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Perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety

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ABSTRACT

Several lines of research have illustrated that negative environments can precipitate psychopathology, particularly in the context of relatively increased biological risk, while social resources can buffer the effects of these environments. However, little research has examined how social resources might buffer proximal biological risk for psychopathology or the neurobiological pathways through which such buffering may be mediated. Here we report that the expression of trait anxiety as a function of threat-related amygdala reactivity is moderated by perceived social support, a resource for coping with adversity. A significant positive correlation between amygdala reactivity and trait anxiety was evident in individuals reporting below average levels of support but not in those reporting average or above average levels. These results were consistent across multiple measures of trait anxiety and were specific to anxiety in that they did not extend to measures of broad negative or positive affect. Our findings illuminate a biological pathway, namely moderation of amygdala-related anxiety, through which social support may confer resilience to psychopathology. Moreover, our results indicate that links between neural reactivity and behavior are not static but rather may be contingent on social resources.

1. Introduction

A substantial literature highlights the critical role of stressful or adverse circumstances in precipitating psychopathology, particularly in relation to individual differences in personality, brain function, and genetic predisposition (Caspi, Hariri, Holmes, Uher, & Moffitt, 2010; Caspi et al., 2003; Costello et al., 2002; Monroe & Simons, 1991). In general, epidemiological studies have reported increased risk for psychopathology, particularly mood and anxiety disorders, in individuals having encountered a variety of adverse or stressful situations including childhood maltreatment, violent crime, divorce, unemployment, and medical illness (Hammen, 2005; Kendler, Karkowski, & Prescott, 1999; Monroe & Simons, 1991). In parallel, human neuroimaging studies have revealed that increased sensitivity of neural circuitries, especially the amygdala, to threat and stress may mediate this risk (Price & Drevets, 2010).

Reactivity of the amygdala to threat-related cues such as emotional faces has been linked to trait anxiety (Fakra et al., 2009), anxiety disorders (Phan, Fitzgerald, Nathan, & Tancer, 2006), and depression (Monk et al., 2008; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002), and therefore represents a well researched biological risk factor for negative psychological outcomes. The link between trait anxiety and amygdala reactivity is particularly robust and seen across many different studies and approaches (Dickie & Armony, 2008; Etkin et al., 2004; Fakra et al., 2009; Haas, Omura, Constable, & Canli, 2007; Hariri, 2009; Killgore & Yurgelun-Todd, 2005; Most, Chun, Johnson, & Kiehl, 2006; Ray et al., 2005; Stein, Simmons, Feinstein, & Paulus, 2007). Thus, this research suggests that variability in anxiety, an individual's behavioral sensitivity to threat and stress, reflects in part both the underlying reactivity of these neural circuitries as well as the risk for psychopathology associated with stress and adversity (Hariri, 2009).

Partly in response to the work emphasizing the harmful psychological effects of negative environments, resiliency research has explored factors that may buffer against negative environments and biological risk leading to positive outcomes even in unfavorable environments (Cohen & Hoberman, 1983; Masten, 2001; Masten & Coatsworth, 1998; Rutter, 2006). One such buffering factor is social support, which typically reflects people in an individual's life (family, friends, neighbors, community members) that are available in times of need and can provide resources such as emotional support (someone with whom to communicate), companionship (someone with whom to spend time and share activities), and instrumental aid (financial and material resources; Cohen & Wills, 1985).

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Social support has been shown to buffer the relationship between negative life events and depressive symptomatology (Cohen & Hoberman, 1983; Cohen, McGowan, Fooskas, & Rose, 1984), and has been associated broadly with well-being and health, both directly and as a buffer against stressful circumstances (Turner, 1981). Interestingly, *perceptions* of social support are often more powerful in predicting the buffering effects of this support than objective measures (Cohen et al., 1984). For example, in a review of the stress and social support literature, Cohen and Wills (1985) concluded that studies assessing perceptions of social support found evidence for the "buffering" effect of social support (social support predicted more positive outcomes only during times of stress), whereas those using more objective measures of social support generally found only a main effect of social support (the support predicted positive outcomes regardless of levels of stress). Thus, individuals' subjective appraisal of their social support may be particularly important in evaluating the effects of social support as a moderator between biological risk and health related outcomes.

In the current study, we asked if perceived social support, a resource for coping with adversity, moderates the link between amygdala reactivity to threat-related cues and the expression of trait anxiety, a well-established personality risk factor for psychopathology (Kendler, Kuhn, & Prescott, 2004; Lahey, 2009). To do so, we used blood oxygen level-dependent functional MRI (BOLD fMRI) to assess threat-related amygdala reactivity in 103 healthy adults. Social support was measured using the Interpersonal Support Evaluation List, a self-report measure of perceived availability of potential social resources including material aid, as well as individuals with whom one can interact and share experiences (Cohen & Hoberman, 1983; Cohen & Wills, 1985). Multiple indices of personality, mood, and affect as well as an index of recent negative life experiences were also assessed via self-report to examine the specificity of links between social support, amygdala reactivity, and trait anxiety.

2. Materials and methods

2.1. Participants

103 participants (45% male; mean age = 44.5 years; SD = 6.8; range: 31–54 years) were recruited from a larger community sample of 1379 middle-aged volunteers who were in good general health and free of major medical or psychiatric illnesses (Fakra et al., 2009; Manuck et al., 2010). Written informed consent according to the guidelines of the University of Pittsburgh's institutional review board was provided by all subjects before their participation in the neuroimaging subcomponent of the larger project. All participants included in these analyses were in good general health and free of the following: (1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or a lifetime history of psychotic symptoms; (2) use of psychotropic, glucocorticoid, or cardiovascular (e.g., antihypertensive or antiarrhythmic) medication; (3) conditions that affect cerebral blood flow and metabolism (e.g., hypertension); and (4) any current *DSM-IV* Axis I disorder as assessed by the nonpatient version of the Structured Clinical Interview for *DSM-IV*. Participants reported their race as follows: 88% reported being European-American, 7% reported being African American, and 4% reported being other races (Asian-American, Multi-racial, or other).

2.2. Amygdala reactivity paradigm

We used a well-characterized and widely used fMRI challenge paradigm that elicits robust bilateral amygdala reactivity to threat-related cues (Bigos et al., 2008; Brown et al., 2005; Fakra et al., 2009; Fisher et al., 2009; Fisher, Meltzer, Ziolko, Price, & Hariri, 2006; Hariri et al., 2009; Manuck, Brown, Forbes, & Hariri, 2007; Manuck et al., 2010). The paradigm consists of 4 blocks of a perceptual face-processing task interleaved with 5 blocks of a sensorimotor control task. During face-processing blocks, participants view a trio of faces (expressing either anger or fear) and select 1 of 2 faces (bottom) that is identical to a target face (top). Angry and fearful facial expressions can represent honest indicators of an ecologically valid threat and have likely been associated with negative outcomes in the past. In this context, we interpret the amygdala activation elicited by our task as being threat-related. Each face-processing block consists of 6 images, balanced for gender and target affect (angry or fearful), all of which were derived from a standard set of pictures of facial affect (Ekman & Friesen, 1976). During the sensorimotor control blocks, participants view a trio of simple geometric shapes (circles and vertical and horizontal ellipses) and select 1 of 2 shapes (bottom) that are identical to a target shape (top). Each sensorimotor control block consists of 6 different shape trios. All blocks are preceded by a brief instruction ("match faces" or "match shapes") that lasts 2 s. In the face-processing blocks, each of the 6 face trios is presented for 4 s with a variable inter-stimulus interval (ISI) of 2–6 s (mean = 4 s), for a total block length of 48 s. In the sensorimotor control block, each of the 6 shape trios is presented for 4 s with a fixed inter-stimulus interval of 2 s, for a total block length of 36 s. Total task time is 390 s.

2.3. BOLD acquisition parameters

Each participant underwent scanning with a Siemens 3-T MAGNETOM Allegra (Siemens AG, Erlangen, Germany), which was developed specifically for advanced brain imaging applications and is characterized by increased T2* sensitivity and fast gradients (slew rate, 400 T/m/s), which minimize echospacing, thereby reducing echoplanar imaging geometric distortions and improving image quality. Blood oxygen level-dependent (BOLD) functional images were acquired with a gradient-echo EPI sequence (TR/TE = 2000/25 milliseconds, FOV = 20 cm, matrix = 64 × 64), covering 34 interleaved axial slices (3 mm). All scanning parameters were selected to optimize the quality of the BOLD signal while maintaining a sufficient number of slices to acquire whole-brain data. Before collecting fMRI data for each participant, we acquired a reference echoplanar imaging scan, which we visually inspected for artifacts (e.g., ghosting) and good signal across the entire volume of acquisition, including the amygdala. Additionally, an autoshimming procedure was conducted before the acquisition of BOLD data in each participant to minimize field inhomogeneities.

2.4. Image processing and analysis

Whole-brain image analysis was completed using the general linear model of SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Images for each participant were realigned to the first volume in the time series to correct for head motion, spatially normalized into standard stereotactic space (Montreal Neurological Institute template) using a 12-parameter affine model, and smoothed to minimize noise and residual difference in gyral anatomy with a Gaussian filter (6 mm FWHM). Voxel-wise signal intensities were ratio-normalized to the whole-brain global mean.

Following preprocessing, linear contrasts employing canonical hemodynamic response functions were used to estimate condition-specific (faces > shapes) contrast images for each individual, which were used in second-level random effects models accounting for scan-to-scan and participant-to-participant variability to determine mean condition-specific regional responses using one-sample *t*-tests (voxel threshold = $p < .05$, FDR-corrected; cluster threshold ≥10 contiguous voxels).

2.4.1. Amygdala regions of interest

BOLD contrast estimates were extracted from functional clusters exhibiting a main effect of task using the above threshold within anatomically defined amygdala regions of interest (ROIs). Due to structural and functional heterogeneity of amygdala nuclei implicated in the processing of threat-related cues, we independently examined the ventral and dorsal amygdala, which encompass the amygdala's principal input and output regions, respectively (Manuck et al., 2010). We constructed hemisphere-specific ROIs using Marsbar (version 0.41) for the ventral amygdala, which encompassed the basolateral complex, and for the dorsal amygdala, which encompassed the central nucleus as well as the sublenticular extended amygdala and nucleus baysalis of Meynert. The ventral amygdala ROIs were anchored by MNI coordinates $x = \pm 21$, $y = -3$, $z = -23$, with widths of 14 mm, 6 mm, and 6 mm along the *x*-, *y*-, and *z*-axes, respectively. The total volume of the ventral amygdala ROI was 1024 mm^3 in each hemisphere. The dorsal amygdala ROI was anchored by the MNI coordinates $x = \pm 21$, $y = -4$, $z = -13$, with widths of 14 mm, 8 mm and 10 mm along the *x*-, *y*-, and *z*-axes, respectively. The total volume of the dorsal amygdala ROI was 1920 mm^3 in each hemisphere. The reported widths reflect the total for the ROI along each axis and are centered on the MNI coordinate anchoring each axis (i.e., with $x = 21$ and width = 14 mm, the range of coordinates included along that axis of the ROI are from $x = 14$ to $x = 28$). The posterior extent of both the dorsal and ventral amygdala was carefully defined to exclude the hippocampus.

2.5. Self-report measures

The *Interpersonal Support Evaluation List* (ISEL) measures the perceived availability of social support through self-report (Cohen & Hoberman, 1983). This measure assesses availability of support across four domains: availability of material aid, availability of someone to talk to about one's problems, availability of a positive comparison when comparing one's self to others, and availability of people with whom one can do things.

The *Revised NEO Personality Inventory* (NEO-PI-R) contains the trait Neuroticism (N) characterized by emotional distress, negative affect, and lack of emotional stability. The N1 subscale of Neuroticism measures Anxiety. Those high on "Anxiety" in this scale are characterized by anxiousness, fearfulness, worrying, and feelings of nervousness. The trait Extraversion (E) is characterized by sociability and tendency to experience positive emotions (Costa & McCrae, 1992, 1995).