

# The Development of Neural Synchrony and Large-Scale Cortical Networks During Adolescence: Relevance for the Pathophysiology of Schizophrenia and Neurodevelopmental Hypothesis

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**Recent data from developmental cognitive neuroscience highlight the profound changes in the organization and function of cortical networks during the transition from adolescence to adulthood. While previous studies have focused on the development of gray and white matter, recent evidence suggests that brain maturation during adolescence extends to fundamental changes in the properties of cortical circuits that in turn promote the precise temporal coding of neural activity. In the current article, we will highlight modifications in the amplitude and synchrony of neural oscillations during adolescence that may be crucial for the emergence of cognitive deficits and psychotic symptoms in schizophrenia. Specifically, we will suggest that schizophrenia is associated with impaired parameters of synchronous oscillations that undergo changes during late brain maturation, suggesting an important role of adolescent brain development for the understanding, treatment, and prevention of the disorder.**

*Key words:* neural synchrony/adolescence/schizophrenia

## Introduction: Schizophrenia and Adolescence

Schizophrenia is a devastating psychotic disorder that affects multiple brain regions and their associated cognitive functions. While cognitive dysfunctions can be observed prior to the onset of psychotic symptoms reaching as far back as to childhood in subjects who subsequently develop the disorder,<sup>1,2</sup> the characteristic expression of psychotic symptoms is in the large majority of cases associated with the transition from adolescence to adulthood.<sup>3,4</sup> Furthermore, the clinical manifestation between the late teens and early 20s is preceded by a prodromal

period of up to 5 years,<sup>5</sup> suggesting a close temporal coincidence between the expression of schizophrenia and adolescence.

This fact has been cited as evidence by several investigators that disturbances in adolescent brain maturation may be crucially involved in the pathophysiology of schizophrenia.<sup>6–8</sup> Yet, the mechanisms underlying this central feature have remained elusive. The question is nonetheless at the very core of the pathophysiology of schizophrenia: Why does the disorder appear in its full spectrum during late brain development? Which neural events during this developmental stage promote the disorganization of cortical networks that lead to the life-long disability?

The neurodevelopmental hypothesis of schizophrenia has been predominantly framed in the context of early (peri- and prenatal) risk factors.<sup>9</sup> The contribution of birth complications, viral infections, and malnutrition has been shown to confer modest effect sizes that are hypothesized to lead to abnormal brain maturation.<sup>10</sup> The focus on early, aberrant brain maturation in the pathophysiology of schizophrenia may also be seen in the wider context of developmental studies that have concentrated to a large extent on early windows of development.

It has been held that the fundamental properties of cortical networks are sculpted mainly in utero and in the early postnatal years, but recent data from a range of disciplines require a reassessment of this notion. Later developmental periods, such as adolescence, are not confined to the refinement of cortical networks but are associated with a fundamental reorganization of large-scale, functional networks that may be relevant for the disorganization of brain functions in schizophrenia.<sup>11–13</sup>

In the following, we shall first review the evidence for changes in the structural and functional properties during adolescence and highlight the maturation of precise temporal coordination as a core phenomenon of this developmental process. Subsequently, we shall review evidence on synchronous, oscillatory activity in schizophrenia. We shall argue that the disorder is characterized by impairments in parameters that undergo maturational changes during the adolescent period. In the final part, possible candidate mechanisms for these changes are discussed as well as the implications of such findings for the understanding, treatment, and prevention of the disorder.

## Brain Development During Adolescence

### *Changes in Anatomy and Neurotransmitter Systems*

Since the seminal findings of Huttenlocher in the late 1970s,<sup>14</sup> which for the first time highlighted the occurrence of late modifications in synaptic connections during human development, schizophrenia researchers have advocated the potential importance of these data for understanding the late manifestation of schizophrenia during the transition from adolescence to adulthood. On the basis of these results, Feinberg<sup>7</sup> initially proposed that the onset of schizophrenia during adolescence is the result of an aberrant pruning process that involves an excess elimination of synaptic contacts.

Subsequent support for this hypothesis came from magnetic resonance imaging (MRI) studies that examined the developmental trajectory of gray matter volume changes during normal adolescence and in patients with childhood-onset schizophrenia (COS). During normal development, these studies revealed progressive patterns of reductions in the volume of cortical areas until early adulthood, which is consistent with findings from post-mortem analyses.<sup>15</sup> This pattern of gray matter loss was found to be accelerated in patients with COS.<sup>16</sup>

Aberrant maturation of white matter pathways during adolescence has also been proposed as a factor in the pathophysiology of schizophrenia.<sup>17</sup> Recent MR studies as well as earlier postmortem data established that myelination increases until early adulthood, specifically for long corticocortical tracts (for a review, see<sup>18</sup>). On the basis of these results, Benes<sup>19</sup> proposed that the myelination in the corticolimbic system may “trigger” the onset of psychosis during late adolescence in susceptible individuals.

Until recently, the focus in developmental research has been on changes in anatomy. However, maturation involves also important modifications of various transmitter systems and their composition of proteins controlling synaptic transmission and cellular excitability. Late-occurring changes in gamma amino butyric acidergic (GABAergic) neurotransmission have been demonstrated (see Hoftman and Lewis<sup>20</sup> in this issue). Similarly, developmental trends have been reported for the dopami-

nergic (see O’Donnell<sup>21</sup> in this issue) and glutamatergic systems<sup>22</sup> and for interactions of these neurotransmitters with GABAergic interneurons. The latter may be of particular relevance for synchronous oscillations because GABAergic interneurons and their interactions with excitatory neurotransmission have been shown to be critical for the generation of high-frequency oscillations.<sup>23</sup> Wang and Gao<sup>24</sup> reported a significant reduction in *N*-Methyl-D-Aspartat (NMDA)-mediated excitatory drive onto fast-spiking interneurons between juvenile and adult rats. In addition, Tseng and O’Donnell<sup>25</sup> found significant changes in the susceptibility of interneurons to dopaminergic D<sub>2</sub> receptor modulation during adolescence. Importantly, D<sub>2</sub> agonists were effective only in adult but not in prepubertal animals.

While these findings suggest important evidence on late-occurring anatomical and physiological modifications, the precise implications of these changes for coordinated network activity are unknown. In the next section, we shall argue that these anatomical and physiological changes impact critically upon the functional properties of large-scale cortical networks.

### *Synchronous Oscillations and the Development of Cortical Networks*

The synchronization of neural oscillations in the delta (0–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gamma band (30–100 Hz) has received increasing attention as a physiological mechanism underlying a wide range of perceptual and cognitive processes.<sup>26</sup> While research has focused on the functional relevance in the mature cortex, there is also ample evidence that synchronized, oscillatory activity plays an important role in structuring the development of cortical networks.<sup>27</sup>

Beginning with early development periods, synchronized oscillatory activity is essential for the shaping of cortical circuits and is a hallmark of the developing nervous system.<sup>28</sup> For example, patterned retinal activity synchronizes the activity of neurons in the neonatal visual cortex and is essential for the selection of appropriate connections.<sup>29,30</sup>

At later stages, the shaping and development of cortical networks are influenced by experience-dependent activity. Modifications of synaptic contacts are dependent upon correlated neural responses.<sup>31</sup> The strengthening and weakening of connections by spike timing-dependent plasticity depend on the precise sequence of pre- and postsynaptic spiking, whereby the critical window is in the range of milliseconds.<sup>32</sup> Evidence indicates that oscillations serve to establish such precise temporal relations between pre- and postsynaptic discharges. Stimulation of neurons during the depolarizing peak of the theta cycle in the hippocampus favors long-term potentiation, whereas stimulation in the trough causes depression.<sup>33</sup> The same relationship holds for oscillations in the beta and gamma frequency range,<sup>34</sup> indicating that

precisely timed theta and beta/gamma oscillations are crucial for the strengthening (consolidation) and weakening (disruption) of synaptic contacts.

#### *Maturation of Neural Oscillations and Synchrony During Adolescence*

Following early developmental periods, changes in the amplitude of neural oscillations and their synchronization continue until early adulthood, suggesting ongoing modifications in network properties. One of the most replicated findings is the change in resting-state oscillations. In the adult brain, resting-state activity is characterized by prominent alpha oscillations over occipital regions while low (delta, theta) and high (beta, gamma) frequencies are attenuated. During adolescence, there is a reduction in the amplitude of oscillations over a wide frequency range, particularly in the delta and theta band,<sup>35</sup> while oscillations in the alpha and beta range become more prominent with age.<sup>36</sup> Topographically, these changes occur more rapidly in posterior than in frontal regions and follow a linear trajectory until age 30.<sup>35</sup>

Changes in the amplitude of oscillations are accompanied by modifications in the synchrony of resting-state oscillations. Thatcher et al<sup>37</sup> investigated changes in the coherence of beta oscillation in children and adolescents between 2 months and 16 years of age. During development, beta-band coherence increased over shorter distances (<6 cm) while long-range coherence (>24 cm) did not vary with age. Pronounced increases in long-range coherence in the alpha band were reported by Srinivasan et al.<sup>38</sup> The authors tested coherence in electroencephalographic (EEG) data in 20 children (6–11 y) and 23 adults (18–23 y). Reduced power over anterior electrodes in children was accompanied by reduced coherence between anterior and posterior periods, indicating a late maturation of long-range coupling between frontal and parietal regions.

Recent studies have also begun to examine the effects of sensory stimulation and cognitive processes on oscillations and synchrony during the adolescent period. Rojas et al<sup>39</sup> examined the 40-Hz auditory steady-state response (SSR) in magnetoencephalographic (MEG) data in 69 participants in the age range of 5–52 years. A marked increase in 40-Hz power was observed during childhood and adolescence and appeared to reach a plateau during early adulthood. A similar protracted development was found in a study by Poulsen et al.<sup>40</sup> In addition to an overall increase in the 40-Hz response during adolescence, SSRs in adults were characterized by a reduced variability and higher peak frequencies than in children.

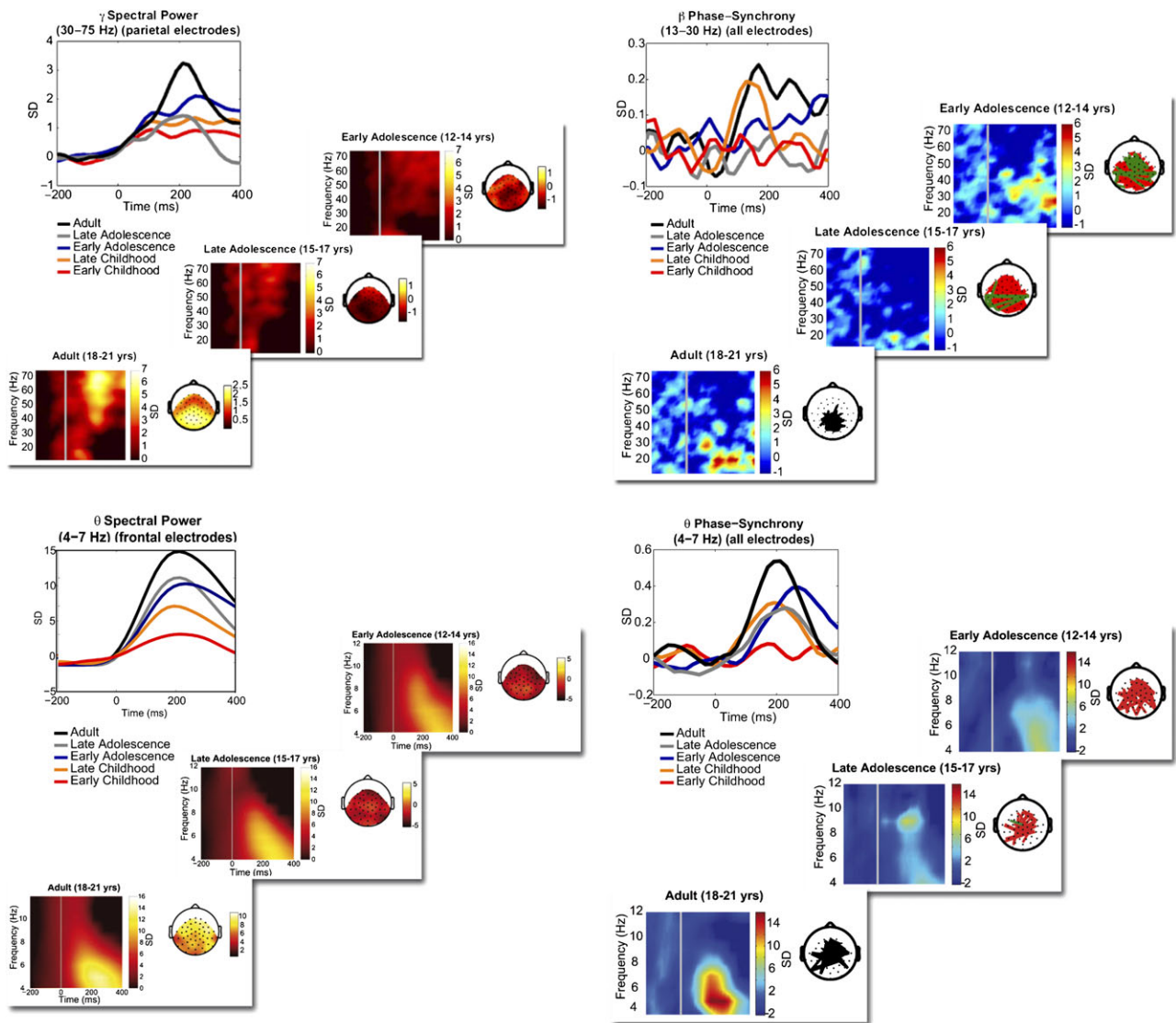
Data on increased amplitude and precision of gamma oscillations in the SSR paradigm are consistent with changes in evoked oscillations during sensory processing. Werkle-Bergner et al<sup>41</sup> tested the amplitude and phase stability of evoked gamma-band oscillations during the

perception of squares and circles in children (10–12 y), young adults (20–26 y), and older adults (70–76 y). Evoked oscillations in children were significantly reduced between 30 and 148 Hz over occipital electrodes relative to adults and did not show a modulation by the size of the stimulus. Moreover, Yordanova et al<sup>42</sup> reported also differences in alpha oscillations between children and adults during an auditory oddball paradigm. In adult participants, phase locking of alpha oscillations was significantly increased while the amplitude was lower than in children. Together with the findings from SSRs, these data suggest that during the adolescent period, cortical circuits undergo a fine-tuning that facilitates sensory processing in auditory and visual cortices.

Late development has also been demonstrated for induced oscillations and their synchronization. In contrast to evoked (stimulus locked) activity, induced oscillations are characterized by variable latencies from trial to trial and reflect self-generated, rhythmic activity that is thought to support higher cognitive functions, such as memory, attention, and consciousness.<sup>26</sup> The development of induced oscillations in the 4- to 80-Hz frequency range was examined in children, adolescent participants, and young adults during the perception of Mooney faces (figure 1) in a recent study by our group.<sup>11</sup> In adult participants, perceptual integration of Mooney faces was accompanied by prominent increases in gamma-band oscillations over parietal electrodes as well as by theta activity over frontal regions. In addition, phase synchrony of induced oscillations, an index for the functional coupling of neural assemblies, was assessed. Long-range synchrony was found in the theta frequency range between frontoparietal electrodes while beta/gamma phase synchrony was focused over parietooccipital electrodes.

During adolescence, apparent changes in these parameters occurred that correlated with improved detection rates and reaction times. In particular, phase synchrony in the beta and gamma band increased until age 14 and was then followed by a reduction during late adolescence (15–17 y) before synchrony increased again sharply in 18- to 21-year olds. This nonlinear development of phase synchrony was accompanied by a reorganization in the topography of phase synchrony patterns in the beta band. Whereas in the mature cortex, phase synchrony was concentrated over parietooccipital regions, younger age groups displayed phase synchrony predominantly between temporal and frontal electrodes, suggesting that an immature proto-network becomes reorganized during the transition from adolescence to adulthood.

Developmental trends were also found for theta- and gamma-band spectral power and theta phase synchrony. Again, changes were particularly marked during the transition from adolescence to adulthood with adult participants showing enhanced theta- and gamma-band oscillations compared with younger age groups. Finally, phase synchrony between frontal



**Fig. 1.** Development of task-related neural synchrony. Left panels—top: Comparison of spectral power of oscillations in the 30- to 75-Hz range over parietal electrodes between 100 and 300 ms during the presentation of Mooney faces at different ages and time-frequency maps (*x*-axis: time; *y*-axis: normalized spectral power in SD) for early adolescent, late adolescent, and adult participants. Bottom panel: Comparison of theta-band oscillations (4–7 Hz) over frontal electrodes between 100 and 300 ms for early adolescent, late adolescent, and adult participants. The data show that amplitude of both theta- and gamma-band oscillations increase significantly during the transition from adolescence to adulthood. Right panels—top: Comparison of phase synchrony in the 13- to 30-Hz frequency range for all electrode pairs between 100 and 300 ms at different ages (top left panel) and phase synchrony charts of oscillations in the beta and gamma band averaged across all electrodes (*x*-axis: time; *y*-axis: normalized phase synchrony in SD) for early adolescent, late adolescent, and adult participants. The phase synchrony of beta-band oscillations increased until early adolescence and was then substantially reduced during late adolescence, suggesting that cortical networks reorganize during the transition from adolescence to adulthood. A linear, late developmental trend was also found for theta-band (4–7 Hz) phase synchrony (bottom) for all electrode pairs between 100 and 300 ms.

and parietal circuits was significantly increased during adolescence.

A similar finding was reported by Müller et al<sup>43</sup> for phase synchrony of evoked and induced delta and theta oscillations during an auditory oddball task. Differences in the synchronization and amplitude of oscillations in EEG data were most prominent between children and young adults. Children were characterized by reduced synchronization in local circuits over frontocentral

electrodes at delta and theta frequencies and reduced long-range synchronization in delta and theta bands. However, this reduced local and long-range synchronization was accompanied by a relative increase in the power of evoked and induced oscillations in the same frequencies. This indicates that, as development progresses, networks oscillating at low frequencies become replaced by more precisely networks oscillating at higher frequencies.

In summary, the current data suggest important, late-occurring modifications in synchrony and amplitude of neural oscillations at different frequencies during the adolescent period. Cortical networks increasingly express high-frequency oscillations in combination with enhanced long-range synchronization. This suggests that precise temporal coding in large-scale networks is an achievement that occurs relatively late during brain maturation.

### **Impairments in Synchronized Oscillations in Schizophrenia: Involvement of Aberrant Brain Development During Adolescence**

#### *Deficits in Synchronized, Oscillatory Activity in Schizophrenia*

Impairments in synchronized, oscillatory activity have emerged recently as a potentially fundamental pathophysiological mechanism in schizophrenia.<sup>44</sup> This is due to the fact that aberrant neural oscillations and their synchronization can account for the enduring deficits in cognition and some of the psychotic symptoms of the disorder. Moreover, deficits in the synchronization of gamma-band oscillations are consistent with current theories emphasizing alterations in the balance between GABAergic and glutamatergic neurotransmission.<sup>45</sup> It is unclear at present, however, to what extent dysfunctions in synchronized, oscillatory activity may also account for the neurodevelopmental profile of the disorder and at which developmental stage such deficits may arise.

The observation that the amplitude and synchrony of neural oscillations undergo important modifications during normal adolescence suggests that in schizophrenia, developmental processes during this period are aberrant and cause impaired temporal coding and cognitive dysfunctions. A comparison between parameters that are impaired in schizophrenia and those involved in adolescent brain maturation supports this hypothesis (see table 1).

Schizophrenia patients are characterized by changes in neural oscillations both during the resting state as well as during cognitive and perceptual stimulation across a wide frequency range.<sup>44</sup> One particularly salient feature of resting-state activity is an increase in slow oscillations, especially over frontal electrodes, which has been interpreted as a sign of physiological inefficiency. In addition, there is evidence for reduced coherence in several spectral bands (for a review, see<sup>46</sup>). Both the amplitude and coherence of those resting-state oscillations that undergo significant changes during adolescence are impaired in schizophrenia.

One of the most consistent findings in schizophrenia is impairment in sensory-evoked oscillations during visual and auditory processing. These dysfunctions involve impaired auditory SSRs to stimulation at 40 Hz<sup>47,48</sup> as well as deficits in the amplitude and phase locking of alpha, beta, and gamma oscillations during visual and auditory processing,<sup>49–51</sup> suggesting an impaired ability to pre-

cisely align oscillatory activity with incoming sensory information. Comparison between the developmental trajectory of stimulus-evoked oscillations, in particular with respect to the maturation of phase locking, and the respective impairments in schizophrenia reveals similarities, suggesting that the developmental fine-tuning of temporal coding in sensory cortices fails during adolescence in schizophrenia patients.

Schizophrenia is also associated with impairments in induced oscillations and their large-scale synchronization that are associated with core symptoms of the disorder.<sup>50,52,53</sup> Phase synchrony of induced oscillations has been shown to be impaired during auditory and visual processing in the beta and gamma range implicating a functional disconnection syndrome.<sup>50,53</sup> Some studies report that these deficits in phase locking are independent of reductions in the power of induced oscillations<sup>53</sup> while other studies have provided evidence for additional circumscribed reductions in induced gamma-band activity, especially over frontal regions.<sup>54</sup>

Developmental findings on the maturation of induced oscillatory activity suggest that this process may be particularly vulnerable to developmental disruptions during adolescence. Our own findings suggest that the full expression of precise synchrony and high-frequency activity is preceded by a transient disruption of long-distance synchronization, probably reflecting a developmental destabilization of functional networks. This supports the notion of a vulnerable phase in late adolescence.

The close correspondence between the developmental changes in the amplitude and synchrony of neural oscillations and the impairments associated with schizophrenia are compatible with our view that deficits in schizophrenia may be associated with aberrant adolescent brain development. However, to obtain more direct evidence, longitudinal studies are required that examine changes in neural synchrony during adolescence in at-risk subjects.

An alternative interpretation is that synchronized, oscillatory activity is normal prior to the breakdown of coordinated network activity and the expression of the full range of psychotic symptoms. In this case, same hitherto unidentified causes would have to be associated that reverse some of the late developmental processes, leading to a deterioration of temporal coordination and as a consequence to psychotic symptomatology. Several facts argue against the hypothesis for such a “physiological regression.” Evidence suggests that impairments in evoked oscillations and resting state are also present in first-degree relatives,<sup>46,55</sup> suggesting that the observed changes in neural oscillations are likely to reflect directly the genetic predisposition of the disorder. In addition, other indices of functional networks, such as functional MRI (fMRI) measures of functional connectivity, have been found to be impaired in subjects who are at risk for developing schizophrenia,<sup>56</sup> suggesting that the specific impairments are already present prior to illness onset.

**Table 1.** Changes in Neural Synchrony in Adolescence and Schizophrenia

Measure	Change During Adolescence	Effect in Schizophrenia
Resting-state oscillations	Reduction in the amplitude of delta and theta oscillations, while alpha oscillations increase. In addition, increased coherence in the alpha and beta band is observed.	Consistent support for increased delta and theta oscillations as well as for reduced alpha-band power. There is evidence for reduced coherence of resting-state oscillations.
Steady-state responses	Increases in the amplitude and peak frequency of auditory SSRs to stimulation at 40 Hz.	Robust reductions in both the amplitude and the phase locking of 40-Hz auditory SSRs.
Evoked oscillations	Increased phase locking of evoked alpha- and gamma-band oscillations during adolescence, possibly accompanied by reductions in the power of evoked oscillations.	Consistent evidence for deficits in phase locking of evoked oscillations in the alpha and gamma bands. Conflicting evidence in regard to abnormalities in the power of evoked oscillations.
Induced oscillations	Pronounced increases in power of induced theta- and gamma-band oscillations. These changes are characterized by increases in long-distance synchronization at low (delta, theta) and high (beta/gamma) frequencies.	Pronounced impairments in beta- and gamma-band phase synchrony as well as reduced theta- and gamma-band power.

*The Neurodevelopmental Hypothesis of Schizophrenia and Neural Oscillations: Early Brain Development and the Onset of Psychosis*

As mentioned earlier, synchronized, neural oscillations are critical during pre- and perinatal development periods. Accordingly, it is possible that the genetic predisposition or early epigenetic factors interfere with rhythmic electrical activity that is crucially involved in the shaping of cortical circuits in pre- and perinatal periods. Thus, abnormal neural oscillations during early development could give rise to abnormal wiring that in turn causes disturbances in temporal coordination, thus initiating a vicious circle that eventually causes a decompensation of the system’s dynamics (figure 2).

Indications for major developmental changes at the transition from late adolescence and adulthood have also been obtained in recent fMRI studies. Galvan and colleagues<sup>57</sup> investigated the development of neural systems involved in reward-seeking behaviors. Interestingly, adolescent participants were characterized by exaggerated nucleus accumbens activity to large reward values relative to children and adults while the activation of the orbitofrontal cortex was similar to children. This study and related work on emotion perception by the same group<sup>58</sup> have led to the hypothesis that adolescent brain maturation involves a transient imbalance between hyperactive subcortical regions and an immature prefrontal cortex that characterizes a unique stage of brain development.

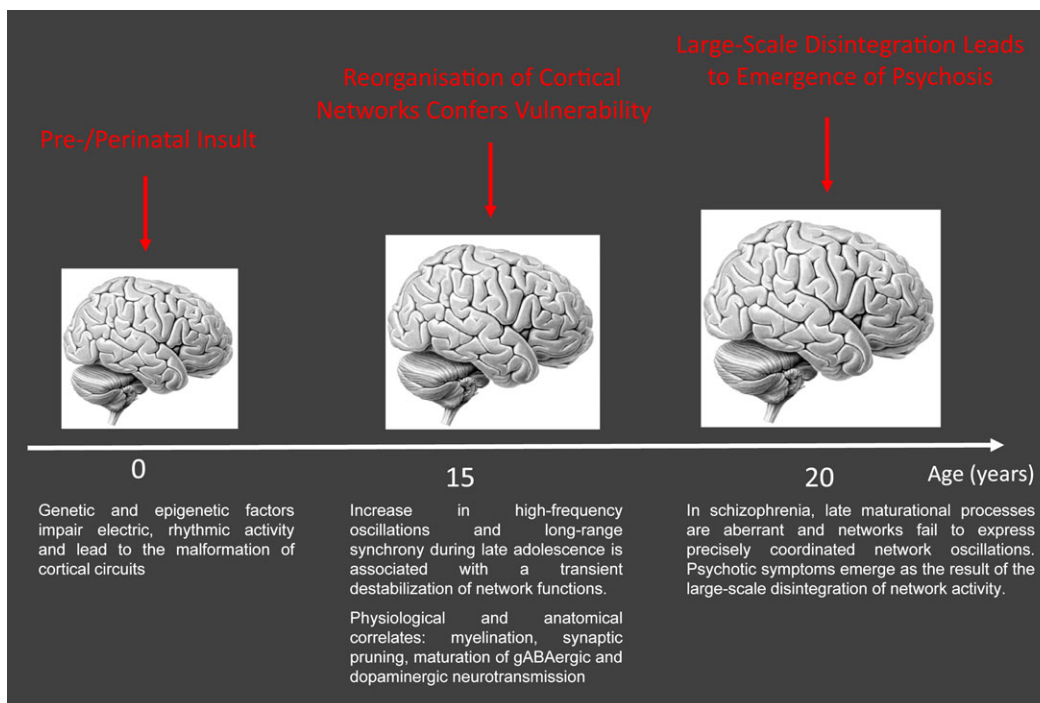
From a dynamical systems perspective, the nonlinear, developmental trajectory of functional networks during adolescence is consistent with idea that phase transitions between different states of a system are characterized by

critical fluctuations.<sup>59</sup> In the adolescent brain, the transient reduction in large-scale synchronization of cortical networks and the concomitant increase of subcortical input could be a condition that favors critical fluctuations. If these become supracritical at the time when the developing system undergoes the phase transition toward the adult state, it could remain in a wrong bifurcation and fail to accomplish the last development steps: (1) the increase in the precision of synchronized, high-frequency oscillations, (2) the integration of frontal and subcortical activity patterns, and (3) the shift in the balance between local and global coordinated brain states.

Taken together, the available evidence suggests the possibility that the late manifestation of schizophrenia may be intimately linked to the nonlinear developmental processes that characterize late adolescence. Accordingly, the emergence of psychotic symptoms would have to be regarded as a consequence of the disintegration of large-scale temporal coordination of distributed cortical networks. While mild psychotic symptoms can be traced back to childhood and are present during the prodrome, full-blown psychotic symptoms nonetheless emerge during late adolescence and early adulthood.

*Changes in Physiological, Anatomical, and Genetic Parameters During Adolescence and the Development of Synchronized, Oscillatory Activity: Implications for Schizophrenia*

The disturbances in the maturation of neural synchrony and large-scale cortical networks during adolescence are likely to reflect aberrant development of several physiological and anatomical parameters that are critical for the



**Fig. 2.** Maturation of neural synchrony and the neurodevelopmental hypothesis of schizophrenia.

generation of synchronous, oscillatory activity. Of these changes, we consider abnormal maturation of white matter fiber pathways to be of particular relevance because corticocortical tracts establish temporal correlations between and within neural assemblies.<sup>60</sup>

Increased myelination during adolescence decreases conduction times and reduces the latency of responses,<sup>61</sup> thereby facilitating the precision with which synchrony can be established between brain regions. Thus, impaired development of white matter pathways could lead to reduced synchrony. However, it is also conceivable that aberrant developmental processes promote the stabilization of connections that are normally pruned away during normal development<sup>62</sup> and that these persistent connections facilitate pathological coactivation of brain regions leading to psychotic symptoms.

Another pathological mechanism could be the profound modifications in GABAergic neurotransmission that occur during late development. For example, the switches in GABA<sub>A</sub> receptor composition<sup>63</sup> could be responsible for the pronounced increases in gamma oscillations during the transition from adolescence to adulthood. The observed reduction in the duration of inhibitory post-synaptic potentials in pyramidal neurons is compatible with this interpretation because this variable is crucial for the precision and frequency of network oscillations.<sup>64</sup>

Recent data from gene expression profile studies indicate that one possible source for disturbances in adolescent brain maturation could be deficits in the expression

of specific genes. Harris et al<sup>65</sup> used whole-genome arrays to measure gene expression in postmortem prefrontal cortex tissue of normal subjects between 0 and 49 years of age. The authors observed continued changes in gene categories during adolescence that are involved in the pathophysiology of schizophrenia, such as neuregulin, and genes involved in myelination and metabolism. These findings support the possibility that late-occurring genetic and epigenetic disturbances could potentially impact upon the anatomical and physiological parameters important for the maturation of neural oscillations during adolescence.

Direct links can also be established with environmental factors, such as cannabis, that may be particularly critical for adolescent brain maturation. Cannabis is currently viewed as an important risk factor for the development of schizophrenia, but the neurobiological processes underlying this relationship are unknown. Bossong and Niesink<sup>66</sup> have proposed that adolescent exposure to  $\Delta^9$ -tetrahydrocannabinol can transiently disturb the physiological control of glutamate and GABA release. As mentioned above, both systems contribute to the generation of synchronized, high-frequency oscillations.

There is also evidence that cannabinoids directly impair synchronized network activity. Robbe et al<sup>67</sup> examined the effects of cannabinoids on theta- and gamma-band activity during working memory in the hippocampus of freely moving rats. Administration of cannabinoids led to a reduction in theta and gamma oscillations, which correlated with the degree of working

memory impairment. In addition, the temporal coordination of cell assemblies was profoundly disrupted while firing rates were only marginally affected, suggesting that cannabinoids are critical for neural oscillations. These findings highlight the possibility that continued abuse of cannabinoids may severely disrupt network activity and the development of cortical networks and thus facilitate the emergence of psychosis.

### Discussion: Implications for Treatment and Prevention

The neurodevelopmental hypothesis of schizophrenia has been predominantly conceptualized in the context of early disturbances in pre- and perinatal brain maturation, while putting less emphasis on the profound changes in the structure, organization, and function of cortical networks that occur during the adolescent period. The findings reviewed above indicate that the maturation of synchronized, oscillatory activity during the transition from adolescence to adulthood involves the modification of important parameters that may be crucial for understanding the pathophysiology of schizophrenia. Furthermore, several anatomical and physiological functions have been identified that are likely to support the continued maturation of neural oscillations that may be abnormal in schizophrenia.

One possible implication is that cortical networks may be considered particularly susceptible for therapeutic interventions during this very same phase. This could involve a wide range of approaches, such as cognitive remediation, targeted pharmacological interventions, and direct manipulation of neural synchrony through biofeedback and possibly transcranial direct current stimulation. However, a necessary prerequisite for such interventions is a more detailed understanding of the changes that occur in the adolescent brain at multiple scales. Modifications in several neurotransmitter systems, the maturation of white matter fiber tracts, and the pruning of cortical connections are likely to impact on the strength, precision, and synchronization of neural oscillations.

The hypothesis that adolescent brain development involves a nonlinear trajectory deserves also attention in its own rights. Late adolescence is a period of major physiological and psychological changes that may obscure the clear differentiation between a turbulent adolescent development and a developmental trajectory leading to schizophrenia. Future studies will need to clarify in more detail the nature and functional meaning of the changes observed in adolescent brain development by employing both functional and structural brain imaging techniques. In particular, studies that examine adolescents at high risk for schizophrenia longitudinally are required that test specifically the hypothesis that large-scale cortical networks disintegrate

during the phase transition between adolescence and adulthood.

Given the obvious relationship between the onset of schizophrenia and adolescent brain development, understanding the physiological and anatomical changes during this developmental period may prove crucial for better therapies and perhaps even prevention of schizophrenia. The field has neglected these changes for too long. It is time to change this balance.

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### References

1. Reichenberg A, Caspi A, Harrington H, et al. Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. *Am J Psychiatry*. 2010;167:160–169.
2. Walker EF, Savoie T, Davis D. Neuromotor precursors of schizophrenia. *Schizophr Bull*. 1994;20:441–451.
3. Kraepelin E. *Dementia Praecox and Paraphrenia*. Edinburgh, UK: E. and S. Livingstone; 1919.
4. Hafner H, Maurer K, Löffler W, Riecher-Rössler A. Schizophrenia and age. *Nervenarzt*. 1991;62:536–548.
5. Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry*. 2001;58:158–164.
6. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44:660–669.
7. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982;17:319–334.
8. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. *J Psychiatr Res*. 1994;28:239–265.
9. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br Med J (Clin Res Ed)*. 1987;295:681–682.
10. Cannon M, Murray RM. Neonatal origins of schizophrenia. *Arch Dis Child*. 1998;78:1–3.
11. Uhlhaas PJ, Roux F, Singer W, Haenschel C, Sireteanu R, Rodriguez E. The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. *Proc Natl Acad Sci U S A*. 2009;106:9866–9871.
12. Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. *PLoS Biol*. 2009;7:e1000157.
13. Casey BJ, Duhoux S, Malter Cohen M. Adolescence: what do transmission, transition, and translation have to do with it? *Neuron*. 2010;67:749–760.



14. Huttenlocher PR. Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res.* 1979;163:195–205.
15. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A.* 2004;101:8174–8179.
16. Thompson PM, Vidal C, Giedd JN, et al. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc Natl Acad Sci U S A.* 2001;98:11650–11655.
17. Woo TU, Crowell AL. Targeting synapses and myelin in the prevention of schizophrenia. *Schizophr Res.* 2005;73:193–207.
18. Paus T. Growth of white matter in the adolescent brain: myelin or axon? *Brain Cogn.* 2010;72:26–35.
19. Benes FM. Why does psychosis develop during adolescence and early adulthood? *Curr Opin Psychiatry.* 2003;16:317–319.
20. Hoftman GD, Lewis DA. Postnatal developmental trajectories of neural circuits in the primate prefrontal cortex: identifying sensitive periods for vulnerability to schizophrenia. *Schizophr Bull.* 2011;37:493–503.
21. O'Donnell P. Adolescent onset of cortical disinhibition in schizophrenia: insights from animal models. *Schizophr Bull.* 2011;37:484–492.
22. Anderson SA, Classey JD, Conde F, Lund JS, Lewis DA. Synchronous development of pyramidal neuron dendritic spines and parvalbumin-immunoreactive chandelier neuron axon terminals in layer III of monkey prefrontal cortex. *Neuroscience.* 1995;67:7–22.
23. Sohal VS, Zhang F, Yizhar O, Deisseroth K. Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature.* 2009;459:698–702.
24. Wang HX, Gao WJ. Cell type-specific development of NMDA receptors in the interneurons of rat prefrontal cortex. *Neuropsychopharmacology.* 2009;34:2028–2040.
25. Tseng KY, O'Donnell P. Dopamine modulation of prefrontal cortical interneurons changes during adolescence. *Cereb Cortex.* 2007;17:1235–1240.
26. Uhlhaas PJ, Pipa G, Lima B, et al. Neural synchrony in cortical networks: history, concept and current status. *Front Integr Neurosci.* 2009;3:17.
27. Uhlhaas PJ, Roux F, Rodriguez E, Rotarska-Jagiela A, Singer W. Neural synchrony and the development of cortical networks. *Trends Cogn Sci.* 2010;14:72–80.
28. Khazipov R, Luhmann HJ. Early patterns of electrical activity in the developing cerebral cortex of humans and rodents. *Trends Neurosci.* 2006;29:414–418.
29. Stellwagen D, Shatz CJ. An instructive role for retinal waves in the development of retinogeniculate connectivity. *Neuron.* 2002;33:357–367.
30. Cang J, Renteria RC, Kaneko M, Liu X, Copenhagen DR, Stryker MP. Development of precise maps in visual cortex requires patterned spontaneous activity in the retina. *Neuron.* 2005;48:797–809.
31. Hebb DO. *The Organization of Behaviour: A Neuropsychological Theory.* New York, NY: Wiley; 1949.
32. Markram H, Lubke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science.* 1997;275:213–215.
33. Huerta PT, Lisman JE. Heightened synaptic plasticity of hippocampal CA1 neurons during a cholinergically induced rhythmic state. *Nature.* 1993;364:723–725.
34. Wespapat V, Tennigkeit F, Singer W. Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *J Neurosci.* 2004;24:9067–9075.
35. Whitford TJ, Rennie CJ, Grieve SM, Clark CR, Gordon E, Williams LM. Brain maturation in adolescence: concurrent changes in neuroanatomy and neurophysiology. *Hum Brain Mapp.* 2007;28:228–237.
36. Gasser T, Verleger R, Bacher P, Sroka L. Development of the EEG of school-age children and adolescents. I. Analysis of band power. *Electroencephalogr Clin Neurophysiol.* 1988;69:91–99.
37. Thatcher RW, North DM, Biver CJ. Development of cortical connections as measured by EEG coherence and phase delays. *Hum Brain Mapp.* 2008;29:1400–1415.
38. Srinivasan R. Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. *Clin Neurophysiol.* 1999;110:1351–1362.
39. Rojas DC, Maharajh K, Teale PD, et al. Development of the 40Hz steady state auditory evoked magnetic field from ages 5 to 52. *Clin Neurophysiol.* 2006;117:110–117.
40. Poulsen C, Picton TW, Paus T. Age-related changes in transient and oscillatory brain responses to auditory stimulation during early adolescence. *Dev Sci.* 2009;12:220–235.
41. Werkle-Bergner M, Shing YL, Muller V, Li SC, Lindenberger U. EEG gamma-band synchronization in visual coding from childhood to old age: evidence from evoked power and inter-trial phase locking. *Clin Neurophysiol.* 2009;120:1291–1302.
42. Yordanova JY, Kolev VN. Developmental changes in the alpha response system. *Electroencephalogr Clin Neurophysiol.* 1996;99:527–538.
43. Muller V, Gruber W, Klimesch W, Lindenberger U. Lifespan differences in cortical dynamics of auditory perception. *Dev Sci.* 2009;12:839–853.
44. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci.* 2010;11:100–113.
45. Lewis DA, Moghaddam B. Cognitive dysfunction in schizophrenia: convergence of gamma-aminobutyric acid and glutamate alterations. *Arch Neurol.* 2006;63:1372–1376.
46. Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iacono W. The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophr Res.* 2008;99:225–237.
47. Spencer KM, Salisbury DF, Shenton ME, McCarley RW. Gamma-band auditory steady-state responses are impaired in first episode psychosis. *Biol Psychiatry.* 2008;64:369–375.
48. Kwon JS, O'Donnell BF, Wallenstein GV, et al. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch Gen Psychiatry.* 1999;56:1001–1005.
49. Haenschel C, Linden DE, Bittner RA, Singer W, Hanslmayr S. Alpha phase locking predicts residual working memory performance in schizophrenia. *Biol Psychiatry.* 2010;68:595–598.
50. Spencer KM, Nestor PG, Niznikiewicz MA, Salisbury DF, Shenton ME, McCarley RW. Abnormal neural synchrony in schizophrenia. *J Neurosci.* 2003;23:7407–7411.
51. Hirano S, Hirano Y, Maekawa T, et al. Abnormal neural oscillatory activity to speech sounds in schizophrenia: a magnetoencephalography study. *J Neurosci.* 2008;28:4897–4903.
52. Ford JM, Mathalon DH, Whitfield S, Faustman WO, Roth WT. Reduced communication between frontal and temporal lobes during talking in schizophrenia. *Biol Psychiatry.* 2002;51:485–492.

53. Uhlhaas PJ, Linden DE, Singer W, et al. Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci.* 2006;26:8168–8175.
54. Cho RY, Konecky RO, Carter CS. Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci U S A.* 2006;103:19878–19883.
55. Hong LE, Summerfelt A, Mitchell BD, et al. Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch Gen Psychiatry.* 2008;65:1008–1016.
56. Crossley NA, Mechelli A, Fusar-Poli P, et al. Superior temporal lobe dysfunction and frontotemporal dysconnectivity in subjects at risk of psychosis and in first-episode psychosis. *Hum Brain Mapp.* 2009;30:4129–4137.
57. Galvan A, Hare TA, Parra CE, et al. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *J Neurosci.* 2006;26:6885–6892.
58. Hare TA, Tottenham N, Galvan A, Voss HU, Glover GH, Casey BJ. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol Psychiatry.* 2008;63:927–934.
59. Haken H. *Principles of Brain Functioning. A Synergetic Approach to Brain Activity, Behavior, and Cognition.* Berlin, Germany: Springer; 1996.
60. Engel AK, König P, Kreiter AK, Singer W. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science.* 1991;252:1177–1179.
61. Salami M, Itami C, Tsumoto T, Kimura F. Change of conduction velocity by regional myelination yields constant latency irrespective of distance between thalamus and cortex. *Proc Natl Acad Sci U S A.* 2003;100:6174–6179.
62. Innocenti GM, Price DJ. Exuberance in the development of cortical networks. *Nat Rev Neurosci.* 2005;6:955–965.
63. Hashimoto T, Nguyen QL, Rotaru D, et al. Protracted developmental trajectories of GABAA receptor alpha1 and alpha2 subunit expression in primate prefrontal cortex. *Biol Psychiatry.* 2009;65:1015–1023.
64. Wang XJ, Buzsáki G. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J Neurosci.* 1996;16:6402–6413.
65. Harris LW, Lockstone HE, Khaitovich P, Weickert CS, Webster MJ, Bahn S. Gene expression in the prefrontal cortex during adolescence: implications for the onset of schizophrenia. *BMC Med Genomics.* 2009;2:28.
66. Bossong MG, Niesink RJ. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Prog Neurobiol.* 2010;92:370–385.
67. Robbe D, Montgomery SM, Thome A, Rueda-Orozco PE, McNaughton BL, Buzsáki G. Cannabinoids reveal importance of spike timing coordination in hippocampal function. *Nat Neurosci.* 2006;9:1526–1533.