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Review

Neuroimaging findings from childhood onset schizophrenia patients and their non-psychotic siblings

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ABSTRACT

Childhood onset schizophrenia (COS), with onset of psychosis before age 13, is a rare form of schizophrenia that represents a more severe and chronic form of the adult onset illness. In this review we examine structural and functional magnetic resonance imaging (MRI) studies of COS and non-psychotic siblings of COS patients in the context of studies of schizophrenia as a whole. Studies of COS to date reveal progressive loss of gray matter volume and cortical thinning, ventricular enlargement, progressive decline in cerebellar volume and a significant but fixed deficit in hippocampal volume. COS is also associated with a slower rate of white matter growth and disrupted local connectivity strength. Sibling studies indicate that non-psychotic siblings of COS patients share many of these brain abnormalities, including decreased cortical thickness and disrupted white matter growth, yet these abnormalities normalize with age. Cross-sectional and longitudinal neuroimaging studies remain some of the few methods for assessing human brain function and play a pivotal role in the quest for understanding the neurobiology of schizophrenia as well as other psychiatric disorders. Parallel studies in non-psychotic siblings provide a unique opportunity to understand both risk and resilience in schizophrenia.

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1. Introduction

Childhood onset schizophrenia (COS) is a rare and severe form of schizophrenia with symptom onset before age 13 (Driver et al., 2013). Longitudinal studies demonstrate that COS is continuous with the more common adult onset schizophrenia (AOS) with regard to symptoms and brain abnormalities (Jacobsen and Rapoport, 1998). Continuity between COS and AOS has also been supported by studies of structural neuroimaging (Rapoport et al., 2005; Sowell et al., 2000), genetics (Addington et al., 2004, 2005), neurocognitive functioning (Asarnow et al., 1987; Gochman et al., 2005), smooth pursuit eye movements (Ross et al., 1999; Sporn et al., 2005), and family studies (Asarnow et al., 2001; Nicolson et al., 2003). The commonalities between COS and AOS indicate that the investigation of COS is a valid model for understanding the neurodevelopmental basis of schizophrenia.

Like research in other cases of early-onset illness, the study of COS may hold unique advantages, as research suggests that early development of schizophrenia symptoms is linked to increased symptom severity and genetic loading of schizophrenia related markers. In fact, many characteristics of COS patients resemble those of patients with severe and poor-outcome AOS (Nicolson and Rapoport, 1999), suggesting that research specific to COS could lead to insights into disease-traits that may be more subtle in an adult-onset patient group. For example, while juvenile and adult-onset schizophrenia patients have a similar premorbid presentation, such as premorbid language delays, motor development delays and social delays (Nicolson et al., 2000; Rapoport et al., 2009; Russell et al., 1989), these early impairments are more apparent and severe for COS patients than for those with later onset of illness (Alaghband-Rad et al., 1995; Hollis, 1995; Rapoport et al., 2005). COS patients also show an increased likelihood of copy number variations (CNVs) compared to AOS patients, suggesting greater genetic salience for neurodevelopmental abnormalities in general (Ahn et al., 2014). Lastly, since early illness onset also decreases the influence of confounding environmental factors (e.g. drug abuse or psychological trauma), COS patients provide a clearer research picture of biological causes of schizophrenia.

Due to the impossibility of obtaining brain tissue during life, particularly in pediatric populations, and the limitations of postmortem studies (scarcity of tissue availability, inability to allow for concomitant correlation with clinical functioning or to perform longitudinal studies), non-invasive magnetic resonance imaging (MRI) of the brain offers an important alternative to studying brain development. This review will address recent structural and functional neuroimaging findings in studies of COS patients and their non-psychotic siblings in the context of studies of schizophrenia as a whole. We will discuss the insights that can be gained by studying abnormal brain development closer to its developmental roots.

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We searched the literature using PubMed and identified major brain regions studied in COS structural and functional MRI research. With additional expert opinion we identified total cerebral volume, ventricles, gray matter thickness, hippocampus, corpus callosum, cerebellum, white matter, and functional activity as major areas of study in COS neuroimaging. Using these brain areas as search terms, in combination with other key words ("schizophrenia", "childhood", "volume", "thickness", "MRI", "siblings", "non-psychotic", "resting", "task") we were able to add depth to our findings. To our knowledge, we have summarized the major findings in COS and all currently published research addressing non-psychotic siblings of COS patients (Table 1). The included AOS research is meant to compare and supplement the major findings in COS.

2. Structural neuroimaging

2.1. Total cerebral volume and ventricles

In clinical studies of brain structure, one of the most basic questions is whether there are overall differences in brain size for a given clinical population. In the case of adult-onset schizophrenia, decreased intracranial volume in adulthood (Haijma et al., 2013; Kahn and Sommer, 2014) and longitudinal decrease in total cerebral volume are well documented (Veijola et al., 2014). In adult patients, it is predicted that brain growth is stunted even before the onset of illness (Haijma et al., 2013). Childhood-onset patients present at initial scan with a smaller overall brain volume and then experience a progressive decline in volume during adolescence (Giedd et al., 1999b). While the clinical meaning of these findings is unclear in COS, clinical correlates have been examined in adult-onset patients. Over a longitudinal window of 9 years, antipsychotic use predicted brain volume loss in one cohort of adult patients (Veijola et al., 2014). In the same study, changes in brain volume were not related to variations in symptom severity or changes in cognitive ability over the 9-year period (Veijola et al., 2014). Similar studies have not been published in the COS field.

Along with decreased total cerebral volume, ventricular enlargement is one of the most replicated findings in schizophrenia (Sayo et al., 2012). Patients with COS have also been found to have larger ventricular volumes (Alaghband-Rad et al., 1997; Mehler and Warnke, 2002) as well as greater progressive increase in ventricular size compared to healthy controls (Giedd et al., 1999b; Rapoport et al., 1997). In particular, significant differences are seen between COS subjects and comparison controls in the lateral ventricles, which enlarge throughout adolescence in COS (Giedd et al., 1999b). These findings suggest fundamental shifts in neurodevelopment in COS.

2.2. Cortical gray matter thickness

Progressive cortical loss in COS was first described in a study by Thompson et al. (2001). This study demonstrated a dynamic wave of gray matter loss, which starts in the parietal and motor cortices and with time advances into the superior frontal, dorsolateral prefrontal and temporal cortices (including the superior temporal gyri). While temporal and dorsolateral prefrontal cortex deficits are among the most severe, they begin in late adolescence and are observed only after the onset of psychotic symptoms. The progressive deterioration in gray matter correlates with overall deterioration in global functioning. This study also sought to determine whether psychosis itself was associated with gray matter loss. Specifically, the study included a third comparison group of non-schizophrenic participants with psychotic symptoms, who were matched for IQ and medication. This group showed subtle but significantly greater gray matter loss compared to normal volunteers, but to a lesser extent than COS. These findings pointed to a successively increasing rate of gray mater loss among the three groups, with normal volunteers experiencing the least amount and COS patients the most amount of thinning. In 2004, triggered by the Thompson study, Gogtay et al. used the same type of analysis to evaluate cortical maturation in typically developing children, describing longitudinal cortical changes between the ages of 4 and 21 years (Gogtay et al., 2004). This study brought important insights into normal brain development, highlighting the different timelines of cortical maturation (with somatosensory and visual cortices developing earlier than association cortices). However, most relevant to COS, the findings of these studies together indicate that COS appears to be an exaggeration of the gray mater loss/maturation patterns observed in typically developing children.

The initial observation of profound cortical thinning in COS, described above, emerged from the study of COS patients through late adolescence. Does the same pattern of loss persist into early adulthood, and if it does, is it to the same degree? A later longitudinal study addressed this question by following COS patients and controls into adulthood (Greenstein et al., 2006). The Greenstein et al. study, found a 7.5% difference in mean cortical thickness ($p = 0.001$) between COS patients ($n = 70$, ages 7 to 26) and age matched healthy controls ($n = 72$), as well as progressive cortical thinning in the parietal, frontal and temporal regions, with parietal thinning normalizing by early adulthood (Greenstein et al., 2006). These results are continuous with findings from adult onset patients, which demonstrate cortical thinning in schizophrenia probands in the frontal and temporal cortices only (Gutierrez-Galve et al., 2015; Nesvag et al., 2008). Together, these findings further support the continuity of COS into AOS and suggest that AOS patients could have similar abnormalities before illness onset. These findings also establish that the profound gray matter thinning in adolescence appears to slow down as the children mature. It remains difficult to conclude whether this lessening rate is part of a resilience process or due to medical treatment.

It has also been established that COS probands do not differ from healthy controls with regard to sex differences in cortical thickness (Weisinger et al., 2013), or with regard to cross-sectional or longitudinal developmental changes in asymmetry (Bakalar et al., 2009). Cortical thickness deficits in COS probands are also largely uninfluenced by clozapine versus olanzapine intake, aside from a small area of the right prefrontal cortex (Mattai et al., 2010). These findings are consistent with AOS, in which age, dose, or type of antipsychotic medication are not significantly linked to changes in cortical thickness (Nesvag et al., 2008).

Using longitudinal MRI data, a recent study assessed maturational trajectories in cortical thickness in COS by comparing growth curves in patients ($n = 102$, ages 7–32) to those in healthy controls ($n = 106$, ages 7–32) (Alexander-Bloch et al., 2014). In addition to confirming a number of areas where COS patients show age-constant cortical thickness deficits compared to controls, the researchers calculated normative developmental modules based on correlations in brain maturation in the healthy volunteers. Across these modules, the only network with significant abnormal cortical growth overlap in COS was the cingulo-fronto-temporal module. These findings highlight that neuroanatomical modularity in cortical thickness may contribute to the development of schizophrenia and therefore indicate alterations in the developmental process rather than focusing on anatomical areas per se.

2.3. Hippocampus

The hippocampus is known as a critical brain structure for learning and memory, and has accordingly been of interest in schizophrenia, in which cognitive deficits remain a primary feature of the disease. Bilateral deficits in hippocampal volume are well documented in schizophrenia (Adriano et al., 2012) and research in COS suggests that the hippocampus is affected by the disease state (Giedd et al., 1999b; Jacobsen et al., 1998). Older studies examining young COS patients demonstrate no initial difference in hippocampal volume (Giedd et al., 1999) but also suggest that the illness itself may eventually cause a decline in hippocampal volume (Giedd et al., 1999b; Jacobsen et al., 1998). In Jacobsen