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Age of Onset of Schizophrenia: Perspectives From Structural Neuroimaging Studies

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Many of the major neuropsychiatric illnesses, including schizophrenia, have a typical age of onset in late adolescence. Late adolescence may reflect a critical period in brain development making it particularly vulnerable for the onset of psychopathology. Neuroimaging studies that focus on this age range may provide unique insights into the onset and course of psychosis. In this review, we examine the evidence from 2 unique longitudinal cohorts that span the ages from early childhood through young adulthood; a study of childhood-onset schizophrenia where patients and siblings are followed from ages 6 through to their early twenties, and an ultra-high risk study where subjects (mean age of 19 years) are studied before and after the onset of psychosis. From the available evidence, we make an argument that subtle, regionally specific, and genetically influenced alterations during developmental age windows influence the course of psychosis and the resultant brain phenotype. The importance of examining trajectories of development and the need for future combined approaches, using multimodal imaging together with molecular studies is discussed.

Key words: schizophrenia/adolescent/brain development/high risk/neural circuitry/prefrontal cortex

Introduction

Schizophrenia is a complex and debilitating brain disorder that typically emerges in late adolescence and early adulthood and is characterized by hallucinations and delusions (commonly known as positive symptoms), social withdrawal, alogia, and flat affect (negative symptoms), and cognitive disabilities. Schizophrenia afflicts approximately 1% of the population worldwide incurring substantial individual, family, and societal costs[1] along with shortened life span.[2]

As is the case with many major neuropsychiatric illnesses, the typical age of onset for schizophrenia is in late adolescence or early twenties, with a slightly later onset in females.[3] Several lines of evidence have suggested that the pathogenesis of the disorder may be rooted in early development[4] and that brain changes during this period are relevant.[5,6] According to the neurodevelopmental theory of schizophrenia proposed by Weinberger[7] and by Murray and Lewis,[8] early brain insults affect prenatal brain development and resultant pathophysiological mechanisms, causing dysfunction of the mature brain predisposing to schizophrenia. While the main protagonist of this notion[7] proposed that schizophrenia results from a second trimester insult, the available evidence suggests that insults at all stages of development are relevant, which may explain the heterogeneity of brain structural abnormalities in schizophrenia.[9–11] Thus, recent clinical, genetic, cognitive, and imaging studies have provided a better conceptualization of the pathophysiology of schizophrenia, and revised neurodevelopmental models have been proposed that implicate early as well as late neurodevelopmental processes.[9,12,13] These revisions posit that quantitative pathogenic biological events are present in early life that undergo various developmental stages predisposed by complex genetic influences[14] and environmental "hits" that continue through all phases of the illness,[15,16] a notion similar to that proposed by others (eg, Keshavan and Hogarty[17]). Alternatively, the available evidence may be explained as reflecting an interaction between the timing of a hit (ie, maturational stages) with the age of onset of the disorder.[9,10,18] In the context of these notions, an examination of the nature and extent of brain changes in

relation to both the timing of schizophrenia onset and brain maturational stage is likely to be informative.

Adolescence is a critical period of neural development, and the relationship between normal brain maturation and onset of psychopathology in this age group has been an area of intense investigation over the past 2 decades.[6,19–24] Recent neuroimaging studies have examined trajectories of brain change during normal development and with the onset of psychopathology, affording a perspective on the relationship between dynamic brain changes and illness onset in disorders such as schizophrenia. Importantly, such trajectories should also be examined from a neuropsychological and functional perspective, however, this is beyond the limits of the present article.[25]

The aim of the present review is to provide an overview on normal and psychiatrically abnormal brain structure during the childhood and adolescent period. We attempt to identify the vulnerabilities during normal brain development that may explain progressive brain changes occurring in schizophrenia and examine the impact of developmental stage at illness onset on the nature and extent of brain changes observed. While we review the literature in general, we focus particularly on the imaging findings of 2 important prospective cohorts of schizophrenia; a longitudinal cohort of childhood-onset schizophrenia (COS) studied at the US National Institute of Mental Health (NIMH), and another longitudinal cohort of ultra-high risk (for schizophrenia; UHR) group being studied in Melbourne, Australia.

Child and Adolescent Brain Development

The increased spatial resolution available with magnetic resonance imaging (MRI) allows a reliable, automated quantitative measurement of several brain regions, which combined with periodic rescanning in pediatric and adult populations, allows us to examine trajectories of brain change longitudinally. Over the past 20 years, longitudinal anatomic brain imaging of children and adolescents has established the trajectories of brain gray matter (GM) and white matter (WM) volumes, cortical thickness, along with finer maps of GM and WM development across time.

Earlier volumetric studies in children and adolescents showed an inverted "*U* shaped" trajectory of GM volumes that peaked at different times in different brain regions.[26] For the first time, it was demonstrated that GM volumes increased during childhood, reaching peak levels around puberty onset, and subsequently declining in the frontal and parietal lobes but not in the temporal lobes, while the WM volumes continued to increase into adulthood.[26] Furthermore, females reached peak GM volumes in the frontal, parietal, and temporal regions about 2 years earlier than males.[27] While this raises intriguing questions given the differences in profile of illness onset in females compared with males[28] with schizophrenia, a recent study examining longitudinal changes in GM did not find an effect of gender,[29] while other studies are equivocal.[30] Subsequent finer mapping revealed that the primary sensorimotor areas were the earliest to mature, while the higher order brain regions (association cortices, typically associated with executive functions and visuospatial processing) such as the dorsolateral prefrontal cortex, inferior parietal lobe, and superior temporal gyrus (STG) matured at much later ages.[20] Some studies have reported that even within the prefrontal cortex (PFC), there is differential functional maturation such that executive abilities of the orbitofrontal cortex (OFC) mature before other executive systems.[31–34] These findings suggest that while structural brain development corresponds with functional milestones in the brain, there may be a lag between structural and functional changes, representing a complex interplay between programmed brain development and the maturation of motor, cognitive, and social functions (eg, [24,35–38]). Thus, clarification of structure-function relationships may provide further insights into the neurodevelopmental framework of schizophrenia and inform the findings related to progressive brain changes before, during, and following illness onset in adolescence.[39–46]

The GM trajectories and regional synaptic counts have led to a hypothesis that the inverted *U* trajectories reflect excess production of synaptic connections followed by pruning.[21,26] This is consistent with postmortem studies, both in humans and primates, as well as a recent evaluation of neural compartments that could explain the volume loss in psychosis and schizophrenia.[47] A landmark study by Huttenlocher[48] showed a slow decline in the number of synapses in the human cerebral cortex during childhood and then a steep fall off during late childhood and adolescence, which was further substantiated by the primate work documenting changes in synaptic density in motor and visual cortices during fetal, postnatal, and postpubertal periods.[49] The relevance of synaptic elimination in the pathophysiology of schizophrenia was initially proposed by Feinberg in the "excessive pruning" hypothesis based on his observations on sleep studies during adolescence.[50] McGlashan and Hoffman[51] subsequently proposed the Developmentally Reduced Synaptic Connectivity (DRSC) model. This model proposed that schizophrenia occurred as a result of critically reduced levels of synaptic connectivity, which in turn, occurred owing to (*a*) developmental disturbances of the synaptogenesis during phases of gestation and early childhood, and/or (*b*) overrapid synaptic pruning during adolescence. The early environmental insults would fit within this DRSC neurodevelopmental model with increased synaptic pruning (reduced synaptic density and dendritic arbor) contributing to psychotic symptoms, leading to an earlier age of onset, and thus poor social and clinical outcome. There is evidence for functional

relevance to these observations. During adolescence, decreases in synaptic density, as well as axon retraction and neuronal loss coincide with an increased ability to solve high-order cognitive tasks,[25,52] although it is not yet clear how the structural and functional trajectories are aligned.

On the other hand, WM volume and density generally increase throughout childhood and adolescence, with volumetric peaks reached in the fifth decade of life.[53] This may lead to greater diversity of functional connectivity and integration of neural circuitry. Gender differences have also been identified with age-related increases being greater in males than females.[54,55] An important advance in discoveries regarding myelin is that in addition to maximizing speed of transmission, myelin modulates both the timing and synchrony of the neuronal firing patterns that develop functional brain networks.[56] Signal transduction can be improved by thicker myelin sheaths, increased axonal diameter, and improved organization of WM tracts and may contribute towards a more optimal level of cognitive ability, behavioral, and emotional development. Paus and colleagues[57] showed rapid localized age-related increases in WM density in corticospinal tracts, while the fronto-temporal pathways showed more pronounced WM density in the language-associated brain regions. This work that has mapped the developmental changes from childhood to adolescence provides an important context for understanding the changes observed in patients with schizophrenia. As mentioned earlier, the changes are heterogenous[58] and may depend on the developmental stage during the first episode of the illness.[9] If this is the case, it would be expected that the changes in patients with schizophrenia having a younger age of illness onset, such as COS, would have more severe consequences, with adverse effects on brain structures that are maturing or yet to mature.

Early-Onset/COS Studies

Studying schizophrenia in very early ages provides a unique opportunity to examine the developmental perspective. In general, childhood manifestation of a typical adult-onset illness tends to show severe phenotype and more salient genetic influences,[59] which is also the case for COS.[60] COS probands and siblings are younger than typical adult-onset patients and their siblings and hence provide an opportunity to observe brain changes closer to the developmental roots. Furthermore, the findings are less likely to be contaminated by environmental factors (see van Os et al[61]) such as substance abuse, which can adversely affect brain structure,[62] and are likely to show more salient genetic influences.[60,63] This has been evident from the ongoing NIMH COS study where, since 1991, probands and siblings have been prospectively studied and scanned every 2 years in what now constitutes the largest sample of very early-onset cases.[15,60,64] This cohort now consists of 117 COS probands with 114 full siblings many of whom have now been scanned 4–5 times at 2-year intervals. The average age of psychosis onset is 10 ± 2 years, and clinically, this cohort resembles chronic, severe, and treatment refractory adult schizophrenia cases and is neurobiologically continuous with the adult illness.[15,65] The majority of patients are maintained on clozapine[66] and show equal gender distribution.

During the adolescent period, patients with COS show progressive ventricular enlargement and a progressive reduction of cortical GM that follows a ''parieto-frontal'' pattern, which appears to be an exaggeration of healthy brain development through adolescence.[15,64,67,68] Furthermore, as hypothesized above, an effect size comparison shows that the GM loss in COS during adolescence is indeed more severe than that seen for adult-onset schizophrenia in later years. Interestingly, the profound and global GM loss in COS seen in the adolescent years appears to slow down and becomes more localized to prefrontal and temporal cortices, as has been seen in most adult studies, which also establishes the biological continuity between the childhood-onset and adult forms.[69] Furthermore, a recent analysis of a large longitudinal COS sample (n = 104; 249 scans; M/F = 57/47) with a matched group of healthy controls (n = 104; 244 scans, M/F = 57/47) showed no significant differential effect of gender on cortical or subcortical brain development (group × age × gender interaction, $P > .05$ and group × gender interaction, $P > .05$; although there were significant gender effects within the controls), suggesting that sex played no role in COS brain development (B. Weisinger, D. Greenstein, A. Mattai, et al., Unpublished data) despite the gender-related differences in the clinical phenotype.

What causes the profound GM loss in COS followed by the slowing down process ''post adolescence'' remains a critical question, and more studies into this age window could provide valuable insights. Although this could be the result of chronic and stable medication treatment in childhood-onset patients, it could also mean that factors specific to late adolescence may also have a protective role in the slowing of GM loss. Our sibling studies (described below) provide an interesting insight into this developmental window.

UHR Studies

UHR cohorts have provided another unique sample to investigate the development of psychosis-related disorders. Based upon a number of criteria including current mental state, state (ie, symptomatic and help-seeking) and trait (ie, family history) characteristics, the UHR group are at an increased risk of developing

psychosis.[70,71] The Melbourne UHR cohorts in the imaging studies have a mean age of around 19 ± 3.5 years, with about 58% male, and almost 50% of those making the transition to psychosis develop a schizophreniform illness.[72] Although the transition from UHR status to a psychotic disorder is not considered inevitable, almost 40% of the initial cohorts made the transition to psychosis over a 12-month period. This provides the opportunity to document early and late dynamic brain changes as psychosis develops and also to assess brain structural changes longitudinally at the earliest stages of illness.[9,18,39] While the hope has been to identify a premorbid marker to evaluate an individual's susceptibility to develop a psychotic illness, examining trajectories of change of these potential markers would be more informative than limiting the assessment to cross-sectional evaluation.[11,73]

In a series of cross-sectional and longitudinal investigations, the Melbourne and other groups investigating UHR individuals have assessed a number of cortical and subcortical structures and contrasted the findings with those in first-episode psychosis and chronic schizophrenia. While changes in various regions have been found more consistently across these regions in patients with established schizophrenia, the findings at or before illness onset have been inconsistent, while progressive changes are apparent particularly in the earliest illness stages.

Meta-analyses of voxel-based morphometry studies in schizophrenia have shown reduced GM volume in anterior cingulate cortex (ACC) and medial frontal cortex, insula bilaterally, medial and lateral temporal lobes, STG, lateral PFC, thalamic, and subcortical regions.[74,75] However, these changes are less apparent in first-episode patients with evidence for cortical progression.[76] Cross-sectional studies in UHR have identified reduced volume in some of these regions pre-psychosis onset, such as the insular cortex[45] and ACC thickness,[77] as well as corpus callosum thickness.[78] In contrast, other findings did not discriminate between those developing psychosis compared with those who did not, including hippocampus and amygdala,[72,79,80] ACC morphology,[81] STG,[82] ventricular size,[83] or midline abnormalities, such as adhesio interthalamica[84] and cavum septum pellucidum.[85]

In contrast to the cross-sectional findings in UHR, longitudinal studies have been more consistent in discriminating UHR developing psychosis from those not progressing to illness. In the first such study, examining longitudinal changes in UHR, baseline scans prior to psychosis onset were compared with follow-up scans taken post psychosis onset or at least 12 months later (in those not developing psychosis). The UHR-psychosis group showed progressive loss of GM in left medial temporal and inferior temporal regions, left OFC, and ACC bilaterally. These changes were not observed in the UHR-non-psychotic individuals.[39,72,80] These findings have since been supported by a study in a separate sample at another research centre investigating a similar cohort,[41] which reported changes in frontal, temporal, and parietal GM in those who transitioned to psychosis, while no changes were seen in patients who did not. Furthermore, these changes were also seen in a genetic cohort from the Edinburgh high-risk study, with findings showing that these changes were not explained by medication.[40]

In order to address some of the methodological issues identified in these studies, such as the relatively thick image slice and small sample size, we combined 2 approaches—a cortical pattern matching technique[68] and a longitudinal cortical surface motion technique.[86] Using this methodology, we examined the cortical surface in detail, although other cortical regions of interest in psychotic disorders, such as the insula and the STG could not be examined because the methodology could not accurately assess cortical surface motion in these deep sulci. We again showed significant reductions (GM retraction) in patients who progressed to psychosis compared with those who did not, with changes localized to the lateral PFC.[42] Furthermore, these changes continued over the first 2–4 years of the illness in a first-episode group.[43] In this latter study, we also demonstrated that the pattern of GM retraction represented an amplification of the normal pattern and that this occurred across the entire brain but reaching significance in lateral PFC.

The PFC has received much attention, especially in consideration of the cognitive and functional deficits associated with schizophrenia including attention, working memory, and executive functioning.[87–90] Hypofunction in the PFC in UHR groups compared with controls has been reported,[91] as well as in neuroleptic-naïve first-episode schizophreniform psychosis.[92]

WM changes also implicate PFC regions. Reduced thickness of the corpus callosum has been found in first episode and chronic schizophrenia as well as in pre-psychotic UHR individuals, consistent with disruption to fiber tracts connecting with PFC.[78,93] In a longitudinal study of WM abnormalities in the Melbourne UHR group, Walterfang and colleagues[94] reported that individuals who later developed psychosis had larger baseline volumes of WM in the frontal lobe, while longitudinally they showed a reduction in WM volume in the region of the left fronto-occipital fasciculus. More recently, Bloemen and colleagues[95] identified lower fractional anisotropy (FA) values in medial frontal cortex, bilaterally in UHR individuals developing psychosis compared with controls, while compared with those not developing psychosis, they reported lower FA in left STG and in a region lateral to the right putamen. Further studies examining the changes in WM over development in UHR subjects should map the trajectories in relation to normal development of WM.

In addition to these structural abnormalities, executive functions are consistently found to be impaired in

schizophrenia, implicating impaired integrity of the PFC.[96] The Melbourne group has reported deficits in spatial working memory (SWM) from before psychosis onset,[97] which are similar in degree to patients with first-episode schizophrenia[98] and established schizophrenia.[99,100] These researchers have also demonstrated that performance on this same SWM task shows an inverted *U* function over the course of development from age 8 to 65 years, with optimal performance reached between ages 25 and 30 years.[36,52] These findings would be consistent with developmental arrest of important functions during adolescence and adulthood as schizophrenia is developing.

As evident from the above summary, results have thus far been difficult to interpret and inconsistent, and understanding the timing of brain changes still requires additional work.[18,101] Longitudinal investigations have generally proved more informative, given that patients have been followed through the period of transition to illness.[9,12,13,39,40,102] However, a neuroanatomical marker to predict the development of psychosis in UHR cohorts is yet to be identified or validated, though there are some possible leads.[103] This may be because neuroanatomical changes within the UHR group need to be placed within the context of normal developmental processes. Alternatively, the observed inconsistencies in this ''transitional'' group could reflect on the interplay of vulnerability vs compensatory processes in the underlying brain. A greater understanding of how environmental factors contribute and/or interact to result in the transition to psychosis could be provided from further studies of this group.

Healthy Sibling Studies

Full siblings share about 50% of the genes with the proband and are also likely to share the environment, particularly in childhood-onset cases due to their younger ages. As a result, non-psychotic siblings of COS probands have provided a valuable contrast group to address whether the observed brain abnormalities are trait markers. Additionally, sibling findings also help to tease out the medication effects on identified brain changes given most of the non-psychotic siblings are unmedicated. Healthy siblings of adult-onset schizophrenia have shown largely negative findings in cortical GM, although some have shown enlarged ventricles, GM loss in frontal and temporal regions, and reduction in thalamic GM volume.[104] Some evidence for the trait nature of GM abnormalities also comes from the twin studies of adult patients. For example, Cannon et al[105] showed that the prefrontal and temporal deficits were genetically influenced, while the parietal deficits were more disease related. Similarly, Ettinger et al[106,107] showed a heterogenous pattern of genetic influence in PFC and thalamus in concordant twins.

Interestingly, studies on non-psychotic siblings of COS patients have shown a pattern of prefrontal and temporal GM deficits in early ages that appear to ''normalize'' by the time the subjects reach late adolescence.[108] This initial observation on 52 healthy COS siblings (113 scans) and 52 matched healthy controls (108 scans) was recently replicated in a ''nonoverlapping'' sample of 47 healthy siblings (68 scans) and 48 matched healthy controls (69 scans). The same pattern of GM deficit normalization by late adolescence was recently replicated (Mattai et al. submitted). These robust findings raise several interesting possibilities. First, it is possible that the GM deficits are an ''age-specific'' endophenotype and only observed in early developmental periods. This could explain the general lack of cortical GM deficits observed in adult studies of schizophrenia siblings, who are generally over age 20. It is possible that if these cases were observed at an early age, evidence of GM deficits could be demonstrated. This notion is consistent with a number of the longitudinal high-risk studies. For example, genetically at risk subjects who developed psychosis in the Edinburgh High Risk study demonstrated medial and lateral temporal lobe abnormalities,[109] whereas the COS siblings remained healthy in late adolescence, post the typical age of onset for schizophrenia. This subsequently resulted in the normalization of cortical GM deficits within this cohort. Alternatively, the causative relationship may be reversed, where the normalization of cortical GM loss may prevent illness onset. Third, these findings may also indicate that following an early genetically driven GM deficit, some yet unknown protective factors are at play, which by late adolescence result in resilience. These observations would also support a ''two/multiple hit'' ''progressive neurodevelopmental'' model of schizophrenia where early GM loss in siblings is probably due to genetic vulnerabilities (first/genetic hit), while the lack of a second/subsequent hit around the typical age of onset in late adolescence, or some yet unknown genetic/environmental protective factors, result in the ''normalization'' of the GM abnormalities. Anatomic MRI does not have the resolution to address the mechanisms behind these observations but may provide clues to future studies. For example, connectivity studies using modalities such as functional imaging across the age range where deficits appear and normalize could highlight the neural circuits that are initially abnormal but normalize with age.

Is There Any Supportive Evidence From Genetic Studies?

Schizophrenia is a complex genetic disorder with heritability estimates up to 80%, which is likely to be the result of many genes of small effect.[14] Structural genomic variants of small or modest size, known as copy number variants, are a common cause of genetic variation in humans and are also being increasingly reported in schizophrenia[110–112] and, as expected, show a higher incidence in the childhood-onset cases.[113] Advances in genetic

neuroimaging methodologies, which combine the genetic and imaging data sets, are now starting to provide insights into the association between risk alleles (small-to-moderate effect size) and the trait nature of morphological and functional brain abnormalities,[114,115] including studies in COS.[116,117] This is based on the assumption that the brain phenotype, if indeed it is an intermediate phenotype,[118,119] is likely to show greater association with the underlying risk alleles than with the overall disease diagnosis. This is supported by our recent observations in COS patients and their siblings, (A. Raznahan, D. Greenstein, Y. Lee, Unpublished data) where increased Val dosing of catechol-*O*-methyltransferase (COMT) Val158Met genotype resulted in accelerated loss of cortical GM in PFC in both COS probands and their healthy siblings, while COMT genotype per se had no diagnostic association in this group. Interestingly, in both COS probands and siblings, the Met-Met genotype appeared to normalize the GM loss but this occurred at an earlier age (late adolescence) in siblings and much later in COS probands, suggesting an "age-dependent" influence of specific genes (Raznahan et al. submitted). These findings suggest that individual risk alleles may influence brain development in schizophrenia in an age and regionally specific manner.

Conclusions

We have summarized the findings from 2 important cohorts with illness onset at different stages of development and different stages of brain maturity. The COS is a unique cohort with an onset before puberty and associated initially with profound structural abnormalities within the parietal and frontal regions and later incorporating temporal regions post adolescence. The UHR group represents a group with an "at risk" mental state, who have a high transition rate to psychosis and who present during adolescence, when frontal lobes normally show their maximal maturational change. When the findings from these differing cohorts are considered together, it suggests that structural changes represent an acceleration of normal maturational processes in childhood and adolescence involving those regions that are programmed to mature at that time. The onset of schizophrenia at these critical periods is likely to disrupt the normal processes of maturation of both GM and WM in these regions, with associated disruption to maturation of relevant functions. In the UHR, these brain changes involve the PFC and STG over the adolescent and young adult period as psychosis is developing. The data from the COS group indicate that the changes are more extensive involving these as well as more posterior, parietal regions at the earlier stages of the illness.

The available evidence is consistent with the presence of subtle regionally and temporally specific neurobiological changes through the course of psychosis, involving early as well as later neurodevelopmental changes that are disrupted with the onset of psychosis.[9] These changes involve an acceleration of normal brain maturational processes that appear to be endophenotypic in nature and influenced by individual genes in an age-specific manner.

A limitation of imaging (particularly structural) studies is that they cannot adequately inform the mechanisms underlying the brain changes. However, they provide a unique opportunity to observe in vivo brain changes, which are not possible with postmortem studies. As stated above, the developmental context is important in thinking about the nature and extent of the brain changes in schizophrenia. Developmentally, a number of processes may be relevant to the structural brain changes observed, including synaptic pruning, myelination, developmental changes in neurotransmitters, such as gamma amino butyric acid/glutamate,[120,121] as well as changes in gene expression in key brain regions during adolescent development.[122–124] Similarly, the impact of stress and hypothalamic-pituitary-adrenal-axis function, with changes in glucocorticoid receptors evident developmentally,[125] could also be relevant as evidenced by the enlarged pituitary size reported immediately prior to and immediately following onset of psychosis.[126–128] Thus, future studies using a complimentary approach that combines neuroimaging and molecular methodologies could provide unique insights.

It is also becoming increasingly clear that schizophrenia is a disorder of functional as well as structural connectivity.[129] Recent advances in neuroimaging methodologies can explore this. For example, resting or task-driven functional imaging and magnetoencephalography can explore brain synchrony and networks that are abnormal in schizophrenia.[130,131] Similarly, diffusion tensor imaging can show structural WM abnormalities in specific tracts.[132] These studies are beginning to provide clues into the abnormal neurocircuitries relevant to schizophrenia during developmentally critical age windows.

An important question is which changes in the brain (functional or structural) lead either to conversion to psychosis (eg, UHR that convert to psychosis) or protection from psychosis (as in healthy siblings or UHR that do not convert). Prospective studies on schizotypal and early psychosis cases before and after the conversion to full syndromic psychosis, as well on young siblings that remain healthy post adolescence, using the multimodal imaging techniques combined with molecular approaches described above may reveal further clues into the factors of resilience or conversion. Such studies are currently underway at NIMH, Melbourne, and other centers.

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