The psychological and neurobiological bases of dispositional negativity

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Here, we highlight recent advances in our understanding of the psychological and neurobiological bases of negative emotionality or what we term *dispositional negativity*, one of the most intensely scrutinized dimensions of childhood temperament and adult personality. A primary focus of our essay concerns the processes linking enduring individual differences in dispositional negativity to momentary emotional experiences and behaviors.

Dispositional Negativity

Dispositional negativity—the tendency to show increased negative affect—is a fundamental dimension of temperament and personality, subsuming a range of narrower traits (e.g., anxious temperament, behavioral inhibition, harm avoidance, neuroticism, and trait anxiety; Caspi, Roberts, & Shiner, 2005). Individual differences in dispositional negativity can be conceptualized as an extended family of complex, multi-componential phenotypes that first emerge early in development, persist into adulthood, and reflect a combination of heritable and non-heritable factors (A. S. Fox & N. H. Kalin, 2014; Ormel et al., 2013; Soto & John, 2014). Key features of this family of phenotypes are expressed similarly across mammalian species, enabling mechanistic studies (Kalin & Shelton, 2003). Dispositional negativity is stable, but not immutable, and can be increased by stress or decreased by cognitive-behavioral or pharmacological treatments, raising the possibility of targeted interventions (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2013).

Trait-State Links Inferred from Self-Report and Behavior

Increased Stressor Reactivity

Self-report data indicate that individuals with elevated levels of dispositional negativity over-react to a variety of stressors. They report exaggerated negative affect in response to hassles and interpersonal conflicts in daily life (Suls & Martin, 2005) and aversive challenges in the laboratory (Matthews, Deary, & Whiteman, 2009). Likewise, individuals with a more negative disposition are prone to exaggerated behavioral, psychophysiological, and neuroendocrine reactions to potential threat (Oler, Fox, Shackman, & Kalin, *in press*). These findings suggest that dispositional negativity represents a diathesis, which enhances the likelihood, magnitude, or duration of negative affect elicited by stressors.

Increased Negative Affect in the Absence of Immediate Stressors

Importantly, individuals with elevated dispositional negativity are also prone to exaggerated negative affect in situations where potential stressors are remote, diffuse, or absent. This kind of pervasive, context-independent negative affect has been described as a tonic or endogenous effect of temperament, given the absence of clear stressors (Gross, Sutton, & Ketelaar, 1998; Watson & Clark, 1984). In the laboratory, dispositionally-negative individuals experience more intense negative thoughts and feelings at 'baseline' or after viewing emotionally-neutral control stimuli (Gross et al., 1998). In daily life, they frequently experience elevated negative affect in comfortable, familiar settings. For example, Bolger and Schilling (1991) used statistical decomposition techniques to demonstrate that nearly 60% of heightened negative affect in daily life reflects tonic differences in distress, in settings where there was no clear concurrent source of stress, more than double that attributable to individual differences in stressor reactivity or

stressor exposure. These observations indicate that context-independent negative affect is a central feature of dispositional negativity.

Increased Stressor Generation and Exposure

Dispositionally-negative individuals often behave in ways that generate hassles and promote social conflict. Increased stressor exposure, in turn, promotes more frequent or intense negative affect. A variety of evidence shows that individuals with high levels of dispositional negativity experience more frequent adversities and conflicts, particularly those of an interpersonal nature (Kendler, Gardner, & Prescott, 2003; Suls & Martin, 2005). Other work suggests that dispositionally-negative individuals play an instrumental role in evoking interpersonal stress and rejection. Their friends and offspring report increased conflict (Berry, Willingham, & Thayer, 2000; Hutteman et al., 2014), their romantic partners report reduced relationship security (Neyer & Voigt, 2004), and their spouses report reduced relationship satisfaction (Malouff, Thorsteinsson, Schutte, Bhullar, & Rooke, 2010). In the laboratory, randomly-assigned social partners judge dispositionally-negative individuals to be more moody, uncomfortable, and negative (Creed & Funder, 1998). This negativity begets negativity; random partners often respond with heightened criticism, contempt, and hostility (Creed & Funder, 1998). This evocative effect may reflect dispositionally-negative individuals' tendency to express less warmth, be less responsive to social partners, escalate negative affect during conflict, and engage in toxic interpersonal behaviors (e.g., contempt and sarcasm; Clark, Kochanska, & Ready, 2000; Wang, Repetti, & Campos, 2011). Other work shows that interventions targeting these kinds of maladaptive socioemotional behaviors reduce conflict and rejection, indicating a causal role (Snyder &

Halford, 2012; Taylor & Alden, 2011). Taken together, these observations provide compelling evidence that dispositionally-negative individuals play an active role in shaping their social environment in ways that increase the likelihood of negative affect

The Neurobiology of Dispositional Negativity

Increased Reactivity to Aversive Laboratory Challenges

Neurobiological research corroborates the link connecting dispositional negativity to heightened stressor reactivity. Imaging studies show that dispositionally-negative individuals are prone to increased or prolonged activation in the dorsal amygdala in response to punctate, threat-related cues (Calder, Ewbank, & Passamonti, 2011; A. S. Fox & N. H. Kalin, 2014; Schuyler et al., 2012)[1]. Metabolic activity in the dorsal or central (Ce) nucleus of the amygdala is stable over time and measurement context (i.e., trait-like), heritable, and associated with heightened reactions to potential threat encountered outside the scanner environment (A. S. Fox & N. H. Kalin, 2014). Moreover, elevated amygdala activity appears to be a shared substrate for different phenotypic presentations of dispositional-negativity (A. J. Shackman et al., 2013). Like the dispositional-negativity phenotype, increased amygdala reactivity to acute threat: (a) predicts the development of future internalizing symptoms (Swartz, Knodt, Radtke, & Hariri, 2015), (b) is heightened in mood and anxiety disorders (Etkin & Wager, 2007; Hamilton et al., 2012), (c) is increased by stress and adversity (Dannlowski et al., 2012), and (d) is decreased by cognitive-

[1] Anatomically, the amygdala is poised to assemble a broad spectrum of emotional reactions via projections to the brain regions that proximally mediate many of the behavioral (e.g., passive and active avoidance), peripheral physiological (e.g., cardiovascular and neuroendocrine activity), and cognitive (e.g., vigilance) features of momentary negative affect (Davis & Whalen, 2001; Freese & Amaral, 2009; Pessoa & Adolphs, 2010; A. J. Shackman & Fox, *in press*).

behavioral and pharmacological treatments for anxiety and depression (Furmark et al., 2002; Paulus, Feinstein, Castillo, Simmons, & Stein, 2005).

Work in animals shows that the amygdala causally contributes to negative affect elicited by threat (Oler, Fox, Shackman, & Kalin, 2016). This is consistent with observations made in humans with naturally-occurring amygdala damage. For example, Patient SM, who has near-complete bilateral destruction of the amygdala, shows a profound lack of fear and anxiety when exposed to frightening movies, haunted houses, tarantulas, and snakes and consistently endorses low levels of dispositional negativity on standard self-report measures (Feinstein, Adolphs, Damasio, & Tranel, 2011). These data suggest that dispositionally-negative individuals' heightened reactivity to threat and other kinds of stressors reflects larger or longer-lasting responses in a distributed neural circuit centered on the amygdala[2].

Trait-like Individual Differences in Stressor Reactivity are Discernible at Rest

Although most human neurobiological research has focused on reactivity to acute threat-related cues—faces, images, and so on—stable individual differences in threat-reactivity can also be discerned in the brain's spontaneous or 'resting' activity. For example, monkeys with elevated amygdala activity at 'baseline' (e.g., in their home-cage) show increased

[2] Although these findings highlight the contributions of the amygdala to trait-like differences in threat reactivity, it is by no means the only relevant region. Mechanistic and imaging work highlights the important contributions of a distributed circuit encompassing the anterior hippocampus, anterior insula/orbitofrontal cortex, and periaqueductal gray (PAG) (A. S. Fox & N. H. Kalin, 2014; A. S. Fox, Oler, Shackman, et al., 2015; A. S. Fox, Oler, Tromp, Fudge, & Kalin, 2015; A. S. Fox et al., 2010; A. S. Fox, Shelton, Oakes, Davidson, & Kalin, 2008; Kalin, Shelton, & Davidson, 2007; Oler et al., 2010; A. J. Shackman et al., 2013). Like the amygdala, activity in each of these regions predicts trait-like individual differences in stressor reactivity.

freezing and elevated levels of the stress-sensitive hormone cortisol when threat is encountered in other contexts (A. S. Fox et al., 2008). Likewise, humans with higher levels of dispositional negativity show increased amygdala activity at rest (Canli et al., 2006). These observations suggest that variation in the basal activity of the amygdala and other regions of the brain (e.g. dorsolateral prefrontal cortex[3]) represent a diathesis for heightened negative affect in response to trait-relevant challenges.

Altered Resting Activity—Traits or States, Tonic or Reactive Differences?

The data reviewed in the prior section would seem to suggest that reactive features of temperament are embodied in the on-going activity of the brain. Yet, it remains unclear whether alterations in 'resting' activity reflect trait-like differences in momentary affect, fleeting states elicited by the novelty or stress of the experimental context, or some combination of the two. After all, most neurophysiological assays are intrusive and can elicit substantial negative affect (Törnqvist, Månsson, Larsson, & Hallström, 2006).

[3] Relations between temperament and resting-state brain activity are not limited to the amygdala—dispositionally-negative monkeys, children, and adults also show greater resting-state activity in the electroencephalogram (EEG) over the right compared to the left prefrontal cortex (PFC) (Oler et al., 2016; Wacker, Chavanon, & Stemmler, 2010). Like the negative phenotype, individual differences in resting prefrontal EEG asymmetry emerge early in life and are relatively stable over time, reliable, heritable, and predictive of the intensity of emotional reactions to aversive stimuli (N. A. Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Smit, Posthuma, Boomsma, & De Geus, 2007; Towers & Allen, 2009; Wheeler, Davidson, & Tomarken, 1993). Like the dispositional-negativity phenotype, resting prefrontal EEG asymmetry: (a) prospectively predicts the first-onset of mood disorders (Nusslock et al., 2011), (b) is exaggerated in patients with anxiety and mood disorders (Thibodeau, Jorgensen, & Kim, 2006), and is normalized by anxiolytic drugs (Oler et al., 2016). Furthermore, direct neurofeedback manipulations of prefrontal EEG attenuate negative affect elicited by subsequent exposure to aversive stimuli (Allen, Harmon-Jones, & Cavender, 2001). With the pharmacological evidence, this suggests that the neural mechanisms responsible for generating this electrophysiological marker causally contribute to trait-like individual differences in threat reactivity. Recent efforts to pinpoint the source of the scalp-recorded EEG asymmetry have highlighted the importance of the dorsolateral prefrontal cortex (dlPFC; A. J. Shackman, McMenamin, Maxwell, Greischar, & Davidson, 2009), consistent with this region's well-established role in regulating momentary affect (Buhle et al., 2014).

More sophisticated psychometric analyses will be required to determine the relative contribution of traits and states to resting-state measures of brain function (Coan, Allen, & McKnight, 2006).

'Tonic' Negative Affect May Reflect Heightened Reactivity to Diffuse Threat

Self-report data show that dispositionally-negative individuals experience heightened negative affect in the absence of clear-cut stressors. Although this could reflect a direct or endogenous effect of dispositional negativity on mood, a wealth of biological evidence suggests that it partially reflects a reaction to stressors that are uncertain, temporally remote (i.e., occurred in the past or may occur in the future), or psychologically diffuse (e.g., a novel or mildly aversive experimental context) (Grupe & Nitschke, 2013). For example, individuals with extreme dispositional negativity show elevated defensive responses (e.g., startle) and experience elevated negative affect during periods of safety embedded within instructed fear paradigms (CS-or inter-cue interval); that is, in the periods before and after the randomized presentation of learned threat cues (CS+) (Barker, Reeb-Sutherland, & Fox, 2014). Conversely, anxiety-reducing drugs selectively dampen sustained negative affect elicited by uncertain threat, while sparing phasic reactions to cues signaling clear and immediate danger (Bradford, Shapiro, & Curtin, 2013). These findings suggest that apparently endogenous increases in negative affect, as described in the self-report literature, likely reflect heightened sensitivity to distal, uncertain stressors, rather than a fixed or 'tonic' consequence of dispositional negativity.

Mechanistic work in rodents suggests that sustained levels of heightened negative affect reflect the central extended amygdala, a neural circuit encompassing the lateral divisions of the Ce and bed nucleus of the stria terminalis (BST) (A. S. Fox, Oler, Tromp, et al., 2015). Consistent with this view, imaging studies show that dispositionally-negative monkeys and humans are marked by heightened activity in the extended amygdala during periods of diffuse or uncertain threat (A. S. Fox et al., 2008; A. J. Shackman et al., *in press;* Somerville, Whalen, & Kelley, 2010). Furthermore, variation in BST activation and functional connectivity predict negative affect, freezing, skin conductance, and cortisol elicited by uncertain danger (Alvarez et al., 2015; Jahn et al., 2010; Kalin, Shelton, Fox, Oakes, & Davidson, 2005; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Somerville et al., 2013). Although this activity is often described as a 'sustained' response to uncertain threat, it has also been found using much briefer challenges (<10 seconds; Grupe, Oathes, & Nitschke, 2013; Mobbs et al., 2010), consistent with the spill-over effects found in fear-potentiated startle studies. Collectively, this work indicates that a circuit[4] centered on the extended amygdala is a key substrate for the kinds of context-independent negative affect that characterize individuals with heightened levels of dispositional negativity (A. J. Shackman & Fox, *in press*)[5].

[4] Individual differences in BST activity may reflect altered communication with the orbitofrontal cortex (OFC). Large-scale imaging studies in monkeys (n = 592) demonstrate that threat-related metabolic activity in the OFC is heritable and predictive of trait-like differences in dispositional negativity (A. S. Fox, Oler, Shackman, et al., 2015). Moreover, selective OFC lesions are associated with decreased passive avoidance of uncertain threat and reduced BST activity in monkeys (A. S. Fox et al., 2010; Kalin et al., 2007), paralleling the consequences of naturally-occurring OFC insults for BST activity in humans (Motzkin et al., 2015).

[5] Deficient filtering of threat-related information from fronto-parietal working memory circuits, leading to elevated rumination over the past and increased worry about the future, may also contribute to context-independent negative affect (Stout, Shackman, Johnson, & Larson, 2014; Stout, Shackman, & Larson, 2013).

Pervasive 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 (Suls & Martin, 2005). Imaging work suggests that the amygdala could contribute to this spill-over of negative mood via a process of stress-induced sensitization. Indeed, there is evidence that brief exposure to acute stressors leads to sustained increases in amygdala activity (Cousijn et al., 2010) and amplifies amygdala reactivity to threat (van Marle, Hermans, Qin, & Fernandez, 2009). Acute stressors can produce even longer-lasting changes—on the order of minutes to hours—in the functional connectivity of the amygdala (Vaisvaser et al., 2013; van Marle, Hermans, Qin, & Fernandez, 2010). Furthermore, these neural spill-over effects are exaggerated among individuals with a more negative disposition (Everaerd, Klumpers, van Wingen, Tendolkar, & Fernandez, 2015). Sensitization of the amygdala following exposure to stress could promote negative affect either directly, by enhancing reactions to mild threat (Grillon & Charney, 2011), or indirectly, by increasing the likelihood that attention will be allocated to threat-related information (Gamer, Schmitz, Tittgemeyer, & Schilbach, 2013; MacLeod & Clarke, 2015).

Increased Stressor Generation and Exposure May Reflect Differences in the Way Social Cues Are Processed

Self-report data indicate that individuals with a more negative disposition are prone to behave in ways that evoke stress. Although the neurobiological mechanisms underlying this recursive Temperament—Environment—Affect relationship remain poorly understood, it is known that damage to the amygdala is associated with heightened, even

pathological levels of social approach and trust (Adolphs, *in press;* van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013). Conversely, imaging studies in neurologically-intact adults indicate that amygdala activation is associated with increased suspicion and is sensitive to betrayal during economic bargaining games (Bhatt, Lohrenz, Camerer, & Montague, 2012). These observations raise the possibility that differences in social-appraisal processes mediated by the amygdala contribute, at least in a distal way, to dispositionally-negative individuals' tendency to experience relationship insecurity, express less warmth and reciprocity, engage in active and passive forms of avoidance, and evoke negative reactions from social partners.

An Integrative Perspective

Recent years have witnessed the emergence of powerful tools for assaying emotion and brain function and new insights into the psychological and neurobiological bases of dispositional negativity.

First, there is clear evidence that dispositionally-negative individuals respond more strongly to explicit stressors and aversive challenges. Variation in threat-reactivity reflects stable individual differences in the sensitivity and functional connectivity of a number of brain regions, including the amygdala. These differences manifest as heightened activation in response to punctate challenges, but they are also evident in the spontaneous, on-going activity of the brain. At present, it remains unclear whether temperament-related variation in resting-state activity and connectivity reflects tonic differences in neurophysiology, momentary states precipitated by diffuse threat, or some combination of the two.

Second, individuals with elevated dispositional negativity often show heightened negative affect in contexts where stressors are diffuse, remote, or absent. Neurobiological research suggests that this reflects alterations in a neural circuit centered on the extended amygdala. Other work indicates that enduring stress-induced changes in amygdala reactivity and functional connectivity may contribute to the spill-over of negative affect across contexts.

Third, individuals with a more negative disposition tend to act in ways that evoke stress, increasing the likelihood of negative affect. Although the neurobiological mechanisms underlying stressor generation have received scant attention, the existing evidentiary record highlights the potential importance of circuitry encompassing the amygdala.

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 dispositional negativity. The vast majority of negative affect experienced by dispositionally-negative individuals in daily life is indiscriminate and cannot be attributed to clear and present stressors (Bolger & Schilling, 1991; Watson & Clark, 1984). In the laboratory, heightened negative affect in safe contexts is generally more sensitive to differences in dispositional negativity and pathological anxiety than that elicited by overt threat (Davis, Walker, Miles, & Grillon, 2010; Duits et al., 2015) and prospectively predicts the first onset of anxiety disorders (Craske et al., 2012).

This pervasive, context-insensitive emotional bias likely reinforces other maladaptive components of the negative phenotype (e.g., avoidance and hyper-vigilance) and may promote the expression of maladaptive interpersonal behaviors that increase the likelihood of conflict, alienation, and rejection.

Conclusions

Individual differences in dispositional negativity can have profound consequences for health, wealth, and happiness (Lahey, 2009). The work that we have reviewed provides an integrative framework for understanding the cascade of psychological and biological processes that bind dispositional negativity to momentary emotional states, to emotional disorders, and to a range of other adverse outcomes.

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