Depression Risk Is Associated With Weakened Synchrony Between the Amygdala and Experienced Emotion

Nim Tottenham, Myrna M. Weissman, Zhishun Wang, Virginia Warner, Marc J. Gameroff, David P. Semanek, Xuejun Hao, Jay A. Gingrich, Bradley S. Peterson, Jonathan Posner, and Ardesheer Talati

ABSTRACT

BACKGROUND: Major depressive disorder (MDD) is associated with aberrant limbic neural responses to emotional stimuli. We assessed how self-generated emotions modulate trial-by-trial limbic activity and whether this brain-emotion synchrony varies by familial MDD risk (regardless of personal MDD history) and neuroticism.

METHODS: Participants (n = 74, mean age = 34 years) were later-generation family members of depressed or nondepressed probands as part of a longitudinal cohort study. Using an emotion induction task, we examined participant-specific modulation of anatomically defined limbic neurobiology. Neuroticism, mental health, and familial parenting style were assessed, and MDD assessments were routinely collected throughout the previous longitudinal assessments of the study.

RESULTS: Participant-specific emotional arousal modulated amygdala and hippocampal activity. Lasso regression identified attenuated right amygdala arousal modulation as being relatively more associated with neuroticism (even though neuroticism was not associated with arousal ratings). Attenuated amygdala modulation and neuroticism were significantly more likely in offspring of parents with MDD. Parental MDD, but not personal history of MDD, predicted attenuated amygdala modulation.

CONCLUSIONS: Attenuated right amygdala modulation by emotional arousal was associated with neuroticism, indicating that the amygdala was less synchronous with emotional experiences in individuals higher in neuroticism. This neurophenotype was predicted by participants’ parental MDD history but not by their own MDD history; that is, it was observed in unaffected and affected offspring of parents with MDD. These data suggest that weak amygdala-emotion synchrony may be a predisposing risk factor for MDD, rather than a result of the illness, and they suggest pathways by which this risk factor for depression is passed intergenerationally.

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A central feature of major depressive disorder (MDD) is impaired emotional functioning (1). Emotion processing has at its core the structural and functional integrity of the limbic system (e.g., amygdala, striatum, hippocampus, anterior cingulate). Collectively, the limbic system is involved in responding, attending, appraising, and learning about emotionally relevant stimuli, and meta-analyses show altered limbic function and structure in MDD [e.g., (2–6)]. Less understood is whether these neurobehavioral alterations signify trait-like risk factors for depression (occurring even in the absence of illness) or state-like phenotypes resulting from depression. Using a familial risk design, the current study addresses this question.

We examined limbic activity as a function of the personality trait neuroticism. Neuroticism, the tendency to exhibit difficulty managing, tolerating, and regulating affect (especially negative) (7), is a leading risk factor for MDD (8–10). Neuroticism is highly heritable and is elevated in nonaffected family members of people with MDD (11). Compared with MDD itself, the dimensional trait of neuroticism may be more valuable in identifying neurobiological correlates of familial MDD risk. Neuroticism, like MDD, has commonly been associated with individual differences in limbic functioning (12). These reasons make neuroticism well suited for studying limbic risk for depression.

Depression has been associated with dysfunction in both arousal and valence dimensions (13,14). Emotional dysfunction associated with depression involves heightened negative affect (1), reduced positive affect (15), and/or an overall flattening of emotional experiences, consistent with the hypothesis that depression derives from a constricted reaction range to differing emotional contexts (16,17). While emotional and
limbic responses are commonly examined using stimuli external to the participant (e.g., faces, images) (4), the clinical experience of MDD typically consists of altered personal experiences of emotion, which are often blunted in depression (18). Here, we used an emotion induction task (19), which may provide an ecologically valid means of assessing limbic function for personally experienced emotion (20–22) in individuals at familial MDD risk. This task allowed us to use participants’ own ratings to identify limbic regions that were modulated by personal experiences and to examine associations between limbic-emotion synchrony and trait neuroticism.

Studying individuals who have already been depressed is informative for identifying neurobiological correlates of MDD but leaves open the question of whether observed phenotypes are risk factors for MDD or are the consequences of living with the illness. Here, we examined limbic modulation by personally experienced emotion in individuals at high risk by virtue of having a family member with MDD. Because these individuals may or may not have had a history of MDD, studying neurobiological correlates of neuroticism may provide insight into neurobiological risk involved in developing MDD.

**METHODS AND MATERIALS**

**Participants**

A longitudinal cohort familial study following relatives of depressed or nondepressed individuals provided a sample with a wide variation of neuroticism and depression risk (23). Participants in the final sample (N = 74) were subsequent family members of depressed or nondepressed probands (generation 1) recruited ~30 years prior (24,25) (Table 1). Data in the current article were obtained at the sixth wave (~year 30) of data collection. Generation 1 probands with moderate to severely impairing MDD were outpatients receiving medication for depression. Nondepressed probands were selected from an epidemiologic sample in the same community with no history of psychiatric illness, as determined by several interviews. Generation 2 spouses were included when appropriate (noted below).

Eighty-six participants completed functional magnetic resonance imaging (fMRI) scanning. Of these, 74 provided usable fMRI data; 12 were excluded from analyses (see Supplemental Methods A1). At the session, there were no group differences in depressive symptoms on the Hamilton Depression Rating Scale between individuals with and without a history of MDD depression ($F_{1,55} = 1.52, \ p = .22$; no MDD history: mean ± SD = 3.19 ± 3.17, MDD history: mean ± SD = 3.12 ± 5.56), and overall scores were low (mean ± SD = 2.10 ± 4.35; range, 0–23; median = 0; mode = 0). Generation 1 comprised only European-American individuals to reduce heterogeneity for future genetic studies, as was the custom when the study began. All family members were European American (non-Hispanic) as well. Procedures were approved by the institutional review boards of Yale and Columbia Universities.

**Assessments**

The diagnostic interview across all waves was the Schedule for Affective Disorders and Schizophrenia—Lifetime (26) (see Supplemental Methods A2). Current neuroticism and depressive symptoms were assessed with the NEO Five-Factor Inventory (27) and the Hamilton Depression Rating Scale (28), respectively. The Parker Parental Bonding Instrument (29) from the current wave of data collection was used; it has been evaluated extensively for its psychometric properties and has demonstrated good test-retest reliability, internal consistency, and validity (30,31), intergenerational transmission (32), and stability over a 20-year assessment period within the current sample (33). This measure, completed by participants, assesses parental warmth and overprotection. These data were highly skewed and thus transformed (see Supplemental Methods A3).

**fMRI Emotion Induction Task**

During fMRI scanning, an emotion induction task (19) designed to elicit personally experienced emotions was used. Participants were told, “You will be shown sentences that describe certain emotions. Try to think about what the emotion feels like. Some people think about situations, or draw on memories of situations, that have made them feel the emotion in the past” (see Supplemental Methods A4). Each trial lasted 35 seconds and consisted of three components (Figure 1): 1) an emotional sentence (20 s), 2) ratings on valence and arousal dimensions (12 s) (34), and 3) center crosshair (3 s). Ratings were presented as Likert-type scales, first for arousal (ranging from −4 [low energy] to 0 [neutral] to 4 [high energy]) and then for valence (ranging from −4 [unpleasant] to 0 [neutral] to 4 [pleasant]). Participants responded with a right hand using a scanner-compatible computer mouse. The first rating bar (arousal) would disappear if no input was provided after 6 seconds, and the second rating bar

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<td>Probands With MDD</td>
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<td>Generation 2: $n = 15$ (10 children and 5 spouses)</td>
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<td>Generation 3: $n = 23$ (grandchildren)</td>
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<td>Generation 2: $n = 10$ (6 children and 4 spouses)</td>
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<td>Generation 3: $n = 26$ (grandchildren)</td>
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MDD, major depressive disorder.
(valence) would appear immediately after the first bar if there was an answer or if the response window timed out. Practice trials with different stimuli were provided.

We conducted two runs (8.5 min each), each comprising 15 complete trials (totaling 30 stimuli and associated ratings). The sentences, presented in a fixed pseudo-randomized order, conveyed the following emotions: angry (trial 3), bored (trial 1), calm (trial 6), disgusted (trial 1), fearful (trial 3), happy (trial 6), sad (trial 5), sleepy (trial 2), surprised (trial 2), and tense (trial 1). Participants’ individual ratings were used for time-course modulation. Missing responses were replaced by the group mean (neuroimaging analyses included a regressor for trials with missing ratings). There was a mean ± SD of 1.24 ± 2.09 missing trials of the 30 trials across participants (mode = 0; median = 0; range, 0–12). The task was presented through goggles (Resonance Technology, Northridge, CA) and programmed in E-Prime (version 1.0; Psychology Software Tools, Pittsburgh, PA).

Image Acquisition
Images were obtained on a GE Healthcare Signa 3T whole-body scanner (GE Healthcare, Milwaukee, WI) operating the E2-M4 platform using a quadrature head coil in receive mode. T1-weighted sagittal images positioned axial functional images parallel to the anterior commissure–posterior commissure line. A 3-dimensional spoiled gradient recall image was acquired for coregistration with axial echo-planar images (repetition time = 2800 ms, echo time = 25 ms, 90° flip angle, single excitation per image, 3-mm thickness, 0.5-mm gap, 24 × 24 cm field of view, 64 × 64 matrix, 43 slices, 189 repetition times per run), providing an effective resolution of 3.75 × 3.75 × 3.5 mm and whole-brain coverage.

fMRI Preprocessing
fMRI data were preprocessed and analyzed with AFNI (Analysis of Functional NeuroImages) (version 16.1.28) (34). Alignment between anatomical and functional scans was performed and then assessed visually, and any data that appeared misaligned were corrected with a rigid body transformation. Images were transformed into Talairach space (resampled to 3 mm³). Preprocessing involved slice timing correction, followed by image registration to the minimum outlier volume, and smoothing with an anisotropic 6-mm Gaussian kernel (full width at half maximum). Time series were normalized to percent signal change to allow comparisons across individual participants by dividing signal intensity at each time point by mean signal intensity for that voxel and multiplying the result by 100. Volumes exceeding 0.3-mm framewise displacement were censored.

Parametric Analysis
General linear modeling (random effects) fit the percent signal change time courses to each regressor, using the dmBLOCK model with amplitude modulation, modeling drift with linear and quadratic factors within each model. The canonical hemodynamic response function was convolved with a boxcar function (20-s duration) indexing the affective sentence presentation (termed FactorA) and the rating period (12 s). Subject-level models included six stimulus regressors (FactorA, FactorA modulated by arousal ratings, FactorA modulated by valence ratings, the rating period, the rating period modulated by arousal ratings, and the rating period modulated by valence ratings) by convolving the stimulus timing with the hemodynamic response function. An additional regressor was added for any trials with missing ratings. Twelve motion parameters (6 rigid body, 6 derivatives) were included as separate regressors. A priori anatomical regions of interest (ROIs) (amygdala, hippocampus, ventral striatum, dorsal anterior cingulate cortex, and ventral anterior cingulate cortex, from the right and left hemispheres [see Supplemental Methods A5]) were selected, motivated by previous literature highlighting their role in MDD and neuroticism (7,15).

Outliers
Prior to analyses, imaging data were inspected for outlier values based on the regressors of interest (i.e., FactorA modulated by arousal ratings and FactorA modulated by valence ratings); participants (n = 2) were excluded using a parametric method if z scores were >4 for any parameter estimates.

Analytic Plan
First, we identified which of the anatomically predefined limbic regions were modulated by participant ratings. The resulting regions were entered into a lasso regression to identify those most strongly associated with neuroticism (revealing the right amygdala), with neuroticism as the dependent variable. To examine family risk, associations between parental MDD history and the right amygdala and neuroticism were tested. Finally, associations between parental MDD history and parental characteristics (warmth, overprotectiveness) were examined.

Statistics
Following fMRI processing, all analyses were performed with extracted ROI data in SPSS version 26 (IBM Corp., Armonk, NY) and JASP 2018 (JASP Team, Amsterdam, the Netherlands) (35). All tests were 2-sided. Greenhouse-Geisser correction was applied when necessary (see Supplemental Methods A6).

Covariates
Unless otherwise noted, all analyses controlled for age (mean centered), gender, and familial relatedness based on a kinship coefficient (36). Analyses with fMRI data also covaried for mean displacement.
RESULTS

Limbic Modulation by Participant-Specific Ratings

Separate parameter estimates (i.e., blood oxygen level-dependent signal modulation), one for FactorA modulated by arousal ratings (arousal) and one for FactorA modulated by valence ratings (valence), were extracted from a priori ROIs. “Modulation” here refers to the parametric modulation of the blood oxygen level-dependent response by participants’ ratings. A region (ROIs) × modulation (arousal vs. valence) × hemisphere repeated-measures ANOVA was performed (see Covariates). This analysis revealed a region × modulation interaction ($F_{2.32,155.62} = 3.96, p = .016, \eta^2_p = .06$ [90% confidence interval (CI), .01 to .10]). Examination of the estimated marginal means showed that only the bilateral amygdala and hippocampus were significantly modulated by arousal ratings (Figure 2). No regions were significantly modulated by valence ratings. There was also a modulation × gender interaction ($F_{1,67} = 4.79, p = .032, \eta^2_p = .07$ [90% CI, .00 to .20]), such that male participants showed greater arousal modulation of limbic regions than female participants. Whole-brain analyses are provided in Supplemental Results B1.

Variable Selection

To reduce the number of ROI features for subsequent behavioral analyses, variable selection was performed with lasso regression (CATREG, SPSS version 26). The four anatomically predefined ROIs that exhibited modulation by participant-specific arousal ratings (i.e., the right and left amygdala and the hippocampus) were entered to predict neuroticism scores (dependent measure) (see Supplemental Methods A7). Of these regions entered, the right amygdala was the variable with the most relative influence on the model because it entered the model first and then steadily negatively affected neuroticism scores (Figure S2A). For visualization purposes only, we generated the scatterplot in Figure S2B illustrating the association between the right amygdala arousal modulation and neuroticism scores. Supplemental Results B2 includes regressions performed for each of the ROIs separately; note that none of these would survive multiple comparisons. These analyses were circular with the lasso regression and were only included to better understand the associations between each ROI and neuroticism scores. A neuroticism whole-brain analysis is provided in Supplemental Results B2.

Neuroticism and Behavioral Ratings

Separate repeated-measures analyses of covariance were performed on the dependent measures of arousal (repeated) and valence (repeated) with neuroticism (continuous score) and stimulus (10 emotion sentences) entered (see Covariates). For arousal, there was a main effect of stimulus ($F_{5,59,294.93} = 14.50, p < 10^{-21}, \eta^2_p = .20$ [90% CI, .13 to .25]) (Figure 3), but there was neither a main effect of neuroticism ($F_{1,58} = 0.73, p =$...
For valence, there was a main effect of stimulus ($F_{5.31,308.21} = 16.71, \ p < 10^{-24}$, $\eta_p^2 = .22$ [90% CI, .15 to .27]) (Figure 3), but there was neither a main effect of neuroticism ($F_{1,58} = 2.01, \ p = .16$, $\eta_p^2 = .03$ [90% CI, .00 to .16]) nor a neuroticism $\times$ stimulus interaction ($F_{9,522} = 0.91, \ p = .52$, $\eta_p^2 = .02$ [90% CI, .00 to .02]) (see Supplemental Materials B3 for additional analyses).

**Associations Between Parental MDD History**

The nature of this sample (high risk for MDD via family history) allowed for testing whether parental depression was associated with right amygdala modulation and neuroticism. Data about parental MDD history (both mothers’ and fathers’) were available from 63 participants; participants who were “married in” to the study (i.e., not biologically related to probands) were excluded from these analyses. Forty-six participants had at least 1 parent with an MDD history (both parents had an MDD history for 11 of these 46 participants). A univariate ANOVA was performed with the independent variable of parental MDD history and the dependent variable of right amygdala arousal modulation (see Covariates). There was a main effect of parental MDD history ($F_{1,57} = 5.47, \ p = .02$, $\eta_p^2 = .09$ [90% CI, .00 to .24]) and gender ($F_{1,57} = 6.44, \ p = .01$, $\eta_p^2 = .10$ [90% CI, .00 to .26]) on amygdala modulation. Individuals with at least 1 parent with an MDD history had lower amygdala arousal modulation than those with no parental history (Figure 4A), and male participants (mean $\pm$ SD = 0.012 $\pm$ 0.025) were more likely to show amygdala arousal modulation, whereas, as a group, female participants did not (mean $\pm$ SD = –0.005 $\pm$ 0.028). This analysis was repeated including the participant’s MDD diagnosis history, and the association between parental MDD history and amygdala arousal modulation remained ($F_{1,53} = 4.34, \ p = .042$, $\eta_p^2 = .08$ [90% CI, .00 to .24]); participants’ own MDD history was not associated with amygdala arousal modulation ($F_{1,53} = 0.03, \ p = .85$, $\eta_p^2 = .00$ [90% CI, .00 to .02]). A follow-up repeated-measures ANOVA with the factor of parent gender (mother vs. father) was performed, and there was no significant parent $\times$ amygdala modulation interaction ($F_{1,57} = 0.90, \ p = .35$, $\eta_p^2 = .02$ [90% CI, .00 to .13]), suggesting that no one parent was more likely to contribute to offsprings’ amygdala modulation. The Supplemental Results include...
whole-brain analyses examining parental MDD effects (Supplemental Results B4), analyses that controlled for current depression symptoms (Supplemental Results B6), and ratings by parental MDD history (Supplemental Results B5).

A univariate ANOVA tested for the association between parental MDD history and neuroticism (see Covariates). There was a main effect of parental MDD history ($F_{1,56} = 5.98, p = .02, \eta^2_p = .10$ [90% CI, .00 to .26]) and age ($F_{1,56} = 4.46, p = .039, \eta^2_p = .08$ [90% CI, .00 to .23]) on neuroticism. Higher neuroticism scores were observed in individuals with parent(s) with an MDD history (Figure 4B) and in younger participants. The association between parental MDD history and neuroticism remained even when including participants’ own MDD histories ($F_{1,51} = 4.69, p = .035, \eta^2_p = .08$ [90% CI, .00 to .25]). A follow-up repeated-measures ANOVA with the factor of parent gender (mother vs. father) was performed, and there was no significant effect of parent gender ($F_{1,56} = 0.11, p = .74, \eta^2_p = .00$ [90% CI, .00 to .08]), suggesting that no one parent was more likely to contribute to offspring’s neuroticism values.

**Parenting Characteristics in Families With MDD History**

Two separate repeated-measures ANOVAs with the factor of parenting behavior (warmth, overprotectiveness) were performed (separately for each parent), using the between-subject variable of parental MDD history (see Covariates). There was a parent MDD history × behavior interaction ($F_{1,57} = 5.49, p = .023, \eta^2_p = .09$ [90% CI, .00 to .24]) for mothers (Figure 5B). Post hoc 1-way ANOVAs showed that in families with at least 1 parent with an MDD history, mothers were rated as expressing less warmth (mean ± SD = −0.219 ± 0.965) compared with families with no parental MDD (mean ± SD = 0.604 ± 0.915) ($F_{1,57} = 8.05, p = .006, \eta^2_p = .12$ [90% CI, .01 to .29]), but there were no differences in overprotectiveness ($F_{1,57} = 0.08, p = .78, \eta^2_p = .02$ [90% CI, .00 to .06]). For fathers, there was a main effect for parent MDD history on behavior ($F_{1,56} = 5.31, p = .025, \eta^2_p = .09$ [90% CI, .00 to .24]) (Figure 5B), such that in families with at least 1 parent with an MDD history, fathers were rated as less warm and less overprotective. For the added control of current depressive symptoms, see Supplemental Results B6.

**Mediation**

To examine whether amygdala arousal modulation mediated the association between parental MDD history and neuroticism or vice versa, two separate mediation tests were performed using the SPSS PROCESS macro (37). Both included parental MDD history as the “A” factor, but the first model included right amygdala arousal modulation as the “B” factor and neuroticism scores as the “C” factor. The second model reversed factors B and C. Both models included age, gender, and kinship factor as covariates. Neither model showed significant mediation (first model [indirect effect = 0.26; bootstrapped CI, −1.32 to 1.88], second model [indirect effect = −0.00; bootstrapped CI, −0.00 to 0.00]).

The PROCESS macro was also used to examine whether parent warmth mediated the association between parental MDD history and neuroticism; this analysis (using the maximum value between mothers and fathers for warmth) showed an indirect effect of warmth (1.78; bootstrapped CI, 0.03 to 4.25) but no direct effect of parental MDD history on neuroticism (3.55; CI, −0.78 to 7.88). The PROCESS macro also examined whether warmth mediated the association between parental MDD history and right amygdala arousal modulation; this analysis showed a direct effect of parental MDD history on amygdala arousal modulation (−0.02; CI, −0.03 to −0.002) but no indirect effect (−0.001; bootstrapped CI, −0.009 to 0.004).

**DISCUSSION**

Here, we investigated associations between familial MDD risk, altered limbic neurobiology, and neuroticism. We observed that parental MDD history was negatively associated with arousal modulation of the right amygdala and positively associated with neuroticism, with amygdala modulation and neuroticism being negatively correlated with each other. This association with parental history was observed regardless of one’s own MDD history. That is, weak amygdala-arousal synchrony and neuroticism were more likely observed in high-risk families, being better predicted by parental MDD than participants’ own MDD history.

Of the limbic regions tested, only the amygdala and hippocampus showed participant-specific arousal modulation. This
finding is consistent with a previous report using this task (19) and with the notion that limbic regions are sensitive to experiences of emotions and amygdala activity. Lesion work has shown that the amygdala is not critical for emotion reporting (42); thus, the current results raise the possibility that emotional experience is represented at the neurobiological level differently in individuals at higher risk for depression. Lack of correspondence between the amygdala and emotion suggests that reported affect may not always be a sensitive enough measure for depression risk. Although speculative, poor arousal-amygdala synchrony conferred by familial risk might be associated with broader emotion regulation difficulties (including alexithymic tendencies) (43). Indeed, studies have observed negative associations between alexithymic symptoms and limbic reactivity (notably in the amygdala (44–47]), and alexithymic symptoms are correlated with neuroticism (48–51).

The role of the amygdala in neuroticism is complex, and reports have been inconsistent (7,40,52), with some studies showing positive relationships and others showing null or negative relationships. Some have suggested that neuroticism is associated with atypical amygdala dynamics (52), with both baseline and reactivity exhibiting alterations at higher levels of neuroticism (and depression) (53–57). The current findings may provide additional support for this hypothesis, showing low synchrony between experienced affect and amygdala at higher levels of neuroticism, without an overall dampening of amygdala reactivity (if anything, there was a positive trend between neuroticism and overall amygdala task reactivity). Because emotions were manipulated using imagined experiences in different situational contexts, ratings were context dependent, and therefore so was the altered amygdala reactivity by extension. Perhaps an overall elevated affective response coupled with attenuated sensitivity to changing emotional cues increases depression risk (16). Relative insensitivity to emotional stimuli (58,59) has been linked to familial risk (via electrophysiological studies and depressive symptoms in healthy individuals (via affective startle) despite normal arousal ratings (60). Together, these findings support the hypothesis that depression risk is associated with weak amygdala synchrony to changing emotional contexts; this hypothesis requires future testing.

Weaker arousal-amygdala synchrony and neuroticism was associated with familial risk. While parental MDD was associated with this neurobehavioral phenotype, there was no significant association with participants’ own MDD diagnostic histories, suggesting that the weak amygdala synchrony and elevated neuroticism observed here were not “scars” of past illness, but instead were risk factors associated with family history. This interpretation is based on the analysis showing that parental MDD history, but not personal MDD history, was associated with right amygdala arousal modulation. This association was found regardless of current depression symptoms, suggesting a trait-like quality. What other phenotypes (e.g., cognitive control (61), religiosity/spirituality (62)) might simultaneously protect high-risk individuals against MDD are not addressed by the current study.

Previous work has shown that neuroticism demonstrates moderate heritability (63,64), being elevated in depressed and nondepressed family members (11), which might indicate a genetic transmission from parent to offspring. At the same time, the transmission may be, in part, interpersonal. In the current study, families with at least 1 parent with an MDD history were described as having less parental warmth (and less overprotectiveness for fathers), and warmth had an indirect effect on the association between parental history and neuroticism. Indeed, treating parental MDD reduces children’s symptoms (65). While the current sample was small, we observed that female participants (regardless of familial risk) were more likely to exhibit attenuated amygdala modulation, providing a potential mechanism for increased risk for depression-related phenotypes in females. Within this same sample, it has previously been shown that among low-risk offspring, females are at greater risk for MDD than males (whereas with high-risk offspring, there were no gender differences) (25). Previous work has shown that disturbed family environments are positively associated with neuroticism (9), with low parental warmth being a common risk factor for neuroticism and MDD (66–68). The association between parental MDD and amygdala-arousal synchrony merits replication with a larger sample, but, if replicated, would implicate poor amygdala synchrony as a risk factor for depression by way of parental MDD.

This study has limitations. The sample size is small—this becomes especially concerning for group differences analyses (e.g., examinations of parental MDD). However, this sample size was constrained three generations prior by the initial proband/control sample. Because of the prospective cohort design, we only had access to the family members that could/would participate. The wide age range motivated the addition of age covariates to analyses; while this helps model some variance, it may also introduce biases into the data (e.g., time since disease onset, episode frequency, aging processes) and introduces additional variance that may lessen power. The parenting measure was retrospectively collected, which may not always agree with prospective measures (69). However, scores on the Parental Bonding Instrument used here have demonstrated stability over 20 years within the current sample that was not influenced by changes in depression (32,33,70), suggesting at least moderate reliability between developmental and current assessments. Although we include tests of mediation here, we hesitate to interpret these findings, as the neuroticism and amygdala data were collected at the same time point. We should be careful interpreting a nonsignificant effect here, but the lack of mediation might suggest that both amygdala modulation and neuroticism were directly affected.
by parental MDD history, but perhaps not through each other. Also note poor amygdala signal reliability (Supplemental Results B7). Although we describe gender differences, the sample was too small to adequately test for gender effects. Finally, the original probands were selected from an ambulatory depression clinic and may not generalize to community samples.

Mapping the neurobiology of depression is challenging because MDD is a constellation of heterogeneous behaviors and personality traits supported by multiple and distinct neural circuits (15). Here, we examined neuroticism, because of its stability, strong psychometric properties (71), and tendency to be elevated in relatives (11), as one aspect of MDD to overcome these challenges. These findings show the value of high-risk designs in assessing neurobiological risk for MDD. They also advocate for consideration of the early caregiving environment for ameliorating MDD risk.

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