Structural Brain Differences in Individuals with Bipolar Disorder: A Developmental Perspective

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Abstract

Background: While the existence of bipolar disorder in early adolescence is becoming more widely accepted, the degree of manifestation in childhood is still unclear. This thesis summarizes findings on neurostructural correlates of adult bipolar disorder compared to more limited research on pediatric bipolar disorder. Then we examined the relationship between mania symptoms and brain structure in a large sample of children.

Methods: We analyzed data from 10,699 9-to-10-year-old children from the Adolescent Brain Cognitive Development (ABCD) Study. We employed structural equation modeling to examine the associations between subsyndromal mania symptoms and cortical grey matter volume and thickness in 68 regions.

Results: After correction for multiple comparisons and controlling for age, sex, race/ethnicity, and scanner model, we found that mania was associated with smaller brain volumes in 54 cortical regions (p_{fdr}-values $\leq .048$). However, none of these effects survived sensitivity analyses that accounted for socioeconomic status, medication use, in-scanner motion, or total intracranial volume (p_{fdr}-values $\geq .299$). There were no significant associations between mania and cortical thickness in any region (p_{fdr}-values $\geq .249$).

Conclusions: Prior studies have identified structural differences in individuals with bipolar disorder, which is supported by the current study's results in children. However, these results do not survive when controlling for additional covariates, possibly due to the young age of the current sample. Future studies should associate subsyndromal mania with cortical volume and thickness longitudinally to refine our understanding of the emergence of structural changes during the prodromal stage, which could be leveraged for improved identification and intervention.

Structural Brain Differences in Individuals with Bipolar Disorder: A Developmental Perspective

Bipolar disorder is a severe psychiatric condition characterized by cycles of manic and depressive episodes. Unlike other psychiatric disorders, the symptoms of bipolar disorder episodically fluctuate between mania and depression (Muneer, 2016). The DSM-5, the current edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, defines a manic episode as "a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy" (American Psychiatric Association, 2013, p. 124). In contrast, a major depressive episode is marked by low mood and/or decreased interest in activities, changes in appetite, trouble sleeping, psychomotor slowing or agitation, loss of energy, feelings of worthlessness, concentration problems, and/or suicidal ideation (American Psychiatric Association, 2013). However, there is substantial heterogeneity, or different symptom presentations, within bipolar disorder.

For example, after listing seven symptoms below the descriptive statement of a manic episode, it is stated that "three (or more) of the following symptoms (four if the mood is only irritable) [must be] present to a significant degree and represent a noticeable change from usual behavior" (American Psychiatric Association, 2013, p. 124), suggesting many different symptom combinations can result in a manic episode. The DSM-5 diagnostic criteria are based on presenting symptoms, which are continually being updated, and the number of symptoms that must be met to receive a diagnosis was subjectively determined (Harrison et al., 2018). Furthermore, different diagnoses overlap substantially in symptoms and are primarily

differentiated by severity and time of onset (Charney et al., 2020). These issues further contribute to the heterogeneity in clinical presentations (Hanford et al., 2016).

All individuals with bipolar disorder are disadvantaged by the challenges of accurately diagnosing this condition, but these difficulties disproportionately affect children and adolescents. A majority of cases first manifest as a depressive episode, which most often occurs during adolescence. However, on average, individuals with bipolar disorder are not accurately diagnosed and treated until ten years after they first sought out mental health services (Van Meter et al., 2021). In addition to delaying relief of symptoms, the large gap between initial symptom presentation and identification could result in misdiagnosis of the first depressive episode as indicative of major depressive disorder (MDD). This is particularly harmful because antidepressants, when taken without a mood stabilizing drug, accelerate and may even induce mania in individuals with bipolar disorder (Lan et al., 2014).

Unfortunately, misdiagnosis is common because the clinical course and combination of symptoms and comorbidities that present in an individual with bipolar disorder vary greatly from patient to patient and are particularly individualistic in areas that reflect impaired cognitive domains (Charney et al., 2020; Chen et al., 2021; Goldstein et al., 2017; Hibar et al., 2018). To address the problem that these individualistic presentations pose to identification and treatment, we look to potential commonalities in the underlying neurobiology of individuals with bipolar disorder. In this literature review, structural evidence for the degenerative effects of bipolar disorder will be explored and ultimately these findings will be extended from the adult literature to early-stage or prodromal children.

Neural structure

Comparing the brains of adults diagnosed with bipolar disorder to the brains of healthy control subjects, there are apparent differences in many areas: prefrontal-limbic networks, amygdala activity, cell pathology, neurochemical transmission, circadian dysregulation, immune and inflammatory responses, neuroplasticity and neurotrophin signaling, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis stress-response system, and intracellular signaling cascades, to name a few (Maletic & Raison, 2014). This review will begin by focusing on the structural elements found in previous research on adults with bipolar disorder. Structural magnetic resonance imaging (MRI) investigations of grey matter reveal perhaps the most salient and heritable structural differences between adults with bipolar disorder and healthy controls (Hanford et al., 2016). In a broad sense, grey matter is simply a collection of neuronal cell bodies (Bear et al., 2016). Cortical grey matter refers to the material between the pia mater, the thin membrane at the surface of the brain that is permeated by many blood vessels, and the grey matter-white matter border deeper in the brain. This grey matter can be measured in terms of cortical thickness, cortical surface area, or cortical volume which is the product of the two (Hanford et al., 2016). The current study will concentrate on cortical thickness and cortical volume of grey matter as these are the most widely studied measures in the bipolar disorder literature.

Bipolar disorder is a progressive disorder in the sense that the incidence of episodes results in increased frequency and severity of subsequent episodes (Maletic & Raison, 2014). We also see increased suicidal risk and further cognitive and functional impairment as the disorder progresses, which is supported by the growing evidence of neurotoxicity associated with these episodes (Lan et al., 2014; Maletic & Raison, 2014; Muneer, 2016). Both manic and major depressive episodes result in damaged neurons and glial elements in the brain (Muneer, 2016;

Chen et al., 2021). This damage is suspected to be a result of the inflammation that occurs with both types of mood episodes (Muneer, 2016). We can also see these changes on a larger structural scale as studies showing changes in cortical thickness can reflect instances of neurotoxicity and degeneration (Lan et al., 2014). When we compare structural differences in the brains of healthy adults to those diagnosed with bipolar disorder, we start filling in some conceptual gaps that remain in the field, such as how symptoms and structure are related.

Existing literature reports thinner cortices and smaller cortical volumes in individuals with bipolar disorder relative to healthy controls in several lobes, but many of the most consistent and widespread findings are regions located in the frontal lobe due to its connections to emotional responses (K. Lim et al., 1999). The regions that are of particular interest for this review are those that were identified in multiple studies in the literature. These include the caudal middle frontal, medial orbitofrontal, and anterior and posterior cingulate cortex regions. Deficits in the caudal middle frontal region have been linked to challenges with working memory tasks and skills like spatial attention (Abé et al., 2016; Lan et al., 2014). The medial orbitofrontal has many connections with the limbic system and is particularly involved in making behavioral choices (Abé et al., 2016; Maller et al., 2014). The cingulate gyrus, including the anterior cingulate cortex (ACC) and the posterior cingulate cortex (PCC), modulates mood and has been linked to symptoms of depression (Abé et al., 2016; Toma et al., 2019). Therefore, thinner cortices and smaller volumes in the ACC and PCC may be associated with deficits in emotion regulation (Abé et al., 2016; Hanford et al., 2016; Kaur et al., 2005; Lan et al., 2014). In some cases, patients with bipolar disorder display larger volume of the ACC relative to healthy controls, which has been tied to the effects of antipsychotic drugs (Hanford et al., 2016). This is consistent with existing theories that structural changes in the ACC may be an early indicator of

susceptibility to psychosis and other emotional regulation issues that may merit prescription of antipsychotics (Maletic & Raison, 2014).

The temporal lobe also contains structural differences present across multiple studies, particular in its superior, middle, and inferior (including the fusiform gyrus) regions. Although several studies found that thinner cortices were widespread across the temporal lobes, the left superior temporal gyrus is a highly specialized region and therefore thinner cortices in this area are of particular interest (Abé et al., 2016; Hanford et al., 2016; Maller et al., 2014). This area houses Wernicke's area, key for processing language, and thus thinner cortices in this region have been associated with auditory hallucinations such as hearing voices, difficulty perceiving others' facial expressions, and other complications that arise with the psychotic-like symptoms of manic episodes (Hanford et al., 2016). The middle and inferior temporal gyrus coordinates visual processing, including the fusiform gyrus which specializes in facial recognition (Abé et al., 2016; Hanford et al., 2016; Hibar et al., 2018). There were also some regions of the parietal and occipital lobes that were reported to show thinner cortices in individuals with bipolar disorder, although these findings were less consistent across the literature (Abé et al., 2016; Hibar et al., 2018; Lan et al., 2014). In some cases, regions where thinner cortices were identified also displayed smaller cortical volumes, but several studies, including those reported in summary papers, determined there were no significant findings for cortical volume (Frazier, Ahn, et al., 2005; Hibar et al., 2018; Rimol et al., 2012).

Bipolar I and bipolar II

The DSM-5 recognizes two types of bipolar disorder: bipolar I and bipolar II. The major difference between the two types is that bipolar II disorder is characterized by hypomanic rather than manic episodes (Abé et al., 2016). The symptoms of hypomania mirror those of mania, but

hypomanic symptoms are generally considered less severe, and the episode only needs to last four consecutive days instead of the week required for bipolar I. It is also important that "the episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic" (American Psychiatric Association, 2013, p. 133). While bipolar I manic episodes may include psychotic symptoms, not everyone experiences these symptoms and thus they are not necessary to receive a diagnosis of bipolar I. Also, bipolar II disorder is characterized by more frequent and longer depressive episodes than bipolar I disorder and is associated with more comorbid conditions (Abé et al., 2016).

Due to the distinctions in symptom presentation, we can reasonably expect that there would be a neurobiological difference found between the two conditions (Abé et al., 2016). In one study, patients with bipolar I disorder displayed thinner cortices relative to patients with bipolar II in the right medial orbitofrontal and left superior temporal areas (Maller et al., 2014). The right medial orbitofrontal region, as previously mentioned, is concerned with behavioral decision-making in unpredictable situations. The superior temporal cortex, which was also identified earlier, is involved in more social matters such as perceiving and processing others' emotions (Maller et al., 2014). Another study identified significantly thinner cortices in individuals with bipolar I disorder in the right dorsomedial prefrontal cortex (dmPFC) and right anterior cingulate cortex (ACC), both of which are associated with emotion dysregulation and executive functioning challenges, and in the right temporal lobe, which is associated with learning and remembering (Abé et al., 2016). This draws a clear direct parallel with previous results of individuals with bipolar I struggling with memory tasks more so than individuals with bipolar II (Abé et al., 2016.) Overall, bipolar I and bipolar II presented similar differences

regionally when compared to healthy controls but the thinner cortices in bipolar I were more widespread and in bipolar II these effects were more specific (Abé et al., 2016).

Structural distinction from major depressive disorder and schizophrenia

Despite sharing many symptoms in common with MDD, bipolar disorder shows unique structural differences. Structural MRIs comparing bipolar disorder patients, MDD patients, and healthy controls found six regions that were significantly thinner in bipolar disorder patients than healthy controls: left inferior parietal, right caudal middle frontal, left superior parietal, right posterior cingulate, right inferior parietal, and right supramarginal regions (Lan et al., 2014). Three of those regions were unique to bipolar disorder, showing thinner cortices relative to MDD: right caudal middle frontal, left inferior parietal, and right precuneus regions (linked with posterior cingulate) (Lan et al., 2014). The strongest and most significant result unique to bipolar disorder was thinner cortices in the right dorsolateral frontal region (including caudal middle frontal) which is tied to executive functioning skills (Chen et al., 2021; Lan et al., 2014). Deficits in executive functioning are a common characteristic of bipolar disorder; thus, finding a neurobiological foundation for this deficit is a significant step to better understanding the origins of the disorder (Maletic & Raison, 2014; Lan et al., 2014; Abé et al., 2016). Below the cortex, bipolar disorder showed smaller volumes that were not mirrored in MDD in the hippocampus and basal ganglia (Maletic & Raison, 2014).

Similarly, individuals with bipolar I that experience psychotic symptoms during mania have symptomatic and functional overlap with individuals with schizophrenia. Differences in structure are often mirrored by deficits in function, so it is no surprise that we see some shared patterns in the regions that show thinner cortices (K. Lim et al., 1999). Both individuals with bipolar disorder and individuals with schizophrenia show thinner cortices relative to healthy

controls in parahippocampal and orbitofrontal regions (Hanford et al., 2016). However, there are also areas that are distinct, such as smaller cortical volumes in patients with schizophrenia in the medial temporal gyrus, inferior temporal gyrus, and fusiform gyrus relative to patients with bipolar disorder, all of which are associated with deficits in facial and object recognition and memory (Rimol et al., 2012). Thus far, this review of the literature reveals a number of key structural regions that are implicated in bipolar disorder. However, studies that focus on adults only may be missing a critical period in the development of bipolar symptoms.

Pediatric bipolar disorder

There are advantages to studying bipolar disorder in children beyond the obvious implications of developing better treatment and interventions. Children who have not yet received a diagnosis will not have the confounding effects of pharmacological treatments, the neurotoxic effects of long-term illness, and the multiple mood episodes commonly found in studies of adults (Frazier, Ahn, et al., 2005). This early period in childhood is called the prodromal stage where subsyndromal symptoms are present. The term subsyndromal refers to the presentation of symptoms that are relevant to a diagnosis but do not meet the threshold for receiving that diagnosis. Subsyndromal symptoms are certainly present for mania in bipolar disorder. About 76% of individuals with bipolar disorder show clinically significant subsyndromal manic symptoms during a depressive episode (Judd et al., 2012).

Children who are genetically at risk for developing bipolar disorder may demonstrate subsyndromal deficits in verbal declarative memory, selective and sustained attention, and working memory. The two most common symptoms are irritability and psychomotor agitation such as pacing or fidgeting. However, it is difficult to identify subsyndromal symptoms without a proper measure. Children’s subsyndromal symptoms are primarily driven by irritability and

psychomotor agitation more so than distinct mood episodes (Frazier, Ahn, et al., 2005; Judd et al., 2012). Subsyndromal manic symptoms can be present for several months prior to the first full-blown episode which has important implications for early identification and intervention (Salzar de Pablo et al., 2020; Correll et al., 2014).

Existing literature on structural abnormalities in children with early-onset bipolar disorder is limited but the findings thus far have been promising. While the majority of studies have found significant relationships between bipolar disorder and primarily cortical thickness in adults, pediatric studies have found almost exclusively significant differences in cortical volume. This could indicate that when this disorder manifests in childhood or early adolescence, the symptoms and morbidity tend to be more severe. The primary findings of thinner cortices in adults with bipolar disorder are paralleled in similar regions with smaller cortical volumes in children and adolescents: caudal middle frontal, lateral orbitofrontal, anterior and posterior cingulate cortex, and superior temporal (including the fusiform gyrus) cortical regions (Frazier, Ahn, et al., 2005; Frazier, Breeze, et al., 2005; Gogtay et al., 2007; C. Lim et al., 2013; Roberts et al., 2022; Toma et al., 2019). Additionally, smaller volume was found the accumbens, amygdala, and frontal pole regions although these were not replicated across many studies (Dickstein et al., 2005; Gogtay et al., 2017; Roberts et al., 2022). On a larger scale of global volume differences, children with bipolar disorder have smaller total cerebral volume or smaller brains (Frazier, Ahn, et al., 2005). The finding of smaller global brain volume is most likely indicative of neurodevelopmental problems associated with the disorder (Frazier, Ahn, et al., 2005). This may be attributed to the fact that early-onset bipolar disorder is generally more severe and impacts more domains of cognitive functioning (Salzar de Pablo et al., 2020; Toma et al., 2019).

Most studies of children and early adolescents demonstrated no differences in cortical thickness relative to healthy controls, but one study by Toma and colleagues (2019) did find cortical thickness differences when comparing children and adolescents diagnosed with bipolar I and bipolar II. The authors found that individuals with an early diagnosis of bipolar I disorder had additional deficits in temporal regions relative to individuals with bipolar II disorder (Toma et al., 2019). Also, individuals suspected to have bipolar II disorder had thinner cortices than those with bipolar I disorder in regions relevant to depressive symptoms, which is consistent with the greater amount of time individuals with bipolar II disorder spend in depressive episodes (Toma et al., 2019). Otherwise, the two subtypes demonstrated large overlap (Toma et al., 2019). Taken together, this literature review demonstrates that while structural differences are apparent in adults with bipolar disorder, fewer studies have examined these associations in pediatric samples. Thus, this thesis aims to fill this gap by examining structural differences in a large sample of children with prodromal mania symptoms.

The current study aims to examine differences in cortical thickness and volume associated with a dimensional measure of subsyndromal mania in children. Much of the previous literature on the association between bipolar disorder and cortical thickness and volume has focused on adult populations. The limited research on cortical differences in children so far has included a pediatric or adolescent sample that had already received a bipolar disorder diagnosis (Dickstein et al., 2005; Gogtay et al., 2017; Frazier, Breeze, et al., 2005; Kaur et al., 2005; Toma et al., 2019). This is a limitation because subthreshold manic symptoms are present for a lengthy prodrome prior to the first manic episode (Correll et al., 2014; Van Meter et al., 2021), which suggests that early stage/prodromal intervention may be possible (Judd et al., 2012; Goldstein et al., 2017). Furthermore, the included studies of structural differences in children had sample

sizes of 50 or smaller with age ranges of 10 years or greater. We propose to advance this research by relating cortical thickness and volume to a continuous measure of subsyndromal mania in the largest community sample of children to date (N = 11,876), where the majority of these children have not yet received their first bipolar diagnosis. By using a sample with a young age range (9-10 years old), we can better capture the critical prodromal period, which has been overlooked in most studies. We hypothesize that children with higher subsyndromal mania scores will display smaller volumes in regions implicated by prior work: caudal middle frontal, orbitofrontal, anterior and posterior cingulate, and temporal regions. Based on the lack of findings showing cortical thickness differences in youth, our analyses of cortical thickness were exploratory.

Method

Participants

The present study used data from the latest release (4.0) of the Adolescent Brain Cognitive Development (ABCD) Study. The ABCD Study is the largest longitudinal study of children to date designed to follow the environmental, genetic, neurobiological, and behavioral correlates of children for at least ten years (Barch et al., 2018). The ABCD Study includes assessment measures that attempt to predict future mental health problems. Participants were 11,876 children ages 9-10 years who completed numerous assessments evaluating physical, cognitive, and academic functioning and underwent neuroimaging and biospecimen collection at 21 sites across the United States. Participants will be continually assessed biannually until ages 19-20 years. To obtain a sample as representative of the general population as possible, the principal investigators partnered with private, public, and charter schools to invite families to participate. Data was securely stored separate from identifying information for the privacy of the

participants. Recruitment occurred in a staggered fashion over two years. Parental consent and children's assent were obtained by the researchers. Participants and their parents were compensated for their time in the study. Of the 11,876 participants, we excluded individuals for missing data, abnormal structural images, or failure to meet quality assurance for the MRI measures, leaving us with 10,699 participants for analyses. A summary of demographics based on the final sample can be found in Table 1. The sample was fairly balanced between males and females and was predominantly non-Hispanic White. Household income demonstrated a skewed distribution with about two-thirds of the sample earning above $50,000 annually and the majority of participants had parents with a Bachelor's degree or higher. Vanderbilt University's Institutional Review Board approved the use of this publicly available, de-identified dataset.

Materials

Subsyndromal mania measure

Among the battery of mental health assessments in the ABCD Study, the measure for subsyndromal mania is of particular interest because children are unlikely to have received their first bipolar disorder diagnosis at this age. The Parent General Behavior Inventory – 10-Item Mania scale (PGBI-10M) was developed from the 73-item Parent General Behavior Inventory (PGBI) and highlights the 10 best items to discriminate subsyndromal bipolar disorder, reflecting manic and biphasic (mixed state including aspects of both mania and depression) symptoms, from frequent comorbid conditions such as unipolar depression and attention-deficit/hyperactivity disorder (ADHD) (Barch et al., 2018; Youngstrom et al., 2008). This measure annually screens children for pediatric bipolar disorder symptoms based on their parents' assessment of their child's behavior. The items included also allow for deviation from the classic DSM-5 diagnostic criteria for bipolar disorder and assess mixed symptoms in addition

to characteristics of traditional mood episodes (Freeman et al., 2012). The ten-item form has been shown to effectively identify bipolar disorder uniquely from closely related disorders like unipolar depression and ADHD (Youngstrom et al., 2008).

Image acquisition, quality assurance, and processing

The ABCD Study collected MRI scans from 21 sites across the country. The data were collected every two years on multiple models of 3 tesla (3T) scanners: General Electric Discovery MR750, Siemens Prisma, Siemens Prisma Fit, Phillips Achieva dStream, and Philips Ingenia. One challenge of scanning children is their propensity to move, therefore, the study used real-time motion correction. The images were processed using brain segmentation and cortical surface reconstruction (Hagler et al., 2019). The images are aligned to a reference brain to standardize the images and trained technicians evaluated the quality of the alignment. Resulting data is parcellated into specific regions of interest (Hagler et al., 2019). For the current study, structural MRI data (cortical volume and thickness) will be used to examine our hypotheses.

Data analysis

Basic descriptive information of the sample was obtained using R Studio. We tested our hypotheses using structural equation modeling in Mplus version 8.4. Cortical thickness and volume measures were related to a dimensional measure of subsyndromal mania symptoms while controlling for age, sex, race/ethnicity, and differences between MRI scanners. Age was included as a covariate based on studies showing our brain structure changes as we age (Frazier, Breeze, et al., 2005; Toma et al., 2019). The sex covariate addressed the fact that males and females have different brain sizes (Frazier, Breeze, et al., 2005; Toma et al., 2019). Race and ethnicity have been shown to be important covariates; we controlled for race/ethnicity based on previous work showing an association between race/ethnicity, SES, and the brain (Assari &

Boyce, 2021). Finally, there are differences between the scanners across the 21 sites in the study that need to be controlled for, thus, scanner model was included as an additional covariate.

The analyses also cluster based on family ID to account for the genetic material shared by twins and siblings in this dataset. Additionally, participants are nested within site, thus this was accounted for by stratifying based on site. The sample was also made as representative of the U.S. population as possible by applying post-stratification weights provided by the ABCD Study, which adjusted the sample to account for discrepancies between the sample and population on key demographics like race/ethnicity. Finally, non-participation weights were applied since those who were included in the final sample differ significantly from those who were excluded for missing data and poor-quality imaging on important demographics like age and sex (Durham et al., 2021). Weighting the data adjusted the sample to make the included and excluded samples more similar to each other. As mentioned previously, participants that were missing data on our key variables were excluded from analysis.

Structural equation modeling was used to examine the relationship between subsyndromal mania symptoms and cortical thickness and cortical volume, while controlling for covariates. Cortical thickness and volume analyses were performed with 68 cortical regions (34 in each hemisphere) based on the Desikan-Killiany atlas. The false discovery rate (FDR) was controlled to account for multiple comparisons. Each brain region was tested as follows:

$$\text{Region} = \beta \times \text{age} + \beta \times \text{sex} + \beta \times \text{race/ethnicity} + \beta \times \text{MRI scanner model} + \beta \times \text{mania}$$

Sensitivity analyses

To further investigate the robustness of the primary findings, family income, medication status, and in-scanner motion were added as additional covariates to control for possible associations between brain structure and SES, medication use, or movement-related effects.

Additionally, we ran a sensitivity analysis with total intracranial volume (TICV) as an additional covariate to account for global differences in cranium size.

Results

Subsyndromal mania is associated with differences in brain structure

Following FDR correction for multiple comparisons and controlling for age, sex, race/ethnicity, and differences in scanner model, cortical grey matter volume was found to be significantly inversely associated with mania scores in many brain regions. Specifically, higher subsyndromal mania scores were associated with smaller cortical volumes in the bilateral banks of superior temporal sulcus, left caudal anterior cingulate, bilateral caudal middle frontal, bilateral entorhinal, bilateral frontal pole, bilateral fusiform, bilateral inferior parietal, bilateral inferior temporal, bilateral insula, left isthmus cingulate, bilateral lateral occipital, bilateral lateral orbitofrontal, bilateral medial orbitofrontal, bilateral middle temporal, bilateral paracentral, bilateral parahippocampal, bilateral pars orbitalis, bilateral postcentral, bilateral posterior cingulate, bilateral precentral, bilateral precuneus, bilateral rostral anterior cingulate, bilateral rostral middle frontal, bilateral superior frontal, bilateral superior temporal, bilateral supramarginal, bilateral temporal pole, and bilateral transverse temporal regions (p_{fdr}-values $\leq$ .048) (Table 2). In terms of cortical thickness, no brain regions were significantly associated with the dimensional measure of subsyndromal mania after controlling for age, sex, race/ethnicity, and scanner model and after FDR-correction (p_{fdr}-values $\geq$ .249) (Table 3).

Structural changes may reflect the effects of confounding variables

Follow-up sensitivity analyses were performed with regional cortical volume and cortical thickness. In addition to the previous covariates mentioned, sensitivity analyses controlled for the additional covariates of socioeconomic status as measured by family income, medication status,

motion in the scanner, and total intracranial volume (TICV). While higher mania scores were associated with smaller cortical volumes in the main analyses, these effects did not survive the addition of the aforementioned covariates during sensitivity analyses. When these additional covariates were included, all significant effects disappeared (p_{fdr}-values $\geq .299$) (Table 4).

Discussion

The results of the current study, which explored associations between subsyndromal mania and brain structure in a large sample of children, demonstrated that the relationship between mania symptoms and structural differences may not be apparent in children age 9-10 years. Our main analyses showed that after controlling for age, sex, race/ethnicity, and scanner model and after correcting for multiple comparisons, greater mania symptoms were associated with smaller brain volumes in many regions, but no differences were apparent in cortical thickness. However, the volume results did not survive after adding additional covariates to account for SES, medication use, movement, and cranial size. To our knowledge, this is the largest study to date (over 10,000 participants) investigating associations between a dimensional measure of subsyndromal mania and cortical thickness and volume in children; thus, we had ample power to find significant associations, if they exist. This may suggest that the relationship between mania symptoms and structural differences may not appear until later in the course of the disorder. These results also suggest that the relationship between mania and brain structure may be due to potential confounds such as SES at this young age.

It is worthwhile to still consider the results of the main analyses even though they did not hold up to further sensitivity analysis testing. The primary findings are largely in line with the regions identified in previous studies. Based on existing work in the field, we anticipated there would be more significant results in cortical volume than cortical thickness for children, which

was supported by our results. There were 54 regions with significant results for cortical volume and no significant regions for cortical thickness. As we predicted, greater mania scores were associated with smaller cortical volumes in all 54 significant regions. The following areas previously mentioned in pediatric/adolescent studies were replicated in the main analyses: left rostral anterior cingulate cortex, right caudal middle frontal lobe, left fusiform, left and right lateral orbitofrontal cortex, left and right postcentral gyrus, left and right posterior cingulate cortex, and left superior temporal lobe (Maletic & Raison, 2014; Kaur et al., 2005; Frazier, Ahn, et al., 2005; Frazier, Breeze, et al., 2005). Furthermore, additional regions found in this study were cited in the adult literature as showing either smaller cortical volume or thinner cortices in individuals with bipolar disorder including the caudal anterior cingulate cortex, entorhinal cortex, inferior parietal lobe, inferior temporal lobe, medial orbitofrontal cortex, middle temporal lobe, parahippocampal gyrus, pars orbitalis, precuneus, rostral middle frontal lobe, superior frontal lobe, supramarginal gyrus, and temporal pole (Hanford et al., 2016; Lan et al., 2014; Abé et al., 2016; Maller et al., 2014). Thus, the regions found in the main analyses are consistent with those implicated in prior work.

However, as mentioned above, these effects do not survive when accounting for the additional covariates of income, medication status, motion in the scanner, and total intracranial volume. There are several reasons why the current study was not able to produce stable effects. First and foremost, it is most likely the case that the sample was too young. Our lack of consistent results could be interpreted to mean that relationships do exist but are not yet strong enough and may become apparent in a few years. This interpretation would be consistent with the average age of onset for bipolar disorder being 18 years to the mid-twenties, suggesting that our sample is too young to show enough symptoms to detect these differences (American

Psychiatric Association, 2013). Additionally, prior work in this area showing reliable differences between mania symptoms and brain structure were based on slightly older samples with all of the studies included in this literature review of children and adolescents having an older average age than the current study. Considering that the initial results of the current study replicate many prior studies, it seems likely that these effects may become significant in a few years' time.

Another possibility for the lack of consistent findings in our study is that more prevalent or severe mania would be needed to produce significant effects. All of the pediatric bipolar studies reviewed here analyzed children and adolescents that had already received a diagnosis of bipolar disorder. Because the ABCD Study is a community-based sample, there are many children in this sample with no manic symptoms. While the methods used in our study were a strength, in that a dimensional measure of subsyndromal mania allowed us to more accurately assess the presence of structural deficits during the prodrome, the use of a sample with fewer manic symptoms than a clinical sample may have made associations more difficult to find. The average mania score for this population was 6.6 (*SD* = 8.86; Table 1). According to the likelihood ratios chart produced by a study that tested the validity of this measure, this score fits into the "low to neutral" (5.0-9.9) likelihood range for risk for bipolar disorder (Youngstrom et al., 2008). However, despite the use of a community sample with fewer mania symptoms present, our sample was large (over 10,000), which is large enough to detect differences, even if small. Additionally, the standard deviation for this measure was larger than the mean, suggesting we had ample variability to test our hypotheses. Therefore, our lack of stable results cannot be wholly attributed to using a community sample with fewer symptoms on average, as this sample still has a large number of children with mania symptoms at clinical levels, which is more than most prior studies.

A final possibility is that the relationship between mania symptoms and structural differences is actually caused by some other variable. This is supported by the finding of significant results in our main analyses for many cortical volume regions, only to have these effects disappear when additional covariates are added. It is well established that individuals from low socioeconomic backgrounds are at increased risk of developing psychopathology (Brito & Noble, 2014). Furthermore, some neuroimaging studies have found evidence for a correlation between SES and changes in brain structure in areas responsible for executive control and emotion, both of which are impacted in bipolar disorder (Brito & Noble, 2014). Medication use may be a confound as well. Although evidence of brain structure effects resulting from the use of psychotropic medications is limited, some studies have shown that lithium is associated with increased grey matter density and/or volume (Hanford et al., 2016; Kaur et al., 2005; Lan et al., 2014; Toma et al., 2019). Children with manic symptoms are more likely to be using anti-psychotic or anti-depressant medications, as the samples in the majority of the reviewed pediatric studies included participants on the medications (Dickstein et al., 2005; Frazier, Ahn, et al., 2005; Frazier, Breeze, et al., 2005; Gogtay et al., 2007; Kaur et al., 2005; Kuang et al., 2022; Roberts et al., 2022; Toma et al., 2019). Additionally, movement in the scanner can impact the quality of MRI images and it is generally more challenging for children than for adults to keep their head completely still during the scan (Frazier, Ahn, et al., 2005; Hagler et al., 2019). A final confounding variable to consider is head size. As mentioned previously, some studies have found globally smaller brain volumes in youth with bipolar disorder, so head size could also impact the size of each volume region. To determine if there are causal effects related to any of these possible confounds, future work needs to test each covariate separately in longitudinal mediation models.

The current study has both strengths and limitations. The large sample size of the ABCD Study dataset provided more than adequate power to find even small effects, which mitigates concerns that our sample had less severe symptoms on average. Alternatively, if we had selected children with only the most severe symptoms, we would have artificially inflated our effect sizes. Furthermore, the narrow age range of the participants in this study reduced the confounding effects of the normative structural brain changes that occur over the course of development. Another strength was that this dataset is a community-based sample, unlike most of the reviewed literature based on clinical samples, which allowed us to capture the complete spectrum of mania symptoms, from no symptoms to many symptoms. Assessing the continuum of mania symptoms is more representative of how these symptoms appear in the general population. A limitation of the current study was the use of parent report only. Although a parent-report measure of subsyndromal mania was administered by the ABCD Study because it is likely more accurate than self-report from a 9- to 10-year-old, the potential for parents to report symptoms inaccurately in the absence of insights from subjective experience was a limitation of the current study.

In sum, while there were initially many cortical regions with significant volume differences when associated with subsyndromal mania that were consistent with the findings from prior research, after accounting for potential confounds like SES, the results became insignificant. In terms of other structural measures, due to the absence of any significant differences in cortical thickness, the primary findings of this study were not consistent with the majority of previous studies on cortical thickness in adults with bipolar disorder. However, our findings did support the limited existing literature on cortical thickness in children with bipolar disorder. The current study can be used as a stepping stone for advancement in the field as it

shows that the relationship between mania symptoms and structural differences is not particularly strong in 9- to 10-year-old children. Future work should map the relationship between mania symptoms and brain structure from 9 years and onward to determine when this association becomes stable. The findings of the current study could be considered as we work to continue to narrow in on structural areas that are characteristic of early-onset bipolar disorder and thus could be utilized as prodromal markers. For example, several studies agree that structural deficiencies in the ACC, with its ties to emotion regulation and abnormal neurodevelopment, may be a key indicator of early-stage bipolar disorder or vulnerability to psychosis (Maletic & Raison, 2014; Kaur et al., 2005; Frazier, Ahn, et al., 2005). Since the ABCD Study is a longitudinal study that will continue to collect symptom and brain data until these children reach young adulthood, future studies using this dataset could track the appearance of significant structural differences in the ACC, and the other regions listed in the main analysis results, as a means of working toward earlier identification, earlier intervention and treatment, and ultimately better outcomes for individuals with bipolar disorder.

References

Abé, C., Ekman, C. J., Sellgren, C., Petrovic, P., Ingvar, M., & Landén, M. (2016). Cortical thickness, volume and surface area in patients with bipolar disorder types I and II. *Journal of psychiatry & neuroscience : JPN*, *41*(4), 240–250. https://doi.org/10.1503/jpn.150093

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Barch, D. M., Albaugh, M. D., Avenevoli, S., Chang, L., Clark, D. B., Glantz, M. D., Hudziak, J. J., Jernigan, T. L., Tapert, S. F., Yurgelun-Todd, D., Alia-Klein, N., Potter, A. S., Paulus, M. P., Prouty, D., Zucker, R. A., & Sher, K. J. (2018). Demographic, physical and mental health assessments in the adolescent brain and cognitive development study: Rationale and description. *Developmental cognitive neuroscience*, *32*, 55–66. https://doi.org/10.1016/j.dcn.2017.10.010

Bear, M. F., Connors, B. W., & Paradiso, M. A. (2016). Neuroscience : exploring the brain / Mark F. Bear, Barry W. Connors, Michael A. Paradiso. (Fourth edition). Wolters Kluwer.

Brito, N. H., & Noble, K. G. (2014). Socioeconomic status and structural brain development. Frontiers in Neuroscience, 8, 276–276. https://doi.org/10.3389/fnins.2014.00276

Charney, A.W., Mullins, N., Park, Y.J. *et al.* (2020). On the diagnostic and neurobiological origins of bipolar disorder. *Transl Psychiatry* 10, 118. https://doi.org/10.1038/s41398-020-0796-8

Correll, C. U., Hauser, M., Penzner, J. B., Auther, A. M., Kafantaris, V., Saito, E., . . . Cornblatt, B. A. (2014). Type and duration of subsyndromal symptoms in youth with bipolar I

disorder prior to their first manic episode. *Bipolar Disorders, 16*(5), 478-492. https://doi.org/10.1111/bdi.12194

Dickstein, D. P., Milham, M. P., Nugent, A. C., Drevets, W. C., Charney, D. S., Pine, D. S., & Leibenluft, E. (2005). Frontotemporal Alterations in Pediatric Bipolar Disorder: Results of a Voxel-Based Morphometry Study. Archives of General Psychiatry, 62(7), 734–741. https://doi.org/10.1001/archpsyc.62.7.734

Durham, E. L., Jeong, H. J., Moore, T. M., Dupont, R. M., Cardenas-Iniguez, C., Cui, Z., Stone, F. E., Berman, M. G., Lahey, B. B., & Kaczkurkin, A. N. (2021). Association of gray matter volumes with general and specific dimensions of psychopathology in children. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *46*(7), 1333–1339. https://doi.org/10.1038/s41386-020-00952-w

Frazier, J. A., Ahn, M. S., DeJong, S., Bent, E. K., Breeze, J. L., & Giuliano, A. J. (2005). Magnetic resonance imaging studies in early-onset bipolar disorder: A critical review. *Harvard Review of Psychiatry, 13*(3), 125-140. https://doi.org/10.1080/10673220591003597

Frazier, J. A., Breeze, J. L., Makris, N., Giuliano, A. S., Herbert, M. R., Seidman, L., . . . Caviness, V. S. (2005). Cortical gray matter differences identified by structural magnetic resonance imaging in pediatric bipolar disorder. *Bipolar Disorders, 7*(6), 555-569. https://doi.org/10.1111/j.1399-5618.2005.00258.x

Freeman, A. J., Youngstrom, E. A., Frazier, T. W., Youngstrom, J. K., Demeter, C., & Findling, R. L. (2012). Portability of a screener for pediatric bipolar disorder to a diverse setting. *Psychological Assessment, 24*(2), 341-351. http://dx.doi.org/10.1037/a0025617

Goldstein, B. I., Birmaher, B., Carlson, G. A., DelBello, M. P., Findling, R. L., Fristad, M., Kowatch, R. A., Miklowitz, D. J., Nery, F. G., Perez-Algorta, G., Van Meter, A., Zeni, C. P., Correll, C. U., Kim, H. W., Wozniak, J., Chang, K. D., Hillegers, M., & Youngstrom, E. A. (2017). The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research. *Bipolar disorders*, *19*(7), 524–543. https://doi.org/10.1111/bdi.12556

Gogtay, N., Ordonez, A., Herman, D. H., Hayashi, K. M., Greenstein, D., Vaituzis, C., Lenane, M., Clasen, L., Sharp, W., Giedd, J. N., Jung, D., Nugent, T. F., 3rd, Toga, A. W., Leibenluft, E., Thompson, P. M., & Rapoport, J. L. (2007). Dynamic mapping of cortical development before and after the onset of pediatric bipolar illness. *Journal of child psychology and psychiatry, and allied disciplines*, *48*(9), 852–862. https://doi.org/10.1111/j.1469-7610.2007.01747.x

Hanford, L. C., Nazarov, A., Hall, G. B., & Sassi, R. B. (2016). Cortical thickness in bipolar disorder: a systematic review. *Bipolar disorders*, *18*(1), 4–18. https://doi.org/10.1111/bdi.12362

Harrison, P., Greddes, J., Turnbridge, E. (2018). The Emerging Neurobiology of Bipolar Disorder. *Trends in Neurosciences*, 41, 1. https://doi.org/10.1016/j.tins.2017.10.006

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Versace, A., Bilderbeck, A. C., Uhlmann, A., Krämer, B., Overs, B., Abé, C., Dima, D., Grotegerd, D., Sprooten, E., Bøen, E., Howells, F. M., Delvecchio, G., Temmingh, H., Starke, J., … Beard, L. M. (2018). Cortical abnormalities in bipolar disorder: an MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. Molecular Psychiatry, 23(4), 932–942. https://doi.org/10.1038/mp.2017.73

Judd, L. L., Schettler, P. J., Akiskal, H., Coryell, W., Fawcett, J., Fiedorowicz, J. G., . . . Keller, M. B. (2012). Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. *Journal of Affective Disorders*, *138*(3), 440-448. https://doi.org/10.1016/j.jad.2011.12.046

Kaur, S., Sassi, R. B., Axelson, D., Nicoletti, M., Brambilla, P., Monkul, E. S., Hatch, J. P., Keshavan, M. S., Ryan, N., Birmaher, B., & Soares, J. C. (2005). Cingulate Cortex Anatomical Abnormalities in Children and Adolescents With Bipolar Disorder. *The American Journal of Psychiatry*, *162*(9), 1637–1643. https://doi.org/10.1176/appi.ajp.162.9.1637

Lan, M. J., Chhetry, B. T., Oquendo, M. A., Sublette, M. E., Sullivan, G., Mann, J. J., & Parsey, R. V. (2014). Cortical thickness differences between bipolar depression and major depressive disorder. *Bipolar disorders*, *16*(4), 378–388. https://doi.org/10.1111/bdi.12175

Lim, C. S., Baldessarini, R. J., Vieta, E., Yucel, M., Bora, E., & Sim, K. (2013). Longitudinal neuroimaging and neuropsychological changes in bipolar disorder patients: Review of the evidence. *Neuroscience and Biobehavioral Reviews*, *37*(3), 418-435. https://doi.org/10.1016/j.neubiorev.2013.01.003

Lim, K. O., Rosenbloom, M. J., Faustman, W. O., Sullivan, E. V., & Pfefferbaum, A. (1999). Cortical gray matter deficit in patients with bipolar disorder. *Schizophrenia Research*, *40*(3), 219-227. http://dx.doi.org/10.1016/S0920-9964(99)00063-8

Maletic, V., & Raison, C. (2014). Integrated neurobiology of bipolar disorder. *Frontiers in psychiatry*, *5*, 98. https://doi.org/10.3389/fpsyt.2014.00098

Maller, J. J., Thaveenthiran, P., Thomson, R. H., McQueen, S., & Fitzgerald, P. B. (2014). Volumetric, cortical thickness and white matter integrity alterations in bipolar disorder type I and II. *Journal of Affective Disorders*, *169*, 118–127. https://doi.org/10.1016/j.jad.2014.08.016

Muneer A. (2016). The Neurobiology of Bipolar Disorder: An Integrated Approach. *Chonnam medical journal*, *52*(1), 18–37. https://doi.org/10.4068/cmj.2016.52.1.18

Roberts, G., Lenroot, R., Overs, B., Fullerton, J., Leung, V., Ridgway, K., . . . Mitchell, P. B. (2022). Accelerated cortical thinning and volume reduction over time in young people at high genetic risk for bipolar disorder. *Psychological Medicine, 52*(7), 1344-1355. https://doi.org/10.1017/S0033291720003153

Rimol, L. M., Nesvåg, R., Hagler, D. J., Jr., Bergmann, Ø., Fennema-Notestine, C., Hartberg, C. B., . . . Dale, A. M. (2012). Cortical volume, surface area, and thickness in schizophrenia and bipolar disorder. *Biological Psychiatry, 71*(6), 552-560. https://doi.org/10.1016/j.biopsych.2011.11.026

Salazar de Pablo, G., Guinart, D., Cornblatt, B. A., Auther, A. M., Carrión, R. E., Carbon, M., Jiménez-Fernández, S., Vernal, D. L., Walitza, S., Gerstenberg, M., Saba, R., Lo Cascio, N., Brandizzi, M., Arango, C., Moreno, C., Van Meter, A., & Correll, C. U. (2020). Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. Journal of Child and Adolescent Psychopharmacology, 30(4), 222–234. https://doi.org/10.1089/cap.2019.0138

Toma, S., Islam, A. H., Metcalfe, A. W. S., Mitchell, R. H. B., Fiksenbaum, L., MacIntosh, B. J., & Goldstein, B. I. (2019). Cortical volume and thickness across bipolar disorder subtypes

in adolescents: A preliminary study. *Journal of Child and Adolescent Psychopharmacology, 29*(2), 141-151. http://dx.doi.org/10.1089/cap.2017.0137

Van Meter, A., Correll, C. U., Ahmad, W., Dulin, M., & Saito, E. (2021). Symptoms and Characteristics of Youth Hospitalized for Depression: Subthreshold Manic Symptoms Can Help Differentiate Bipolar from Unipolar Depression. *Journal of child and adolescent psychopharmacology*, *31*(8), 545–552. https://doi.org/10.1089/cap.2021.0057

Youngstrom, E. A., Frazier, T. W., Demeter, C., Calabrese, J. R., & Findling, R. L. (2008). Developing a 10-item mania scale from the Parent General Behavior Inventory for children and adolescents. *The Journal of clinical psychiatry*, *69*(5), 831–839. https://doi.org/10.4088/jcp.v69n0517

Table 1

Demographics of the sample (N = 10,699)

	Mean	*SD*
Age (months)	119.07	7.50
PGBI-10M Score	6.60	8.86
	N	*%*
Gender		
Female	5,137	48.01
Male	5,562	51.99
Race-Ethnicity		
White	5,615	52.48
Hispanic	2,197	20.53
African American	1,551	14.50
Other	1,336	12.49
Household Annual Income		
< $5,000	354	3.31
$5,000-$11,999	376	3.51
$12,000-$15,999	254	2.37
$16,000-$24,999	465	4.35
$25,000-$34,999	584	5.46
$35,000-$49,999	827	7.73
$50,000-$74,999	1,350	12.62
$75,000-$99,999	1,445	13.51
$100,000-$199,999	3,006	28.10
≥ $200,000	1,134	10.60
Missing	904	8.45
Parental Education		
No degree	541	5.06
Highschool degree/GED	1,285	12.01
Some college	1,750	16.36
Associate's degree	1,387	12.96
Bachelor's degree	3,041	28.42
Master's degree	2,056	19.22
Professional/Doctoral degree	639	5.97

Table 2

Associations between subsyndromal mania and grey matter volume of 68 cortical regions

	β	p_{fdr}	R^2
Left banks of superior temporal sulcus	-0.031	**.008**	0.07
Left caudal anterior cingulate	-0.028	**.014**	0.04
Left caudal middle frontal	-0.024	**.035**	0.10
Left cuneus	0.002	.837	0.12
Left entorhinal	-0.027	**.014**	0.11
Left frontal pole	-0.031	**.008**	0.11
Left fusiform	-0.043	**<.001**	0.19
Left inferior parietal	-0.028	**.015**	0.10
Left inferior temporal	-0.029	**.008**	0.21
Left insula	-0.037	**<.001**	0.18
Left isthmus cingulate	-0.022	**.048**	0.14
Left lateral occipital	-0.034	**.003**	0.22
Left lateral orbitofrontal	-0.029	**.008**	0.19
Left lingual	-0.014	.219	0.11
Left medial orbitofrontal	-0.028	**.010**	0.23
Left middle temporal	-0.029	**.010**	0.19
Left paracentral	-0.032	**.008**	0.08
Left parahippocampal	-0.029	**.013**	0.05
Left pars opercularis	-0.007	.545	0.08
Left pars orbitalis	-0.029	**.014**	0.13
Left pars triangularis	-0.011	.351	0.08
Left pericalcarine	0.002	.895	0.04
Left postcentral	-0.030	**.008**	0.16
Left posterior cingulate	-0.040	**<.001**	0.10
Left precentral	-0.040	**<.001**	0.19
Left precuneus	-0.027	**.018**	0.19
Left rostral anterior cingulate	-0.029	**.013**	0.09
Left rostral middle frontal	-0.043	**<.001**	0.17
Left superior frontal	-0.048	**<.001**	0.17
Left superior parietal	-0.013	.244	0.15
Left superior temporal	-0.050	**<.001**	0.14
Left supramarginal	-0.042	**<.001**	0.15
Left temporal pole	-0.030	**.013**	0.10
Left transverse temporal	-0.044	**<.001**	0.07
Right banks of superior temporal sulcus	-0.026	**.024**	0.10
Right caudal anterior cingulate	-0.023	.053	0.04
Right caudal middle frontal	-0.031	**.008**	0.09
Right cuneus	-0.015	.197	0.13
Right entorhinal	-0.040	**<.001**	0.10
Right frontal pole	-0.023	**.041**	0.12
Right fusiform	-0.047	**<.001**	0.20
Right inferior parietal	-0.026	**.020**	0.18
Right inferior temporal	-0.040	**<.001**	0.21
Right insula	-0.048	**<.001**	0.20
Right isthmus cingulate	-0.005	.698	0.11
Right lateral occipital	-0.028	**.010**	0.25
Right lateral orbitofrontal	-0.032	**.003**	0.22
Right lingual	-0.015	.219	0.09
Right medial orbitofrontal	-0.028	**.014**	0.15
Right middle temporal	-0.045	**<.001**	0.22

Right paracentral	-0.023	**.047**	0.08
Right parahippocampal	-0.033	**.006**	0.05
Right pars opercularis	-0.022	.053	0.08
Right pars orbitalis	-0.026	**.024**	0.11
Right pars triangularis	-0.014	.219	0.08
Right pericalcarine	-0.006	.633	0.05
Right postcentral	-0.037	**<.001**	0.14
Right posterior cingulate	-0.033	**.006**	0.10
Right precentral	-0.035	**.003**	0.17
Right precuneus	-0.027	**.015**	0.21
Right rostral anterior cingulate	-0.029	**.014**	0.07
Right rostral middle frontal	-0.026	**.024**	0.16
Right superior frontal	-0.041	**<.001**	0.18
Right superior parietal	-0.013	.260	0.17
Right superior temporal	-0.038	**<.001**	0.12
Right supramarginal	-0.036	**.003**	0.11
Right temporal pole	-0.038	**.003**	0.06
Right transverse temporal	-0.031	**.008**	0.09

Table 3

Associations between subsyndromal mania and cortical thickness of 68 cortical regions

	β	p_{fdr}	R^2
Left banks of superior temporal sulcus	-0.007	.996	0.03
Left caudal anterior cingulate	-0.001	.996	0.05
Left caudal middle frontal	0.000	.996	0.04
Left cuneus	0.005	.996	0.08
Left entorhinal	0.003	.996	0.04
Left frontal pole	0.008	.996	0.02
Left fusiform	-0.004	.996	0.04
Left inferior parietal	0.000	.996	0.10
Left inferior temporal	-0.008	.996	0.04
Left insula	-0.013	.996	0.07
Left isthmus cingulate	0.012	.996	0.02
Left lateral occipital	-0.015	.901	0.27
Left lateral orbitofrontal	-0.021	.709	0.04
Left lingual	-0.011	.996	0.14
Left medial orbitofrontal	-0.008	.996	0.06
Left middle temporal	-0.002	.996	0.10
Left paracentral	0.000	.996	0.08
Left parahippocampal	-0.020	.709	0.06
Left pars opercularis	0.007	.996	0.04
Left pars orbitalis	0.008	.996	0.02
Left pars triangularis	0.001	.996	0.02
Left pericalcarine	0.003	.996	0.09
Left postcentral	-0.009	.996	0.12
Left posterior cingulate	0.008	.996	0.05
Left precentral	-0.007	.996	0.07
Left precuneus	-0.002	.996	0.09
Left rostral anterior cingulate	-0.003	.996	0.08
Left rostral middle frontal	-0.004	.996	0.08
Left superior frontal	0.015	.996	0.05
Left superior parietal	-0.001	.996	0.09
Left superior temporal	0.004	.996	0.09
Left supramarginal	-0.002	.996	0.12
Left temporal pole	0.008	.996	0.01
Left transverse temporal	0.000	.996	0.04
Right banks of superior temporal sulcus	0.006	.996	0.04
Right caudal anterior cingulate	0.006	.996	0.01
Right caudal middle frontal	0.007	.996	0.02
Right cuneus	-0.009	.996	0.11
Right entorhinal	0.000	.996	0.03
Right frontal pole	0.007	.996	0.03
Right fusiform	-0.005	.996	0.10
Right inferior parietal	-0.001	.996	0.12
Right inferior temporal	-0.007	.996	0.09
Right insula	-0.016	.996	0.06
Right isthmus cingulate	0.032	.249	0.02
Right lateral occipital	-0.013	.996	0.28
Right lateral orbitofrontal	-0.004	.996	0.04
Right lingual	-0.011	.996	0.11
Right medial orbitofrontal	-0.002	.996	0.04
Right middle temporal	0.004	.996	0.13

Right paracentral	0.005	.996	0.034
Right parahippocampal	-0.012	.996	0.09
Right pars opercularis	0.028	.249	0.04
Right pars orbitalis	0.010	.996	0.04
Right pars triangularis	0.023	.709	0.02
Right pericalcarine	-0.012	.996	0.08
Right postcentral	-0.001	.996	0.10
Right posterior cingulate	0.005	.996	0.01
Right precentral	-0.007	.996	0.03
Right precuneus	0.002	.996	0.05
Right rostral anterior cingulate	0.008	.996	0.04
Right rostral middle frontal	0.021	.709	0.03
Right superior frontal	0.028	.249	0.04
Right superior parietal	0.001	.996	0.07
Right superior temporal	0.006	.996	0.05
Right supramarginal	-0.006	.996	0.17
Right temporal pole	-0.007	.996	0.04
Right transverse temporal	0.010	.996	0.07

Table 4

Associations between subsyndromal mania and gray matter volume including the additional covariates of income, medication, in-scanner motion, and total intracranial volume.

		β	p_{fdr}	R^2
Income, medication, in-scanner motion	Left banks of superior temporal sulcus	-0.053	.858	0.13
	Right banks of superior temporal sulcus	0.000	.998	0.21
	Left caudal anterior cingulate	0.001	.998	0.05
	Left caudal middle frontal	-0.092	.858	0.17
	Right caudal middle frontal	-0.107	.782	0.17
	Left entorhinal	-0.015	.998	0.18
	Right entorhinal	-0.033	.998	0.15
	Left frontal pole	-0.039	.946	0.15
	Right frontal pole	-0.025	.998	0.18
	Left fusiform	0.057	.858	0.30
	Right fusiform	0.047	.941	0.18
	Left inferior parietal	-0.017	.998	0.18
	Right inferior parietal	0.005	.998	0.27
	Left inferior temporal	-0.045	.929	0.28
	Right inferior temporal	0.032	.998	0.24
	Left insula	0.055	.929	0.25
	Right insula	0.000	.998	0.27
	Left isthmus cingulate	0.061	.858	0.26
	Left lateral occipital	-0.063	.858	0.25
	Right lateral occipital	-0.074	.858	0.32
	Left lateral orbitofrontal	0.045	.929	0.30
	Right lateral orbitofrontal	0.067	.858	0.32
	Left medial orbitofrontal	0.018	.998	0.33
	Right medial orbitofrontal	0.077	.858	0.32
	Left middle temporal	-0.027	.998	0.25
	Right middle temporal	-0.023	.998	0.34
	Left paracentral	-0.064	.858	0.11
	Right paracentral	0.061	.858	0.16
	Left parahippocampal	0.048	.929	0.08
	Right parahippocampal	0.059	.858	0.11
	Left pars orbitalis	0.037	.998	0.21
	Right pars orbitalis	-0.003	.998	0.16
	Left postcentral	-0.039	.946	0.22
	Right postcentral	-0.012	.998	0.24
	Left posterior cingulate	-0.021	.998	0.14
	Right posterior cingulate	-0.014	.998	0.25
	Left precentral	-0.052	.925	0.33
	Right precentral	-0.003	.998	0.23
	Left precuneus	0.006	.998	0.25
	Right precuneus	0.006	.998	0.24
	Left rostral anterior cingulate	-0.007	.998	0.14
	Right rostral anterior cingulate	-0.010	.998	0.17
	Left rostral middle frontal	0.000	.998	0.16
	Right rostral middle frontal	0.042	.936	0.22
	Left superior frontal	-0.083	.858	0.22
	Right superior frontal	0.007	.998	0.23
	Left superior temporal	0.073	.858	0.19
	Right superior temporal	0.025	.998	0.19
	Left supramarginal	0.028	.998	0.25

	Right supramarginal	-0.008	.998	0.21
	Left temporal pole	0.133	.544	0.17
	Right temporal pole	0.090	.858	0.08
	Left transverse temporal	-0.011	.998	0.11
	Right transverse temporal	-0.007	.998	0.15
Total ICV	Left banks of superior temporal sulcus	-0.010	.673	0.21
	Right banks of superior temporal sulcus	-0.004	.923	0.27
	Left caudal anterior cingulate	-0.009	.699	0.15
	Left caudal middle frontal	-0.001	.983	0.28
	Right caudal middle frontal	-0.007	.775	0.27
	Left entorhinal	-0.014	.569	0.17
	Right entorhinal	-0.028	.299	0.14
	Left frontal pole	-0.015	.565	0.20
	Right frontal pole	-0.007	.775	0.20
	Left fusiform	-0.015	.391	0.44
	Right fusiform	-0.018	.299	0.47
	Left inferior parietal	-0.003	.937	0.31
	Right inferior parietal	-0.001	.983	0.39
	Left inferior temporal	-0.003	.923	0.43
	Right inferior temporal	-0.014	.453	0.44
	Left insula	-0.008	.699	0.47
	Right insula	-0.020	.299	0.46
	Left isthmus cingulate	0.002	.937	0.34
	Left lateral occipital	-0.012	.569	0.38
	Right lateral occipital	-0.005	.795	0.43
	Left lateral orbitofrontal	0.002	.937	0.52
	Right lateral orbitofrontal	-0.001	.937	0.54
	Left medial orbitofrontal	-0.001	.937	0.47
	Right medial orbitofrontal	0.001	.937	0.44
	Left middle temporal	-0.002	.937	0.44
	Right middle temporal	-0.016	.391	0.51
	Left paracentral	-0.009	.699	0.27
	Right paracentral	0.000	.983	0.26
	Left parahippocampal	-0.010	.695	0.17
	Right parahippocampal	-0.012	.588	0.19
	Left pars orbitalis	-0.007	.775	0.29
	Right pars orbitalis	-0.005	.912	0.26
	Left postcentral	-0.004	.923	0.34
	Right postcentral	-0.010	.673	0.38
	Left posterior cingulate	-0.013	.569	0.33
	Right posterior cingulate	-0.006	.775	0.34
	Left precentral	-0.012	.569	0.44
	Right precentral	-0.008	.703	0.41
	Left precuneus	0.002	.937	0.46
	Right precuneus	0.002	.937	0.48
	Left rostral anterior cingulate	-0.002	.937	0.32
	Right rostral anterior cingulate	-0.007	.775	0.24
	Left rostral middle frontal	-0.016	.391	0.42
	Right rostral middle frontal	0.000	.983	0.38
	Left superior frontal	-0.017	.391	0.49
	Right superior frontal	-0.011	.569	0.47
	Left superior temporal	-0.021	.299	0.43
	Right superior temporal	-0.007	.775	0.45
	Left supramarginal	-0.018	.391	0.36
	Right supramarginal	-0.010	.673	0.33
	Left temporal pole	-0.013	.588	0.19

Right temporal pole	-0.021	.391	0.16
Left transverse temporal	-0.023	.299	0.21
Right transverse temporal	-0.009	.699	0.25

Note. ICV = Intracranial volume

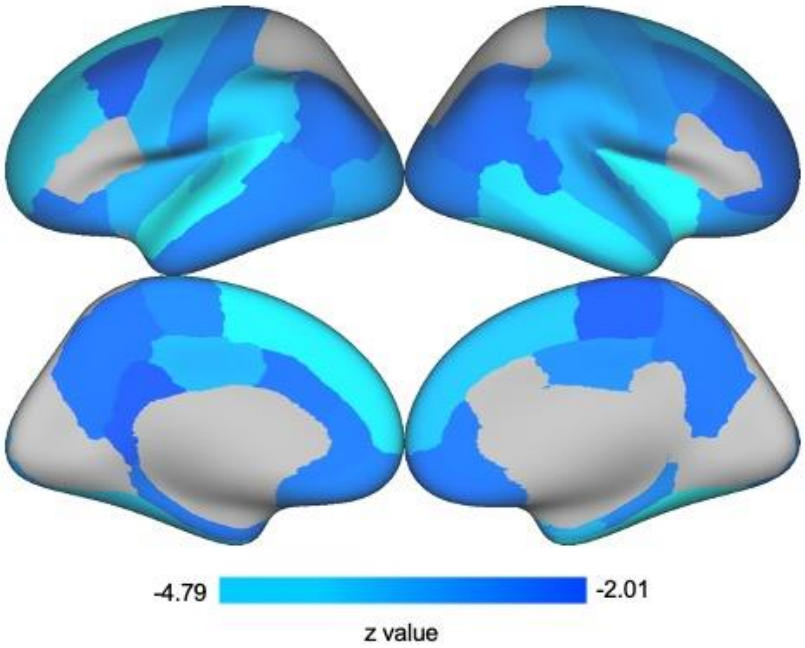

Figure 1. Regions with significant associations between cortical volume and subsyndromal mania. Higher subsyndromal mania scores were associated with significantly smaller cortical grey matter volumes in many regions in the brain. No regions remained significant after the addition of income, medication status, motion in the scanner, and total intracranial volume as additional covariates during sensitivity analyses.