

The Neurobiology of Dispositional Negativity and Attentional Biases to Threat: Implications for Understanding Anxiety Disorders in Adults and Youth

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Abstract

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

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

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

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Introduction

When extreme, anxiety—a sustained state of apprehension, arousal, and vigilance in the absence of immediate danger—can become debilitating (LeDoux, 2015). Anxiety disorders, which often first emerge early in development (Kessler et al., 2005), are the most common family of psychiatric disorders and contribute to the etiology of co-morbid depression and substance abuse (DiLuca & Olesen, 2014; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Collectively, these disorders impose a staggering burden on both public health—more than 100 million life-years lost to disability—and the economy, with billions of dollars devoted to healthcare costs and lost productivity (Collins et al., 2011; Whiteford et al., 2013). These data underscore the need to develop a deeper understanding of the neurocognitive mechanisms that support the development and maintenance of anxiety disorders. Here we review recent work highlighting the importance of the amygdala. We begin by describing dispositional negativity, an important temperamental risk factor for the development of anxiety disorders, depression, and other kinds of stress-sensitive psychopathology. Next, we review new evidence that the amygdala supports stable individual differences in dispositional negativity across the lifespan and contributes to the development of anxiety and mood disorders among individuals exposed to stress. Hyper-vigilance and attentional biases to threat-related¹ cues are key features of dispositional negativity in both children and adults and there is growing evidence that they contribute to the

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

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

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

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

The Consequences of Elevated Dispositional Negativity for Mental Illness

Dispositional negativity is a prominent risk factor for some of the most common and burdensome mental illnesses, including anxiety disorders, depression, and co-morbid substance abuse (Clauss & Blackford, 2012; Conway, Craske, Zinbarg, & Mineka, 2016; Hakulinen et al., 2015; Kendler & Gardner, 2014; Soldz & Vaillant, 1999; Watson & Naragon-Gainey, 2014; S. Wilson, Vaidyanathan, Miller, McGue, & Iacono, 2014; Zinberg, et al., 2016). The magnitude of these associations is substantial; a recent meta-analysis incorporating 175 cross-sectional studies reported that the mean Cohen's d across mood, anxiety, and substance use disorders was 1.65, ranging from $d \cong 2$ for anxiety disorders to $d = .77$ for alcohol use disorder (Kotov, Gamez, Schmidt, & Watson, 2010). Among children, recent work suggests that nearly half of those with stable and extreme levels of behavioral inhibition—a core facet of dispositional negativity—are diagnosed with social anxiety disorder later in life ($N = 692$; risk ratio = 3.4; Clauss & Blackford, 2012). Other work suggests that dispositional negativity is among the strongest prospective predictors of disorder onset in adults ($k = 46$ studies; mean Cohen's $d = .63$; Ormel et al., 2013) and adolescents (Craske et al., 2012; Zinbarg, et al., 2016). For example, adult data from the Zurich Cohort Study ($n = 591$) indicates that a one standard-deviation increase in dispositional negativity at the time of the baseline assessment in 1988 increased the odds of developing a major depressive episode by 41% and an anxiety disorder by 32% during the twenty year (1988-2008) follow-up period (Hengartner, Ajdacic-Gross, Wyss, Angst, & Rossler, 2016). These relations are particularly evident among individuals exposed to stress and negative life events (e.g., childhood maltreatment; Kopala-Sibley et al., 2016; Kopala-Sibley et al., 2016; Vinkers et al., 2014), suggesting that high levels of dispositional negativity represent a diathesis for the internalizing spectrum of disorders (i.e., anxiety and depression). Among adults with a history of internalizing disorders, higher levels of dispositional negativity are associated with a greater number of co-morbid diagnoses (Hengartner, Kawohl, Haker, Rossler, & Ajdacic-Gross, 2016) and a more pessimistic prognosis (Berlanga, Heinze, Torres, Apiquian, & Cabellero, 1999; Duggan, Lee, & Murray, 1990; Faravelli, Ambonetti, Pallanti, & Pazzagli, 1986; Hirschfeld, Klerman, Andreasen, Clayton, & Keller, 1986; Kendler, Neale, Kessler, & Heath, 1993; Ormel, Oldehinkel, & Vollebergh, 2004; Quilty et al., 2008; Scott, Williams, Brittlebank, & Ferrier, 1995; Weissman, Prusoff, & Klerman, 1978). For example, Steunenbergh and colleagues found that individuals with above-median levels of dispositional negativity were 2.8-times more likely to relapse or experience a new depressive episode across a six-year follow-up period (Steunenbergh, Beekman, Deeg, & Kerkhof, 2010). Importantly, dispositional negativity continues to predict self-reported anxious and depressive symptoms after eliminating overlapping item content (Uliaszek et al., 2009).

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

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

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

Relevance of the Amygdala to Dispositional Negativity

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

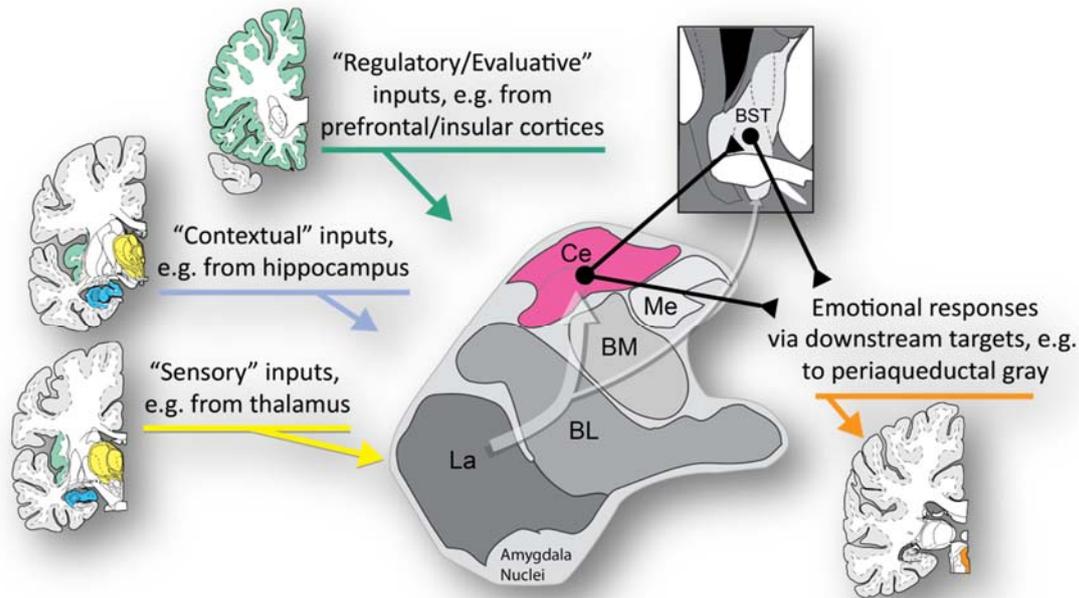


Figure 1: Simplified schematic of amygdala circuitry relevant to dispositional negativity, attentional biases, and hyper-vigilance to threat.

Among humans and other primates, 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, are poised to modulate sensory cortex. Portions of this figure were adapted with permission from the atlas of Mai and colleagues (Mai, Paxinos, & Voss, 2007).

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

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

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

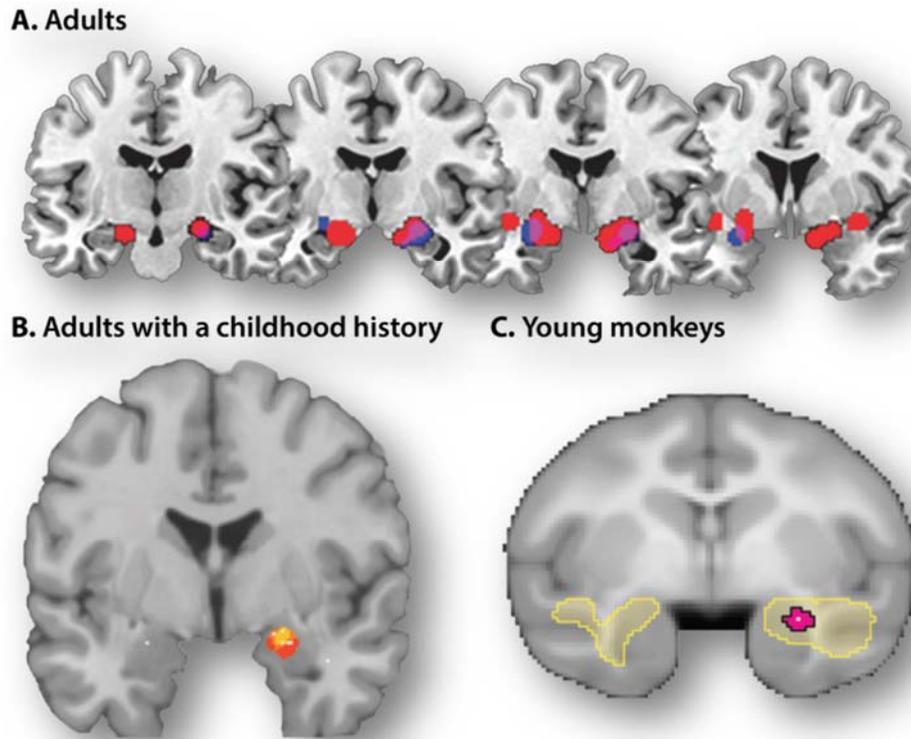


Figure 2: The dorsal amygdala is more reactive to threat-related cues in individuals with a more negative disposition.

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

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

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

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

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

3. Prospectively predicts heightened internalizing symptoms among adolescents and young adults exposed to stress, trauma, or negative life events (Admon et al., 2009; McLaughlin et al., 2014; Swartz, Knodt, Radtke, & Hariri, 2015). For example, McLaughlin and colleagues showed that adolescents marked by a more reactive amygdala at initial assessment experienced heightened posttraumatic stress symptoms 9 months later, following exposure to the terrorist attacks at the 2013 Boston Marathon (McLaughlin et al., 2014).
4. Is attenuated by clinically effective cognitive-behavioral and pharmacological (e.g., benzodiazepine) treatments for anxiety and depression in adults (Arce, Simmons, Lovero, Stein, & Paulus, 2008; Brown et al., 2015; Felmingham et al., 2007; Furmark et al., 2002; Harmer, Mackay, Reid, Cowen, & Goodwin, 2006; Paulus, Feinstein, Castillo, Simmons, & Stein, 2005; Phan et al., 2013; Sheline et al., 2001; Strawn, Wehry, DelBello, Rynn, & Strakowski, 2012; Windischberger et al., 2010). As yet, the impact of treatment on pediatric amygdala function has received little attention and remains unclear (Maslowsky et al., 2010; Strawn et al., 2012).

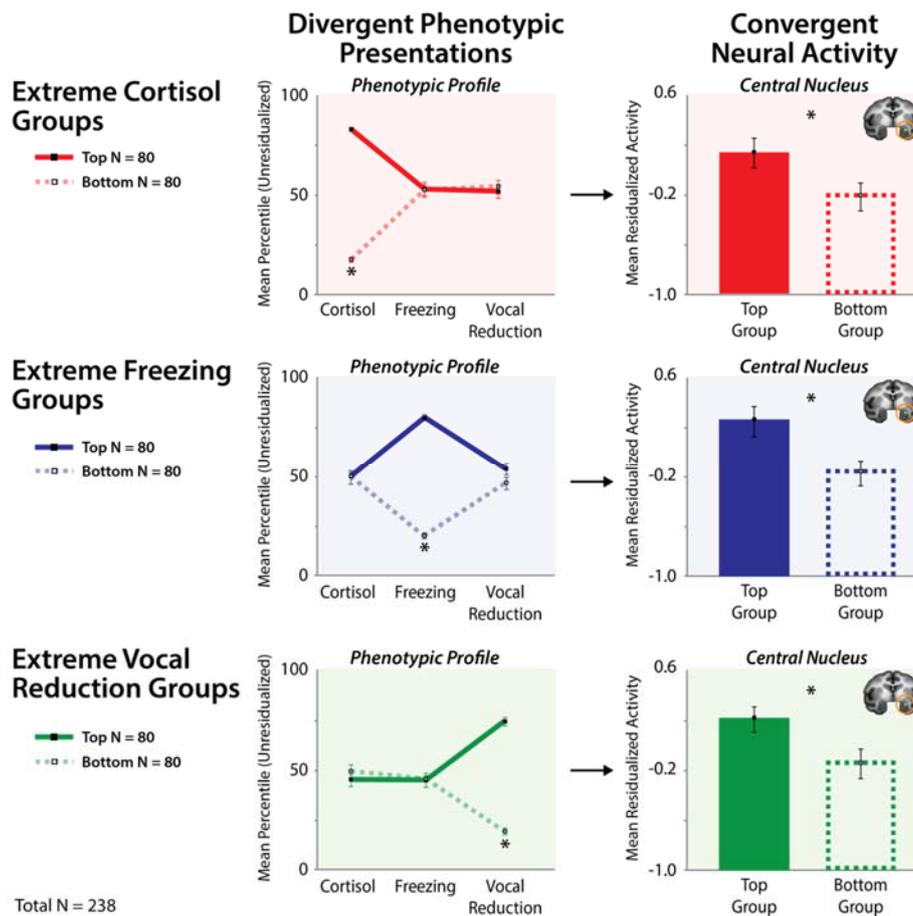


Figure 3: Elevated amygdala activity is a shared substrate for different phenotypic presentations of dispositional negativity.

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

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

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

Mechanistic Work Indicates that the Amygdala Causally Contributes to Extreme Anxiety

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

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

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

Attentional Biases to Threat-Related Cues

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

Threat-Related Cues Grab Attention

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

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

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

Relevance of Attention to Dispositional Negativity and Anxiety Disorders

Heightened vigilance and exaggerated risk assessment behaviors are hallmarks of both dispositional negativity and anxiety disorders (Grupe & Nitschke, 2013), particularly generalized anxiety disorder (Salum et al., 2013; Waters, Bradley, & Mogg, 2014). Like many patients with anxiety disorders, adults, adolescents, and children with a more negative disposition are biased to allocate excess attention to threat-related cues, even when they are irrelevant to the task at hand (Aue & Okon-Singer, 2015; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Cole, Zapp, Fetting, & Perez-Edgar, 2016; Dudeney, Sharpe, & Hunt, 2015; LoBue & Perez-Edgar, 2014; Van Bockstaele et al., 2014) (for thoughtful discussions of heterogeneity, see Naim et al., 2015; Roy, Dennis, & Warner, 2015; Waters et al., 2015; Mogg, and Bradley, 2016; Montagner et al., 2016)². In particular, recent meta-analyses indicate that children and adolescents with elevated levels of dispositional negativity or frank anxiety disorders show a significantly greater attentional bias for threat-related stimuli when compared to typical youth ($k = 44$ studies; mean Cohen's $d = 0.21$) or when compared emotionally neutral stimuli ($k = 16$ studies; mean Cohen's $d = 0.54$; Dudeney et al., 2015). The latter effect is similar in magnitude to that reported in studies of adults ($k = 101$ studies; mean Cohen's $d = 0.45$; Bar-Haim et al., 2007). On average, dispositionally negative adults are more likely to initially orient their gaze towards threat-related cues in free-viewing tasks; quicker to fixate threat-related targets in visual search tasks; and slower to disengage from threat-related distractors in spatial cueing, visual search, and dot-probe³ tasks (Armstrong & Olatunji, 2012; Cisler & Koster, 2010; Rudaizky, Basanovic, & MacLeod, 2014). Recent work employing tasks designed to more cleanly dissociate biases in attentional engagement from disengagement (i.e., release-from-capture paradigm) suggests that adults with a more negative disposition are particularly impaired in disengaging from threat-related cues (Sheppes et al., 2013). Whether this is also evident in youth remains unknown.

A range of evidence motivates the hypothesis that attentional biases to threat-related cues contribute to the development and maintenance of extreme anxiety. From a longitudinal perspective, attentional biases to threat-related cues have been shown to moderate the impact of dispositional negativity on the development of internalizing symptoms in youth. For example, Pérez-Edgar, Fox, and colleagues have demonstrated that among youth with an early childhood history of extreme dispositional negativity, it is the subset who also shows an attentional bias to threat-related cues on the dot-probe task that is most likely to exhibit social withdrawal and elevated anxiety symptoms later in development, at ages 5 and 15 (Perez-Edgar, Bar-Haim, et al., 2010; Perez-Edgar et al., 2011; White et al., in press). Likewise, there is emerging evidence that clinically effective cognitive-behavioral and pharmacological treatments for anxiety also tend to reduce attentional biases to threat-related cues (Murphy, Yiend, Lester, Cowen, & Harmer, 2009; Reinecke, Waldenmaier, Cooper, & Harmer, 2013; Van Bockstaele et al., 2014). Direct support for this hypothesis comes from studies using computer-based interventions targeting attentional biases to threat. In non-clinical samples, attention modification has been shown to reduce distress, behavioral signs of anxiety, and intrusive thoughts elicited during subsequent exposure to cognitive stressors, public speaking challenges, and worry inductions in adults and children (Bar-Haim, Morag, & Glickman, 2011; Dennis & O'Toole, 2014; MacLeod & Mathews, 2012). In adult clinical samples, medium-to-small treatment effects have been consistently observed compared to placebo training (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; MacLeod & Clarke, 2015; Mogg, & Bradley, 2016). Results have been somewhat less consistent in pediatric clinical samples, with some studies reporting positive effects compared to placebo (Eldar et al., 2012; Riemann, Kuckertz, Rozenman,

² Or show more complex patterns of initial vigilance followed by avoidance (Armstrong & Olatunji, 2012; Di Simplicio et al., 2014; Onnis, Dadds, & Bryant, 2011; Weierich, Treat, & Hollingworth, 2008; Zvielli, Bernstein, & Koster, 2014; Mogg, & Bradley, 2016).

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

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

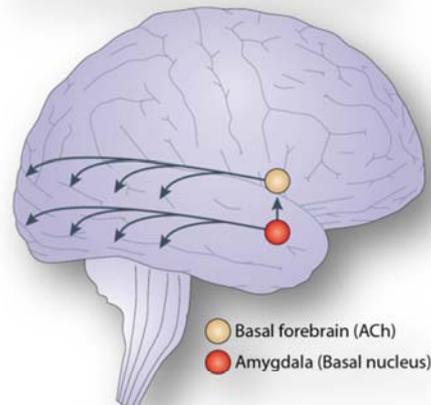
Relevance of the Amygdala to Hyper-Vigilance and Attentional Biases to Threat

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

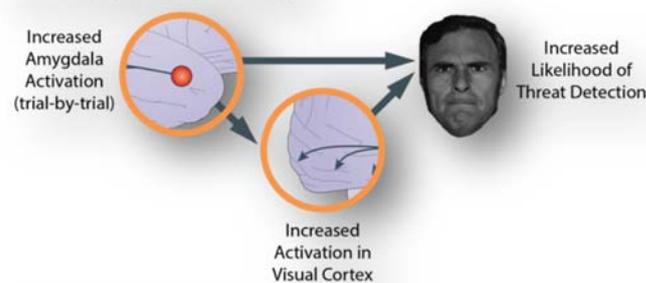
As shown in Figure 4a, anatomical tracing studies in nonhuman primates and mechanistic studies in rodents demonstrate that the amygdala is well-positioned to prioritize the processing of threat and other salient stimuli. Enhanced attention can occur via at least two mechanisms: *directly*, via projections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

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

A. Amygdala connectivity



B. Amygdala activity



C. Amygdala damage

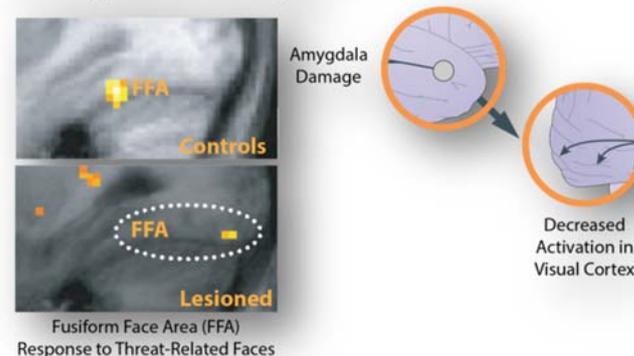


Figure 4: The amygdala plays a key role in enhancing attention to threat-relevant information.

A. Amygdala connectivity. Invasive 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 via direct projections to sensory cortex as well as indirectly, via projections to ascending neurotransmitter systems in the basal forebrain and brain stem. In turn, these transmitter systems can enhance the signal-to-noise ratio of neuronal processing in cortical sensory regions. In this simplified illustration, selected projections from the basal forebrain cholinergic (ACh) system to the visual cortex are depicted.

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

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

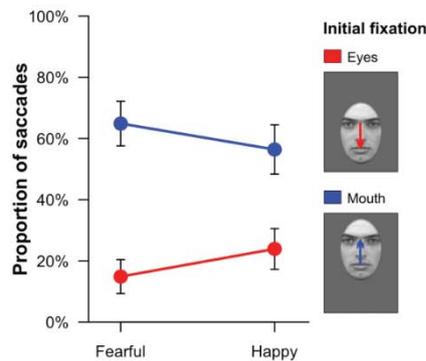
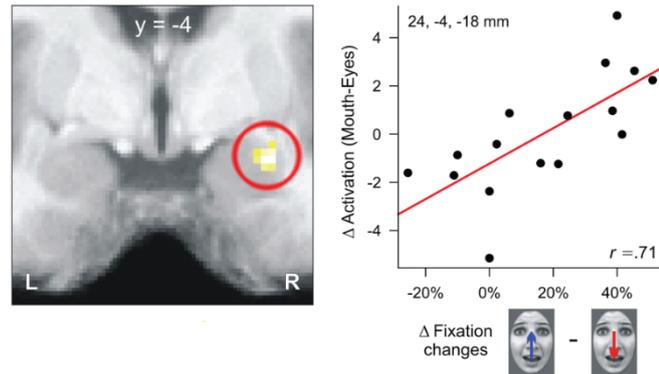
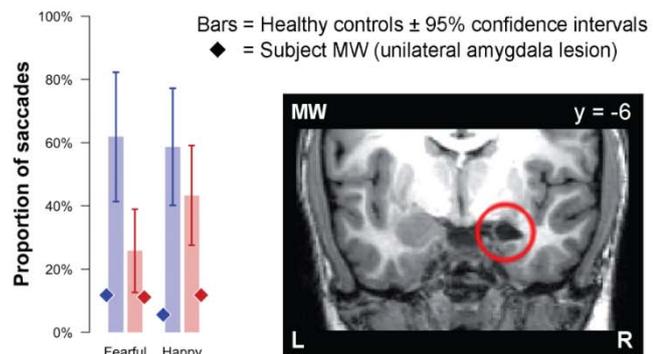
A. Attentional exploration of faces**Fixation density****Saccades****B. Amygdala activity and attentional orienting****C. Amygdala damage impairs reflexive orienting**

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

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

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

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

Other work suggests that the amygdala is not necessarily the passive recipient of threat-related information streaming in from the environment. In addition to biasing selection and increasing the depth of processing, there is compelling evidence that the amygdala plays a key role in redirecting gaze (i.e., overt attention) to those features of the face, such as the eyes and brow, that are most diagnostic of threat, trustworthiness, anger, and fear (Oosterhof & Todorov, 2008, 2009; Smith, Cottrell, Gosselin, & Schyns, 2005). Using a combination of eye tracking and brain imaging, Gamer and colleagues have demonstrated that human adults are biased to reflexively attend the eye and brow region of the face, that this bias is most pronounced for threat-related (i.e., fearful) facial expressions, and that individuals with greater amygdala activation are more likely to shift their gaze to the eyes (Gamer & Buchel, 2009; Scheller, Buchel, & Gamer, 2012) (Figure 5a, b). Similar effects have been obtained for complex non-social cues; subjects are biased to fixate the visual features most predictive of threat and this tendency co-varies with trial-by-trial fluctuations in amygdala activation (Eippert, Gamer, & Buchel, 2012). With regard to faces, this attentional bias is exaggerated among adults with a more negative disposition (Perlman et al., 2009) or social anxiety disorder (Boll, Bartholomaeus, Peter, Lupke, & Gamer, 2016). Importantly, patients with circumscribed amygdala damage do not show reflexive saccades to the eyes (Gamer, et al., 2013) (Figure 5c). Instead, they tend to fixate the mouth, both in laboratory assessments and real-world social interactions (Adolphs et al., 2005; Spezio, Huang, Castelli, & Adolphs, 2007), and

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

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

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

Future Challenges

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

1. *Which brain circuits underlie hyper-vigilance and attentional biases to threat in anxious youth?*

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

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

2. ***How do different aspects of attention contribute to the development of anxiety disorders?*** In this review, we have treated hyper-vigilance and attentional biases to threat-related information as virtually synonymous. Yet, there is a growing recognition that the amount of attention allocated to threat-related cues can be fruitfully decomposed into several key constituents: (i) the likelihood that task-relevant threat will be detected and attention will be re-oriented (i.e., heightened 'vigilance'), (ii) the likelihood that task-irrelevant threat will capture attention or bias behavior (i.e., reduced attentional control or selectivity), (iii) the rapidity of disengagement from threat, and (iv) the degree of attentional avoidance (or maintenance) during sustained, free-viewing tasks (Richards, Benson, Donnelly, & Hadwin, 2014). Although work by Gamer and colleagues demonstrates that the amygdala plays a crucial role in the initial re-orienting to threat-diagnostic features of the face (Gamer & Buchel, 2009; Gamer et al., 2013), relatively little is known about the clinical relevance or neurobiology of these other kinds of attentional biases in adults or youth. Addressing these important issues will require the integration of eye tracking with brain imaging or electrophysiological assays in individuals with anxiety disorders or varying levels of familial or dispositional risk. Longitudinal studies in high-risk populations (e.g., patient offspring, individuals with a more negative disposition) would be especially valuable.
3. ***How do different components of the extended amygdala contribute to risk?*** Like attention, the amygdala is a complex, heterogeneous construct and can be divided into meaningful sub-components or nuclei (Fox & Kalin, 2014; Freese & Amaral, 2009; Swanson & Petrovich, 1998) (Figure 1). These nuclei are a key component of the central extended amygdala, a larger anatomical complex that runs from the dorsal amygdala (Ce), through the substantia innominata (SI), to the BST and the shell of the nucleus accumbens (Alheid & Heimer, 1988; Heimer et al., 1999; Oler et al., 2012; Yilmazer-Hanke, 2012; Shackman & Fox., 2016). Recent mechanistic work in rodents demonstrates that specific nuclei, circuits, and neuronal populations within the extended amygdala make dissociable contributions to fear and anxiety. Some of these sub-components promote rapid responses to immediate danger, some promote sustained responses in the face of novelty and uncertain threat, some support both kinds of response, and still others appear to dampen fear- and anxiety-related responses (Botta et al., 2015; Daniel & Rainnie, 2016; Davis et al., 2010; Duvarci, Bauer, & Pare, 2009; Kim et al., 2013; Tovote et al., 2015; Walker & Davis, 2008).

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

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

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

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

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

6. **What mechanisms underlie individual differences in risk?** Much of the data that we have reviewed comes from brain imaging studies. Aside from unresolved questions about the origins and significance of the measured signals (Logothetis, 2008), the most important limitation of imaging studies is that they cannot address causation. A crucial challenge for future studies is to develop a mechanistic understanding of the brain circuits that confer increased risk for the development of internalizing disorders in adults and youth. Addressing this fundamental question requires coordinated research efforts in humans and nonhuman animal models. This could be achieved by combining mechanistic techniques in animals with the same whole-brain imaging strategies routinely used in humans, enabling the development of bidirectional

translational models (Borsook, Becerra, & Hargreaves, 2006; Casey et al., 2013; Desai et al., 2011; Ferenczi et al., 2016; Fox et al., 2010; Kaiser & Feng, 2015). Nonhuman primate models are likely to be particularly useful for modeling and understanding the neurobiology of dispositional negativity because monkeys and humans share similar genes and brains (Freese & Amaral, 2009; Gibbs et al., 2007; Preuss, 2007), which endow the two species with a shared repertoire of complex social, emotional, and cognitive behaviors (Belmonte et al., 2015; Kalin & Shelton, 2003; Preuss, 2007; Wise, 2008). Furthermore, well-established techniques already exist for studying both dispositional negativity and attention in nonhuman primates (Hadj-Bouziane et al., 2012; Noudoost, Albarran, & Moore, 2014; Oler et al., 2016). Human studies will be crucial for determining whether those mechanisms identified using animal models are conserved across species and, hence, relevant to understanding human affect and human disorders. In human studies, imaging approaches can be applied to patients with circumscribed brain damage (Motzkin, Philippi, Oler, et al., 2015; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014, 2015). Alternatively, fMRI or EEG can be combined with noninvasive perturbation techniques (Bestmann & Feredoes, 2013; Reinhart & Woodman, 2014), neurofeedback (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015; Greer, Trujillo, Glover, & Knutson, 2014; Stoeckel et al., 2014), cognitive-behavioral interventions (Britton et al., 2015; Schnyer et al., 2015), or more passive psychological manipulations (i.e., temporally unpredictable auditory stimuli; Herry et al., 2007). 'Gameified' approaches may be particularly useful for studies of youth. Prospective longitudinal imaging studies represent another fruitful approach to identifying candidate mechanisms, especially in relation to the development of internalizing disorders (Admon, Milad, & Hendler, 2013; Burghy et al., 2012; Herringa et al., 2013; McLaughlin et al., 2014; Swartz, Williamson, et al., 2015).

Conclusions

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

Acknowledgements

Authors acknowledge assistance from L. Friedman, S. Haas, and J. Smith and support from the European Research Council (ERC-2013-StG-336305.), German Research Foundation (GA 1621/2-1), National Institute of Health (DA040717 and MH107444), University of California, and University of Maryland. Authors declare no conflicts of interest.

References

- Admon, R., Lubin, G., Stern, O., Rosenberg, K., Sela, L., Ben-Ami, H., & Hendler, T. (2009). Human vulnerability to stress depends on amygdala's predisposition and hippocampal plasticity. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 14120-14125. <http://dx.doi.org/10.1073/pnas.0903183106>
- Admon, R., Milad, M. R., & Hendler, T. (2013). A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. *Trends in Cognitive Sciences*, *17*, 337-347. <http://dx.doi.org/10.1016/j.tics.2013.05.005>
- Adolphs, R. (*in press*). Consequences of developmental bilateral amygdala lesions in humans. In D. G. Amaral & R. Adolphs (Eds.), *Living without an amygdala*. NY: Guilford Press.
- Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature*, *433*, 68-72. <http://dx.doi.org/10.1038/nature03086>
- Alheid, G. F., & Heimer, L. (1988). New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata. *Neuroscience*, *27*, 1-39. [http://dx.doi.org/10.1016/0306-4522\(88\)90217-5](http://dx.doi.org/10.1016/0306-4522(88)90217-5)

- Alvarez, R. P., Kirlic, N., Misaki, M., Bodurka, J., Rhudy, J. L., Paulus, M. P., & Drevets, W. C. (2015). Increased anterior insula activity in anxious individuals is linked to diminished perceived control. *Translational Psychiatry*, 5, e591. <http://dx.doi.org/10.1038/tp.2015.84>
- Anticevic, A., Cole, M. W., Repovs, G., Savic, A., Driesen, N. R., Yang, G., . . . Krystal, J. H. (2013). Connectivity, pharmacology, and computation: toward a mechanistic understanding of neural system dysfunction in schizophrenia. *Frontiers in Psychiatry*, 4, 169. <http://dx.doi.org/10.3389/fpsy.2013.00169>
- Arce, E., Simmons, A. N., Lovero, K. L., Stein, M. B., & Paulus, M. P. (2008). Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology*, 196(4), 661-672. <http://dx.doi.org/10.1007/s00213-007-1004-8>
- Armstrong, T., & Olatunji, B. O. (2012). Eye tracking of attention in the affective disorders: a meta-analytic review and synthesis. *Clinical Psychology Review*, 32, 704-723. <http://dx.doi.org/10.1016/j.cpr.2012.09.004>
- Aue, T., & Okon-Singer, H. (2015). Expectancy biases in fear and anxiety and their link to biases in attention. *Clinical Psychology Review*, 42, 83-95. <http://dx.doi.org/10.1016/j.cpr.2015.08.005>
- Avery, S. N., Clauss, J. A., & Blackford, J. U. (2016). The human BNST: Functional role in anxiety and addiction. *Neuropsychopharmacology*, 41, 126-141. <http://dx.doi.org/10.1038/npp.2015.185>
- Avery, S. N., Clauss, J. A., Winder, D. G., Woodward, N., Heckers, S., & Blackford, J. U. (2014). BNST neurocircuitry in humans. *Neuroimage*, 91, 311-323. <http://dx.doi.org/10.1016/j.neuroimage.2014.01.017>
- Bach, D. R., Hurlemann, R., & Dolan, R. J. (2015). Impaired threat prioritisation after selective bilateral amygdala lesions. *Cortex*, 63, 206-213. <http://dx.doi.org/10.1016/j.cortex.2014.08.017>
- Ball, T. M., Sullivan, S., Flagan, T., Hitchcock, C. A., Simmons, A., Paulus, M. P., & Stein, M. B. (2012). Selective effects of social anxiety, anxiety sensitivity, and negative affectivity on the neural bases of emotional face processing. *Neuroimage*, 59, 1879-1887. <http://dx.doi.org/10.1016/j.neuroimage.2011.08.074>
- Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. *Psychological Bulletin*, 133, 1-24. <http://dx.doi.org/10.1037/0033-2909.133.1.1>
- Bar-Haim, Y., Morag, I., & Glickman, S. (2011). Training anxious children to disengage attention from threat: a randomized controlled trial. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 52, 861-869. <http://dx.doi.org/10.1111/j.1469-7610.2011.02368.x>
- Barlow, D. H., Ellard, K. K., Sauer-Zavala, S., Bullis, J. R., & Carl, J. R. (2014). The origins of neuroticism. *Perspectives on Psychological Science*, 9, 481-496. <http://dx.doi.org/10.1177/1745691614544528>
- Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2013). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science*, 2, 344-365. <http://dx.doi.org/10.1177/2167702613505532>
- Becker, M. W. (2009). Panic search: fear produces efficient visual search for nonthreatening objects. *Psychological Science*, 20, 435-437. <http://dx.doi.org/10.1111/j.1467-9280.2009.02303.x>
- Beesdo, K., Lau, J. Y., Guyer, A. E., McClure-Tone, E. B., Monk, C. S., Nelson, E. E., . . . Pine, D. S. (2009). Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. *Archives of General Psychiatry*, 66, 275-285. <http://dx.doi.org/10.1001/archgenpsychiatry.2008.545>
- Belmonte, J. C., Callaway, E. M., Churchland, P., Caddick, S. J., Feng, G., Homanics, G. E., . . . Zhang, F. (2015). Brains, genes, and primates. *Neuron*, 86, 617-631. <http://dx.doi.org/10.1016/j.neuron.2015.03.021>
- Bennett, K., Manassis, K., Duda, S., Bagnell, A., Bernstein, G. A., Garland, E. J., . . . Wilansky, P. (2015). Preventing child and adolescent anxiety disorders: Overview of systematic reviews. *Depression and Anxiety*, 32, 909-918. <http://dx.doi.org/10.1002/da.22400>
- Berkman, E. T., & Falk, E. B. (2013). Beyond brain mapping: Using neural measures to predict real-world outcomes. *Current Directions in Psychological Science*, 22, 45-50. <http://dx.doi.org/10.1177/0963721412469394>
- Berlanga, C., Heinze, G., Torres, M., Apiquian, R., & Cabellero, A. (1999). Personality and clinical predictors of recurrence in depression. *Psychiatric Services*, 50, 376-380. <http://dx.doi.org/10.1176/ps.50.3.376>
- Bestmann, S., & Feredoes, E. (2013). Combined neurostimulation and neuroimaging in cognitive neuroscience: past, present, and future. *Annals of the New York Academy of Sciences*, 1296, 11-30. <http://dx.doi.org/10.1111/nyas.12110>

- Blackford, J. U., Allen, A. H., Cowan, R. L., & Avery, S. N. (2013). Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. *Social Cognitive and Affect Neuroscience*, 8, 143-150. <http://dx.doi.org/10.1093/scan/nsr078>
- Blackford, J. U., Avery, S. N., Cowan, R. L., Shelton, R. C., & Zald, D. H. (2011). Sustained amygdala response to both novel and newly familiar faces characterizes inhibited temperament. *Social Cognitive and Affect Neuroscience*, 6, 621-629. <http://dx.doi.org/10.1093/scan/nsq073>
- Blackford, J. U., Avery, S. N., Shelton, R. C., & Zald, D. H. (2009). Amygdala temporal dynamics: temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neuroscience*, 10, 145. <http://dx.doi.org/10.1186/1471-2202-10-145>
- Blairy, S., Herrera, p., & Hess, U. (1999). Mimicry and the judgment of emotional facial expressions. *Journal of Nonverbal Behavior*, 23, 5-41. <http://dx.doi.org/10.1023/A:1021370825283>
- Bocanegra, B. R., & Zeelenberg, R. (2009). Emotion improves and impairs early vision. *Psychological Science*, 20, 707-713. <http://dx.doi.org/10.1111/j.1467-9280.2009.02354.x>
- Bocanegra, B. R., & Zeelenberg, R. (2011). Emotional cues enhance the attentional effects on spatial and temporal resolution. *Psychonomic Bulletin & Review*, 18, 1071-1076. <http://dx.doi.org/10.3758/s13423-011-0156-z>
- Boehme, S., Ritter, V., Tefikow, S., Stangier, U., Strauss, B., Miltner, W. H., & Straube, T. (2015). Neural correlates of emotional interference in social anxiety disorder. *PLoS ONE*, 10, e0128608. <http://dx.doi.org/10.1371/journal.pone.0128608>
- Boissy, A. (1995). Fear and fearfulness in animals. *Quarterly Review of Biology*, 70, 165-191. <http://dx.doi.org/10.1086/418981>
- Boll, S., Bartholomaeus, M., Peter, U., Lupke, U., & Gamer, M. (2016). Attentional mechanisms of social perception are biased in social phobia. *Journal of Anxiety Disorders*, 40, 83-93. <http://dx.doi.org/10.1016/j.janxdis.2016.04.004>
- Borsook, D., Becerra, L., & Hargreaves, R. (2006). A role for fMRI in optimizing CNS drug development. *Nature Reviews Drug Discovery*, 5, 411-424. <http://dx.doi.org/10.1038/nrd2027>
- Botta, P., Demmou, L., Kasugai, Y., Markovic, M., Xu, C., Fadok, J. P., . . . Luthi, A. (2015). Regulating anxiety with extrasynaptic inhibition. *Nature Neuroscience*, 18, 1493-1500. <http://dx.doi.org/10.1038/nn.4102>
- Britton, J. C., Bar-Haim, Y., Clementi, M. A., Sankin, L. S., Chen, G., Shechner, T., . . . Pine, D. S. (2013). Training-associated changes and stability of attention bias in youth: Implications for Attention Bias Modification Treatment for pediatric anxiety. *Developmental Cognitive Neuroscience*, 4, 52-64. <http://dx.doi.org/10.1016/j.dcn.2012.11.001>
- Britton, J. C., Suway, J. G., Clementi, M. A., Fox, N. A., Pine, D. S., & Bar-Haim, Y. (2015). Neural changes with attention bias modification for anxiety: a randomized trial. *Social Cognitive and Affective Neuroscience*, 10, 913-920. <http://dx.doi.org/10.1093/scan/nsu141>
- Brown, G. G., Ostrowitzki, S., Stein, M. B., von Kienlin, M., Liu, T. T., Simmons, A., . . . Paulus, M. (2015). Temporal profile of brain response to alprazolam in patients with generalized anxiety disorder. *Psychiatry Research*, 233, 394-401. <http://dx.doi.org/10.1016/j.psychresns.2015.06.016>
- Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., . . . Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience*, 15, 1736-1741. <http://dx.doi.org/10.1038/nn.3257>
- Bystritsky, A. (2006). Treatment-resistant anxiety disorders. *Molecular Psychiatry*, 11, 805-814. <http://dx.doi.org/10.1038/sj.mp.4001852>
- Calder, A. J., Ewbank, M. P., & Passamonti, L. (2011). Personality influences the neural responses to viewing facial expressions of emotion. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366, 1684-1701. <http://dx.doi.org/10.1098/rstb.2010.0362>
- Carretie, L. (2014). Exogenous (automatic) attention to emotional stimuli: a review. *Cognitive, Affective and Behavioral Neuroscience*, 14, 1228-1258. <http://dx.doi.org/10.3758/s13415-014-0270-2>
- Casey, B. J., Craddock, N., Cuthbert, B. N., Hyman, S. E., Lee, F. S., & Ressler, K. J. (2013). DSM-5 and RDoC: progress in psychiatry research? *Nature Reviews Neuroscience*, 14, 810-814. <http://dx.doi.org/10.1038/nrn3621>
- Caspi, A., Roberts, B. W., & Shiner, R. L. (2005). Personality development: stability and change. *Annual Review of Psychology*, 56, 453-484. <http://dx.doi.org/10.1146/annurev.psych.55.090902.141913>

- Cavanagh, J. F., & Shackman, A. J. (2015). Frontal midline theta reflects anxiety and cognitive control: Meta-analytic evidence. *Journal of Physiology, Paris*, 109, 3-15. <http://dx.doi.org/10.1016/j.jphysparis.2014.04.003>
- Chang, L. J., Gianaros, P. J., Manuck, S. B., Krishnan, A., & Wager, T. D. (2015). A sensitive and specific neural signature for picture-induced negative affect. *PLOS Biology*, 13, e1002180. <http://dx.doi.org/10.1371/journal.pbio.1002180>
- Chase, H. W., Eickhoff, S. B., Laird, A. R., & Hogarth, L. (2011). The neural basis of drug stimulus processing and craving: an activation likelihood estimation meta-analysis. *Biological Psychiatry*, 70, 785-793. <http://dx.doi.org/10.1016/j.biopsych.2011.05.025>
- Choi, J. S., & Kim, J. J. (2010). Amygdala regulates risk of predation in rats foraging in a dynamic fear environment. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 21773-21777. <http://dx.doi.org/10.1073/pnas.1010079108>
- Chronis-Tuscano, A., Rubin, K. H., O'Brien, K. A., Coplan, R. J., Thomas, S. R., Dougherty, L. R., . . . Wimsatt, M. (2015). Preliminary evaluation of a multimodal early intervention program for behaviorally inhibited preschoolers. *Journal of Consulting and Clinical Psychology*, 83, 534-540. <http://dx.doi.org/10.1037/a0039043>
- Chun, M. M., Golomb, J. D., & Turk-Browne, N. B. (2011). A taxonomy of external and internal attention. *Annual Review of Psychology*, 62, 73-101. <http://dx.doi.org/10.1146/annurev.psych.093008.100427>
- Cisler, J. M., & Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*, 30, 203-216. <http://dx.doi.org/10.1016/j.cpr.2009.11.003>
- Clauss, J. A., & Blackford, J. U. (2012). Behavioral inhibition and risk for developing social anxiety disorder: a meta-analytic study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51, 1066-1075. <http://dx.doi.org/10.1016/j.jaac.2012.08.002>
- Coan, J. A., & Allen, J. J. B. (2007). *Handbook of emotion elicitation and assessment*. NY: Oxford University Press.
- Cole, C. E., Zapp, D. J., Fettig, N. B., & Perez-Edgar, K. (2016). Impact of attention biases to threat and effortful control on individual variations in negative affect and social withdrawal in very young children. *Journal of Experimental Child Psychology*, 141, 210-221. <http://dx.doi.org/10.1016/j.jecp.2015.09.012>
- Collins, P. Y., Patel, V., Joestl, S. S., March, D., Insel, T. R., Daar, A. S., . . . Stein, D. J. (2011). Grand challenges in global mental health. *Nature*, 475, 27-30. <http://dx.doi.org/10.1038/475027a>
- Conway, C. C., Craske, M. G., Zinbarg, R. E., & Mineka, S. (2016). Pathological personality traits and naturalistic course of internalizing disorders among high-risk young adults. *Depression and Anxiety*, 33, 84-93. <http://dx.doi.org/10.1002/da.22404>
- Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. (2008). Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews*, 58, 57-70. <http://dx.doi.org/10.1016/j.brainresrev.2007.10.012>
- Cousijn, H., Rijpkema, M., Qin, S., van Marle, H. J., Franke, B., Hermans, E. J., . . . Fernandez, G. (2010). Acute stress modulates genotype effects on amygdala processing in humans. *Proceedings of the National Academy of Sciences of the United States of America*, 107, 9867-9872. <http://dx.doi.org/10.1073/pnas.1003514107>
- Craske, M. G., Wolitzky-Taylor, K. B., Mineka, S., Zinbarg, R., Waters, A. M., Vrshek-Schallhorn, S., . . . Ornitz, E. (2012). Elevated responding to safe conditions as a specific risk factor for anxiety versus depressive disorders: evidence from a longitudinal investigation. *Journal of Abnormal Psychology*, 121, 315-324. <http://dx.doi.org/10.1037/a0025738>
- Creed, A. T., & Funder, D. C. (1998). Social anxiety: from the inside and outside. *Personality and Individual Differences*, 25, 19-33. [http://dx.doi.org/10.1016/S0191-8869\(98\)00037-3](http://dx.doi.org/10.1016/S0191-8869(98)00037-3)
- Dal Monte, O., Costa, V. D., Noble, P. L., Murray, E. A., & Averbach, B. B. (2015). Amygdala lesions in rhesus macaques decrease attention to threat. *Nature Communications*, 6, 10161. <http://dx.doi.org/10.1038/ncomms10161>
- Daniel, S. E., & Raine, D. G. (2016). Stress modulation of opposing circuits in the bed nucleus of the stria terminalis. *Neuropsychopharmacology*, 41, 103-125. <http://dx.doi.org/10.1038/npp.2015.178>
- Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., . . . Kugel, H. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry*, 71, 286-293. <http://dx.doi.org/10.1016/j.biopsych.2011.10.021>

- Davis, M., Walker, D. L., Miles, L., & Grillon, C. (2010). Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. *Neuropsychopharmacology*, *35*, 105-135. <http://dx.doi.org/10.1038/npp.2009.109>
- Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Molecular Psychiatry*, *6*, 13-34. <http://dx.doi.org/10.1038/sj.mp.4000812>
- deBettencourt, M. T., Cohen, J. D., Lee, R. F., Norman, K. A., & Turk-Browne, N. B. (2015). Closed-loop training of attention with real-time brain imaging. *Nature Neuroscience*, *18*, 470-475. <http://dx.doi.org/10.1038/nn.3940>
- Dennis, T. A., & O'Toole, L. (2014). Mental health on the go: Effects of a gamified attention bias modification mobile application in trait anxious adults. *Clinical Psychological Science*, *2*, 576-590. <http://dx.doi.org/10.1177/2167702614522228>
- Desai, M., Kahn, I., Knoblich, U., Bernstein, J., Atallah, H., Yang, A., . . . Boyden, E. S. (2011). Mapping brain networks in awake mice using combined optical neural control and fMRI. *Journal of Neurophysiology*, *105*, 1393-1405. <http://dx.doi.org/10.1152/jn.00828.2010>
- Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience*, *18*, 193-222. <http://dx.doi.org/10.1146/annurev.ne.18.030195.001205>
- Di Simplicio, M., Doallo, S., Costoloni, G., Rohenkohl, G., Nobre, A. C., & Harmer, C. J. (2014). 'Can you look me in the face?' Short-term SSRI administration reverts avoidant ocular face exploration in subjects at risk for psychopathology. *Neuropsychopharmacology*, *39*, 3059-3066. <http://dx.doi.org/10.1038/npp.2014.159>
- DiLuca, M., & Olesen, J. (2014). The cost of brain diseases: a burden or a challenge? *Neuron*, *82*, 1205-1208. <http://dx.doi.org/10.1016/j.neuron.2014.05.044>
- Dimberg, U. (1988). Facial electromyography and the experience of emotion. *Journal of Psychophysiology*, *2*, 277-282.
- Dudeny, J., Sharpe, L., & Hunt, C. (2015). Attentional bias towards threatening stimuli in children with anxiety: A meta-analysis. *Clinical Psychology Review*, *40*, 66-75. <http://dx.doi.org/10.1016/j.cpr.2015.05.007>
- Duggan, C. F., Lee, A. S., & Murray, R. M. (1990). Does personality predict long-term outcome in depression? *British Journal of Psychiatry*, *157*, 19-24. <http://dx.doi.org/10.1192/bjp.157.1.19>
- Dunning, J. P., Auriemmo, A., Castille, C., & Hajcak, G. (2010). In the face of anger: Startle modulation to graded facial expressions. *Psychophysiology*, *47*, 874-878. <http://dx.doi.org/10.1111/j.1469-8986.2010.01007.x>
- Dunsmoor, J. E., Mitroff, S. R., & LaBar, K. S. (2009). Generalization of conditioned fear along a dimension of increasing fear intensity. *Learning and Memory*, *16*, 460-469. <http://dx.doi.org/10.1101/lm.1431609>
- Duvarci, S., Bauer, E. P., & Pare, D. (2009). The bed nucleus of the stria terminalis mediates inter-individual variations in anxiety and fear. *Journal of Neuroscience*, *29*, 10357-10361. <http://dx.doi.org/10.1523/JNEUROSCI.2119-09.2009>
- Eippert, F., Gamer, M., & Buchel, C. (2012). Neurobiological mechanisms underlying the blocking effect in aversive learning. *Journal of Neuroscience*, *32*, 13164-13176. <http://dx.doi.org/10.1523/JNEUROSCI.1210-12.2012>
- Eldar, S., Apter, A., Lotan, D., Edgar, K. P., Naim, R., Fox, N. A., . . . Bar-Haim, Y. (2012). Attention bias modification treatment for pediatric anxiety disorders: a randomized controlled trial. *American Journal of Psychiatry*, *169*, 213-220. <http://dx.doi.org/10.1176/appi.ajp.2011.11060886>
- Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, *164*, 1476-1488. <http://dx.doi.org/10.1176/appi.ajp.2007.07030504>
- Everaerd, D., Klumpers, F., van Wingen, G., Tendolkar, I., & Fernandez, G. (2015). Association between neuroticism and amygdala responsivity emerges under stressful conditions. *Neuroimage*, *112*, 218-224. <http://dx.doi.org/10.1016/j.neuroimage.2015.03.014>
- Ewbank, M. P., Lawrence, A. D., Passamonti, L., Keane, J., Peers, P. V., & Calder, A. J. (2009). Anxiety predicts a differential neural response to attended and unattended facial signals of anger and fear. *Neuroimage*, *44*, 1144-1151. <http://dx.doi.org/10.1016/j.neuroimage.2008.09.056>
- Faravelli, C., Ambonetti, A., Pallanti, S., & Pazzagli, A. (1986). Depressive relapses and incomplete recovery from index episode. *American Journal of Psychiatry*, *7*, 888-891.
- Feinstein, J. S., Adolphs, R., Damasio, A., & Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current Biology*, *21*, 1-5. <http://dx.doi.org/10.1016/j.cub.2010.11.042>

- Felmington, K., Kemp, A., Williams, L., Das, P., Hughes, G., Peduto, A., & Bryant, R. (2007). Changes in anterior cingulate and amygdala after cognitive behavior therapy of posttraumatic stress disorder. *Psychological Science, 18*, 127-129. <http://dx.doi.org/10.1111/j.1467-9280.2007.01860.x>
- Ferenczi, E. A., Zalocusky, K. A., Liston, C., Grosenick, L., Warden, M. R., Amatya, D., . . . Deisseroth, K. (2016). Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science, 351*, aac9698. <http://dx.doi.org/10.1126/science.aac9698>
- Forbes, E. E., Hariri, A. R., Martin, S. L., Silk, J. S., Moyles, D. L., Fisher, P. M., . . . Dahl, R. E. (2009). Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *American Journal of Psychiatry, 166*, 64-73. <http://dx.doi.org/10.1176/appi.ajp.2008.07081336>
- Fornito, A., Zalesky, A., & Breakspear, M. (2015). The connectomics of brain disorders. *Nature Review Neuroscience, 16*, 159-172. <http://dx.doi.org/10.1038/nrn3901>
- Fox, A. S., & Kalin, N. H. (2014). A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. *American Journal of Psychiatry, 171*, 1162-1173. <http://dx.doi.org/10.1176/appi.ajp.2014.14040449>
- Fox, A. S., Oler, J. A., Shackman, A. J., Shelton, S. E., Raveendran, M., McKay, D. R., . . . Kalin, N. H. (2015). Intergenerational neural mediators of early-life anxious temperament. *Proceedings of the National Academy of Sciences USA, 112*, 9118-9122. <http://dx.doi.org/10.1073/pnas.1508593112>
- Fox, A. S., Oler, J. A., Shelton, S. E., Nanda, S. A., Davidson, R. J., Roseboom, P. H., & Kalin, N. H. (2012). Central amygdala nucleus (Ce) gene expression linked to increased trait-like Ce metabolism and anxious temperament in young primates. *Proceedings of the National Academy of Sciences of the United States of America, 109*, 18108-18113. <http://dx.doi.org/10.1073/pnas.1206723109>
- Fox, A. S., Oler, J. A., Tromp, D. P., Fudge, J. L., & Kalin, N. H. (2015). Extending the amygdala in theories of threat processing. *Trends in Neurosciences, 38*, 319-329. <http://dx.doi.org/10.1016/j.tins.2015.03.002>
- Fox, A. S., Shelton, S. E., Oakes, T. R., Converse, A. K., Davidson, R. J., & Kalin, N. H. (2010). Orbitofrontal cortex lesions alter anxiety-related activity in the primate bed nucleus of stria terminalis. *Journal of Neuroscience, 30*, 7023-7027. <http://dx.doi.org/10.1523/JNEUROSCI.5952-09.2010>
- Fox, A. S., Shelton, S. E., Oakes, T. R., Davidson, R. J., & Kalin, N. H. (2008). Trait-like brain activity during adolescence predicts anxious temperament in primates. *PLoS ONE, 3*, e2570. <http://dx.doi.org/10.1371/journal.pone.0002570>
- Fraley, R. C., & Roberts, B. W. (2005). Patterns of continuity: a dynamic model for conceptualizing the stability of individual differences in psychological constructs across the life course. *Psychological Review, 112*, 60-74. <http://dx.doi.org/10.1037/0033-295X.112.1.60>
- Freese, J. L., & Amaral, D. G. (2009). Neuroanatomy of the primate amygdala. In P. J. Whalen & E. A. Phelps (Eds.), *The human amygdala* (pp. 3-42). NY: Guilford.
- Fried, I., MacDonald, K. A., & Wilson, C. L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron, 18*, 753-765. [http://dx.doi.org/10.1016/S0896-6273\(00\)80315-3](http://dx.doi.org/10.1016/S0896-6273(00)80315-3)
- Furmark, T., Tillfors, M., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B., & Fredrikson, M. (2002). Common changes in cerebral blood flow in patients with social phobia treated with citalopram or cognitive-behavioral therapy. *Archives of General Psychiatry, 59*, 425-433. <http://dx.doi.org/10.1001/archpsyc.59.5.425>
- Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., . . . Politi, P. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of Psychiatry and Neuroscience, 34*, 418-432.
- Gamer, M., & Buchel, C. (2009). Amygdala activation predicts gaze toward fearful eyes. *Journal of Neuroscience, 29*, 9123-9126. <http://dx.doi.org/10.1523/JNEUROSCI.1883-09.2009>
- Gamer, M., Schmitz, A. K., Tittgemeyer, M., & Schilbach, L. (2013). The human amygdala drives reflexive orienting towards facial features. *Current Biology, 23*, R917-918. <http://dx.doi.org/10.1016/j.cub.2013.09.008>
- Gamer, M., Zurowski, B., & Buchel, C. (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 9400-9405. <http://dx.doi.org/10.1073/pnas.1000985107>
- Gibbs, R. A., Rogers, J., Katze, M. G., Bumgarner, R., Weinstock, G. M., Mardis, E. R., . . . Ziegler, A. S. (2007). Evolutionary and biomedical insights from the rhesus macaque genome. *Science, 316*, 222-234. <http://dx.doi.org/10.1126/science.1139247>

- Gosling, S. D., & Mason, W. (2015). Internet research in psychology. *Annual Review of Psychology*, 66, 877-902. <http://dx.doi.org/10.1146/annurev-psych-010814-015321>
- Gothard, K. M., Battaglia, F. P., Erickson, C. A., Spitler, K. M., & Amaral, D. G. (2007). Neural responses to facial expression and face identity in the monkey amygdala. *Journal of Neurophysiology*, 97, 1671-1683. <http://dx.doi.org/10.1152/jn.00714.2006>
- Greer, S. M., Trujillo, A. J., Glover, G. H., & Knutson, B. (2014). Control of nucleus accumbens activity with neurofeedback. *Neuroimage*, 96, 237-244. <http://dx.doi.org/10.1016/j.neuroimage.2014.03.073>
- Griebel, G., & Holmes, A. (2013). 50 years of hurdles and hope in anxiolytic drug discovery. *Nature Reviews Drug Discovery*, 12, 667-687. <http://dx.doi.org/10.1038/nrd4075>
- Grillon, C., & Charney, D. R. (2011). In the face of fear: anxiety sensitizes defensive responses to fearful faces. *Psychophysiology*, 48, 1745-1752. <http://dx.doi.org/10.1111/j.1469-8986.2011.01268.x>
- Grupe, D. W., & Nitschke, J. B. (2013). Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*, 14, 488-501. <http://dx.doi.org/10.1038/nrn3524>
- Hadj-Bouziane, F., Liu, N., Bell, A. H., Gothard, K. M., Luh, W. M., Tootell, R. B., . . . Ungerleider, L. G. (2012). Amygdala lesions disrupt modulation of functional MRI activity evoked by facial expression in the monkey inferior temporal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 109, E3640-3648. <http://dx.doi.org/10.1073/pnas.1218406109>
- Hakulinen, C., Elovainio, M., Pulkki-Raback, L., Virtanen, M., Kivimaki, M., & Jokela, M. (2015). Personality and depressive symptoms: Individual participant meta-analysis of 10 cohort studies. *Depression and Anxiety*, 32, 461-470. <http://dx.doi.org/10.1002/da.22376>
- Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. *American Journal of Psychiatry*, 169, 693-703. <http://dx.doi.org/10.1176/appi.ajp.2012.11071105>
- Hare, T. A., Tottenham, N., Galvan, A., Voss, H. U., Glover, G. H., & Casey, B. J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biological Psychiatry*, 63, 927-934. <http://dx.doi.org/10.1016/j.biopsych.2008.03.015>
- Harmer, C. J., Mackay, C. E., Reid, C. B., Cowen, P. J., & Goodwin, G. M. (2006). Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biological Psychiatry*, 59, 816-820. <http://dx.doi.org/10.1016/j.biopsych.2005.10.015>
- Heimer, L., de Olmos, J. S., Alheid, G. F., Pearson, J., Sakamoto, N., Shinoda, K., . . . Switzer, R. C. (1999). The human basal forebrain. In F. E. Bloom, A. Björklund & T. Hökfelt (Eds.), *Handbook of chemical neuroanatomy* (pp. 57-226). NY: Elsevier.
- Heller, A. S., Fox, A. S., Wing, E., Mayer, K., Vack, N. J., & Davidson, R. J. (2015). Affective neurodynamics predict prolonged real-world emotional responses. *Journal of Neuroscience*, 35, 10503-10509. <http://dx.doi.org/10.1523/JNEUROSCI.0569-15.2015>
- Hengartner, M. P., Ajdacic-Gross, V., Wyss, C., Angst, J., & Rössler, W. (2016). Relationship between personality and psychopathology in a longitudinal community study: a test of the predisposition model. *Psychological Medicine*, 46, 1693-1705. <http://dx.doi.org/10.1017/S0033291716000210>
- Hengartner, M. P., Kawohl, W., Haker, H., Rössler, W., & Ajdacic-Gross, V. (2016). Big Five personality traits may inform public health policy and preventive medicine: Evidence from a cross-sectional and a prospective longitudinal epidemiologic study in a Swiss community. *Journal of Psychosomatic Research*, 84, 44-51. <http://dx.doi.org/10.1016/j.jpsychores.2016.03.012>
- Herringa, R. J., Birn, R. M., Ruttle, P. L., Burghy, C. A., Stodola, D. E., Davidson, R. J., & Essex, M. J. (2013). Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proceedings of the National Academy of Sciences of the United States of America*, 110, 19119-19124. <http://dx.doi.org/10.1073/pnas.1310766110>
- Herry, C., Bach, D. R., Esposito, F., Di Salle, F., Perrig, W. J., Scheffler, K., . . . Seifritz, E. (2007). Processing of temporal unpredictability in human and animal amygdala. *Journal of Neuroscience*, 27, 5958-5966. <http://dx.doi.org/10.1523/JNEUROSCI.5218-06.2007>
- Hess, U., Sabourin, G., & Kleck, R. E. (2007). Postauricular and eyeblink startle responses to facial expressions. *Psychophysiology*, 44, 431-435. <http://dx.doi.org/10.1111/j.1469-8986.2007.00516.x>

- Hirschfeld, R. M., Klerman, G. L., Andreasen, N. C., Clayton, P. J., & Keller, M. B. (1986). Psycho-social predictors of chronicity in depressed patients. *British Journal of Psychiatry*, *148*, 648-654. <http://dx.doi.org/10.1192/bjp.148.6.648>
- Hoffman, K. L., Gothard, K. M., Schmid, M. C., & Logothetis, N. K. (2007). Facial-expression and gaze-selective responses in the monkey amygdala. *Current Biology*, *17*, 766-772. <http://dx.doi.org/10.1016/j.cub.2007.03.040>
- Hudson, N. W., & Fraley, R. C. (2015). Volitional personality trait change: Can people choose to change their personality traits? *Journal of Personality and Social Psychology*, *109*, 490-507. <http://dx.doi.org/10.1037/pspp0000021>
- Insel, T. R. (2012). Next-generation treatments for mental disorders. *Science Translational Medicine*, *4*, 155ps119. <http://dx.doi.org/10.1126/scitranslmed.3004873>
- Izquierdo, A., Suda, R. K., & Murray, E. A. (2005). Comparison of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in rhesus monkeys. *Journal of Neuroscience*, *25*, 8534-8542. <http://dx.doi.org/10.1523/JNEUROSCI.1232-05.2005>
- Jahn, A. L., Fox, A. S., Abercrombie, H. C., Shelton, S. E., Oakes, T. R., Davidson, R. J., & Kalin, N. H. (2010). Subgenual prefrontal cortex activity predicts individual differences in hypothalamic-pituitary-adrenal activity across different contexts. *Biological Psychiatry*, *67*, 175-181. <http://dx.doi.org/10.1016/j.biopsych.2009.07.039>
- Janak, P. H., & Tye, K. M. (2015). From circuits to behaviour in the amygdala. *Nature*, *517*, 284-292. <http://dx.doi.org/10.1038/nature14188>
- Jeronimus, B. F., Riese, H., Sanderman, R., & Ormel, J. (2014). Mutual reinforcement between neuroticism and life experiences: a five-wave, 16-year study to test reciprocal causation. *Journal of Personality and Social Psychology*, *107*, 751-764. <http://dx.doi.org/10.1037/a0037009>
- Jokela, M., Hakulinen, C., Singh-Manoux, A., & Kivimaki, M. (2014). Personality change associated with chronic diseases: pooled analysis of four prospective cohort studies. *Psychological Medicine*, *44*, 2629-2640. <http://dx.doi.org/10.1017/S0033291714000257>
- Jokela, M., Kivimaki, M., Elovainio, M., & Keltikangas-Jarvinen, L. (2009). Personality and having children: a two-way relationship. *Journal of Personality and Social Psychology*, *96*, 218-230. <http://dx.doi.org/10.1037/a0014058>
- Kagan, J., Reznick, J. S., & Snidman, N. (1988). Biological bases of childhood shyness. *Science*, *240*, 167-171. <http://dx.doi.org/10.1126/science.3353713>
- Kaiser, T., & Feng, G. (2015). Modeling psychiatric disorders for developing effective treatments. *Nature Medicine*, *21*, 979-988. <http://dx.doi.org/10.1038/nm.3935>
- Kalin, N. H., Fox, A. S., Kovner, R., Riedel, M. K., Fekete, E. M., Roseboom, P. H., . . . Oler, J. A. (2016). Overexpressing corticotropin-releasing hormone in the primate amygdala increases anxious temperament and alters its neural circuit. *Biological Psychiatry*. <http://dx.doi.org/10.1016/j.biopsych.2016.01.010>
- Kalin, N. H., & Shelton, S. E. (2003). Nonhuman primate models to study anxiety, emotion regulation, and psychopathology. *Annals of the New York Academy of Sciences*, *1008*, 189-200. <http://dx.doi.org/10.1196/annals.1301.021>
- Kalin, N. H., Shelton, S. E., & Davidson, R. J. (2004). The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. *Journal of Neuroscience*, *24*, 5506-5515. <http://dx.doi.org/10.1523/JNEUROSCI.0292-04.2004>
- Kalin, N. H., Shelton, S. E., Fox, A. S., Oakes, T. R., & Davidson, R. J. (2005). Brain regions associated with the expression and contextual regulation of anxiety in primates. *Biological Psychiatry*, *58*, 796-804. <http://dx.doi.org/10.1016/j.biopsych.2005.05.021>
- Kappenman, E. S., Farrens, J. L., Luck, S. J., & Proudfit, G. H. (2014). Behavioral and ERP measures of attentional bias to threat in the dot-probe task: poor reliability and lack of correlation with anxiety. *Front Psychol*, *5*, 1368. <http://dx.doi.org/10.3389/fpsyg.2014.01368>
- Kappenman, E. S., MacNamara, A., & Proudfit, G. H. (2015). Electrocardiac evidence for rapid allocation of attention to threat in the dot-probe task. *Social Cognitive and Affective Neuroscience*, *10*(4), 577-583. <http://dx.doi.org/10.1093/scan/nsu098>
- Kendler, K. S., & Gardner, C. O. (2014). Sex differences in the pathways to major depression: a study of opposite-sex twin pairs. *American Journal of Psychiatry*, *171*, 426-435. <http://dx.doi.org/10.1176/appi.ajp.2013.13101375>

- Kendler, K. S., Neale, M. C., Kessler, R. C., & Heath, A. C. (1993). A longitudinal twin study of personality and major depression in women. *Archives of General Psychiatry*, *50*, 853-862. <http://dx.doi.org/10.1001/archpsyc.1993.01820230023002>
- Kessler, R. C., Berglund, P. A., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, *62*, 593-602. <http://dx.doi.org/10.1001/archpsyc.62.6.593>
- Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H. U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research*, *21*, 169-184. <http://dx.doi.org/10.1002/mpr.1359>
- Kim, S. Y., Adhikari, A., Lee, S. Y., Marshel, J. H., Kim, C. K., Mallory, C. S., . . . Deisseroth, K. (2013). Diverging neural pathways assemble a behavioural state from separable features in anxiety. *Nature*, *496*, 219-223. <http://dx.doi.org/10.1038/nature12018>
- Klumpers, F., Morgan, B., Terburg, D., Stein, D. J., & van Honk, J. (2015). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. *Social Cognitive and Affective Neuroscience*, nsu164. <http://dx.doi.org/10.1093/scan/nsu164>
- Knutson, B., Wolkowitz, O. M., Cole, S. W., Chan, T., Moore, E. A., Johnson, R. C., . . . Reus, V. I. (1998). Selective alteration of personality and social behavior by serotonergic intervention. *American Journal of Psychiatry*, *155*, 373-379. <http://dx.doi.org/10.1176/ajp.155.3.373>
- Kopala-Sibley, D. C., Danzig, A. P., Kotov, R., Bromet, E. J., Carlson, G. A., Olino, T. M., . . . Klein, D. N. (in press). Negative emotionality and its facets moderate the effects of exposure to hurricane Sandy on children's postdisaster depression and anxiety symptoms. *Journal of Abnormal Psychology*. <http://dx.doi.org/10.1037/abn0000152>
- Kopala-Sibley, D. C., Kotov, R., Bromet, E. J., Carlson, G. A., Danzig, A. P., Black, S. R., & Klein, D. N. (2016). Personality diatheses and Hurricane Sandy: effects on post-disaster depression. *Psychological Medicine*, *46*, 865-875. <http://dx.doi.org/10.1017/S0033291715002378>
- Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychological Bulletin*, *136*, 768-821. <http://dx.doi.org/10.1037/a0020327>
- Kouider, S., Eger, E., Dolan, R. J., & Henson, R. N. (2009). Activity in face-responsive brain regions is modulated by invisible, attended faces: evidence from masked priming. *Cerebral Cortex*, *19*, 13-23. <http://dx.doi.org/10.1093/cercor/bhn048>
- Kuhn, S., & Gallinat, J. (2011). Common biology of craving across legal and illegal drugs - a quantitative meta-analysis of cue-reactivity brain response. *European Journal of Neuroscience*, *33*, 1318-1326. <http://dx.doi.org/10.1111/j.1460-9568.2010.07590.x>
- Laceulle, O. M., Nederhof, E., Karreman, A., Ormel, J., & Van Aken, M. A. G. (2011). Stressful events and temperament change during early and middle adolescence: The Trails study. *European Journal of Personality*, *26*, 276-284. <http://dx.doi.org/10.1002/per.832>
- Laidlaw, K. E., Foulsham, T., Kuhn, G., & Kingstone, A. (2011). Potential social interactions are important to social attention. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 5548-5553. <http://dx.doi.org/10.1073/pnas.1017022108>
- Lake, R. I., Eaves, L. J., Maes, H. H., Heath, A. C., & Martin, N. G. (2000). Further evidence against the environmental transmission of individual differences in neuroticism from a collaborative study of 45,850 twins and relatives on two continents. *Behavior Genetics*, *30*, 223-233. <http://dx.doi.org/10.1023/A:1001918408984>
- Lau, J. Y. (2015). Commentary: A glass half full or half empty? Cognitive bias modification for mental health problems in children and adolescents--reflections on the meta-analysis by Cristea et al. (2015). *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*, 735-737. <http://dx.doi.org/10.1111/jcpp.12436>
- LeDoux, J. E. (2012). Rethinking the emotional brain. *Neuron*, *73*, 653-676. <http://dx.doi.org/10.1016/j.neuron.2012.02.004>
- LeDoux, J. E. (2015). *Anxious. Using the brain to understand and treat fear and anxiety*. NY: Viking.
- Lewis-Peacock, J. A., & Norman, K. A. (2014). Multi-voxel pattern analysis of fMRI data. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (5th ed., pp. 911-920). Cambridge, MA: MIT Press.

- Lim, S. L., Padmala, S., & Pessoa, L. (2009). Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 16841-16846. <http://dx.doi.org/10.1073/pnas.0904551106>
- Lindquist, K. A., Wager, T. D., Kober, H., Bliss-Moreau, E., & Barrett, L. F. (2012). The brain basis of emotion: A meta-analytic review. *Behavioral and Brain Sciences*, *35*, 121-143. <http://dx.doi.org/10.1017/S0140525X11000446>
- Linetzky, M., Pergamin-Hight, L., Pine, D. S., & Bar-Haim, Y. (2015). Quantitative evaluation of the clinical efficacy of attention bias modification treatment for anxiety disorders. *Depression and Anxiety*, *32*, 383-391. <http://dx.doi.org/10.1002/da.22344>
- LoBue, V., & Perez-Edgar, K. (2014). Sensitivity to social and non-social threats in temperamentally shy children at-risk for anxiety. *Developmental Science*, *17*, 239-247. <http://dx.doi.org/10.1111/desc.12110>
- Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*, 869-878. <http://dx.doi.org/10.1038/nature06976>
- Lopez, R. B., Hofmann, W., Wagner, D. D., Kelley, W. M., & Heatherton, T. F. (2014). Neural predictors of giving in to temptation in daily life. *Psychological Science*, *25*(7), 1337-1344. <http://dx.doi.org/10.1177/0956797614531492>
- Ludtke, O., Roberts, B. W., Trautwein, U., & Nagy, G. (2011). A random walk down university avenue: life paths, life events, and personality trait change at the transition to university life. *Journal of Personality and Social Psychology*, *101*, 620-637. <http://dx.doi.org/10.1037/a0023743>
- MacLeod, C., & Clarke, P. J. F. (2015). The attentional bias modification approach to anxiety intervention. *Clinical Psychological Science*, *3*, 58-78. <http://dx.doi.org/10.1177/2167702614560749>
- MacLeod, C., & Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annual Review of Clinical Psychology*, *8*, 189-217. <http://dx.doi.org/10.1146/annurev-clinpsy-032511-143052>
- Magidson, J. F., Roberts, B. W., Collado-Rodriguez, A., & Lejuez, C. W. (2014). Theory-driven intervention for changing personality: expectancy value theory, behavioral activation, and conscientiousness. *Developmental Psychology*, *50*, 1442-1450. <http://dx.doi.org/10.1037/a0030583>
- Mai, J. K., Paxinos, G., & Voss, T. (2007). *Atlas of the human brain* (3rd ed.). San Diego, CA: Academic Press.
- Markovic, J., Anderson, A. K., & Todd, R. M. (2014). Tuning to the significant: neural and genetic processes underlying affective enhancement of visual perception and memory. *Behavioural Brain Research*, *259*, 229-241. <http://dx.doi.org/10.1016/j.bbr.2013.11.018>
- Marsh, A. A., Ambady, N., & Kleck, R. E. (2005). The effects of fear and anger facial expressions on approach- and avoidance-related behaviors. *Emotion*, *5*, 119-124. <http://dx.doi.org/10.1037/1528-3542.5.1.119>
- Maslowsky, J., Mogg, K., Bradley, B. P., McClure-Tone, E., Ernst, M., Pine, D. S., & Monk, C. S. (2010). A preliminary investigation of neural correlates of treatment in adolescents with Generalized Anxiety Disorder. *Journal of Child and Adolescent Psychopharmacology*, *20*, 105-111. <http://dx.doi.org/10.1089/cap.2009.0049>
- Mason, W. A., Capitanio, J. P., Machado, C. J., Mendoza, S. P., & Amaral, D. G. (2006). Amygdalectomy and responsiveness to novelty in rhesus monkeys (*Macaca mulatta*): generality and individual consistency of effects. *Emotion*, *6*, 73-81. <http://dx.doi.org/10.1037/1528-3542.6.1.73>
- McClure, E. B., Monk, C. S., Nelson, E. E., Parrish, J. M., Adler, A., Blair, R. J., . . . Pine, D. S. (2007). Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. *Archives of General Psychiatry*, *64*, 97-106. <http://dx.doi.org/10.1001/archpsyc.64.1.97>
- McLaughlin, K. A., Busso, D. S., Duys, A., Green, J. G., Alves, S., Way, M., & Sheridan, M. A. (2014). Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depression and Anxiety*, *31*, 834-842. <http://dx.doi.org/10.1002/da.22284>
- McMenamin, B. W., Langeslag, S. J., Sirbu, M., Padmala, S., & Pessoa, L. (2014). Network organization unfolds over time during periods of anxious anticipation. *Journal of Neuroscience*, *34*, 11261-11273. <http://dx.doi.org/10.1523/JNEUROSCI.1579-14.2014>
- Mihalopoulos, C., Vos, T., Rapee, R. M., Pirkis, J., Chatterton, M. L., Lee, Y. C., & Carter, R. (2015). The population cost-effectiveness of a parenting intervention designed to prevent anxiety disorders in children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*, 1026-1033. <http://dx.doi.org/10.1111/jcpp.12438>

- Mobbs, D., & Kim, J. J. (2015). Neuroethological studies of fear, anxiety, and risky decision-making in rodents and humans. *Current Opinion in Behavioral Sciences*, 5, 8-15. <http://dx.doi.org/10.1016/j.cobeha.2015.06.005>
- Mogg, K., & Bradley, B. P. (2016). Anxiety and attention to threat: Cognitive mechanisms and treatment with attention bias modification. *Behaviour Research and Therapy*, 87, 76-108. <http://dx.doi.org/10.1016/j.brat.2016.08.001>
- Monk, C. S., Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Louro, H. M., . . . Pine, D. S. (2008). Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Archives of General Psychiatry*, 65, 568-576. <http://dx.doi.org/10.1001/archpsyc.65.5.568>
- Montagner, R., Mogg, K., Bradley, B. P., Pine, D. S., Czykiel, M. S., Miguel, E. C., . . . Salum, G. A. (2016). Attentional bias to threat in children at-risk for emotional disorders: role of gender and type of maternal emotional disorder. *European Child and Adolescent Psychiatry*, 25, 735-742. <http://dx.doi.org/10.1007/s00787-015-0792-3>
- Motzkin, J. C., Philippi, C. L., Oler, J. A., Kalin, N. H., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex damage alters resting blood flow to the bed nucleus of stria terminalis. *Cortex*, 64, 281-288. <http://dx.doi.org/10.1016/j.cortex.2014.11.013>
- Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2014). Ventromedial prefrontal cortex lesions alter neural and physiological correlates of anticipation. *Journal of Neuroscience*, 34, 10430-10437. <http://dx.doi.org/10.1523/JNEUROSCI.1446-14.2014>
- Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex is critical for the regulation of amygdala activity in humans. *Biological Psychiatry*, 77, 276-284. <http://dx.doi.org/10.1016/j.biopsych.2014.02.014>
- Murphy, S. E., Yiend, J., Lester, K. J., Cowen, P. J., & Harmer, C. J. (2009). Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers. *International Journal of Neuropsychopharmacology*, 12, 169-179. <http://dx.doi.org/10.1017/S1461145708009164>
- Naim, R., Abend, R., Wald, I., Eldar, S., Levi, O., Fruchter, E., . . . Bar-Haim, Y. (2015). Threat-related attention bias variability and posttraumatic stress. *American Journal of Psychiatry*, 172, 1242-1250. <http://dx.doi.org/10.1176/appi.ajp.2015.14121579>
- Namburi, P., Al-Hasani, R., Calhoun, G. G., Bruchas, M. R., & Tye, K. M. (2016). Architectural representation of valence in the limbic system. *Neuropsychopharmacology*, 41, 1697-1715. <http://dx.doi.org/10.1038/npp.2015.358>
- Noudoost, B., Albarran, E., & Moore, T. (2014). Neural signatures, circuitry, and modulators of selective attention. In M. S. Gazzaniga & G. R. Mangun (Eds.), *The cognitive neurosciences* (5th ed., pp. 233-243). Cambridge, MA: MIT Press.
- Okon-Singer, H., Hendler, T., Pessoa, L., & Shackman, A. J. (2015). The neurobiology of emotion-cognition interactions: Fundamental questions and strategies for future research. *Frontiers in Human Neuroscience*, 9. <http://dx.doi.org/10.3389/fnhum.2015.00282>
- Okon-Singer, H., Stout, D. M., Stockbridge, M. D., Gamer, M., Fox, A. S., & Shackman, A. J. (in press). The interplay of emotion and cognition. In A. S. Fox, R. C. Lapate, A. J. Shackman & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed.). NY: Oxford University Press.
- Olderbak, S., Hildebrandt, A., Pinkpank, T., Sommer, W., & Wilhelm, O. (2014). Psychometric challenges and proposed solutions when scoring facial emotion expression codes. *Behavior Research Methods*, 46, 992-1006. <http://dx.doi.org/10.3758/s13428-013-0421-3>
- Oler, J. A., Birn, R. M., Patriat, R., Fox, A. S., Shelton, S. E., Burghy, C. A., . . . Kalin, N. H. (2012). Evidence for coordinated functional activity within the extended amygdala of non-human and human primates. *Neuroimage*, 61, 1059-1066. <http://dx.doi.org/10.1016/j.neuroimage.2012.03.045>
- Oler, J. A., Fox, A. S., Shackman, A. J., & Kalin, N. H. (2016). The central nucleus of the amygdala is a critical substrate for individual differences in anxiety. In D. G. Amaral & R. Adolphs (Eds.), *Living without an amygdala*. NY: Guilford.
- Oler, J. A., Fox, A. S., Shelton, S. E., Rogers, J., Dyer, T. D., Davidson, R. J., . . . Kalin, N. H. (2010). Amygdalar and hippocampal substrates of anxious temperament differ in their heritability. *Nature*, 466, 864-868. <http://dx.doi.org/10.1038/nature09282>

- Onnis, R., Dadds, M. R., & Bryant, R. A. (2011). Is there a mutual relationship between opposite attentional biases underlying anxiety? *Emotion, 11*, 582-594. <http://dx.doi.org/10.1037/a0022019>
- Oosterhof, N. N., & Todorov, A. (2008). The functional basis of face evaluation. *Proceedings of the National Academy of Sciences of the United States of America, 105*, 11087-11092. <http://dx.doi.org/10.1073/pnas.0805664105>
- Oosterhof, N. N., & Todorov, A. (2009). Shared perceptual basis of emotional expressions and trustworthiness impressions from faces. *Emotion, 9*, 128-133. <http://dx.doi.org/10.1037/a0014520>
- Ormel, J., Jeronimus, B. F., Kotov, R., Riese, H., Bos, E. H., Hankin, B., . . . Oldehinkel, A. J. (2013). Neuroticism and common mental disorders: meaning and utility of a complex relationship. *Clinical Psychology Review, 33*, 686-697. <http://dx.doi.org/10.1016/j.cpr.2013.04.003>
- Ormel, J., Oldehinkel, A. J., & Vollebergh, W. (2004). Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Archives of General Psychiatry, 61*, 990-996. <http://dx.doi.org/10.1001/archpsyc.61.10.990>
- Parker, P. D., Ludtke, O., Trautwein, U., & Roberts, B. W. (2012). Personality and relationship quality during the transition from high school to early adulthood. *Journal of Personality, 80*, 1061-1089. <http://dx.doi.org/10.1111/j.1467-6494.2012.00766.x>
- Paulus, M. P., Feinstein, J. S., Castillo, G., Simmons, A. N., & Stein, M. B. (2005). Dose-dependent decrease of activation in bilateral amygdala and insula by lorazepam during emotion processing. *Archives of General Psychiatry, 62*, 282-288. <http://dx.doi.org/10.1001/archpsyc.62.3.282>
- Perez-Edgar, K., Bar-Haim, Y., McDermott, J. M., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2010). Attention biases to threat and behavioral inhibition in early childhood shape adolescent social withdrawal. *Emotion, 10*, 349-357. <http://dx.doi.org/10.1037/a0018486>
- Perez-Edgar, K., McDermott, J. N., Korelitz, K., Degnan, K. A., Curby, T. W., Pine, D. S., & Fox, N. A. (2010). Patterns of sustained attention in infancy shape the developmental trajectory of social behavior from toddlerhood through adolescence. *Developmental Psychology, 46*, 1723-1730. <http://dx.doi.org/10.1037/a0021064>
- Perez-Edgar, K., Reeb-Sutherland, B. C., McDermott, J. M., White, L. K., Henderson, H. A., Degnan, K. A., . . . Fox, N. A. (2011). Attention biases to threat link behavioral inhibition to social withdrawal over time in very young children. *Journal of Abnormal Child Psychology, 39*, 885-895. <http://dx.doi.org/10.1007/s10802-011-9495-5>
- Perlman, S. B., Morris, J. P., Vander Wyk, B. C., Green, S. R., Doyle, J. L., & Pelphrey, K. A. (2009). Individual differences in personality predict how people look at faces. *PLoS ONE, 4*, e5952. <http://dx.doi.org/10.1371/journal.pone.0005952>
- Pessoa, L. (2013). *The cognitive-emotional brain: From interactions to integration*. Cambridge, MA: MIT Press. <http://dx.doi.org/10.7551/mitpress/9780262019569.001.0001>
- Petersen, S. E., & Sporns, O. (2015). Brain networks and cognitive architectures. *Neuron, 88*, 207-219. <http://dx.doi.org/10.1016/j.neuron.2015.09.027>
- Pfeiffer, U. J., Vogeley, K., & Schilbach, L. (2013). From gaze cueing to dual eye-tracking: novel approaches to investigate the neural correlates of gaze in social interaction. *Neuroscience and Biobehavioral Reviews, 37*, 2516-2528. <http://dx.doi.org/10.1016/j.neubiorev.2013.07.017>
- Phan, K. L., Coccaro, E. F., Angstadt, M., Kreger, K. J., Mayberg, H. S., Liberzon, I., & Stein, M. B. (2013). Corticolimbic brain reactivity to social signals of threat before and after sertraline treatment in generalized social phobia. *Biological Psychiatry, 73*, 329-336. <http://dx.doi.org/10.1016/j.biopsych.2012.10.003>
- Phelps, E. A., Ling, S., & Carrasco, M. (2006). Emotion facilitates perception and potentiates the perceptual benefits of attention. *Psychological Science, 17*, 292-299. <http://dx.doi.org/10.1111/j.1467-9280.2006.01701.x>
- Pichon, S., Miendlarzewska, E. A., Eryilmaz, H., & Vuilleumier, P. (2015). Cumulative activation during positive and negative events and state anxiety predicts subsequent inertia of amygdala reactivity. *Social Cognitive and Affective Neuroscience, 10*, 180-190. <http://dx.doi.org/10.1093/scan/nsu044>
- Pine, D. S., & Fox, N. A. (2015). Childhood antecedents and risk for adult mental disorders. *Annual Review of Psychology, 66*, 459-485. <http://dx.doi.org/10.1146/annurev-psych-010814-015038>

- Pourtois, G., Schettino, A., & Vuilleumier, P. (2013). Brain mechanisms for emotional influences on perception and attention: what is magic and what is not. *Biological Psychology*, *92*, 492-512.
<http://dx.doi.org/10.1016/j.biopsycho.2012.02.007>
- Power, R. A., & Pluess, M. (2015). Heritability estimates of the Big Five personality traits based on common genetic variants. *Translational Psychiatry*, *5*, e604. <http://dx.doi.org/10.1038/tp.2015.96>
- Preuss, T. M. (2007). Primate brain evolution in phylogenetic context. In J. H. Kaas & T. M. Preuss (Eds.), *Evolution of Nervous Systems* (Vol. 4, pp. 3-34). NY: Elsevier. <http://dx.doi.org/10.1016/B0-12-370878-8/00005-7>
- Price, R. B., Allen, K. B., Silk, J. S., Ladouceur, C. D., Ryan, N. D., Dahl, R. E., . . . Siegle, G. J. (2016). Vigilance in the laboratory predicts avoidance in the real world: A dimensional analysis of neural, behavioral, and ecological momentary data in anxious youth. *Developmental Cognitive Neuroscience*, *19*, 128-136.
<http://dx.doi.org/10.1016/j.dcn.2016.03.001>
- Price, R. B., Siegle, G. J., Silk, J. S., Ladouceur, C. D., McFarland, A., Dahl, R. E., & Ryan, N. D. (2014). Looking under the hood of the dot-probe task: an fMRI study in anxious youth. *Depression and Anxiety*, *31*, 178-187.
<http://dx.doi.org/10.1002/da.22255>
- Quilty, L. C., De Fruyt, F., Rolland, J. P., Kennedy, S. H., Rouillon, P. F., & Bagby, R. M. (2008). Dimensional personality traits and treatment outcome in patients with major depressive disorder. *Journal of Affective Disorders*, *108*, 241-250. <http://dx.doi.org/10.1016/j.jad.2007.10.022>
- Reinecke, A., Waldenmaier, L., Cooper, M. J., & Harmer, C. J. (2013). Changes in automatic threat processing precede and predict clinical changes with exposure-based cognitive-behavior therapy for panic disorder. *Biological Psychiatry*, *73*, 1064-1070. <http://dx.doi.org/10.1016/j.biopsycho.2013.02.005>
- Reinhart, R. M., & Woodman, G. F. (2014). Causal control of medial-frontal cortex governs electrophysiological and behavioral indices of performance monitoring and learning. *Journal of Neuroscience*, *34*, 4214-4227.
<http://dx.doi.org/10.1523/JNEUROSCI.5421-13.2014>
- Richards, H. J., Benson, V., Donnelly, N., & Hadwin, J. A. (2014). Exploring the function of selective attention and hypervigilance for threat in anxiety. *Clinical Psychology Review*, *34*, 1-13.
<http://dx.doi.org/10.1016/j.cpr.2013.10.006>
- Riemann, B. C., Kuckertz, J. M., Rozenman, M., Weersing, V. R., & Amir, N. (2013). Augmentation of youth cognitive behavioral and pharmacological interventions with attention modification: a preliminary investigation. *Depression and Anxiety*, *30*, 822-828. <http://dx.doi.org/10.1002/da.22127>
- Roberts, B. W., Caspi, A., & Moffitt, T. E. (2003). Work experiences and personality development in young adulthood. *Journal of Personality and Social Psychology*, *84*, 582-593. <http://dx.doi.org/10.1037/0022-3514.84.3.582>
- Roberts, B. W., & DeVecchio, W. F. (2000). The rank-order consistency of personality traits from childhood to old age: a quantitative review of longitudinal studies. *Psychological Bulletin*, *126*, 3-25.
<http://dx.doi.org/10.1037/0033-2909.126.1.3>
- Roberts, B. W., & Mroczek, D. (2008). Personality trait change in adulthood. *Current Directions in Psychological Science*, *17*, 31-35. <http://dx.doi.org/10.1111/j.1467-8721.2008.00543.x>
- Robins, R. W., Caspi, A., & Moffitt, T. E. (2002). It's not just who you're with, it's who you are: Personality and relationship experiences across multiple relationships. *Journal of Personality*, *70*, 925-964.
<http://dx.doi.org/10.1111/1467-6494.05028>
- Rotshtein, P., Richardson, M. P., Winston, J. S., Kiebel, S. J., Vuilleumier, P., Eimer, M., . . . Dolan, R. J. (2010). Amygdala damage affects event-related potentials for fearful faces at specific time windows. *Human Brain Mapping*, *31*, 1089-1105. <http://dx.doi.org/10.1002/hbm.20921>
- Roy, A. K., Dennis, T. A., & Warner, C. M. (2015). A critical review of attentional threat bias and its role in the treatment of pediatric anxiety disorders. *Journal of Cognitive Psychotherapy*, *29*, 171-184.
<http://dx.doi.org/10.1891/0889-8391.29.3.171>
- Rudaizky, D., Basanovic, J., & MacLeod, C. (2014). Biased attentional engagement with, and disengagement from, negative information: independent cognitive pathways to anxiety vulnerability? *Cognitive Emotion*, *28*, 245-259.
<http://dx.doi.org/10.1080/02699931.2013.815154>
- Sabatinelli, D., Fortune, E. E., Li, Q., Siddiqui, A., Krafft, C., Oliver, W. T., . . . Jeffries, J. (2011). Emotional perception: Meta-analyses of face and natural scene processing. *Neuroimage*, *54*, 2524-2533.
<http://dx.doi.org/10.1016/j.neuroimage.2010.10.011>

- Salum, G. A., Mogg, K., Bradley, B. P., Gadelha, A., Pan, P., Tamanaha, A. C., . . . Pine, D. S. (2013). Threat bias in attention orienting: evidence of specificity in a large community-based study. *Psychological Medicine*, *43*, 733-745. <http://dx.doi.org/10.1017/S0033291712001651>
- Sano, A., Phillips, A. J., Yu, A. Z., McHill, A. W., Taylor, S., Jaques, N., . . . Picard, R. W. (2015). *Recognizing academic performance, sleep quality, stress level, and mental health using personality traits, wearable sensors and mobile phones*. Paper presented at the 12th International IEEE Conference on Wearable and Implantable Body Sensor Networks. <http://dx.doi.org/10.1109/bsn.2015.7299420>
- Scheller, E., Buchel, C., & Gamer, M. (2012). Diagnostic features of emotional expressions are processed preferentially. *PLoS ONE*, *7*, e41792. <http://dx.doi.org/10.1371/journal.pone.0041792>
- Schnyer, D. M., Beevers, C. G., deBettencourt, M. T., Sherman, S. M., Cohen, J. D., Norman, K. A., & Turk-Browne, N. B. (2015). Neurocognitive therapeutics: from concept to application in the treatment of negative attention bias. *Biology of Mood & Anxiety Disorders*, *5*, 1. <http://dx.doi.org/10.1186/s13587-015-0016-y>
- Schuyler, B. S., Kral, T. R., Jacquart, J., Burghy, C. A., Weng, H. Y., Perlman, D. M., . . . Davidson, R. J. (2012). Temporal dynamics of emotional responding: amygdala recovery predicts emotional traits. *Social Cognitive and Affective Neuroscience*, *9*, 176-181. <http://dx.doi.org/10.1093/scan/nss131>
- Scott, J., Williams, J. M., Brittlebank, A., & Ferrier, I. N. (1995). The relationship between premorbid neuroticism, cognitive dysfunction and persistence of depression: a 1-year follow-up. *Journal of Affective Disorders*, *33*, 167-172. [http://dx.doi.org/10.1016/0165-0327\(94\)00085-N](http://dx.doi.org/10.1016/0165-0327(94)00085-N)
- Seo, D., Tsou, K. A., Ansell, E. B., Potenza, M. N., & Sinha, R. (2014). Cumulative adversity sensitizes neural response to acute stress: association with health symptoms. *Neuropsychopharmacology*, *39*, 670-680. <http://dx.doi.org/10.1038/npp.2013.250>
- Sergerie, K., Chochol, C., & Armony, J. L. (2008). The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *32*, 811-830. <http://dx.doi.org/10.1016/j.neubiorev.2007.12.002>
- Servaas, M. N., Geerligs, L., Renken, R. J., Marsman, J. B., Ormel, J., Riese, H., & Aleman, A. (2014). Connectomics and neuroticism: An altered functional network organization. *Neuropsychopharmacology*, *40*, 296-304. <http://dx.doi.org/10.1038/npp.2014.169>
- Sescousse, G., Caldu, X., Segura, B., & Dreher, J. C. (2013). Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *37*, 681-696. <http://dx.doi.org/10.1016/j.neubiorev.2013.02.002>
- Shackman, A. J., & Fox, A. S. (2016). Contributions of the central extended amygdala to fear and anxiety. *Journal of Neuroscience*, *36*, 8050-8063. <http://dx.doi.org/10.1523/JNEUROSCI.0982-16.2016>
- 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. *Proceedings of the National Academy of Sciences of the United States of America*, *110*, 6145-6150. <http://dx.doi.org/10.1073/pnas.1214364110>
- Shackman, A. J., Fox, A. S., & Seminowicz, D. A. (2015). The cognitive-emotional brain: Opportunities and challenges for understanding neuropsychiatric disorders. *Behavioral and Brain Sciences*, *38*, e86. <http://dx.doi.org/10.1017/s0140525x15000679>
- Shackman, A. J., Salomons, T. V., Slagter, H. A., Fox, A. S., Winter, J. J., & Davidson, R. J. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nature Reviews Neuroscience*, *12*, 154-167. <http://dx.doi.org/10.1038/nrn2994>
- Shackman, A. J., Stockbridge, M. D., LeMay, E. P., & Fox, A. S. (in press). The psychological and neurobiological bases of dispositional negativity. In A. S. Fox, R. C. Lapate, A. J. Shackman & R. J. Davidson (Eds.), *The nature of emotion. Fundamental questions* (2nd ed.). NY: Oxford University Press.
- Shackman, A. J., Tromp, D. P. M., Stockbridge, M. D., Kaplan, C. M., Tillman, R. M., & Fox, A. S. (in press). Dispositional negativity: An integrative psychological and neurobiological perspective. *Psychological Bulletin*. <http://dx.doi.org/10.1037/bul0000073>
- Sheline, Y. I., Barch, D. M., Donnelly, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry*, *50*, 651-658. [http://dx.doi.org/10.1016/S0006-3223\(01\)01263-X](http://dx.doi.org/10.1016/S0006-3223(01)01263-X)

- Sheppes, G., Luria, R., Fukuda, K., & Gross, J. J. (2013). There's more to anxiety than meets the eye: Isolating threat-related attentional engagement and disengagement biases. *Emotion, 13*, 520-528. <http://dx.doi.org/10.1037/a0031236>
- Sladky, R., Baldinger, P., Kranz, G. S., Trostl, J., Hoflich, A., Lanzenberger, R., . . . Windischberger, C. (2013). High-resolution functional MRI of the human amygdala at 7 T. *European Journal of Radiology, 82*, 728-733. <http://dx.doi.org/10.1016/j.ejrad.2011.09.025>
- Smith, D. J., Escott-Price, V., Davies, G., Bailey, M. E. S., Conde, L. C., Ward, J., . . . O'Donovan, M. (2015). Genome-wide analysis of over 106,000 individuals identifies 9 neuroticism-associated loci. *bioRxiv*.
- Smith, M. L., Cottrell, G. W., Gosselin, F., & Schyns, P. G. (2005). Transmitting and decoding facial expressions. *Psychological Science, 16*, 184-189. <http://dx.doi.org/10.1111/j.0956-7976.2005.00801.x>
- Soldz, S., & Vaillant, G. E. (1999). The big five personality traits and the life course: A 45-year longitudinal study. *Journal of Research in Personality, 33*, 208-232. <http://dx.doi.org/10.1006/jrpe.1999.2243>
- Somerville, L. H., Wagner, D. D., Wig, G. S., Moran, J. M., Whalen, P. J., & Kelley, W. M. (2013). Interactions between transient and sustained neural signals support the generation and regulation of anxious emotion. *Cerebral Cortex, 23*, 49-60. <http://dx.doi.org/10.1093/cercor/bhr373>
- Soskin, D. P., Carl, J. R., Alpert, J., & Fava, M. (2012). Antidepressant effects on emotional temperament: toward a biobehavioral research paradigm for major depressive disorder. *CNS Neuroscience & Therapeutics, 18*, 441-451. <http://dx.doi.org/10.1111/j.1755-5949.2012.00318.x>
- Soto, C. J., & John, O. P. (2014). Traits in transition: the structure of parent-reported personality traits from early childhood to early adulthood. *Journal of Personality, 82*, 182-199. <http://dx.doi.org/10.1111/jopy.12044>
- Soto, C. J., John, O. P., Gosling, S. D., & Potter, J. (2011). Age differences in personality traits from 10 to 65: Big Five domains and facets in a large cross-sectional sample. *Journal of Personality and Social Psychology, 100*, 330-348. <http://dx.doi.org/10.1037/a0021717>
- Spezio, M. L., Huang, P. Y., Castelli, F., & Adolphs, R. (2007). Amygdala damage impairs eye contact during conversations with real people. *Journal of Neuroscience, 27*, 3994-3997. <http://dx.doi.org/10.1523/JNEUROSCI.3789-06.2007>
- Springer, U. S., Rosas, A., McGetrick, J., & Bowers, D. (2007). Differences in startle reactivity during the perception of angry and fearful faces. *Emotion, 7*, 516-525. <http://dx.doi.org/10.1037/1528-3542.7.3.516>
- Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry, 164*, 318-327. <http://dx.doi.org/10.1176/ajp.2007.164.2.318>
- Steunenberg, B., Beekman, A. T., Deeg, D. J., & Kerkhof, A. J. (2010). Personality predicts recurrence of late-life depression. *Journal of Affective Disorders, 123*, 164-172. <http://dx.doi.org/10.1016/j.jad.2009.08.002>
- Stoeckel, L. E., Garrison, K. A., Ghosh, S., Wightton, P., Hanlon, C. A., Gilman, J. M., . . . Evins, A. E. (2014). Optimizing real time fMRI neurofeedback for therapeutic discovery and development. *Neuroimage: Clinical, 5*, 245-255. <http://dx.doi.org/10.1016/j.nicl.2014.07.002>
- Strawn, J. R., Wehry, A. M., DeBello, M. P., Rynn, M. A., & Strakowski, S. (2012). Establishing the neurobiologic basis of treatment in children and adolescents with generalized anxiety disorder. *Depression and Anxiety, 29*, 328-339. <http://dx.doi.org/10.1002/da.21913>
- Swanson, L. W., & Petrovich, G. D. (1998). What is the amygdala? *Trends in the Neurosciences, 21*, 323-331. [http://dx.doi.org/10.1016/S0166-2236\(98\)01265-X](http://dx.doi.org/10.1016/S0166-2236(98)01265-X)
- Swartz, J. R., Knodt, A. R., Radtke, S. R., & Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron, 85*, 505-511. <http://dx.doi.org/10.1016/j.neuron.2014.12.055>
- Swartz, J. R., Williamson, D. E., & Hariri, A. R. (2015). Developmental change in amygdala reactivity during adolescence: effects of family history of depression and stressful life events. *American Journal of Psychiatry, 172*(3), 276-283. <http://dx.doi.org/10.1176/appi.ajp.2014.14020195>
- Tang, D. W., Fellows, L. K., Small, D. M., & Dagher, A. (2012). Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. *Physiology and Behavior, 106*, 317-324. <http://dx.doi.org/10.1016/j.physbeh.2012.03.009>
- Tang, Y. Y., Holzel, B. K., & Posner, M. I. (2015). The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience, 16*, 213-225. <http://dx.doi.org/10.1038/nrn3916>

- Thomas, K. M., Drevets, W. C., Dahl, R. E., Ryan, N. D., Birmaher, B., Eccard, C. H., . . . Casey, B. J. (2001). Amygdala response to fearful faces in anxious and depressed children. *Archives of General Psychiatry*, *58*, 1057-1063. <http://dx.doi.org/10.1001/archpsyc.58.11.1057>
- Torrise, S., O'Connell, K., Davis, A., Reynolds, R., Balderston, N., Fudge, J. L., . . . Ernst, M. (2015). Resting state connectivity of the bed nucleus of the stria terminalis at ultra-high field. *Human Brain Mapping*, *36*, 4076-4088. <http://dx.doi.org/10.1002/hbm.22899>
- Tovote, P., Fadok, J. P., & Luthi, A. (2015). Neuronal circuits for fear and anxiety. *Nature Reviews Neuroscience*, *16*, 317-331. <http://dx.doi.org/10.1038/nrn3945>
- Tranel, D., Gullickson, G., Koch, M., & Adolphs, R. (2006). Altered experience of emotion following bilateral amygdala damage. *Cognitive Neuropsychiatry*, *11*, 219-232. <http://dx.doi.org/10.1080/13546800444000281>
- Turk-Browne, N. B. (2013). Functional interactions as big data in the human brain. *Science*, *342*, 580-584. <http://dx.doi.org/10.1126/science.1238409>
- Turkheimer, E., Pettersson, E., & Horn, E. E. (2014). A phenotypic null hypothesis for the genetics of personality. *Annual Review of Psychology*, *65*, 515-540. <http://dx.doi.org/10.1146/annurev-psych-113011-143752>
- Uliaszek, A. A., Hauner, K. K., Zinbarg, R. E., Craske, M. G., Mineka, S., Griffith, J. W., & Rose, R. D. (2009). An examination of content overlap and disorder-specific predictions in the associations of neuroticism with anxiety and depression. *Journal of Research in Personality*, *43*, 785-794. <http://dx.doi.org/10.1016/j.jrp.2009.05.009>
- Vaisvaser, S., Lin, T., Admon, R., Podlipsky, I., Greenman, Y., Stern, N., . . . Hendler, T. (2013). Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Frontiers Human Neuroscience*, *7*, 313. <http://dx.doi.org/10.3389/fnhum.2013.00313>
- Van Bockstaele, B., Verschuere, B., Tibboel, H., De Houwer, J., Crombez, G., & Koster, E. H. (2014). A review of current evidence for the causal impact of attentional bias on fear and anxiety. *Psychological Bulletin*, *140*, 682-721. <http://dx.doi.org/10.1037/a0034834>
- van den Bulk, B. G., Meens, P. H., van Lang, N. D., de Voogd, E. L., van der Wee, N. J., Rombouts, S. A., . . . Vermeiren, R. R. (2014). Amygdala activation during emotional face processing in adolescents with affective disorders: the role of underlying depression and anxiety symptoms. *Frontiers in Human Neuroscience*, *8*, 393. <http://dx.doi.org/10.3389/fnhum.2014.00393>
- van der Zwaag, W., Da Costa, S. E., Zurcher, N. R., Adams, R. B., Jr., & Hadjikhani, N. (2012). A 7 tesla fMRI study of amygdala responses to fearful faces. *Brain Topography*, *25*, 125-128. <http://dx.doi.org/10.1007/s10548-012-0219-0>
- van Marle, H. J., Hermans, E. J., Qin, S., & Fernandez, G. (2009). From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. *Biological Psychiatry*, *66*, 649-655. <http://dx.doi.org/10.1016/j.biopsych.2009.05.014>
- van Marle, H. J., Hermans, E. J., Qin, S., & Fernandez, G. (2010). Enhanced resting-state connectivity of amygdala in the immediate aftermath of acute psychological stress. *Neuroimage*, *53*, 348-354. <http://dx.doi.org/10.1016/j.neuroimage.2010.05.070>
- van Wingen, G. A., Geuze, E., Vermetten, E., & Fernandez, G. (2011). Perceived threat predicts the neural sequelae of combat stress. *Molecular Psychiatry*, *16*, 664-671. <http://dx.doi.org/10.1038/mp.2010.132>
- Vinkers, C. H., Joels, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W., & Boks, M. P. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety*, *31*, 737-745. <http://dx.doi.org/10.1002/da.22262>
- Vuilleumier, P., Armony, J. L., Clarke, K., Husain, M., Driver, J., & Dolan, R. J. (2002). Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect. *Neuropsychologia*, *40*, 2156-2166. [http://dx.doi.org/10.1016/S0028-3932\(02\)00045-3](http://dx.doi.org/10.1016/S0028-3932(02)00045-3)
- 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. *Nature Neuroscience*, *7*, 1271-1278. <http://dx.doi.org/10.1038/nn1341>
- Vukasovic, T., & Bratko, D. (2015). Heritability of personality: A meta-analysis of behavior genetic studies. *Psychological Bulletin*, *141*, 769-785. <http://dx.doi.org/10.1037/bul0000017>
- Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C. W., & Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *New England Journal of Medicine*, *368*, 1388-1397. <http://dx.doi.org/10.1056/NEJMoa1204471>

- Walker, D. L., & Davis, M. (2008). Role of the extended amygdala in short-duration versus sustained fear: a tribute to Dr. Lennart Heimer. *Brain Structure Function*, 213, 29-42. <http://dx.doi.org/10.1007/s00429-008-0183-3>
- Wang, S., Tudusciuc, O., Mamelak, A. N., Ross, I. B., Adolphs, R., & Rutishauser, U. (2014). Neurons in the human amygdala selective for perceived emotion. *Proceedings of the National Academy of Sciences of the United States of America*, 111, E3110-3119. <http://dx.doi.org/10.1073/pnas.1323342111>
- Waters, A. M., Bradley, B. P., & Mogg, K. (2014). Biased attention to threat in paediatric anxiety disorders (generalized anxiety disorder, social phobia, specific phobia, separation anxiety disorder) as a function of 'distress' versus 'fear' diagnostic categorization. *Psychological Medicine*, 44, 607-616. <http://dx.doi.org/10.1017/S0033291713000779>
- Waters, A. M., Pittaway, M., Mogg, K., Bradley, B. P., & Pine, D. S. (2013). Attention training towards positive stimuli in clinically anxious children. *Developmental Cognitive Neuroscience*, 4, 77-84. <http://dx.doi.org/10.1016/j.dcn.2012.09.004>
- Waters, A. M., Zimmer-Gembeck, M. J., Craske, M. G., Pine, D. S., Bradley, B. P., & Mogg, K. (2015). Look for good and never give up: A novel attention training treatment for childhood anxiety disorders. *Behaviour Research and Therapy*, 73, 111-123. <http://dx.doi.org/10.1016/j.brat.2015.08.005>
- Watson, D., & Naragon-Gainey, K. (2014). Personality, emotions, and the emotional disorders. *Clinical Psychological Science*, 2, 422-442. <http://dx.doi.org/10.1177/2167702614536162>
- Weierich, M. R., Treat, T. A., & Hollingworth, A. (2008). Theories and measurement of visual attentional processing in anxiety. *Cognition and Emotion*, 22, 985-1018. <http://dx.doi.org/10.1080/02699930701597601>
- Weissman, M. M., Prusoff, B. A., & Klerman, G. L. (1978). Personality and the prediction of long-term outcome of depression. *American Journal of Psychiatry*, 135, 797-800. <http://dx.doi.org/10.1176/ajp.135.7.797>
- White, L. K., Degnan, K. A., Henderson, H. A., Pérez-Edgar, K. A., Walker, O. L., Shechner, T., . . . Fox, N. A. (in press). Developmental relations between behavioral inhibition, anxiety, and attention biases to threat and positive information. *Child Development*.
- Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., . . . Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet*, 382, 1575-1586. [http://dx.doi.org/10.1016/S0140-6736\(13\)61611-6](http://dx.doi.org/10.1016/S0140-6736(13)61611-6)
- WHO, W. H. O. (2007). *Economic aspects of mental health in children and adolescents*. Geneva: WHO.
- Wieser, M. J., & Keil, A. (2014). Fearful faces heighten the cortical representation of contextual threat. *Neuroimage*, 86, 317-325. <http://dx.doi.org/10.1016/j.neuroimage.2013.10.008>
- Wilson, S., Vaidyanathan, U., Miller, M. B., McGue, M., & Iacono, W. G. (2014). Premorbid risk factors for major depressive disorder: are they associated with early onset and recurrent course? *Development and Psychopathology*, 26, 1477-1493. <http://dx.doi.org/10.1017/S0954579414001151>
- Wilson, S. J., Smyth, J. M., & MacLean, R. R. (2014). Integrating ecological momentary assessment and functional brain imaging methods: new avenues for studying and treating tobacco dependence. *Nicotine and Tobacco Research*, 16 Suppl 2, S102-110. <http://dx.doi.org/10.1093/ntr/ntt129>
- Windischberger, C., Lanzenberger, R., Holik, A., Spindelegger, C., Stein, P., Moser, U., . . . Kasper, S. (2010). Area-specific modulation of neural activation comparing escitalopram and citalopram revealed by pharmacofMRI: a randomized cross-over study. *Neuroimage*, 49, 1161-1170. <http://dx.doi.org/10.1016/j.neuroimage.2009.10.013>
- Wise, S. P. (2008). Forward frontal fields: phylogeny and fundamental function. *Trends in Neurosciences*, 31, 599-608. <http://dx.doi.org/10.1016/j.tins.2008.08.008>
- Wrzus, C., & Mehl, M. R. (2015). Lab and/or field? Measuring personality processes and their social consequences. *European Journal of Personality*, 29, 250-271. <http://dx.doi.org/10.1002/per.1986>
- Yilmazer-Hanke, D. M. (2012). Amygdala. In J. K. Mai & G. Paxinos (Eds.), *The human nervous system* (pp. 759-834). San Diego: Academic Press. <http://dx.doi.org/10.1016/B978-0-12-374236-0.10022-7>
- Zinbarg, R. E., Mineka, S., Bobova, L., Craske, M. G., Vrshek-Schallhorn, S., Griffith, J. W., . . . Anand, D. (2016). Testing a hierarchical model of neuroticism and its cognitive facets: Latent structure and prospective prediction of first onsets of anxiety and unipolar mood disorders during 3 years in late adolescence. *Clinical Psychological Science*, 4, 805-824. <http://dx.doi.org/10.1177/2167702615618162>
- Zvielli, A., Bernstein, A., & Koster, E. H. (2014). Dynamics of attentional bias to threat in anxious adults: bias towards and/or away? *PLoS ONE*, 9, e104025. <http://dx.doi.org/10.1371/journal.pone.0104025>