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REVIEW ARTICLE

Functional and clinical insights from neuroimaging studies in childhood-onset schizophrenia

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Childhood-onset schizophrenia is a rare pediatric onset psychiatric disorder continuous with and typically more severe than its adult counterpart. Neuroimaging research conducted on this population has revealed similarly severe neural abnormalities. When taken as a whole, neuroimaging research in this population shows generally decreased cortical gray matter coupled with white matter connectivity abnormalities, suggesting an anatomical basis for deficits in executive function. Subcortical abnormalities are pronounced in limbic structures, where volumetric deficits are likely related to social skill deficits, and cerebellar deficits that have been correlated to cognitive abnormalities. Structures relevant to motor processing also show a significant alteration, with volumetric increase in basal ganglia structures likely due to antipsychotic administration. Neuroimaging of this disorder shows an important clinical image of exaggerated cortical loss, altered white matter connectivity, and differences in structural development of subcortical areas during the course of development and provides important background to the disease state.

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Introduction

Schizophrenia is a chronic, debilitating psychiatric disorder that affects approximately 1% of the population and represents a tremendous cost on society.[1] Childhood-onset schizophrenia (COS), diagnosed before the age of 13, is a rare and severe form of this disorder that is continuous with its adult counterpart.[2–4]. The clinical presentation of COS is identical to that of chronic, severe, and treatment-refractory adult-onset schizophrenia (AOS) with psychosis, delusions, disorganization, flat affect, and social withdrawal.[5] Characterized by its non-episodic course, COS shows similar but more severe abnormalities on neurobiological,[3] cognitive,[6] as well as familial[7] measures. Prospective anatomic brain MRI studies of COS (discussed later in detail) establish further continuity between COS and AOS, as, with age, the gray matter (GM) deficit pattern seen in COS merges into a deficit pattern that is characteristic of AOS.[8] Due to the myriad of psychiatric disorders that can manifest with psychotic symptoms, the likelihood of misdiagnosis of COS is high.[9–11] Familiarity with the nature of COS is imperative to pediatric clinicians, as misdiagnosis is a legitimate concern. Over the past 2 decades, neuroimaging and genetic research has brought new insights into functional and neural abnormalities in COS patients, as well as the developmental course of the disease in the brain as it matures.[12]

The overarching picture painted by these studies is not far from that of adult onset schizophrenia (AOS). COS patients have smaller brain volume in general, largely due to the difference in gray matter.[13] The pattern of gray matter volume loss that occurs in COS during adolescence appears to be an exaggeration of normal gray matter maturation,[14–17] while white matter development seems lagging compared to controls.[18,19] Early-onset disorders generally follow the trend of more severe prognosis and a greater genetic component; thus, insights into COS also offer clinicians especially useful etiologic and genetic information. COS appears to have significant genetic salience, perhaps greater than that seen for AOS,[20] with greater clusters of schizophrenia spectrum disorders in relatives,[4] as well as greater frequency of rare allelic variants, which often take the form of a copy number variation[21] or chromosomal abnormalities.[12,22] COS also features a high genetic overlap with autism spectrum disorders (ASD).[22] COS is also noteworthy for its increased instance of multimodality hallucinations, especially visual hallucinations.[23]

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An important question for the schizophrenia field has been the diagnostic specificity of neuroimaging findings and whether they are influenced by medication exposure. This is particularly important in pediatric psychosis, as often there is phenotypic overlap in various forms of psychosis and other comorbidities such as autism spectrum disorders. In order to attribute neurobiological observation to a specific disorder, it becomes crucial to make sure that a specific phenotype is being studied. Observations from COS neuroimaging studies have helped answer many of these questions. These studies have shown that COS imaging findings are diagnostically specific,[15] are unlikely to be due to medication influence,[15] are likely to be endophenotypes shared by healthy COS siblings,[24] and brain abnormalities are influenced by the dimensional nature of psychosis.[12]

Magnetic resonance imaging (MRI) technology has enabled a noninvasive foray into the developing brain of COS patients. Through neuroimaging, researchers and clinicians can glean insight into the anatomical bases for psychiatric symptoms in the COS population. It is important for clinicians to understand the biological course of COS especially because of is rarity and clinical profile, and early treatment has a drastic effect on patient outcome.[25] As literature on neuroimaging becomes more comprehensive, eventually diagnosis may be assisted by biological measures, instead of relying only on symptom report and observation of symptoms during delimited periods of time.

The goal of this review is to summarize trends in neuroimaging research of COS as it pertains to cortical, subcortical, and white matter differences, as well as how these anatomical and functional findings may help to explain the clinical phenomenology and functionality of COS patients. Our methodology in compiling these findings involved searching through PubMed for several key terms, including "childhood-onset schizophrenia," "schizophrenia," "cortex," "cerebellum," "ventricle," "basal ganglia," "amygdala," "hippocampus," "fMRI," "neuroimaging," "DTI," "corpus callosum," "white matter," and "gray matter." After this initial acquisition of articles, additional literature was found by combing through the works of the principal investigators of both the National Institute of Mental Health (NIMH) cohort and the University of California–Los Angeles (UCLA) cohort on COS. Additional research was found by variations in suffixes of search terms and papers referenced in discussion sections of the principle papers found. Controls in both cases are normal volunteers controlled for IQ, past psychiatric history, serious medical illness, and age.

Cortical Structures

Cortical structure abnormalities in COS populations have the strongest relation to clinical symptom profile of all their neural deficits. Cortical thinning in schizophrenia patients has been demonstrated repeatedly in AOS populations.[26,27] The trend is similar but more profound in COS patients, though the effect appears more robust[8,15] and not influenced by gender.[28] Cortical thickness in non-psychotic full siblings of COS patients was shown to depict similar significant deficits in the prefrontal, left temporal, right inferior temporal, and parietal cortices; however these appeared to normalize by age 17,[29] suggesting that this cortical thinning in COS patients is due in part to a genetic component.

Prefrontal cortex abnormalities are among the most reported in both COS and AOS, and have been generally agreed to represent the neural pathway of working memory deficits in schizophrenia.[30] Temporal lobe volumes abnormalities are similarly commonly reported, with temporal cortical gray matter decrease as the most replicated finding in COS patients.[12,16,29,31,32] This is in concordance with temporal cortical thickness deficits noted in AOS patients.[33] Both of these cortical deficits are, broadly speaking, likely implicated in compromised normative functioning. Temporal lobe structures are implicated in both emotion processing and auditory processing, and the symptom profile of COS patients is inclusive of deficits in social functioning, which are characterized by social withdrawal[34] and auditory hallucinations, among other modalities. Working memory is involved in any task that involves holding salient information in mind, such as directions to a novel location. Being unable to navigate a new area compromises the ability of COS patients to lead independent and fully functional lifestyles.

Prefrontal and temporal cortical deficits are present throughout the disease course,[29,31] yet the pattern of thinning appears to begin at the parietal lobe and spread toward the frontal and temporal areas.[35,36] Later neuroimaging studies have shown a deficit pattern similar to AOS patients, with reductions in thickness confined primarily to the superior temporal and frontal lobes,[8,26,27] providing evidence for the normalization of parietal deficits by adulthood.[8,37] The early age deficit pattern appears to be, as previously mentioned, an exaggerated form of normal developmental "pruning," and may demonstrate the neural correlate of one of the few distinguishing characteristics between COS and AOS. It seems as though COS patients undergo an early parietal deficit that is not so much abnormal as it is poorly timed; the normal maturational curve of parietal development is similar, yet delayed, compared to the COS population.[8]

There is no reported reduction in occipital thickness in COS, but there are some functional MRI studies that point towards altered functional connectivity. In 2012, White *et al*[38] found that a sample of 25 adolescent and childhood onset schizophrenia patients had significantly lower

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volume of activation in the occipital lobe in response to a flashing checkerboard stimulus when compared to normal volunteers, but demonstrated preserved local functional connectivity. The lower volume of activation points toward abnormal processing of visual stimuli, as they typically travel from v1 to other regions in the occipital lobe. White *et al* cite a parallel study performed in AOS patients that failed to find significant differences between early visual processing in patients and controls,[39] and acknowledge that differences in processing could be due to differences in age, illness duration, medication effects, paradigm, or analysis.[38] It is difficult to conclude the effect of this abnormal processing, but it could be implicated in the abnormally high rate of visual hallucination in COS[23] as compared to AOS patients, which is further supported by the lack of abnormal processing in AOS.[39] The NIMH COS cohort uncovered the opposite trend when utilizing a resting state as opposed to task-based fMRI task; the data it has found support a dysfunctional intramodular connectivity between neighboring regions in a variety of areas, including the ventral occipital cortex.[40] While these studies are contradictory, in AOS studies, decreased superior occipital volume and local occipital functional activity have been noted as well,[41] indicating that reduced long distance connectivity may be an age effect. It is difficult to conclude the effects of this degradation based on the discrepancies in the literature, but due to the fact that primary visual processing occurs in the occipital lobe, it is possible that altered connectivity in COS patients is the basis for the high rate of visual hallucination seen in this patient population. Additionally, aberrant connectivity in COS patients would seem a likely basis of the higher prevalence of multimodality hallucinations.[23] Perhaps, because of onset of illness prior to normal developmental pruning, connectivity between different sensory cortices is still intact, enabling the greater frequency of visual, olfactory, and tactile hallucinations.

More recently, connectivity findings in COS and AOS were found to also be predictive of network topology in patients, with reduced strength of functional connectivity over short distances and preserved global functional connectivity indicating reduced clustering and modularity, as well as increased global efficiency of COS networks throughout the brain.[42] As stated previously, modularity of networks in COS patients has been shown to be significantly reduced due to a decrease of intramodule connections between neighboring regions.[40] AOS findings have found similar decreased clustering and local connectivity,[43] and, in both COS and AOS, decreased clustering has been found in a variety of regions implicated in schizophrenia.[40] Additionally, the very anatomical identity of the brain regions comprising these individual modules is believed to be different between COS patients and controls.[44] The sum lesson of these more recent findings appears to be the changing conceptualization of schizophrenia as a disease of individual brain regions to instead a disease of global dysmodularity and abnormal connectivity. These new hypotheses make intuitive sense as causes for both disorganization and hallucination as symptoms of schizophrenia; however, more concrete evidence linking the clinical manifestation of disorganization to abnormal network topology and community structure would provide more clear and solid footing for these hypotheses.

One of the cortical locations with the most strikingly different modular partition and local connectivity is the insula[40] (specifically, the right anterior insula), which is believed to contribute to processing of emotional information coming from visual or auditory modalities, as well as the ability to distinguish between the self and outside stimuli.[45] Insular cortex thinning has been showed to occur in AOS patients previously,[46] but only one study has examined insular cortex abnormalities in COS patients and found significantly decreased left, right, and bilateral insula volumes relative to controls.[47] An inability to engage in interoception in addition to mishandling of emotionally salient visual or auditory modalities might explain confusion in processing positive information and ultimately hallucinations of various modalities. More studies of varying methods are necessary for further insight into the role of the insula in COS.

Increased ventricular volume is one of the hallmark features of schizophrenia,[48] and COS is no different. Ventricular volume increases may represent a complement to the gray matter decreases that accompany them, with both showing a compounding trend of deficit. Neuroimaging studies have shown consistently larger ventricular size in COS patients, especially in the lateral ventricles.[49–51] There is evidence for increased[50,52] and unchanged fourth ventricle volume in COS patients, though there are limited data on adolescent onset schizophrenia, pointing towards larger fourth ventricle volumes at baseline without data over time.[53] Ventricular volume increases are typically related to the equally landmark feature of decreased gray matter in schizophrenia populations.[14] Progressive increases in ventricular volume and ventricle-brain ratio have been reported in conjunction with reductions in the midsagittal thalamic area[54]; however, there are lower power studies that failed to detect statistically significant differences between groups.[55] While increased ventricular volume is a hallmark of schizophrenia, it is difficult to relate to any specific biophysiological mechanism of disease pathology or specific type of symptoms.

Subcortical Structures

Subcortical structures of relevance in COS populations include those related to emotional processing, which are

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associated with inappropriate and flat emotional responses, and those related to motor processing, which many antipsychotic medications affect. One of the most studied subcortical structures in COS populations is the hippocampus, and for good reason. Findings of hippocampal abnormalities in AOS are among the most robust, and excitotoxic damage to the hippocampus is a key facet of multiple hypotheses of mechanisms of schizophrenia onset,[56,57] including that of the early fixed hippocampal deficit theory and the glutamate hypothesis.[58] Hippocampal abnormalities in the context of COS seem to be markers of initial deficits, as stress has a profound effect on hippocampal neuron development. Hippocampal deficits may be due to a combination of stress (trauma or hypoxia during birth)[59] and genetic influence,[60] and act, after damage has passed some critical threshold,[61–63] as a catalyst for other deficits that manifest as the classical symptom profile of COS patients. In AOS, hippocampal volume deficits are frequently reported,[56,64,65] as well as shape abnormality and asymmetry that resemble an exaggeration of control subject asymmetries.[66,67] In contrast, volumetric findings in COS patients are relatively inconsistent, with newer studies depicting bilateral deficits in hippocampal volume relative to control subjects[68,69] and older studies reporting left unilateral deficits and insignificant differences between patients and controls.[70,71] The most robust data on the developmental course of the hippocampus demonstrate fixed longitudinal volume decreases,[59] indicating that significant hippocampal volume decreases observed in COS[72] do not vary by time.

Recent literature suggests the presence of anterior hippocampal shape abnormalities in COS patients, containing primarily CA1 hippocampal neurons,[73] which are linked to the earlier mentioned excitotoxicity hypothesis in schizophrenia.[74] Deformities in this region are closely related to positive symptom severity and are correlated with antipsychotic dosage,[75] showing the significance of hippocampal changes to the disease course. Studies on related disorders (with adolescent onset) have found additional hippocampal abnormalities in those patients with obsessive-compulsive symptoms and antisocial violent behavior,[76,77] which highlights the relevance of hippocampal abnormalities to psychiatric disorders in general.

Closely following the hippocampus in significance in schizophrenia is the amygdala. The amygdala is globally recognized as vital to emotional processing as well as social communication.[78] In AOS subjects, both abnormal amygdala activation[79] and decreased volume[80] have been noted. Research into amygdala volume in COS patients has been inconsistent, and is largely undependable without a sufficient number of subjects and due to the previous limitations of imaging software.[81] Earlier studies bypassed this limitation by utilizing hand tracing methodology to determine amygdala volume, and found either no significant change in amygdala formation,[71,72] increased right amygdala volume,[32] or increased bilateral volume.[70] Speculation on the significance of these anatomical differences is hardly worthwhile without more consistent data and higher subject numbers, especially because of the lack of reproducibility of a single anatomist's tracing of the amygdala in order to calculate volume. Studies in the analysis of amygdala structure and function in COS are ongoing, as advancing imaging modalities allow clearer distinction between the hippocampus and the amygdala. Improvements in methodology and higher resolution imaging will hopefully enable more consistent findings in amygdala function and volume. Regardless, amygdala size and functionality are of great importance due to the centrality of the amygdala's role in emotional/social processing[78] and in fear processing,[82,83] which are both very heavily implicated in the clinical profile of COS.

The cerebellum has been thought to play a very large role in schizophrenia, with 2 classes of clinical symptoms at the forefront of these theories: neurological soft signs (NSS) and cognitive dysmetria (CD).[84] The former are sensory and motor anomalies in the absence of any obvious localized lesion, and in the case of schizophrenic patients, take the form of odd posture, dysfunction in various motor tasks, and sensory prediction. The functioning of the cerebellum has also been strongly linked to cognition in schizophrenia, indicating the likelihood of schizophrenia being a condition of impaired network connectivity and thus CD.[85] In AOS, reports of smaller cerebellar volumes have been reported in conjunction with reports of NSS.[86] The majority of COS literature echoes these findings, with the exception of one study on cerebellar volumes in both adolescent and childhood onset schizophrenia that found inconclusive results. This can be discounted by its nonhomogeneous and small sample size.[53] There is a divergent trajectory of cerebellar volume between COS patients and controls, with progressive loss noted in COS patients.[87,88] Vermis volume is noted as decreased in both AOS and COS,[87] and has been positively correlated with post-onset IQ and Global Assessment of Functioning Score (GAS) in AOS,[89] COS,[87] childhood tumor,[90] Joubert syndrome,[91] and fragile X.[92] Given that vermis volume is altered and correlated with IQ in a variety of developmental disorders, that the vermis is noted to reach maturity later comparatively to other parts of the brain, and that vermis volume is preserved in siblings of COS patients, there is strong evidence that vermis volume is a marker of the progression of the disease state and potentially reflects a compensatory mechanism.[87] Aside from vermis volume, both COS patients and their siblings differed with controls in total, right, and left inferior cerebellar growth trajectories, with patients

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and siblings showing a decrease over time.[87] This, coupled with a recent study that found, by utilizing volume-based morphometry, that siblings of COS patients had decreased cerebellar GM than controls in the cerebellum, point towards cerebellar morphology being an endophenotype of COS.[93] Cerebellar size was also correlated to performance on the Weather Prediction Task (WPT), and cerebellar size has been tied to cognition in the past.

The basal ganglia are a series of nuclei that are implicated in dopamine release, so their involvement in COS can be inferred based on the role of dopamine antagonists in COS treatment alone. Coordination deficits and involuntary dyskinetic movement abnormalities in children have also been correlated with later onset of schizophrenia.[94,95] Pallidum and putamen enlargement have been reported in both AOS[80] and COS studies,[54,55,96] and are linked with administration of first-generation antipsychotics in AOS patients.[54,55,96,97] Caudate, putamen, and globus pallidus increases in COS patients have been found to be markedly increased and correlated with neuroleptic exposure, as well as age of exposure,[55] though these increases were found to normalize over time.[54] With regard to the nucleus accumbens, Ballmaier *et al* found no significant difference between patients and controls in a study of 12 patients, but did find volume to be significantly related to specific thought disorder features.[98] The lack of medication-naïve studies on basal ganglia volume, formation, and functional activity make it difficult to deduce any direct effects of the disease state on this structure. However, one study utilizing primarily atypical antipsychotics, which are uncorrelated with basal ganglia volume, found bilateral enlargement of the caudate nucleus in early onset schizophrenia patients.[50] An earlier mentioned study discussing VBM also found reduced caudate regional volume in siblings of COS patients, suggesting a further endophenotype dysfunction of schizophrenia.[93] Generally speaking, it appears as though basal ganglia volumes observed to date are largely the result of antipsychotic influence on brain structures, highlighting the value of medication-naïve studies to help elucidate the primary effects of basal ganglia structures and functions in COS. Overall, the portrait of subcortical abnormalities in schizophrenia seems largely representative of underlying neural deficits that have cascading effects in cortical phenomena.

White Matter

The largest white matter tract in the brain is the corpus callosum, but insight in COS research is inconsistent in its findings. The most recent study on corpus callosum formation in COS features the largest sample size to date and provides evidence for a lack of abnormality in COS populations,[99] while other studies have found a significant decrease in developmental trajectory for the area of the splenium after adjustment for total cerebral volume.[100] Contrary to the most recent literature, an older study described larger total, anterior, and posterior corpus callosum areas; however, this study had a smaller sample size and adjusted for smaller brain volumes in patients with schizophrenia.[101] While these data are difficult to interpret, deletion of chromosome 22q11 (a mutation linked to greater incidence of COS) has been correlated to increased midbody corpus callosum area relative to both controls and COS patients.[102] Additionally, recent literature points toward altered structural integrity of the corpus callosum in AOS patients,[103] indicating the need for further studies in order to reach conclusive results.

Diffusion tensor imaging (DTI) data are limited in COS populations, but findings have been interesting and support theories about aberrant connectivity negatively affecting cognition and social processing in COS populations. Using DTI in conjunction with language testing in 18 COS patients, Clark *et al*[104] found data pointing toward the idea that COS patients have more disturbed structural connectivity, and as such, severe linguistic impairments. Functional connectivity research on COS patients accompanies these studies of linguistic processing: Different patterns of functional specialization for semantic and syntactic processing of language have been identified in COS patients relative to controls.[105] In addition, neuroleptic dosage has been negatively correlated with functional activity in the left frontal gyrus during a semantic judgment task.[105] These linguistic impairments show a connecting point of dysfunction in both cognitive and social processing, though they are likely not the only such bridges. These linguistic problems represent another barrier between COS populations and typical development, and by extension, quality of life and ability to live independently.

As previously mentioned, issues with connectivity in the cortex seem just as important as volume and shape abnormalities in COS patients. A recent study of white matter abnormalities in 39 COS patients and 39 of their siblings using DTI found significant evidence of impaired white matter connectivity in COS patients and their healthy siblings relative to controls, especially in the left and right cuneus.[106] This offers evidence of significant white matter impairment in both COS patients and their healthy siblings. However, in the case of global white matter development, early white matter growth deficits in non-psychotic siblings of COS patients normalized over time,[18] showing the complex interaction of state and trait markers with age and at least one part of the disease state that is possibly compensated for over time in siblings of patients. Altered white matter connectivity of this kind would likely have an additive effect on executive functioning with cortical abnormalities discussed previously.

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In sum, the white matter findings at present depict decelerated white matter growth and disrupted white matter connectivity.

Summary

While less abundant than in other fields, neuroimaging data in COS have enabled some key observations in relation to the disorder, including progressive cortical thinning, fixed longitudinal hippocampal volume loss, aberrant basal ganglia development, ventricular enlargement, disrupted white matter connectivity, and slowed white matter growth. COS patients must deal with multiple challenges rooted in cognitive deficits that make quality of life poorer by limiting appropriate professional roles relative to their capabilities. They must also face the compounding and possibly more stifling social processing limitations linked to aberrant linguistic processing, temporal abnormalities, and inability to perform adequate reality testing with regards to internal stimuli.

Among the most striking findings is the correlation between cortical thinning and executive/cognitive deficits in patients. These contribute largely to the burden of disease in schizophrenia, as they are the most likely to prevent patients from functioning independently. Subcortical deficits generally encompass limbic abnormalities, which seem to play some role in altered social interaction and other emotional deficits in COS populations, and those seemingly more related to motor deficits. The latter of these are further confounded by the effect of antipsychotic medications on motor circuits, particularly those in the basal ganglia. White matter volumetric deficits in COS patients depict abnormal global connectivity that would have a compound effect with cortical deficits on normative functioning.

Future directions for COS neuroimaging research are inherently constrained by small sample size; however, it is clear that both functional neuroimaging and DTI would be a good direction for future research to go. At present, there is very little in the way of functional neuroimaging in COS patients who are participating in various task-based paradigms. A body of functional connectivity research exists with regard to a resting state paradigm and has provided a different conceptual framework with which to model COS. Task-based functional neuroimaging data will allow researchers to further test current frameworks related to module construction and connectivity in COS, and enable perhaps deeper insight as to the mechanism behind noted deficits in patients and if such deficits are state or trait markers. Volume/voxel-based morphometry research is also in its infancy with regard to COS and is promising as a methodology to observe global brain anatomical and functional abnormalities in patients.

The overarching portrait of COS from a neuroimaging perspective is generally one of progressive decline in cortical and many subcortical structures. However its clinical correlates and salience remain difficult to pinpoint. Additional neuroimaging research coupled with genetic data are important in order to help provide clinicians greater insight into disease mechanisms and etiology, and will hopefully ultimately lead to the development of more accurate tools for both diagnosis and preventative care of COS in the future.

Disclosures

The authors do not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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