Published in final edited form as:
Child Adolesc Psychiatr Clin N Am. 2013 October ; 22(4): 689–714. doi:10.1016/j.chc.2013.06.003.

Gray Matter Alterations in Schizophrenia High-Risk Youth and Early-Onset Schizophrenia: A Review of Structural MRI Findings

Benjamin K. Brent, M.D., M.S.[a,b,c,d], **Heidi W. Thermenos, Ph.D.**[a,b,c,d], **Matcheri S. Keshavan, M.D.**[a,b,c], and **Larry J. Seidman, Ph.D.**[a,b,c,d]

[a]Harvard Medical School, Boston, MA, USA

[b]Massachusetts Mental Health Center Division of Public Psychiatry, Boston, MA, USA

[c]Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA

[d]Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Synopsis

The purpose of this article is to provide a review of the literature on structural MRI findings in pediatric and young adult populations at clinical or genetic high-risk for schizophrenia, as well as in early-onset schizophrenia. The authors discuss the implications of this research for understanding the pathophysiology of schizophrenia and for early intervention strategies for prevention of the illness. The evidence linking brain structural changes in pre-psychosis development and early-onset schizophrenia with disruptions of normal neurodevelopmental processes during childhood and/or adolescence are described. In addition, the authors outline future directions for research to address current knowledge gaps regarding the neurobiological basis of brain structural abnormalities in schizophrenia and to help improve the utility of these abnormalities for preventative interventions.

Keywords

schizophrenia; structural MRI; high-risk; prodrome; early-onset schizophrenia; childhood-onset schizophrenia

Corresponding Author: Benjamin K. Brent, M.D., M.S., Department of Psychiatry, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, Phone: 617-754-1262, Fax: 617-754-1250, bbrent@bidmc.harvard.edu.
Co-Author
Heidi W. Thermenos, Ph.D., Athinoula A. Martinos Imaging Center, Building 149, 2nd Floor (Room 2602E), 13th Street, Charlestown, MA 02129, Phone: 617-726-2065, Fax: 617-726-4078, hthermen@bidmc.harvard.edu
Co-Author
Matcheri S. Keshavan, M.D., Massachusetts Mental Health Center, 75 Fenwood Road, Boston, MA 02115, Phone: 617-754-1236, Fax: 617-754-1250, mkeshava@bidmc.harvard.edu
Co-Author
Larry J. Seidman, Ph.D., Massachusetts Mental Health Center, 75 Fenwood Road, Boston, MA 02115, Phone: 617-754-1238, Fax: 617-754-1250, lseidman@bidmc.harvard.edu

Disclosures: Dr. Brent reports no financial disclosures or conflicts of interest.
Dr. Thermenos reports no financial disclosures or conflicts of interest.
Dr. Keshavan reports no financial disclosures or conflicts of interest.
Dr. Seidman reports no financial disclosures or conflicts of interest.

Introduction

Neuroimaging studies over the last four decades have provided overwhelming evidence that schizophrenia is a disorder involving widespread abnormalities of brain structure[1]. It is thought that the neurobiological processes underlying these structural abnormalities are central to the pathophysiology of schizophrenia[2]. However, the specific mechanisms involved in producing the structural deficits of schizophrenia remain incompletely understood. While no focal brain abnormality has been identified unequivocally, structural abnormalities including enlargement of the lateral and third ventricles, and reduced lateral temporal cortical, medial temporal, and prefrontal lobe volumes are consistently reported in persons with schizophrenia[1]. Further, alterations of brain structure are linked with key psychotic symptoms (e.g., auditory hallucinations[3], delusions[4]), neurocognitive deficits[5], and social dysfunction[6] in schizophrenia.

Neurodevelopmental models hypothesize that pathological processes occurring during "early" (i.e., perinatally) and/or "late" (i.e., adolescent/young adult) brain development (e.g., aberrant migration of neuronal precursor cells during gestation and/or excessive dendritic pruning during adolescence) may be key to the emergence of the brain structural alterations occurring in schizophrenia[7, 8]. Growing evidence from studies of typically developing children shows that brain maturational processes continue well into adolescence[9]. Neuroimaging studies, for example, reveal changes in the rates of gray to white matter (WM) during the second decade of life, with increases in WM (largely comprised of myelinated axon bundles) accompanied by reductions in gray matter ([GM]; an index of cellular and unmyelinated fiber density)[10, 11]. It is thought that, at least in part, these findings are indicative of changes in cellular-level processes, such as myelinization by oligodendrocytes (increased WM) and neuronal apoptosis resulting in dendritic pruning (GM reduction), which together contribute to improved regional communication and more efficient neuronal coding over the course of adolescence[12]. Additionally, several studies suggest a characteristic temporal pattern of GM reduction, with structural decrements proceeding from posterior cortical areas (e.g., parietal cortex) during childhood to anterior brain regions (e.g., prefrontal cortex (PFC)) during late adolescence and early adulthood[13, 14]. It has been hypothesized that this lag in PFC GM maturation may result in an "imbalance" during adolescence between earlier developing mesolimbic structures mediating responses to pleasurable stimuli (i.e., the brain's reward circuitry) and less fully-developed prefrontal brain areas involved in response inhibition and cognitive control[12]. Thus, the trajectories of structural brain changes in normal development are increasingly believed to provide a neurobiological basis for the increase in impulsivity and risk-taking behavior that contribute to making adolescence a period of heightened risk for the emergence of a broad range of psychopathology, including schizophrenia[15].

Several lines of evidence provide substantial support for the neurodevelopmental hypothesis that alterations of normal brain maturational processes are implicated in the characteristic structural abnormalities of schizophrenia. This evidence, reviewed extensively elsewhere[2, 16, 17], includes:

1. Neuropathological findings in schizophrenia consistent with microneuroanatomical alterations (e.g., abnormal laminal organization and orientation of neurons) associated with gestational development in the prefrontal, cingulate, and lateral temporal cortices, as well as the hippocampus[18–20].
2. Structural MRI observations of abnormal prefrontal and/or temporal cortical surface morphology in adult[21] and early-onset schizophrenia (EOS)[22], as well as in adolescents at genetic high risk (GHR) for schizophrenia [23], that are thought to reflect perturbations of gyrification during early development.

3. Reduced cortical neuropil and somal size found in post mortem studies of schizophrenia[24, 25], suggestive of dysregulated apoptosis and/or synaptic pruning in adolescence

4. Immunohistochemical and genetic linkage and association studies[26] implicating gene mutations in persons with schizophrenia that are thought to disrupt normal cortical developmental processes – e.g., early synaptogenesis (e.g., RELN[27]) and changes in dendritic spines during adolescence (e.g., DISC 1[28]).

5. Animal models showing that early alterations of GM development produce later abnormalities of adolescent cortical function that are analogous to those observed in schizophrenia[29].

Despite the accumulating evidence for brain dysmaturation during childhood and adolescent development in schizophrenia, many questions regarding the pathophysiology of the structural brain abnormalities of schizophrenia remain unanswered. For example, it is not clear when GM loss first begins during development[1] – e.g., whether less GM in schizophrenia is the product of primarily early (intrauterine/perinatal), or late (peri-adolescent/early adult) dysmaturational processes, or some combination of the two. Further, how environmental, or epigenetic risk and/or protective factors might influence the course of neurodevelopment, or how alterations of brain structure are specifically linked to the emergence of psychotic symptoms have yet to be determined. Additionally, it is acknowledged that although there has been significant growth in neuroscientific understanding of normal brain development, relatively few studies have focused directly on youth (age less than 18 years) who develop schizophrenia (i.e., EOS)[30], or adolescents or young adults (age less than 30 years) at risk for the illness (whether by virtue of family relatedness to a person with schizophrenia (GHR), or as a result of symptoms or functional decline thought to be indicative of clinical high-risk (CHR) for full blown psychosis). Characterizing the structural brain changes observed in studies of youth/young adults at GHR or CHR for schizophrenia, as well as in EOS, may be critical to refining current understanding of the timing and pathophysiology of these alterations. It may also help us to identify individuals who could benefit from early treatment interventions. Toward this end, we provide a selective review of structural MRI findings in pediatric at-risk populations and EOS. Our goal is to identify the common findings and gaps in current knowledge regarding structural brain changes associated with the trajectory of schizophrenia risk in youth and young adult development in order to provide future directions for research.

Structural MRI Findings in Genetic High-Risk for Schizophrenia Individuals

Based on the evidence regarding the strong heritability of schizophrenia – approximately 60–80% of the liability to schizophrenia is due to genes[31] -- GHR structural magnetic resonance imaging (MRI) research has focused on the identification of neural abnormalities during the adolescent and young adult development of non-psychotic, first-degree relatives of persons with schizophrenia. This work is motivated by the drive to understand brain development prior to psychosis and to observe it largely without medication and illness state-related confounds that commonly complicate schizophrenia research. According to the GHR model[32], it is hypothesized that schizophrenia results from the cumulative vulnerability of multiple genetic and environmental factors, each associated with relatively small effects. Prior to the onset of psychosis, subclinical neuroanatomical, or other abnormalities (e.g., reduced hippocampal GM volume, or neurocognitive deficits) are thought to be reliably detectable and expressed in non-psychotic, first-degree relatives of patients, who on average share 50% of genes with their affected family member[33]. A particular strength of the GHR approach is that it allows for the identification of neural markers of schizophrenia risk preceding psychosis-like symptoms. Findings from GHR

research, therefore, could contribute to greater understanding of pathophysiological processes associated with early development, as well as to the identification of vulnerability markers that may be particularly useful for early detection strategies for psychosis prevention[7, 34]. Additionally, longitudinal GHR research in children and adolescents may be able to distinguish temporally distal neuroanatomical abnormalities associated with schizophrenia risk from those more closely linked to the timing of psychosis onset[7].

Recently, our group has carried out a comprehensive review[35] of all GHR MRI studies involving individuals 30 years of age or younger, bringing together the results from 14 independent research groups, 12 of whom have contributed structural MRI data (Table 1). It should be noted that studies included in this review employed a variety of MRI morphometric techniques (e.g., voxel-based morphometry and manual parcellation), as well as differing MRI software packages (e.g., Statistical Parametric Mapping (SPM), FreeSurfer) and methods to correct for multiple comparisons (e.g., whole brain vs. region-of-interest (ROI)). Below, we summarize the main findings.

Cross-sectional findings

In cross-sectional analyses, GHR youth have most consistently shown evidence for smaller prefrontal cortical (PFC) GM, including reduced cortical thickness[36–38], volume (inferior frontal gyrus[39–42], frontal pole[43], medial prefrontal cortex[43]), and/or gyral surface area[44] compared to controls. Other brain areas where GHR have reliably shown less GM in comparison to controls include: temporal cortex (decreased bilateral superior temporal gyrus volume[45, 46] and surface area[47], bilateral temporal lobe cortical thinning[36, 37]), parietal cortex (decreased GM volume[37, 42, 48] and reduced cortical thickness[38, 49]), and medial temporal/limbic regions (hippocampus[50–55], parahippocampus[36, 56], anterior cingulate cortex[36, 57]). More variable findings have been reported with respect to smaller GM in GHR versus controls in occipital cortex, cerebellum, amygdala, thalamus, and basal ganglia[35]. Significant associations between higher levels of attenuated psychotic symptoms and smaller GM in PFC[57–59], temporal cortex[60–62], parietal cortex[59], amygdala[59, 61, 62], and cerebellum[61, 62] in GHR youth and/or young adults have been reported. Regarding age-related neural alterations, significantly less GM has been observed in GHR samples with children as young as age 7 years[48]. However, there is insufficient data regarding neural alterations at specific ages, or developmental periods (e.g., middle childhood versus adolescence), to draw firm conclusions about the onset of GM loss in GHR youth[35]. Only one research group has found greater GM in GHR youth compared to controls[40]. This included increased cortical thickness of PFC (inferior orbital, middle frontal gyri), temporal cortex (right superior temporal gyrus), and parietal cortex (angular gyrus, inferior parietal cortex)[40]. Thus, there is substantial evidence, most consistently involving PFC and hippocampus, of less GM volume in HR subjects than controls.

Longitudinal findings

Two research groups (Pittsburgh High Risk (PHR) and Edinburgh (EHR)) have carried out longitudinal studies of GHR first-degree adolescent and/or young adult relatives of patients with adult onset schizophrenia. Consistent with the cross-sectional findings, both groups showed progressive reductions of PFC volume over time (1 year follow up (PHR), and 10 year follow up (EHR)) in GHR compared to controls[49, 58, 63]. Further, progressive decline in PFC GM has been linked with greater symptom levels in GHR individuals, including those who developed schizophrenia[59, 63]. Similar associations between increasing levels of symptoms and significant deceases in temporal cortical GM volume over time have also been reported[59, 63]. An association between greater symptom severity and progressive decline in parietal cortex volume is reported in one study[59].

A third research group has carried out a longitudinal GHR study focused on the development of brain structure in the "very healthy" siblings of individuals with childhood onset schizophrenia ([COS]; i.e., schizophrenia occurring in affected individuals < age 13). As with GHR studies involving first-degree relatives of people with adult-onset schizophrenia, COS relatives initially show significant GM reductions of PFC, temporal, and parietal cortex[37, 38]. However, over time these structural alterations were found to normalize, with no significant GM cortical decrements detected among COS relatives compared to controls by the end of adolescence (ages 17 to 20)[38]. Of note, none of the non-affected COS siblings developed psychosis during the follow-up period and, thus, may have comprised particularly resilient individuals. By contrast, on the basis of findings from studies involving families with strong evidence of genetic loading (i.e., EHR, in which relatives had at least two affected family members[63]), or in the offspring of persons with schizophrenia (i.e., PHR[49]), there is mounting evidence for accelerated reduction in PFM GM in GHR individuals, particularly those who become symptomatic or go on to develop schizophrenia (~10%).

Structural MRI Findings in Clinical High-Risk Individuals

Clinical high-risk (CHR) studies have provided an alternative approach to the investigation of alterations of neural structure associated with schizophrenia risk in adolescents and young adults based on the presence of clinical risk syndromes indicative of the "need-for-care"[64] – i.e., low level, attenuated positive symptoms; brief intermittent psychotic symptoms; or, genetic risk accompanied by functional decline[64]. Since approximately 20 percent of persons meeting "prodromal" criteria convert to psychosis within one year of initial assessment, and 35% over about 3 years[65], CHR studies provide a method for examining brain structural alterations proximal to the emergence of frank psychosis, which could ultimately elucidate pathophysiological processes most closely associated with illness onset[7]. Structural MRI findings in CHR studies have been the subject of several recent systematic and critical reviews[66, 67]. As with the GHR literature, structural MRI studies of CHR individuals have employed a wide-range of imaging methods, and MRI morphometric analytic techniques. Here, we summarize the structural MRI findings in CHR youth from 11 independent research groups and one multicenter study, as well as from two meta-analyses (Table 2).

Cross-sectional findings

Overall, studies of CHR individuals show brain structural alterations that are neuroanatomically similar to, but less severe than those commonly reported in established schizophrenia[68]. For example, compared to controls, CHR groups have shown both smaller GM volume and cortical thinning in PFC[69–76], lateral temporal cortex[69, 72, 73, 75–80] (particularly superior temporal gyrus (STG)), and, to a lesser extent, parietal cortex[72, 81]. Further, in the largest structural MRI study of CHR to date, which involved data collected from five clinical sites, CHR individuals showed significantly less GM in the PFC bilaterally compared to controls[82]. Less PFC GM has also been associated with impaired executive function[74] and greater symptoms severity[71] in CHR, while smaller STG GM has been linked with deficits involving semantic fluency[77].

Structural alterations of limbic brain areas and insula are also among the most consistently reported findings in CHR individuals compared to controls. This includes less bilateral[83–85] and ipsilateral[86, 87] hippocampal GM volume, aberrant surface morphology[80, 87–90] and smaller GM[70, 76, 82, 85, 91] in anterior cingulate and paracingulate cortex, as well as asymmetry[92] and smaller GM volume [69, 70, 93, 94] of the insula. In several studies, structural alterations of anterior cingulate[89] and insula[93, 94] have been significantly associated with

greater negative symptom levels in CHR. Structural abnormalities in CHR involving the cuneus[95], caudate[96], anterior limb of the internal capsule[97], and the presence of cavum septum pellucidum[98, 99] are less frequently assessed and less consistently reported. In one study, CHR individuals showed less total whole brain volume[100] compared to controls. Only one study has reported no significant differences in any brain structures in CHR persons versus controls[101].

Cross-sectional comparisons of CHR who transition to psychosis (CHR-t) to non-converters or controls have provided evidence for smaller GM volume in PFC[102, 103] and temporal cortical (STG[69, 88]) GM among CHR-t. CHR-t have also shown aberrant anterior cingulate morphology[89], smaller insula bilaterally[94] and on the right[69], as well as both greater[84] and smaller[104] hippocampal, or parahippocampal[82] GM volume. One study reported greater pituitary volume in CHR-t, which may potentially reflect greater exposure to environmental stress in persons who transition to psychosis[105]. An additional study of dykinesia in CHR has reported smaller striatal volume in CHR-t with a trend association between less striatal GM and greater dyskinetic symptoms[106]. Finally, a study of CHR persons exposed to herpes simplex virus 1 (HSV1) showed smaller GM volume of the cuneus among HSV1 positive CHR-t[106]. Overall, cross-sectional studies have shown smaller GM volume in frontal-temporal and medial temporal/limbic structures in CHR individuals compared to controls, with significantly less GM in these brain areas among individuals who transition to psychosis than in non-converters.

Longitudinal findings

In longitudinal studies, comparisons of structural brain alterations in CHR compared to controls have shown progressive GM loss in PFC (orbitofrontal cortex[76, 102]), lateral temporal cortex (STG[102, 107]), parietal cortex[102], cingulate gyrus[76], parahippocampus[76], fusiform cortex[76], insula[94], and cerebellum[76, 102]. Further, studies comparing structural changes in CHR-t to CHR non-converters have shown evidence for reductions over time in PFC[81] and temporal cortex[107], as well as in the cerebellum[108].

Meta-analyses of CHR structural MRI studies

The clinical diversity of CHR youth and the heterogeneity of MRI morphometric techniques used across studies together have posed a challenge to interpreting CHR structural findings regarding the neural alterations most closely linked to the risk for transitioning to psychosis. To shed further light on the neural correlates associated with the transition to psychosis, Smieskova and colleagues conducted a meta-analysis of structural MRI findings in both GHR and CHR, comparing HR individuals who transitioned to psychosis (HR-t) with non-coverters[67]. Overall, HR-t showed significantly decreased GM volume in PFC, temporal cortex, the limbic system, and cerebellum, compared to non-converters[67]. A subsequent meta-analysis by Fusar-Poli and colleagues[66] of voxel-based morphometric studies in GHR and CHR showed smaller GM volume in the PFC, temporal cortex (STG), anterior cingulate, parahippocampus, and precuneus in HR individuals[66]. In the same meta-analysis, a comparison of HR-t to non-converters revealed less GM in PFC (inferior frontal gyrus) and temporal cortex (STG) in HR-t. A comparison of CHR to GHR in the same meta-analysis showed smaller GM volume in the anterior cingulate bilaterally in CHR, while GHR showed less GM in the left hippocampal gyrus, insula, and right temporal cortex (STG) compared to CHR individuals [66]. Taken together, these meta-analyses show smaller PFC, STG, and medial temporal structures across HR populations, as well as converging evidence for reduced fronto-temporal GM volume in HR individuals who develop psychosis.

Early-Onset and Childhood-Onset Schizophrenia

Schizophrenia beginning in adolescence (EOS, age 13–18) or childhood (COS, < age 13) occurs rarely (approximately 4% of cases[109]), but is generally more clinically and neurobiologically severe than the adult-onset illness[110]. In particular, the brain structural abnormalities observed in COS have been shown to be significantly greater than in adults with schizophrenia[110]. Research over the last two decades regarding the pattern of neural alterations in COS, premorbid risk factors, and neurocognitive deficits in non-affected family members have provided strong evidence suggesting the neurobiological continuity between COS/EOS and adult-onset schizophrenia[111]. Further, because of evidence for greater genetic vulnerability[110] in COS (e.g., increased familiarity[110], cytogenetic abnormalities[112], and copy number variants[112]), it is increasingly believed that studies of brain structural alterations in children and adolescents with schizophrenia may be particularly valuable to understanding the neurobiological basis of the GM abnormalities associated with the illness overall. Below, we summarize the findings from structural MRI studies of EOS and COS carried out by 15 independent research groups world-wide (Table 3). It should be noted that roughly half of the studies included in this review have been carried out by the NIMH research group[110], which has focused on COS. Further, as with the HR structural MRI literature, there is considerable variability in terms of the MRI morphometric techniques and data analytic methods employed across studies.

Cross-sectional findings

Similar to findings in adult onset schizophrenia, structural MRI studies of EOS and COS have consistently shown smaller GM volume in PFC[113–119] and the temporal[114, 119–122] and parietal[113, 117, 123] cortices in EOS and COS compared to controls. Abnormalities of PFC thickness[22], cortical folding[124], and asymmetry[125] have also been reported. Additionally, less STG volume has been linked with both greater symptom severity, as well as earlier age of illness onset[121]. However, several cross-sectional studies have found enlargement of temporal cortical structures[126–128], raising the possibility that, alternatively, temporal GM volume reduction may occur developmentally later[128]. In contrast to HR and adult-onset schizophrenia, decreased hippocampal GM is less commonly reported in COS[129], with several studies showing no significant alterations compared to controls in hippocampal volume[130–132]. Other commonly reported structural findings in EOS and COS include: smaller whole brain volume[113, 126, 130, 132, 133], greater lateral ventricular volume[130, 134–136], and smaller GM in the cerebellum[137–139] and thalamus[115, 130, 140]. Fewer, and less consistent structural alterations are reported regarding the amygdala[127, 141], parahippocampus[119], insula[116], fusiform gyrus[116], basal ganglia[130], fornix[142, 143], corpus callosum[144, 145], and cavum septum pellucidum[146]. In two studies, no structural brain abnormalities in any brain areas in EOS versus controls were found[147, 148]. Thus, cross-sectional EOS and COS studies have provided consistent evidence for smaller whole brain volume, enlargement of lateral ventricles, in conjunction with smaller PFC and (somewhat less consistently) STG GM.

Longitudinal findings

Longitudinal studies comparing brain structure changes in EOS and COS to controls have shown progressive decreases in GM volume involving PFC[149–151] and the temporal[120, 150, 151] and parietal[149, 151] cortices in conjunction with decreases over time in cortical thickness in PFC[152] and temporal cortex[152]. Particularly noteworthy were results from a 5 year longitudinal study conducted by the NIMH group[151], which revealed a temporal pattern of significant GM volume loss in COS compared to controls, with the earliest deficits seen in the parietal cortex, followed by progression during adolescence to

the temporal lobes, and lastly to the prefrontal cortex. Additional brain regions in which volumetric decrements have been observed over time in EOS and COS compared to controls include: the cerebellum[137, 153], hippocampus[120, 154], thalamus[155], and corpus callosum[156]. Finally, progressive enlargement of the lateral ventricles has also been found in COS compared to controls[140, 154]. Across longitudinal studies, EOS and COS individuals have most consistently shown decrements in GM volume in fronto-temporal and parietal cortices over time.

Summary

Here, we reviewed the structural neuroimaging literature in youth and young adults at high-risk for schizophrenia and in EOS and COS. The most consistent finding was that, compared to normal development, there is accelerated fronto-temporal cortical GM volume reduction across the spectrum of schizophrenia risk and in EOS/COS. Specifically, progressive GM decline in these brain regions occurs in HR youth and young adults who eventually transition to psychosis, and also occurs during adolescence in persons with EOS/COS. Progressive volumetric decline and morphological alterations of limbic structures (e.g., hippocampus, parahippocampus, anterior cingulate) are also prominent among HR individuals who later develop psychosis. Structural alterations over time in limbic areas are less common in COS, although there is some evidence to suggest that these abnormalities may emerge as COS individuals are followed through the end of adolescence.

Overall, these structural neuroimaging findings are broadly consistent with the hypothesis that schizophrenia involves, at least partly, the disruption of normal neurodevelopment occurring during childhood and/or adolescence. Structural MRI findings in HR individuals suggest the potential involvement of both early and late brain dysmaturational processes in the trajectory of GM alterations during pre-psychosis development. For example, evidence for altered surface morphology of PFC[44] and STG[47] in GHR individuals are thought to potentially reflect abnormalities of neuronal migration and mini-columnar formation during gestation[2, 16]. At the same time, it has been proposed that GM volume loss in frontal-temporal brain regions of CHR individuals who transition to psychosis[102, 107] could reflect dysregulation of synaptic pruning during adolescence[68]. Further, the progressive reduction in GM from posterior (parietal) to anterior (prefrontal) cortical brain areas over time found in COS follows the pattern of decline in GM observed during typically developing adolescents[13, 14], and, thus, has been interpreted as an indication of aberrant acceleration of normal brain maturational processes[157]. Although speculative, taken together these findings lend support to the “2-hit” model proposed by Keshavan and colleagues[2, 7, 8], in which neural dysmaturation occurring during early development is thought to produce a vulnerability to later abnormalities of adolescent brain development that ultimately result in the emergence of psychosis.

Nevertheless, despite the evolving evidence implicating aberrant neural developmental processes in the pathophysiology of schizophrenia, it is acknowledged that the findings from both GHR and CHR structural MRI studies are quite variable and difficult to replicate[35, 158]. Issues pertaining to the clinical heterogeneity of CHR and GHR subjects, as well as the diversity of neuroimaging methods employed for acquisition and analysis of MRI data have been identified as central to the difficulties of comparing results between research groups[35, 158]. As a result, in part, structural MRI findings currently lack sufficient specificity and sensitivity to be used clinically to identify biomarkers for the prospective identification of individuals at risk for developing schizophrenia.

However, we suggest that future neuroimaging studies of GHR/CHR and EOS/COS populations might take several further steps in order to address the gaps in current

knowledge regarding premorbid and prodromal structural brain alterations preceding schizophrenia onset, and to address the challenges of improving the clinical applicability of structural MRI findings to early intervention and prevention strategies for persons at risk for psychosis. First, the predictive value of structural MRI findings might be enhanced if the volumetric or morphological alterations observed in CHR and GHR individuals are incorporated within a multivariate approach, in which structural changes are combined with clinical and neurocognitive measures in models to predict later psychopathology[159]. Additionally, there is recent evidence suggesting that the use of machine learning techniques to identify patterns of structural abnormalities associated with the transition to psychosis in HR individuals could be used prospectively to improve the predictive specificity of structural MRI findings during the pre-psychosis period[73, 160]. Second, given the extensive clinical and neurobiological overlap between schizophrenia and bipolar affective disorder[161], studies of young first-degree relatives of probands across the psychotic spectrum may help determine which structural MRI abnormalities are most specific to schizophrenia risk[162]. Third, while our review is limited to structural MRI findings, how GM alterations develop in conjunction with changes in WM, impairments of brain function, cognitive deficits, as well as other potential markers of schizophrenia risk (e.g., inflammatory markers and oxidative stress), all of which appear to evolve during the early phase of schizophrenia[163], remains to be determined. Future longitudinal studies need to address these questions and control for diagnostic variability, as well as differences of age and gender. Fourth, the potential influence of early (e.g., perinatal complications) and later (e.g., substance misuse, psychosocial stress) environmental stress on neural development in the context of risk needs to be clarified in an effort to elucidate the neurobiology of schizophrenia, and to identify the risk markers that can be most useful to early intervention strategies to preempt illness onset. Finally, given the evidence reviewed here of early developmental pathology underlying schizophrenia risk, future research on younger individuals at GHR (i.e., preteen children) will be critical to the further clarification of the origins of brain structural abnormalities associated with the development of schizophrenia.

Acknowledgments

Grant support and other acknowledgements:

This project was supported in part by a KL2 Medical Research Investigator Training (MeRIT) award from Harvard Catalyst and The Harvard Clinical and Translational Science Center, NIH KL2 RR 025757 (BKB), NIMH MH081928, MH065571, and MH092840, and the Commonwealth Research Center of the Massachusetts Department of Mental Health, SCDMH82101008006 (LJS), and by NIMH RO1 64023, 78113 and, KO2 01180 (MSK).

References

1. Shenton ME, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. Schizophr Res. 2001; 49(1–2):1–52. [PubMed: 11343862]
2. Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. Dev Psychopathol. 1999; 11(3):525–543. [PubMed: 10532623]
3. Palaniyappan L, Balain V, Radua J, Liddle PF. Structural correlates of auditory hallucinations in schizophrenia: a meta-analysis. Schizophr Res. 2012; 137(1–3):169–173. [PubMed: 22341902]
4. Palaniyappan L, Mallikarjun P, Joseph V, et al. Reality distortion is related to the structure of the salience network in schizophrenia. Psychol Med. 2011; 41(8):1701–1708. [PubMed: 21144116]
5. Seidman LJ, Yurgelun-Todd D, Kremen WS, et al. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. Biol Psychiatry. 1994; 35(4):235–246. [PubMed: 8186328]

6. Mitelman SA, Shihabuddin L, et al. MRI assessment of gray and white matter distribution in Brodmann's areas of the cortex in patients with schizophrenia with good and poor outcomes. Am J Psychiatry. 2003; 160(12):2154–2168. [PubMed: 14638586]
7. Cannon TD, van Erp TG, Bearden CE, et al. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. Schizophr Bull. 2003; 29(4):653–669. [PubMed: 14989405]
8. Keshavan MS, Anderson S, Pettegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. Journal of Psychiatric Research. 1994; 28(3): 239–265. [PubMed: 7932285]
9. Paus T. Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci. 2005; 9(2):60–68. [PubMed: 15668098]
10. Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999; 2(10):861–863. [PubMed: 10491603]
11. Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. Dev Med Child Neurol. 2002; 44(1):4–16. [PubMed: 11811649]
12. Ernst M, Mueller SC. The adolescent brain: insights from functional neuroimaging research. Dev Neurobiol. 2008; 68(6):729–743. [PubMed: 18383544]
13. 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(21):8174–8179. [PubMed: 15148381]
14. Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. Neuroscientist. 2004; 10(4):372–392. [PubMed: 15271264]
15. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? Nat Rev Neurosci. 2008; 9(12):947–957. [PubMed: 19002191]
16. Keshavan, MS.; Bhojraj, T. Gray matter alterations in schizophrenia: are they reversible. New York: Routledge; 2011.
17. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol. 2000; 12(3):501–527. [PubMed: 11014750]
18. Akbarian S, Bunney WE Jr, Potkin SG, et al. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry. 1993; 50(3):169–177. [PubMed: 7679891]
19. Bunney WE, Bunney BG. Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. Brain Res Brain Res Rev. 2000; 31(2–3):138–146. [PubMed: 10719142]
20. Chana G, Landau S, Beasley C, et al. Two-dimensional assessment of cytoarchitecture in the anterior cingulate cortex in major depressive disorder, bipolar disorder, and schizophrenia: evidence for decreased neuronal somal size and increased neuronal density. Biol Psychiatry. 2003; 53(12):1086–1098. [PubMed: 12814860]
21. Vogeley K, Schneider-Axmann T, Pfeiffer U, et al. Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. Am J Psychiatry. 2000; 157(1):34–39. [PubMed: 10618010]
22. White T, Andreasen NC, Nopoulos P, Magnotta V. Gyrification abnormalities in childhood- and adolescent-onset schizophrenia. Biol Psychiatry. 2003; 54(4):418–426. [PubMed: 12915286]
23. Jou RJ, Hardan AY, Keshavan MS. Reduced cortical folding in individuals at high risk for schizophrenia: a pilot study. Schizophr Res. 2005; 75(2–3):309–313. [PubMed: 15885522]
24. Pierri JN, Volk CL, Auh S, et al. Decreased somal size of deep layer 3 pyramidal neurons in the prefrontal cortex of subjects with schizophrenia. Arch Gen Psychiatry. 2001; 58(5):466–473. [PubMed: 11343526]
25. Rajkowska G, Selemon LD, Goldman-Rakic PS. Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. Arch Gen Psychiatry. 1998; 55(3):215–224. [PubMed: 9510215]
26. Bennett MR. Schizophrenia: susceptibility genes, dendritic-spine pathology and gray matter loss. Prog Neurobiol. 2011; 95(3):275–300. [PubMed: 21907759]

27. Fatemi SH, Earle JA, McMenomy T. Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. Mol Psychiatry. 2000; 5(6): 654–663. 571. [PubMed: 11126396]
28. Gill M, Donohoe G, et al. What have the genomics ever done for the psychoses? Psychol Med. 2010; 40(4):529–540. [PubMed: 19818200]
29. Lipska BK, Weinberger DR. Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and apomorphine-induced stereotypic behaviors in the rat. Brain Res Dev Brain Res. 1993; 75(2):213–222.
30. McGorry P. Transition to adulthood: the critical period for pre-emptive, disease-modifying care for schizophrenia and related disorders. Schizophr Bull. 2011; 37(3):524–530. [PubMed: 21505119]
31. MacDonald AW, Schulz SC. What we know: findings that every theory of schizophrenia should explain. Schizophr Bull. 2009; 35(3):493–508. [PubMed: 19329559]
32. Stone WS, Faraone SV, Seidman LJ, et al. Searching for the liability to schizophrenia: concepts and methods underlying genetic high-risk studies of adolescents. J Child Adolesc Psychopharmacol. 2005; 15(3):403–417. [PubMed: 16092907]
33. Agnew-Blais J, Seidman LJ. Neurocognition in youth and young adults under age 30 at familial risk for schizophrenia: A quantitative and qualitative review. Cogn Neuropsychiatry. 2012
34. Keshavan MS, DeLisi LE, Seidman LJ. Early and broadly defined psychosis risk mental states. Schizophr Res. 2011; 126(1–3):1–10. [PubMed: 21123033]
35. Thermenos HW, Keshavan MS, et al. Neuroimaging of youg relatives of persons with schizophrenia: a developmental perspective from schizotaxia to schizophrenia. Am J Med Genet B Neuropsychiatr Genet. 2013 (Accepted).
36. Byun MS, Kim JS, Jung WH, et al. Regional cortical thinning in subjects with high genetic loading for schizophrenia. Schizophr Res. 2012; 141(2–3):197–203. [PubMed: 22998933]
37. Gogtay N, Greenstein D, Lenane M, et al. Cortical brain development in nonpsychotic siblings of patients with childhood-onset schizophrenia. Arch Gen Psychiatry. 2007; 64(7):772–780. [PubMed: 17606811]
38. Mattai AA, Weisinger B, Greenstein D, et al. Normalization of cortical gray matter deficits in nonpsychotic siblings of patients with childhood-onset schizophrenia. J Am Acad Child Adolesc Psychiatry. 2011; 50(7):697–704. [PubMed: 21703497]
39. Harms MP, Wang L, Campanella C, et al. Structural abnormalities in gyri of the prefrontal cortex in individuals with schizophrenia and their unaffected siblings. Br J Psychiatry. 2010; 196(2):150–157. [PubMed: 20118463]
40. Li X, Alapati V, Jackson C, Xia S, et al. Structural abnormalities in language circuits in genetic high-risk subjects and schizophrenia patients. Psychiatry Res. 2012; 201(3):182–189. [PubMed: 22512952]
41. Francis AN, Seidman LJ, Jabbar GA, et al. Alterations in brain structures underlying language function in young adults at high familial risk for schizophrenia. Schizophr Res. 2012; 141(1):65–71. [PubMed: 22892286]
42. Bhojraj TS, Francis AN, Rajarethinam R, et al. Verbal fluency deficits and altered lateralization of language brain areas in individuals genetically predisposed to schizophrenia. Schizophr Res. 2009; 115(2–3):202–208. [PubMed: 19840895]
43. Rosso IM, Makris N, Thermenos HW, et al. Regional prefrontal cortex gray matter volumes in youth at familial risk for schizophrenia from the Harvard Adolescent High Risk Study. Schizophr Res. 2010; 123(1):15–21. [PubMed: 20705433]
44. Prasad KM, Sanders R, Sweeney J, et al. Neurological abnormalities among offspring of persons with schizophrenia: relation to premorbid psychopathology. Schizophr Res. 2009; 108(1–3):163–169. [PubMed: 19108992]
45. Bhojraj TS, Prasad KM, Eack SM, et al. Do inter-regional gray-matter volumetric correlations reflect altered functional connectivity in high-risk offspring of schizophrenia patients? Schizophr Res. 2010; 118(1–3):62–68. [PubMed: 20171847]
46. Rajarethinam R, Sahni S, Rosenberg DR, Keshavan MS. Reduced superior temporal gyrus volume in young offspring of patients with schizophrenia. Am J Psychiatry. 2004; 161(6):1121–1124. [PubMed: 15169705]

47. Bhojraj TS, Sweeney JA, Prasad KM, et al. Progressive alterations of the auditory association areas in young non-psychotic offspring of schizophrenia patients. J Psychiatr Res. 2011b; 45(2):205–212. [PubMed: 20541772]
48. Gogtay N, Sporn A, Clasen LS, et al. Structural brain MRI abnormalities in healthy siblings of patients with childhood-onset schizophrenia. Am J Psychiatry. 2003; 160(3):569–571. [PubMed: 12611841]
49. Prasad KM, Goradia D, Eack S, et al. Cortical surface characteristics among offspring of schizophrenia subjects. Schizophr Res. 2010; 116(2–3):143–151. [PubMed: 19962858]
50. Dougherty MK, Gu H, Bizzell J, et al. Differences in subcortical structures in young adolescents at familial risk for schizophrenia: a preliminary study. Psychiatry Res. 2012; 204(2–3):68–74. [PubMed: 23146250]
51. Ho BC, Magnotta V. Hippocampal volume deficits and shape deformities in young biological relatives of schizophrenia probands. Neuroimage. 2010; 49(4):3385–3393. [PubMed: 19941961]
52. Keshavan MS, Dick E, Mankowski I, et al. Decreased left amygdala and hippocampal volumes in young offspring at risk for schizophrenia. Schizophr Res. 2002; 58(2–3):173–183. [PubMed: 12409156]
53. Keshavan MS, Montrose DM, Pierri JN, et al. Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. Prog Neuropsychopharmacol Biol Psychiatry. 1997; 21(8):1285–1295. [PubMed: 9460092]
54. Lawrie SM, Whalley H, Kestelman JN, et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. Lancet. 1999; 353(9146):30–33. [PubMed: 10023948]
55. Sismanlar SG, Anik Y, Coskun A, et al. The volumetric differences of the fronto-temporal region in young offspring of schizophrenic patients. Eur Child Adolesc Psychiatry. 2010; 19(2):151–157. [PubMed: 19711026]
56. Karnik-Henry MS, Wang L, Barch DM, et al. Medial temporal lobe structure and cognition in individuals with schizophrenia and in their non-psychotic siblings. Schizophr Res. 2012; 138(2–3): 128–135. [PubMed: 22542243]
57. Diwadkar VA, Montrose DM, Dworakowski D, et al. Genetically predisposed offspring with schizotypal features: an ultra high-risk group for schizophrenia? Prog Neuropsychopharmacol Biol Psychiatry. 2006; 30(2):230–238. [PubMed: 16318899]
58. Harris JM, Whalley H, Yates S, et al. Abnormal cortical folding in high-risk individuals: a predictor of the development of schizophrenia? Biol Psychiatry. 2004; 56(3):182–189. [PubMed: 15271587]
59. Bhojraj TS, Sweeney JA, Prasad KM, et al. Gray matter loss in young relatives at risk for schizophrenia: relation with prodromal psychopathology. Neuroimage. 2011a; 54 (Suppl 1):S272–279. [PubMed: 20441795]
60. Lymer GK, Job DE, William T, et al. Brain-behaviour relationships in people at high genetic risk of schizophrenia. Neuroimage. 2006; 33(1):275–285. [PubMed: 16926102]
61. Job DE, Whalley HC, McIntosh AM, et al. Grey matter changes can improve the prediction of chizophrenia in subjects at high risk. BMC Med. 2006; 4:29. [PubMed: 17156415]
62. Job DE, Whalley HC, Johnstone EC, Lawrie SM. Grey matter changes over time in high risk subjects developing schizophrenia. Neuroimage. 2005; 25(4):1023–1030. [PubMed: 15850721]
63. McIntosh AM, Owens DC, Moorhead WJ, et al. Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. Biol Psychiatry. 2011; 69(10):953–958. [PubMed: 21168123]
64. Wood SJ, Pantelis C, Velakoulis D, et al. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. Schizophr Bull. 2008; 34(2):322–329. [PubMed: 18199631]
65. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 2012; 69(3):220–229. [PubMed: 22393215]
66. Fusar-Poli P, Borgwardt S, Crescini A, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. Neurosci Biobehav Rev. 2011; 35(5):1175–1185. [PubMed: 21168439]

67. Smieskova R, Fusar-Poli P, Allen P, et al. Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. Neurosci Biobehav Rev. 2010; 34(8):1207–1222. [PubMed: 20144653]
68. Jung WH, Borgwardt S, Fusar-Poli P, Kwon JS. Gray matter volumetric abnormalities associated with the onset of psychosis. Front Psychiatry. 2012; 3:101. [PubMed: 23227013]
69. Borgwardt SJ, Riecher-Rossler A, Dazzan P, et al. Regional gray matter volume abnormalities in the at risk mental state. Biol Psychiatry. 2007b; 61(10):1148–1156. [PubMed: 17098213]
70. Fusar-Poli P, Broome MR, Woolley JB, et al. Altered brain function directly related to structural abnormalities in people at ultra high risk of psychosis: longitudinal VBM-fMRI study. J Psychiatr Res. 2011; 45(2):190–198. [PubMed: 20580022]
71. Iwashiro N, Suga M, Takano Y, et al. Localized gray matter volume reductions in the pars triangularis of the inferior frontal gyrus in individuals at clinical high-risk for psychosis and first episode for schizophrenia. Schizophr Res. 2012; 137(1–3):124–131. [PubMed: 22425035]
72. Jung WH, Kim JS, Jang JH, et al. Cortical thickness reduction in individuals at ultra-high-risk for psychosis. Schizophr Bull. 2011; 37(4):839–849. [PubMed: 20026559]
73. Koutsouleris N, Schmitt GJ, Gaser C, et al. Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. Br J Psychiatry. 2009; 195(3):218–226. [PubMed: 19721111]
74. Koutsouleris N, Patschurek-Kliche K, Scheuerecker J, et al. Neuroanatomical correlates of executive dysfunction in the at-risk mental state for psychosis. Schizophr Res. 2010; 123(2–3): 160–174. [PubMed: 20826078]
75. Meisenzahl EM, Koutsouleris N, Gaser C, et al. Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. Schizophr Res. 2008; 102(1–3):150–162. [PubMed: 18439804]
76. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. Lancet. 2003; 361(9354): 281–288. [PubMed: 12559861]
77. Meijer JH, Schmitz N, Nieman DH, et al. Semantic fluency deficits and reduced grey matter before transition to psychosis: a voxelwise correlational analysis. Psychiatry Res. 2011; 194(1):1–6. [PubMed: 21831606]
78. Shin KS, Jung WH, Kim JS, et al. Neuromagnetic auditory response and its relation to cortical thickness in ultra-high-risk for psychosis. Schizophr Res. 2012; 140(1–3):93–98. [PubMed: 22759440]
79. Takahashi T, Wood SJ, Yung AR, et al. Superior temporal gyrus volume in antipsychotic-naive people at risk of psychosis. Br J Psychiatry. 2010; 196(3):206–211. [PubMed: 20194543]
80. Ziermans TB, Schothorst PF, Schnack HG, et al. Progressive structural brain changes during development of psychosis. Schizophr Bull. 2012; 38(3):519–530. [PubMed: 20929968]
81. Dazzan P, Soulsby B, Mechelli A, et al. Volumetric abnormalities predating the onset of schizophrenia and affective psychoses: an MRI study in subjects at ultrahigh risk of psychosis. Schizophr Bull. 2012; 38(5):1083–1091. [PubMed: 21518921]
82. Mechelli A, Riecher-Rossler A, Meisenzahl EM, et al. Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study. Arch Gen Psychiatry. 2011; 68(5):489–495. [PubMed: 21536978]
83. Hurlemann R, Jessen F, Wagner M, et al. Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state. Psychol Med. 2008; 38(6):843–851. [PubMed: 18387213]
84. Phillips LJ, Velakoulis D, Pantelis C, et al. Non-reduction in hippocampal volume is associated with higher risk of psychosis. Schizophr Res. 2002; 58(2–3):145–158. [PubMed: 12409154]
85. Witthaus H, Kaufmann C, Bohner G, et al. Gray matter abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. Psychiatry Res. 2009; 173(3):163–169. [PubMed: 19616415]
86. Wood SJ, Kennedy D, Phillips LJ, et al. Hippocampal pathology in individuals at ultra-high risk for psychosis: a multimodal magnetic resonance study. Neuroimage. 2010; 52(1):62–68. [PubMed: 20399273]

87. Wood SJ, Yucel M, Velakoulis D, et al. Hippocampal and anterior cingulate morphology in subjects at ultra-high-risk for psychosis: the role of family history of psychotic illness. Schizophr Res. 2005; 75(2–3):295–301. [PubMed: 15885520]

88. Borgwardt SJ, McGuire PK, Aston J, et al. Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. Br J Psychiatry Suppl. 2007b; 51:s69–75. [PubMed: 18055941]

89. Fornito A, Yung AR, Wood SJ, et al. Anatomic abnormalities of the anterior cingulate cortex before psychosis onset: an MRI study of ultra-high-risk individuals. Biol Psychiatry. 2008; 64(9): 758–765. [PubMed: 18639238]

90. Yucel M, Wood SJ, Phillips LJ, et al. Morphology of the anterior cingulate cortex in young men at ultra-high risk of developing a psychotic illness. Br J Psychiatry. 2003; 182:518–524. [PubMed: 12777343]

91. Bohner G, Milakara D, Witthaus H, et al. MTR abnormalities in subjects at ultra-high risk for schizophrenia and first-episode schizophrenic patients compared to healthy controls. Schizophr Res. 2012; 137(1–3):85–90. [PubMed: 22377101]

92. Haller S, Borgwardt SJ, Schindler C, et al. Can cortical thickness asymmetry analysis contribute to detection of at-risk mental state and first-episode psychosis? A pilot study. Radiology. 2009; 250(1):212–221. [PubMed: 19092095]

93. Smieskova R, Fusar-Poli P, Aston J, et al. Insular volume abnormalities associated with different transition probabilities to psychosis. Psychol Med. 2012; 42(8):1613–1625. [PubMed: 22126702]

94. Takahashi T, Wood SJ, Yung AR, et al. Insular cortex gray matter changes in individuals at ultra-high-risk of developing psychosis. Schizophr Res. 2009; 111(1–3):94–102. [PubMed: 19349150]

95. Whitford TJ, Wood SJ, Yung A, et al. Structural abnormalities in the cuneus associated with Herpes Simplex Virus (type 1) infection in people at ultra high risk of developing psychosis. Schizophr Res. 2012; 135(1–3):175–180. [PubMed: 22244184]

96. Hannan KL, Wood SJ, Yung AR, et al. Caudate nucleus volume in individuals at ultra-high risk of psychosis: a cross-sectional magnetic resonance imaging study. Psychiatry Res. 2010; 182(3):223–230. [PubMed: 20488675]

97. Han HJ, Jung WH, Jang JH, et al. Reduced volume in the anterior internal capsule but its maintained correlation with the frontal gray matter in subjects at ultra-high risk for psychosis. Psychiatry Res. 2012; 204(2–3):82–90. [PubMed: 23217576]

98. Choi JS, Kang DH, Park JY, et al. Cavum septum pellucidum in subjects at ultra-high risk for psychosis: compared with first-degree relatives of patients with schizophrenia and healthy volunteers. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(5):1326–1330. [PubMed: 18513845]

99. Takahashi T, Yung AR, Yucel M, et al. Prevalence of large cavum septi pellucidi in ultra high-risk individuals and patients with psychotic disorders. Schizophr Res. 2008; 105(1–3):236–244. [PubMed: 18693084]

100. Velakoulis D, Wood SJ, Wong MT, et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. Arch Gen Psychiatry. 2006; 63(2):139–149. [PubMed: 16461856]

101. Ziermans TB, Durston S, Sprong M, et al. No evidence for structural brain changes in young adolescents at ultra high risk for psychosis. Schizophr Res. 2009; 112(1–3):1–6. [PubMed: 19419840]

102. Borgwardt SJ, McGuire PK, Aston J, et al. Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. Schizophr Res. 2008; 106(2–3):108–114. [PubMed: 18789654]

103. Sun D, Phillips L, Velakoulis D, et al. Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. Schizophr Res. 2009; 108(1–3):85–92. [PubMed: 19138834]

104. Witthaus H, Mendes U, Brune M, et al. Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia. J Psychiatry Neurosci. 2010; 35(1):33–40. [PubMed: 20040244]

105. Garner B, Pariante CM, Wood SJ, et al. Pituitary volume predicts future transition to psychosis in individuals at ultra-high risk of developing psychosis. Biol Psychiatry. 2005; 58(5):417–423. [PubMed: 16026767]
106. Mittal VA, Daley M, Shiode MF, et al. Striatal volumes and dyskinetic movements in youth at high-risk for psychosis. Schizophr Res. 2010; 123(1):68–70. [PubMed: 20732793]
107. Takahashi T, Wood SJ, Yung AR, et al. Progressive gray matter reduction of the superior temporal gyrus during transition to psychosis. Arch Gen Psychiatry. 2009; 66(4):366–376. [PubMed: 19349306]
108. Walterfang M, Yung A, Wood AG, et al. Corpus callosum shape alterations in individuals prior to the onset of psychosis. Schizophr Res. 2008; 103(1–3):1–10. [PubMed: 18562178]
109. Cannon M, Jones P, Huttunen MO, et al. School performance in Finnish children and later development of schizophrenia: a population-based longitudinal study. Arch Gen Psychiatry. 1999; 56(5):457–463. [PubMed: 10232301]
110. Nicolson R, et al. Childhood-onset schizophrenia: rare but worth studying. Biol Psychiatry. 1999; 46(10):1418–1428. [PubMed: 10578456]
111. Gogtay N. Cortical brain development in schizophrenia: insights from neuroimaging studies in childhood-onset schizophrenia. Schizophr Bull. 2008; 34(1):30–36. [PubMed: 17906336]
112. Addington AM, Rapoport JL. The genetics of childhood-onset schizophrenia: when madness strikes the prepubsecent. Current Psychiatry Reports. 2009; 11(2):156–161. [PubMed: 19302770]
113. El-Sayed M, Steen RG, Poe MD, et al. Brain volumes in psychotic youth with schizophrenia and mood disorders. J Psychiatry Neurosci. 2010; 35(4):229–236. [PubMed: 20569649]
114. Gogtay N, Weisinger B, Bakalar JL, et al. Psychotic symptoms and gray matter deficits in clinical pediatric populations. Schizophr Res. 2012; 140(1–3):149–154. [PubMed: 22835806]
115. James AC, James S, Smith DM, Javaloyes A. Cerebellar, prefrontal cortex, and thalamic volumes over two time points in adolescent-onset schizophrenia. Am J Psychiatry. 2004; 161(6):1023–1029. [PubMed: 15169690]
116. Paillere-Martinot M, Caclin A, Artiges E, et al. Cerebral gray and white matter reductions and clinical correlates in patients with early onset schizophrenia. Schizophr Res. 2001; 50(1–2):19–26. [PubMed: 11378311]
117. Reig S, Parellada M, Castro-Fornieles J, et al. Multicenter study of brain volume abnormalities in children and adolescent-onset psychosis. Schizophr Bull. 2011; 37(6):1270–1280. [PubMed: 20478821]
118. Vidal CN, Rapoport JL, Hayashi KM, et al. Dynamically spreading frontal and cingulate deficits mapped in adolescents with schizophrenia. Arch Gen Psychiatry. 2006; 63(1):25–34. [PubMed: 16389194]
119. Yoshihara Y, Sugihara G, Matsumoto H, et al. Voxel-based structural magnetic resonance imaging (MRI) study of patients with early onset schizophrenia. Ann Gen Psychiatry. 2008; 7:25. [PubMed: 19102744]
120. Jacobsen LK, Giedd JN, Castellanos FX, et al. Progressive reduction of temporal lobe structures in childhood-onset schizophrenia. Am J Psychiatry. 1998; 155(5):678–685. [PubMed: 9585721]
121. Matsumoto H, Simmons A, Williams S, et al. Superior temporal gyrus abnormalities in early-onset schizophrenia: similarities and differences with adult-onset schizophrenia. Am J Psychiatry. 2001a; 158(8):1299–1304. [PubMed: 11481166]
122. Tang J, Liao Y, Zhou B, et al. Decrease in temporal gyrus gray matter volume in first-episode, early onset schizophrenia: an MRI study. PLoS One. 2012; 7(7):e40247. [PubMed: 22802957]
123. Kumra S, Robinson P, Tambyraja R, et al. Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders. J Am Acad Child Adolesc Psychiatry. 2012; 51(2):171–180. [PubMed: 22265363]
124. Penttila J, Paillere-Martinot ML, Martinot JL, et al. Global and temporal cortical folding in patients with early-onset schizophrenia. J Am Acad Child Adolesc Psychiatry. 2008; 47(10): 1125–1132. [PubMed: 18725863]
125. Clark GM, Crow TJ, Barrick TR, Collinson SL, James AC, Roberts N, Mackay CE. Asymmetry loss is local rather than global in adolescent onset schizophrenia. Schizophr Res. 2010; 120(1–3): 84–86. [PubMed: 20452748]

126. Jacobsen LK, Giedd JN, Vaituzis AC, et al. Temporal lobe morphology in childhood-onset schizophrenia. Am J Psychiatry. 1996; 153(3):355–361. [PubMed: 8610822]

127. Levitt JG, Blanton RE, Caplan R, et al. Medial temporal lobe in childhood-onset schizophrenia. Psychiatry Res. 2001; 108(1):17–27. [PubMed: 11677064]

128. Taylor JL, Blanton RE, Levitt JG, et al. Superior temporal gyrus differences in childhood-onset schizophrenia. Schizophr Res. 2005; 73(2–3):235–241. [PubMed: 15653266]

129. Nugent TF 3rd, Herman DH, Ordonez A, et al. Dynamic mapping of hippocampal development in childhood onset schizophrenia. Schizophr Res. 2007; 90(1–3):62–70. [PubMed: 17161938]

130. Frazier JA, Giedd JN, Hamburger SD, et al. Brain anatomic magnetic resonance imaging in childhood-onset schizophrenia. Arch Gen Psychiatry. 1996; 53(7):617–624. [PubMed: 8660128]

131. Jacobsen LK, Giedd JN, Tanrikut C, et al. Three-dimensional cortical morphometry of the planum temporale in childhood-onset schizophrenia. American Journal of Psychiatry. 1997a; 154(5):685–687. [PubMed: 9137128]

132. Matsumoto H, Simmons A, Williams S, et al. Structural magnetic imaging of the hippocampus in early onset schizophrenia. Biol Psychiatry. 2001b; 49(10):824–831. [PubMed: 11343679]

133. Collinson SL, Mackay CE, James AC, et al. Brain volume, asymmetry and intellectual impairment in relation to sex in early-onset schizophrenia. Br J Psychiatry. 2003; 183:114–120. [PubMed: 12893664]

134. Hata K, Iida J, Iwasaka H, Negoro H, Kishimoto T. Association between minor physical anomalies and lateral ventricular enlargement in childhood and adolescent onset schizophrenia. Acta Psychiatr Scand. 2003; 108(2):147–151. [PubMed: 12823172]

135. Juuhl-Langseth M, Rimol LM, Rasmussen IA Jr, et al. Comprehensive segmentation of subcortical brain volumes in early onset schizophrenia reveals limited structural abnormalities. Psychiatry Res. 2012; 203(1):14–23. [PubMed: 22917502]

136. Sowell ER, Levitt J, Thompson PM, et al. Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images. Am J Psychiatry. 2000; 157(9):1475–1484. [PubMed: 10964865]

137. Greenstein D, Lenroot R, Clausen L, et al. Cerebellar development in childhood onset schizophrenia and non-psychotic siblings. Psychiatry Res. 2011; 193(3):131–137. [PubMed: 21803550]

138. Kumra S, Giedd JN, Vaituzis AC, et al. Childhood-onset psychotic disorders: magnetic resonance imaging of volumetric differences in brain structure. Am J Psychiatry. 2000; 157(9):1467–1474. [PubMed: 10964864]

139. Jacobsen LK, Giedd JN, Berquin PC, et al. Quantitative morphology of the cerebellum and fourth ventricle in childhood-onset schizophrenia. Am J Psychiatry. 1997b; 154(12):1663–1669. [PubMed: 9396943]

140. Rapoport JL, Giedd J, Kumra S, et al. Childhood-onset schizophrenia. Progressive ventricular change during adolescence. Arch Gen Psychiatry. 1997; 54(10):897–903. [PubMed: 9337768]

141. Frazier JA, Hodge SM, Breeze JL, et al. Diagnostic and sex effects on limbic volumes in early-onset bipolar disorder and schizophrenia. Schizophr Bull. 2008; 34(1):37–46. [PubMed: 18003631]

142. Davies DC, Wardell AM, Woolsey R, James AC. Enlargement of the fornix in early-onset schizophrenia: a quantitative MRI study. Neurosci Lett. 2001; 301(3):163–166. [PubMed: 11257423]

143. Kendi M, Kendi AT, Lehericy S, et al. Structural and diffusion tensor imaging of the fornix in childhood- and adolescent-onset schizophrenia. J Am Acad Child Adolesc Psychiatry. 2008; 47(7):826–832. [PubMed: 18520955]

144. Jacobsen LK, Giedd JN, Rajapakse JC, et al. Quantitative magnetic resonance imaging of the corpus callosum in childhood onset schizophrenia. Psychiatry Res. 1997; 68(2–3):77–86. [PubMed: 9104755]

145. Johnson SL, Greenstein D, Clasen L, et al. Absence of anatomic corpus callosal abnormalities in childhood-onset schizophrenia patients and healthy siblings. Psychiatry Res. 2013; 211(1):11–16. [PubMed: 23154096]

146. Nopoulos PC, Giedd JN, Andreasen NC, Rapoport JL. Frequency and severity of enlarged cavum septi pellucidi in childhood-onset schizophrenia. Am J Psychiatry. 1998; 155(8):1074–1079. [PubMed: 9699696]
147. James AC, Javaloyes A, James S, Smith DM. Evidence for non-progressive changes in adolescent-onset schizophrenia: follow-up magnetic resonance imaging study. Br J Psychiatry. 2002; 180:339–344. [PubMed: 11925357]
148. Pagsberg AK, Baare WF, Raabjerg Christensen AM, et al. Structural brain abnormalities in early onset first-episode psychosis. J Neural Transm. 2007; 114(4):489–498. [PubMed: 17024324]
149. Arango C, Rapado-Castro M, Reig S, et al. Progressive brain changes in children and adolescents with first-episode psychosis. Arch Gen Psychiatry. 2012; 69(1):16–26. [PubMed: 22213785]
150. Rapoport JL, Giedd JN, Blumenthal J, et al. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. Arch Gen Psychiatry. 1999; 56(7):649–654. [PubMed: 10401513]
151. 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(20):11650–11655. [PubMed: 11573002]
152. Greenstein D, Lerch J, Shaw P, et al. Childhood onset schizophrenia: cortical brain abnormalities as young adults. J Child Psychol Psychiatry. 2006; 47(10):1003–1012. [PubMed: 17073979]
153. Keller A, Castellanos FX, Vaituzis AC, et al. Progressive loss of cerebellar volume in childhood-onset schizophrenia. Am J Psychiatry. 2003a; 160(1):128–133. [PubMed: 12505811]
154. Giedd JN, Jeffries NO, Blumenthal J, et al. Childhood-onset schizophrenia: progressive brain changes during adolescence. Biol Psychiatry. 1999; 46(7):892–898. [PubMed: 10509172]
155. Janssen J, Aleman-Gomez Y, Reig S, et al. Regional specificity of thalamic volume deficits in male adolescents with early-onset psychosis. Br J Psychiatry. 2012; 200(1):30–36. [PubMed: 22116979]
156. Keller A, Jeffries NO, Blumenthal J, et al. Corpus callosum development in childhood-onset schizophrenia. Schizophr Res. 2003b; 62(1–2):105–114. [PubMed: 12765750]
157. Rapoport JL, Addington AM, Frangou S, et al. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 2005; 10(5):434–449. [PubMed: 15700048]
158. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry. 2013; 70(1):107–120. [PubMed: 23165428]
159. Shah J, Eack SM, Montrose DM, et al. Multivariate prediction of emerging psychosis in adolescents at high risk for schizophrenia. Schizophr Res. 2012; 141(2–3):189–196. [PubMed: 23010485]
160. Koutsouleris N, Gaser C, Bottlender R, et al. Use of neuroanatomical pattern regression to predict the structural brain dynamics of vulnerability and transition to psychosis. Schizophr Res. 2010; 123(2–3):175–187. [PubMed: 20850276]
161. Sublette ME, Oquendo MA, Mann JJ. Rational approaches to the neurobiologic study of youth at risk for bipolar disorder and suicide. Bipolar Disord. 2006; 8(5 Pt 2):526–542. [PubMed: 17042826]
162. Ivleva EI, Bidesi AS, Thomas BP, et al. Brain gray matter phenotypes across the psychosis dimension. Psychiatry Res. 2012; 204(1):13–24. [PubMed: 23177922]
163. Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, “just the facts”: what we know in 2008 Part 3: neurobiology. Schizophr Res. 2008; 106(2–3):89–107. [PubMed: 18799287]

Key Points

1. Structural MRI evidence indicates that the adolescent/young adult development of individuals at genetic and clinical high-risk for schizophrenia, as well as of persons with early-onset schizophrenia, is associated with smaller brain volumes, particularly in fronto-temporal cortical areas.
2. There is evidence implicating the disruption of both “early” (i.e., perinatal) and “late” (i.e., adolescent) normal neurodevelopmental processes, which lends support to the “two hit” neurodevelopmental model of schizophrenia.
3. Future longitudinal studies that control for diagnostic variability, age and gender effects, and which examine the evolution of structural brain changes in at-risk youth/young adults in the context of evolving changes of white matter, brain function, and neurocognition will contribute to improving the clinical applicability of structural MRI findings during the premorbid and prodromal periods to early intervention strategies for illness prevention.

Table 1

Structural MRI findings from studies of genetic high-risk for schizophrenia individuals less than age 30

Group	Author (Year)	Study type	Results
Pittsburgh	Keshavan et al. (1997)	Cross-sectional	-Smaller L amygdala and enlarged 3rd ventricle
	Keshavan et al. (2002)	Cross-sectional	-Smaller bilateral amygdala-hippocampal complex and intracranial volume
	Rajarethinam et al. (2004)	Cross-sectional	-Smaller superior temporal gyrus bilaterally
	Jou et al. (2005)	Cross-sectional	-Altered gyrification of L anterior cortical surface
	Diwadkar et al. (2006)	Cross-sectional	-GHR showed smaller PFC GM
			-GHR with symptoms showed smaller PFC, thalamus, and cuneus GM vs. GHR without symptoms
	Bhojraj et al. (2009)	Cross-sectional	-Smaller L PT, R Heschl's gyrus, L supramarginal and R angular gyri
			-Reversed PT asymmetry, exaggerated Heschl's gyrus asymmetry, attenuated supramarginal/angular gyri
	Prasad et al. (2010)	Longitudinal	-Reduced gyral surface area in fronto-parietal lobes
			-Increased gyral cortical thinning
			-Shrinkage of total surface area (bilateral frontal/occipital cortices) at 1-yr follow-up.
	Bhojraj et al. (2010)	Cross-sectional	-Smaller bilateral lateral temporal, R inferior parietal, and L posterior cingulate cortices
			-Smaller bilateral precuneus and R DLPFC
	Bhojraj et al., (2011a)	Longitudinal	-Reduced bilateral lateral orbitofrontal, L rostral anterior cingulate, L medial PFC, R inferior frontal gyrus, and L frontal pole over time in GHR
			-Smaller volumes predicted greater severity of symptoms at baseline and at follow-up
			-Smaller baseline volumes and longitudinal decrease in volumes predicted greater severity of prodromal symptoms over time
	Bhojraj et al. (2011b)	Longitudinal	-L surface area in auditory association cortex and laterality index showed decline over time in GHR
Edinburgh	Lawrie et al. (1999)	Cross-sectional	-Smaller L amygdala-hippocampal complex volume and bilateral thalamus in GHR
	Harris et al. (2004)	Cross-sectional	-Increased R PFC gyrification index in GHR who developed schizophrenia
	Job et al. (2005)	Longitudinal	-GHR with symptoms showed reduction in L superior lateral hippocampal surface, L fusiform gyrus, L uncus, L inferior temporal gyrus, and L STG
	Job et al. (2006)	Longitudinal	-Changes over time in inferior temporal gyrus were significantly predictive of developing schizophrenia in GHR
	Lymer et al. (2006)	Cross-sectional	-L superior temporal gyrus GM density associated with schizotypal symptoms in GHR
	McIntosh et al (2011)	Longitudinal	-Smaller bilateral PFC volume in GHR vs. controls at baseline
			-GHR who transition to psychosis show significant reduction in bilateral PFC volume
			-GHR as a whole show significant reductions in whole-brain volume, L and R temporal lobes, and L frontal lobe volume
NIMH	Gogtay et al. (2003)	Cross-sectional	-Smaller total cerebral, frontal and parietal lobe GM volume in GHR
	Gogtay et al. (2007)	Cross-sectional	-Smaller GM in L PFC and bilateral temporal cortices in GHR
	Mattai et al. (2011)	Longitudinal	-Smaller baseline GM in bilateral PFC, L temporal cortex, and parietal cortex that normalized by age 17
NYU	Li et al. (2012)	Cross-sectional	-Thinning of inferior frontal gyrus GM volume in GHR
			-Increased cortical thickness in PFC, temporal and parietal cortices in GHR
Iowa	Ho et al. (2010)	Cross-sectional	-Smaller bilateral hippocampal volume in GHR

Group	Author (Year)	Study type	Results
WU	Harms et al. (2010)	Cross-sectional	-Smaller inferior frontal gyrus GM in GHR
	Karnik-Henry et al. (2012)	Cross-sectional	-Thinner parahippocampal volume in GHR
Harvard AHRS	Rosso et al. (2010)	Cross-sectional	-Smaller bilateral vmPFC and frontal pole GM volume in GHR
			-vmPFC volume negatively correlated with schizotypal symptoms in GHR
UNC	Dougherty et al. (2012)	Cross-sectional	-Greater positive association between age and hippocampal and basal gangliar volumes in GHR
Turkey	Sismanlar et al. (2010)	Cross-sectional	-Smaller bilateral hippocampal volume in GHR
Korea	Byun et al. (2012)	Cross-sectional	-Cortical thinning in R anterior cingulate, L paracingulate, PCC, bilateral frontal pole, vmPFC, and occipital cortex
Harvard LHRS	Francis et al. (2012)	Cross-sectional	-Smaller L pars triangularis and R pars orbitalis volumes in GHR with reversal of L>R pars orbitalis lateralization

Abbreviations: AHRS = Adolescent High-Risk Study; DLPFC = dorsolateral prefrontal cortex GHR = genetic high-risk; GM = gray matter; L = left; PFC = prefrontal cortex; LHRS = Language High-Risk Study; NYU = New York University; PCC = posterior cingulate cortex; PT = pars triangularis; R = right; STG = superior temporal gyrus; UNC = University of North Carolina; vmPFC = ventromedial prefrontal cortex; WU = Washington University. Note: for a comprehensive listing of all structural MRI findings in GHR individuals, see Thermenos et al., 2013.

Table 2

Structural MRI findings from studies of clinical high-risk for schizophrenia individuals

Group	Author (Year)	Study type	Results
Melbourne	Phillips et al. (2002)	Cross-sectional	-Smaller hippocampal volume bilaterally in CHR
			-Larger L hippocampal volume in CHR-t vs. CHR-n, but no differences compared to controls
	Pantelis et al. (2003)	Longitudinal	-Smaller GM in R medial temporal, lateral temporal, and inferior frontal and bilateral cingulate cortices at baseline
			-CHR-t showed reduced GM in L parahippocampal, fusiform, orbitofrontal, and cerebellar cortices and cingulate gyri over time
			-CHR-n showed reduced cerebellar GM
	Yucel et al. (2003)	Cross-sectional	-Interrupted L anterior cingulate sulcus in CHR vs. controls, but no differences between CHR-t and CHR-n
	Garner et al. (2005)	Cross-sectional	-Larger baseline pituitary vol. in CHR-t vs. CHR-n
	Wood et al. (2005)	Cross-sectional	-Smaller hippocampal volume and less L anterior cingulate folding in CHR with GHR vs. CHR without GHR
	Velakoulis et al. (2006)	Cross-sectional	-Normal baseline hippocampal and amygdala volume in CHR
			-Smaller whole-brain volumes in CHR vs. controls
	Fornito et al. (2008)	Longitudinal	-Bilateral thinning of anterior cingulate in CHR-t also associated with negative symptoms
			-Baseline anterior cingulate differences in CHR-t vs. CHR-n predicted time to psychosis onset
	Takahashi et al. (2008)	Cross-sectional	-No increased prevalence of cavum septi pellucidi enlargement in CHR
	Walterfang et al. (2008)	Cross-sectional	-Smaller anterior corpus callosum in CHR-t vs. CHR-n
	Sun et al. (2009)	Longitudinal	-Greater brain contraction in R PFC in CHR-t vs. CHR-over time
	Takahaski et al., (2009)	Longitudinal	-Smaller baseline insula bilaterally in CHR-t vs. CHR-n, and in R insula vs. controls
			-Reduced GM of bilateral insula in CHR-t vs. CHR-n and controls
	Hannan et al. (2010)	Cross-sectional	-No differences in caudate volume in CHR at baseline vs. controls or in CHR-t vs. CHR-n
	Takahashi et al. (2010)	Cross-sectional	-Smaller STG bilaterally at baseline in CHR vs. controls
	Wood et al. (2010)	Cross-sectional	-Smaller L hippocampal volume in CHR vs. controls
	Dazzan et al. (2012)	Longitudinal	-Smaller frontal cortex volume in CHR-t vs. CHR-n at baseline
			-Reduced parietal cortex and temporal cortex (trend) in CHR-t vs. CHR-n
	Whitford et al. (2012)	Cross-sectional	-Smaller cuneus in CHR-HSV1+ vs. CHR-HSV1− and controls
Basel	Borgwardt et al. (2007a)	Cross-sectional	-Smaller GM at baseline in posterior cingulate and precuneus bilaterally and L superior parietal lobule in CHR-t vs. controls
	Borgwardt et al. (2007b)	Longitudinal	-Smaller L insula, STG, cingulate gyrus, and precuneus in CHR vs. controls
			-Reduced R insula, inferior frontal and STG in CHR-t vs. CHR-n
	Borgwardt et al. (2008)	Longitudinal	-Reduced orbitofrontal, superior frontal, inferior temporal, parietal cortex, and cerebellum in CHR-t vs. controls over time
	Haller et al. (2009)	Cross-sectional	-Whole brain cortical thickness asymmetry in CHR vs. controls
	Koutsouleris et al. (2009)	Cross-sectional	-Smaller GM volume in fronto-temporal and limbic structures in CHR-L vs. controls
			-Alterations of bilateral temporal and limbic structures in CHR-E vs. controls
			-Alterations of PFC in CHR-t vs. CHR-n and controls
	Buehlmann et al. (2010)	Cross-sectional	-Asymmetry between L and R hippocampus in CHR vs. controls
	Smieskova et al. (2012)	Cross-sectional	-Smaller insula GM volume bilaterally in CHR-E at baseline vs. CHR-L

Group	Author (Year)	Study type	Results
			-Insular alterations associated with negative symptoms in CHR
	Walter et al (2012)	Longitudinal	-Reduced hippocampal volume in CHR over time vs. controls
			-No hippocampal volume differences in CHR-t vs. CHR-n
Berlin	Witthaus et al. (2009)	Cross-sectional	-Smaller GM volume in cingulate gyrus bilaterally, R inferior frontal, R STG, and bilateral cingulate cortex in CHR
	Witthaus et al. (2010)	Cross-sectional	-Smaller corpus and tail volume of hippocampus bilaterally in CHR vs. controls
			-Smaller R hippocampal tail volume in CHR-t vs. CHR-n
	Bohner et al. (2012)	Cross-sectional	-Smaller cingulate gyrus GM in CHR vs. controls
Seoul	Choi et al. (2008)	Cross-sectional	- Higher incidence of cavum septum pellucidum in CHR vs. controls
	Jung et al. (2011)	Cross-sectional	-Reduced cortical thickness in PFC, anterior cingulate cortex, inferior parietal cortex, STG and parahippocampal cortex vs. controls
	Han et al. (2012)	Cross-sectional	-Smaller ALIC volume in CHR vs. controls
	Soon Shin et al. (2012)	Cross-sectional	-Reduced cortical thickness in L Heschl's gyrus in CHR vs. controls
Munich	Meisenzahl et al. (2008)	Cross-sectional	-Smaller GM volume in frontal, lateral temporal, and medial temporal areas in CHR vs. controls
London	Fusar-Poli et al. (2009)	Longitudinal	-Smaller middle and medial frontal gyrus, insula and anterior cingulate cortex volume in CHR vs. controls at baseline
			-No structural differences in CHR and controls at follow up
	Fusar-Poli et al. (2011)	Longitudinal	-Smaller GM volume in L middle and medial frontal gyri in CHR vs. controls at baseline
Utrecht	Ziermans et al. (2009)	Cross-sectional	-No structural difference in CHR vs. controls
	Ziermans et al. (2012)	Longitudinal	-Greater loss of total brain volume in CHR-t vs. CHR-n and controls
			-Cortical thinning in L anterior cingulate, precuneus, and temporo-parietal-occipital areas in CHR-t vs. CHR-n and controls
Amsterdam	Meijer et al. (2011)	Cross-sectional	-Smaller baseline GM density in R STG, MTG, R insula, and L anterior cingulate in CHR-t vs. CHR-n
			-GM reductions correlated with semantic fluency in CHR
Bonn	Hurlemann et al. (2008)	Cross-sectional	-Smaller bilateral hippocampal volume in CHR-L and CHR-E vs. controls
Tokyo	Iwashiro et al. (2012)	Cross-sectional	-Smaller bilateral PT volume in CHR vs. controls
			-Reduced PT vol. correlated with prodromal symptoms in CHR
Los Angeles	Mittal et al. (2010)	Cross-sectional	-Smaller baseline striatal GM volume in CHR-t vs. CHR-n
			-Trend association between reduced GM vol. in CHR-t and increased dyskinetic movements
Multicenter	Mechelli et al. (2011)	Cross-sectional	-Smaller frontal GM volume in CHR vs. controls at baseline
			-Smaller baseline L parahippocampal GM volume in CHR-t vs. CHR-n

Abbreviations: ALIC = anterior limb of internal capsule; CHR = clinical high-risk; CHR-E = early course clinical high-risk; CHR-HSV1+ = clinical high-risk with herpes simplex virus 1; CHR-HSV- = clinical high-risk without herpes simplex virus 1; CHR-L clinical high-risk of long duration; CHR-n = clinical high-risk without transition to psychosis; CHR-t = clinical high-risk with transition to psychosis; GM = gray matter; L = left; MTG = middle temporal gyrus; PFC = prefrontal cortex; PT = pars triangularis; R = right; STG = superior temporal gyrus

Table 3

Structural MRI findings from studies of early-onset and childhood-onset schizophrenia individuals

Group	Author (Year)	Study type	Results
NIMH	Frazier et al. (1996)	Cross-sectional	-Smaller total brain and thalamic vol. and increased basal gangliar vol., as well as increased lateral ventricular vol. in COS vs. controls
	Jacobsen et al. (1996)	Cross-sectional	-Smaller total cerebral vol. in COS vs. controls
	Jacobsen et al. (1997a)	Cross-sectional	-Smaller cerebellar volume in COS vs. controls
	Jacobsen et al. (1997b)	Cross-sectional	-Larger corpus callosum vol. in COS vs. controls
	Rapoport et al. (1997)	Longitudinal	-Reduced thalamic GM volume and increased lateral ventricular volume over time in COS vs. controls
	Jacobsen et al. (1998)	Longitudinal	-Reduced R temporal lobe, bilateral STG, and L hippocampus vol. over time in COS vs. controls
			-Reduced R STS volume associated with symptom severity
	Nopoulos et al. (1998)	Cross-sectional	-Enlarged cavum septum pellucidi in COS vs. controls
	Giedd et al. (1999)	Longitudinal	-Reduced total brain vol. and hippocampus and increase lateral ventricular vol. over time in COS vs. controls
	Rapoport et al. (1999)	Cross-sectional	-Four times smaller fronto-temporal GM volume in COS vs. controls
	Kumra et al. (2000)	Cross-sectional	-Reduced total cerebral vol. in COS vs. controls
	Thompson et al. (2001)	Longitudinal	-Smaller parietal cortical GM volume with progressive GM volume loss in temporal cortex, followed by PFC over 5 years in COS vs. controls
	Keller et al. (2003a)	Longitudinal	-Reduced cerebellar GM volume over time in COS vs. controls
	Keller et al. (2003b)	Longitudinal	-Reduced volume of splenium of corpus callosum in COS over time vs. controls
	Greenstein et al. (2006)	Longitudinal	-Reduced cortical thickness in temporal cortex over time in COS vs. controls
	Nugent et al. (2007)	Cross-sectional	-Smaller bilateral total hippocampal volume in COS vs. controls
	Bakalar et al. (2009)	Longitudinal	-No baseline or follow-up asymmetry of lateral or medial cortical surface in COS vs. controls
	Greenstein et al. (2011)	Longitudinal	-Reduced cerebellar GM at baseline and over time in COS vs. controls
	Gogtay et al. (2012)	Cross-sectional	-Smaller PFC and temporal GM volume in COS vs. psychosis NOS
	Johnson et al. (2013)	Cross-sectional	-No corpus callosum vol. differences in COS vs. controls
UCLA	Sowell et al. (2000)	Cross-sectional	-Increased lateral ventricular vol. in EOS vs. controls
	Levitt et al. (2001)	Cross-sectional	-Larger L amygdala vol. in EOS vs. controls
	Marquardt et al. (2005)	Cross-sectional	-Anterior cingulate asymmetry in EOS vs. controls
	Taylor et al. (2005)	Cross-sectional	-Greater posterior STG in EOS vs. controls
Iowa	White et al. (2003)	Cross-sectional	-Reduced cortical thickness and surface morphology in fronto-temporo-parietal lobes in EOS vs. controls
	Clark et al. (2010)	Cross-sectional	-Loss of planum temporale asymmetry in EOS vs. controls
Minnesota	Kendi et al. (2008)	Cross-sectional	-Smaller fornix volume in EOS vs. controls
	Kumra et al. (2012)	Cross-sectional	-Smaller L parietal volume in EOS vs. controls
Harvard	Frazier et al. (2005)	Cross-sectional	-Smaller L amygdala vol. in males with EOS vs. controls
UNC	El-Sayed et al. (2010)	Cross-sectional	-Smaller whole brain volume and frontal-parietal GM in EOS vs. controls
Madrid	Reig et al. (2011)	Cross-sectional	-Smaller frontal/parietal cortical GM in EOS vs. controls
	Aranyo et al. (2011)	Longitudinal	-Reduced frontal/parietal GM over time in EOS vs. controls
	Janssen et al. (2012)	Cross-sectional	-Smaller thalamic volume in EOS vs. controls
Oxford	Davies et al. (2001)	Cross-sectional	-Larger fornix in EOS vs. controls

Group	Author (Year)	Study type	Results
	James et al. (2002)	Cross-sectional	-No GM volume differences in EOS vs. controls
	Collinson et al. (2003)	Cross-sectional	-Smaller total brain volume in EOS vs. controls
	James et al. (2004)	Cross-sectional	-Smaller PFC and thalamic volume in EOS vs. controls
London	Matsumoto et al. (2001a)	Longitudinal	-Reduced total and R STG GM in EOS vs. controls over time
			-Severity of symptoms associated with reduced STG vol. and correlated with age of onset in EOS
	Matsumoto et al. (2001b)	Longitudinal	-Smaller GM whole brain vol. in EOS vs. controls
	Hadjul et al. (2004)	Cross-sectional	-No asymmetries of hemispheric lateralization in EOS vs. controls
Orsay	Pailière-Martinot et al. (2001)	Cross-sectional	-Smaller PFC, L insula, parahippocampal and fusiform GM volume in EOS vs. controls
	Penttila et al. (2008)	Cross-sectional	-Smaller global sulcal indices in both hemispheres in EOS vs. controls
Copenhagen	Pagsberg et al. (2007)	Cross-sectional	-No GM volume differences in EOS vs. controls
Oslo	Juuhl-Langseth et al. (2012)	Cross-sectional	-Bilateral enlargement of lateral and 4^{th} ventricle and bilateral enlargement of caudate in EOS vs. controls
Changsha	Tang et al. (2012)	Cross-sectional	-Smaller L STG/MTG GM volume in EOS vs. controls
			-Smaller L STG/MTG negatively correlated with positive symptoms in EOS
Osaka	Hata et al. (2003)	Cross-sectional	-Enlargement of lateral ventricles in EOS vs. controls
			-Positive correlation between lateral ventricular enlargement and minor physical abnormalities in EOS
Hamamatsu	Yoshihara et al. (2008)	Cross-sectional	-Smaller parahippocampal and inferior frontal GM volume in EOS vs. controls

Abbreviations: COS = childhood-onset schizophrenia; EOS = early-onset schizophrenia; GM = gray matter; L = left; MTG = middle temporal gyrus; NIMH = National Institute of Mental Health; NOS = not otherwise specified; PFC = prefrontal cortex; R = right; STG = superior temporal gyrus; UCLA = University of California, Los Angeles; UNC = University of North Carolina