatment) that can precipitate acute mental illness in dispositionally vulnerable individuals (Hein and Monk, 2017; McCrory et al., 2017; Shackman et al., 2016a; Teicher et al., 2016).
3. Prospectively predicts heightened internalizing symptoms among adolescents and young adults exposed to stress, trauma, or negative life events (Admon et al., 2009; Stevens et al., 2017; Swartz et al., 2015a). 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). Among preschool-aged children, amygdala activation prospectively predicts heightened negative affect (Gaffrey et al., 2016).
4. Is attenuated by clinically effective cognitive-behavioral and pharmacological (e.g., benzodiazepine) treatments for anxiety and depression in adults

[c]A video record of the stimulation is available at: https://doi.org/10.1016/j.neuropsychologia.2018.03.019.

(Månsson et al., 2016; Shackman et al., 2016a). More recent work shows that amygdala reactivity is also dampened by low to moderate doses of ethyl alcohol (Hur et al., 2018), a well-established anxiolytic that, like the benzodiazepines, enhances inhibitory neurotransmission in the Ce (Bartholow et al., 2012; Kaye et al., 2017; Sharko et al., 2016). These observations suggest that the amygdala causally contributes to pathological anxiety in humans, consistent with the mechanistic work reviewed in the prior section.

2.7 Interim conclusions

Dispositional negativity is a well-established diathesis for the internalizing spectrum of disorders. Children and adults with a more negative disposition are more likely to develop anxiety disorders and depression if they experience the appropriate precipitants (e.g., negative life events, chronic stress). Dispositional negativity can be conceptualized as an extended family of complex phenotypes that reflect multiple brain circuits and molecular pathways. Converging lines of epidemiological, imaging, mechanistic, and clinical evidence suggest that specific populations of neurons in the amygdala, particularly those harbored within the Ce: (a) underlie core features of dispositional negativity in humans and other mammals, (b) exert bidirectional control over defensive responses to threat and subjective feelings of fear and anxiety, and (c) causally contribute to the development of anxiety and mood disorders.

3 The nature, consequences, and neurobiology of attentional biases to threat

Alterations in vigilance, risk assessment, and other aspects of attention are hallmarks of dispositional negativity and anxiety (Blanchard et al., 2001; Grupe and Nitschke, 2013; Shackman et al., 2016a). Attention is a fundamental property of perception and cognition. Attentional mechanisms prioritize the most relevant sources of information while inhibiting or ignoring potential distractions and competing courses of action (Desimone and 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 remembered. Thus, attention involves both stimulus selection and the intensity of processing once a stimulus has been selected.

3.1 The nature of attentional biases to threat

Threat-related stimuli—whether learned (CS+) and unlearned (e.g., spiders)—can strongly influence 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 (Shackman et al., 2016a). 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 detection of the stimuli (Shackman et al., 2016a).

3.2 Relevance of attentional biases to dispositional negativity and anxiety disorders

Heightened vigilance and exaggerated risk assessment behaviors to threat-related cues are hallmarks of dispositional negativity and pathological anxiety (Grupe and Nitschke, 2013). Like many patients with anxiety disorders, adults and youth with a more negative disposition tend to allocate excess attention to threat-related cues, even when they are task irrelevant (Pérez-Edgar et al., 2017; Shackman et al., 2016a; Silvers et al., 2017). On average, dispositionally negative adults are more likely to initially orient their gaze toward 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 (Armstrong and Olatunji, 2012; Cisler and Koster, 2010; Rudaizky et al., 2014; Sheppes et al., 2013). Meta-analyses indicate that youth with elevated levels of dispositional negativity or 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 to emotionally neutral stimuli ($k = 16$ studies; mean Cohen's $d = 0.54$; Dudeney et al., 2015). Although the latter effect is similar to that reported in adult studies ($k = 101$ studies; mean Cohen's $d = 0.45$; Bar-Haim et al., 2007), recent large-scale studies suggest that the size of these effects is likely to be somewhat misleading. For example, a recent meta-analysis of clinical studies using various dot-probe[d] tasks failed to uncover evidence of a significant threat bias in 1005 anxiety patients (Kruijt et al., 2018). Eye-tracking studies have often failed to demonstrate enhanced threat detection or hypervigilance in pathologically anxious adults, although they have revealed consistent evidence of sustained attention to threat (e.g., increased dwell time) (Lazarov et al., 2016, 2019), consistent with evidence that adults with a more negative disposition are particularly impaired in disengaging from threat-related cues (Sheppes et al., 2013). Using data gleaned from a large ($N = 1291$) international sample of youth, Abend and colleagues reported a zero-order correlation of $r = 0.08$ between anxiety symptoms and attentional biases to threat, again, indexed using the dot-probe (Abend et al., 2018). The modest size of this association likely reflects multiple factors, including the suboptimal psychometric properties of dot-probe tasks (McNally, 2018; Price et al., 2015; Rodebaugh et al., 2016), an exclusive reliance on social threat (angry faces), and unmeasured heterogeneity in the nature of attentional biases (e.g., initial vigilance followed by avoidance; Armstrong and Olatunji, 2012; Di Simplicio et al., 2014; Mogg et al., 2017; Naim et al., 2015; Onnis et al., 2011; Roy et al., 2015; Waters et al., 2015; Weierich et al., 2008; Zvielli et al., 2014). Developing tools for reliably quantifying these more nuanced cognitive biases represents a crucial direction for future research (Liu et al., 2018; MacLeod, 2019).

[d]In the "dot-probe" paradigm, subjects view 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 ms), 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.

3.3 Attentional biases to threat causally contribute to pathological anxiety

Several lines of evidence suggest that attentional biases to threat-related cues can causally contribute to the development of pathological anxiety. Attentional biases to threat have been shown to promote inflated estimates of threat intensity or likelihood (Aue and Okon-Singer, 2015)—a key feature of extreme anxiety (Grupe and Nitschke, 2013; Stuijfzand et al., 2018)—and to foreshadow the development of social inhibition in children (Kiel and Buss, 2011). 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. Among youth with an early history of extreme dispositional negativity, it is the subset who also show an attentional bias to threat who are most likely to exhibit social withdrawal and elevated anxiety symptoms in the future (Pérez-Edgar et al., 2010a, 2011; White et al., 2017). Moreover, there is some evidence that clinically effective cognitive-behavioral and pharmacological treatments for anxiety can reduce attentional biases to threat-related cues, with greater therapeutic gains among patients showing larger reductions in attentional biases (Hadwin and Richards, 2016; Reinholdt-Dunne et al., 2015; Shackman et al., 2016a). Direct support for a causal role comes from meta-analyses of computer-based interventions aimed at reducing attentional biases to threat, often termed "attention bias modification" (ABM). For example, Heeren and colleagues reported a small-to-medium reduction in social anxiety symptoms ($g = 0.27$) and reactivity to a public speaking challenge ($g = 0.46$) ($N = 1043$; Heeren et al., 2015). Among adult clinical samples, small-to-medium treatment effects have been observed when ABM is compared to placebo training (Linetzky et al., 2015; MacLeod and Clarke, 2015; Price et al., 2016b), although the precise size and consistency of such effects remain contentious (Cristea, 2018; Cristea et al., 2015; Grafton et al., 2017, 2018; Kruijt and Carlbring, 2018; Mogg and Bradley, 2016, 2018; Mogg et al., 2017). Results have been less consistent in pediatric clinical samples (Hardee et al., 2013; Liu et al., 2018; Shackman et al., 2016a). Broadly speaking, across this literature the most promising clinical effects have been found in studies where ABM was delivered in the clinic or laboratory and produced evidence of "target engagement," that is, a demonstrable reduction in attentional biases to threat-related cues (Grafton et al., 2017; MacLeod and Grafton, 2016; Mogg and Bradley, 2018; Notebaert et al., 2018b; Price et al., 2016b). Indeed, Heeren and colleagues reported a substantial between-study covariation ($k = 8$ studies, $r = 0.90$) between ABM-induced reductions in attentional biases and experimentally elicited anxiety (Heeren et al., 2015). On balance, these observations are consistent with the idea that attentional biases to threat can causally contribute to the development of anxiety disorders.

3.4 Relevance of the amygdala to attentional biases to threat

The neural mechanisms underlying attentional biases to threat remain poorly understood, particularly in youth. Nonetheless, there is compelling evidence that the prioritized processing of threat-related cues reflects the influence of neural circuits

encompassing the amygdala. Imaging and single unit recording studies 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 (Méndez-Bértolo et al., 2016; Minxha et al., 2017; Shackman et al., 2016a). Increased amygdala activation is even observed using subliminal or task-irrelevant emotional stimuli (Brooks et al., 2012; Cromheeke and Mueller, 2014; Hung et al., 2018; Krug and Carter, 2010) and has been associated with more severe symptoms in pediatric anxiety patients (Monk et al., 2008). Among children, heightened amygdala activation is associated with enhanced detection of threat-related faces in a crowed array and, among those exposed to early deprivation, greater amygdala activation is associated with elevated anxiety symptoms (Silvers et al., 2017). Among adults, individuals with a more negative disposition show heightened amygdala activation and enhanced attentional capture (i.e., response slowing) to threat-related cues, even when they are task irrelevant (Ewbank et al., 2009). Likewise, adults and children with anxiety disorders have been shown to exhibit increased amygdala activation and exaggerated behavioral interference when performing standard "emotional attention" tasks (e.g., emotional Stroop, dot-probe; Boehme et al., 2015; Price et al., 2016a).

As shown in Fig. 5A, anatomical tracing studies in nonhuman primates and mechanistic studies in rodents indicate 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 excitatory projections from the basolateral (BL) nucleus of the amygdala (Fig. 1) to the relevant areas of sensory cortex (e.g., fusiform face area) and *indirectly*, via projections from the basal nuclei and Ce 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 and Whalen, 2001; Freese and 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—consistent with single unit recording studies in monkeys (Peck et al., 2014)—and demonstrate that this association is statistically mediated by enhanced activation in the relevant areas of sensory cortex (Lim et al., 2009) (Fig. 5B). Determining whether this distributed amygdalo-cortical circuitry is altered in individuals with a negative disposition or anxiety disorder remains an important challenge for the future.

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 attentional biases 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. Fig. 1) and amplifies attentional biases to angry faces in a 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 et al., 2004).

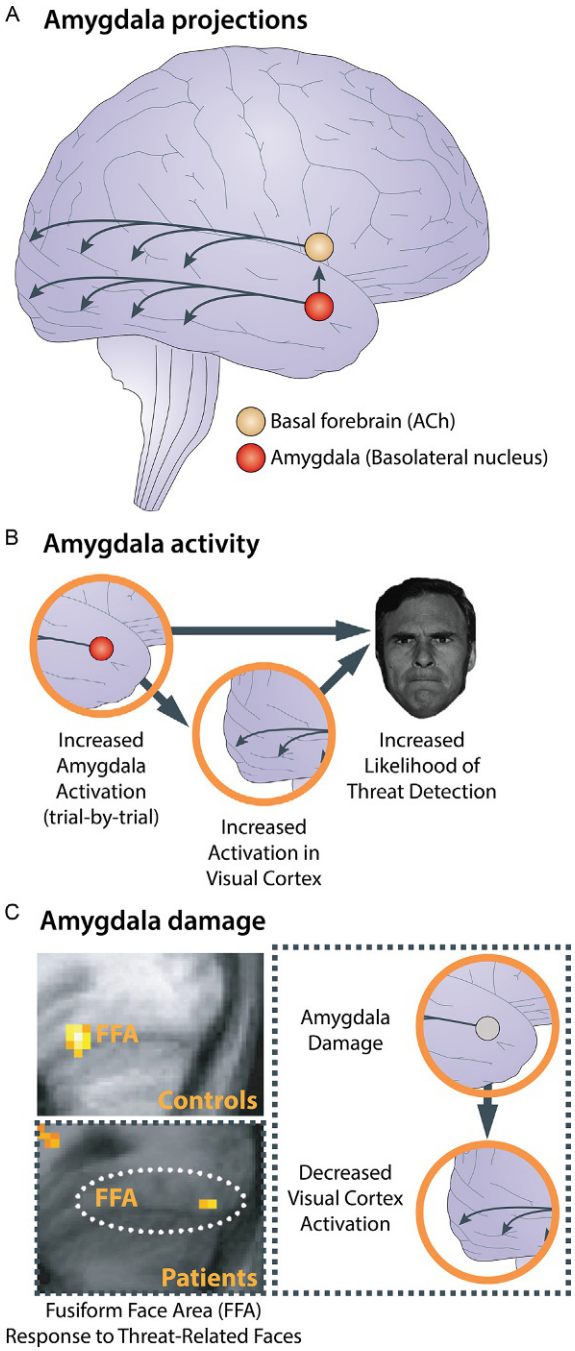

FIG. 5

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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) (Fig. 5C) and inferior temporal cortex in monkeys (Hadj-Bouziane et al., 2012). In humans, amygdala damage disrupts the prioritized processing of threat-related faces in crowded stimulus arrays (Bach et al., 2015). Likewise, monkeys' normal preference for viewing conspecific faces is disrupted by fiber-sparing (excitotoxic) lesions of the amygdala (Taubert et al., 2018).[e]

Other work suggests that the amygdala can actively tune attention. 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

FIG. 5

The amygdala plays a key role in enhancing attention to threat-relevant information. (A) Amygdala projections. Anatomical tracing studies in monkeys and mechanistic studies in rodents indicate that the amygdala can enhance vigilance and prioritize the processing of threat-relevant information *directly*, via monosynaptic projections from the basolateral nucleus (BL; see Fig. 1) to sensory cortex, and *indirectly*, via projections from the basal nuclei and central nucleus (Ce) to ascending neuromodulatory 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. Using fMRI, 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 amygdala activation and detection performance were explained by increased activation in the visual cortex, consistent with work in animals. (C) Amygdala damage. In a seminal study, Vuilleumier et al. (2004) 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 in humans. This observation has since been replicated using more selective chemical lesions in monkeys (Hadj-Bouziane et al., 2012). Abbreviations: *ACh*, acetylcholine; *FFA*, fusiform face area.

Portions of this figure were adapted with permission from Tang, Y.Y., Holzel, B.K., Posner, M.I., 2015. The neuroscience of mindfulness meditation. Nat. Rev. Neurosci. 16, 213–225; Vuilleumier, P., Richardson, M.P., Armony, J.L., Driver, J., Dolan, R.J., 2004. Distant influences of amygdala lesion on visual cortical activation during emotional face processing. Nat. Neurosci. 7, 1271–1278.

[e]Opposing effects have been reported for a rare group of patients with selective BLA damage (i.e., sparing Ce). BL patients have difficulty ignoring task-irrelevant threat, show prolonged attention to potentially threat-diagnostic facial features, and exhibit enhanced recognition of dynamic fearful facial expressions (de Gelder et al., 2014; Terburg et al., 2012). Building on mechanistic work in rodents, these observations have been interpreted as evidence that BL normally inhibits vigilance-related processes orchestrated by the Ce (Terburg et al., 2018).

of threat, trustworthiness, anger, and fear (Oosterhof and Todorov, 2008, 2009; Smith et al., 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 and Buchel, 2009; Scheller et al., 2012) (Fig. 6A and 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 et al., 2012). With regard to faces, this kind of attentional bias is exaggerated among adults with a more negative disposition (Perlman et al., 2009) and those with social anxiety disorder (Boll et al., 2016). Importantly, patients with circumscribed amygdala damage do not show reflexive saccades to the eyes (Gamer et al., 2013) (Fig. 6C). Instead, they tend to fixate the mouth, both in laboratory assessments and real-world social interactions (Adolphs et al., 2005; Spezio et al., 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 et al., 2015). These converging lines of neurophysiological and mechanistic evidence indicate that the amygdala is crucial for re-allocating attention to threat-diagnostic social cues in adults. A key challenge for the future is establishing whether the amygdala performs a similar role IN other clinical populations and youth.

3.5 Pervasive hypervigilance may reflect stress-induced sensitization of the amygdala

Hypervigilance in inappropriate or maladaptive settings is a core feature of extreme anxiety (Grupe and Nitschke, 2013; Notebaert et al., 2017, 2018a). 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 acute experimental stressors (e.g., threat-of-shock, aversive film clips) potentiate defensive reactions (i.e., startle) to threat-related facial expressions (Grillon and Charney, 2011), cause persistent increases in spontaneous amygdala activity (Cousijn et al., 2010)—consistent with rodent studies (Ahrens et al., 2018)—and potentiate amygdala reactivity to threat-related faces (Pichon et al., 2015; van Marle et al., 2009). Acute stressors produce even longer-lasting changes (i.e., minutes to hours) in amygdala functional connectivity (Hermans et al., 2017; Vaisvaser et al., 2013; van Marle et al., 2010). Moreover, these kinds of neurobiological "spill-over" effects are amplified among individuals with a more negative disposition. For example, a large-scale imaging study ($n = 120$) showed that dispositionally negative individuals exhibit potentiated activation to threat-related faces following acute stressor exposure (Everaerd et al., 2015). Persistent amygdala sensitization could promote pervasive anxiety and "spillover" of negative affect by increasing the likelihood that attention is allocated to threat-related cues in the environment (Grupe and Nitschke, 2013; Macatee et al., 2017; Shackman et al., 2016b). Understanding the relevance of these pathways to the development of anxiety disorders

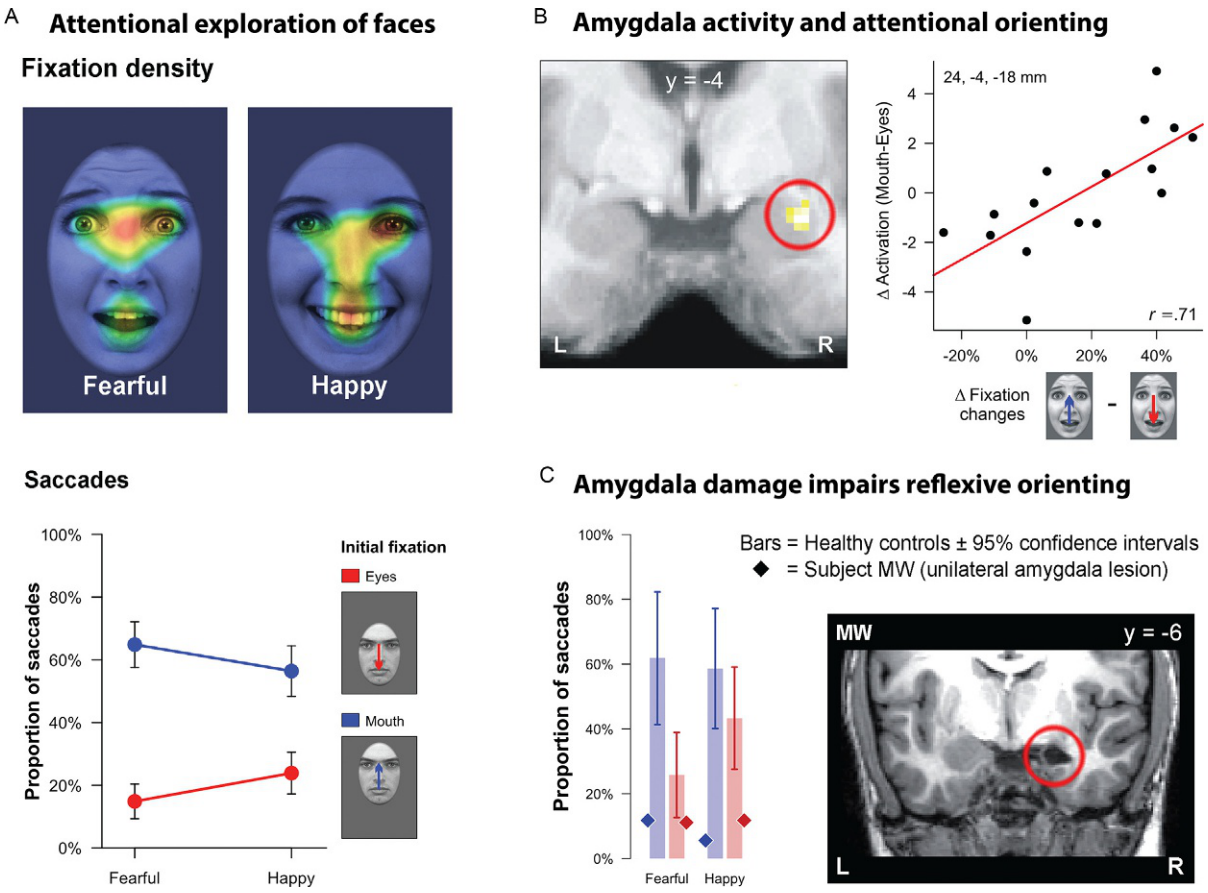

FIG. 6

The amygdala plays a key role in orienting overt attention to potentially 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 et al., 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 and Buchel, 2009). (C) Amygdala damage impairs reflexive orienting. Patient MW has selective damage to the right amygdala (*red ring*) and shows a profound reduction in reflexive saccades to the eye region of the face (Gamer et al., 2013). Abbreviations: *L*, left hemisphere; *R*, right hemisphere.

is important because the roots of anxiety disorders often extend into childhood (Kessler et al., 2007) and mental illnesses that emerge before adulthood impose a substantially higher economic burden than those that emerge in mid or later life (Lee et al., 2014; WHO, 2007).

3.6 Interim conclusions

Hypervigilance is a core feature of the anxiety disorders and dispositional negativity and, on average, adults and youth with a more negative disposition tend to allocate excess attention to potentially threat-related cues, even when they are task irrelevant (Shackman et al., 2016a). Like other candidate biomarkers, the magnitude of this cross-sectional association is too small to be clinically useful, at least when assessed using the popular, but psychometrically flawed dot-probe task (Abend et al., 2018; Fu and Pérez-Edgar, 2019; Kruijt et al., 2018; Rodebaugh et al., 2016). Preliminary work using new paradigms and new behavioral measures, including eye tracking, suggests that patients with anxiety disorders and individuals with a more negative disposition are more likely to dwell on threat-related cues and are more likely to shift attention to potentially threat-diagnostic features of the environment (Boll et al., 2016; Lazarov et al., 2016, 2019; Perlman et al., 2009; Sheppes et al., 2013). Attentional biases to threat prospectively predict the first emergence of anxiety symptoms in youth and interventions that attenuate attentional biases to threat have been shown to reduce pathological anxiety in adults, indicating a causal contribution (Grafton et al., 2017; White et al., 2017).

Converging lines of neuroimaging, electrophysiological, and mechanistic research indicate that the amygdala plays a crucial role in prioritizing the processing of threat-related cues (Bach et al., 2015; Gamer et al., 2013; Hadj-Bouziane et al., 2012; Lim et al., 2009; Peck et al., 2014; Vuilleumier et al., 2004). Individuals with a more negative disposition and patients with anxiety disorders show exaggerated behavioral interference and elevated amygdala activation when performing emotional attention tasks (Boehme et al., 2015; Ewbank et al., 2009; Price et al., 2016a). Exposure to acute stressors increases the on-going activity of the amygdala and potentiates reactivity to threat-related cues encountered in the future, suggesting a substrate for the kinds of mood spillover effects and inappropriate deployment of attentional resources that characterize individuals with a more negative disposition and many anxiety patients (Cousijn et al., 2010; Everaerd et al., 2015; Shackman et al., 2016b).

4 The nature, consequences, and neurobiology of executive deficits

4.1 The nature of executive function and cognitive control

Lapses in concentration and problems with cognitive function are clinically significant features of anxiety disorders and other psychiatric illnesses (American Psychiatric Association, 2013). Yet the contributions of executive function and cognitive control—the basic building blocks of intelligence and complex everyday cognition—to pathological anxiety have received considerably less empirical attention

than attentional biases to threat. Executive function refers to the processes involved in *shifting* between mental sets or tasks, *updating* and monitoring working memory (e.g., *n*-back continuous performance task), and *inhibiting* prepotent responses (Banich, 2009; Miyake and Friedman, 2012; Miyake et al., 2000). Cognitive control encompasses a range of processes—including attention, inhibition, and learning—that are engaged when automatic or habitual responses are insufficient to sustain goal-directed behavior, as with the inhibitory facet of executive function (Shackman et al., 2011b). Like fear and anxiety, cognitive control is a component of the NIMH Research Domain Criteria (RDoC) (Clark et al., 2017b; Kozak and Cuthbert, 2016). Common assays of cognitive control include variants of the Anti-Saccade, Eriksen Flanker, Go/No-Go, Simon, Stop-Signal, and Stroop tasks. Here, we use "executive control" as a rubric for executive function and cognitive control.

4.2 Relevance of executive control deficits to dispositional negativity and anxiety disorders

Converging lines of educational, epidemiological, developmental, and experimental research suggest that dispositional negativity is associated with deficits in executive control. Increased dispositional negativity is associated with reduced educational attainment (Damian et al., 2015; Hengartner et al., 2016b; Hill et al., 2017; Nagel et al., 2018a, b) and fluid intelligence (Dubois et al., 2018). Dispositional negativity is genetically correlated with reduced educational attainment ($r_G = -0.22$, $N = 328{,}917$) (Nagel et al., 2018a), lower intelligence ($r_G = -0.21$, $N = 170{,}911$) (Savage et al., 2018), and lower executive function ($r_G = -44$, $N = 1207$ twins) (Gustavson et al., in press), suggesting shared molecular underpinnings. In laboratory settings, children and adults with a more negative disposition are prone to executive control deficits when performing standard emotionally neutral tasks, that is, in the absence of threat-related cues (Basten et al., 2011; Beaudreau et al., 2013; Berggren and Derakshan, 2013; Bishop, 2009; Derakshan and Eysenck, 2009; Derryberry and Reed, 2002; Eysenck and Derakshan, 2011; Eysenck et al., 2007; Gustavson et al., 2017; Gustavson and Miyake, 2016; Muris et al., 2004, 2008; Osinsky et al., 2012). For example, adults with a more negative disposition tend to commit more errors in task-switching and inhibitory control paradigms (Ansari and Derakshan, 2011; Basten et al., 2011; Derakshan et al., 2009a, b; Garner et al., 2009; Goodwin and Sher, 1992; Orem et al., 2008; Pacheco-Unguetti et al., 2009, 2010; Wieser et al., 2009). Clinical samples reveal a broadly similar pattern (Aupperle et al., 2012; Hallion et al., 2017; Polak et al., 2012; Scott et al., 2015; Stefanopoulou et al., 2014; Wright et al., 2014). Nevertheless, the limited number, breadth, and quality of clinical studies signals the need for additional research (McTeague et al., 2016; Snyder et al., 2015).

4.3 Executive control deficits causally contribute to pathological anxiety

Longitudinal studies show that executive control difficulties are prospectively associated with greater anxiety, worry, and rumination in the future (Aupperle et al., 2012; Bredemeier and Berenbaum, 2013; Crowe et al., 2007; De Lissnyder et al., 2012;

Duchesne et al., 2010; Pérez-Edgar et al., 2014; Snyder et al., 2014; Whitmer and Banich, 2007; Zhang et al., 2015). In a nationally representative sample of 2605 American adults, decrements in set shifting, updating, and inhibition conferred robust risk of developing generalized anxiety disorder (GAD) across the 9-year follow-up period (e.g., odds ratios for updating >6.00; Zainal and Newman, 2018). Likewise, a recent meta-analysis uncovered evidence of cognitive impairment—including lower IQ (−0.19 SD) and academic performance—in first-degree relatives of individuals with MDD ($N = 8468$) (MacKenzie et al., 2019), suggesting a causal role. Conversely, there is emerging evidence that interventions targeting cognitive control can ameliorate anxiety symptoms, reinforcing the conclusion that executive control deficits causally contribute to the development of pathological anxiety (e.g., Cohen et al., 2014, 2015).

4.4 The neurobiology of executive control

Executive control is often associated with the prefrontal cortex (PFC). Historically, this view was motivated by early evidence of impairments in goal-directed behavior and complex cognition in monkeys and humans with selective damage to the lateral PFC (Bianchi and Macdonald, 1922; Duncan, 1986; Ferrier, 1886; Grafman, 1994; Knight, 1984; Passingham, 1993). Recent meta-analyses of the functional neuroimaging literature have extended this perspective, suggesting that executive control reflects the coordinated function of several large-scale brain circuits, including the *frontoparietal network* (dlPFC, intraparietal sulcus) and *cingulo-opercular network* (midcingulate cortex, anterior insula, frontal operculum) (Chen et al., 2018; Hung et al., 2018; Li et al., 2017; McKenna et al., 2017) (Fig. 7).

4.5 Relevance of executive control networks to dispositional negativity and anxiety disorders

To our knowledge, only three functional neuroimaging studies have examined relations between dispositional negativity and executive control. Two studies reported *increased* engagement of frontoparietal control networks, while a third, much smaller study reported *decreased* engagement. Fales and colleagues showed that dispositional negativity enhanced activation of frontoparietal regions on control-demanding trials of a complex *n*-back task in the absence of overt differences in performance ($N = 96$; Fales et al., 2008). Likewise, Basten and colleagues found enhanced dlPFC activation on control-demanding (i.e. incongruent) trials of the widely used Stroop task ($N = 46$; Basten et al., 2011). Here, the positive association between dispositional negativity and dlPFC activation remained significant after controlling for performance decrements among subjects with a more negative disposition. Finally, Bishop used a compound attentional-search/response-conflict paradigm to reveal reduced dlPFC activation and slower target identification among individuals with a more negative disposition ($N = 17$; Bishop, 2009). While the results of these three studies preclude strong conclusions, the overall pattern aligns with the hypothesis that dispositionally negative individuals tend to inefficiently allocate executive control resources, requiring greater effort or neural engagement to achieve similar (or worse) ends

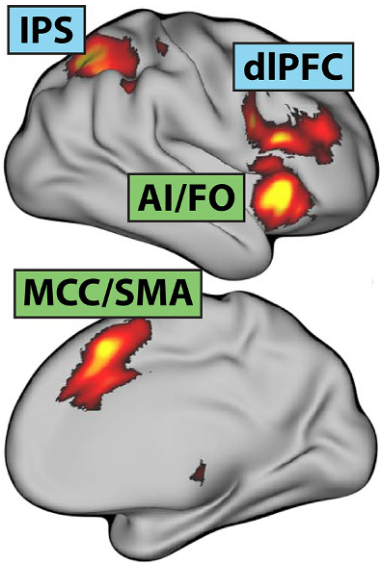

FIG. 7

Executive control networks. The frontoparietal (*blue*) and cingulo-opercular (*green*) networks are sensitive to a broad spectrum of executive function and cognitive control tasks. Abbreviations: *AI*, anterior insula; *dlPFC*, dorsolateral prefrontal cortex; *FO*, frontal operculum; *IPS*, intraparietal sulcus; *MCC*, midcingulate cortex; *SMA*, supplementary motor area.

This figure was adapted with permission from Li, Q., Yang, G., Li, Z., Qi, Y., Cole, M.W., Liu, X., 2017. Conflict detection and resolution rely on a combination of common and distinct cognitive control networks. Neurosci. Biobehav. Rev. 83, 123–131.

(Berggren and Derakshan, 2013; Eysenck and Derakshan, 2011; Eysenck et al., 2007). At present, even less is known about the relevance of executive control networks to clinical anxiety. A comprehensive recent meta-analysis of neuroimaging studies failed to uncover any significant regional differences in activation during the performance of emotionally neutral executive control tasks, although this may reflect the disproportionate representation of obsessive-compulsive compulsive disorder (OCD) samples ($k = 32$ studies; McTeague et al., 2016, 2017). Given the consequences of executive control deficits for the development of pathological anxiety (Zainal and Newman, 2018), additional research in adults and youth is clearly warranted.

5 Emerging evidence for the interplay of attentional biases and executive control

While most research has focused on attentional biases to threat or deficits in executive control in isolation, an emerging body of data and theory suggests that these processes are intimately related and can reciprocally interact (Bishop, 2008, 2009;

Bishop and Forster, 2013; Derakshan et al., 2009a; Eysenck and Derakshan, 2011; Eysenck et al., 2007; Iordan et al., 2013; Mogg and Bradley, 2016, 2018; Mogg et al., 2017; Tottenham and Gabard-Durnam, 2017). From a conceptual perspective, such interactions are most likely to occur when there is competition between task-irrelevant threat-related cues and on-going goals, as with a variety of "emotional conflict" tasks (e.g., emotional Stroop). Monitoring and adjudicating this conflict demands executive control resources, rendering them less available for on-going cognitive performance (Shackman et al., 2011b) or anxiety regulation (Buhle et al., 2014). Consistent with this view, there is evidence that excessive allocation of attention and working memory capacity to threat disrupts on-going performance and hijacks regions of the frontoparietal network, and that these adverse consequences are more pronounced among individuals with a negative disposition (Hur et al., 2015; Moran, 2016; Robinson et al., 2013; Shackman et al., 2006, 2011a; Stout et al., 2013) or psychiatric disorder (Schweizer et al., in press). Other work demonstrates that attentional biases to threat are *enhanced* among dispositionally negative individuals marked by poor cognitive control and that they are *reduced* under conditions that facilitate cognitive control (Derryberry and Reed, 2002; Hadwin and Richards, 2016; Hur et al., 2016; Lonigan and Vasey, 2009; Susa et al., 2012; Taylor et al., 2010).

Given the many ways in which attentional biases to threat and executive control can potentially interact, and the numerous mono- and polysynaptic pathways linking the amygdala to regions involved in executive control, the underlying neural circuitry is likely to be complex and at least somewhat task-dependent (Benarroch, 2015; Etkin et al., 2015; Freese and Amaral, 2009; Mogg and Bradley, 2018). Nevertheless, recent meta-analyses of the functional neuroimaging literature reveal a remarkably consistent engagement of regions within the frontoparietal and cingular-opercular networks (Fig. 7) across a wide range of emotional interference tasks ($k = 10$–48 studies; Chen et al., 2018; Cromheeke and Mueller, 2014; Hung et al., 2018; Song et al., 2017; Xu et al., 2016). Work focused on adult anxiety patients has begun to document aberrant functional connectivity between the amygdala and these control regions, as well as diminished mPFC responses to threat distractors (Bishop, 2008; Blackford and Pine, 2012; Carpenter et al., 2015; Ding et al., 2011; Etkin et al., 2015; Kim et al., 2010; Liao et al., 2010; Monk et al., 2006, 2008; Price et al., 2011; Shin et al., 2005; Stein et al., 2002; Sussman et al., 2016; Sylvester et al., 2012; Tillfors et al., 2001). While most of the work remains undone, these observations suggest that dispositional negativity and anxiety disorders disrupt the balance between attention and control—*amplifying* the attentional salience of threat and *attenuating* executive control—leading to less effective or less efficient performance (Berggren and Derakshan, 2013; Eysenck et al., 2007; Snyder et al., 2015).

6 Future challenges

The data that we have reviewed provide new insights into the neurocognitive mechanisms that support individual differences in dispositional negativity and that link this disposition to the development of anxiety disorders and other psychiatric

diseases. Yet, it is clear that our understanding remains far from complete. Throughout the review, we highlighted a number of specific conceptual and methodological challenges for future research in this area. Here, we outline some broader questions for the field and offer some strategies for starting to address them (for general recommendations about best practices, see Fox et al., 2018a).

1. *How do different aspects of attention contribute to the development of anxiety disorders?* In this review, we have treated hypervigilance and attentional biases to threat-related information as virtually synonymous. Yet, there is a growing recognition that the amount of attention allocated to threat-related cues can be decomposed into several constituents: (i) the likelihood that task-relevant threat will be detected and attention will be re-oriented, (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 (Mogg and Bradley, 2018; Richards et al., 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 and Buchel, 2009; Gamer et al., 2013), much less is known about the clinical relevance or neurobiology of these other biases in adults or youth. Addressing this 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 would be especially valuable.
2. *How do different components of the amygdala contribute to risk?* Like attention, the amygdala can be divided into meaningful sub-components or nuclei (Freese and Amaral, 2009; Yilmazer-Hanke, 2012) (Fig. 1). Developing a deeper understanding of this heterogeneity and its relevance to the development of anxiety disorders and other stress-sensitive mental illnesses requires that we first acknowledge it. Although investigators need to be cautious when assigning specific labels (e.g., 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 amygdala (e.g., "in the region of the Ce"). The use of high-field MRI or specialized analytic approaches (e.g., spatially unsmoothed data) may also prove useful (Fox and Shackman, 2019; Hur et al., 2018; Tillman et al., 2018).
3. *Which brain circuits are associated with individual differences in risk?* There is widespread consensus that dispositional negativity, hypervigilance for threat, and executive control deficits—like other psychologically and psychiatrically relevant processes—reflect the coordinated activity of distributed brain circuits (Okon-Singer et al., 2015; Pessoa, 2013; Shackman et al., 2015). Yet most imaging investigators (including our team) have relied heavily on localization strategies, where function is mapped to isolated brain structures. Unfortunately,

this approach tends to promote the development of models in which a small number of territories—the amygdala, dlPFC, and MCC, for example—do all or most of the "heavy lifting." Overcoming this important barrier requires that we accelerate the transition from localization strategies to network-based approaches (Fornito et al., 2015; Guloksuz et al., 2017; McMenamin et al., 2014; Servaas et al., 2014). Information-based approaches, such as multivoxel classifier approaches, provide another powerful tool for discovering the distributed functional networks associated with emotional states, traits, and disorders (Kragel et al., 2018; Woo et al., 2017). Developing robust and generalizable (i.e., task- and sample-general) classifiers that are firmly grounded in overt behavior or subjective report are more likely to be useful for therapeutics development and more likely to successfully translate to the clinic (Hur et al., 2019; Shackman and Fox, 2018; Shackman and Wager, 2019).

4. *How relevant are individual differences in brain function to anxiety-related experience and behavior in the real world?* Most psychophysiological and imaging studies of anxiety and anxiety-relevant cognitive mechanisms (e.g., attention bias, attention control) rely on a limited number of well controlled, but highly artificial manipulations (e.g., static emotional faces, unpleasant images, threat-of-shock), collected under unnatural conditions (Coan and Allen, 2007; Fox et al., 2018a). Although this approach has afforded many important insights, the real-world or "translational" significance of the circuits identified in the laboratory often remain unclear. 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 *field* (Anderson et al., 2018) or in the *laboratory* (e.g., during semi-structured interactions or using commercially available virtual reality techniques; Creed and Funder, 1998; Kroes et al., 2017; Pérez-Edgar et al., 2010b; Stolz et al., 2019; Thomson et al., 2019). Work combining fMRI with ecological momentary assessment (EMA) and other 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 older children (Berkman and Falk, 2013; Forbes et al., 2009; Heller et al., 2015; Lopez et al., 2014; Price et al., 2016a; Wilson et al., 2014). The development of robust mobile eye trackers (Liu et al., 2018), the emergence of commercial software for automated facial analytics (Olderbak et al., 2014), and the widespread dissemination of "smart" mobile technologies afford new opportunities for intensively quantifying social attention, arousal, behavior, mood, and anxiety-relevant features of the environment (Boukhechba et al., 2018; Chow et al., 2017; Mohr et al., 2017; Picard, 2018; Saeb et al., 2016; Shackman et al., 2018b; Stingone et al., 2017). Networked sensors in smartphones and other wearables are already woven into the fabric of our lives. In the United States, 77% of adults and 94% of young adults (<30 years) own smartphones (Pew Research Center (Producer), 2018).

Because data are repeatedly captured in the real world, smartphone-based EMA circumvents the mnemonic biases that can distort daily diaries, clinical assessments, and other retrospective "snapshots" (Ebner-Priemer and Trull, 2009; Kanning et al., 2013; Shiffman et al., 2008; Solhan et al., 2009; Stone et al., 2007; Tost et al., 2015). Smartwatches and other wearable sensors (e.g., actigraphy, GPS) go a step further, eliminating the need for subjects to repeatedly respond to surveys and providing continuous and objective measures (movies) of anxiety-relevant behaviors (Gambhir et al., 2018). Moreover, digital tracking can provide behavioral phenotypes (e.g., locomotion, sleep, social avoidance) that are directly comparable between humans and animals (Freimer and Mohr, 2019; Hong et al., 2015), facilitating the development of cross-species models and enhancing opportunities for mechanistic insight (Fox and Shackman, 2019; Shackman and Fox, 2016). 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) in the real world, close to clinical end-points (Price et al., 2016a). This approach promises a depth of understanding that cannot be achieved using either animal models or isolated measures of brain function and represents a key step to establishing the clinical and therapeutic relevance of these brain circuits.

5. *What mechanisms underlie individual differences in risk?* Much of the data that we have reviewed come 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 necessity or sufficiency. A crucial challenge for the future is to develop a mechanistic understanding of the brain regions and functional circuits that confer increased risk for the development of anxiety 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 (Birn et al., 2014; Fox and Shackman, 2019; Kalin, 2017; Terburg et al., 2018). Nonhuman primate models are likely to be particularly useful for modeling and understanding the molecular and cellular neurobiology of dispositional negativity because monkeys and humans share similar genes and brains, which endow the two species with a shared repertoire of complex social, emotional, and cognitive behaviors (Fox and Shackman, 2019). Furthermore, well-established techniques already exist for studying both dispositional negativity and attention in nonhuman primates (Hadj-Bouziane et al., 2012; Noudoost et al., 2014; Oler et al., 2016).

Human studies will also be crucial. After all, anxiety disorders are defined and diagnosed on the basis of subjective symptoms and human studies are essential for understanding the neural mechanisms supporting the experience of fear and anxiety

(LeDoux and Hofmann, 2018; Pankevich et al., 2014; Pine and LeDoux, 2017; Zoellner and Foa, 2016). Human studies are also important for identifying the features of animal models that are conserved and, hence, most relevant to understanding human disease and to developing improved interventions for human suffering (forward translation; Birn et al., 2014; Hyman, 2016; Pankevich et al., 2014). In humans, imaging approaches can be applied to patients with circumscribed brain damage (Adolphs, 2016; Motzkin et al., 2014, 2015a, b; Spunt et al., 2015). Alternatively, fMRI or EEG can be combined with noninvasive perturbation techniques (Bestmann and Feredoes, 2013; Dubois et al., n.d.; Reinhart and Woodman, 2014), neurofeedback (deBettencourt et al., 2015; Greer et al., 2014; Stoeckel et al., 2014), cognitive-behavioral interventions (Britton et al., 2015; Schnyer et al., 2015), pharmacological interventions (Paulus et al., 2005; Wager et al., 2013), or more passive psychological manipulations (i.e., temporally unpredictable auditory stimuli; Herry et al., 2007). Prospective longitudinal imaging studies represent another important approach to identifying candidate mechanisms, especially in relation to the development of internalizing disorders (Admon et al., 2013; Burghy et al., 2012; Herringa et al., 2013; McLaughlin et al., 2014; Swartz et al., 2015b).

7 Conclusions

The work that we have reviewed highlights the importance of amygdala, frontoparietal, and cingular-opercular circuits to individual differences in dispositional negativity and two prominent intermediate phenotypes: threat-related attentional biases and deficits in executive control. Collectively, these observations provide an integrative translational framework for understanding the development and maintenance of anxiety and mood disorders in adults and youth and set the stage for developing improved strategies for preventing or treating them.

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