Cortical Morphology Characteristics of Young Offspring of Patients With Schizophrenia or Bipolar Disorder

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Objective: Cortical surface area and thickness abnormalities have been observed in patients with schizophrenia and bipolar disorders; however, no study thus far has examined cortical morphologic measurements in children and adolescents at genetic risk for the disorders comparatively.

Method: One hundred thirty-seven participants, including 36 offspring of patients with schizophrenia (SzO), 54 offspring of patients with bipolar disorder (BpO), and 47 offspring of community controls (CcO), 6 to 17 years old, were assessed with clinical and neuroimaging methods. Sixty-nine percent of the sample was reassessed at a 27.6-month (mean) follow-up. Cortical surface reconstruction was applied to measure cortical area and thickness using FreeSurfer; mixed-effects models were used to investigate cross-sectional and longitudinal differences in global and lobar morphologic measurements.

Results: The SzO group exhibited a cross-sectional decrease in global, parietal, and occipital lobe surface area compared with the CcO group, and in the occipital lobe compared with the BpO group. In the SzO group, global and parietal surface area values were inversely associated with attenuated positive and negative prodromal symptom scores. No cross-sectional differences in cortical thickness were observed. Division of the sample by pubertal status showed group-by-time interactions in the pubertal and postpubertal SzO subgroup, with less longitudinal decrease in cortical surface area and thickness than in the CcO and BpO subgroups, respectively.

Conclusion: The SzO, but not the BpO, group was characterized by cross-sectional decreases in surface area, and this was associated with prodromal symptoms. Longitudinal changes in cortical morphology associated with risk for schizophrenia may be expressed differently according to developmental stage.

Key words: bipolar disorder, schizophrenia, neuroimaging, gray matter

J Am Acad Child Adolesc Psychiatry 2017;56(1):79–88.

Schizophrenia and bipolar disorder are chronic, disabling conditions that are considered to originate during neurodevelopment.[1] Despite efforts to conceptualize them jointly, owing to evidence pointing to an epidemiologic, clinical, genetic, and biological overlap, the 2 disorders continue to exhibit distinctive features that support current diagnostic categorization.[2] Although phenotypic overlap has been found mostly in the chronic phase of the disorders, it has been suggested that much of the divergence takes place in the preclinical stage of the illness.[1]

Schizophrenia and bipolar disorders have a multifactorial origin, stemming from a gene-by-environment interaction; first-degree relatives show an approximate 10% risk of developing the illness over their lifetime.[3] Healthy relatives have been reported to exhibit some phenotypic features shown by patients, although to a lesser degree. The study of child and adolescent offspring of patients provides the opportunity to assess the neural imprint of genetic vulnerability to disease, and allows for the study of preclinical features and the interaction between illness-related processes and normal brain maturation.

A previous study from our team found that child and adolescent offspring of patients with schizophrenia (SzO), compared with offspring of community controls (CcO) and offspring of patients with bipolar disorder (BpO), showed cross-sectional global and regional gray matter volume decreases similar to those observed in samples of adult patients with schizophrenia, whereas no volumetric changes were observed in BpO. Our results suggested that gray matter volume abnormalities in child and adolescent high-risk offspring may be specific to SzO.[4] Gray matter volume is defined as the amount of gray matter located between the gray-white interface and the pia mater, and is a function of cortical surface area (SA) and thickness (CTH), with each of these 3 measurements being potentially heritable.[5] Evidence from the macaque embryo has suggested that SA, which has been related to the number of cortical columns, originates from the symmetrical division of progenitor cells in the

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ventricular and subventricular layers, whereas CTH, which depends on the number of cells within a microcolumn, is formed by the asymmetrical division of radial glia in these cortical regions.[6] Longitudinal studies in humans have shown that gray matter volume, in association with SA and CTH, continues to grow from birth until late childhood in a region-specific manner.[7] This is followed by a decrease of these measures during adolescence, when the cerebral cortex has been postulated to flatten, involving decreases in CTH and SA,[5,8] a process that is influenced by hormonal changes during puberty.[9]

Schizophrenia and bipolar disorders have been associated with widespread cross-sectional cortical thinning and decreased SA compared with controls, when assessed independently.[10,11] However, the few studies that have directly compared the 2 disorders have reported more severe and widespread decreases for CTH in schizophrenia compared with bipolar disorder[12-14] and decreases in SA exclusive to schizophrenia.[14]

Thus far, a limited number of studies have examined cortical morphology characteristics in child and adolescent SzO or BpO groups. Prasad *et al.*[15] observed a cross-sectional decrease in SA in the frontoparietal lobes and decreased parietal CTH in SzO offspring aged 10 to 20 years, compared with healthy controls. One-year follow-up of these participants showed decreased global SA, especially in the bilateral frontal and occipital regions, and preservation of CTH in the SzO group compared with controls. In a more recent study by Bois *et al.*[16] of young adults aged 16 to 25 years, individuals at familial risk for schizophrenia exhibited no baseline differences in SA or CTH compared with controls, although those who developed psychotic symptoms over time had significantly larger baseline SA than individuals who remained well. Ten-year follow-up analyses showed less decrease in cortical SA and more prominent decreases in CTH in the frontal, cingulate, and occipital lobes in individuals at familial risk for schizophrenia compared with controls. To our knowledge, only 1 study has assessed CTH in young relatives of patients with bipolar disorder: Papmeyer *et al.*[17] reported a cross-sectional decrease in CTH in parahippocampal and fusiform regions in a sample aged 16 to 25 years. We are unaware of any study providing measurements of SA in young first-degree relatives of patients with bipolar disorder.

This evidence indicates that abnormal cortical morphology in schizophrenia and bipolar disorder could be related to familial risk; however, no study has compared young relatives of patients with schizophrenia with those of patients with bipolar disorder. Therefore, we set out to examine cross-sectional and longitudinal measurements of CTH and SA in SzO and BpO groups simultaneously, and to examine the effect of pubertal stage on these findings. Given the high rates of mental health disorders that characterize these samples[18] and their potential to influence brain morphology,[19] we used a community control group as a comparison, to confirm that changes in brain structure were related to risk status and not to co-occurring mental health conditions. A second objective was to assess the relation between cortical morphology and clinical symptoms and functionality. Based on previous findings, we hypothesized that the SzO group would show widespread decreases in SA and CTH, globally and regionally, compared with the BpO and CcO groups. Conversely, we speculated that the BpO group would show changes only in CTH, whereas SA would remain intact compared with the CcO group.

METHOD

Participants

The study was conducted in the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona, Spain. The protocol was approved by the local ethics review board. All participants provided written informed consent or assent. For participants younger than 18 years at the time of assessment, parents provided written informed consent and participants provided assent. The recruitment and evaluation of this sample have been described in detail elsewhere.[20]

Patients with a diagnosis of schizophrenia or bipolar disorder from adult psychiatry units with offspring 6 to 17 years old were identified and invited to participate in the study. The exclusion criteria for proband parents were intellectual disability and drug or medically induced psychosis or mania. Exclusion criteria for offspring included intellectual disability, head injury with loss of consciousness, or severe neurological conditions. Community control parents were recruited through advertisements posted in primary health care centers and other community locations within the same geographic area as the patients. The exclusion criteria were intellectual disability, severe neurological conditions and personal or first-degree family history of schizophrenia or bipolar spectrum disorders. All 6- to 17-year-old offspring of community control parents were invited to participate in the study; exclusion criteria were the same as those for high-risk offspring. To decrease selection bias, parents who stated they were specifically motivated to participate because of concerns about school performance or emotional or behavioral problems in their offspring were excluded.

The SzO group was composed of 36 participants, the BpO group was composed of 54 participants, and the CcO group was composed of 47 participants. All families were contacted for a 2-year follow-up: of the total 139 participants, we were able to assess 94 longitudinally (23 in SzO group [63.9% of baseline], 35 in BpO group [64.8%], and 34 in CcO group [72.3%]; $\chi^2 = 0.88$; $p = .64$) at a mean interval of 27.6 months (standard deviation 4.2 months). Longitudinal assessments included the same assessments as at baseline. Reasons for incomplete follow-up included wearing dental braces, refusal to undergo scanning, and change of residence. Baseline volumetric data for this sample have been reported as part of a 2-center study in collaboration with the Hospital Gregorio Marañon of Madrid, Spain.[4]

Clinical Assessment

The assessment of the participating family was carried out at the outpatient service of the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona. The families received compensation for their time and travel expenses.

Clinical and cognitive assessments were performed by experienced psychiatrists and psychologists. Parental and offspring interviews were conducted by different team members who were blinded to the others' assessment. Clinical diagnoses were based on the Spanish version of the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders[21] for parents and offspring at least 18 years old. Offspring younger than 18 years were assessed by child and