Abnormal Cortical Growth in Schizophrenia Targets Normative Modules of Synchronized Development

Aaron F. Alexander-Bloch, Philip T. Reiss, Judith Rapoport, Harry McAdams, Jay N. Giedd, Ed T. Bullmore, and Nitin Gogtay

Background: Schizophrenia is a disorder of brain connectivity and altered neurodevelopmental processes. Cross-sectional case-control studies in different age groups have suggested that deficits in cortical thickness in childhood-onset schizophrenia may normalize over time, suggesting a disorder-related difference in cortical growth trajectories.

Methods: We acquired magnetic resonance imaging scans repeated over several years for each subject, in a sample of 106 patients with childhood-onset schizophrenia and 102 age-matched healthy volunteers. Using semiparametric regression, we modeled the effect of schizophrenia on the growth curve of cortical thickness in ~80,000 locations across the cortex, in the age range 8 to 30 years. In addition, we derived normative developmental modules composed of cortical regions with similar maturational trajectories for cortical thickness in typical brain development.

Results: We found abnormal nonlinear growth processes in prefrontal and temporal areas that have previously been implicated in schizophrenia, distinguishing for the first time between cortical areas with age-constant deficits in cortical thickness and areas whose maturational trajectories are altered in schizophrenia. In addition, we showed that when the brain is divided into five normative developmental modules, the areas with abnormal cortical growth overlap significantly only with the cingulo-fronto-temporal module.

Conclusions: These findings suggest that abnormal cortical development in schizophrenia may be modularized or constrained by the normal community structure of developmental modules of the human brain connectome.

Key Words: Neuroimaging, penalized splines, psychosis, system, topology

Schizophrenia is increasingly understood to emerge from the abnormal development of relationships or connectivity between functional or anatomical areas of the brain. Magnetic resonance imaging (MRI) has demonstrated a wide range of disruptions in gray matter and white matter in schizophrenia (1–5). Disrupted structural and functional connectivity between brain regions has also been found with many imaging modalities (6–9). One hypothesis is that these disruptions reflect a pathology of neurodevelopment (1–5,10,11), with particular vulnerability in adolescence (12).

Childhood-onset schizophrenia (COS), a rare and severe form of schizophrenia that begins before age 13, provides a unique opportunity to explicitly test hypotheses about alterations in brain development. The cellular substrates of developmental change in MRI measures of cortical thickness are not known with certainty, but there is reason to think that processes of synaptic pruning and axonal myelination, which are ongoing during adolescence, could contribute to macroscopic shrinkage of cortical thickness during this time period (13). Previous studies of COS patients have demonstrated that cortical thickness of frontal and temporal lobe regions is reduced most severely in early adolescence and may partially normalize in early adulthood (14,15). These cross-sectional data imply, but do not directly demonstrate, that schizophrenia may be associated with abnormal maturational trajectories for frontal and temporal cortical thickness.

Human brain networks can be studied at the scale of MRI by estimating the structural covariance between cortical regions as a measure of anatomical connectivity (16). It has recently been shown that brain regions that have strong structural covariance also tend to have synchronized rates of maturational change over the course of adolescence (17). Specifically, graph analysis of longitudinal MRI data has demonstrated a community structure of developmental modules, each module comprising a group of cortical areas with growth curves that are similar to each other and different from the growth curves of areas in other modules (18). These developmental modules correspond quite closely to the modules of adult anatomical networks, implying that synchronized growth processes in adolescence are important to the formation or consolidation of the normal adult connectome. It is important to note that the overlap between structural covariance and white matter connectivity, while substantial, is also incomplete (19). It is plausible that shared genetic and environmental influences lead to interregional correlations in brain anatomy, even in the absence of a direct white matter connection between the areas (16). New data on modular development of human cortex during normal adolescence have not yet been translated to inform the analysis of hypothetically abnormal cortical development in people with schizophrenia.

Here, we studied a large sample of MRI data from patients with COS (n = 102; 7–32 years) and age-matched healthy volunteers (n = 106; 7–32 years). Participants were scanned on

From the Child Psychiatry Branch (AFA-B, JR, HM, JNG, NG), National Institute of Mental Health, Bethesda, Maryland; Brain Mapping Unit (AFA-B, ETB), Behavioural & Clinical Neuroscience Institute, University of Cambridge, Cambridge, United Kingdom; David Geffen School of Medicine at UCLA (AFA-B), Los Angeles, California; New York University School of Medicine (PTR); and Nathan S. Kline Institute for Psychiatric Research (PTR), New York, New York; and Cambridgeshire & Peterborough National Health Service Foundation Trust (ETB), Cambridge; and ImmunoPsychiatry, Alternative Discovery & Development (ETB), GlaxoSmithKline, Stevenage, United Kingdom.

Authors ETB and NG contributed equally to this work.

Address correspondence to Aaron F. Alexander-Bloch, Ph.D., National Institute of Mental Health, Child Psychiatry Branch, 10 Center Drive, Bldg 10, Room 3N202, Bethesda, MD 20892-1600; E-mail: aalexanderbloch@gmail.com.

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average 2.6 times, with at least 2 years between consecutive scans (range = 1–6 longitudinal scans per participant). We used semiparametric regression based on penalized splines (20,21) to model the nonlinear growth curves or relationships between age and mean cortical thickness at each of 80,000 locations (vertices) of the cortex. This analysis allowed us to test directly the hypothesis that schizophrenia is associated specifically with abnormal cortical thickness maturation during adolescence. We were also able to locate these regions of abnormal cortical maturation in the context of the normal community structure of developmental modules. This allowed us to test the hypothesis that abnormal cortical maturation in schizophrenia is modularized or constrained by the normative community structure of developmental modules.

Methods and Materials

Sample and Image Processing

The sample included 525 longitudinal structural MRI scans from 208 subjects, including 103 people with COS (age range 7–32; see Table S1 in Supplement 1 for demographic information). All scans were acquired on the same 1.5T Signa scanner (General Electric, Milwaukee, Wisconsin) located at the National Institutes of Health Clinical Center in Bethesda, Maryland, using a T1-weighted fast spoiled gradient echo sequence: echo time 5 milliseconds; repetition time 24 milliseconds; flip angle 45 degrees; matrix 256 × 256 × 124; field of view 24 cm. The Montreal Neurological Institute CIVET pipeline estimated cortical thickness at ~40,000 vertices per hemisphere, as previously described (22–24). This study was approved by the National Institutes of Health Institutional Review Board.

We conducted two main streams of analysis, using penalized cubic splines to estimate the nonlinear relationship between age and cortical thickness at each cortical vertex (Figure 1), where the resulting curves represent group-level averages over subjects. We first tested the null hypothesis that there is zero between-group difference (COS versus healthy volunteers) in mean cortical growth curves. Since the spline-based model was specified to differentiate age-invariant (trait) from age-dependent (trajectory) effects of diagnosis on mean cortical thickness, we could distinguish group differences in these two aspects of cortical thickness. Having thus identified vertices where cortical thickness trajectories were significantly different between groups, we then explored the secondary hypothesis that regions of abnormal growth might be concentrated in one or a few developmental modules of the normal human brain connectome. To address this

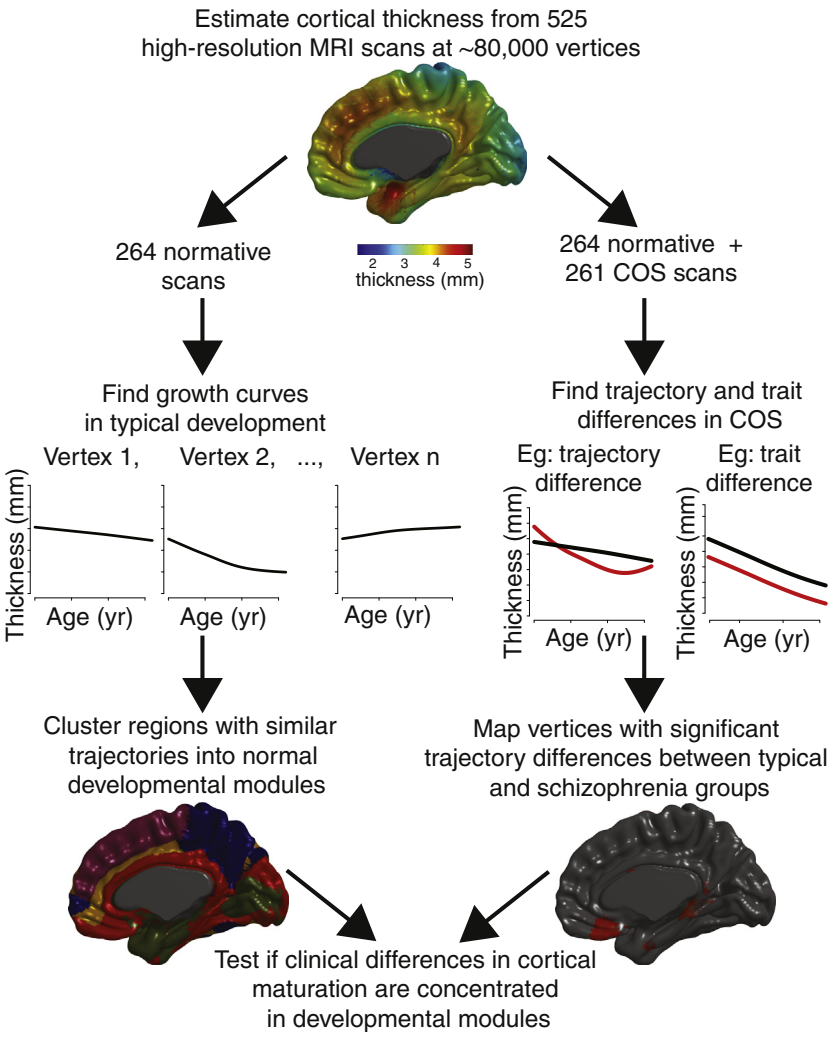

Figure 1. Schematic of streams of analysis. As part of the intramural National Institute of Mental Health study of typical development and childhood-onset schizophrenia (COS), 525 high-resolution magnetic resonance imaging (MRI) scans were acquired on 208 subjects, 102 with COS. For each scan, thickness was estimated at ~80,000 cortical vertices via the Montreal Neurological Institute CIVET pipeline, and penalized splines were used to estimate maturational trajectories (thickness as a function of age). Using only healthy subjects, developmental modules were derived by clustering vertices with similarly shaped maturational trajectories. Using both healthy subjects and subjects with COS, schizophrenia-related alterations in cortical maturation were tested for all cortical vertices. Finally, it was determined whether schizophrenia-related alterations in maturational trajectories were influenced by the organization of normative developmental modules.

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