Elevated Amygdala Activity in Youth With Familial Risk for Depression: A Potential Marker of Low Resilience

Supplementary Information

Supplemental Methods

Details about the parent study (also see (1–3)):

The goal of the larger parent study from which the current subjects were recruited was to screen a large number of undergraduate students for a range of symptoms of psychopathology and then to identify predictors of certain symptom categories, such as depression and suicidality (1, 2), subclinical psychotic symptoms (3) and substance abuse, as well as correlates of specific "risk states", such as familial risk for depression (the current study). Subjects who met certain criteria (i.e., had a minimum score on the BDI or PDI scales, see below) were invited to participate in a clinician interview, MRI scan and on-line longitudinal follow-up (every 6 months).

In this parent study, a total of 1047 subjects were screened between 2011 and 2014 via on-campus mental health screenings conducted at four undergraduate institutions in the Boston area. Of those screened participants, 520 met criteria (BDI score $>$ 5, BDI item #9 $>$ 0, or PDI score $>$ 7) for a clinician interview, and 40 of these 520 met diagnostic criteria for major depressive disorder according to DSM-IV criteria. A total of 131 subjects were scanned, 112 of the scanned participants had met screening criteria for a clinician interview, and 23 met criteria for major depressive disorder.

Participants excluded from the analyses of the current study:

Subjects who: 1) met criteria for major depressive disorder at baseline based on the SCID (n = 23) or 2) had a family history of psychiatric illnesses other than depression (n = 28) or reported being adopted (n = 1) were excluded from all analyses. Also, three subjects were excluded because of unclear information or reported uncertainty regarding their family psychiatric history. Lastly, four subjects (two FH+ and two FH-) were excluded from the fMRI analyses following quality control procedures (due to a brain

abnormality detected on the anatomical scan, incomplete questionnaire data, excessive head motion (> 2 mm) and slice placement error, respectively).

Within the remaining 45 subjects in the FH- group: one run/subject of the four fMRI runs was excluded from the analyses due to excessive head motion (> 2 mm absolute head motion) for 3 subjects, and one run was excluded because the subject did not perform the dot-detection task at the criterion accuracy rate (> 40%) during that run. Thus, for 41 of the 45 FH- subjects, all four runs of the fMRI data were included; for 4 subjects, 3 runs were included. All of the data for the 27 FH+ subjects were included in the analyses.

Details about the self-report measures used in the current analyses:

The Conner Davidson Resilience Scale (CD-RISC):

The 25-item CD-RISC was used to measure resilience levels. Features of resilience measured by the CD-RISC include 5 primary factors: 1) tenacity 2) trust in one's instincts 3) acceptance of change and positive relationships 4) control and 5) spirituality (4). This scale has been shown to have good test-retest validity, internal consistency, convergent and divergent validity (4), as well as good cross-cultural validity (5–8). Given these characteristics, it has become widely used in a range of populations, including college-aged individuals (9, 10).

The Beck Depression Inventory (BDI):

The BDI is a commonly used self-report questionnaire that measures the core symptoms of depression. It consists of 21 questions that assess the severity of symptom dimensions that characterize depression (e.g., concentration, interest, sleep, suicidal ideation). To capture the presence and severity of a symptom, each question allows for at least 4 possible responses. The BDI total score ranges from 0 – 63 to reflect the overall presence and severity of symptoms (high total score = more severe depressive symptoms). This dimensional variation in individual item scores and total scores (varying from no symptoms to severe symptoms) allows for the identification of subclinical depression (people who are endorsing clinically relevant symptoms of depression without reaching clinical criteria for depression). One study found that

the average BDI total score in university students was 7.5 (11); similarly, the average BDI total of subjects in the current study was 7.5 (n = 72).

The Peters et al Delusions Inventory (PDI):

The PDI has been frequently used to assess delusion-like experiences in the general, non-clinical population (3, 12). The average PDI score found in a large study of healthy individuals was 6.7 (13), which is similar to what we find in the current population (current study mean = 5.7; n = 72).

The State and Trait Anxiety Inventory (STAI):

The STAI is a 20 item self-report questionnaire that measures both general (trait) anxiety and transient, in-the-moment (state) anxiety (14). Scores range from 20-80, with higher scores indicating high levels of anxiety. In one study of a non-clinical population, average state and trait sub-scale scores of the STAI were 31.5 and 37, respectively (15), similar to the mean values found in the current study (STAI-S/STAI-T mean = 30.2/32.5; n = 72).

Additional information about the MRI data acquisition and preprocessing:

MRI data acquisition:

Nine scans were collected from each subject using a 3T Seimens Tim Trio scanner (Iselin, NJ) and a 12-channel head coil (16). Two of these were analyzed in the current study: 1) a high-resolution multi-echo T1-weighted magnetization prepared gradient-echo image (MEMPRAGE) (144 coronal slices special resolution 1.2 mm isotropic, TR = 2.2 sec, TE = 1.54 ms, flip angle = 7º, FOV 230), 2) four BOLD scans (each 3.33 minutes in duration, TR = 2000 ms, TE = 30 ms; 33 axial slices; 128 images per slice, 3 mm isotropic voxels) during which the looming paradigm was presented.

MRI data preprocessing:

Functional volumes were motion corrected using the Analysis of Functional NeuroImages (AFNI) algorithm (10), corrected for temporal drift, normalized for signal intensity. Normalized data were spatially smoothed (full width at half maximum = 6 mm) using a three-dimensional spatial filter. Each subject's individual cortical surface was morphed onto an average spherical surface using a common spherical surface coordinate system. Functional data were analyzed using a general linear model with random effects.

Supplemental Tables

	DIPS				**PMv**				**Amygdala**			
	FH-		**FH+**		**FH-**		**FH+**		**FH-**		**FH+**	
Condition	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**
Face Approach	0.35 (.23)	0.28 (.25)	0.30 (.25)	0.29 (.29)	0.05 (.18)	0.45 (.19)	-0.01 (.16)	-0.01 (.15)	0.05 (.16)	0.05 (.17)	0.02 (.16)	0.01 (.18)
Face Withdrawal	0.28 (.22)	0.22 (.23)	0.21 (.24)	0.21 (.28)	0.06 (.17)	0.05 (.20)	-0.05 (.17)	-0.05 (.17)	0.07 (.15)	0.05 (.14)	-0.04 (.15)	-0.05 (.16)
Car Approach	0.45 (.27)	0.36 (.29)	0.35 (.30)	0.33 (.32)	0.09 (.21)	0.06 (.24)	-0.01 (.17)	-0.02 (.17)	0.02 (.16)	-0.01 (.17)	-0.05 (.17)	-0.05 (.16)
Car Withdrawal	0.34 (.29)	0.28 (.27)	0.29 (.21)	0.30 (.25)	0.06 (.18)	0.04 (.19)	-0.03 (.15)	-0.03 (.14)	0.02 (.17)	0.01 (.16)	-0.05 (.18)	-0.07 (.16)

Table S1: Mean BOLD signal extracted from the three *a priori* anatomical regions-of-interest for each condition of the looming paradigm for those with (FH+) and without (FH-) a family history of depression. Standard deviations are in parentheses. DIPS, dorsal intraparietal sulcus; PMv, ventral premotor cortex; L, left hemisphere; R, right hemisphere.

	Left Amygdala		**Right Amygdala**	
Variable	Correlation Coefficient (r)	p-value	Correlation Coefficient (r)	p-value
Childhood adversity[a]	0.10	0.61	0.09	0.65
Depressive symptoms[b]	-0.15	0.45	0.08	0.68
Psychotic experiences[c]	0.07	0.72	0.26	0.20
State anxiety[d]	-0.08	0.71	-0.21	0.30
Trait anxiety[e]	-0.07	0.71	-0.09	0.66

Table S2: Correlations between amygdala responses to looming faces (extracted using the anatomically-defined amygdala ROIs) and symptoms in the FH+ group.

There were no significant correlations between left or right amygdala activation to Approaching vs. Withdrawing Faces and measures of childhood adversity, depressive symptoms, psychotic experiences (delusion-like beliefs), or state or trait anxiety levels in the subjects with a family history of depression (the FH+ group).

[a] Measured using the Childhood Trauma Questionnaire; [b] Measured using the Beck Depression Inventory; [c] Measured using Peters et al. Delusions Inventory; [d] Measured using the Spielberger State Anxiety Inventory; [e] Measured using the Spielberger Trait Anxiety Inventory.

Supplemental Figures

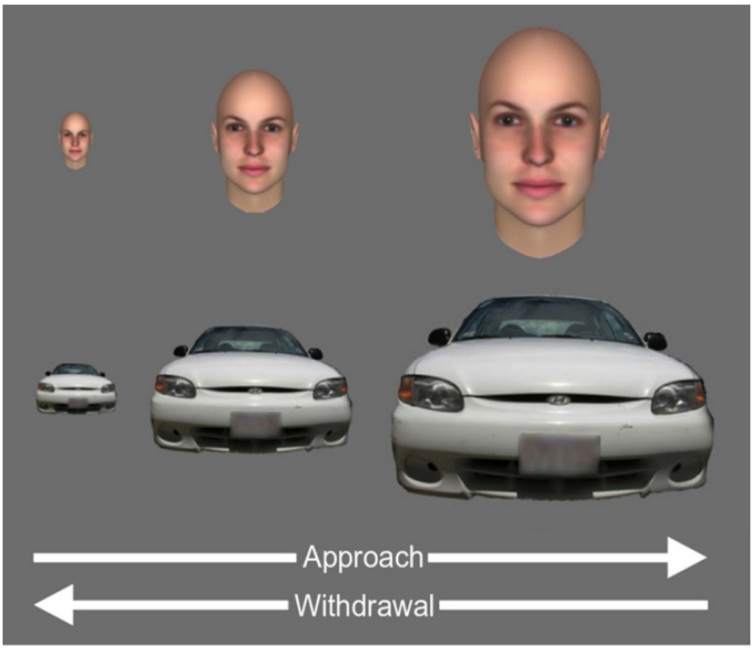

Figure S1. The looming paradigm.

During the paradigm, faces and cars appear to move toward or away from the subject at the pace of walking. The minimum and maximum stimulus size is 3.1 º x 3.1 º and 17.2 º x 17.2 º, respectively; see Holt et al, J Neurosci 2014 (17) for further details. Five dots appeared for a variable duration (500-1500 ms) during each 16 second block at a random location in the image. Subjects were instructed to press a button whenever a dot appeared.

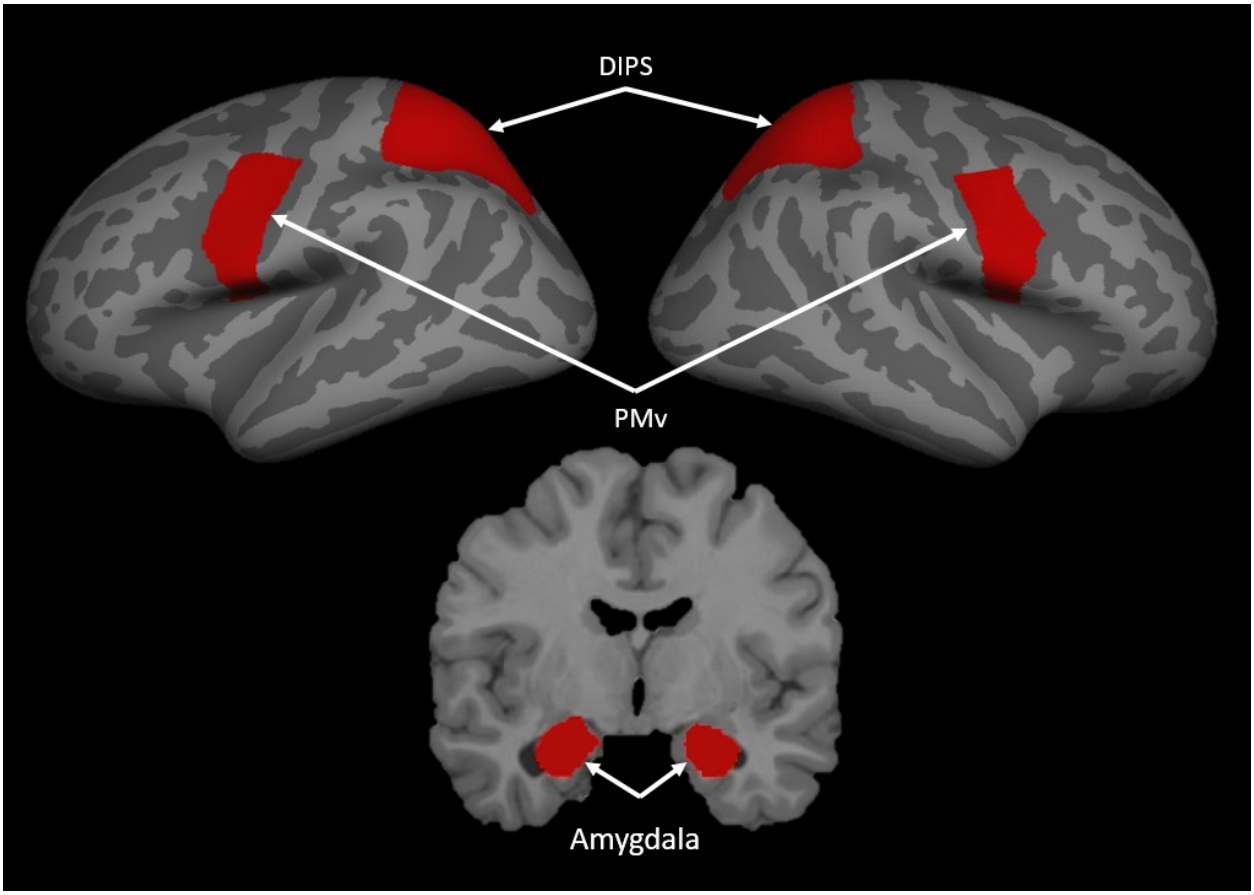

Figure S2. The anatomical regions-of-interest.

The three *a priori* regions-of-interest (defined in the anatomical scan of each individual participant using FreeSurfer) of this study are shown in red on an average brain (fsaverage): the ventral premotor cortex (PMv), dorsal intraparietal sulcus (DIPS), and amygdala.

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