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Neuroimaging Findings from Childhood Onset Schizophrenia Patients and their Non-Psychotic Siblings

Anna E. Ordóñez, M.D., M.A.S.^{*}, Zoe Luscher, B.S.^{*}, and Nitin Gogtay, M.D.

Child Psychiatry Branch, National Institute of Mental Health, NIH

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.

Keywords

schizophrenia; neuroimaging; childhood; endophenotype; siblings

1.1 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 regards to symptoms and brain abnormalities (Jacobsen and Rapoport, 1998). Continuity between COS

Corresponding Author: Nitin Gogtay, M.D. Address: Child Psychiatry Branch, NIMH, NIH, Building 10, Rm 3N202, 10 Center Drive, MSC-1600 Bethesda, MD 20892, Phone: (301) 435-4494, Fax: (301) 402-7160, ; Email: gogtayn@mail.nih.gov.

^{*}Equal contribution

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and AOS has also been supported by studies of structural neuroimaging (Rapoport et al., 2005; Sowell et al., 2000), genetics (Addington et al., 2005; Addington et al., 2004), 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.

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. The included AOS research is meant to compare and supplement the major findings in COS.

1.2 Structural Neuroimaging

1.2.1 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 (Alagband-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.

1.2.2 Cortical Gray Matter Thickness

Progressive cortical loss in COS was first described in a study by Thompson et al., in 2001 (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 grey matter correlates with overall deterioration in global functioning. This study also sought to determine whether psychosis itself was associated with grey 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 grey 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 grey matter 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 regards to sex differences in cortical thickness (Weisinger et al., 2013), or with regards 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.

1.2.3 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., 1999a) but also suggest that the illness itself may eventually cause a decline in hippocampal volume (Giedd et al., 1999b; Jacobsen et al., 1998). In the Jacobsen et al. study, for example, schizophrenic children demonstrated a 14.3% decline in hippocampal volume in the first two years of study enrollment (Jacobsen et al., 1998). This poses the question of whether differences in findings regarding hippocampal volume trajectories are related to the time elapsed since initial onset of illness, or the time covered by longitudinal studies.

Contrary to some of the above described earlier findings, a number of subsequent larger prospective studies (Mattai et al., 2011a; Nugent et al., 2007) demonstrate fixed longitudinal volumetric deficits in COS patients compared to controls. Of these, the 2011 Matai et al. study had the largest sample (89 COS probands, 78 siblings and 79 controls) and highlighted prior findings (Giedd et al., 1999b; Nugent et al., 2007) that suggest that the hippocampal deficits observed in COS are significant but do not vary over time. These findings are consistent with the animal model of schizophrenia suggested by Lipska et al. in 1993 (Lipska et al., 1993), in which ventral hippocampal lesions in the neonatal (but not adult) rat lead to exaggerated mesolimbic dopamine response to stress and amphetamines in adulthood. Of particular note in this model was that the rats with the early ventral hippocampal lesions didn't manifest the specific behavioral changes until early adulthood. These findings are consistent with an early fixed hippocampal deficit, which manifests after an initial quiescent period due to increased stress or particular substances.

From an anatomic perspective, subregional shape abnormalities have also been described in adult schizophrenia (Csernansky et al., 2002; Narr et al., 2004) and COS (Johnson et al., 2013b). Specifically, the Johnson et al. study found that COS patients demonstrate inward deformations on both sides of the anterior hippocampus, and greater differences have been associated with increased symptom severity. The affected hippocampal regions are commonly associated with hippocampal CA1 pyramidal neurons, whose migration is disrupted by genetic differences associated with schizophrenia (e.g. disruption of the *Disc1* gene) (Booth et al., 2014). The CA1 neurons serve as a connection between the hippocampus and the prefrontal cortex, which is also widely implicated in schizophrenia (Godsil et al., 2013). While the exact involvement of hippocampal abnormalities in COS is unclear, it is possible that abnormal neurodevelopment in these interconnected regions holds further information regarding symptom development.

1.2.4 Corpus Callosum

The majority of patients with schizophrenia manifest neurological soft signs that include errors in sensory integration, motor coordination, and inhibition (Chan et al., 2010). These processing deficits, thought to arise due to decreased interhemispheric neural communication, have been associated with irregularities in the corpus callosum (Bersani et al., 2011). This connective region has been extensively studied in AOS, and while not all studies agree, meta-analyses have associated schizophrenia with a reduced midsagittal cross-sectional area in the corpus callosum (Arnone et al., 2008; Woodruff et al., 1995). In the Arnone, et al. meta-analysis, first episode patients were more likely to have decreased

corpus callosum areas, and chronic patients were more likely to demonstrate an increase in area (Arnone et al., 2008). A more recent study of first-episode and chronic schizophrenia patients found decreased corpus callosum area and volume in all patients, but in comparing first-episode and chronic patients reported that chronicity contributed to greater decrease in four of five corpus callosum area segments; in fact, this particular study reported that first-episode patients only differed from healthy controls in two of five area regions (Collinson et al., 2014). One longitudinal study of the corpus callosum in adult-onset chronic schizophrenia patients demonstrated progressive decline in callosal size, with poor-outcome patients demonstrating more pronounced decline (Mitelman et al., 2009).

The research regarding the corpus callosum in COS is less abundant but no less heterogeneous. The most recent and largest to-date longitudinal study in COS (n=90, 235 scans) (Johnson et al., 2013a) found no differences in total corpus callosum cross-sectional area or in any subregions of the cross-section. This study also found no differences in developmental trajectories of any measurement of corpus callosum area or volume (Johnson et al., 2013a). These results contrast those from an earlier, smaller study in the same group, which also reported normal initial total corpus callosum area, but showed a progressive decrease in the splenium area, which connects occipital cortical areas, beginning at age 22 (Keller et al., 2003b). An earlier study of brain volumes in COS patients found no difference in callosal volume in patients compared to healthy controls (Kumra et al., 2000). One study has examined corpus callosum area in healthy siblings of COS patients, and these results were also not significant (Johnson et al., 2013a). The heterogeneity of these findings suggests that the behavioral deficits in sensorimotor integration in COS may originate not in callosal connections but in the interaction of multiple networks, possibly reflecting a dysfunction in predictive processing (Ford and Mathalon, 2012; Frith et al., 2000; Picard and Friston, 2014).

1.2.5 Cerebellum

The cerebellum is of particular interest to studies of psychiatric disorders due to its highly heritable development (Wallace et al., 2006). The cerebellum has traditionally been viewed as a motor structure, but more recent evidence suggests that it may also contribute to higher cognitive functions (Middleton and Strick, 1998), and it has garnered attention as a key site of dysregulated circuitry in schizophrenia (Andreasen and Pierson, 2008). In line with this, cerebellar deficits have been linked to COS (Keller et al., 2003a). An early cross-sectional study of COS patients between the ages of 9 and 18 demonstrated decreased cerebellar volume relative to controls in the vermis (11.7% smaller), midsagittal inferior posterior lobe area (10.9% smaller) and midsagittal inferior posterior lobe (8.9% smaller) (Jacobsen et al., 1997). Later research suggests that the volumetric deficits found in this study may have been due to a progressive loss over time. For example, while a longitudinal study of COS patients between ages 8 and 24 found no initial differences in the cerebellum, follow-up scans revealed significant cerebellar volume decrease that was not seen in healthy subjects (Keller et al., 2003a). Studies of AOS have reported a similar progressive decline in cerebellar volume (Kong et al., 2012), or a smaller cerebellar volume during the first episode in AOS (Bottmer et al., 2005).

We recently further examined the cerebellum in COS patients in relation to their siblings in a prospective design with a large sample (94 COS patients between ages 6.5 and 29 and their 80 non-psychotic siblings)(Greenstein et al., 2011). The results indicated that COS subjects had smaller bilateral anterior lobes and anterior and total vermis volumes compared to controls (Greenstein et al., 2011). Siblings did not differ from healthy controls initially, but demonstrated decreased cerebellar volume over time in the total and right cerebellum, left inferior posterior, left superior posterior, and superior vermis (Greenstein et al., 2011).

Many of the findings in COS cerebellar volume are similar to those found in AOS patients, continuing to support the continuity between COS and later-onset schizophrenia. The presence of cerebellar atrophy in healthy siblings of COS patients, as well as the presence of abnormalities in AOS patients during the first episode, suggests that the cerebellar trajectory described is likely related to genetic risk for schizophrenia.

1.2.6 White Matter

The dysconnectivity hypothesis of schizophrenia was brought to the forefront of schizophrenia research in 1995, when researchers first proposed that aspects of the illness could be due to aberrant (increased or decreased) connectivity between brain regions as opposed to localized abnormalities within regions (Pettersson-Yeo et al., 2011). Studies of white matter, axonal connective tissue in the brain, allow investigation into differences in neural architecture and the dysconnectivity that bolster this hypothesis. White matter abnormalities have been demonstrated in both AOS and COS patients. Using tensor-based morphometry, Gogtay et al. demonstrated that teenage COS patients have a slower rate of white matter growth per year, particularly in the right hemisphere, and that deficits in growth are associated with lower functioning in terms of the Children's Global Assessment Scale (Gogtay et al., 2008). Adults with schizophrenia maintain deficits in white matter longitudinally, supporting continuity between COS and AOS brain morphology (Kahn and Sommer, 2014).

Diffusion tensor imaging (DTI), which examines directional diffusion of water in the brain to assume structural integrity in neural axons, has led to less conclusive results. The largest study of DTI in COS to date (n=39) examined eleven regions of interest based on white matter findings in the aforementioned Gogtay et al. paper, and found decreased white matter integrity in the bilateral cuneus, a portion of the occipital lobe (Moran et al., 2015). In another DTI study, COS patients exhibited a decrease in white matter integrity in relation to their level of linguistic impairment (Clark et al., 2012). Overall, DTI research in COS is limited, and inconsistent with the frontal abnormalities demonstrated by AOS DTI research (Samartzis et al., 2014) and clearly needs more observations with larger samples and better image resolution.

1.3 Functional Magnetic Resonance Imaging

Functional imaging studies have broadened our ability to explore abnormalities in brain circuitry. These types of studies are difficult to perform in the COS population due to difficulties engaging patients with severe illness in various tasks. This is in great part why resting state fMRI studies have been more feasible in this population and the most likely

reason that only one task-based fMRI study has been published to date with a focus on COS. Borofsky et al. examined language processing in COS, demonstrating that COS patients have overall reduced activity compared to healthy controls during both semantic and syntactic language processing tasks (Borofsky et al., 2010). The differences in activation were not related to performance on the task, as there were no group differences in success rate.

Brain function has been more extensively examined in COS through resting state functional magnetic resonance imaging (R-fMRI), in which brain activity is recorded during rest as opposed to during a task. R-fMRI studies examine patterns in blood oxygen level dependent (BOLD) signal and use correlations between activity in anatomically-distinct brain regions to infer long-distance connectivity (van den Heuvel and Hulshoff Pol, 2010). These type of inferences regarding connectivity are particularly useful in understanding the dysconnectivity model of schizophrenia, which suggests that schizophrenia is in part due to aberrant communication between brain regions in addition to the previously described volumetric differences (van den Heuvel and Fornito, 2014).

R-fMRI has been used to examine dysconnectivity in a number of different ways including seed-based analysis, spatial independent component analysis and graph-theory based methods (Yu et al., 2012). Studies of resting state in AOS are more abundant and support the dysconnectivity model of schizophrenia (Yu et al., 2012). To date, there are three published studies of R-fMRI in COS, all focusing on graph theory approach (Alexander-Bloch et al., 2012; Alexander-Bloch et al., 2010; Alexander-Bloch et al., 2013). These resting state studies have demonstrated a decreased local connectivity strength in COS that is partially balanced by increased global network efficiency relative to healthy controls.

1.4 Healthy Siblings

Knowledge regarding healthy siblings of patients with heritable illnesses is invaluable in clinical research because it allows researchers to make important conclusions regarding the contribution of genetic background to an illness state versus an illness predisposition. Healthy siblings of COS patients, who share an average of 50% of their genetic material, can add context to neuroimaging findings and act as an additional control group (Moran et al., 2013). In the most rudimentary form, phenotypic differences between patients and genetically related controls suggest that the patient phenotype is related to the expression of symptoms. In other words, consistent differences between patients and their siblings can be explained by the disease state, assuming that the healthy sibling group and unrelated healthy control group do not differ. On the other end of the spectrum, similarities between healthy and ill siblings despite the difference in their health can relate phenotypes to genetic vulnerability that may not contribute directly to symptoms. In each case, the assumption is that the patient group and the healthy, unrelated control group have a different phenotype, and that the siblings may be more similar to either of the other two groups.

Though COS sibling studies are not as common as studies of COS probands, they have added greatly to the depth of schizophrenia research (Moran et al., 2013). Due to the early onset nature of COS, siblings of COS patients enter studies early and provide an excellent

means to study non-symptomatic neurodevelopment in subjects with a genetic predisposition for schizophrenia, addressing the state vs. trait question.

1.4.1 State Markers

State markers are characteristics unique to the disease state that do not occur in healthy siblings of patients despite their predisposition for the illness. One obvious state marker of schizophrenia is diagnostic-level psychosis, which non-psychotic siblings do not experience despite their predisposition. The brain area most consistently identified as a state marker for schizophrenia through COS studies is the hippocampus, which demonstrates volumetric deficits in probands but not their non-psychotic siblings (Mattai et al., 2011a). In a study by Mattai et al, COS patients consistently had a decreased hippocampal volume, and the developmental trajectory in probands, siblings and healthy controls were all similar (Mattai et al., 2011a). In other words, the mean hippocampal volume of COS patients was lower than the sibling and healthy control group at every point in time, but the patient developmental trajectory was consistent with all other groups.

1.4.2 Trait Markers

Herein, trait markers are defined as phenotypes of schizophrenia that may be related to predisposition for the illness. They are similarities between patients and their healthy siblings that occur despite differences in psychiatric phenotype, and that do not occur in the general healthy population. For example, it is widely known that first-degree relatives of patients with schizophrenia may exhibit a deficit in sensory gating (e.g. tuning out white noise), which, though not directly related to the illness, may be related to underlying pathology (Freedman et al., 1987). Non-psychotic siblings of COS patients share a number of characteristic abnormalities with their affected relatives, including differences in cerebral volume, gray matter thickness, and white matter growth (Gogtay et al., 2007; Gogtay et al., 2012; Gogtay et al., 2003).

Studies of healthy siblings of COS patients suggest that initial decreased cortical thickness is a heritable risk factor as opposed to a state marker for the illness (Gogtay et al., 2007). Two non-overlapping studies of unaffected siblings ($n = 52$, 113 scans; ages 8 to 28 and $n=43$, 68 scans, ages 5 to 26 years) versus healthy controls ($n = 52$, 108 scans and $n = 86$, 136 scans) demonstrated no significant difference in mean cortical thickness between the two groups, however the sibling group had a pattern of early restricted grey matter loss (Gogtay et al., 2007; Mattai et al., 2011b). Both studies examined cortical thickness in siblings by region, revealing grey matter deficits in prefrontal, temporal, and parietal areas during early life (Gogtay et al., 2007; Mattai et al., 2011b). Each of these deficits, though initially similar to those seen in young COS patients, were undetectable by adulthood mostly due to faster rates of cortical thinning in the healthy control group (Gogtay et al., 2007; Mattai et al., 2011b). The volume normalization may help explain inconsistent results from similar studies of cortical thickness in healthy siblings of adult-onset patients (Boos et al., 2012), as sibling cortical thickness seems to depend on the age of the sibling sample. Furthermore, siblings of COS patients have also been shown to exhibit deficits in white matter growth during adolescence at early stages in life, however the growth rate normalizes by adulthood in healthy siblings, suggesting that white matter growth represents an endophenotype (Gogtay

et al., 2012). One DTI study has also examined regions of interest in non-psychotic siblings of COS patients, demonstrating deficits in fractional anisotropy in the bilateral cuneus, a characteristic shared between patients and their siblings (Moran et al., 2015). These results represent additional evidence of white matter abnormalities as an endophenotype in schizophrenia.

One task-based fMRI study has been conducted with a COS sibling population. In this study, Wagshal et al. demonstrated that healthy siblings of COS patients showed aberrant frontal and striatal activation relative to healthy controls during a cognitive skill learning task (Wagshal et al., 2014). Activation was measured throughout learning, and healthy siblings demonstrated increased frontal activation during an initial slow learning period and then decreased activation after training (Wagshal et al., 2014). The striatal activation in healthy siblings was also different from controls, decreasing steadily throughout the learning process instead of remaining constant over time (Wagshal et al., 2014). If feasible, it would be interesting to conduct a similar study in COS patients, in order to understand to what extent these findings may represent a functional endophenotype.

To our knowledge, no R-fMRI studies have been published describing functional connectivity in healthy siblings of COS patients. However, preliminary findings from our unpublished data (Rebecca Berman et al.) suggest the sibling phenotype is intermediate, similar to that seen for structural abnormalities, and suggesting a potential functional trait marker.

1.5 Summary

COS represents a unique and promising research opportunity to help understand the neurodevelopment and brain abnormalities in schizophrenia as a whole. Because the majority of patients with schizophrenia do not develop the illness until young adulthood, few studies have the opportunity to track patients during the significant life-altering brain changes of adolescence. Longitudinal studies of COS patients and their unaffected siblings (as potential carriers both of disease traits as well as of resiliency factors) can help answer questions regarding schizophrenia-specific neurodevelopment and resilience.

Structural neuroimaging studies in COS to date have revealed progressive loss of gray matter volume and cortical thinning, ventricular enlargement, progressive decline in cerebellar and hippocampal volume, and slower rate of white matter growth. Corpus callosum findings are heterogeneous and amygdala findings are overall negative. Sibling studies have revealed potential disease traits in the manifestation of decreased gray matter and progressive decrease in cerebellar volume. Structural neuroimaging in healthy siblings of patients demonstrate that healthy children at genetic risk for schizophrenia share disrupted white matter growth and initial decreases in cortical thickness with their affected siblings. In healthy siblings, findings that lose significance after early development and thus indicate possible neurodevelopmental processes that convey risk if maintained, as well as potential restitutive or protective processes.

Functional neuroimaging studies in COS are fewer in number. The majority of functional research in COS has examined the COS brain in resting state, and these studies demonstrate disrupted local connectivity strength in patient populations relative to healthy controls. The research to date can be related to the dysconnectivity model of schizophrenia. One task-based study in patients demonstrates lower activity in a language processing task, and one study of healthy siblings of COS patients demonstrates aberrant activity during cognitive skill learning. Because no functional studies to date examine both COS patients and their siblings, it has been difficult to draw further conclusions than the former.

While neuroimaging studies remain limited in their ability to provide information about brain activity at the molecular level, as well as the relatively small sample sizes, few longitudinal studies, and scarce population studies in the field, they remain our only direct access to the live brain. Continued advances in neuroimaging and genetic methodology, increased correlation between genetic, functional and multi-modal neuroimaging findings, using longitudinal designs across early to late age spectrum of children and adults with schizophrenia as well as their siblings, will remain pivotal in the quest for understanding the neurobiology of this devastating illness.

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Table 1
Key neuroimaging studies in patients with childhood-onset schizophrenia and/or their non-psychotic siblings

Area of Study	Citation	N	Key Findings
fMRI, resting state	Alexander-Bloch et al. 2010	COS (n=13, mean age =18, SD =4); healthy controls (n=19, mean age=19, SD=4)	decreased local connectivity strength and increased global network efficiency in COS patients relative to HCs
fMRI, resting state	Alexander-Bloch et al., 2012	COS (n=19, mean age =18.7, SD=4.9, range=12.2-30.4); healthy controls (n=20, mean age =19.7, SD=5, range=13.2-33.7)	decreased local connectivity strength and increased global network efficiency in COS patients relative to HCs
cortical thickness	Alexander-Bloch et al., 2014	COS (n=106, 261 scans; mean age at scan =17.4, range=7-32); healthy controls (n=102, 264 scans; mean age at scan=17.2, range=8-33)	age-constant cortical thickness deficits in COS versus HCs; COS deficits are localized to one of five cortical growth modules (the cingulo-fronto-temporal module)
brain asymetry	Bakalar et al., 2009	COS (n=49, 117 scans; mean age scan 1=14.72); healthy controls (n=50, 125 scans; mean scan 1 age=15.15)	no difference in cross-sectional or longitudinal developmental changes in asymmetry in COS patients versus HCs
fMRI, task	Borofsky et al., 2010	COS (n=14; mean age=13.34, SD=2.14); healthy controls (n=14; mean age=12.37, SD=2.39)	reduced brain activity during semantic and syntactic language processing tasks in COS patients versus HCs, unrelated to performance on the task
white matter	Clark et al., 2012	COS (n=18, mean age=14.3); healthy controls (n=25, mean age=14.2)	decreased white matter integrity in relation to linguistic impairment in COS patients versus HCs
hippocampus	Gied et al., 1999	COS (n=42; mean age=14.4, SD=2.3); healthy controls (n=72; mean age =13.8, SD=2.5);	COS patients demonstrate no initial difference in hippocampal volume versus HCs, but develop a deficit that worsens in time since onset
ventricles	Giedd et al., 1999	COS (n=42; mean age=14.4, SD=2.3); healthy controls (n=72; mean age =13.8, SD=2.5);	lateral ventricles enlarge throughout adolescence in COS versus HCs
whole brain, ventricles	Giedd et al., 1999	COS (n=42; mean age=14.4, SD=2.3); healthy controls (n=72; mean age =13.8, SD=2.5);	smaller initial overall brain volume and progressive decline in volume during adolescence in COS versus HCs
cerebral volume	Gogtay et al., 2003	non-psychotic siblings of COS patients (n=15, mean age = 19.14, SD=5.99); healthy controls (n=32, mean age = 18.75, SD=6.02)	smaller total cerebral volume & smaller total, frontal, & parietal gray matter volumes in SIBS than HCs
cortical gray matter	Gogtay et al., 2007	non-psychotic siblings (n=52, 113 scans; age 8-28 years); healthy controls (n=52, 1-8 scans)	cortical gray matter deficits in the left prefrontal, bilateral temporal, right prefrontal, and inferior parietal cortices in SIBs versus HCs; deficits disappear by age 20; higher GAS scores related to normalization of cortical deficits
white matter	Gogtay et al., 2008	COS (n=12; mean baseline age=14.1; mean follow-up age=18.7); healthy controls (n=12; mean baseline age=18.0)	slower rate of white matter growth per year in teenage COS patients versus HCs, particularly in the right hemisphere; deficits associated with lower functioning
white matter growth	Gogtay et al., 2012	non-psychotic siblings of COS patients (n=49, mean age = 16.1, SD=5.3); healthy controls (n=57, mean age =16.9, SD=5.3)	slower parietal white matter growth rates in SIBs relative to HCs, at younger (7-14) ages, normalizing at older ages
cortical thickness	Greenstein et al., 2006	COS (n=70, 162 scans; mean age at scan 1=14.47); healthy controls (n=72, 168 scans; mean age at scan 1=14.35)	progressive cortical thinning in parietal, frontal and temporal cortex regions in COS patients relative to HCs; parietal thinning normalized by early adulthood
cerebellum	Greenstein et al., 2011	COS (n=94); non-psychotic siblings (n=80), healthy controls (n=110)	smaller bilateral anterior cerebellar lobes and anterior and total vermis volumes in COS versus HCs; no difference initially between SIBs and HCs, but decreased volume over time in the total and right cerebellum, left inferior posterior, left superior posterior, and superior vermis

Area of Study	Citation	N	Key Findings
cerebellum	Jacobsen et al., 1997	COS (n=24; mean age =14.1, SD=2.2); healthy controls (n=52)	decreased cerebellar volume in COS versus HCs in the vermis, midsagittal inferior posterior lobe area and midsagittal inferior posterior lobe
hippocampus	Jacobsen et al., 1998	COS (n=10, 20 scans; mean baseline age =15.2, mean follow-up age=17.4); healthy controls (n=17, 34 scans; mean baseline age =14.2, mean follow-up age =16.4)	no initial difference in hippocampal volume in COS versus HCs, but a deficit that worsens in time since illness onset in COS
corpus callosum	Johnson et al., 2013a	COS (n=98, 235 scans; mean age=17.3, SD=4); non-psychotic siblings (n=71, 153 scans; mean age=17.6, SD=5.2); healthy controls (n=100, 253 scans; mean age=17.2, SD=4.9)	no difference in cross-sectional area of the corpus callosum in COS versus HCs, or within any subregions of the cross section. There were no differences in developmental trajectories of any measurement of corpus callosum area or volume. Non-psychotic siblings of COS patients show no differences in corpus callosum area compared to HCs
hippocampus	Johnson et al., 2013b	COS (n=103, 225 scans); non-psychotic siblings (n=79, 169 scans); healthy controls (n=101, 255 scans); age-range=9-29	inward deformations on both sides of the anterior hippocampus in COS versus HCs; greater differences associated with increased symptom severity
cerebellum	Keller et al., 2003a	COS (n=55, 113 scans; ages 8-24); healthy controls (n=56, 110 scans, age-matched)	progressive loss of cerebellar volume in adolescence in COS patients versus HCs
corpus callosum	Keller et al., 2003b	COS (n=50; 108 scans); healthy controls (n=50; 101 scans)	smaller splenium (posterior corpus callosum) in COS versus HCs, starting at age 22.4 with differences increasing with age
hippocampus	Kumra et al 2000	COS (n=44); psychotic disorder NOS (n=27); healthy controls (n=106)	no difference in hippocampus volume in COS versus HCs at illness onset in COS
corpus callosum	Kumra et al., 2000	COS (n=44); psychotic disorder NOS (n=27); healthy controls (n=106)	no difference in callosal volume in COS versus HCs
cortical thickness	Mattai et al., 2010	COS patients taking clozapine (n=12, 37 scans); COS patients taking olanzapine (n=12, 33 scans)	clozapine and olanzapine differ in their influence on cortical thickness in COS in the right prefrontal cortex, but in no other areas
hippocampus	Mattai et al., 2011a	COS (n=98, 198 scans; mean age=17.5, SD=4.2); non-psychotic siblings (n=78, 172 scans; mean age=17.9, SD=6.9); healthy controls (n=79, 198 scans; mean age=17.3, SD=4.9)	fixed longitudinal hippocampal volumetric deficits in COS patients versus HCs and SIBs; no differences in volume or volume trajectory between SIBs and HCs
cortical gray matter	Mattai et al., 2011b	non-psychotic siblings (n=43, 68 scans; ages 5-26); healthy controls (n=86, 136 scans)	gray matter deficits in bilateral prefrontal and left temporal cortices in SIBs younger than 17 versus HCs; smaller deficits in parietal & right inferior temporal cortices, compared to HCs; deficits normalize with age
white matter	Moran et al., 2014	COS (n=29, mean age=19.7, SD=5.7); non-psychotic siblings n=39, mean age=18.1, SD=7.4), healthy controls (n=50, mean age =19.3, SD=6.3)	of 11 regions of interest in a DTI study, decreased FA (white matter integrity) in the bilateral cuneus in COS patients and SIBs relative to HCs
hippocampus	Nugent et al., 2007	COS (n=29, 87 scans; mean age=17.6, SD=3.7); healthy controls (n=31, 94 scans; mean age = 17.5, SD=3.5)	fixed longitudinal volumetric deficits in the hippocampus of COS patients compared to HCs
ventricles	Rapoport et al., 1997	COS (n=16; mean age scan 1=14.8, mean age scan 2=16.8); healthy controls (n=24; mean age scan 1=14.3, mean age scan 2=16.7)	greater progressive increase in ventricular size in COS versus HCs
cortical thickness	Thompson et al., 2001	COS (n=12, mean age scan 1=13.9); healthy controls (n=12, mean age scan 1=13.5)	progressive cortical loss in COS versus HCs, starting at parietal and motor cortices and advancing into the superior frontal, dorsolateral prefrontal and temporal cortices
fMRI, task	Wagshal et al., 2014	non-psychotic siblings (n=16); healthy controls (n=45)	aberrant frontal & striatal activation in SIBs vs. HCs during a cognitive skill learning task

Area of Study	Citation	N	Key Findings
cortical thickness	Weisinger et al., 2011	COS (n=104, 249 scans); healthy controls (n=104, 244 scans)	no difference in sex-related cortical thickness in COS patients compared to HCs

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