

The Adolescent Brain: Implications for the Understanding, Pathophysiology, and Treatment of Schizophrenia

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The typical onset of schizophrenia during the transition from late adolescence to adulthood is one of its central features. However, the neurodevelopmental hypothesis of schizophrenia has largely focused on the contribution of early development events. In this issue, we summarize data from a range of perspectives that emphasize the profound modifications occurring in anatomy, physiology, and functional properties of cortical networks during adolescence that may be important for the emergence of psychosis, enduring cognitive, and physiological deficits as well as for the treatment and prevention of the disorder. The contributions by Hoftman and Lewis¹ and O'Donnell² show major modifications in GABAergic, glutamatergic, and dopaminergic neurotransmission and their interactions during the adolescent period that may be abnormal in schizophrenia. Gogtay et al.³ highlight data from longitudinal anatomical imaging studies that have examined the trajectory of brain maturation in childhood-onset schizophrenia (COS) and in subjects at ultrahigh risk (UHR). Their findings converge on the possibility that in schizophrenia, there is an excess pruning of synaptic contacts during adolescence that leads to reductions in gray matter (GM) volume. The consequences of the co-occurring changes in anatomy and transmitter systems for properties of large-scale cortical networks are discussed by Uhlhaas and Singer.⁴ They highlight that precisely synchronized neural oscillations emerge only during late adolescence. Accordingly, in schizophrenia, there may be a failure to express important neural synchrony parameters during adolescence, causing the emergence of psychosis as well as contributing to cognitive deficits. The commentary by McGorry⁵ discusses the implications of these findings from the perspective of treatment and prevention.

There is little doubt today that schizophrenia is a disorder of brain development.⁶ Yet, the nature and timing of developmental disturbances are a matter of debate.

The neurodevelopmental hypothesis of schizophrenia was proposed in the late 1980s^{7,8} to highlight the fact

that the disorder is the end product of an abnormal trajectory in the maturation of cortical circuits that possibly begins already in utero. The association with several prenatal and perinatal risk factors,⁹ the presence of cognitive deficits in childhood,¹⁰ as well as the success of certain animal models with circumscribed brain defects during early brain development in modeling the clinical phenotype in adulthood¹¹ all point to the important role of early adverse events in the pathophysiology of schizophrenia.

However, this perspective leaves another central question unanswered, namely the late manifestation of the disorder and the contribution of aberrant maturational processes during adolescence (see ref.¹² for a recent perspective). Indeed, a central question for schizophrenia research is: Why does schizophrenia emerge during late adolescence? This fact has been known since the initial descriptions of Dementia Praecox by Emil Kraepelin,¹³ yet remains one of the unsolved mysteries of the disorder.

Neurodevelopmental theories have taken different perspectives toward this problem. Weinberger⁸ proposed that an insult in the second trimester interacts with the molecular and anatomical changes during adolescence. One particularly important event for the manifestation of psychosis during adolescence according to Weinberger is the functional integration of the frontal cortex into extended cortical networks.

Other investigators have emphasized the active contribution of adolescent brain maturation toward the pathophysiology of schizophrenia. According to the late neurodevelopmental model,¹⁴ brain development during adolescence does not only serve as a trigger for the expression of psychosis but also is itself abnormal. Feinberg¹⁵ in the 1980s suggested on the basis of the groundbreaking work of Huttenlocher¹⁶ that in schizophrenia, the pruning of synaptic contacts is increased. The late manifestation of schizophrenia would therefore be “caused” by excessive synaptic elimination during adolescence.

While these perspectives represent important milestones in the history of schizophrenia research, there has been in recent years a surprising absence of systematic investigations and discussions into the potential role of adolescent brain development for the pathophysiology of schizophrenia (for exceptions see ref.^{17–20}). This may be explained by the dominance of early neurodevelopmental models in schizophrenia research and the focus on early critical periods in developmental neuroscience in general.

Recent studies using functional and anatomical imaging as well as electrophysiology now clearly point to the decisive role of adolescence in profoundly reorganizing cortical networks.^{21–24} Because these changes coincide with the manifestation of major psychiatric disorders, such as schizophrenia,²⁵ the possible contribution of these developmental events toward the emergence of psychosis and their role in contributing to the enduring cognitive and physiological deficits requires reassessment. This issue is particularly pertinent giving the current emphasis on the identification of subjects who are at-risk for the development of schizophrenia that could lead to better treatments and eventually to the prevention of the disorder.²⁶ However, for this objective to be successful, a necessary prerequisite is a more detailed understanding of normal brain development that allows the differentiation between pathological vs normal developmental trajectories.

The current theme provides an update of recent findings on the relevance of adolescent brain maturation for the pathophysiology of schizophrenia. The article by O'Donnell² summarizes changes in dopaminergic neurotransmission in rodent cortex, highlighting the profound alterations in the properties of dopaminergic neurotransmission, and the interaction with GABAergic interneurons during adolescence. Data from his laboratory demonstrate that while D₂ agonists are strongly excitatory over fast-spiking interneurons in the adult cortex, in juvenile rats, they have a weak or no effect, suggesting that the excitation-inhibition balance with prefrontal cortex (PFC) is refined.²⁷ Because disinhibition of PFC has been demonstrated in animal models of schizophrenia,²⁸ one possible hypothesis is that this phenomenon is linked to the abnormal maturation of the excitation-inhibition balance during adolescence.

For this hypothesis to be tested, O'Donnell² summarizes the utility of animal models toward identifying aberrant maturation of cortical circuits in schizophrenia. In his view, this approach allows the identification of cellular, synaptic, and circuit elements that may be abnormal in schizophrenia. Accordingly, animal models could be of crucial importance for developing novel therapeutic targets.

The article by Hoftman and Lewis¹ expands this perspective by summarizing a large body of work on the developmental trajectories of cortical circuits underlying working memory in primate dorsolateral PFC

(DLPFC). The authors focus on the maturation of glutamatergic and GABAergic circuits during different stages of development and identify potential windows of vulnerability.

One central finding according to Hoftman and Lewis¹ is the possible role of aberrant maturation of excitatory glutamatergic circuits during adolescence. As pointed out above, it has been proposed that the pruning of synaptic contacts in schizophrenia is abnormal.¹⁵ Hoftman and Lewis¹ suggest that one source for the observed reductions in GM during adolescence in schizophrenia could be the alterations in dendritic spine density and somal volume of deep layer 3 pyramidal neurons. Interestingly, spine density in DLPFC undergoes marked changes in postnatal development.²⁹ In addition, the authors provide intriguing evidence that the eliminated synapses are fully functional and not, as previously assumed, immature.³⁰

An important aspect of the pathophysiology of schizophrenia that is emphasized by several contributors (O'Donnell,² Hoftman and Lewis¹, and Uhlhaas and Singer⁴) is GABAergic interneurons.³¹ Hoftman and Lewis¹ summarize evidence to suggest that markers of parvalbumine-positive interneurons, such as the number of axon terminals of basket cells, change markedly during postnatal development until adulthood. In addition, there are substantial refinements during the adolescent period in the subcomposition of GABA_A receptors that affect the strength and speed of GABAergic transmission.

Gogtay et al.³ provide an overview of longitudinal studies that have examined brain development in patients with COS and in subjects at UHR. During normal adolescence, there is a reduction in GM until early adulthood²³ that is consistent with postmortem and animal studies indicating synaptic pruning. In COS patients, progressive reductions of cortical GM have been observed³² that could represent an exaggeration of the process seen during normal adolescence. Importantly, healthy siblings of COS patients have also reduced GM volumes,³³ but prefrontal and temporal GM deficits normalize by late adolescence. Thus, aberrant anatomical development during adolescence may be genetically influenced but environmental factors may also have a role.

In the second part of their article, Gogtay and colleagues³ summarize data from UHR cohorts that potentially allow the identification of brain changes prior to the onset of disorder. One major finding is that there may be progressive changes in GM and white matter (WM) that distinguish subjects who developed psychosis from those who did not, indicating the occurrence of late anatomical changes that may be related to the manifestation of psychosis.^{34,35} Although these findings are promising, the authors also note that neuroanatomical marker which can predict the development of psychosis have yet to be identified and that further longitudinal studies are required to reach a more detailed understanding of how environmental factors contribute to aberrant developmental processes.

The article by Uhlhaas and Singer⁴ examines the consequences of changes in anatomy and neurotransmitter systems for neural oscillations and their synchronization. In recent years, the possibility that schizophrenia involves a dysfunction in the synchronization of neural oscillations has received widespread interest as a potential mechanism to explain the cognitive dysfunctions and certain symptoms of the disorder.³⁶ However, it is currently unclear to what extent neural synchrony could also be involved in aberrant development of cortical networks in schizophrenia.

In their article, two important observations are made. First, synchronized neural oscillations are a prerequisite for the development of cortical circuits during early development periods and the continued anatomical modifications require precise temporal coordination. Second, neural synchrony is only fully expressed during the adolescent period that corresponds with changes in GABAergic neurotransmission and myelination of corticocortical pathways.

A comparison between those aspects of neural synchrony that undergo important modifications during normal adolescence and the deficits observed in schizophrenia furthermore highlights the possibility that the late maturation of cortical networks is abnormal in schizophrenia. This fact may also be related to the nonlinear developmental trajectory of cortical networks during the transition from adolescence to adulthood. Adolescence may involve a transient destabilization of coordinated network properties that increases the risk for vulnerable individuals to express a psychosis during this period.

Which implications have these findings for the treatment and perhaps prevention of schizophrenia? This important question is addressed in a commentary by McGorry.⁵ He questions the primacy of traditional neurodevelopmental approaches that have emphasized the contribution of an early deficit or lesion while neglecting the major changes in brain development and their interaction with the environment that occur during adolescence. According to McGorry, this approach has also impeded research into creating effective interventions during the perionset stages of schizophrenia.

To this end, he emphasizes the need to depart from traditional diagnostic practices and adopt a clinical staging approach.³⁷ This is particularly relevant for early intervention because there is a large overlap between nonspecific complaints and symptoms that are indicative for a major psychiatric disorder. As a consequence, young people with psychosis but also adolescents with other disorders require novel clinical interventions that reduce stigma and delay of treatment.

Conclusions

This themed issue has attempted to provide an update on recent findings from anatomy, physiology, and brain imaging that all point to fundamental changes in the ado-

lescent brain. These findings may stimulate novel perspectives and research into the relevance of adolescent brain maturation for the pathophysiology of schizophrenia. A necessary prerequisite for such a step will be, however, a more detailed understanding of the changes at multiple scales. Future research that aims to identify pathways that underlie the emergence of psychosis is likely to require an integrative approach from transmitter systems to large-scale cortical networks. Such studies may then point to crucial maturational processes in subjects who are at risk for developing schizophrenia and which could promote the disorganization of large-scale cortical networks. The multifaceted modifications of the adolescent brain require such an approach and point to the imminent need to improve early intervention and treatment of the disorder.

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