Functional and Structural Amygdala – Anterior Cingulate Connectivity Correlates with Attentional Bias to Masked Fearful Faces

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Note

Functional and structural amygdala – Anterior cingulate connectivity correlates with attentional bias to masked fearful faces

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ABSTRACT

An attentional bias to threat has been causally related to anxiety. Recent research has linked nonconscious attentional bias to threat with variability in the integrity of the amygdala – anterior cingulate pathway, which sheds light on the neuroanatomical basis for a behavioral precursor to anxiety. However, the extent to which structural variability in amygdala – anterior cingulate integrity relates to the functional connectivity within this pathway and how such functional connectivity may relate to attention bias behavior, remain critical missing pieces of the puzzle. In 15 individuals we measured the structural integrity of the amygdala – prefrontal pathway with diffusion tensor-weighted MRI (magnetic resonance imaging), amygdala-seeded intrinsic functional connectivity to the anterior cingulate, and attentional bias toward backward masked fearful faces with a dot-probe task. We found that greater biases in attention to threat predicted greater levels of uncinate fasciculus integrity, greater positive amygdala – anterior cingulate functional connectivity, and greater amygdala coupling with a broader social perception network including the superior temporal sulcus, tempoparietal junction (TPJ), and somatosensory cortex. Additionally, greater levels of uncinate fasciculus integrity correlated with greater levels of amygdala – anterior cingulate intrinsic functional connectivity. Thus, high bias individuals displayed a heightened degree of amygdala – anterior cingulate connectivity during basal conditions, which we believe predisposes these individuals to focus their attention on signals of threat within their environment.

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1. Introduction

Stimuli that signal the existence of potential threat are afforded greater attentional resources (Ohman, Flykt, & Esteves, 2001). This attentional bias to threat is exaggerated in individuals with heightened anxiety (MacLeod & Mathews, 1988), even when awareness is restricted by backward masking and threat is preattentively processed (Fox, 2002; Mogg &
Bradley, 2002). Furthermore, individual differences in pre-attentive attentional bias to threat predict cortisol reactivity to stress (Fox, Cahill, & Zoukou, 2010). Critically, an attentional bias to threat is not only correlated with anxiety, but also appears to play a causal role in the development of anxious symptoms (Mathews & MacLeod, 2002). Thus, understanding the underlying neural correlates of individual variability in attentional bias to threat has important implications for the understanding of stress and anxiety.

Neuroimaging research has linked the facilitation of spatial attention by backward masked threats to elevated blood oxygen level dependant (BOLD) activity in an amygdala, anterior cingulate cortex (ACC), posterior superior temporal sulcus (pSTS), and visual cortex network (Carlson, Reinke, & Habib, 2009). Within this network, the amygdala appears to automatically detect crude preattentive representations of threat vs. non-threat information (Morris, De Gelder, Weiskrantz, & Dolan, 2001; Morris, Ohman, & Dolan, 1998; Whalen et al., 1998), while the ACC appears to be involved in monitoring and resolving potential emotional conflicts (Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). The end product is a rapid prioritization of visual cortical processing within the retinotopic location of potential threat (Carlson & Reinke, 2010; Carlson, Reinke, LaMontagne, & Habib, 2011). Anatomically, attentional bias to preattentive threat is predictive of greater ACC gray matter volume (Carlson et al., 2012) and greater fiber integrity within the uncinate fasciculus amygdala — ACC white matter pathway (Carlson, Cha, Harmon-Jones, Mujica-Parodi, & Hajcak, 2013). Given these anatomical associations, high bias individuals should display a heightened degree of amygdala — ACC intrinsic functional connectivity, which ultimately predisposes these individuals to focus their attention on signals of environmental threat. However, the extent to which variability in amygdala — ACC structural integrity relates to variability in the functional integrity of this network as it relates to attentional bias to masked threat is unclear.

Here, we measured the structural integrity of the uncinate fasciculus with diffusion tensor-weighted MRI (magnetic resonance imaging), amygdala-seeded intrinsic or resting-state functional connectivity with the ACC, and measured attentional bias with a backward masked fearful face dot-probe task. We hypothesized that greater biases in attention to backward masked threats would predict (1) greater levels of uncinate fasciculus fiber integrity, (2) greater positive amygdala — ACC intrinsic functional connectivity, and (3) greater levels of uncinate fasciculus integrity would correlate with greater levels of amygdala — ACC intrinsic functional connectivity.

2. Methods

2.1. Participants

Fifteen consenting young adults (6 male) between the ages of 19 and 23 (M = 20.80, SD = 1.21) participated in this study. All individuals reported being right handed. The Institutional Review Board of Stony Brook University approved this study and participants were compensated for their time ($70.00).

2.2. Task

The task used here has been described in detail in earlier publications (Carlson et al., 2012; Carlson, Mujica-Parodi, Harmon-Jones, & Hajcak, 2012; Carlson & Reinke, 2008). Behavioral data were collected outside of the scanner. Briefly, trials started with a central fixation cue (+; 1000 msec) followed by face stimuli (5 × 7° of visual angle) simultaneously presented to the left and right of fixation (separated by 14°). Initial faces were displayed for 33 msec and then masked (100 msec). A target dot appeared either on the left or the right and remained until the participant responded. Trials used to calculate attention bias scores contained one fearful and one neutral face. There were 40 congruent (target dot presented on the same side as the fearful face) and 40 incongruent (target dot presented on the same side as the neutral face) trials. Attention bias scores are calculated as congruent – incongruent reaction times (on correct trials with reaction times between 150 and 750 msec). Participants used an E-Prime response box with their right hand to indicate the location of the dot. The task also contained 40 neutral–neutral trials.

Participants then completed a task to assess awareness of the masked faces. This task was identical to the dot-probe task in all aspects through the backward masking procedure. After the masking procedure participants were asked to indicate with the response box whether they saw: a fearful face on the left, a fearful face on the right, or two neutral faces. There were 60 randomly presented trials.

2.3. Functional (fMRI)

After completing the behavioral task 5 min of eyes closed “resting-state” fMRI data was collected. A 3-T Siemens Trio whole body scanner was used to acquire 150 T2*-weighted whole-brain volumes with an echo planar imaging (EPI) sequence sensitive to BOLD signal using the following parameters: TR = 2000 msec, TE = 23 msec, Flip Angle = 83°, Matrix Dimensions = 96 × 96, FOV = 224 × 224 mm, Slices = 35, Slice Thickness = 4 mm, Gap = 0. Standard preprocessing procedures were performed in Statistical Parameter Mapping (SPM8), including image realignment, slice timing correction, normalization to standard Montreal Neurological Institute (MNI) space, and spatial smoothing with a Gaussian full-width-at-half-maximum 6 mm filter. Preprocessed images were filtered between .01 Hz and .1 Hz in the Functional Connectivity Toolbox v13 (Whitfield-Gabrieli et al., 2011), and entered in a first-level General Linear Model regressing out time courses from principle components associated with white matter and cerebrospinal fluid. Based on earlier work implicating the left amygdala in attentional bias to threat, a left amygdala seed mask for the functional connectivity analyses was derived from the Harvard-Oxford subcortical structural atlas (www.fmrib.ox.ac.uk/fsl/fslview/). This 1st-level analysis yielded a left amygdala seeded intrinsic functional connectivity map for each individual. We constructed a second-level model in SPM with attention bias scores as a regressor of interest. For our a priori target region, we derived ACC masks for each hemisphere. Our region of interest (ROI) analyses were family-wise error (FWE) small volume corrected (SVC) for 6 mm radius-spheres at ±4, 46, –4 (coordinates from...
which ACC BOLD activity showed significant association with attention-related amygdala activity in an earlier study; Carlson et al., 2009. For the completeness, we did the same analysis on right amygdala-seeded connectivity maps.

2.4. Diffusion tensor imaging

Diffusion tensor images (DTIs) were collected after fMRI acquisition using the following parameters: TR = 5500 msec, TE = 93 msec, FOV = 220 x 220 mm, Matrix = 120 x 220 x 220, Voxel size = 1.7 x 1.7 x 3.0 mm, EPI factor = 128, slices = 40, slice thickness 3 mm, Bandwidth 1396 Hz/pixel, generalized autocalibrating partially parallel acquisition (GRAPPA) acceleration factor = 2. The series contained two initial images without diffusion weighting and with diffusion weighting along 40 non-collinear directions (b = 800 secm−2).

We employed standard DTI preprocessing steps in FSL 4.1.9 (FMRIB Software Library; www.fmrib.ox.ac.uk/fsl) to correct for eddy current distortions and head motion. We then fitted a diffusion tensor model at each voxel by running the DTIFIT function in FSL. This yielded individual fractional anisotropy images, which we used for voxel-wise statistical analysis using Tract-Based Spatial Statistics (TBSS), part of FSL (Smith et al., 2006). TBSS projects all subjects’ FA data onto a mean FA tract skeleton, before applying voxel-wise cross-subject statistics. We conducted a correlation test between FA voxels and attention bias scores, using Randomize 2.9 in FSL, which, unlike the earlier version, corrects for inflated significance in small samples (Ref. http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/Theory). We focused our analysis on the uncinate fasciculus, based on our previous work (Carlson et al., 2013); the mean FA skeleton within the John Hopkins University white matter pathway atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslview/) was assessed in each hemisphere separately. Results were FWE corrected, applying TFCE (Threshold-Free Cluster Enhancement) option in Randomize. For better visibility, significant skeletonized FA voxels were flattened using ‘tbss_fill’ in FSL. We extracted mean FA values from the significant clusters, and correlated with significant clusters of amygdala – ACC functional connectivity.

3. Results

Overall, participants displayed an attentional bias to threat (mean difference = −10.31 msec, SD = 12.99, t14 = −3.08, puncorrected = .004). However, participants’ performance on the post-task assessment of awareness was above chance (t14 = 2.54, pone-tailed = .01). Therefore, as suggested in the literature (Wiens, 2006), participants’ level of awareness was controlled for and partialled out in subsequent analyses. Level of awareness did not significantly correlate with task performance (r = .30, p = .28), but the direction of this correlation would suggest that as awareness of threat increases attentional bias to threat decreases (i.e., our results can not be attributed to an attentional bias to consciously detected threat). Nevertheless, in the current study, we do not claim that backward masking resulted in unconscious processing per se, but rather a restricted level of automatic preattentive processing that may be at a pre-threshold level of conscious processing in some individuals.

We first tested whether the fiber integrity of the uncinate fasciculus was correlated with attentional bias to masked threat. Within the uncinate fasciculus we found a correlated cluster within the left hemisphere tract proximal to the ACC (MNI −25, 25, 14; Fig. 1c) at corrected punc = .05 (Tract Based Spatial Statistics; TBSS). In the right hemisphere tract this association was weaker and not significant at a corrected level (puncorrected = .02). This association was specific to the left uncinate fasciculus as whole brain while matter (i.e., average FA values) did not correlate with attention bias scores (p > .44). We performed a follow-up analysis using average values extracted from the significant cluster in the left uncinate fasciculus. This revealed the effect remained significant when controlling for age (Pfefferbaum et al., 2000) and awareness (Wiens, 2006), r partial = −.84, p < .001. We then assessed the degree to which intrinsic functional coupling between the amygdala and ACC was correlated with attentional bias to threat. As displayed in Fig. 1b, left amygdala – ACC intrinsic functional connectivity from resting-state fMRI was correlated with attentional bias to masked threat, maximum voxel (MNI 8, 46, 4): t svc = 5.16, psvc < .05, r partial = −.69, pone-tailed = .002 and r partial = −.72, pone-tailed = .003 when controlling for age (Pfefferbaum et al., 2000) and awareness (Wiens, 2006). As presented in Table 1, additional whole brain targets of intrinsic left amygdala connectivity correlating with attention bias scores included areas of the occipital cortex, posterior insula, posterior superior temporal sulcus (pSTS), tempoparietal junction (TPJ), and somatosensory cortex (SS). Correlations with attention bias on right amygdala – ACC connectivity maps were not significant at a corrected level (Peak p svc > .38, puncorrected < .01). Finally, we explored the relationship between structural and functional measures of amygdala – ACC connectivity. As can be seen in Fig. 1d, the mean FA value of the uncinate fasciculus cluster was significantly correlated with the mean value of the functional connectivity cluster, r = .47, pone-tailed = .039.

4. Discussion

Individual differences in attentional bias to threat were linked to differential intrinsic connectivity in the amygdala – ACC network. High bias individuals displayed greater intrinsic functional coupling, while low bias individuals displayed diminished or negative coupling, suggesting an inhibitory relationship in these individuals. Additionally, we confirmed earlier work showing that the structural integrity of this pathway is correlated with greater biases in attention to nonconscious threat (Carlson et al., 2013). Furthermore, consistent with prior work on the relation between brain structure and function (e.g., the default mode network; Greicius, Supekar, Menon, & Dougherty, 2009), our results directly link variability in intrinsic functional connectivity within the amygdala – ACC pathway to the structural integrity of uncinate fasciculus white matter.

The current results add to a growing body of work implicating the amygdala – ACC system in attention bias behavior (Armony & Dolan, 2002; Carlson et al., 2012; Carlson et al., 2013; 2009). Cognitive processing biases are thought to manifest when multiple stimulus representations compete for...
Attention (Mathews & MacLeod, 2002). Within this framework, the ACC monitors and resolves potential conflicts (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Etkin et al., 2006), while the amygdala appraises environmental stimuli for their threat potential (Adolphs et al., 1999) and “biases” the monitoring system to favor stimuli with a high potential for threat. Our results provide evidence that greater amygdala–ACC functional connectivity under basal conditions correlates with attentional bias to masked threat, which may predispose high bias individuals to focus on threat.

Beyond amygdala–ACC intrinsic coupling, we found that high bias individuals also display heightened intrinsic functional connectivity between the amygdala and social perception/cognition-related areas such as the TPJ, pSTS, and SS cortex. Respectively, these regions have been shown to be involved in processing others’ intentions/thoughts (Saxe & Kanwisher, 2003), dynamic aspects of face perception, such as eye gaze direction and expression (Haxby, Hoffman, & Gobbini, 2000; Hoffman & Haxby, 2000; Puce, Allison, Bentin, Gore, & McCarthy, 1998), in addition to the recognition of others’ affective states (presumably through simulation; Adolphs et al., 2000). Amygdala–pSTS coupling has previously been linked to nonconscious fearful face processing (Jiang & He, 2006) and attentional responses to such faces (Carlson et al., 2009). Other visual areas such as the cuneus/lingual gyrus and occipito-temporal cortex displayed heightened intrinsic connectivity with the amygdala in high bias individuals. Thus, the amygdala appears to be broadly connected with visual processing cortical regions including those associated with social perception, which may be linked to preattentive perceptions of others’ affective states and intentions, in high bias individuals. It is unclear if this facilitation of social perceptual regions is specific to the social stimuli used in this task (i.e., fearful faces) or if this network is more broadly engaged in threat- or salience-elicited attention. Further research will be needed to address the specificity of this network and to further dissect the attentional response to threat in order to identify the specific roles that each structure plays in mediating this behavior. In particular, it is unclear exactly how activity in the amygdala–ACC system translates into facilitated visual perceptual processing in the context of attentional bias to threat. Research suggests that the amygdala has direct projections back to areas of visual cortex (Adolphs, 2004). Additional research suggests that the amygdala projects to the diffuse modulatory centers including...
the acetylcholine producing cells in the nucleus basalis, which has been implicated in animal models of emotional attention (Holland & Gallagher, 1999) and the gray matter near this region correlates with attention bias to threat (Carlson et al., 2012). Prior research has shown that the attentional response to visual threat facilitates visual cortical activity (Carlson & Reinke, 2010; Carlson et al., 2012). Nonconscious attention bias to threat is correlated with anterior cingulate cortex gray matter volume: a voxel-based morphometry result and replication. Neuroimage, 59(2), 1713–1718.


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