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COMMENTARY

Future of Days Past: Neurodevelopment and Schizophrenia

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Since a proposal in 1986 that schizophrenia involved early neurodevelopmental deviations beginning in intrauterine life that showed varying expressivity as relevant neural systems matured, our understanding of the developmental components of the pathogenesis of schizophrenia has substantially evolved. This commentary highlights recent genetic and epigenetic evidence that prenatal development is a critical period for the expression of schizophrenia risk. Studies of gene expression have been fairly consistent in showing that genes implicated in schizophrenia show relatively greater expression during fetal than postnatal life. Consistent molecular evidence of early environmental perturbations contributing to risk has emerged from studies of epigenetic marks in the brain genome as potential environmental footprints and these also highlight the prenatal period. Analyses of gene expression in placenta dramatically identify the intrauterine environment as a direct point of impact of a component of schizophrenia genetic risk. Together, the enrichment of transcriptional and epigenetic associations with schizophrenia during fetal life suggest that both genetic and environmental risk for schizophrenia have a particular molecular impact on early development, possibly because of genetic biases in environmental sensitivity.

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A Personal History Perspective

There were 4 pivotal experiences in my early years at the NIH that prompted me to propose in 1986 a "neurodevelopmental hypothesis of schizophrenia."[1] While the notion that this disorder had components of its origins beginning in early life was nothing new, and had been the subject of considerable discussion in the prior literature,[2–4] the emergence of a new generation of anatomical studies of the brain in patients with schizophrenia led to a reinvention of this concept. The first of these experiences involved my trying to make sense out of the finding of relatively enlarged ventricles on CT scans of patients with schizophrenia. While this also was not a new observation and in fact harkened back to pneumoencephalography studies of the 1920s, the landmark report with CT by Eve Johnstone and colleagues[5] at Northwick Park in 1976 put this finding back in the news. While the Johnstone et al report involved a small group of patients mostly in their seventh decade of life, my colleagues and I at the NIH also observed relatively enlarged ventricles even in acutely ill and in first episode patients, leading me to wonder whether these findings pre-existed the diagnosis.[6,7] We also found to our surprise that ventricular size did not correlate with length of illness, implying that it might not reflect a neurodegenerative process.[6] I became further enamored of this conclusion when we found (the second of these "experiences") that poor early childhood social adjustment was associated with larger ventricles during adulthood.[8] This led me to wonder, to paraphrase Kraepelin, that the childhood difficulties of individuals later to manifest schizophrenia were expressions of the "morbid pathology" during this earlier phase of life. At the same time, I was working with Prof. Paul Yakovlev in his brain collection at the Armed Forces Institute of Pathology, studying whole brain sections stained with nissl and giesma (for myelin) of cases with schizophrenia.[9] I was struck, as was he and many of the experienced neuropathologists who studied schizophrenia during the first half of the twentieth century, by the absence of gliosis in the brains of patients with this diagnosis. Prof. Yakolev, who had defined many of the developmental abnormalities of midline structures (the "schizencephalies"), opined that if there were pathology in the schizophrenia brain, it was not likely to be of adult onset. And finally, while studying for my neurology board specialty examination, I read *Neurology of Hereditary Metabolic Diseases of Children* by Lyons and Adams. I was struck by the principle that the clinical expression of intrauterine insults varied postnatally because as the brain matures the neural systems that mediate symptoms change. One of the

remarkable observations highlighted in the book was that several congenital encephalopathies associated with psychosis do not show psychotic symptoms until adolescence, even though the pathology is present from before birth. Could schizophrenia possibly involve early developmental pathology that was waiting to show itself as a psychosis until neural systems that could mediate psychosis reached an appropriate state of postnatal maturation?

These were the basic tenets of my original proposal in 1986 which was then amplified in a more cited manuscript in 1987.[10] The basic principle was that schizophrenia involved early neurodevelopmental deviations, beginning in intrauterine life and that the expression of the associated pathology showed varying expressivity as relevant neural systems matured. Thus, early childhood deficits in developmental milestones and social and intellectual function were seen as manifestations of cortical dysfunction during that phase of development, while psychosis required a further maturation of cortical-limbic circuitries, as also seemed to be the case with traditional neurological disorders associated with psychosis (eg, epilepsy, metachromatic leukodystrophy, Huntington's Disease).

Over the past 30 years, our understanding of the developmental components of the pathogenesis of schizophrenia has substantially evolved.[11,12] From early data that were circumstantial at best, we now have objective molecular data linking intrauterine life to schizophrenia risk. My own view of the "neurodevelopmental hypothesis" also has changed in several respects, particularly in terms of 2 of my original inspirational experiences. Indeed, I have become increasingly doubtful of the conclusions that I reached from the CT studies, as it has become a glaringly inconvenient truth that numerous artifacts and epiphenomena plague in vivo imaging studies and raise doubt about whether the findings reported in patients reflect underlying structural pathology.[13] The lack of gliosis has, I believe, held as an indicator of the lack of an active degenerative process in the schizophrenic brain. Recent interest in a role for CNS inflammation in the adult brain suggested by several largely preliminary studies of peripheral blood and PET imaging have not been confirmed in more rigorous and detailed investigations.[14,15] Overall, the accumulating evidence for a critical role of early brain development in the origins of schizophrenia has become substantial and compelling. What follows are selected examples of this evidence.

Genes and Developmental Risk

The sea change in our understanding of the causative factors that account for schizophrenia and the role of early developmental events have followed the discovery of risk genes and genomic loci. From large population based genome-wide genotyping and sequencing studies, the genetic risk landscape has been at least partially illuminated. This landscape includes microscopic chromosomal aberrations called copy number variations and loss of function point mutations which are moderately penetrant in predicting a schizophrenia diagnosis.[16] These deleterious variations in coding sequences are likely damaging to brain development, but they are rare and found in approximately 2% of individuals with the diagnosis of schizophrenia. Even within this 2%, they are factors that increase risk and are not pathogenic causes in and of themselves. They also are associated with other developmental disorders including intellectual disability, autism, and epilepsy and show much greater penetrance in these contexts than in schizophrenia. Studies of expression of genes affected by these rare variants suggest that they are expressed in human brain during fetal life and that in silico informatics analyses further implicate these genes as important in basic neural developmental processes.[15]

In contrast to the more penetrant but rare variations, most risk for schizophrenia across heterogeneous clinical populations is explained by inheritance of many common alleles across the genome.[17] These common alleles, however, which likely number in the many hundreds, have very small effects on risk at the individual locus level. For example, allele frequency differences between samples of patients with schizophrenia and control subjects at any given allele is on the order of 2%, and the odds ratios of increased risk are in general less than 1.2-fold for any given risk associated allele. Most of these common variants do not involve protein coding sequences and presumably do not alter amino acid composition. Rather, their influence on brain development and function is likely related to gene processing (eg, expression, splicing) via transcription factor and epigenetic mechanisms. In silico bioinformatics analyses of genes within loci that show common variant association across the genome implicate many early developmental processes.[18]

It is important to note that evidence showing a link between genes implicated in risk for schizophrenia and early development biology is circumstantial and does not establish a neurodevelopmental origin for illness pathogenesis. A more compelling approach is direct analysis of gene expression in brain tissue, contrasting fetal to postnatal brain. A number of recent reports have described this approach, and the data are fairly consistent that genes implicated in schizophrenia show relatively greater expression during fetal than postnatal life.[11,19,20] This suggests, at the least, that regulation of these genes during fetal life implicates a specific role for them in early brain development. As an example, Birnbaum et al[19] surveyed sets of genes associated with schizophrenia using a microarray method and observed significantly preferential expression of this gene set during fetal life. Similar results were found for gene sets implicated in autism and syndromal neurodevelopmental disorders. Gene sets associated with neurodegenerative disorders showed relative increased expression during late life. Jaffe et al[20], using more comprehensive RNA sequencing, surveyed similar sets of genes and confirmed all of these observations.

Environment and Developmental Risk

From archival twin studies, it is clear that genes alone are not sufficient etiological factors in determining illness; environmental modifiers are likely important but they are difficult to objectify. Fairly consistent circumstantial evidence of environmental adversity during early development influencing risk for schizophrenia has come from studies of complications during pregnancy such as premature birth, preeclampsia, intrauterine infection, and immune incompatibility.[21] Molecular evidence of early life perturbations contributing to risk has emerged from recent studies of epigenetic marks in the brain genome as potential environmental footprints related to risk.[22,23] For example, Jaffe et al[23] studied DNA methylation (DNAm) in prefrontal cortex in normal brain across the lifespan starting in early prenatal life and defined the changing epigenetic state characterizing different life stages. Remarkably, they found that recent schizophrenia genome wide association study (GWAS) significant loci were enriched for epigenetic changes associated with fetal life, while DNAm changes characterizing the early adult period when illness is typically diagnosed were actually significantly depleted of Psychiatric Genomics Consortium risk loci. More remarkably, DNAm differences between control brains and brains of individuals dying in their 40s and 50s with the diagnosis of schizophrenia were enriched for the fetal epigenetic marks and not for DNAm changes related to postnatal experience. This study also demonstrated that almost two-thirds of the schizophrenia GWAS significant SNPs were strong meQTLs, meaning they were associated with variation in nearby DNAm, a sign of genetic variation in environmental sensitivity. Together, the enrichment of transcriptional and epigenetic associations with schizophrenia genetic risk during fetal life, at least those epigenetic changes that leave an enduring footprint in the brains of adult patients with this diagnosis, suggest that both genetic and environmental risk for schizophrenia have a particular molecular impact on early development, possibly because of genetic biases in environmental sensitivity.

An association between genomic risk loci and fetal epigenetic marks and expression of fetal transcripts represents strong molecular evidence that genetic and environmental risk for schizophrenia influences early brain development, but it does not prove a role for events associated with this time of life. Potentially stronger evidence of such proof has come from a recent genetic study that dramatically sharpened the focus on the early fetal environment as a key effector of genetic risk for schizophrenia and the genome of risk as a determinant of sensitivity to intra uterine stress. Ursini et al.[24] identified an interaction between obstetrical complications (adverse intrauterine and perinatal events with likely impact on fetal health) and schizophrenia polygenic risk, such that the variance of schizophrenia explained by the polygenic risk score based on SNPs marking GWAS significant loci and its prediction accuracy increased significantly and synergistically when including obstetrical complications in the statistical model. The interaction of polygenic risk with obstetrical adversity implicated a potential role for placental health, and analyses of placenta-specific gene expression revealed that genes within the most clinically significant schizophrenia risk loci were enriched in expression in the placenta, and dynamically regulated in placenta from complicated pregnancies. Interestingly, placenta gene expression data revealed much larger effects in placenta from males compared with female offspring, potentially shedding light on a longstanding mystery about schizophrenia and other developmental behavioral disorders—the preponderance of males affected. Moreover, the genomic loci containing genes dynamically regulated in placenta were then used to generate a novel polygene risk score, called PlacPRS, which predicted complicated pregnancies. In silico biological pathway analyses revealed that the schizophrenia risk associated genes dynamically regulated in placenta reflect aspects of cellular stress, an orthogonal biology to schizophrenia associated genes typically linked with brain development and function, such as, synaptic function and calcium signaling. Moreover, the placental gene set was strongly co-expressed with immune and inflammation genes. These results implicate placenta biology as a point of direct impact of genetic risk, suggesting that a fraction of the schizophrenia risk genes sensitize the placenta to environmental stress and increase the probability of a developmental insult to the fetus and a complicated pregnancy.

Future of Past Days

The foregoing discussion highlights convergent data implicating prenatal brain development as a critical period for shaping genetic and environmental risk for schizophrenia. The diverse and protean effects of schizophrenia risk on brain development may be parsimoniously conceptualized as introducing developmental "noise," subtle and diverse perturbations in the construction and tuning of early brain circuits or synaptic organization. This perspective places schizophrenia on a continuum of neurodevelopmental disorders, with some shared common mechanisms with autism, intellectual disability, and syndromic developmental disorders, though with less biological "noise" (ie, more bufferable developmental deviation) and thus a later relative age of onset and functional capacity. In my original disquisition about brain development and schizophrenia, I highlighted the deterministic role of brain maturation in the clinical expression of psychosis and suggested that what is unique about schizophrenia is neither its pathology nor its cause, but the interaction of the pathology with the normal course of maturation of the brain systems affected by it.[1,10] I further suggested that the syndrome might not be considered as a disease, but rather a state of brain development and function based

on an altered developmental trajectory with changing repercussions throughout life. I proffered that the pathology in schizophrenia "may not reflect a discrete event or illness process at all, but rather one end of the developmental spectrum that for genetic and/or other reasons 0.5% of the population will fall into."[10] My current view of this suggestion has not been altered by the recent evidence, which is largely consistent with the assumptions of this perspective. In a later and more developed discussion of this subject, along with Pat Levitt, we borrowed concepts from Conrad Waddington in suggesting that as individuals on a particular developmental trajectory move forward, "the subtle course corrections from early cell differentiation and circuit construction become increasingly amplified and compounded as the phenotypic endpoint becomes increasingly mature and the circuits involved take on increasingly complex functions."[2] Schizophrenia, we suggested, involved developmental alterations in cortical microcircuitry, involving the interplay between glutamate and GABA neurons (now popularly referred to as "excitatory-inhibitory balance"), in molecular trajectories that converge on relatively late maturating mechanisms for tuning cortical circuitry.

A critical assumption of the neurodevelopmental model is that the pathological process is compensable early in life and then relatively decompensates later in life. This pattern contrasts with more typical early onset neurodevelopmental disorders, such as cerebral palsy, autism, and intellectual disability, which presumably involve greater developmental pathology or involvement of neural functions not compensable early in life. Interesting, the principle of an early developmental abnormality in cortical circuitry having a delayed impact on later developing cortical functions has been tested in a number of animal models and found to be biologically plausible.[25,26] Views on clinical and preclinical research paradigms are discussed by Meyer-Lindenberg[27] and Anderson[28] in this issue.

Lastly, the neurodevelopmental model of schizophrenia is not merely a research heuristic but holds diagnostic and therapeutic implications. As clinical practice aspires to "precision-medicine," stratifying patients by underlying biology or genetic background for improved therapeutic efficacy and reduced untoward effects may eventually become point-of-care. We can reasonably expect that the clinical translation of schizophrenia genetic risk will yield insight into disease mechanisms, novel targets for therapeutic intervention, and perhaps in a neurodevelopmental manner, even prediction and prophylaxis, well before the onset of the diagnostic syndrome.

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