Neuroscience Reviews

Schizophrenia: Who dreamed this one up?

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Jean Frazier raised several interesting questions in her keynote address at the 29th Annual NADD Conference in Denver. She focused on the relationship between two very complex syndromes—autism and schizophrenia spectrum disorders. The neurobiological, genetic, and phenomenological boundaries between these neurodevelopmental disorders suggest that there is an overlap between them. Recent genetic research suggests that these boundary issues can be extended to subtypes of IDD and epilepsy. In the next several updates, we will delve into these complex problems and hopefully do justice to Dr. Frazier’s excellent presentations.

Ongoing developments in the neurosciences have changed the historical boundaries between developmental disorders. Leo Kanner first described autism in the 1940’s. Since that time, our conceptual models of autism have morphed in several directions. In the 1970’s the British Working Group separated autism from Childhood Schizophrenia. During this time our
clinician-researchers also used the Research Diagnostic Criteria to define schizophrenia. Both moves help separate autism from the schizophrenias. The publication of the *DSM-III* expanded on the descriptive approaches pioneered by Kraeplin and Schneider and away from Bleuler’s two-tiered, longitudinal approach. Bleuler also introduced the term “autism” to denote a pattern of egocentric thought and social isolation as a primary feature of the schizophrenias. The shift towards descriptive psychiatry was now in high gear.

It wasn’t long before the original subtypes of schizophrenia became victims of the awakening neuroscience revolution. With these changes the boundary between schizophrenia and mood disorders opened the doorway for schizoaffective disorder. Yet there was more. Researchers focused on additional heterogeneity of the schizophrenias based on age of onset, neurobiological subtypes, variations in longitudinal course, differences in positive versus negative symptoms, neuropsychological studies of associated cognitive impairments, and issues related to treatment resistance. In the process attention shifted to a neurodevelopmental model of schizophrenia and a dimensional model that gave rise to schizophrenia spectrum disorders (SSD). The spectrum concept expanded to now include mood disorders, Obsessive-compulsive disorder, and autism (ASD), once the myth of categorical purity cracked as the entropic forces became obvious.

Geneticists and molecular psychiatrists are stirring boundaries between SSD and ASD. There is increased interest in the relationship between PDD and childhood onset schizophrenia, and the emergence of schizophrenia in adults with childhood ASD. The use of genome wide scans (GWAS) added new concepts to our vocabulary—namely copy number variants of multiple genes that appeared in both disorders. Neuroimaging and neuropathological studies suggested differences in neurophysiology and anatomy of various neuronal systems. The
differences suggest that epigenetic factors (changes in gene action without changing DNA) play a role in the differences based on differences in regulating gene activation. The neurodevelopmental model of both schizophrenia and autism spectrum disorders require us to address differences in the patterns of neuronal maturation and interconnections; myelin formation, timing of postnatal changes in specific cells lines; and age related changes in white matter tract development, dendrite development, and pruning. Now interest is moving toward micro-RNA and regulation of protein synthesis outside the nucleus, neuro-immunological activation, and the complex role of mitochondria in brain development.

The good old days are gone for a simple “two-hit” model. Neurodevelopmental models point out the evolving nature of SSD. During childhood there are nonspecific aberrations in attention/cognition, motor development, memory, and social relatedness during and early adolescence childhood. Yet the emergence of the adult-onset phenotype of schizophrenia is a relatively late developing phenomenon. Latest models describe overexuberant dendritic pruning, failure of white matter maturation and tract formation during late adolescence. We can assume that the derailment of regulatory signals for key genes precedes both the neuroanatomical and clinical onset of schizophrenia. The transition period between prodromal symptoms and the duration of untreated psychotic symptoms suggest an ongoing process. Recent evidence suggests that only about 40% of high risk probands with prodromal symptoms go on to develop syndromal schizophrenia. There are hints that omega 3 fatty acids may have a useful role in prevention but are less beneficial than antipsychotics once the transition has occurred. Cannabinoids (marijuana) and other drugs of abuse and psychosocial and environmental toxins may be key factors in the transformation.
As a rule schizophrenia is a disorder of youth; ASD is one that begins in early childhood. Both are influenced by the presence of IDD. How then do we make sense of the differences between ASD and SSD?

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