Cortical thinning in persons at increased familial risk for major depression

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The brain disturbances that place a person at risk for developing depression are unknown. We imaged the brains of 131 individuals, ages 6 to 54 years, who were biological descendants (children or grandchildren) of individuals identified as having either moderate to severe, recurrent, and functionally debilitating depression or as having no lifetime history of depression. We compared cortical thickness across high- and low-risk groups, detecting large expanses of cortical thinning across the lateral surface of the right cerebral hemisphere in persons at high risk. Thinning correlated with measures of current symptom severity, inattention, and visual memory for social and emotional stimuli. Mediator analyses indicated that cortical thickness mediated the associations of familial risk with inattention, visual memory, and clinical symptoms. These findings suggest that cortical thinning in the right hemisphere produces disturbances in arousal, attention, and memory for social stimuli, which in turn may increase the risk of developing depressive illness.

anatomy | cortex | imaging | MRI | cognition

Major depressive disorder (MDD) is a highly familial illness (1). It is the leading cause of disability worldwide for persons 15 to 44 years of age (2), and it is associated with increased mortality resulting from cardiovascular disorder (3), poor personal care (4), and suicide (5). Genetic and environmental factors and their interactions are important in its pathogenesis (6), but the abnormalities of brain structure and function that mediate these effects have not yet been identified. Brain-imaging studies have suggested the involvement of the limbic system and related frontal cortices in persons suffering from MDD, although findings from those studies have been inconsistent and have had relatively small effect sizes. Moreover, studies reporting abnormalities in brain structure and function in already-affected individuals have been unable to discern whether those abnormalities represent the causes of depressive illness, the compensatory neural responses that help to promote recovery or the attenuation of symptoms, the epiphenomenal effects of chronic illness or stress, or the effects of prior or ongoing treatment.

To address these limitations of prior neurobiological studies of already-affected individuals, we undertook a study of brain structure in individuals who are at high familial risk for developing MDD. These individuals belonged to a 3-generation cohort in which the first 2 generations have been followed for more than 20 years. The first generation (G1) comprised 2 groups of adults: 1 group that was clinically ascertained during treatment of moderate to severe, recurrent, and functionally debilitating MDD; and a control group composed of a sample of matched adults, ascertained from the same community, who had no discernible lifetime history of depression. The second generation (G2) comprised the biological offspring of the first generation, and the third generation (G3) comprised the offspring of the second generation. Longitudinal assessments in this sample (7) and in similar 2-generation studies (8, 9) have helped define the natural history of depression in the offspring of depressed individuals, with elevated rates of anxiety disorders before puberty usually being the harbinger of MDD that begins in mid- to late adolescence and that tends to be more severe, more recurrent in adulthood, and less responsive to treatment than nonfamilial MDD.

A prior electroencephalographic study of this cohort demonstrated greater alpha asymmetry in posterior leads of persons in G2 who had 2 depressed parents compared with offspring who had 1 or no depressed parents (10). The increased asymmetry derived from relatively less activity in parietotemporal leads over the right hemisphere and was independent of a personal lifetime history of MDD. The findings suggested that reduced right parietotemporal activity is a trait marker for vulnerability to developing MDD, prompting us to expect that in the present anatomical imaging study we would detect abnormalities in structure of the right parietotemporal cortices in individuals at elevated familial risk for depression.

Results

We imaged 131 individuals, 66 (12 children, 54 adults) in the high-risk group and 65 in the low-risk group (31 children, 34 adults). As expected, the frequency of lifetime MDD was significantly greater in the high-risk group ($n = 37$, 56%) than in the low-risk group ($n = 15$, 23%) ($\chi^2 = 13.54$, df = 1, $P = 0.0002$), as was the frequency of lifetime anxiety disorder (high-risk group: $n = 34$, 52%; low-risk group: $n = 14$, 21%; $\chi^2 = 11.42$, df = 1, $P = 0.0007$). These rates of lifetime MDD and anxiety disorder in the low-risk group were comparable to those reported in community surveys (11–13). At the time of MRI scanning, the high-risk group had significantly more current MDD (high-risk group: $n = 16$, 25%; low-risk group: $n = 7$, 11%; $\chi^2 = 4.28$, df = 1, $P < 0.05$) but not anxiety disorder (high-risk group: $n = 23$, 35%; low-risk group: $n = 16$, 25%; $\chi^2 = 1.79$, df = 1, $P = 0.18$) compared with the low-risk group, and the groups were similar in the severity ratings of depression and anxiety symptoms (Hamilton anxiety rating scale score (14) in high-risk adults = 5.2 [SD 6.1]; in low-risk adults = 4.6 [SD 6.0]; $t = 0.41$, df = 80, $P = 0.68$; Hamilton anxiety rating scale score (15) in high-risk adults = 5.0 [SD 5.4]; in low-risk adults = 5.1 [SD 7.3]; $t = 0.04$, df = 80, $P = 0.97$).

Maps of cortical thickness demonstrated broad expanses of statistically significant thinning in the lateral aspect of the right hemisphere in the high-risk group, including the inferior and middle frontal gyri, somatosensory and motor cortices, dorsal and inferior parietal regions, the inferior occipital gyrus, and posterior temporal cortex (Fig. 1). Thinning was absent in the lateral aspect of the left hemisphere of the high-risk group. The average reduction in cortical thickness in the lateral aspect of the right hemisphere of the high-risk group was 0.87 mm (range 0.55–1.36 mm), representing a 28% reduction in the 3-mm average cortical thickness of the low-risk group. Additional areas of thinning included the dorsal

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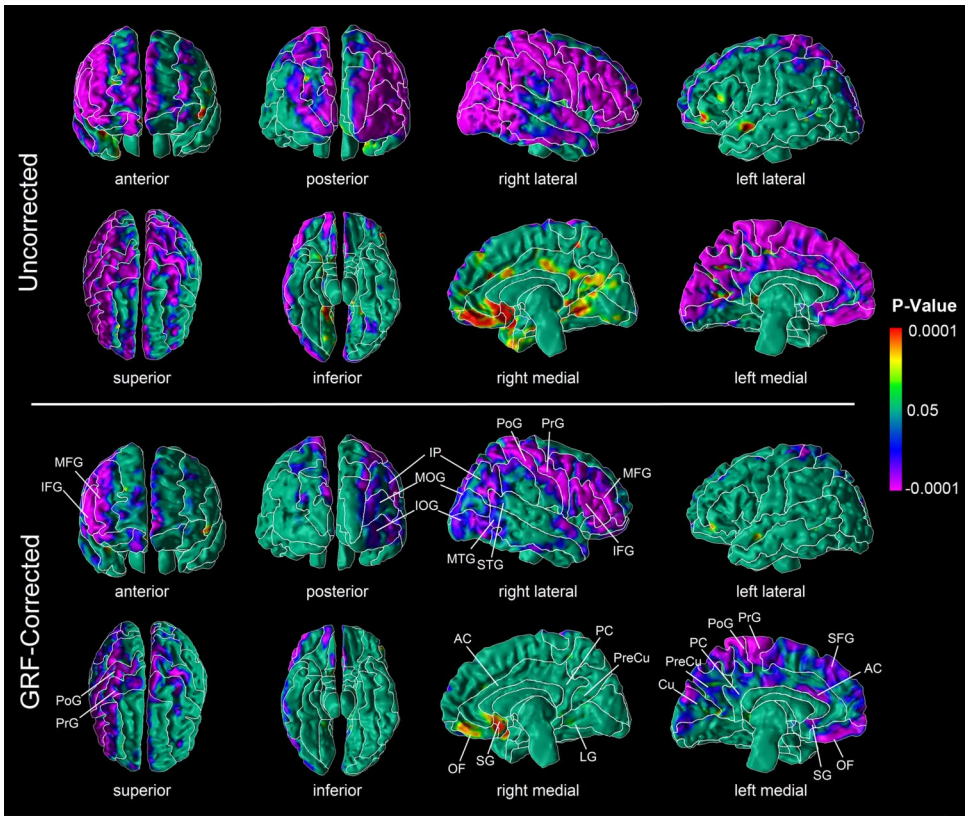

Fig. 1. Maps of group differences in cortical thickness. At each point on the cerebral surface, the statistical significance (probability values) of differences in cortical thickness across groups (high vs. low risk) in participants from generations G2 and G3 are color coded. Warm colors (yellow, orange, and red) represent significantly thicker cortices in the high-risk group; cooler colors (blue and purple) represent thinner cortices in that group. The color bar indicates the color-coding of p-values for testing of statistical significance at each point on the surface of the brain. Cortical thickness was rescaled for overall brain size, and the statistical models controlled for the degree of familial relatedness, the age, and the sex of all participants. (*Upper*) P-values thresholded at $P < 0.05$ without correction for multiple statistical comparisons. (*Lower*) P-values thresholded at $P < 0.05$ after correction for multiple comparisons using the theory of Gaussian random fields (GRF) on a 2D manifold. Cu, cuneus; IF, inferior frontal gyrus; IOG, inferior occipital gyrus; IP, inferior parietal lobule; LG, lingual gyrus; MGF, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OF, orbitofrontal cortex; PC, posterior cingulate; PoG, postcentral gyrus; PreCu, precuneus; PrG, precentral gyrus; SG, subgenual cortex; STG, superior temporal gyrus.

aspect of tissue along the interhemispheric sulcus of the left hemisphere, including the superior frontal gyrus and the parietal, precuneus, and cuneate cortices, the subgenual cortex, and the anterior and posterior cingulate cortices. Areas of statistically significant cortical thickening in the high-risk group were detected in the subgenual cortex, anterior and posterior cingulate gyrus, and medial orbitofrontal cortex of the right hemisphere. These findings did not change appreciably when the statistical models covaried for the presence of lifetime depression or anxiety disorders or when individuals who had a lifetime history of either or both of these disorders were excluded from the analyses (SI). Findings were similar in analyses of children and adults separately (SI), and no interaction of age with risk group was detected. Analyses of cortical volumes revealed regional differences across groups that were similar to those detected using measures of cortical thickness (SI).

Although cortical thickness was not associated with a lifetime history of MDD or anxiety disorder, cortical thickness did correlate significantly with the severity of current depression and anxiety symptoms at the time of scan, but primarily in the left rather than in the right hemisphere. Z-scores for measures of current severity correlated significantly and inversely with thickness of the temporal, parietal, and occipital cortices in the left hemisphere, a smaller portion of the parietal and occipital cortices in the right hemisphere, a large portion of the posterior cingulate and precuneate cortices in the right hemisphere, the fusiform and lingual gyri in the inferior temporal cortices bilaterally, and the left orbitofrontal cortex (Fig. 2). These findings were detected in the high- and low-risk groups separately when covarying for age and sex, and in both groups combined when covarying for age, sex, and risk status; moreover, they were detected for depression, anxiety, and combined depression and anxiety scores (SI).

The impressive thinning of the cortical mantle in the right hemisphere of the high-risk compared with the low-risk group, and its independence both from a prior history of MDD or anxiety disorder and from current depressive or anxiety symptoms, naturally raise the questions of what the functional consequences of the cortical thinning may be and how those functional consequences may increase the risk for developing MDD or anxiety. The right cerebral hemisphere is thought to be dominant in mediating certain forms of attention and visuospatial memory (16, 17). We therefore assessed the correlations of cortical thickness with measures of inattention and visual memory. Both measures correlated with cortical thickness more strongly and over a larger spatial extent in the right hemisphere than in the left, in each risk group individually and in both groups together. Thinner cortices in the right hemisphere were associated with greater degrees of inattention and with poorer performance on immediate and delayed visual memory tasks (Fig. 3), even though measures of inattention and visual memory were not themselves significantly intercorrelated ($r = -.09$, $df = 116$, $P = 0.35$) (SI). The patterns of correlation for the visual memory scores were similar for immediate and delayed recall and for subtest scores on tests of memory for faces and family pictures (not shown). The pattern of statistically significant correlations, moreover, was strikingly similar to the general pattern of group differences in cortical thickness across both hemispheres. The correlations of cortical thickness with measures of inattention and visual memory, together with the thinner cortices detected in the high-risk group, predicted that the high-risk group would report significantly more inattentiveness and would score lower on measures of visual memory than would the low-risk group, and this group difference, in fact, is what we found (for delayed visual memory, low-risk group: 108.6 [SD 12.0]; high-risk group: 102.0 [SD 15.2], $F = 7.1$, $df = 1,117$, $P < 0.009$; for inattention, low-risk group: 3.8 [SD 4.6]; high-risk group: 6.2 [SD 5.2], $F = 6.9$, $df = 1,115$, $P < 0.01$).

The possibility that cortical thinning of the right hemisphere could produce inattention for social and emotional stimuli, and that inattention to social stimuli could produce depressive symptoms or MDD, predicted that the degree of inattentiveness in our sample could account for a significant proportion of the lifetime rates of MDD and anxiety disorder (the latter being regarded as the

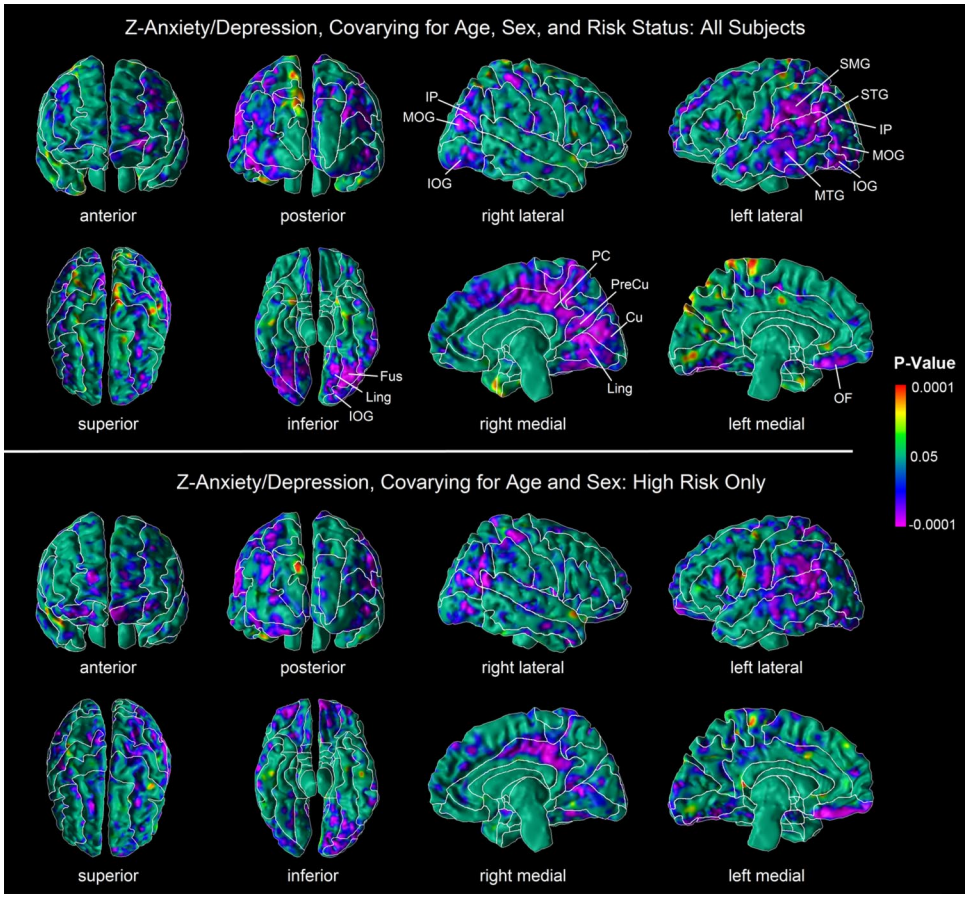

Fig. 2. Correlations of cortical thickness with current symptom severity. (*Top*) Correlations of cortical thickness with the sum of the z-depression and z-anxiety measures in children and adults of both risk groups combined while covarying for age, sex, and risk status of each participant. (*Bottom*) Analogous correlations in the high-risk group only. Similar findings were obtained for each severity measure separately and in each risk group separately (see SI). Significant inverse correlations are evident in the right and left inferior parietal and occipital cortices, the left middle and superior temporal gyri, the right posterior cingulate and precuneus cortices, the inferior temporal cortices bilaterally, and the left orbitofrontal cortex. Because these analyses were post hoc, the maps are not GRF-corrected for multiple comparisons. Cu, cuneus; Fus, fusiform gyrus; IOG, inferior occipital gyrus; IP, inferior parietal lobule; LG, lingual gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; OF, orbitofrontal cortex; PC, posterior cingulate; PreCu, precuneus; SMG, supramarginal gyrus; STG, superior temporal gyrus.

childhood precursor for MDD) in both groups combined. Indeed, this prediction was confirmed for MDD alone (1-tailed $t = 1.82$, $df = 113$, $P < 0.035$), for anxiety disorder alone (1-tailed $t = 1.66$, $df = 113$, $P < 0.05$), and for either MDD or anxiety disorder (1-tailed $t = 1.88$, $df = 113$, $P < 0.03$) while covarying for age and sex. The degree of inattentiveness also accounted for the severity of MDD or anxiety symptoms at the time of scan ($\beta = 0.45$, $df = 108$, $P < 0.0001$ and $\beta = 0.37$, $df = 108$, $P < 0.0001$, respectively, while covarying for age and sex).

We tested more formally the hypothesis that cortical thinning may have mediated the relationships between familial risk, inattention, and MDD using a series of mediator analyses (SI) (18) that permit stronger causal inferences than do simple bivariate correlations. These analyses demonstrated that cortical thickness significantly mediated the association of familial risk status with scores for both inattention and visual memory, effects that were by far most prominent in the right hemisphere and in the same regions where we detected the associations of cortical thickness with risk status (Fig. 4). Furthermore, we found modest evidence that inattention, but not visual memory scores, mediated the relationship of cortical thickness with the severity of MDD and anxiety symptoms. Mediator analyses clearly indicated, in contrast, that MDD and anxiety disorders and symptoms did not mediate the relationship of cortical thickness with measures of inattention and visual memory (SI).

Discussion

These findings strongly suggest that the predisposition to familial depression derives from disturbances of cortical gray matter in the right cerebral hemisphere. The 28% average reduction in cortical thickness of the right hemisphere is remarkable for its magnitude and spatial extent, rivaling the magnitude and extent of cortical morphological abnormalities reported in the most severe neuropsychiatric disorders, including schizophrenia and Alzheimer's diseases (19, 20), and is perhaps all the more remarkable given that the thinning is present even in persons who have never suffered from MDD or anxiety disorder but who are biological descendants of a depressed relative. The presence of the findings in individuals with and without a prior lifetime history of depression who were at increased familial risk for MDD suggests that these abnormalities are not simply a consequence of previously having been depressed or having been treated for depression. Rather, the findings suggest that thinning of the cortical mantle in the right hemisphere probably constitutes a familial trait vulnerability for the development of MDD. Whether that familial risk is of a genetic or epigenetic origin, or some combination of these etiologies (6), cannot be determined from the present data set. Nevertheless, the presence of the findings across a wide age range, the presence of the findings in children of the sample when analyzed separately, the absence of an interaction of age with risk group, and the increased rates of anxiety disorders and MDD in childhood and adolescence that have been documented previously in this cohort (1) suggest that the determinants of the cortical thinning probably are operative early in development, either in utero or during early childhood.

Previous studies support the possibility that the right hemisphere, particularly its posterior portion, is involved in the pathogenesis of depressive illness. Depressed individuals exhibit selective impairment on right-hemisphere tasks (21), and they have right-hemisphere performance deficits in paradigms that employ the presentation or perception of lateralized stimuli (22). Some electrophysiological studies also have reported decreased brain activity over the right posterior cortex in individuals with either current (16, 23) or remitted (24) depression, similar to findings reported in studies of regional cerebral blood flow (25).

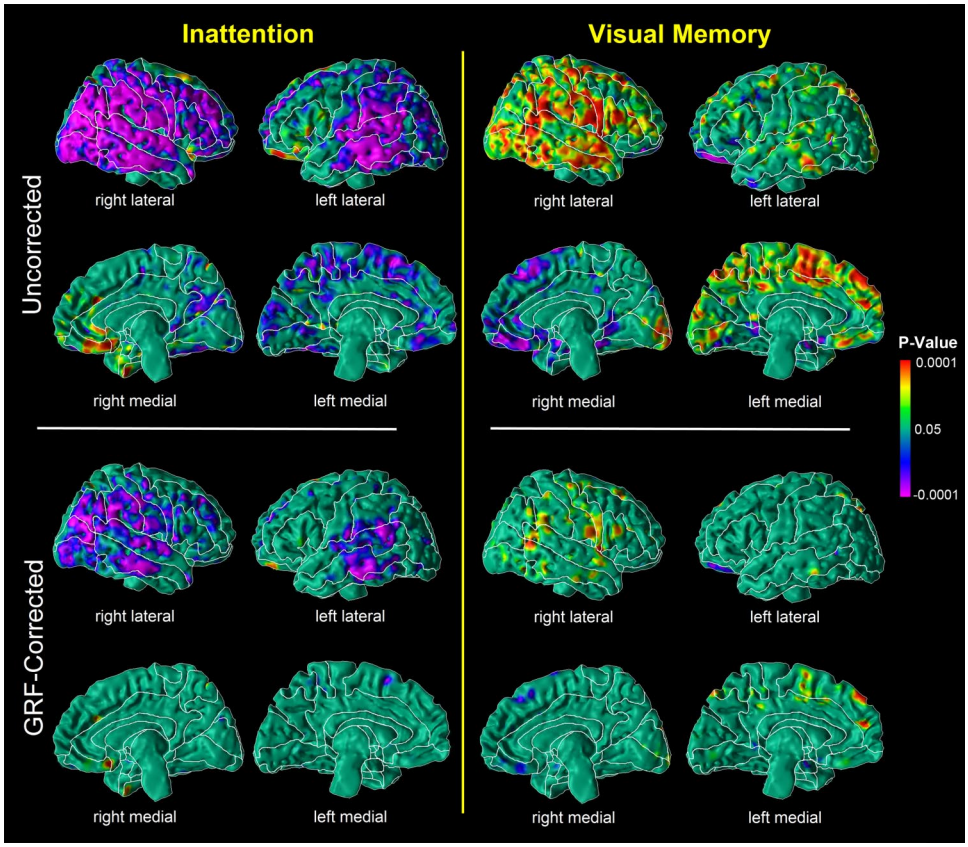

Fig. 3. Correlations of cortical thickness with behavioral measures. Warm colors (yellow, orange, and red) represent significant positive correlations. Cooler colors (blue and purple) represent inverse correlations between cortical thickness and the behavioral measure. Statistical models for the correlations accounted for the degree of familial relatedness, age, and sex of the participants. Correlations are shown for high- and low-risk groups combined, although similar maps were found in both the high- and low-risk groups separately (data not shown). Findings did not change appreciably when covarying also for risk status, indicating that these correlations are not driven by differences in cortical thickness or memory scores across the 2 risk groups. Correlations are especially strong in the lateral surface of the right compared with the left hemisphere, and the general patterns of correlation are similar to those detected when comparing cortical thickness in the high- and low-risk groups (see Fig. 1). Maps that correct for multiple comparisons using the theory of Gaussian random fields (GRF) are shown in the lower half of each panel. (*Left*) Greater inattention accompanied proportionately thinner cortices (n = 117). (*Right*) Worse visual memory performance accompanied proportionately thinner cortices (n = 119).

Taken together, these findings indicate that (*i*) individuals who currently are symptomatic have the most prominent thinning of the cortex, not only in the posterior right hemisphere but also, even more prominently, in the posterior left hemisphere; (*ii*) cortical thinning contributed equally to both depressive and anxiety symptoms; and (*iii*) cortical thinning contributed to those symptoms in both the high- and low-risk groups, not only in the subjects with the greatest familial risk for depression. Note that the participants who were at low familial risk as defined in this study were not necessarily at zero familial risk, because persons who had prior histories of MDD had married into the cohort, thereby undoubtedly adding some degree of familial risk to our low-risk cohort. Nevertheless, when we defined "high risk" as any person with a parental history of MDD, even if that parent had married into the cohort, the

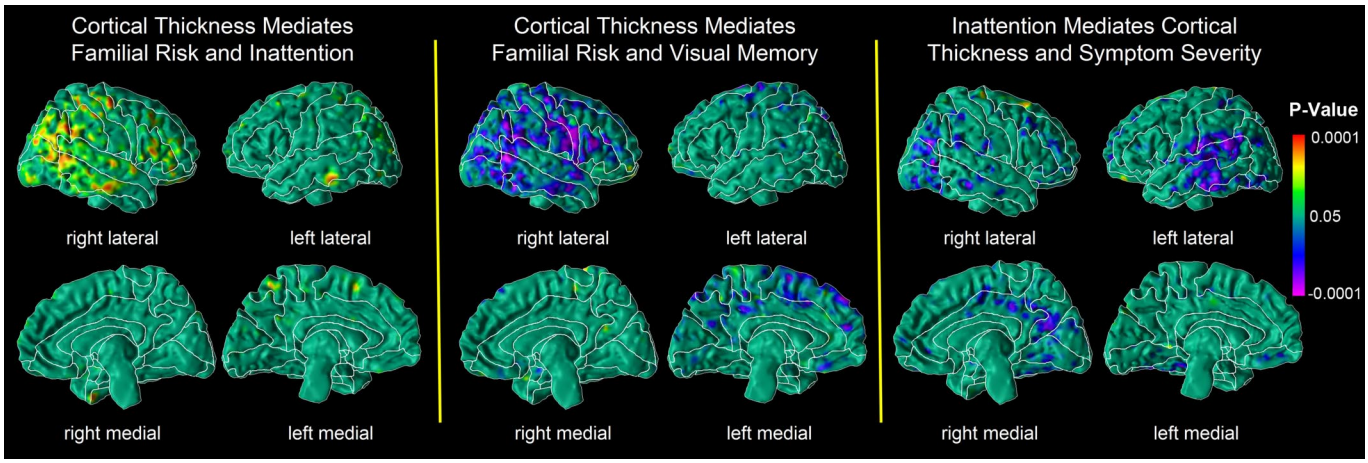

Fig. 4. Mediator analyses. (*Left*) P-values are plotted for regression models that test whether cortical thickness mediates the association of familial risk with measures of inattention. Significant mediator effects were detected throughout the right hemisphere, particularly its posterior portions (n =117). (*Middle*) P-values are plotted for regression models that test whether cortical thickness mediates the association of familial risk with measures of visual memory. Significant mediator effects were detected throughout the right hemisphere (n = 119). (*Right*) P-values are plotted for regression models that test whether inattention mediates the association of cortical thickness with the severity of anxiety symptoms. Significant mediator effects were detected in the mid-temporal and inferior parietal cortices of the left hemisphere as well as in the posterior right hemisphere (n = 133). Similar results were obtained for mediator analyses with depressive symptoms as the dependent variable (SI). Because these analyses were intended to confirm the hypothesized mediating effects in post hoc analyses, the p-values are not corrected for multiple statistical comparisons (n =113).

findings were unchanged from those reported here, in which we defined high and low risk on the basis of biological descent from G1 (data not shown).

The spatial patterns for the correlations of cortical thickness with measures of inattention and visual memory and their similarity to the pattern of cortical thinning in individuals in the high-risk group provide clues to the possible mechanisms through which cortical thinning of the right hemisphere may predispose an individual to depressive illness. The right hemisphere long has been thought to subserve certain forms of attention, arousal, and vigilance (17). A prior study of startle amplitude in a subset of persons in G2 and G3 of this cohort reported an exaggerated startle response in the high-risk group compared with the low-risk group (26), suggesting that exaggerated phasic arousal in these individuals in response to abrupt, startling stimuli may be linked to these right-hemisphere abnormalities (27) and may have contributed to the disturbances in attention that these participants reported. This interpretation is consistent with a recent magnetoencephalography report of reduced activity over the right temporoparietal cortex in depressed persons relative to controls during the viewing of emotionally arousing pictures, indicating that depressed individuals have difficulty activating cortices that subserve the arousal dimension of emotion (16). Furthermore, this putative arousal and vigilance system is thought to support the perception of social and emotional cues from the environment in both the visual and verbal domains, because many psychological and lesion studies in humans and nonhuman primates have suggested that the right hemisphere is dominant for the processing and recall (28) of emotional faces (29), emotion-denoting words (30, 31), emotional information embedded within linguistic prosody (32), and emotional meaning (31, 33). These functions are thought to place an individual in an emotional space within an interpersonal world (34), and disturbances in arousal and attention may predispose an individual to developing emotional disturbances within that interpersonal world.

This interpretation of the functional consequences of cortical thinning in the right hemisphere is consistent with the nature of the stimuli that were used to assess visual memory, i.e., faces and family pictures, stimuli that are fundamentally both social and emotional. Excessive thinning of right hemisphere cortices in the high-risk group probably contributed to impairments in the processing of these social and emotional stimuli, perhaps because of the impaired functioning of attention and arousal systems based within the right hemisphere. Impaired processing of social and emotional stimuli in the environment in turn probably predisposes these individuals to the development of affective illness.

Mediator analyses suggested that right hemisphere cortical thinning mediates the association of familial risk with inattention and visual memory problems, and that inattention in turn mediates the association of cortical thinning with the severity of MDD and anxiety symptoms (Fig. 5). Although the mediating effects of inattention were present in the posterior portion of the right hemisphere, they were most prominent in the temporal and inferior parietal cortices of the left hemisphere, in mirror-image locations of the regions associated with familial risk in the right hemisphere. These various mediator effects did not change when covarying for risk status in the mediator analysis (not shown), indicating that statistical significance was not driven simply by inclusion of the 2 risk groups and their associations with each of the dependent and mediator variables. We calculated the magnitude of the mediator effects at each point of the cortical surface and found that for points where p-values were < 0.005, the mediators consistently accounted for $> 40\%$ of the total effects of the associations that those variables mediated (SI).

Taken together, these analyses suggest that, although cortical thinning in the right hemisphere mediates the association of familial risk for MDD with inattention and impaired visual memory, inattention mediates the relationship between cortical thinning and the severity of MDD and anxiety symptoms most prominently when

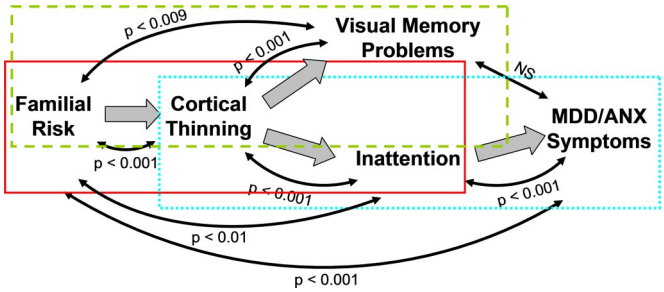

Fig. 5. Model of pathogenesis. Line arrows and adjacent p-values indicate significant bivariate associations. The correlation analyses that generated the p-values are described in the text, except for those involving cortical thickness, which are depicted in the statistical maps of Fig. 1. Block arrows indicate the directions of hypothesized causal influence within mediating pathways. The solid red box encloses the statistically significant mediator analysis in which cortical thinning mediates the associations of familial risk with measures of inattention. The dashed green box encloses the statistically significant mediator analysis in which cortical thinning mediates the associations of familial risk with measures of visual memory. The dotted blue box encloses the statistically significant mediator analysis in which inattention mediates the association of cortical thinning with the symptoms of MMD or anxiety. A familial risk for MDD produces cortical thinning of the right hemisphere. Cortical thinning in turn disrupts attention and arousal processes, as well as visual memory for social stimuli. These disruptions in turn increase the risk for developing MDD. ANX, anxiety disorder; MDD, major depressive disorder; NS, not significant.

cortical thinning also is present in analogous portions of the left hemisphere. We note that cortices in these portions of the left hemisphere were indeed thinner on average in the high-risk group than in the low-risk group (SI), but the thinning was not nearly as great as in the right hemisphere and, in fact, did not reach the level of statistical significance (Fig. 1). Furthermore, these findings suggest that cortical thinning of the right hemisphere in persons who are at increased familial risk for depression may produce inattention and visual memory problems even in the absence of MDD or anxiety. Additional thinning of the corresponding cortical regions in the left hemisphere contributes further to inattentiveness and, in fact, is required to produce the symptoms of MDD or anxiety in persons at either high or low familial risk for depression. The possibilities that familial risk predisposes an individual to MDD and anxiety by virtue of the presence of cortical thinning of the right hemisphere as a trait vulnerability and that additional thinning in the cortex of the left hemisphere is required to manifest symptoms are supported by our findings that thinning in the posterior cortices of both hemispheres, but particularly the left hemisphere, correlated with current symptom severity (Fig. 2).

Differences in cortical thickness between the high- and low-risk groups in regions other than the lateral aspect of the right hemisphere warrant comment. For example, we detected prominent cortical thinning of the mesial wall in the left hemisphere. Although we are uncertain of the functional consequences of these findings, we note that cortical thicknesses here generally followed the same pattern of correlation with measures of inattention and visual memory as did cortical thickness in the lateral aspect of the right hemisphere (Fig. 3), suggesting that all these cortical regions may contribute to attention and visual memory processes. Weighing somewhat against this interpretation, however, is that the mediator analyses indicated that the cortices of the left mesial wall did not significantly mediate the relationship of familial risk with measures of inattention or visual memory (Fig. 4). The mesial wall of the cerebral surface does, nevertheless, contain several regions that contribute to emotional processing, including the mesial prefrontal cortex that helps regulate emotions (35), the medial orbitofrontal cortex that participates in the processing of reward and other hedonic qualities of learned experience (36), and the ventral anterior and posterior cingulate cortices, which may contribute to

the emotional qualities of free associative thought (37). Finally, our findings of right-hemisphere thickening and left-hemisphere thinning of the subgenual cingulate cortex are consistent with variable reports of abnormal metabolism (38), gray matter volume (38, 39), and glial cell reductions (40) in this region in adults who have familial MDD. These portions of the cingulate and mesial prefrontal cortices are important components of the limbic system, and they are intimately connected to other limbic structures, such as the amygdala, hypothalamus, brainstem autonomic nuclei, and dorsal prefrontal cortex, regions that are of central importance in the processing of emotions and probably are mediators of the neurovegetative, somatic, and cognitive symptoms of MDD.

Whether these findings will generalize to all forms of familial depression is unknown. MDD is a heterogeneous illness, with multiple genetic and environmental determinants. Certainly, studying multiple offspring of a limited number of probands in G1 enhanced our ability to detect the neurobiological correlates of some forms of familial MDD. Nevertheless, these participants were offspring from numerous families, and the MDD to which they were prone undoubtedly was heterogeneous across families. Therefore, the prominent abnormalities in cortical thickness that we observed despite this heterogeneity of causes suggests that the thinning probably represents a common final pathway that mediates the effects of multiple genetic and epigenetic influences on the risk for developing MDD.

Materials and Methods

We scanned 131 individuals, ages 6 to 54 years, who were descended from a total of 58 distinct families from G1. The high-risk group contained 66 individuals (comprising 12 children, defined as persons younger than 18 years of age, and 54 adults), and the low-risk group contained 65 individuals (31 children, 34 adults). The diagnostic interviews across all waves (1) were conducted using a semistructured diagnostic instrument (the Schedule for Affective Disorders and Schizophrenia–Lifetime Version for adults, and a child version of the instrument that was modified for the *Diagnostic and Statistical Manual of Mental Disorders*, edition 4 (41) for participants 6 to 17 years of age) (42). Assessments at the time of scan also included measures of inattention, hyperactivity, and impulsivity using the DuPaul-Barkeley Attention Deficit Hyperactivity Disorder rating scale (43); measures of immediate and delayed memory functioning using the Wechsler Memory Scales for adults or the Children's Memory Scales for participants younger than 18 years of age (44, 45); the Children's Depression Rating Scale-Revised (46) or the Hamilton Depression Rating Scale (14) to measure depressive symptoms in children or adults, respectively; and the Revised Children's Manifest Anxiety Scale (47) or Hamilton Anxiety Rating Scale (15) to measure anxiety symptoms in children and adults, respectively. We constructed an index of the severity of either depressive or anxiety symptoms across children and adults for use in correlation analyses by converting the respective measure in each age group into a z score for each participant, and those z scores then were combined across age groups into a single variable for each symptom domain, either ''z-depression,'' ''z-anxiety,'' or ''z-depresssion/anxiety'' (the sum of z-depression and z-anxiety scores across all participants).

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