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Update on Neurodevelopment and Schizophrenia

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Mini Review

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Abstract

In the last two decades, neuroscientific studies have focused on the "previous" of the psychosis, particularly of schizophrenia. Abnormal maturation of brain structures have been widely held to underlie schizophrenia. Early and late developmental processes are involved. Such a stepwise developmental pathophysiology of the illness may result from several factors playing a role singly, or in combination. In recent years, 108 schizophrenia-associated genetic loci that may predispose to neurodevelopmental alteration have been disclosed by the genome-wide association studies (GWAS); there are considerable, common polymorphisms overlapping with autism and bipolar disorder, suggesting the idea of a spectrum. Further research is needed to clarify whether childhood neurodevelopmental disorders and adult psychiatric disorders lie on a neurodevelopmental continuum or spectrum.

Mini Review

In the last two decades, neuroscientific studies have focused on the "previous" of the psychosis, particularly of schizophrenia; genetic, epigenetic, and endophenotypic findings tend to define the classical concept of vulnerability to schizophrenia in a biological and detectable manner, which clearly lies in disturbances of brain development.

Neurodevelopment is a delicate process of sequential, timely changes leading to growth and assumption of something appearing as a definite form, which involves both the brain and other nervous structures and functions as well.

Abnormal maturation of brain structures have been widely held to underlie schizophrenia. During intrauterine or early postnatal life, the alteration of neuronal proliferation, migration, differentiation, and elimination, or neurogenetic processes, may lead to impaired neural infrastructure and abnormal brain maturation predisposing to premorbid dysfunction as well as psychopathology emerging later in adolescence or early adulthood [1]. During adolescence, deviations in later emerging processes, such as synaptic/axonal pruning or neuronal apoptosis and/or myelination processes may be involved in the pathgenesis of schizophrenia [2]. These "late" developmental processes, designed to optimize the excitatory/inhibitory balance in the cortical and subcortical regions, may lead to illness onset during adolescence of early adulthood.

Such a stepwise developmental pathophysiology of the illness may result from several factors playing a role singly, or in combination.

First, genetic factors may predispose to an excess synaptic elimination, increased neuronal apoptosis, decreased cell somal size, or a combination of these processes during adolescence. Such changes might result from altered expression of genes that are critical for neurodevelopmental processes such as glutamatergic NMDA/AMPA receptor expression, brain-derived

neurotrophic factor levels, or altered dynamics of dopaminergic and GABAergic neurotransmitter systems [3-5].

Second, hormonal changes, especially of the reproductive steroids, could modulate brain maturational processes such as synaptic pruning and/or myelination [6].

Third, psychosocial environmental factors might play a significant role as well. It is known that environmental enrichment leads to increased spine density and dendritic arborization [7]. Likewise, environmental impoverishment or stress could conceivably lead to the opposite, that is, increased fallout of synapses and/or neurons and decreased neuronal viability [8,9]. Among environmental factors, toxic, infectious, and metabolic ones are putatively involved during pregnancy; perinatal complications and early relational experiences are involved in this process from birth onward, whereas during adolescence, a window of vulnerability opens to the harmful effects of cannabis use and other stressful life events and conditions van Os, et al. 2010. According to the epigenetic model, environmental factors have an impact on gene expression via changes in DNA methylation and chromatin structure that, in turn, may play a role in the etiology of schizophrenia [10].

In recent years, 108 schizophrenia-associated genetic loci that may predispose to neurodevelopmental alteration have been disclosed by the genome-wide association studies (GWAS); this supports the view that schizophrenia may be caused by multiple common genes, each conferring a small effect. Moreover, International consortia involving GWAS studies have generated evidence for a number of common polymorphisms that associate with schizophrenia (such as the major histocompatibility complex region at 6p22–p21; neuregulin on chromosome 8, transcription factor 4 on chromosome 18q21.2; and 2q32.1) [11]. Interestingly, there are considerable, common polymorphisms overlapping with autism and bipolar disorder, suggesting the idea of a spectrum.

The idea of a spectrum emerging from the neurodevlopmental hypothesis has been reinforced by many clinical and other phenotypic similarities between schizophrenia and childhood neurodevelopmental syndromes. First, schizophrenia shares with childhood neurodevelopmental disorders impairments of cognition, which are often present before psychotic breakdown, a greater frequency in males, and associations with varying degrees of developmental delay, neurological soft signs and motor abnormalities. Second, there is a significant comorbidity between them that is obscured by the use of diagnostic hierarchies or exclusions. Third, a number of environmental risk factors, particularly those impacting on early brain development, are shared across these disorders.

Thus, further research is needed to clarify whether childhood neurodevelopmental disorders (such as intellectual disability, autism spectrum disorders and ADHD) and adult psychiatric disorders (including both schizophrenia and bipolar disorder), rather than being discrete entities from an etiological perspective, lie on a neurodevelopmental continuum or spectrum. In this view, the major clinical syndromes may reflect the severity, timing and predominant pattern of abnormal brain development and resulting functional abnormalities, as well as the modifying effects of other genetic and epigenetic factors.

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