

Dispositional Negativity: An Integrative Psychological and Neurobiological Perspective

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Dispositional negativity—the propensity to experience and express more frequent, intense, or enduring negative affect—is a fundamental dimension of childhood temperament and adult personality. Elevated levels of dispositional negativity can have profound consequences for health, wealth, and happiness, drawing the attention of clinicians, researchers, and policymakers. Here, we highlight recent advances in our understanding of the psychological and neurobiological processes linking stable individual differences in dispositional negativity to momentary emotional states. Self-report data suggest that 3 key pathways—increased stressor reactivity, tonic increases in negative affect, and increased stressor exposure—explain most of the heightened negative affect that characterizes individuals with a more negative disposition. Of these 3 pathways, tonically elevated, indiscriminate negative affect appears to be most central to daily life and most relevant to the development of psychopathology. New behavioral and biological data provide insights into the neural systems underlying these 3 pathways and motivate the hypothesis that seemingly “tonic” increases in negative affect may actually reflect increased reactivity to stressors that are remote, uncertain, or diffuse. Research focused on humans, monkeys, and rodents suggests that this indiscriminate negative affect reflects trait-like variation in the activity and connectivity of several key brain regions, including the central extended amygdala and parts of the prefrontal cortex. Collectively, these observations provide an integrative psychobiological framework for understanding the dynamic cascade of processes that bind emotional traits to emotional states and, ultimately, to emotional disorders and other kinds of adverse outcomes.

Keywords: affective neuroscience, central extended amygdala, fear and anxiety, fMRI, neuroimaging

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Humans, monkeys, and other animals show marked individual differences in temperament, the tendency to experience fear, anger, disgust, joy, and other fleeting emotional states (Gosling, 2008).¹ This distinction between emotional traits and emotional states has its origins in antiquity. More than 2,000 years ago, the Roman intellectual Cicero drew a sharp distinction between anxious temperament (*anxietas*) and anxiety (*angor*; Eysenck, 1983). Like many contemporary researchers, he characterized traits as the proneness to experience particular emotional states (*proclivitas*). Our own working definition is that traits represent enduring emo-

tional and cognitive biases that first emerge early in life, but continue to evolve and grow in complexity across the life span

¹“Emotion” is a fuzzy, contentious category that conventionally includes valenced processes (e.g., action tendencies, attention, motivated learning, overt behavior, subjective feelings, and alterations in peripheral physiology) that are triggered by specific external or internal antecedents, such as actual or remembered threat in the case of fear (Anderson & Adolphs, 2014; Beck, 2015; Gendron & Barrett, 2009; Izard, 2010; Lapate & Shackman, in press).

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(Shiner, *in press-b*). Emotional traits account, in a probabilistic manner, for consistency in thoughts, feelings, physiology, and actions across time and situations (Caspi, Roberts, & Shiner, 2005; Fleeson, 2001; Shiner, *in press-a*; Shiner et al., 2012). Like other psychological constructs that vary across individuals, emotional traits reflect the combined influence of genes and experience on brain structure and function (Polderman et al., 2015).

The study of temperament has proven theoretically informative and practically important. Individual differences in temperament and personality have profound consequences for health, wealth, and happiness. Accordingly, temperament has increasingly drawn the attention of educators, social scientists, neurobiologists, clinicians, economists, and public policymakers (Duckworth & Allred, 2012; Ferguson, Heckman, & Corr, 2011; Lahey, 2009; Moffitt, Poulton, & Caspi, 2013; Roberts, Kuncel, Shiner, Caspi, & Goldberg, 2007). Despite this growing interest, fundamental questions about the nature and origins of temperament have remained unresolved. One of the most basic questions concerns the nature of the relations between trait-like differences in temperament and more transient emotional experiences and behaviors (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2013; Epstein, 1994). As the pioneering psychologist David Funder noted, traits “describe patterns and consistencies in behavior, but they don’t explain where those patterns and consistencies come from” (Funder, 1994; p. 126).

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Here, we highlight recent advances in our understanding of the psychological and neurobiological processes linking emotional traits to emotional states, focusing on *dispositional negativity*, one of the most intensively studied dimensions of temperament and personality. We begin by describing the nature of dispositional negativity and surveying its association with well-being and disease. Next, we review self-report and behavioral data suggesting that three key pathways—increased stressor reactivity, tonic increases in negative affect, and increased stressor exposure—explain most of the heightened negative affect characteristic of individuals with a negative disposition (Figure 1). In the third section of the review, we explore recent advances in our understanding of the neural systems underlying these three pathways, focusing especially on studies of fear and anxiety.

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This work motivates the hypothesis that seemingly “tonic” increases in negative affect may actually reflect increased reactivity to stressors that are uncertain, temporally remote, or perceptually diffuse (e.g., an unfamiliar experimental context, a pitch-black room; Figure 2). These observations raise a number of interesting new questions. We conclude by outlining several strategies for addressing them and for developing a deeper understanding of the pathways linking emotional traits to momentary emotional states and, ultimately, to psychopathology and other kinds of adverse outcomes.

Method

The goal of our review was to integrate psychological and biological perspectives on dispositional negativity into a coherent theoretical framework. Accordingly, it includes 601 citations covering the period between 1966 and 2016, with the major emphasis on recent research (median year of publication = 2010.5, $SD = 8.2$; in-press publications were coded as 2016). This body of research encompasses laboratory, field (e.g., daily diary, ecological momentary assessment), and epidemiological research. It includes published studies of mice, rats, monkeys, and humans, including studies of children, adolescents, adults, and elders. Although most of the work is focused on unselected individuals, we also highlight relevant evidence gleaned from studies of psychiatric and neurological patients. Of necessity, we draw on published articles and reviews from a broad spectrum of scholarly disciplines, from psychology and psychiatry to genetics and neuroscience. For all articles, backward citation checks were used to increase coverage. Although our aims and scope precluded the use of formal meta-analytic techniques, to maximize reproducibility and generalizability we place special emphasis on evidence gleaned from meta-analyses and large-scale studies, including prospective longitudinal studies and nationally representative samples.

The Nature and Consequences of Elevated Dispositional Negativity

Dispositional negativity or “negative emotionality”—the propensity to experience and express more frequent, intense, or en-

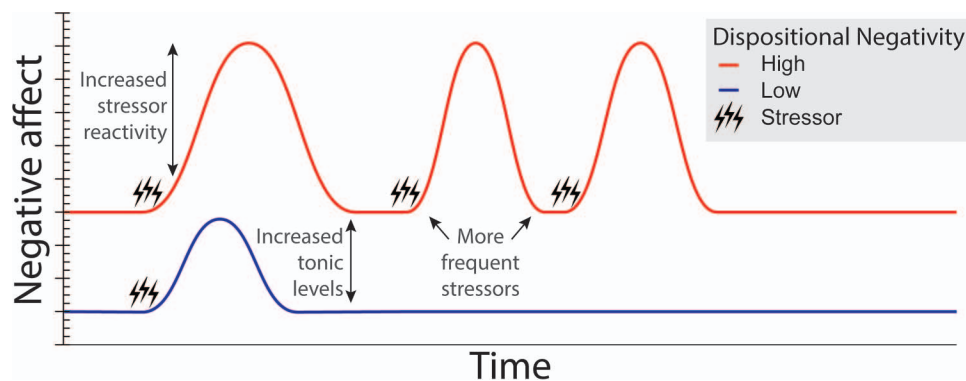


FIGURE 1

Figure 1. Pathways linking dispositional negativity (trait) to increased momentary negative affect (state). Questionnaire and behavioral data suggest that three key pathways—increased stressor reactivity, increased tonic levels of negative affect, and more frequent stressors—explain most of the heightened negative affect characteristic of individuals with a negative disposition. Lines depict hypothesized fluctuations in momentary negative affect in individuals with high (red) and low (blue) levels of dispositional negativity, respectively. Acute stressors (e.g., daily hassles, social conflict, and negative life events) are indicated by black lightning bolts. See the online article for the color version of this figure.

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during negative affect—is a fundamental dimension of childhood temperament and adult personality. Individuals with a more negative disposition tend to be anxious, guilt-prone, insecure, moody, critical, angry, and dissatisfied. They perceive the world as dangerous and threatening and themselves as inadequate (Barlow et al., 2013; Caspi et al., 2005; L. A. Clark & Watson, 2008; Lahey, 2009). Dispositional negativity is sometimes parsed into two midlevel dimensions: *anxious distress*, encompassing feelings of anxiety, fear, and depression and *irritable distress*, encompassing feelings of anger, frustration, and hostility (Caspi et al., 2005). At present, there is greater theoretical consensus about the nature and significance of anxious distress (Caspi et al., 2005; Ormel et al., 2013; Soto & John, 2016) and it has received more empirical attention (Barlow et al., 2013). Anxious distress, in turn, subsumes a variety of narrower facet traits, including anxious temperament, anxiety sensitivity, behavioral inhibition, harm avoidance, neuroticism, and trait anxiety (Barlow et al., 2013; Caspi et al., 2005; Markon, Krueger, & Watson, 2005; van den Berg et al., 2014; Widiger, 2009).²

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We conceptualize dispositional negativity as an extended family of closely related phenotypes that first emerge early in development, persist into adulthood, and reflect a combination of heritable and nonheritable factors (A. S. Fox & Kalin, 2014; Lake, Eaves, Maes, Heath, & Martin, 2000; Ormel et al., 2013; Power & Pluess, 2015; Smith et al., 2016; Soto & John, 2014; Turkheimer, Pettersson, & Horn, 2014; Vukasovic & Bratko, 2015). Among adults, concordance between self- and informant-reported (e.g., friends, family members, coworkers) dispositional negativity is substantial (Connolly, Kavanagh, & Viswesvaran, 2007; Kurtz, Puher, & Cross, 2012), particularly when multiple informants are employed (McCrae & Costa, 1987), suggesting that it is more than just a negative response bias. Core features of this phenotypic family—including increased behavioral inhibition, heightened vigilance, and other signs of fear and anxiety—are expressed similarly across mammalian species, enabling mechanistic studies to be performed in rodents and monkeys (Boissy, 1995; Mobbs & Kim, 2015; Oler, Fox, Shackman, & Kalin, 2016). Although the molecular underpinnings of dispositional negativity and its neural substrates remain poorly understood (Bastiaansen et al., 2014; Bogdan, Pagliaccio, Baranger, & Hariri, 2016; Christian et al., 2009), some promising candidates have recently been identified in humans (Buckholtz et al., 2008; Okbay et al., in press), monkeys (Alishch et al., 2014; A. S. Fox et al., 2012; Kalin et al., 2016; Oler et al., 2009; Rogers et al., 2013; Roseboom et al., 2014), and rodents (Turner, Clinton, Thompson, Watson, & Akil, 2011).

Dispositional negativity is stable, but not immutable, and like other emotional traits continues to develop and change across the life span (Fraley & Roberts, 2005; Roberts & DelVecchio, 2000; Roberts & Mroczek, 2008; Roberts, Walton, & Viechtbauer, 2006). In fact, 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). Several large ($n = 4,850–1,267,218$) international studies indicate that, from about age 14 on, women tend to report higher levels of dispositional negativity than men (De Bolle et al., 2015; Schmitt, Realo, Voracek, & Allik, 2008; Soto et al., 2011).

A range of evidence indicates that dispositional negativity can be increased by stress, trauma, and negative life events (e.g., death

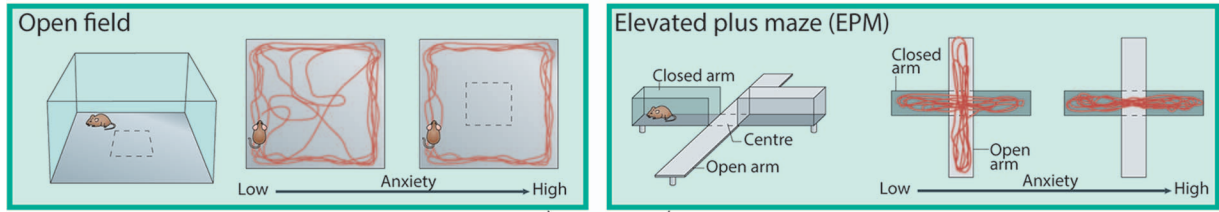
of a spouse, birth of a child, chronic disease; Barlow et al., 2013; Hensley et al., 2012; Hutteman, Bleidorn, Kerestes, et al., 2014; Jeronimus, Riese, Sanderman, & Ormel, 2014; Jokela, Hakulinen, Singh-Manoux, & Kivimaki, 2014; Jokela, Kivimaki, Elovainio, & Keltikangas-Jarvinen, 2009; Koskenvuo, Langinvainio, Kaprio, & Sarna, 1984; Laceulle, Nederhof, Karreman, Ormel, & Van Aken, 2012; Le, Donnellan, & Conger, 2013; Lockenhoff, Terracciano, Patriciu, Eaton, & Costa, 2009; Ludtke, Roberts, Trautwein, & Nagy, 2011; Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008; Mroczek & Spiro, 2003; Parker, Ludtke, Trautwein, & Roberts, 2012; Riese et al., 2014; Roberts, Caspi, & Moffitt, 2003; Roberts & Chapman, 2000; Robins, Caspi, & Moffitt, 2002). But importantly, it can also be decreased by positive experiences (e.g., job promotion, marriage; Costa, Herbst, McCrae, & Siegler, 2000; Hensley et al., 2012; Jeronimus, Ormel, Aleman, Penninx, & Riese, 2013; Le et al., 2013; Mroczek & Spiro, 2003; Neyer & Asendorpf, 2001; Roberts & Chapman, 2000; Scollon & Diener, 2006) and by 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; Soskin, Carl, Alpert, & Fava, 2012). These data raise the possibility of developing strategies for identifying high-risk individuals and intervening to prevent the onset of more severe sequelae. Identifying the psychological and neurobiological mechanisms governing the malleability of temperament is a particularly important avenue for future research, one that promises to provide new targets for intervention (A. S. Fox et al., 2012).

There is clear evidence that dispositionally negative individuals tend to experience heightened levels of momentary negative affect. Self-report measures of dispositional negativity (trait) and negative affect (state) are strongly correlated (Lieberman et al., 2016; Matthews, Deary, & Whiteman, 2009; Watson & Clark, 1984, 1992). In fact, a recent meta-analysis incorporating data from more than 30,000 individuals showed that dispositional negativity explains 30–50% of the variance in negative affect (Steel, Schmidt, & Shultz, 2008). Ratings obtained from other informants, such as clinicians and spouses, yield similar conclusions, indicating that these trait–state relations are not an artifact of response biases (Lieberman et al., 2016; McCrae & Costa, 1991; Soto & John, 2016; Steel et al., 2008; Watson & Clark, 1984).

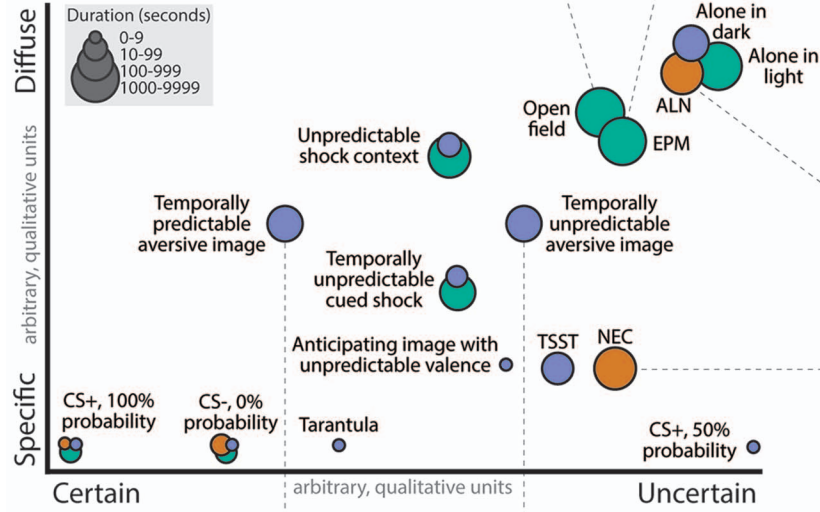
It merits comment that the impact of dispositional negativity on momentary emotional experience is not limited to negative affect. Individuals with a more negative disposition are also prone to lower levels of positive affect (Aldinger et al., 2014; Gable, Reis, & Elliot, 2000; Jacobs et al., 2011; Soto & John, 2016; Watson & Clark, 1984; Zautra, Affleck, Tennen, Reich, & Davis, 2005) and subjective wellbeing (Steel et al., 2008), perhaps reflecting a

² While there are potential benefits to focusing on narrowly defined phenotypic traits (Block, 1995, 2010; Clifford, Lemery-Chalfant, & Goldsmith, 2015; K. H. Rubin & Asendorpf, 1993), adopting a narrow perspective substantially reduces the size and scope of the relevant evidentiary record. At present, very little is known about how some facets of dispositional negativity—including anger, guilt, and shame—contribute to adverse outcomes (Kopala-Sibley, Danzig, et al., 2016), making this an important challenge for future research. From a public health perspective, focusing on broad phenotypes that confer elevated risk for a range of adverse outcomes maximizes the opportunity to develop broad-spectrum interventions (Barlow, Ellard, Sauer-Zavala, Bullis, & Carl, 2014; Chronis-Tuscano et al., 2015; Moffitt et al., 2013).

A. Rodents



D. Comparison of paradigms



B. Nonhuman primates



C. Humans

Example negative uncertain countdown:

3 5 [Image of a barking dog] 7 2 1 4 8 [Image of a crying boy] 7 5 ...

Example negative certain countdown:

2 1 [Image of a shark's mouth] 5 4 3 2 1 [Image of a sad child's face] 4 3 ...

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Figure 2 (opposite).

suppressive consequence of negative affect on reward and appetitive motivation (i.e., sometimes termed *stress-induced anhedonia*; Pizzagalli, 2014).

Dispositional negativity predicts a multitude of practically important outcomes, from satisfaction and wealth to marital stability and disease. Increased dispositional negativity is associated with lower levels of educational attainment (Damian, Su, Shanahan, Trautwein, & Roberts, 2015; Hengartner, Kawohl, Haker, Rossler, & Ajdacic-Gross, 2016) and occupational success (Furnham & Cheng, 2013; Heineck, 2011; Hengartner, Kawohl, et al., 2016; Ng, Eby, Sorensen, & Feldman, 2005; Shanahan, Bauldry, Roberts, Macmillan, & Russo, 2014; Soldz & Vaillant, 1999; Spurk & Abele, 2011; Sutin, Costa, Miech, & Eaton, 2009; Uysal & Pohlmeier, 2011; Viinikainen, Kokko, Pulkkinen, & Pehkonen, 2010). In a representative U.S. sample of 81,000 high school students, individuals who were 1 *SD* above the mean lost the equivalent of half an academic year in educational attainment and \$3,628 in annual income by the time they reached midlife compared to those 1 *SD* below the mean (in 2014 dollars; Damian et al., 2015).

Individuals with elevated dispositional negativity report reduced satisfaction with their lives (Dyrenforth, Kashy, Donnellan, &

Lucas, 2010; Soto & Luhmann, 2013), jobs (Wayne, Musisca, & Fleeson, 2004), friends (R. E. Wilson, Harris, & Vazire, 2015), and spouses (Dyrenforth et al., 2010; Solomon & Jackson, 2014). In fact, elevated levels of dispositional negativity in adolescence have been shown to predict lower levels of job satisfaction 50 years later (Staw, Bell, & Clausen, 1986) and lower levels of psychological well-being 36 years later (Abbott et al., 2008). Heightened dispositional negativity is also a strong predictor of future loneliness (Pressman et al., 2005; Stokes, 1985) and divorce (Karney & Bradbury, 1995; Kurdek, 1993). In one particularly compelling example, 278 married couples were longitudinally assessed between 1936 and 1981 (Kelly & Conley, 1987). Of these, 50 divorced. Self- and acquaintance-ratings of husbands' and wives' dispositional negativity at the initial assessment were among the strongest prenuptial predictors of divorce across the 45-year follow-up period. Similar results have been reported for spouses with preexisting anxiety disorders—for example, the odds of getting divorced among patients with a premarital diagnosis of generalized anxiety disorder is 1.7-fold greater than psychiatrically healthy controls (Kessler, Walters, & Forthofer, 1998). More frequent marital dissolution is, in turn, associated with reduced reproductive success. In a prospective study of more than 1,500

Figure 2 (opposite). Different kinds of threat. (A) Rodents (green). In rats and mice, the open field test and the elevated plus maze (EPM) are commonly used to assess emotional responses to diffuse threat. In the open field, rodents are placed into a relatively large, brightly lit, and unfamiliar context. In the elevated plus maze, rodents are placed in a maze with two open arms and two arms enclosed by walls. Freezing and avoidance of the center of the open field or the open arms of the maze provide behavioral “read-outs” of negative affect. Adapted from “Neuronal Circuits for Fear and Anxiety,” by P. Tovote, J. P. Fadok, and A. Luthi, 2015, *Nature Reviews Neuroscience*, 16, p. 325. Copyright, 2015 by Nature Publishing Group. Adapted with permission. (B) Nonhuman primates (orange). In monkeys, the human “intruder” paradigm can be used to quantify naturalistic defensive behaviors, neuroendocrine activity, and brain metabolic activity associated with exposure to a range of threats. In the “alone” (ALN) condition, the monkey is simply placed in the testing cage. This novel, diffusely threatening context elicits low levels of freezing and cortisol and a moderate frequency of alarm and separation calls. In the “no eye contact” (NEC) condition (A, left), the intruder presents his or her profile while avoiding eye contact. This elicits passive defenses, including freezing and vocal reductions, similar to procedures used for quantifying behavioral inhibition in children. Adapted from “A Translational Neuroscience Approach to Understanding the Development of Social Anxiety Disorder and Its Pathophysiology,” by A. S. Fox and N. H. Kalin, 2014, *American Journal of Psychiatry*, 171, p. 1164. Copyright, 2014 by the American Psychiatric Association. Adapted with permission. (C) Humans (purple). In humans, a wide variety of paradigms have been used to probe responses to uncertain, diffuse, or remote threat. Oftentimes, these involve the unpredictable presentation of electric shocks or, as shown in this panel, aversive images. For example, Somerville and colleagues assessed neural activity associated with the temporally certain or uncertain presentation of aversive images. Adapted from “Interactions Between Transient and Sustained Neural Signals Support the Generation and Regulation of Anxious Emotion,” by L. H. Somerville, D. D. Wagner, G. S. Wig, J. M. Moran, P. J. Whalen, and W. M. Kelley, 2013, *Cerebral Cortex*, 23, p. 51. Copyright, 2013 by Oxford University Press. Adapted with permission. (D) Comparison of paradigms (scatter plot). Threats differ along several key dimensions, including certainty (*x*-axis), physical or temporal imminence, diffuseness (*y*-axis; specific cues vs. real or virtual contexts), and duration (dot size). Here we present some common paradigms used in rodents (green), nonhuman primates (orange), and humans (purple). Studies were chosen for illustrative purposes. We did not attempt a comprehensive review of the literature and, necessarily, the locations of particular paradigms along the two dimensions of the scatter plot are approximate and somewhat arbitrary. Interestingly, many paradigms confound multiple dimensions (e.g., *if* vs. *when* threat will occur) and, because of temporal constraints imposed by conventional fMRI techniques, human imaging studies have mostly focused on the relatively brief (<2 min) anticipation of uncertain threat. Studies (duration)—Rodents: *Alone in brightly lit cage* (900 s; D. L. Walker & Davis, 1997); *CS+*, 100% probability (30 s; Duvarci et al., 2009); *CS-*, 0% probability (30; Duvarci et al., 2009); *EPM* (900 s; Tye et al., 2011); *open field* (1,080 s; Tye et al., 2011); *temporally unpredictable cued shock* ($M = 162$ s; Miles, Davis, & Walker, 2011); *Unpredictable shock context* (1,200 s; Luyten et al., 2012). Monkeys: *ALN* (1,800 s; A. S. Fox et al., 2008); *CS+*, 100% probability (4 s; Winslow, Noble, & Davis, 2007); *CS-*, 0% probability (10 s; Kalin, Shelton, Davidson, & Lynn, 1996); *NEC* (1,800 s; A. S. Fox et al., 2008). Humans: *alone in dark room* (120 s; Grillon, Pellowski, Merikangas, & Davis, 1997); *anticipating image with unpredictable valence* (5 s; Grupe et al., 2013); *CS+*, 100% probability (8 s; Gazendam et al., 2013); *CS+*, 50% probability (3 s; Buchel, Morris, Dolan, & Friston, 1998); *CS-*, 0% shock probability (conditioned safety cue; 8 s; Gazendam et al., 2013); *tarantula (video clip of approach)*; 4 s; Mobbs et al., 2010); *temporally unpredictable aversive image* (115 s; Somerville et al., 2013); *temporally unpredictable cued shock* ($M = 140$ s; Mobberg & Curtin, 2009); *Trier Social Stress Test (TSST)*; 780 s; http://topics.sciencedirect.com/topics/page/Trier_social_stress_test); *virtual reality context paired with unpredictable shock* (40 s; Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011). See the online article for the color version of this figure.

Finnish adults, a 1 *SD* increase in dispositional negativity decreased the odds of having a second and third child by 11% and 15%, respectively, largely due to the higher frequency of marital dissolution and divorce (Jokela et al., 2009).

From the perspective of physical health, dispositional negativity is associated with sleep problems (Hintsanen et al., 2014), metabolic syndrome (Phillips et al., 2010), elevated cholesterol levels (Hengartner, Kawohl, et al., 2016), and a wide variety of other physical diseases and subjective health complaints (e.g., coronary heart disease; Deary, Weiss, & Batty, 2010; Gale et al., 2016; Iacovino, Bogdan, & Oltmanns, 2016; Jokela, Pulkki-Råback, Elovainio, & Kivimäki, 2014; Lahey, 2009; Mund & Neyer, 2015). Among nearly 7,000 older adults (mean age = 68.4 years) followed as part of the Health and Retirement study, a 1 *SD* increase in dispositional negativity prospectively increased the odds of being diagnosed with a heart condition by 24%, lung disease by 29%, and hypertension by 37% during the 4-year follow-up period (Weston, Hill, & Jackson, 2015). Increased morbidity partially reflects dispositional negativity's association with unhealthy behaviors, such as chronic tobacco and substance use (Gale et al., 2016; Hakulinen, Hintsanen, et al., 2015; Hengartner, Kawohl, et al., 2016; Kotov, Gamez, Schmidt, & Watson, 2010; Leventhal et al., 2012; Malouff, Thorsteinsson, Rooke, & Schutte, 2007; Soldz & Vaillant, 1999), and likely contributes to premature mortality among individuals with a more negative disposition (Chapman, Fiscella, Kawachi, & Duberstein, 2010; Jackson, Connolly, Garrison, Leveille, & Connolly, 2015; Terracciano, Lockenhoff, Zonderman, Ferrucci, & Costa, 2008; R. S. Wilson et al., 2005).

Dispositional negativity is also a key risk factor for anxiety disorders, depression, and substance abuse (Clauss & Blackford, 2012; Conway, Craske, Zinbarg, & Mineka, 2016; Grav, Stordal, Romild, & Hellzen, 2012; Hakulinen, Elovainio, et al., 2015; Hengartner, Kawohl, et al., 2016; Kendler & Gardner, 2014; Soldz & Vaillant, 1999; Watson & Naragon-Gainey, 2014; S. Wilson, Vaidyanathan, Miller, McGue, & Iacono, 2014)—psychiatric disorders that are highly prevalent, debilitating, and often challenging to treat (Bystritsky, 2006; Collins et al., 2011; DiLuca & Olesen, 2014; Griebel & Holmes, 2013; Insel, 2012; Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Whiteford et al., 2013). The magnitude of these associations is substantial: A meta-analysis incorporating 175 studies reported that the mean Cohen's *d* across mood, anxiety, and substance use disorders was 1.65, ranging from $d \cong 2$ for dysthymia and anxiety disorders to $d = .77$ for alcohol use disorder (Kotov et al., 2010). Elevated dispositional negativity is among the strongest prospective predictors of future internalizing disorders ($k = 46$ studies; mean Cohen's $d = .63$; Ormel et al., 2013; see also D. A. Clark, Durbin, Hicks, Iacono, & McGue, in press; Laceulle, Ormel, Vollebergh, van Aken, & Nederhof, 2014; Naragon-Gainey & Watson, 2014; Zinbarg et al., in press). For example, data from the Zurich Cohort Study ($n = 591$) indicate that a 1 *SD* 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 20-year follow-up period (Hengartner, Ajdacic-Gross, Wyss, Angst, & Rossler, 2016). These relations are evident after eliminating overlapping item content (Uliaszek et al., 2009). They also appear to be strengthened by exposure to stress (Kopala-Sibley, Kotov, et al., 2016; Kopala-Sibley, Danzig, et al.,

2016; Vinkers et al., 2014), suggesting that high levels of dispositional negativity represent a diathesis (Monroe & Simons, 1991) for the internalizing spectrum of disorders (i.e., anxiety and depression). Among patients with a history of internalizing disorders, higher levels of dispositional negativity are associated with a greater number of comorbid diagnoses (Hengartner, Kawohl, et al., 2016) and a more pessimistic prognosis (Berlenga, Heinze, Torres, Apiquian, & Cabellero, 1999; Duggan, Lee, & Murray, 1990; Faravelli, Ambonetti, Pallanti, & Pazzagli, 1986; Hirschfeld, Klerman, Andreasen, Clayton, & Keller, 1986; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Ormel, Oldehinkel, & Vollebergh, 2004; Quilty et al., 2008; Scott, Williams, Brittlebank, & Ferrier, 1995; Spinhoven et al., 2011; Weissman, Prusoff, & Klerman, 1978). For example, Steunenber 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 6-year follow-up period (Steunenber, Beekman, Deeg, & Kerkhof, 2010). Among parents, higher levels of dispositional negativity are also associated with elevated clinician and teacher ratings of internalizing symptoms in their offspring (Ellenbogen & Hodgins, 2004). Determining the biological and psychological mechanisms underlying this intergenerational transmission of psychopathology remains an important challenge for future research.

Given this panoply of adverse, often comorbid outcomes, dispositional negativity imposes a tremendous burden on health care providers and the global economy (Goodwin, Hoven, Lyons, & Stein, 2002; ten Have, Oldehinkel, Vollebergh, & Ormel, 2005). Indeed, a recent Dutch study estimated that each individual in the upper quartile of the dispositional negativity distribution is associated with \$6,362 in excess costs each year, largely due to increased use of health services and loss of productivity (in 2015 dollars; Cuijpers et al., 2010). In a population the size of the United States, this would translate to \$388 billion annually or nearly a third of federal discretionary spending.

Trait-State Links Inferred From Self-Report and Behavior

Despite its profound significance for health and wealth, the processes linking individual differences in dispositional negativity (trait) to heightened negative affect (state) have only recently begun to come into focus. As shown schematically in Figure 1, self-report data from the past several decades suggest that three interrelated processes explain most of the heightened negative affect characteristic of individuals with a more negative disposition:

1. *Increased stressor reactivity*: Dispositionally negative individuals report elevated negative affect in response to a range of stressors, including negative life events, daily hassles, interpersonal conflicts, and aversive laboratory challenges.
2. *Increased negative affect in the absence of clear stressors*: Dispositionally negative individuals frequently report exaggerated apprehension and distress in relaxed and familiar settings, when potential stressors are remote, diffuse, or altogether absent. This pervasive, context-independent negative affect has been described as a "tonic" or "endogenous" effect of temperament, given the absence of a clear external source

of distress (Gross, Sutton, & Ketelaar, 1998; Watson & Clark, 1984).

3. *Increased stressor exposure and generation:* Individuals with a more negative disposition tend to act in ways that increase the likelihood of experiencing hassles, conflict, and rejection, particularly during times of heightened stress. Increased exposure to stressors, in turn, promotes more frequent, intense, or persistent negative affect.

Increased Stressor Reactivity

Individuals with a more negative disposition are emotionally volatile and tend to overreact to novelty, threat, and other stressors. In one particularly compelling example, Hengartner and colleagues assessed reactions to an “active shooter” incident that recently occurred on the campus of a Swiss university (Hengartner, van der Linden, Bohleber, & von Wyl, 2016). During the incident, an alarm sounded continuously while more than 100 heavily armed police officers secured the site. Three hours later, the “all clear” signal was given, and students and staff were allowed to leave their shelters. Online surveys revealed that individuals with a more negative disposition retrospectively reported (6–26 days later) experiencing elevated levels of fear, worry, and terror during the incident.

Experience-sampling studies show that individuals with high levels of dispositional negativity also tend to report elevated levels of negative affect in response to more mundane hassles and interpersonal conflicts in the home, school, and workplace (Bolger, 1990; Bolger & Schilling, 1991; Gable et al., 2000; Komulainen et al., 2014; Leger, Charles, Turiano, & Almeida, 2016; Mroczek & Almeida, 2004; Suls & Martin, 2005; Tan et al., 2012; Zautra et al., 2005). Heightened reactivity to everyday stressors, in turn, predicts the onset of future internalizing symptoms and episodes, characterizes patients with acute anxiety disorders and depression, and remits with pharmacological therapy (Farmer & Kashdan, 2015; Tan et al., 2012; van Winkel et al., 2015; Wichers et al., 2009).

In the laboratory, individuals with a more negative disposition report elevated distress in response to standardized aversive challenges (e.g., amputation film clips; Gross et al., 1998; Matthews et al., 2009), suggesting that heightened emotional reactivity is not an artifact of systematic response biases, mnemonic distortions, or differences in stressor exposure. These self-report data are consistent with evidence that dispositionally negative children, adults, and monkeys show exaggerated behavioral (e.g., avoidance, crying, inhibition), psychophysiological (e.g., startle, skin conductance), and neuroendocrine (e.g., cortisol) reactions to novelty and potential threat (Brooker et al., 2013; Buss et al., 2003; Hengartner, van der Linden, et al., 2016; Kagan, Snidman, Kahn, & Towsley, 2007; Norris, Larsen, & Cacioppo, 2007; Oler et al., 2016; Schmidt & Fox, 1998; Shackman et al., 2013; Vaidyanathan, Patrick, & Cuthbert, 2009).

Taken together, these observations indicate that dispositional negativity represents a diathesis that serves to enhance the likelihood, intensity, or duration of negative affect elicited by a range of common stressors. Heightened stressor reactivity also appears to causally contribute to the development and recurrence of pathological anxiety and depression.

Increased Negative Affect in the Absence of Clear Stressors

Dispositionally negative individuals often report heightened negative affect in the absence of clear and imminent stressors (Watson & Clark, 1984). In controlled laboratory settings, dispositionally negative adolescents and adults report more intense or frequent negative thoughts and feelings at “baseline,” while viewing emotionally neutral control stimuli or simply relaxing (Craske et al., 2009; Glue, Wilson, Coupland, Ball, & Nutt, 1995; Gross et al., 1998; Larsen & Ketelaar, 1989, 1991; Watson & Clark, 1984). Likewise, children with a more negative disposition show elevated heart rate at “baseline” (Reznick et al., 1986). In their daily lives, dispositionally negative adults report elevated negative affect in comfortable, familiar settings, such as their home (Suls & Martin, 2005). In a seminal study, Bolger and Schilling (1991) leveraged 6 weeks of daily reports collected from more than 300 individuals to show that individuals with a more negative disposition report elevated distress in daily life. Next, they used statistical decomposition techniques (i.e., hierarchical linear modeling) to show that nearly 60% of this effect reflects “tonic” differences in distress, in settings where their subjects did not report a clear concurrent source of stress, more than double the variance attributable to either stressor reactivity or stressor exposure.

Heightened negative affect in the absence of clear exogenous stressors may reflect dispositionally negative individuals’ tendency to experience spillover of negative affect across sequential moments, contexts, or days (Houben, Van Den Noortgate, & Kuppens, 2015; Judge, Simon, Hurst, & Kelley, 2014; Koval & Kuppens, 2012; Suls & Martin, 2005). Data from several large U.S. studies ($ns > 1,000$) show that individuals with heightened levels of dispositional negativity tend to carry negative affect from work to home and vice versa (Horwitz, Luong, & Charles, 2008; Wayne et al., 2004). Spill-over and emotional inertia has also been observed in patients with internalizing disorders (Houben et al., 2015; Newman & Fisher, 2013; Peeters, Nicolson, Berkhof, Delspaul, & deVries, 2003). Among patients, spillover and inertia predict the severity of symptoms (Brose, Schmiedek, Koval, & Kuppens, 2015; Houben et al., 2015; Koval, Kuppens, Allen, & Sheeber, 2012; Newman & Fisher, 2013), foreshadow future episodes (van de Leemput et al., 2014), improve with treatment (Newman & Fisher, 2013), and predict treatment response (Newman & Fisher, 2013). This may reflect maladaptive emotion regulation. Individuals with a more negative disposition are prone to worrying about the future and ruminating about the past (Grupe & Nitschke, 2013; Nolan, Roberts, & Gotlib, 1998; Wupperman & Neumann, 2006) and these maladaptive coping strategies tend to promote pervasive negative affect in otherwise quiescent settings (Barlow et al., 2013; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008).

In short, several decades of self-report research demonstrates that persistently elevated, context-independent negative affect is a key feature of dispositional negativity. More recently acquired experience-sampling data suggest that spillover and inertia of negative affect play a role in the development and recurrence of internalizing disorders.

Increased Stressor Exposure and Generation

Like the anxiety disorders (American Psychiatric Association, 2013), dispositional negativity is thought to be associated with heightened avoidance of punishment and potential threat (Barlow et al., 2013; Cavanagh & Shackman, 2015; Gray & McNaughton, 2000; Grupe & Nitschke, 2013; Hengartner, van der Linden, et al., 2016). Yet there is also compelling evidence that dispositionally negative individuals are more frequently exposed to hassles, stressors, and more severe kinds of adversity. In fact, converging lines of prospective-longitudinal (Carter, Garber, Ciesla, & Cole, 2006; Fergusson & Horwood, 1987; Headey & Wearing, 1989; Kercher, Rapee, & Schniering, 2009; Lakdawalla & Hankin, 2008; Ludtke et al., 2011; Magnus, Diener, Fujita, & Pavot, 1993; Ormel & Wohlfarth, 1991; Riese et al., 2014; Specht, Egloff, & Schmukle, 2011; van Os, Park, & Jones, 2001; Vollrath, 2000; Wetter & Hankin, 2009; Whittington & Huppert, 1998), behavioral-genetic (Billig, Hershberger, Iacono, & McGue, 1996; Kandler, Bleidorn, Riemann, Angleitner, & Spinath, 2012; Middeldorp et al., 2008; Power et al., 2013; Saudino, Pedersen, Lichtenstein, McClearn, & Plomin, 1997), and daily diary data (Berry, Willingham, & Thayer, 2000; Bolger & Schilling, 1991; Bolger & Zuckerman, 1995; J. P. David, Green, Martin, & Suls, 1997; Gunthert, Cohen, & Armeli, 1999; Hankin, 2010; Hankin, Fraley, & Abela, 2005; Leger et al., 2016; Marco & Suls, 1993; Suls, Green, & Hillis, 1998) from more than 70,000 individuals in the United States and abroad, some followed for as long as 16 years, demonstrate that adolescents and adults with high levels of dispositional negativity report more frequent personal difficulties and conflicts, particularly those of an interpersonal nature. Similar effects have been reported in children and adults with internalizing disorders (J. L. Allen & Rapee, 2009; Farmer & Kashdan, 2015; Hoehn-Saric, McLeod, Funderburk, & Kowalski, 2004; Kendler & Karkowski-Shuman, 1997; Kendler, Karkowski, & Prescott, 1999; Liu & Alloy, 2010; Liu, Kraines, Massing-Schaffer, & Alloy, 2014).

Increased stressor exposure has been observed using subjective ratings and more objective experimenter ratings of stressor intensity (Gleason, Powers, & Oltmanns, 2012; Iacovino et al., 2016; Jeronimus et al., 2014). For example, data from the Virginia Twin Registry ($n > 7,000$) indicates that dispositional negativity strongly predicts job loss, marital problems, and conflicts with family and coworkers, but is unrelated to random misfortunes (e.g., robbery; Kendler, Gardner, & Prescott, 2003). Analyses of nearly 1,000 data sets from the Dunedin longitudinal sample show that individuals with a more negative disposition at age 18 report progressively higher levels of conflict and abuse in romantic relationships across young adulthood (Robins et al., 2002). Using digital audio recorders, Mehl and colleagues showed that individuals with higher levels of dispositional negativity were more likely to argue in their daily lives (Mehl, Gosling, & Pennebaker, 2006). Leveraging survey data collected from 900 AmeriCorps volunteers pseudorandomly assigned to 100 teams, Klein, Lim, Saltz, and Mayer (2014) demonstrated that levels of dispositional negativity at the time of employment strongly influenced the formation of spontaneous social networks 10 months later. Individuals with a more negative disposition tended to become central to what they termed *adversarial networks* (i.e., are disliked by many teammates) and to show low centrality in both friendship and advice networks (Klein et al., 2004). Among children and adolescents,

elevated levels of dispositional negativity are prospectively associated with peer rejection, social exclusion, victimization, and reduced friendship quality (Coplan, Arbeau, & Armer, 2008; Gazelle, 2008; Gazelle & Ladd, 2003; Ladd, Kochenderfer-Ladd, Eggum, Kochel, & McConnell, 2011; K. Rubin, Bowker, & Gazelle, 2010; K. H. Rubin, Wojslawowicz, Rose-Krasnor, Booth-LaForce, & Burgess, 2006; H. R. Snyder et al., 2015; Strauss, Frame, & Forehand, 1987). In short, there is compelling evidence that elevated levels of dispositional negativity are associated with increased exposure to a range of psychosocial stressors across the life span.

Other work suggests that dispositionally negative individuals play an instrumental role in generating stressors; that they tend to act in ways that increase the likelihood or chronicity of negative life events (e.g., divorce, financial difficulties) and daily hassles (e.g., interpersonal conflict, social rejection). In adulthood, their friends report more frequent conflict and heightened irritation (Berry et al., 2000), their romantic partners report reduced relationship security (Neyer & Voigt, 2004), their spouses report reduced marital and sexual satisfaction (Dyrenforth et al., 2010; Malouff, Thorsteinsson, Schutte, Bhullar, & Rooke, 2010; Solomon & Jackson, 2014; Watson, Hubbard, & Wiese, 2000; Watson & Humrichouse, 2006), and their offspring report more frequent parent-child conflict (Hutteman, Bleidorn, Kereste, et al., 2014). Likewise, the parents of children with a more negative disposition describe their relationship with their offspring as challenging and emotionally exhausting (Shamir-Essakow, Ungerer, Rapee, & Safier, 2004). Similar effects have been reported for the parents of children with anxiety disorders (Lebowitz, Scharfstein, & Jones, 2014; Lebowitz et al., 2013).

These kinds of informant reports are complemented by laboratory studies showing that randomly assigned social partners judge dispositionally negative adults to be moody, uncomfortable, and negative (Creed & Funder, 1998). This negativity begets negativity and random partners tend to respond with elevated levels of criticism, contempt, and hostility (Creed & Funder, 1998) and to judge the interaction more negatively (Heerey & Kring, 2007). Likewise, dispositionally negative children tend to evoke more negative reactions from unfamiliar peers (Stewart & Rubin, 1995; O. L. Walker, Degnan, Fox, & Henderson, 2015).

Heightened interpersonal stress and social rejection may stem from dispositionally negative individuals' tendency to express lower levels of warmth and empathy; to be less responsive and disclosing to relationship partners; to overreact and escalate negative affect during conflicts (e.g., angry venting, hostile or aggressive confrontation); and to engage in toxic interpersonal behaviors (i.e., criticism, contempt, and sarcasm), particularly during periods of heightened stress (Ackerman & Corretti, 2015; L. A. Clark, Kochanska, & Ready, 2000; Connor-Smith & Flachsbart, 2007; Cote & Moskowitz, 1998; de Haan, Dekovic, & Prinzie, 2012; Donnellan, Assad, Robins, & Conger, 2007; Donnellan, Conger, & Bryant, 2004; Ellenbogen & Hodgins, 2004; Kendler & Karkowski-Shuman, 1997; Kochanska, Clark, & Goldman, 1997; McNulty, 2008; Neyer & Asendorpf, 2001; Prinzie, Stams, Deković, Reijntjes, & Belsky, 2009; Romero-Canyas, Downey, Berenson, Ayduk, & Kang, 2010; Vater & Schröder-Abé, 2015; Wang,

Fn3 Repetti, & Campos, 2011).³ Likewise, individuals with anxiety disorders are prone to more frequent and intense conflict with their partners and spouses (Johnson, Cohen, Kasen, & Brook, 2004; Metz, Majdandžić, & Bogels, 2016).

Studies of patients with social phobia in semistructured “getting acquainted” tasks suggests that these and other maladaptive expressive behaviors elicit negative affect in others which, in turn, promotes discord, alienation, and rejection (Alden & Taylor, 2004; Plasencia, Alden, & Taylor, 2011). Similar results have been found in more naturalistic observational and experience-sampling studies (Pasch, Bradbury, & Davila, 1997; Zaider, Heimberg, & Iida, 2010). Interventions targeting these maladaptive behaviors reduce conflict and rejection, indicating a causal role (D. K. Snyder & Halford, 2012; Taylor & Alden, 2011).

In sum, individuals with a more negative disposition and patients with internalizing disorders actively, if unintentionally, shape their environment in ways that generate stress. Increased exposure to hassles, conflict, and other, more severe psychosocial stressors (e.g., divorce), in turn, tends to promote more intense or pervasive negative affect or even internalizing symptoms (Henderson & Moran, 1983).

The Psychophysiology and Neurobiology of Dispositional Negativity

The self-report and behavioral data that we have reviewed suggest that the link between dispositional negativity and heightened levels of momentary negative affect reflects a combination of increased stressor reactivity, tonic or “endogenous” increases in negative affect, and increased stressor exposure (Figure 1). As described in more detail below, brain imaging, neuropsychological, and more mechanistic kinds of data gleaned from animal models strongly corroborate the link binding dispositional negativity to heightened stressor reactivity. But biological data raise the possibility that seemingly “tonic” increases in negative affect may actually reflect increased reactivity⁴ to stressors that are mild, remote, uncertain, or diffuse (Figure 2). This is likely to be exacerbated by stress-induced sensitization of brain regions, such as the amygdala, that play a key role in assembling states of fear and anxiety.⁵ While the neurobiological mechanisms underlying increased stressor generation and exposure remain largely opaque, the existing neurobiological record suggests that the tendency to behave in ways that promote interpersonal conflict and evoke social rejection may reflect variation in the function of circuits that underlie the appraisal of emotionally salient social cues.

Increased Reactivity to Aversive Challenges in the Laboratory

AQ: 3 Decades ago, Allport (1966) suggested that “traits are cortical [or] subcortical . . . dispositions having the capacity to gate or guide specific phasic reactions” (p. 3). To this day, most neurobiologically grounded models of dispositional negativity remain rooted in the idea that temperament and personality reflect differences in the magnitude or likelihood of reactions to punctate, trait-relevant challenges (e.g., conflict, criticism, punishment, danger; Eysenck, 1967; Goldsmith et al., 1987; Kagan, Reznick, & Snidman, 1988; Reiss, 1997; Spielberger, 1966; Zuckerman, 1976).⁶

Fn6 Consistent with this perspective, there is clear evidence that humans and monkeys with a more negative disposition show heightened

reactions to threat-related cues in a number of brain regions, including the amygdala, anterior hippocampus, anterior insula, bed nucleus of the stria terminalis (BST), midcingulate cortex, orbitofrontal cortex (OFC), and periaqueductal gray (Avery, Clauss, & Blackford, 2016; Calder, Ewbank, & Passamonti, 2011; Cavanagh & Shackman, 2015; A. S. Fox & Kalin, 2014; A. S. Fox, Oler, Shackman, et al., 2015; A. S. Fox, Oler, Tromp, Fudge, & Kalin, 2015; Shackman & Fox, 2016; Shackman et al., 2011).

Here, we focus on the most intensively scrutinized of these regions, the amygdala. The amygdala is a heterogeneous collection of nuclei buried beneath the temporal lobe (Freese & Amaral, 2009; Yilmazer-Hanke, 2012). As shown in Figure 3, the amygdala is poised 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) components of momentary negative affect (M. Davis & Whalen, 2001; Freese & Amaral, 2009). Lesion, imaging, and electrophysiological evidence demonstrate that the amygdala can trigger shifts of attention to threat-relevant social cues (e.g., eyes) and that reentrant projections from the basolateral nucleus of the amygdala to

³ Drawing on a unique body of anthropological research conducted in subject’s own homes,

Wang and colleagues provide a vivid description of this negative interpersonal style: Ed Anderson . . . scored high on . . . [dispositional negativity] and reported high job stress. He is married to Rhoda and together they have three young daughters . . . On Day 1 of videotaping, Ed returned home and was immediately very engaged with his family members . . . However, he appeared somewhat irritated during these interactions with Rhoda and his daughters, and often sighed, rubbed his head in annoyance, and used a mildly sarcastic tone. At the start of dinner, Ed learned from an apologetic Rhoda that the fish she had made would not be ready for another 20 minutes. Although Ed said “OK, I’ll eat it later,” he made several references to the dinner that showed a critical undertone . . . Several minutes into the meal, Ed silently left the table and began loudly crunching on chips. Rhoda continued to be apologetic about the delay with the fish, but Ed told her “I’m not even really hungry” . . . Although Ed continued to inquire when the fish would be ready, he ultimately rejected the fish when it came out of the oven. After dinner, Ed continued to show irritation (e.g., raised eyebrows, annoyed looks, sighs, sarcastic tone).

(Wang et al., 2011, p. 451)

⁴ This is similar to what others have conceptualized as a reduced threshold for responding (Davidson, 1998; Reznick et al., 1986).

⁵ A growing number of researchers draw a sharp distinction between states of “fear” and “anxiety” (e.g., Barlow, 2000; D. C. Blanchard & Pearson, in press; M. Davis, Walker, Miles, & Grillon, 2010; LeDoux, 2015). Yet lay people, scholars in other areas, the American Psychiatric Association’s *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013), and even domain experts—at least in unguarded moments—often use these terms interchangeably or inconsistently. As one psychiatrist (Gaylin, 1979) noted almost 40 years ago, “The word ‘anxiety’ has become confused. It has so many meanings in so many languages, that . . . it has come to be a synonym for the generic term ‘fear’” (p. 18). Other commentators have emphasized the difficulty of drawing sharp operational boundaries between the terms (Perusini & Fanselow, 2015). To avoid misunderstanding, we recommend that researchers eschew these problematic redefinitions of everyday language (Shackman & Fox, 2016).

⁶ The revised reinforcement sensitivity theory is one notable exception (Corr, 2008; Gray & McNaughton, 2000; Reuter, Cooper, Smillie, Markett, & Montag, 2015).

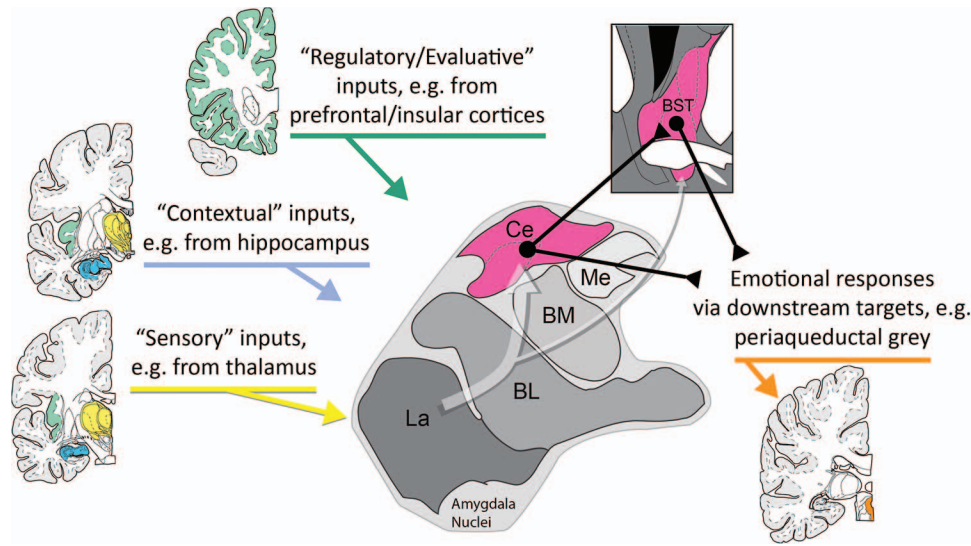


Figure 3. Central extended amygdala circuitry. Simplified schematic of key inputs and outputs to the central extended amygdala (magenta) in humans and other primates. The central amygdala encompasses the central nucleus of the amygdala (Ce) and neighboring bed nucleus of the stria terminalis (BST). As shown by the translucent white arrow at the center of the figure, most sensory (yellow), contextual (blue), and regulatory (green) inputs to the central extended amygdala are indirect (i.e., polysynaptic), and first pass through adjacent amygdala nuclei before arriving at the Ce. In primates, projections linking the Ce to the BST are predominantly unidirectional (Ce → BST). The Ce and BST are poised to orchestrate or trigger momentary negative affect via projections to downstream effector regions (orange). Adapted from “Atlas of the Human Brain (3rd ed.),” by J. K. Mai, G. Paxinos, and T. Voss, 2007, pp. 113, 135, 149, 157, 165, and 187. Copyright, 2007 by Academic Press. Adapted with permission. BL = basolateral; BM = basomedial; La = lateral; Me = medial nuclei of the amygdala. See the online article for the color version of this figure.

the visual cortex and superior colliculus play a crucial role in prioritizing the processing of threat-relevant cues (Shackman, Kaplan, et al., in press). The amygdala is also poised to promote nonspecific states of vigilance via projections to ascending neurochemical systems (i.e., acetylcholine, dopamine, norepinephrine) in the basal forebrain and brainstem that can modulate the responsiveness of sensory cortex to incoming information (Arnsten, 2009, 2015; M. Davis & Whalen, 2001; Freese & Amaral, 2009).

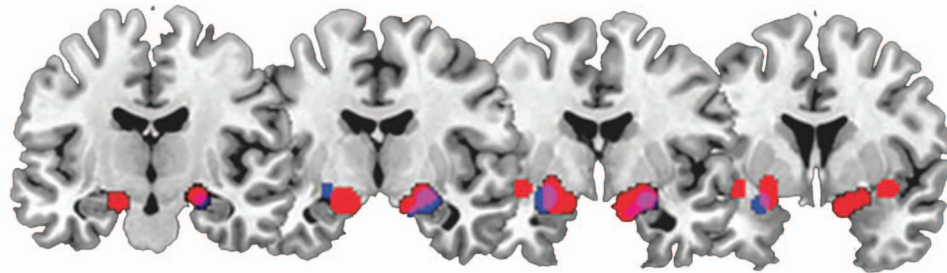
Imaging studies show that dispositionally negative individuals show increased or prolonged activation in the dorsal amygdala in response to novelty or potential threat (Blackford, Avery, Shelton, & Zald, 2009; Calder et al., 2011; Fonzo et al., 2015; A. S. Fox & Kalin, 2014; Schuyler et al., 2014; Stein, Simmons, Feinstein, & Paulus, 2007; Figures 4a, 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 in adults and youth with a more negative disposition (Blackford, Allen, Cowan, & Avery, 2013; Blackford, Avery, Cowan, Shelton, & Zald, 2011; Hare et al., 2008).

Large-scale ($n = 238\text{--}592$) positron emission tomography (PET) studies in juvenile monkeys show that threat-related metabolic activity in the dorsal amygdala, in the region of the central (Ce) nucleus (Figure 4c), is stable over time and context (i.e., trait-like), heritable, and associated with heightened behavioral and neuroendocrine reactions to threat (A. S. Fox & Kalin, 2014; A. S. Fox, Oler, Shackman, et al., 2015; A. S. Fox et al., 2012; Oler et al., 2010; Shackman et al., 2013). For example, Fox and colleagues reported that metabolic activity in the Ce during prolonged exposure to an unfamiliar human

intruder’s profile (Figure 2b) showed an intraclass correlation of 0.64 across three occasions over a 1.1-year span, similar to the concurrent retest stability of dispositional negativity in young monkeys (intraclass correlation = 0.72; A. S. Fox et al., 2012) and the 5-year stability of dispositional negativity in humans (partial $R = .60$; $n = 56,735$; Hakulinen, Elovainio, et al., 2015). Other work in nonhuman primates demonstrates that elevated amygdala activity is a core substrate for different presentations of dispositional negativity (Figure 5). Like humans, monkeys express dispositional negativity in different ways. Some individuals characteristically respond to potential threat with high levels of the stress-sensitive hormone cortisol and middling levels of behavioral inhibition, whereas others show the reverse profile. What all of these individuals share is heightened threat-related activity in the Ce (Shackman et al., 2013). Together, these observations show that individual differences in dispositional negativity partially reflect trait-like individual differences in amygdala function in

The amygdala’s contribution to dispositional negativity appears to be causal. In monkeys and rodents, selective lesions of the amygdala, particularly the Ce, markedly reduce the expression of fear and anxiety elicited by a broad spectrum of learned and innate threats (Calhoun & Tye, 2015; J. S. Choi & Kim, 2010; Izquierdo, Suda, & Murray, 2005; Janak & Tye, 2015; Kalin et al., 2016; Kalin, Shelton, & Davidson, 2004; Mason, Capitanio, Machado, Mendoza, & Amaral, 2006; Tovote, Fadok, & Luthi, 2015). These experimental findings in animals are consistent with observations made of humans with circumscribed amygdala damage (Adolphs, in press; Feinstein, Adolphs, Damasio, & Tranel, 2011; Klumpers, Morgan, Terburg, Stein, & van Honk, in press). Patient S. M.,

A. Adults



B. Adults with a childhood history

C. Young monkeys

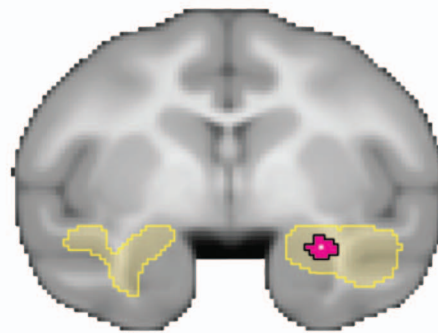
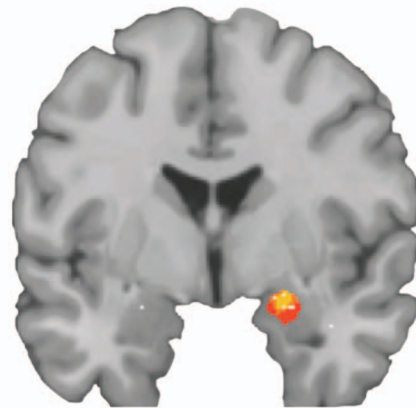


Figure 4. The dorsal amygdala is more reactive to acute threat-related cues in dispositionally negative individuals. (A) Adults with elevated dispositional negativity. Meta-analysis of six published imaging studies reveals consistently elevated activation bilaterally in the vicinity of the dorsal amygdala (Calder et al., 2011). Significant relations with dispositional negativity (trait) are shown in blue, significant relations with momentary negative affect (state) are shown in red, and the overlap is shown in purple. Adapted from “Personality Influences the Neural Responses to Viewing Facial Expressions of Emotion,” by A. J. Calder, M. P. Ewbank, and L. Passamonti, 2011, *Philosophical Transactions of the Royal Society B: Biological Sciences*, 366, p. 1691. Copyright, 2011 by the Royal Society. Adapted with permission. (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. Six of eight amygdala peaks overlapped (yellow) in the dorsal amygdala; four of the peaks extended into the region shown in red. Adapted from “A Translational Neuroscience Approach to Understanding the Development of Social Anxiety Disorder and Its Pathophysiology,” by A. S. Fox and N. H. Kalin, 2014, *American Journal of Psychiatry*, 171, p. 1165. Copyright, 2014 by the American Psychiatric Association. Adapted with permission. (C) Young monkeys. Using high-resolution 18-fluorodeoxyglucose-positron emission tomography acquired from 238 young rhesus monkeys, Oler and colleagues (2010) demonstrated that threat-related activity in the right central nucleus (i.e., dorsal amygdala) predicts stable 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. Adapted from “Amygdalar and Hippocampal Substrates of Anxious Temperament Differ in Their Heritability,” by J. A. Oler, A. S. Fox, S. E. Shelton, J. Rogers, T. D. Dyer, R. J. Davidson, . . . N. H. Kalin, 2010, *Nature*, 466, p. 865. Copyright, 2010 by Nature Publishing Group. Adapted with permission. See the online article for the color version of this figure.

who has near-complete bilateral destruction of the amygdala, shows a profound lack of negative affect when exposed to frightening movies, haunted houses, tarantulas, snakes, and even real-world assaults (Feinstein et al., 2011).⁷ Importantly, she also reports abnormally low levels of dispositional negativity on standardized psychometric measures (Feinstein et al., 2011), consistent with informal clinician ratings of temperament (Tranel, Gullickson, Koch, & Adolphs, 2006).

Other work suggests that elevated amygdala reactivity contributes to the development of pathological anxiety and depression. Activity in

the amygdala covaries with changes in threat-elicited peripheral physiology (e.g., startle potentiation, skin conductance) and

⁷ 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.” (Feinstein et al., 2011, p. 307)

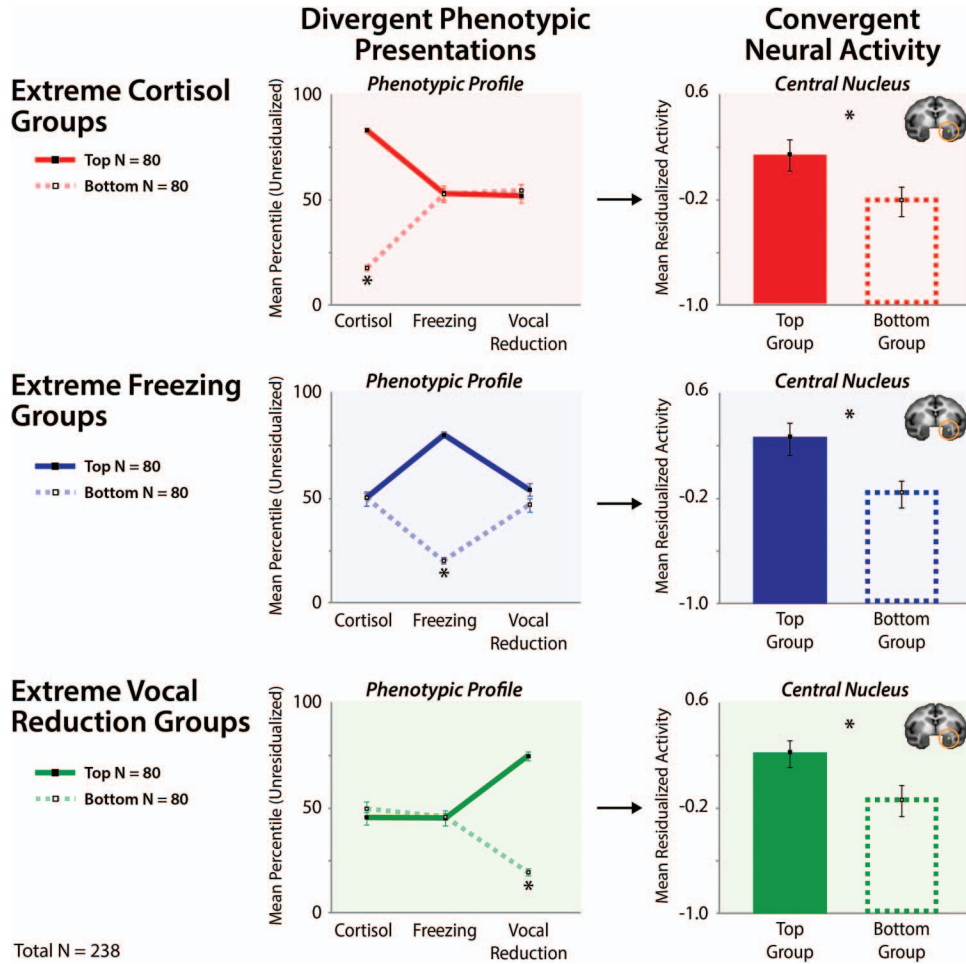


Figure 5. Elevated amygdala activity is a shared substrate for different phenotypic presentations of dispositional negativity. Shackman and colleagues (2013) used a well-established monkey model of childhood dispositional negativity and high-resolution 18-fluorodeoxyglucose-positron emission tomography 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 ($N = 80/\text{group}$; total $N = 238$) 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 on average) evinced greater metabolic activity in the Ce compared with those with low levels ($ps < .05$). Adapted from “Neural Mechanisms Underlying Heterogeneity in the Presentation of Anxious Temperament,” by A. J. Shackman, A. S. Fox, J. A. Oler, S. E. Shelton, R. J. Davidson, and N. H. Kalin, 2013, *Proceedings of the National Academy of Sciences of the United States of America*, 110, p. s5. Copyright, 2013 by the National Academy of Sciences of the United States of America. Adapted with permission. See the online article for the color version of this figure.

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self-reported arousal (Cheng, Knight, Smith, & Helmstetter, 2006; Cheng, Richards, & Helmstetter, 2007; Knight, Nguyen, & Bandettini, 2005; Kragel & LaBar, 2015; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; van Well, Visser, Scholte, & Kindt, 2012; Wood, Ver Hoef, & Knight, 2014). Amygdala reactivity 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), and predicts the development of internalizing symptoms following exposure to stress or trauma (Admon et al., 2009; McLaughlin et al., 2014; Swartz, Knodt, Radtke, & Hariri, 2015). Amygdala reactivity is elevated in children and adults diagnosed with internalizing disorders (Etkin & Wager, 2007; Hamilton et al., 2012; Thomas et

al., 2001) and is reduced by clinically effective treatments for anxiety and depression (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; Windischberger et al., 2010).

In sum, converging lines of epidemiological, physiological, and mechanistic evidence indicate that dispositionally negative individuals' exaggerated reactivity to threat and other aversive challenges partially reflects larger or longer-lasting responses in the dorsal amygdala. Like dispositional negativity, individual differences in amygdala reactivity are trait-like and elevated levels of reactivity predict the future development of internalizing symptoms among individuals exposed to stress.

Trait-Like Individual Differences in Reactivity Are Discernible at “Rest”

Although most neurobiological research has focused on reactivity to acute stressors and threat-related cues—aversive cues, faces, images, films, and so on—individual differences in threat-reactivity can also be discerned in the brain's spontaneous or “resting” activity. For example, monkeys with elevated metabolic activity in the amygdala at “baseline”—in their home-cage with a familiar cage-mate—show increased freezing and elevated levels of cortisol when threat is encountered in other contexts (A. S. Fox, Shelton, Oakes, Davidson, & Kalin, 2008). Likewise, humans with higher levels of dispositional negativity show heightened activity in the amygdala at rest, as indexed by 18-fluorodeoxyglucose PET or perfusion functional MRI (fMRI; Abercrombie et al., 1998; Canli et al., 2006; Kaczurkin et al., *in press*).

Monkeys, children, and adults with a more negative disposition also show greater electroencephalographic (EEG) activity over the right compared to the left prefrontal cortex (PFC) at “rest” (Figure 6a; Buss et al., 2003; Davidson, Jackson, & Kalin, 2000; N. A. Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kalin, Larson, Shelton, & Davidson, 1998; Oler et al., 2016; Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009; Wacker, Chavanon, & Stemmler, 2010). Like dispositional negativity and amygdala reactivity, individual differences in resting prefrontal EEG asymmetry first emerge early in life and are relatively stable over time, heritable, and predict the intensity of negative affect elicited by aversive laboratory challenges (Buss et al., 2003; Davidson et al., 2000; N. A. Fox et al., 2005; Kalin et al., 1998; Smit, Posthuma, Boomsma, & De Geus, 2007; Tomarken, Davidson, Wheeler, & Kinney, 1992; Towers & Allen, 2009; Wheeler, Davidson, & Tomarken, 1993).

Like amygdala reactivity, individual differences in prefrontal EEG asymmetry also confer increased risk for the development of internalizing disorders. This asymmetric pattern of “resting” activity prospectively predicts the first-onset of mood disorders (Nusslock et al., 2011), is exaggerated in patients with internalizing disorders (Thibodeau, Jorgensen, & Kim, 2006), and is normalized by anxiolytic drugs (Davidson, Kalin, & Shelton, 1993; Davidson, Kalin, & Shelton, 1992). Furthermore, neurofeedback interventions targeting this pattern of scalp electrical activity cause lasting reductions in stress reactivity (J. J. Allen,

Harmon-Jones, & Cavender, 2001). Along with the pharmacological evidence, this suggests that the neural circuit or circuits responsible for generating this marker make a causal contribution to individual differences in dispositional negativity. Recent efforts to pinpoint the source of the scalp-recorded EEG asymmetry have highlighted the importance of the dorsolateral prefrontal cortex (dlPFC; Shackman et al., 2009; Figure 6b), consistent with this region's role in regulating momentary negative affect (Buhle et al., 2014).

Other work by our group suggests that the dlPFC and Ce form a coherent, evolutionarily conserved functional circuit. Reduced functional connectivity between the two regions is associated with pathological anxiety in children and elevated levels of dispositional negativity in monkeys (Birn et al., 2014; Figure 6c). Selective lesions of the amygdala, including the Ce, are associated with chronically reduced metabolism in the dlPFC (Machado, Snyder, Cherry, Lavenex, & Amaral, 2008), reinforcing the idea that these regions represent an integrated functional circuit. A key challenge for future studies will be to use mechanistic techniques to clarify the functional architecture and causal contribution of this circuit to extreme anxiety.

Collectively, these data show that individuals with a more negative disposition, who are prone to hyper-react to potential threat, show altered activity in the amygdala and dlPFC in the absence of explicit threat. These observations suggest that variation in the basal activity and functional connectivity of these regions represents a diathesis for heightened negative affect, given an appropriate trait-relevant challenge. More broadly, they indicate that reactive features of dispositional negativity can be discerned in the spontaneous, ongoing activity of the brain, even under sedation (Birn et al., 2014).

Altered “Resting” Activity: States or Traits, Reactive or Tonic Differences?

At present, it remains unclear whether alterations in “resting” activity reflect heightened reactivity to the experimental setting, which often entails a mixture of acute and diffuse threats; “tonic” differences in negative affect (Gross et al., 1998; Watson & Clark, 1984); or more likely some combination of the two processes. It is clear that most neurophysiological assays are intrusive and can elicit substantial negative affect. 18-fluorodeoxyglucose PET requires the injection of a radiotracer. EEG and PET studies in monkeys entail unexpected separation from cage-mates and manual restraint. In humans, resting EEG procedures have been shown to increase negative affect (Blackhart, Kline, Donohue, LaRowe, & Joiner, 2002). MRI data collection requires subjects to lie motionless in a spatially confined, often dark tube while being bombarded by loud noise for tens of minutes. Not surprisingly, MRI procedures have been shown to elicit feelings ranging from mild apprehension to severe panic, to increase cortisol levels, and to activate the sympathetic nervous system in both children and adults (Eatough, Shirtcliff, Hanson, & Pollak, 2009; Lueken, Muehlhan, Evens, Wittchen, & Kirschbaum, 2012; Melendez & McCrank, 1993; Muehlhan et al., 2013; Törnqvist, Månsson, Larsson, & Hallström, 2006; Tyc, Fairclough, Fletcher, Leigh, & Mulhern, 1995). Furthermore, MRI-induced negative affect is amplified in individuals with a more negative disposition (Harris, Cum-

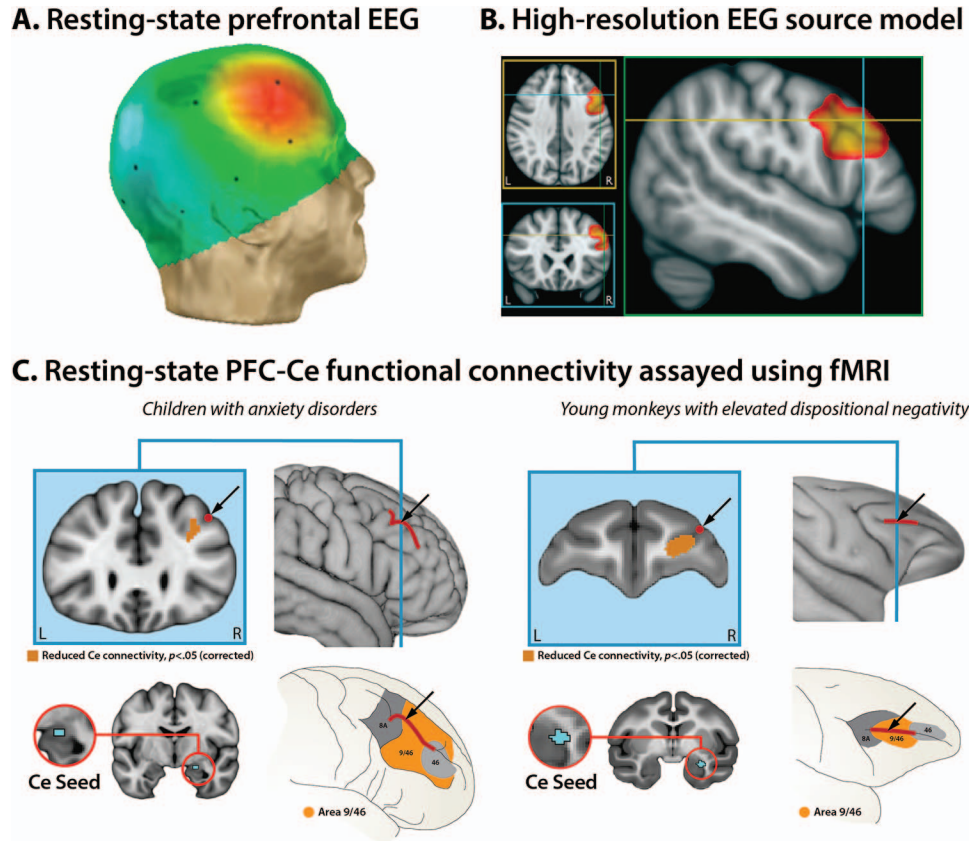


Figure 6. Individuals with a more negative disposition show altered resting-state activity and functional connectivity in a circuit encompassing the right dorsolateral prefrontal cortex (PFC). (A) Resting-state prefrontal electroencephalography (EEG). Monkeys, children, and adults with a more negative disposition show greater resting-state activity on the scalp overlying the right compared to the left dorsolateral PFC. Figure depicts typical EEG scalp topography. Adapted from “Cognitive Vulnerability and Frontal Brain Asymmetry: Common Predictors of First Prospective Depressive Episode,” by R. Nusslock, A. J. Shackman, E. Harmon-Jones, L. B. Alloy, J. A. Coan, and L. Y. Abramson, 2011, *Journal of Abnormal Psychology*, 120, p. 501. Copyright, 2011 by the American Psychological Association. Adapted with permission. (B) High-resolution EEG source model. Shackman and colleagues (2009) used 128-channel EEG recordings and distributed source modeling techniques to provide evidence that this scalp-recorded asymmetry likely reflects increased activity in the right dorsolateral prefrontal cortex (PFC; yellow-orange cluster). Adapted from “Right Dorsolateral Prefrontal Cortical Activity and Behavioral Inhibition,” by A. J. Shackman, B. W. McMenamin, J. S. Maxwell, L. L. Greischar, and R. J. Davidson, 2009, *Psychological Science*, 20, p. 1503. Copyright, 2009 by Sage Publications. Adapted with permission. (C) Resting-state functional connectivity between the dorsolateral PFC and the central (Ce) nucleus assayed using functional MRI (fMRI). Birn and colleagues (2014) demonstrated that children with anxiety disorders (left) and young monkeys with elevated levels of dispositional negativity (right) both show reduced functional connectivity between the Ce (cyan region in the red rings) and right dorsolateral PFC (black arrows). Pediatric data were collected while patients were quietly resting. Nonhuman primate data were collected under sedation, eliminating potential individual differences in scanner-elicited apprehension. Adapted from “Evolutionarily Conserved Dysfunction of Prefrontal-Amygdalar Connectivity in Early-Life Anxiety,” by R. M. Birn, A. J. Shackman, J. A. Oler, L. E. Williams, D. R. McFarlin, G. M. Rogers, . . . N. H. Kalin, 2014, *Molecular Psychiatry*, 19, p. 919. Copyright, 2014 by Nature Publishing Group. Adapted with permission. See the online article for the color version of this figure.

ming, & Menzies, 2004; Harris, Robinson, & Menzies, 2001), even with prior acclimation in a mock scanner (Shechner et al., 2013). Psychometric analyses (e.g., latent state-trait or generalizability-theory models) indicate that resting-state prefrontal EEG asymmetry reflects the joint contribution of traits and states, in about equal measure (Coan, Allen, & McKnight,

2006; Hagemann, Hewig, Seifert, Naumann, & Bartussek, 2005; Hagemann, Naumann, Thayer, & Bartussek, 2002; Tomarken et al., 1992). But as yet, the relative contribution of traits and states to PET and fMRI measures of brain function remains unknown, making this another important avenue for future research.

“Tonic” Increases in Self-Reported Negative Affect May Reflect Heightened Reactivity to Uncertain or Diffuse Threat

Questionnaire data collected in the laboratory and in the field indicate that dispositionally negative individuals often report heightened negative affect in the absence of clear and immediate external stressors. Although this may reflect a “tonic” or direct effect of temperament on mood (Watson & Clark, 1984), a wealth of psychophysiological and behavioral evidence suggests that persistent negative affect may reflect increased reactivity to stressors that are mild, uncertain, remote, or diffuse (D. M. Clark, 2001; M. Davis, Walker, Miles, & Grillon, 2010; Grupe & Nitschke, 2013).

For example, children, adolescents, and adults with a more negative disposition show exaggerated psychophysiological responses (e.g., startle, skin conductance) and report heightened negative affect during periods of explicit safety (i.e., conditioned stimulus [CS]–, intercue interval, CS+ paired with a safety cue) embedded within instructed and associative fear learning paradigms—that is, during the interstitial periods before and after the randomized presentation of genuine threat (CS+; Baas, van Ooijen, Goudriaan, & Kenemans, 2008; Barker et al., 2015; Barker, Reeb-Sutherland, & Fox, 2014; Chan & Lovibond, 1996; Craske et al., 2009; Gazendam et al., 2015; Gazendam, Kamphuis, & Kindt, 2013; Grillon, 2002; Grillon & Ameli, 2001; Haaker et al., 2015; Jovanovic et al., 2014; Reeb-Sutherland et al., 2009; Schmidt & Fox, 1998). Conceptually similar effects have been found in monkeys (Shackman, Fox, et al., in press; Shiba et al., 2014) and in patients with anxiety disorders (Duits et al., 2015). In fact, a comprehensive recent meta-analysis incorporating data from more than 2,000 individuals showed that patients consistently respond more strongly than controls to safety cues (CS–: Cohen’s $d = .30$, $p < .001$), whereas the two groups do not consistently differ in their response to acute threat (CS+: Cohen’s $d = .07$, $p = .41$; Duits et al., 2015).

Research using more naturalistic challenges in children also highlights the importance of contextually inappropriate negative affect. For example, dispositionally negative children show elevated psychophysiological defensive responses to neutral faces (Waters, Neumann, Henry, Craske, & Ornitz, 2008). Relative to typical children, 2-year-olds with an extremely negative disposition show only modestly elevated negative affect in response to high-threat challenges (e.g., approaching robotic spider: typical children: ~32% time; negative children: ~45% time), whereas group differences are dramatically larger during interspersed low-threat challenges (e.g., puppet show: typical children: ~28%; negative children: ~65% time; Buss, 2011). Moreover, contextually inappropriate negative affect in the laboratory at age 2 predicts elevated parent- and teacher-reports of anxiety in preschool and kindergarten and heightened wariness around unfamiliar peers at age 5 (Buss, 2011; Buss et al., 2013).

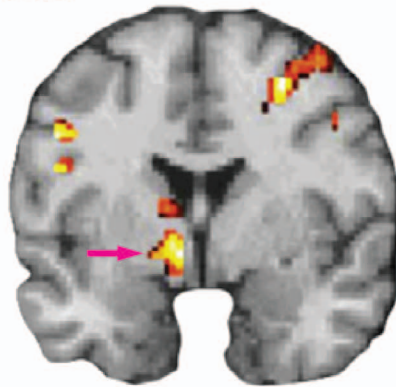
Among adults, indiscriminate or contextually inappropriate negative affect has also been associated with increased avoidance of the aversive learning context. Grillon (2002), for example, showed that subjects who were unable to correctly report the shock-cue contingency following the training phase of a simple differential fear conditioning paradigm (CS+ cue paired with noxious electric shock compared to an unpaired CS– cue) were nearly 4 times more likely to fail to return for a follow-up session ($n = 125$, risk ratio =

3.80, $p < .005$). Furthermore, well-established anxiolytic compounds, like ethyl alcohol and benzodiazepines, have been shown to dampen persistent negative affect elicited by uncertain threat in a dose-dependent manner, while sparing phasic reactions to cues associated with clear and imminent danger (Bradford, Shapiro, & Curtin, 2013; Glue et al., 1995; Grillon et al., 2006; Hefner & Curtin, 2012; Hefner, Jaber, Grant, & Curtin, 2009; Hefner, Moberg, Hachiya, & Curtin, 2013; Moberg & Curtin, 2009).

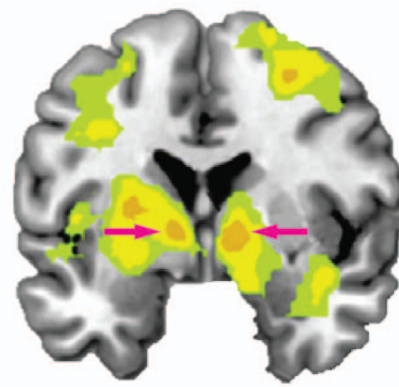
This body of psychophysiological and behavioral research motivates the hypothesis that seemingly endogenous increases in negative affect, as described in the self-report literature, may reflect heightened sensitivity to weak, distal, or uncertain stressors, rather than a fixed or “tonic” consequence of temperament. At a more granular level, this may reflect difficulties discriminating threat from safety, overgeneralization of threat to perceptually similar safety cues (i.e., a broader tuning of threat-detection mechanisms and higher tolerance of false alarms; cf. Nettle & Bateson, 2012; Pollak & Kistler, 2002), or problems using or learning to use safety-related information to regulate momentary negative affect, leading to mood spillover or affective inertia (Davidson, Fox, & Kalin, 2007; Davidson et al., 2000; Grupe & Nitschke, 2013; Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Lissek, 2012).

Mechanistic work in rodents (Calhoun & Tye, 2015; M. Davis et al., 2010; Gungor & Paré, in press; Tovote et al., 2015) suggests that defensive responses to diffuse, uncertain threats (Figure 2a) are organized by the central extended amygdala, an anatomical concept encompassing the Ce and the lateral division of BST (magenta regions in Figure 3; Alheid & Heimer, 1988; A. S. Fox, Oler, Tromp, et al., 2015; Shackman & Fox, 2016; Yilmazer-Hanke, 2012). Like humans with high levels of dispositional negativity, some rodents show poor discrimination of cues associated with danger and safety (i.e., elevated fear and anxiety in response to CS–; often termed *overgeneralization*; Lissek, 2012) and heightened defensive responses during sustained exposure to diffusely threatening contexts (e.g., the cage paired with cued fear learning or the elevated plus-maze; Duvarci, Bauer, & Paré, 2009). Selective lesions of the BST reduce these maladaptive emotional responses, while sparing more adaptive, phasic responses to cues signaling imminent danger (CS+; Duvarci et al., 2009). Anatomically, both the Ce and BST are poised to orchestrate key features of sustained negative affect—including alterations in arousal, behavioral inhibition, and neuroendocrine activation—via dense mono- and polysynaptic (e.g., via the medial division of the Ce) projections to brainstem and subcortical effector regions (M. Davis et al., 2010; M. Davis & Whalen, 2001; A. S. Fox, Oler, Tromp, et al., 2015; Freese & Amaral, 2009).

Recent imaging work in humans and monkeys demonstrates that individuals with a more negative disposition show heightened activity in the BST during prolonged periods of diffuse or uncertain threat (Figures 2c and 7a, b; A. S. Fox et al., 2008; Shackman, Fox, et al., in press; Somerville, Whalen, & Kelley, 2010), with parallel effects reported for patients with anxiety disorders (Münsterkötter et al., 2015; Straube, Mentzel, & Miltner, 2007; Yassa, Hazlett, Stark, & Hoehn-Saric, 2012). Work in nonhuman primates shows that threat-related metabolic activity in the BST is heritable and genetically correlated with individual differences in dispositional negativity, suggesting that it contributes to the intergenerational transmission of this dispositional phenotype (A. S. Fox, Oler, Shackman, et al., 2015; Figure 7b). In humans and monkeys, F7

A. Adults

Somerville et al., 2010



Mobbs et al., 2010

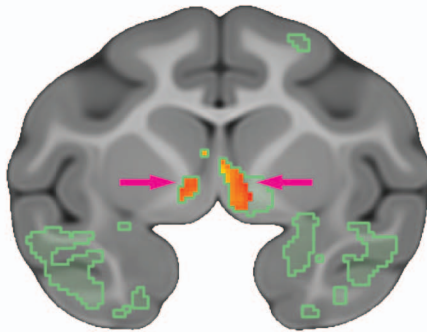
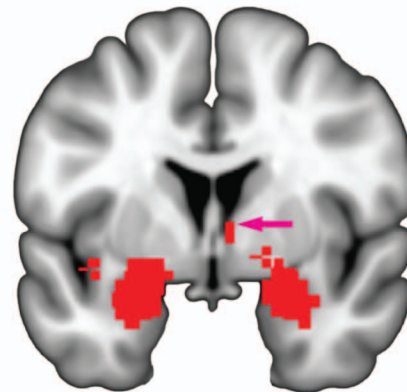
B. Young monkeys**C. Automated meta-analysis**

Figure 7. Individuals with a more negative disposition show heightened activity in the bed nucleus of the stria terminalis (BST) during periods of diffuse or uncertain threat. Clusters in the vicinity of the BST are indicated by magenta arrows. (A) Adult humans. Recent human functional MRI studies reveal increased activation in the BST in response to uncertain threat. Left panel adapted from “Human Bed Nucleus of the Stria Terminalis Indexes Hypervigilant Threat Monitoring,” by L. H. Somerville, P. J. Whalen, and W. M. Kelley, 2010, *Biological Psychiatry*, 68, p. 421. Copyright, 2010 by Elsevier. Adapted with permission. Right panel adapted from “Neural Activity Associated With Monitoring the Oscillating Threat Value of a Tarantula,” by D. Mobbs, R. Yu, J. B. Rowe, H. Eich, O. FeldmanHall, and T. Dalgleish, 2010, *Proceedings of the National Academy of Sciences of the United States of America*, 107, p. 20584. Copyright, 2010 by the National Academy of Sciences of the United States of America. Adapted with permission. (B) Young monkeys. Using high-resolution 18-fluorodeoxyglucose positron emission tomography acquired from 592 young rhesus macaques, Fox and colleagues demonstrated that activity in the right BST is heritable and mediates heritable individual differences in dispositional negativity. Regions where activity predicted dispositional negativity are outlined in green. Adapted from “Intergenerational Neural Mediators of Early-Life Anxious Temperament,” by A. S. Fox, J. A. Oler, A. J. Shackman, S. E. Shelton, M. Raveendran, D. R. McKay, . . . N. H. Kalin, 2015, *Proceedings of the National Academy of Sciences of the United States of America*, 112, p. 9120. Copyright, 2015 by the National Academy of Sciences of the United States of America. Adapted with permission. (C) Automated meta-analysis. An automated neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) meta-analysis of 312 brain imaging studies featuring the term *anxiety* revealed several significant regions (red; $Z > 6.0$ and false discovery rate $q < .05$, whole-brain corrected), including the BST. See the online article for the color version of this figure.

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BST activity and functional connectivity covary with self-reported negative affect, freezing, skin conductance, cardiovascular activity, and cortisol elicited by uncertain or diffuse threat (Alvarez et al., 2015; Banihashemi, Sheu, Midei, & Gianaros, 2015; Jahn et al., 2010; Kalin, Shelton, Fox, Oakes, & Davidson, 2005; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Somerville et al., 2013), consistent with a causal contribution to momentary

negative affect. At present, the consequences of selective BST lesions have yet to be unexplored in humans or nonhuman primates.

BST activity is often described as a “sustained” response to uncertain threat. Yet, mechanistic work in rodents suggests that BST engagement could begin quite early, between 4 and 60 s following the onset of threat-related cues (M. Davis et al., 2010).

Consistent with this, a number of human imaging studies have found transient activation in the BST in response to punctate threats (Figure 7a), such as a 4-s video clip of an approaching tarantula (J. M. Choi, Padmala, & Pessoa, 2012; Grupe, Oathes, & Nitschke, 2013; Klumbers et al., 2015; Mobbs et al., 2010). Likewise, a recent large-scale imaging study ($n = 168$) reported phasic activation of the BST in response to 4-s shock-predictive cues (Klumbers et al., 2015). In fact, imaging studies of fear and anxiety consistently reveal activation in the central extended amygdala—including the BST and the dorsal amygdala in the region of the Ce—across a range of populations, paradigms, and time-scales (Figure 7c). This and other recent work in humans and rodents highlights the importance of these two closely related regions for triggering responses to a broad spectrum of aversive challenges (Shackman & Fox, 2016).⁸

Fn8

Individual differences in the function of the central extended amygdala may reflect altered communication with the OFC (cf. “regulatory/evaluative” inputs in Figure 3). Large-scale imaging studies in monkeys ($n = 592$) reveal that threat-related metabolic activity in the posterior OFC/anterior insula is heritable and, like the BST, genetically correlated with individual differences in dispositional negativity (A. S. Fox, Oler, Shackman, et al., 2015). Aspiration lesions of the OFC markedly reduce passive avoidance of potential threat (i.e., freezing; Kalin, Shelton, & Davidson, 2007; Rudebeck, Saunders, Prescott, Chau, & Murray, 2013), and this appears to be mediated by downstream changes in BST metabolism (A. S. Fox et al., 2010). Reduced BST activity has also been found in humans with OFC damage (Motzkin, Philippi, Oler, et al., 2015), suggesting that this circuit is conserved across primate species. Interestingly, viral vector manipulations that increase metabolic activity in the Ce—the other major component of the central extended amygdala—are associated with elevated metabolic activity in the OFC, increased functional connectivity between the Ce and OFC, and heightened signs of fear and anxiety during prolonged exposure to threat (Kalin et al., 2016). Conversely, Ce lesions are associated with reduced metabolic activity in the OFC (Machado et al., 2008). In other words, perturbations targeting one region (e.g., OFC or Ce damage) propagate to the others (e.g., reduced BST or OFC metabolism) and damage to either the Ce or OFC reduces, but does not abolish, defensive responses to threat.

Collectively, these imaging and mechanistic findings suggest that the extended amygdala and OFC form a functionally integrated circuit that plays a crucial role in detecting and organizing persistent responses to uncertain threat.⁹ Much remains unknown about this circuit, including the necessity of the primate BST to persistent negative affect, the differential contributions of its three constituents (Ce, BST, OFC), the nature of their interactions with one another and other brain regions associated with dispositional negativity (e.g., dlPFC, periaqueductal gray), and the relevance of this circuit to persistent, contextually inappropriate negative affect in the real world.

Fn9

“Tonic” Increases in Self-Reported Negative Affect May Reflect Stress-Induced Sensitization

Self-report data indicate that individuals with a more negative disposition tend to carry negative affect from stressful to less stressful contexts (e.g., work to home) and to behave in ways that

promote interpersonal conflict during times of heightened stress (Suls & Martin, 2005; Wang et al., 2011).⁴ Recent work in humans suggests that the amygdala could contribute to the spillover of negative mood via stress-induced sensitization, consistent with models derived from animal research (Rosen & Schulkin, 1998). In particular, there is evidence that acute stressors (e.g., threat-of-shock, aversive film clips) potentiate defensive reactions (i.e., startle) to threat-related facial expressions (Grillon & Charney, 2011), cause persistent increases in spontaneous amygdala activity (Cousijn et al., 2010), and potentiate amygdala reactivity to threat-related faces (Pichon, Miendlarzewska, Eryilmaz, & Vuilleumier, 2015; van Marle, Hermans, Qin, & Fernandez, 2009). Acute stressors produce even longer-lasting changes (i.e., minutes to hours) in amygdala functional connectivity (Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernandez, 2010). Furthermore, these neurobiological spillover effects are exaggerated in individuals with a more negative disposition. In particular, a recent large-scale imaging study ($n = 120$) showed that dispositionally negative individuals exhibit potentiated activation to threat-related faces following acute stressor exposure (Everaerd et al., 2015).

Persistent amygdala sensitization could promote negative affect either directly, by potentiating emotional reactions to mild threat (Grillon & Charney, 2011), or indirectly, by increasing the likelihood that attention will be allocated to threat-related cues in the surrounding environment. Circuits centered on the amygdala play a central role in allocating attentional resources to threat and a rapidly growing body of longitudinal (Perez-Edgar, Bar-Haim, et al., 2010; Perez-Edgar et al., 2011; White et al., in press) and clinical-intervention studies (Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; MacLeod & Clarke, 2015) indicate that attentional biases to threat causally contribute to the development and maintenance of extreme anxiety and distress (Shackman, Kaplan, et al., in press). For example, computer-based interventions target-

⁸ Inspired by the seminal work of Michael Davis, David Walker, and their colleagues (M. Davis, 1998, 2006; M. Davis, Walker, & Lee, 1997; M. Davis et al., 2010; Grillon, 2008; D. L. Walker & Davis, 2008; D. L. Walker, Miles, & Davis, 2009; D. L. Walker, Toufexis, & Davis, 2003), it is widely thought that phasic and sustained responses to threat reflect dissociable circuits centered on the Ce and the BST, respectively. Indeed, a version of this influential hypothesis has been incorporated into the National Institute of Mental Health Research Domain Criteria as acute threat (“fear”) and potential threat (“anxiety”; cf. <https://www.nimh.nih.gov/research-priorities/rdoc/constructs/potential-threat-anxiety.shtml>; <https://www.nimh.nih.gov/research-priorities/rdoc/negative-valence-systems-workshop-proceedings.shtml>; Kozak & Cuthbert, 2016). But as described in greater detail elsewhere (Calhoun & Tye, 2015; Gungor & Paré, in press; Janak & Tye, 2015; Shackman & Fox, 2016; Tovote et al., 2015), more recent observations in rodents, monkeys, and humans make it clear that the central extended amygdala forms a tightly interconnected functional unit and that claims of strict functional segregation are no longer tenable.

⁹ Other mechanisms, including overgeneralization of threat to perceptually similar safety cues or contexts (Camp et al., 2012; Ciochi et al., 2010; Ghosh & Chattarji, 2015; Kheirbek et al., 2012; Laufer, Israeli, & Paz, 2016; Lissek et al., 2014; Shaban et al., 2006) and deficient filtering of threat-related information from working memory (Stout, Shackman, Johnson, & Larson, 2015; Stout, Shackman, & Larson, 2013), are also likely to be important. In fact, given the central role of working memory in goal-directed cognition (e.g., attention, imagination, memory retrieval), emotion regulation (e.g., worry), and behavior, aberrant gating of threat-related information from working memory storage may represent a key source of sustained apprehension and negative affect in humans (Mobbs et al., 2015; Stout et al., 2013).

ing attentional biases to threat have been shown to reduce self-reported negative affect, behavioral signs of anxiety, and intrusive thoughts elicited by aversive challenges, such as public speaking tasks (Dennis & O'Toole, 2014; MacLeod & Mathews, 2012). Likewise, psychological manipulations that potentiate amygdala reactivity (e.g., exposure to loud, unpredictable trains of auditory stimuli) also enhance attentional biases to threat (Herry et al., 2007).

Collectively, these observations indicate that exposure to stress alters the activity and connectivity of the amygdala in ways that could promote contextually inappropriate negative affect in individuals with a negative disposition. A key challenge for the future will be to understand whether this reflects sensitization of circuits involved in orchestrating states of negative affect or a downstream consequence of changes in circuits involved in detecting and attending to threat.

Increased Stressor Exposure and Generation May Reflect Maladaptive Information Processing and Choices

Self-report data indicate that individuals with a more negative disposition tend to behave in ways that increase the likelihood of hassles, social conflict, interpersonal rejection, and other stressors (e.g., unemployment, divorce).⁴ At present, the neurobiological mechanisms underlying these kinds of recursive temperament–environment–affect relations have received little attention and remain poorly understood. Nonetheless, it is known that the amygdala and other brain regions involved in dispositional negativity can influence information processing and bias decision-making in ways that could promote stress. Imaging studies provide evidence that amygdala activation is associated with reduced trust and is sensitive to potential threat and betrayal during simple economic bargaining games (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008; Bhatt, Lohrenz, Camerer, & Montague, 2012; Gaspic et al., 2011; Li, Xiao, Houser, & Montague, 2009). Conversely, amygdala damage is associated with heightened, even pathological levels of approach and trust (Adolphs, Tranel, & Damasio, 1998; Feinstein et al., 2011; Kennedy, Glascher, Tyszka, & Adolphs, 2009; van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013). Patient studies suggest that the amygdala also plays a role in inhibiting approach in the face of potentially aversive outcomes (i.e., monetary loss aversion; De Martino, Camerer, & Adolphs, 2010). Imaging studies have linked the amygdala to reactive aggression and punishment (Coccaro, McCloskey, Fitzgerald, & Phan, 2007; Treadway et al., 2014), consistent with limited mechanistic work in rodents (Nelson & Trainor, 2007). These observations raise the possibility that stable individual differences in amygdala function contribute to dispositionally negative individuals' tendency to engage in behaviors—including reduced self-disclosure, heightened inhibition and avoidance, escalation during conflict—that promote social discord and rejection. Via its role in pessimism (Sharot, Riccardi, Raio, & Phelps, 2007) and loss aversion, it is plausible that the amygdala contributes, albeit in a more distal way, to the development or maintenance of other stressors (e.g., lost opportunities for financial or social success, difficulties escaping or improving adverse situations and relationships, avoidance of medical professionals and other potential sources of “bad news”). While speculative, the

development of more ecologically valid tasks (Jarcho et al., 2013; Somerville, Heatherton, & Kelley, 2006), in combination with longitudinal imaging studies, makes these hypotheses increasingly tractable.

An Integrative Perspective on the Processes Linking Dispositional Negativity to Momentary Emotional Experience and Behavior

The past 2 decades have witnessed the emergence of powerful tools for assaying emotion and brain function and a number of important insights into the pathways linking stable individual differences in temperament to momentary emotional experience, behavior, and peripheral physiology. These observations provide an integrative framework for understanding the role of dispositional negativity in the development of a broad spectrum of adverse outcomes.

First, there is clear evidence that dispositionally negative individuals respond more strongly to explicit stressors and aversive challenges in the laboratory and in their daily lives. Variation in threat-reactivity reflects stable individual differences in the activity and functional connectivity of several brain regions, including the dorsal amygdala and dlPFC, that have been implicated in the etiology and maintenance of internalizing disorders and substance abuse (Figures 3–6; Chase, Eickhoff, Laird, & Hogarth, 2011; Etkin & Wager, 2007; Hamilton et al., 2012; Kuhn & Gallinat, 2011; McLaughlin et al., 2014; Swartz, Knodt, et al., 2015; Tang, Fellows, Small, & Dagher, 2012; Thibodeau et al., 2006; R. A. Wise & Koob, 2014). These differences manifest as heightened activation in response to punctate challenges, but they are also evident in ongoing brain activity, in the absence of explicit tasks or mood manipulations (Figure 6). At present, it remains unclear whether temperament-related variation in resting-state activity and functional connectivity reflects increased reactivity to the measurement context, which is often novel or mildly aversive; tonic differences in neurophysiology; or some combination of the two.

Second, while increased threat-reactivity is important, individuals with a more negative disposition often report elevated levels of negative affect in contexts where stressors are uncertain, psychologically diffuse, or temporally remote. Mechanistic work in rodents and imaging research in humans and monkeys suggests that persistent, contextually indiscriminate negative affect reflects alterations in a neural circuit encompassing the extended amygdala and OFC (Figures 3 and 7). Other work indicates that persistent changes in amygdala reactivity and functional connectivity following exposure to acute stress could contribute to the spillover of negative mood across contexts.

Third, individuals with a more negative disposition tend to behave in ways that evoke or intensify interpersonal conflict and social rejection, increasing the likelihood that they will experience momentary negative affect. Although the neurobiological mechanisms underlying stressor generation have received scant attention, the existing evidence highlights the potential importance of an amygdala-centered circuit responsible for evaluating the trustworthiness and approachability of other individuals.

Of these three pathways, the tendency to experience sustained levels of heightened negative affect in response to diffuse, uncertain, or remote threat appears to be most central to daily function (Bolger & Schilling, 1991). The vast majority of negative affect

experienced by dispositionally negative individuals in their daily lives appears to be indiscriminate and cannot be attributed to clear and immediate stressors. In the laboratory, heightened negative affect in explicitly or implicitly safe contexts is generally more discriminative of dispositional negativity and pathological anxiety than that elicited by overt threat (M. Davis et al., 2010; Duits et al., 2015; Watson & Clark, 1984). This tendency is amplified by exposure to early adversity (e.g., abuse, neglect, loss of caregiver; Wolitzky-Taylor et al., 2014) and it predicts the first onset of anxiety disorders in adolescents (Craske et al., 2012) and the intensification of internalizing symptoms in children and adults (Barker et al., 2015; Lenaert et al., 2014).

This pervasive, context-insensitive emotional bias likely reinforces other components of the negative phenotype, such as elevated avoidance and hyper-vigilance, and may serve to promote the expression of deleterious behaviors that elicit social rejection (Barlow et al., 2013; Carter et al., 2006; Cramer et al., 2012a, 2012b; Grupe & Nitschke, 2013; Jeronimus et al., 2014; Nettle & Bateson, 2012). This reciprocal cycle of maladaptive social transactions may help to explain why dispositionally negative individuals experience lower levels of occupational, financial, and marital success and are more likely to develop internalizing disorders.

A Roadmap to Future Challenges

The data that we have reviewed provide new insights into the psychological and neurobiological mechanisms that support individual differences in dispositional negativity and the processes that link this disposition to more transient states of negative affect. Yet, it is clear that our understanding remains far from complete. Throughout the review, we highlighted a number of specific conceptual challenges for future research in this area. Here, we outline some broader questions for the field and offer some methodological strategies for beginning to address them.¹⁰

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How Does the Brain Represent and Respond to Different Kinds of Threat?

A major challenge for future research is to understand how the central extended amygdala, OFC, and other key brain regions represent and respond to different kinds of threat (Figure 2). Threats differ along several key dimensions—including their certainty, imminence (i.e., physical distance or temporal latency), diffuseness (i.e., cues vs. contexts), and duration (D.C. Blanchard, Griebel, & Blanchard, 2001; D. C. Blanchard & Pearson, in press; R. J. Blanchard, Blanchard, & Hori, 1989; M. Davis et al., 2010; Fanselow, 1989, 1994; Fanselow & Lester, 1988). There is compelling evidence that these dimensions are psychiatrically important (Craske et al., 2012; M. Davis et al., 2010; Duits et al., 2015; Shackman, Stockbridge, LeMay, & Fox, in press) and pharmacologically dissociable (D. C. Blanchard, Griebel, & Blanchard, 2003; Bradford et al., 2013; M. Davis et al., 2010; Kalin & Shelton, 1989). Yet, we know remarkably little about how the human brain represents and differentially responds to them. Although some important advances have been made (Mobbs et al., 2010; Somerville et al., 2013), progress has been slowed by the use of paradigms and assays that confound these dimensions (e.g., *if* vs. *when* threat will occur; *brief-cues* vs. *prolonged-contexts*).

Drawing strong inferences about the neural systems supporting phasic and sustained responses to different dimensions of threat

requires the use of well-matched tasks, both in humans (Luck, 2005; Shackman et al., 2006) and in animals (Hammack, Todd, Kocho-Schellenberg, & Bouton, 2015). Conditions must be equated for motor requirements and perceptual characteristics, including paired reinforcers (e.g., shocks, aversive images). Investigators should be cautious when comparing neural activity across conditions that markedly differ in duration or number of trials (i.e., in the precision of the estimated activation), as in paradigms where long blocks of uncertain threat are compared to more punctate aversive challenges. Parametric manipulations of threat probability (*if* threat will occur), imminence (*when* or *where* it will occur), and duration (as in Bradford et al., 2013; Mobbs et al., 2010) would be particularly useful. The use of dynamic parametric tasks (e.g., where threat imminence or probability is smoothly and continuously varied) would also afford powerful new opportunities for understanding the kinds of uncertainty most relevant to fear and anxiety (Bach & Dolan, 2012; de Berker et al., 2016) and for identifying circuits involved in triggering behavioral and physiological “phase transitions” (e.g., from vigilance to behavioral inhibition to active defense; Mobbs, Hagan, Dalgleish, Silston, & Prevost, 2015; Mobbs & Kim, 2015). Putative double dissociations (e.g., regions sensitive to certain vs. uncertain threat) need to be rigorously assessed by testing the appropriate Region \times Condition interaction (as in Somerville et al., 2010). Absent that, strong claims of anatomical dissociation are unwarranted. Likewise, concluding that a particular brain region is “not involved” in a complex, multidimensional psychological function, like “fear,” based on a null statistical test or a single assay is unwarranted.

Emotional disorders are defined and diagnosed on the basis of symptoms (i.e., feelings) and human imaging studies will be particularly valuable for understanding the neural mechanisms underlying the subjective experience of different kinds of threat-elicited negative affect (e.g., Chang, Gianaros, Manuck, Krishnan, & Wager, 2015; Satpute et al., 2013; Somerville et al., 2013), something that cannot be assessed in animal models (Anderson & Adolphs, 2014; LeDoux, 2015). To this end, it is will be critical for human studies to verify the presence of target emotions separately for each task or condition (Shackman et al., 2006) and examine relations with ongoing neural activity. For correlational techniques, such as fMRI and EEG, trial-by-trial relations between neural signals and emotional experience provide the strongest and most direct link between the brain and self-reported emotion (Atlas, Bolger, Lindquist, & Wager, 2010; Lim, Padmala, & Pessoa, 2009). Multivoxel classifier approaches, in which machine learning techniques are used to identify patterns of activation predictive of subjective emotional states, are also likely to be fruitful (Chang et al., 2015; Krishnan et al., 2016; Wager et al., 2013; Woo et al., 2014).

¹⁰ For more general recommendations about best practices, see Button et al. (2013a, 2013b); Chalmers et al. (2014); S. P. David et al. (2013); Howells, Sena, and Macleod (2014); Ioannidis, Greenland, et al. (2014); Ioannidis, Munafo, Fusar-Poli, Nosek, and David (2014); Lueken et al. (2016); Poldrack et al. (2016); Stelzer, Lohmann, Mueller, Buschmann, and Turner (2014); Steward and Balice-Gordon (2014).

Which Brain Circuits Underlie Individual Differences in Dispositional Negativity?

It is widely believed that dispositional negativity, like other psychologically and psychiatrically relevant processes, reflects the coordinated activity of distributed brain circuits (Shackman, Fox, & Seminowicz, 2015). Here, we reviewed recent work highlighting the importance of five functional circuits: (a) projections from the Ce and BST to the subcortical and brainstem regions that proximally mediate key somatomotor and neuroendocrine features of momentary negative affect (Figure 3), (b) projections from the Ce to neurotransmitter systems in the basal forebrain and brainstem that modulate sensory processing and promote vigilance (Figure 3), (c) projections from the basolateral amygdala to the visual cortex and superior colliculus that play a role in redirecting or amplifying the amount of attention allocated to threat-relevant cues, (d) a polysynaptic circuit encompassing the Ce and dlPFC that is associated with differences in dispositional negativity in monkeys and anxiety disorders in children (Figure 6c), and (e) a circuit encompassing the central extended amygdala and OFC that covaries with dispositional negativity and supports heightened reactivity to a broad spectrum of aversive challenges (Figures 4, 5, and 7), including contexts associated with diffuse or temporally remote threat. Naturally, other circuits are likely to prove important. More broadly, our understanding of the neural circuits underlying dispositional negativity and momentary negative affect remains in its infancy (Calhoun & Tye, 2015; Janak & Tye, 2015; Okon-Singer, Hendler, Pessoa, & Shackman, 2015; Shackman et al., 2015; Tovote et al., 2015). 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., 2015; Turk-Browne, 2013).

It will also be important to determine the specificity of these circuits to different components of dispositional negativity (e.g., anxious distress vs. irritable distress) and assess whether they are equally relevant to all disorders on the internalizing spectrum (e.g., generalized anxiety disorder vs. major depression). The existing evidentiary record suggests that many of the brain regions that we have highlighted likely contribute to multiple components and disorders, a one-to-many mapping (Shackman et al., 2015). The amygdala, for example, has been linked to anxiety disorders (Etkin & Wager, 2007), depression (Hamilton et al., 2012), substance abuse (Chase et al., 2011; Kuhn & Gallinat, 2011; Tang et al., 2012), psychopathy (Koenigs, Baskin-Sommers, Zeier, & Newman, 2011), and autism (Nacewicz et al., 2006).

What Mechanisms Underlie Individual Differences in Dispositional Negativity?

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 these techniques is that they cannot address causation. A crucial challenge for future studies is to develop a mechanistic understanding of the neural circuits that underlie dispositional negativity and control the expression of negative affect. Addressing these fundamental questions mandates coordinated research efforts in humans and nonhuman animal

models. This could be achieved by combining mechanistic approaches (e.g., viral vector, chemogenetic, or optogenetic 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; A. S. Fox et al., 2010). The enhanced precision afforded by optogenetic and chemogenetic techniques would also open the door to identifying the specific molecules, cells, and subregions of the central extended amygdala that mediate effects detected in imaging studies (cf. Ferenczi et al., 2016). 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 common repertoire of complex socioemotional responses to potential threat and enable the use of similar behavioral assays (A. S. Fox & Kalin, 2014; Kaiser & Feng, 2015; Oler et al., 2016).

In humans, imaging approaches can be applied to patients with circumscribed brain damage (Adolphs, 2016; Motzkin, Philippi, Oler, et al., 2015; Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2014, 2015; Spunt et al., 2015). Alternatively, fMRI or EEG can be combined with noninvasive perturbation techniques (Bestmann & Ferdedoes, 2013; Reinhart & Woodman, 2014), neurofeedback (deBettencourt, Cohen, Lee, Norman, & Turk-Browne, 2015; Greer, Trujillo, Glover, & Knutson, 2014; Stoeckel et al., 2014), pharmacological manipulations (Duff et al., 2015; Paulus et al., 2005), or cognitive-behavioral interventions (Britton et al., 2015; Schnyer et al., 2015). Prospective longitudinal imaging studies represent another fruitful approach to identifying candidate mechanisms, especially in relation to the development of internalizing disorders and other kinds of adverse outcomes (Admon, Milad, & Hendler, 2013; Burghy et al., 2012; Heringa et al., 2013; McLaughlin et al., 2014; Swartz, Williamson, et al., 2015). From a broader perspective, human studies will be crucial for identifying the features of animal models that are conserved across species and, hence, most relevant to developing improved interventions for human suffering (Birn et al., 2014). They also afford an opportunity to develop objective biomarkers of psychiatric disease or disease-risk (Borsook et al., 2006; Borsook, Hargreaves, Bountra, & Porreca, 2014; J. Davis et al., 2015; R. G. Wise & Preston, 2010) and for generating novel hypotheses that can be mechanistically assessed in animal models (“reverse translation”; Ferenczi et al., 2016; Janak & Tye, 2015).

What Is the Relevance of Individual Differences in Brain Function for Negative Affect in Daily Life?

Biological studies of dispositional negativity and negative affect in humans rely on a limited number of well-controlled, but highly artificial manipulations—fearful and angry faces, aversive sounds and images, electric shocks, and so on—collected under unnatural conditions. Most of these manipulations are only mildly threatening, when compared to the kinds of stressors regularly encountered in daily life or those routinely used in animal models (LeDoux, 2015; Levenson, in press; Shackman et al., 2006), and are subject to self-selection biases, precluding the study of individuals with more extreme dispositions (Scherer, 1986). Consequently, the real-world significance of neural systems identified in the laboratory,

including the five circuits that we have highlighted, remains unclear.

Given the limitations of ambulatory measures of brain activity—there is no “fMRI helmet” as yet—addressing these fundamental questions requires integrating assays of brain function and behavior acquired in the scanner with measures of negative affect and motivated behavior assessed under naturalistic conditions in the laboratory (e.g., during semistructured 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 underscores the value of this approach for identifying the neural systems associated with naturalistic variation in mood and behavior, a central goal of psychology, psychiatry, and the behavioral neurosciences (Berkman & Falk, 2013; Forbes et al., 2009; Heller et al., in press; Lopez, Hofmann, Wagner, Kelley, & Heatherton, 2014; S. J. Wilson, Smyth, & MacLean, 2014). To our knowledge, this approach has yet to be applied to the study of dispositional negativity, although ongoing work by our group has begun to do so.

The development of robust mobile eye trackers, the emergence of commercial software for automated analyses of facial expressions (Olderbak, Hildebrandt, Pinkpank, Sommer, & Wilhelm, 2014), and the widespread dissemination of smart-phone and other kinds of “wearable” technology afford additional opportunities for objectively, efficiently, and unobtrusively quantifying social attention and context, negative affect, and motivated behavior in situ (Gosling & Mason, 2015; Onnela & Rauch, 2016; 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 persistent, contextually inappropriate negative affect and pathology-promoting behaviors (e.g., social withdrawal, avoidance, and hyper-vigilance) in the real world, close to clinically relevant end-points. This approach promises a depth of understanding that cannot be achieved using either animal models or isolated measures of brain function. Even in the absence of biological measures, these new tools promise important clues about the dynamics of negative affect in daily life (e.g., spillover of mood across sequential contexts and assessments) and the social factors and coping behaviors that help govern the momentary expression of dispositional negativity.

Conclusions

Dispositional negativity has enormous consequences for global health, wealth, and happiness. Self-report data suggest that three key pathways—increased stressor reactivity, tonic increases in negative affect, and increased stressor exposure—explain most of the heightened negative affect characteristic of individuals with a more negative disposition. Of these three pathways, indiscriminate negative affect appears to be the most central to daily life and most relevant to the development and maintenance of anxiety disorders and depression. Mechanistic and imaging studies in humans, monkeys, and rodents suggest that sustained, indiscriminate negative affect reflects variation in the activity and connectivity of several key brain regions, including the central extended amygdala and OFC. These observations provide an integrative framework for understanding the cascading network of psychological and biological processes that bind emotional traits to emotional states and

emotional disorders and, ultimately, for guiding the development of more effective prevention and treatment strategies.

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