Published in final edited form as:

Biol Psychiatry. 2014 September 15; 76(6): 432–433. doi:10.1016/j.biopsych.2014.07.003.

Finding Pieces to the Puzzle of Brain Structure in Schizophrenia

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The neurodevelopmental origins of schizophrenia have been suspected for more than a century, and the last half century of neuroimaging research has further supported the idea that anomalous brain growth trajectories underlie risk for psychotic syndromes. The article by Alexander-Bloch *et al.* (1) (this issue) marks significant progress in assembling the data necessary to define the healthy trajectories of brain development and how these processes may go awry in people who develop schizophrenia. The article is a technical tour de force, applying sophisticated neuroimaging and statistical methods to map age-associated growth curves and assess their differences between a group of people who have childhood-onset schizophrenia (COS) and a healthy comparison group.

The results importantly highlight that most of the differences between groups reflected cortical thickness reductions in the COS group that did not change over time (i.e., there existed trait differences that did not appear to evolve during the time of the study). There were also some difference in trajectories over time, the clearest of which reflected faster than normal reductions (or earlier reductions) in cortical thickness in the COS group. Of course, this study was conducted in COS individuals only after they already had developed schizophrenia, so it remains tantalizing to consider what differences in growth trajectory might have preceded onset, possibly marking the specific biological processes and patterns of gene expression that may lead up to onset of psychopathology.

It further remains unclear to what extent either the trait or trajectory effects might be consequences of either the illness or the treatments used. The authors indicate the range of possible explanations, including degenerative processes that may accompany the illness and might lead to the observed findings. The authors further note the potential confound with treatments received, and indeed this unusual sample of COS patients included many treated with clozapine, a drug which may also have its own unique impact on cortical volume and growth in this population (2), but there are so far not sufficient data to indicate that this is likely.

The authors state: “It is important to note that our finding of accelerated reductions in cortical thickness is theoretically consistent with a process of neurodegeneration that occurs after the onset of the disease, as opposed to a developmental process that begins before the start of symptoms” [(1), page 444]. While it is true that the findings are consistent with degeneration, there is no evidence to distinguish this from accelerated normal remodeling

processes, and the authors highlight that the alternatives will need to be assessed in future, larger studies of both healthy and at-risk samples.

The findings call for comparisons with other groups at risk for developing mental illness. In this respect, recent results from the North American Prodrome Longitudinal Study (NAPLS) are of high interest (3). The NAPLS study examined cortical thickness, comparing clinical high-risk individuals who would go on to convert to schizophrenia during the study period with those who did not convert. Although the follow-up scans in the NAPLS study also followed the onset of psychosis in those who converted, and therefore it could not be determined if the changes may have preceded or only followed the onset of more severe symptoms, the NAPLS study does make it clearer that preonset to postonset changes follow a trajectory involving cortical thinning. Additional analyses in the NAPLS study make it seem unlikely that antipsychotic drug exposure can account for the tissue reduction.

There are further intriguing convergences in the neuroanatomical loci implicated across the COS and NAPLS studies. In the COS study, the primary locus of maturational trajectory differences was found within one of five identified developmental modules—the cingulo-fronto-temporal module. The authors remain quite circumspect in their interpretation of these findings, but the overall localization is potentially consistent with a wealth of other data implicating dysfunctional circuits heavily dependent on this module [for reviews, see (4,5)].

There is even further convergence between the COS and NAPLS studies in localization of trajectory differences to key cortical regions in the right frontal lobe and more specifically within orbitofrontal/ventrolateral regions. Might this cortical territory, implicated in other research with response inhibition functions and stress modulation, be the locus of change in part because of failure in stress circuits? Or might there be a failure in other circuits leading these components of the stress-modulating circuitry to become overloaded and therefore dysfunctional?

With this in mind, another finding of the NAPLS study resonates with a stress mediation hypothesis. Specifically, cellular markers of neuroinflammation, most often associated with non-resilient stress responses, were found among individuals who converted, and the increases in pro-inflammatory signaling were strongly associated with the cortical gray matter decreases. These complementary articles therefore may further stimulate interest in stress-related factors operating during adolescence, in identifying individuals who are most vulnerable to adverse consequences in the face of these stressors and in designing interventions that can promote stress resilience in at-risk populations.

It is also intriguing that prior work on clozapine implicated regions analogous to human inferior frontal cortex (rodent infralimbic cortex) as a locus of unique changes in molecular expression, possibly linked to this agent's unique clinical profile (6), and this profile may be shared with olanzapine (7). Thus, there are both potential experiential and treatment-related hypotheses that might be examined to determine if this localization of tissue loss can be replicated in other samples of people with schizophrenia who have been studied longitudinally under different treatments. From this perspective, it is worth considering the

possibility that the cortical changes are not an artifact of treatment with clozapine (or any other agent) but instead that clozapine or similar agents may offer the best available treatment for individuals who have the unique combinations of diathesis and stress that precipitate psychosis at an early age—this would be compatible with clinical insights gathered over decades of intensive study at the National Institute of Mental Health Child Psychiatry Branch.

Of course, it should be appreciated that this article's focus on COS may limit the generality of the findings to other psychotic disorders, since COS is a distinctive syndrome in several respects, often characterized by more severe psychopathology and neuropathology. Nevertheless, the overlap of COS with adult-onset schizophrenia suggests that, unless proven otherwise, these clues may well apply to schizophrenia more generally.

National Institute of Mental Health Director Tom Insel once commented that the revolution in genetics and genomics was helping to “fill in the edge pieces” of the enormous puzzle that is schizophrenia. This contribution from Alexander-Bloch *et al.* (1), while raising many questions, does provide some persuasive evidence and is helping to complete an important section of the puzzle that must depend ultimately on changes in brain structure and the functions that are dependent on these structures.

Acknowledgments

The preparation of this manuscript was supported by the Michael E. Tennenbaum Family Center for the Biology of Creativity and a grant from the National Institute of Mental Health (R01MH101478).

Over the past 2 years, Dr. Bilder has received honoraria or consulting fees from Catenion, EnVivo/Forum, Takeda-Lundbeck, and ThinkNow, Inc.

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