Archival Report

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

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ABSTRACT

BACKGROUND: Amygdala overactivity has been frequently observed in patients with depression, as well as in nondepressed relatives of patients with depression. A remaining unanswered question is whether elevated amygdala activity in those with familial risk for depression is related to the presence of subthreshold symptoms or to a trait-level vulnerability for illness.

METHODS: To examine this question, functional magnetic resonance imaging data were collected in nondepressed young adults with (family history [FH+]) (n = 27) or without (FH−) (n = 45) a first-degree relative with a history of depression while they viewed images of "looming" or withdrawing stimuli (faces and cars) that varied in salience by virtue of their apparent proximity to the subject. Activation of the amygdala and 2 other regions known to exhibit responses to looming stimuli, the dorsal intraparietal sulcus (DIPS) and ventral premotor cortex (PMv), were measured, as well as levels of resilience, anxiety, and psychotic and depressive symptoms.

RESULTS: Compared with the FH− group, the FH+ group exhibited significantly greater responses of the amygdala, but not the dorsal intraparietal sulcus or ventral premotor cortex, to looming face stimuli. Moreover, amygdala responses in the FH+ group were negatively correlated with levels of resilience and unrelated to levels of subthreshold symptoms of psychopathology.

CONCLUSIONS: These findings indicate that elevated amygdala activity in nondepressed young adults with a familial history of depression is more closely linked to poor resilience than to current symptom state.

Keywords: Amygdala, Depression, Familial risk, fMRI, Resilience, Youth

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As the leading cause of disability worldwide (1), depression is a major worldwide health concern. With the increasing prevalence of depression (2,3), its economic and public health toll will likely escalate, as rising treatment needs strain already limited mental health resources. Further, many people receiving treatment for depression respond inadequately to available treatment options and develop persistent or recurrent depression (4). Therefore, to address the societal burden of depression, public health approaches such as early identification of at-risk individuals and prevention must be established. However, providing timely preventative measures or early treatment strategies relies on the identification of the most susceptible individuals (5). One vulnerable group is those individuals with a family history of depression (family history positive [FH+]), as they have a threefold greater likelihood of developing depression in their lifetime than those without such a family history (family history negative [FH−]) (6). However, further risk stratification within this group is necessary to develop cost-effective, prevention-focused public health initiatives. Thus, by examining both

markers of risk and protective factors, we can more accurately identify individuals with the highest risk of developing depression who will benefit most from preventive interventions.

One general category of protective factors is referred to as emotional resilience (7,8). Resilience, as defined by the American Psychological Association, is a capacity to adapt well when facing adversity or significant sources of stress, or the constellation of skills or traits that enable one to "bounce back" from difficult experiences (9). It can also be defined operationally as a positive outcome following stressors (10). The building blocks of resilience are likely heterogeneous in terms of both the cognitive/affective processes and neurobiological mechanisms involved (7,11) and thus have been little studied using neuroimaging methods to date. However, given that self-report measures of resilience, such as the Connor-Davidson Resilience Scale (CD-RISC) (12), can predict positive outcomes following stressors (13,14), even cross-sectional investigations of the neurobiology of resilience may begin to shed light on the interplay between biological and

environmentally determined aspects of resilience and psychopathology risk.

To investigate the neurobiology of depression risk and protective factors such as resilience, the networks of the brain most commonly implicated in the biology of depression must be examined. Much research on depression has focused on the amygdala (15). In addition, some current models of depression have linked attentional deficits and abnormal cognitive control of emotion to core symptoms of the illness (16). Evidence for attentional deficits in patients with depression includes reports of abnormal attentional shifting (17), slowed reaction times (18), and mood-congruent attentional biases (19). Supporting this model, both resting-state (20–22) and task-based (17,18,21) functional magnetic resonance imaging (fMRI) studies of depression have revealed involvement of circuitry supporting emotional processing and attention/cognitive control, such as the amygdala-centered and dorsal attention/frontoparietal networks, respectively. The functions of the amygdala-centered/limbic and attentional networks are closely linked; for example, the amygdala rapidly processes salient stimuli and then interacts with attention and cognitive control networks to influence behavioral responses (23–25). The dorsal attention network is involved in orienting attention to spatial cues and in cognitive control, and these processes can be influenced by input from the amygdala and other emotion-processing brain areas (26). Regions of the dorsal attention network, such as the dorsal intraparietal sulcus (DIPS) and ventral premotor cortex (PMv), support goal-directed attention and visuospatial processing (26), which are processes that are affected in depression (17).

Neuroimaging studies of depression have identified abnormalities in both networks, repeatedly detecting abnormalities in amygdala responses to emotional and neutral faces in patients with depression (27–29), as well as altered activation of frontoparietal regions of the dorsal attention network during visuospatial processing (29–31). One meta-analysis of functional connectivity studies of depressed individuals showed that regions of the dorsal attention network are among the brain regions most frequently affected in clinical depression (20). Similar findings within the amygdala and attentional regions have been reported for clinically remitted patients and in never-depressed FH+ individuals (32–36), indicating that such abnormal activation patterns may not represent state-dependent effects of depression. Furthermore, a recent meta-analysis (37) showed that cognitive (including attentional) deficits and deficits in visual scanning (38) are present in FH+ individuals when compared with control subjects. However, it remains unclear whether such changes in the function of the amygdala and attentional networks in unaffected relatives of individuals with depression reflect effects of subthreshold levels of symptoms, a marker of resilience (in the face of genetic vulnerability), or a heightened susceptibility for future illness.

To investigate this question further, in the current study we measured amygdala and frontoparietal cortical responses to dynamic social (faces) and nonsocial (cars) stimuli in young adults with or without a first-degree relative with a history of depression. Specifically, we used a paradigm that activates areas of the dorsal attentional network (dorsal parietal cortex and PMv) as well as the amygdala.

Therefore, first, we determined whether, in our cohort, the amygdala showed greater responses in nondepressed FH+ youths than in FH− youths, as others have reported. Second, we tested whether the FH+ group showed greater responses of the dorsal attentional network than the FH− group, consistent with prior findings in patients with depression. Third, we tested whether the predicted higher responsivity of these regions in the familial high-risk group was related to trait-like levels of emotional resilience or to subthreshold depressive or anxiety symptoms.

METHODS AND MATERIALS

Overall Study Design

This study was conducted in a subset of subjects who participated in a larger study of mental health in college students (39), in which on-campus screenings were conducted at several Boston-area universities. During these screenings, self-report questionnaires measuring a range of symptoms were administered (39). One of the goals of the study was to further characterize young people with subthreshold symptoms of psychopathology, with mildly to moderately elevated scores on a measure of depression (the Beck Depression Inventory [BDI]) (40) and/or a measure of psychotic experiences (the Peters et al. Delusions Inventory [PDI]) (41). Students with elevated scores (BDI total score >5 or >0 on BDI item 9 [measuring suicidal ideation], or PDI total score >7) and a small number of students with no depressive symptoms (total BDI scores of 0) were invited to participate in 1) a brief clinical assessment (administered by a Ph.D.-or M.D.-level clinician) in which the mood module of the Structured Clinical Interview for DSM-IV Axis I Disorders was administered, 2) a baseline neuroimaging session, and 3) longitudinal follow-up assessments conducted at 6-month intervals (self-report scales completed online; analyses including the longitudinal data will be reported separately). The neuroimaging session included 1 T1 anatomical scan and 4 blood oxygen level–dependent (BOLD) scans (see Supplemental Methods for scan parameters), during which subjects viewed dynamic face and car stimuli and performed a low-level attentional task (24). Subjects with neurological disorders or serious medical illnesses, substance abuse or dependence, or contradictions to MRI scanning were excluded from participating in the scanning session. The presence or absence of a family history of depression in first-degree family members was assessed at baseline using 2 self-report questionnaires, which included questions about the psychiatric history of subjects' family members. Resilience levels were measured using the CD-RISC (see Supplemental Methods for further details).

Participants

A total of 131 subjects were scanned. For the current study, the data of 2 groups of subjects within this cohort were examined: those with a first-degree relative with depression (family history postive [FH+]) (n = 29) and those without a first-degree relative with depression (family history negative [FH−]) (n = 47). Data of 4 subjects (2 FH+ and 2 FH−) were excluded following quality control procedures. See Supplemental Methods for additional information about the participants who were screened and the exclusion criteria.

All 72 subjects included in the analyses (27 FH+ and 45 FH−) did not meet DSM-IV criteria for depression at the time of

scanning, based on the Structured Clinical Interview for DSM-IV Axis I Disorders. FH− subjects reported that their first-degree relatives were without a history of any mental illness. FH+ subjects reported the presence of a family history of unipolar depression in at least one first-degree relative.

The study protocol, including informed consent procedures, was approved by the Partners HealthCare and Harvard University Institutional Review Boards, and written informed consent was obtained from all subjects.

Functional MRI Paradigm

As described in Holt *et al.* (24), during each functional scan, subjects viewed 2 types of stimuli: images of human faces (with neutral expressions) and images of cars. Each stimulus appeared to be moving toward or away from the subject at the speed of walking (112 cm/s) (Supplemental Figure S1). This paradigm involves visuospatial processing of approaching stimuli, which robustly activates frontoparietal regions of the dorsal attentional network (23,24). Images of faces with neutral expressions were presented because some previous work has identified significant differences 1) between control subjects and patients with depression (42) and 2) between individuals with and without familial risk for mood disorders (43) in amygdala responses only to neutral (not to emotional) faces. Each of 4 conditions (Face Approach, Face Withdrawal, Car Approach, Car Withdrawal) was presented for 16 seconds. In each run, subjects viewed 2 blocks of each of the 4 stimuli (8 blocks total), randomly presented. During each of the 4 conditions, subjects performed a simple dot-detection task; to distribute spatial attention evenly across the approach and withdrawal conditions, subjects were asked to press a button, while maintaining fixation, whenever a dot appeared at a random location on the screen. The percentage of responses was calculated for each condition, in each subject. A run was excluded if the subject responded to <40% of the dots during that run, as in Holt *et al.* (24).

MRI Data Analysis

Data were analyzed using the FreeSurfer analysis stream (http://surfer.nmr.mgh.harvard.edu), with standard pre-processing methods and quality assessment procedures (see Supplemental Methods for details). Images were spatially smoothed with a 6-mm Gaussian kernel (full width at half maximum) and a 3-dimensional spatial filter.

Anatomical Region-of-Interest Analysis. In the primary, hypothesis-testing analysis of this study, 3 a priori anatomical regions of interest (ROIs) (the DIPS, PMv, and amygdala) (Supplemental Figure S2) were defined in each subject's T1 anatomical scan, using an automated parcellation method that relies on well-known anatomical landmarks (44). We focused on the amygdala because of the extensive prior literature demonstrating amygdala abnormalities in patients with depression (15,45) and their first-degree relatives (34,35). The DIPS and PMv were also examined because these two regions are central nodes of the dorsal attention network (which has shown abnormalities in patients with depression and in first-degree relatives of patients with depression, as described above) and because these two regions are robustly engaged

by the task used here, showing significantly greater responses to approaching (i.e., appearing to "loom" toward the subject), compared with withdrawing, face stimuli in prior studies (24,46). Hereafter, we refer to the approaching versus withdrawing response or contrast as the looming response.

BOLD responses were extracted from each ROI for each condition. The average BOLD response to each face and car condition was compared with the BOLD response to the crosshair baseline condition. The two contrasts of interest were 1) approach versus withdrawal (the looming response) for each stimulus type (faces, cars) and 2) all faces versus all cars. These contrasts were chosen based on prior work demonstrating that the DIPS and PMv regions respond preferentially to looming stimuli, particularly faces (24), and that the amygdala responds preferentially to face stimuli, compared with nonface objects such as car stimuli (47,48). A repeated-measures analysis of variance, using a 3 region (DIPS, PMv, amygdala) × 2 hemisphere (left, right) × 2 condition (approach, withdrawal) × 2 stimuli (faces, cars) × 2 group (FH−, FH+) factorial design, was performed, to test our predictions that compared with the FH− group, the FH+ group would show 1) greater amygdala responses to faces (both to looming faces and to all faces vs. all cars) and 2) greater DIPS and PMv response to looming faces.

Correlational Analyses. ROIs that showed significant between-group effects were then used to conduct correlational and regression analyses to test whether changes in brain function associated with having a family history of depression were correlated with resilience levels [measured using the CD-RISC (12)] and/or with levels of subsyndromal depressive, psychotic-like, and anxiety symptoms [measured using the BDI, PDI (41), and Spielberger State-Trait Anxiety Inventory (49), respectively].

Secondary, Voxelwise Analysis. Subsequently, a secondary, voxelwise analysis was conducted for the purpose of further localizing the findings of the anatomical ROI analysis (see Results). This analysis was conducted using a Monte Carlo simulation (10,000 iterations) whole-brain correction, using 2 cluster-forming height thresholds of $p = .001$ and $p = .05$. In addition, percent signal change data extracted from these maps (limited to regions showing between-group differences in the anatomical ROI analysis) were used to confirm the findings of the regression and correlational analyses conducted using the anatomical ROIs.

RESULTS

Participant Characteristics and Performance on the Dot-Detection Task

There were no significant differences between the FH− and FH+ groups in age, gender, ethnicity, childhood adversity levels, or baseline symptom or resilience levels (Table 1).

Analyses of subjects' behavioral performance during scanning showed no main effects of group in response rates during the dot-detection task ($F_{1,70} = 2.2$, $p = .14$). A significant group × condition effect ($F_{1,70} = 4.3$, $p = .04$) was driven by greater accuracy of the FH+ group (vs. the FH− group) during

Table 1. Demographic Information and Symptom Levels of the Participants

	FH− (n = 45)[a]				FH+ (n = 27)[a]			
	Mean	Min	Max	SD	Mean	Min	Max	SD
Age, Years	19.49	18	22	1.31	19.59	18	24	1.60
Depressive Symptoms[b]	6.71	0	20	5.50	8.93	0	17	3.90
Psychotic Experiences[c]	6.11	0	18	3.93	5.07	0	12	3.22
Resilience[d]	73.10	38	100	16.44	73.89	57	95	9.70
State Anxiety[e]	28.58	0	56	16.72	32.85	0	62	18.27
Trait Anxiety[f]	31.31	0	59	17.70	34.41	0	57	17.35
Childhood Adversity[g]	30.11	0	48	8.93	31.96	0	77	17.47
Gender, Male/Female, n	12/33				9/18			
Race, %								
Caucasian	51				44			
African American	27				37			
Asian	15				7			
Other	8				12			
Ethnicity, Hispanic, %	15				0			

The FH− and FH+ groups showed no significant differences in age, education, gender, ethnicity, levels of symptoms of depression, psychotic experiences, suicidality, resilience, anxiety, and levels of childhood adversity, based on independent-sample t tests. There were no significant differences between groups in gender (Pearson's $\chi^2_1 = 0.3630$, $p = .547$).

FH+, family history of depression; FH−, no family history of depression.

[a]Resilience levels negatively correlated with depressive symptoms within the FH− group ($r = -.61$, $p < .01$) but not within the FH+ group ($r = -.10$, $p = .61$).

[b]Measured using the Beck Depression Inventory.

[c]Measured using the Peters et al. Delusions Inventory.

[d]Measured using the Connor-Davidson Resilience Scale.

[e]Measured using the Spielberger State Anxiety Inventory.

[f]Measured using Spielberger Trait Anxiety Inventory.

[g]Measured using the Childhood Trauma Questionnaire.

the Car Withdrawal condition ($t_{26} = 2.1$, $p = .04$). Given that this result would not have any influence on our a priori hypotheses, it was not explored further.

Functional MRI

Hypothesis Testing: Anatomical ROI Analysis. As expected, the repeated-measures analysis of variance revealed a main effect of condition ($F_{1,70} = 12.88$, $p = .001$) due to the significant activation to looming (Approach > Withdrawal) stimuli. Also, there was a significant 3-way interaction among group, condition, and stimulus type ($F_{1,1} = 4.96$, $p = .029$), which was due to a greater response of the FH+ group compared with the FH− group to looming faces in the bilateral amygdala (left [$t_{70} = -2.89$, $p = 5 \times 10^{-3}$], right [$t_{70} = -2.02$, $p = .04$]) (Figure 1 and Supplemental Table S1), with a trend toward a similar difference between the 2 groups in the bilateral PMv (left [$t_{70} = -1.92$, $p = .06$], right [$t_{70} = -1.83$, $p = .07$]) but not in the DIPS (left [$t_{70} = -0.67$, $p = .50$], right [$t_{70} = -0.76$, $p = .45$]). There was no group × stimulus or group × stimulus × region interaction, indicating that there was no between-group difference in the responses of the amygdala or of the other 2 regions to faces compared with cars. Also, for all 3 ROIs, there were no differences between the 2 groups in responses to looming cars.

Follow-up repeated-measures analysis of variances conducted within each group revealed a significant interaction between region and stimulus for both the FH− and FH+ groups. This interaction was due to a significantly greater response to face compared with car stimuli in the left amygdala in both groups (FH− group [$t_{44} = 3.50$, $p = .001$], FH+ group [$t_{26} = 2.50$, $p = .02$]) and in the right amygdala in the FH− group, with a similar trend in the FH+ group (right: FH− group [$t_{44} = 3.39$, $p = .002$], FH+ group [$t_{26} = 1.93$, $p = .06$]).

Secondary, Voxelwise Analysis: Faces Approach Versus Withdrawal. To localize the between-group difference observed in the amygdala in the anatomical ROI analysis, a secondary voxelwise analysis of the Faces Approach versus Faces Withdrawal contrast was conducted. No significant clusters were observed at the cluster-forming threshold of $p = .001$; however, at $p = .05$, a cluster within the left amygdala was present, owing to a significantly greater response of the FH+ group compared with the FH− group (Montreal Neurological Institute coordinates [x, y, z] of the peak voxel: $-26, -5, -23$ [$z = 4.5$, $p = 6.6 \times 10^{-6}$]). A similar (slightly weaker) pattern of findings was observed for the right amygdala ($30, -8, -17$ [$z = 3.9$, $p = 1 \times 10^{-4}$]) (Figure 2). Follow-up 1-sample t tests confirmed that the FH+ group, but not the FH− group, showed significant responses of the left amygdala to looming faces ($-26, -5, -23$ [$z = 4.4$, $p = 1 \times 10^{-5}$]). There was no significant activation at this threshold in the right amygdala in either group.

Regression Analysis

A regression analysis using a multivariate general linear model was then conducted to test whether changes in brain function
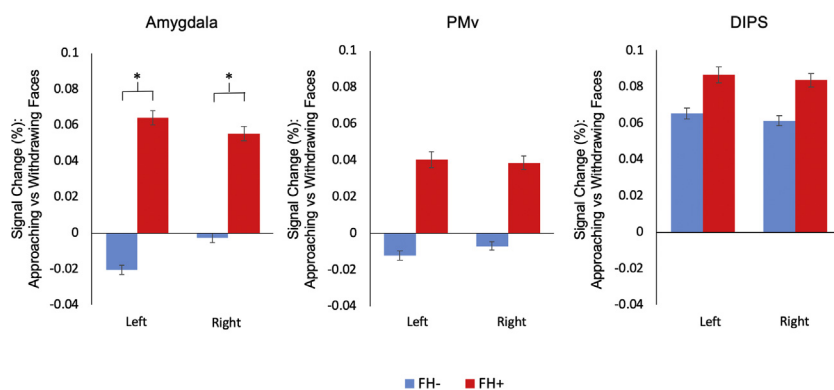
Figure 1. Results of the region-of-interest analysis. Bar plots of mean percent signal change (approaching vs. withdrawing [looming] faces) of the amygdala, ventral premotor cortex (PMv), and dorsal intraparietal sulcus (DIPS) regions of interest for the groups with (FH+) and without (FH−) a family history of depression are displayed. The FH+ group showed a significantly greater response to looming faces in the left and right amygdala compared with the FH− group (left [t_{70} = −2.89, p = 5 × 10^{-3}], right [t_{70} = −2.02, p = .04]). *p < .05.

associated with having a family history of depression were associated with resilience or symptom levels. The regression analysis was performed with amygdala BOLD response, extracted from the left and right amygdala anatomical ROIs, as the dependent variable, group (FH+/FH−) as a between-subjects factor, and resilience/symptom scores as covariates. Significant interactions between group and resilience or symptom levels on amygdala response were followed up with Pearson's correlations (2-tailed). There was a significant interaction between group and resilience levels for the responses of the left, but not of the right, amygdala (left amygdala [$F_{1,55}$ = 8.94, p = .004], right amygdala [$F_{1,55}$ = 1.69, p = .20]). There were no significant interactions between group and levels of depressive (BDI), psychotic-like (PDI), or anxiety (Spielberger State-Trait Anxiety Inventory) symptoms for either the left or right amygdala responses. Follow-up correlations showed that levels of resilience were negatively correlated with responses of the left amygdala to looming faces in the FH+ group (r = −.41, p = .03) (Figure 3). This correlation remained significant after controlling for levels of subthreshold symptoms of depression and anxiety. In contrast, the FH− group did not show any significant correlations between amygdala responses to looming faces and resilience levels (left: p = .09; right: p = .71) (Figure 3). There were no correlations between resilience levels and amygdala responses to faces overall (compared with cars) in either the FH+ or FH− group (all p > .3).

Because having a history of childhood adversity is linked to an increased risk for developing depression (50), we repeated this analysis controlling for levels of childhood adversity, measured using the Childhood Trauma Questionnaire (51). The correlation between resilience levels and amygdala responses to looming faces in the FH+ group remained significant after controlling for childhood adversity (r = −.42, p = .03). Also, there were no correlations between amygdala responses to looming faces and baseline levels of subsyndromal depression, anxiety, psychotic experiences, or levels of childhood adversity in the FH+ group (all ps > .20) (Supplemental Table S2).

Last, to confirm the above findings by repeating the analyses using a slightly different approach, we conducted these correlational analyses using 3 functionally defined amygdala ROIs, which were derived from between-group comparison maps that were generated using 3 thresholds (p = .05, p = .01, and p = .001). These analyses revealed significant negative correlations between resilience levels and amygdala responses, regardless of the ROI used (Table 2).

DISCUSSION

Summary of Main Findings

Consistent with prior work, this study demonstrated that nondepressed young adults with a first-degree relative who had a history of depression display greater amygdala responsivity than nondepressed young adults without such a family history (33–35). Further analyses revealed that this pattern of responses was not related to the presence of subthreshold symptoms of psychopathology but rather to low resilience levels. However, a parietofrontal cortical network involved in attention did not show the same pattern of significantly elevated responsivity as seen in the amygdala in the relatives, suggesting that attentional systems may be disrupted in depressive illness but not in an at-risk cohort.

Amygdala Dysregulation as a Marker of Low Resilience and Risk for Illness

Potentially related to these results, one recent study found that lower resting-state connectivity of the amygdala with the orbitofrontal cortex in adolescents at risk for depression predicted the later development of depression (52); another prior study found that higher basal levels of amygdala activity was associated with low, self-reported resilience in older adults (53). Taken together with the current results, these findings suggest that specific patterns of disrupted amygdala function (i.e., increases in basal or stimulus-elicited activity and reduced functional coupling with prefrontal cortical regions) may be linked to poor resilience and vulnerability to depression. However, exactly how poor resilience and depression risk are manifested and linked biologically remains to be understood.

Resilience

While the definition of resilience and its components continues to be debated, it is likely the result of a combination of a range of biological and environmental factors influencing one's
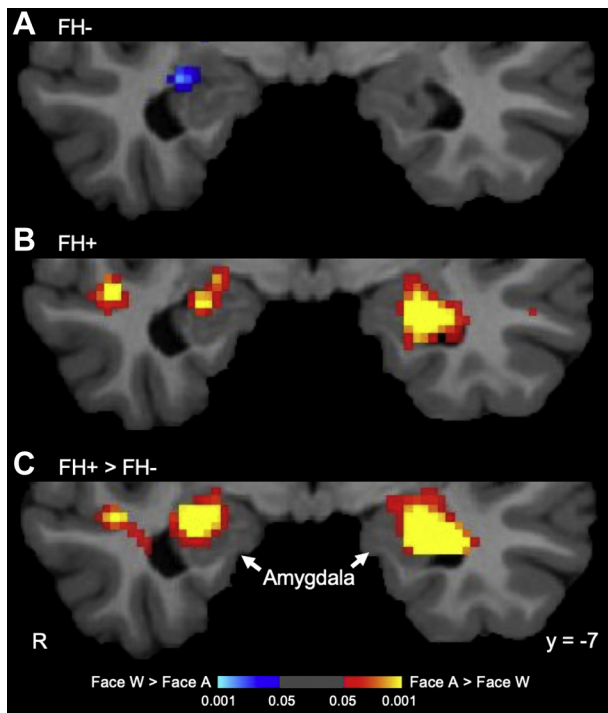
Figure 2. Results of the voxelwise analyses. These whole brain–corrected maps ($p <$ .05) display the amygdala responses to looming faces in **(A)** the group without a family history of depression (FH−) and **(B)** the group with a family history of depression (FH+) and **(C)** the comparison between the responses of the two groups. Only the FH+ group (not the FH− group) showed a significant response to looming faces, in the left amygdala. A, Approach condition; R, right; W, Withdrawal condition.

response to adversity ([54]). In previous studies, resilience as measured by the self-report scale used here, the CD-RISC, has been shown to moderate the relationship between adverse events and severity of subsequent symptoms of anxiety and depression ([13],[14]), as well as predict treatment response in patients with depression ([55]) and posttraumatic stress disorder ([56]), irrespective of symptom severity. Together, these findings suggest that this self-report scale measures an aspect of resilience that predicts both risk for the development of psychopathology and the capacity for rapid recovery from it.

In our sample, average resilience levels did not differ between the FH+ and FH− groups. However, only the FH+ subjects with lower resilience levels showed elevated amygdala responses to looming faces. Thus, in future studies, amygdala responses to salient stimuli and/or self-reported resilience levels could be tested as potential components of a tool for identifying individuals, among those with genetic risk for depression (conferring a threefold increase in risk), who have a particularly elevated risk for depression due to other, perhaps nonfamilial, factors.

Specific Effect on Amygdala Responses to Looming Faces

Interestingly, in the current study, we did not find evidence for overall amygdala dysfunction in those with familial risk for depression, as amygdala responses to faces overall (in comparison with responses to cars) was not elevated in this group, nor were amygdala responses to faces (compared with cars) negatively correlated with resilience levels in either group. This may be due to the robustness of face-elicited responses of the amygdala (as compared with amygdala responses to nonface stimuli) in most individuals; there may not be sufficient variance in these responses to reveal a dimensional relationship with resilience levels, in contrast to the variance observed in amygdala responses to salient [e.g., approaching and on a collision course with the body, or emotional ([24],[57])] versus nonsalient or safe-appearing (e.g., withdrawing or emotionally neutral) face images.

Task Performance

There were no differences between the 2 groups in performance of the dot-detection task that was performed while the approaching and withdrawing face stimuli were presented, suggesting that differences between the 2 groups in levels of attention to the stimuli were not present and thus cannot account for the between-group differences in amygdala responses. The FH+ group did perform significantly better on the task than the FH− group during the Withdrawing Cars condition, perhaps reflecting a generally greater level of vigilance that was only detectable during a rather nonsalient condition.

Dorsal Attention Network

We found no significant between-group differences in the responses of the DIPS, and only a trend toward an elevated response of the PMv, in the FH+ compared with the FH− individuals. Thus, these results do not provide support for the hypothesis that primary abnormalities in the dorsal attentional system are responsible for attention-related abnormalities in individuals at risk for depression. One possible interpretation of this pattern of findings is that attentional abnormalities in depression and depression risk are primarily due to consequences of alterations in amygdala function (or in an amygdala-centered network of regions), rather than due to fundamental changes in the neural circuitry that controls attention. However, it is also important to note that the task used here did not engage all circuitry involved in attentional control; for example, the ventral "bottom-up" attention network was not examined. Thus, additional studies will be needed to fully evaluate the neural systems mediating the various forms of attention in individuals with risk factors for developing depression.

Elevated Responses of the Amygdala as a Transdiagnostic Risk Factor

Current models of depression ([8],[58]) propose that a vulnerability to depression may remain dormant for years, without leading to a depressive episode. Thus, a combination of factors, including environmental events and hormonal changes, as well as protective biological and psychosocial factors, may determine whether clinically impairing depressive symptoms emerge in vulnerable individuals. Notably, recent evidence suggests that this model of depression may in fact correspond to a more general model of psychopathology; some neural
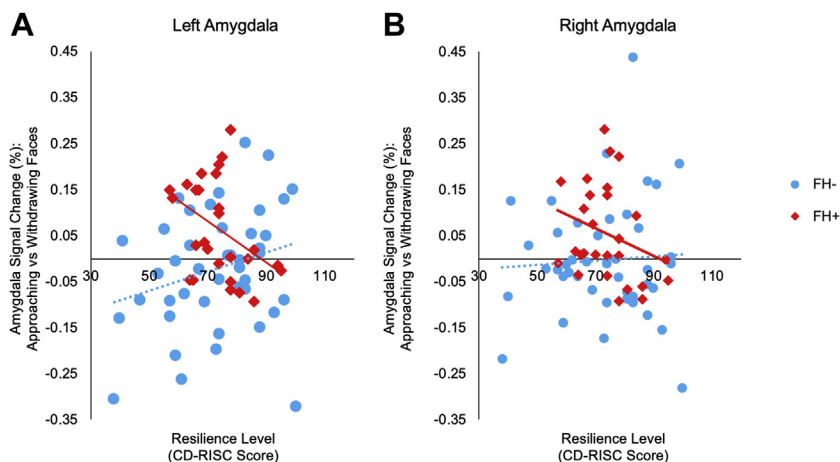
Figure 3. Correlations between amygdala responses and resilience levels. For these correlational analyses, responses of the left and right amygdala for each subject were extracted using anatomically defined regions of interest generated by FreeSurfer from the T1 scan of each subject. The scatter plot in **(A)** illustrates the significant correlation between resilience level (as measured by the Connor-Davidson Resilience Scale [CD-RISC]) and the response of the left amygdala to looming faces in the group with a family history of depression (FH+) ($r = -.41$, $p = .03$, $n = 27$), whereas there was no significant correlation between responses of the left amygdala and resilience levels in the group without a family history of depression (FH−) ($r = .26$, $p = .09$). Moreover, the correlations between responses of the left amygdala and resilience levels in the FH+ and FH− groups were significantly different from each other ($z = -2.48$, $p = .02$). **(B)** Responses of the right amygdala to looming faces were not significantly correlated with resilience levels in the FH+ ($r = -.28$, $p = .16$) or FH− ($r = .05$, $p = .71$) groups.

"vulnerability markers," such as heightened amygdala responses to salient social stimuli, may not be specific to depression risk (59–63). For example, two studies have shown that the response of the amygdala to threatening stimuli prior to a traumatic event predicts the later development of posttraumatic stress disorder symptoms (59,64), and a third study showed that amygdala responses to negatively valenced faces predicted the later development of internalizing symptoms (65). The current data are generally in line with this and other evidence for amygdala dysfunction as a transdiagnostic marker of psychopathology risk. Specifically, taken together with prior work, these results suggest that reactivity of the amygdala in response to salient social stimuli may be a marker of vulnerability for the context-dependent emergence of psychopathology related to a reduced capacity to tolerate stress (i.e., low resilience).

Limitations and Future Directions

Resilience is a complex construct with no agreed-upon operational definition. Thus, one limitation of this study is that resilience was measured using only one self-report questionnaire. Future studies can include additional measures that have been linked to resilience, such as physiologic and epigenetic markers, and test whether those and the putative marker of resilience described here, low or "normal" amygdala reactivity to salient social stimuli, can be used to prospectively predict outcomes (i.e., resilient or not) following stressful events. Follow-up work can also determine whether specific resilience-boosting interventions can influence amygdala function, psychological responses to environmental stressors, and psychiatric outcomes. Future studies can also expand on the experimental design of the functional MRI paradigm used here, including increasing the representation of different ethnicities in the social (face) stimuli, as well as the types of social and nonsocial stimuli.

Lastly, it is also important to emphasize that it is not possible to distinguish here, given the design of the current study, between an effect of greater loading for genetic variants associated with depression (6) and the influence of growing up with a depressed relative and the associated environmental stressors that may accompany that experience. Follow-up studies can investigate whether aversive childhood experiences associated with the stress of familial depression are closely linked to elevated amygdala responses in at-risk individuals, or whether there is instead (or in addition) a strongly genetic basis for this phenotype.

Table 2. Correlations Between Amygdala Responses to Looming Faces and Levels of Resilience

	Region of Interest					
	Left Amygdala		Right Amygdala		Left + Right Amygdala	
Region of Interest Definition	Correlation Coefficient (*r*)	*p* Value	Correlation Coefficient (*r*)	*p* Value	Correlation Coefficient (*r*)	*p* Value
Anatomical (FreeSurfer Segmentation)	−.41	.03	−.28	.16	−.36	.06
Functional (Voxel Threshold .05)	−.52	.01	−.42	.03	−.50	.01
Functional (Voxel Threshold .01)	−.52	.01	−.36	.06	−.46	.01
Functional (Voxel Threshold .001)	−.49	.01	−.35	.07	−.45	.02

Amygdala responses for each subject were extracted using regions of interest that were either defined anatomically (in the primary analysis) or defined using the between-group comparison (family history of depression vs. no family history of depression) voxelwise maps generated using 3 different thresholds ($p = .05$, $p = .01$, and $p = .001$). Significant correlations with resilience levels (measured using the Connor-Davidson Resilience Scale) in the family history–positive group [$n = 27$] are observed regardless of the type of amygdala region of interest used to extract the functional magnetic resonance imaging data.

Conclusions

These findings show that a specific pattern of amygdala function (higher responses to salient social information) in those with familial risk for depression is linked to lower resilience within this group. In the future these results could potentially provide a component of a quantitative tool that could be used to stratify individuals with a family history of depression into high and low risk groups. Such a tool is a prerequisite for the development of objective screening strategies, individualized risk profiles and targeted preventive interventions.

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