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Childhood onset schizophrenia: support for a progressive neurodevelopmental disorder

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Abstract

Structural brain abnormalities have become an established feature of schizophrenia and increasing evidence points towards the progressive nature of these abnormalities. The brain abnormalities are most profound in early onset cases, which have a severe, treatment refractory phenotype and more salient genetic features. Unique insights could thus be gained in schizophrenia pathology from studying the earliest manifestations of the illness. This paper reviews and updates the findings on anatomic brain development in patients with very early onset schizophrenia while showing preliminary data from ongoing studies. Collectively, our studies demonstrate that childhood-onset schizophrenia (COS) subjects show progressive loss of gray matter, delayed/disrupted white matter (WM) growth, and a progressive decline in cerebellar volume, some of which are shared by their healthy siblings. The developmental patterns or the ‘trajectories’ of brain development are often more striking than anatomic brain differences at any one point in time; highlighting the importance of longitudinal studies. The sibling findings of partially shared gray matter (GM) deficits which appear to normalize with age, along with other genetic analyses, provide evidence that the brain developmental ‘patterns/trajectories’ for several regions at particular ages could be useful endophenotypes (trait markers).

Keywords

Anatomic; MRI; Brain; Childhood-onset; Schizophrenia; Imaging; Progressive

1. Introduction

Early onset patients with schizophrenia have been noted since the first descriptions of the disorder (Nicolson and Rapoport, 1999). In general early onset disorders are more severe, may be more homogeneous, less influenced by environmental and secondary effects of illness or its treatment, and may have more salient genetic causes (Childs and Sriver, 1986).

Since 1990, children and adolescents with very early onset of schizophrenia (defined as onset of psychosis before their 13th birthday) have been recruited from North America at the National Institute of Mental Health (NIMH) for prospective longitudinal brain imaging,

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Conflicts of interest

Both authors have no conflicts of interest to declare.

genetic, and treatment studies. These very early onset cases are rare and clinically resemble chronic, severe, and treatment refractory adult onset schizophrenia (AOS) cases. Prospective normative studies of healthy children across ages 4–25 (Giedd et al., 1999) and healthy monozygotic and dizygotic twins have provided comparison groups to gain insights into brain developmental trajectories and the genetic control of (Lenroot and Giedd, 2008). To date 112 COS patients and their first-degree relatives have been studied prospectively. Clinical follow-up into adult years, brain imaging, neuropsychological and physiological testing have established the continuity of COS with the adult onset disorder (Rapoport et al., 2005). Of greatest interest however, are aspects of pediatric cases that are more strikingly abnormal than those for older patients. The areas that have emerged in particular are: more marked pre-psychotic neurodevelopmental problems, abnormal developmental trajectories during adolescence and more striking abnormalities in anatomic brain measures (such as cortical thickness) (Gogtay and Rapoport, 2007; Rapoport and Gogtay, 2008), and a high rate of cytogenetic abnormalities (Rapoport et al., 2005) and rare copy number variants (Walsh et al., 2008).

Here we review and update the findings on anatomic brain development in patients with very early onset schizophrenia and their healthy full siblings while showing preliminary data from ongoing studies. Collectively our studies demonstrate that the developmental patterns or the ‘trajectories’ of brain development are often more striking than anatomic brain differences at any one point in time, thus highlighting the importance of longitudinal studies. There are widespread abnormalities in the development of the cerebral cortex, white matter, hippocampus, and cerebellum. We have extended these studies to the longitudinal brain development in healthy full siblings, which along with other genetic analyses provide evidence that the brain developmental ‘patterns/trajectories’ for several regions at particular ages could be useful endophenotypes for genetic research.

2. NIMH COS cohort and imaging

2.1. COS subjects and their healthy siblings

Since 1990, prescreening of over 3000 case records, over 400 in-person screenings, and over 200 inpatient drug free observations, has yielded 115 patients meeting unmodified DSM-IIIIR/IV criteria for schizophrenia with the onset of psychosis before age 13 at an average rate of 6–7 new cases per year. Patients with significant medical problems, substance abuse, or an IQ below 70 prior to the onset of psychotic symptoms were excluded. Further details of patient selection are described elsewhere (McKenna et al., 1994; Kumra, 2000). All full siblings of COS subjects also participated and were scanned prospectively every two years along with COS probands and underwent structured psychiatric interviews.

2.2. Control subjects

Healthy controls are part of a larger sample of volunteers recruited from the community as part of a prospective study of normal brain development (Giedd et al., 1999). Controls are free of lifetime medical or psychiatric disorders as determined by clinical examination and standardized interview. Psychiatric illness in a first-degree relative was also exclusionary.

2.3. MRI acquisition and image analysis

All analyses over the past 20 years have been done on images acquired on 1.5 T scanner.

Briefly, T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained with 3D spoiled gradient recalled echo in the steady state on a 1.5-T General Electric Signa scanner (Milwaukee, WI). Imaging parameters were echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256×192 , number of excitations equals 1, and 24 cm field of view. Head placement was standardized as previously described (Castellanos et al., 2001). The MRI analyses are done in collaboration with two centers; the Montreal Neurological Institute (MNI) for automated processing and with Paul Thompson at University of California Los Angeles (UCLA) neuroimaging laboratory for surface pattern matching and tensor based morphometry analyses. The details of each methodology are published elsewhere (Thompson et al., 2001a,b; Lerch and Evans, 2005).

2.4. Cortical development in COS

Morphometric studies of COS populations have provided unique insights into schizophrenia brain development. Initial COS studies using whole lobe volumetric measures showed profound and global GM loss with ventricular expansion in COS (Rapoport et al., 1997, 1999; Rapoport and Inoff-Germain, 2000; Gogtay, 2008). With novel neuroimaging methodology, finer-scale brain mapping on the longitudinal data revealed that the GM loss in COS had a characteristic back-to-front (parieto-frontal-temporal) pattern of spread during adolescent years (Thompson et al., 2001a,2001b) which appears to be an exaggeration of the healthy GM developmental pattern (Gogtay et al., 2004a,b); perhaps reflecting lack of inhibitory controls on the normal maturational GM loss (Schoop et al., 1997; Sowell et al., 2001).

Whether the GM loss is progressive throughout the course of the illness or whether it is a phenomenon that is most strikingly seen only until late adolescence is an important question. Adult-onset studies using voxel based morphometry (VBM) or cortical thickness mapping methods show predominantly cortical GM loss in prefrontal and superior temporal cortices (Kuperberg et al., 2003; White et al., 2003; Wiegand et al., 2004; Narr et al., 2005). While a majority of the adult studies have used cross-sectional data, recent prospective studies show evidence for progressive GM loss. A recent analysis of first-episode adult-onset patients scanned 4 times over a year exhibited a back-to-front wave of cortical gray matter loss, with greatest losses in the 3 months after psychosis onset, but proceeding into the frontal cortices a year later; replicating the pattern first reported in COS (Thompson et al., 2008). More significantly, a recent meta analysis of 14 longitudinal studies also supported progressive GM loss (Dr. Stephen Lawrie, U.K., personal communication). Consistent with the adult studies, the profound GM loss in COS during adolescence became less marked and more circumscribed to the prefrontal and superior temporal cortices after age 20 (Greenstein et al., 2006). A replication study with non-overlapping COS subject scans since the 2006 paper, showed a similar pattern (Fig. 1C; Dr. Greenstein, unpublished data). Interestingly, the dorsal parietal regions, which normalized by age 24, are also the regions which show

minimal deficits in healthy siblings (discussed later), suggesting that the parietal GM deficits in COS could be disease (state) related rather than a trait marker (see Fig. 1C).

Thus the GM deficits in schizophrenia may reflect a disease process that is pronounced earlier in the illness and/or at an earlier age, perhaps reflecting a stronger genetic vulnerability interacting with the early brain developmental windows (Pantelis et al., 2003) and exaggerated (dysregulated) neurodevelopment (Woods, 1998; Lieberman, 1999; Lieberman et al., 2005). It is also possible that the structural GM differences are most dynamic in the first years around psychosis onset and then vary with the illness over time perhaps influenced by other environmental, or illness related factors such as medication exposure. Indeed a similar pattern of brain changes has also been tracked as psychosis develops in those at risk (Pantelis et al., 2007) (Fig. 2).

2.5. Diagnostic specificity of GM findings in COS and medication effects

The diagnostic specificity of the GM trajectories was explored by comparing individuals with COS and children who were 'ruled out' as having schizophrenia. These children had similar initial presentation and medication exposure but received other psychiatric diagnoses after thorough inpatient evaluation (Kumra et al., 1998). A group of 32 children had atypical psychosis with striking affective lability and comorbid ADHD that were provisionally labeled by our group as multi-dimensionally impaired (MDI). These were followed longitudinally and at 2–10-year follow-up none converted to schizophrenia, but a surprising 40% converted to Bipolar I disorder and had pre–post-onset scans.

The developmental trajectories for Bipolar I children (with psychosis) showed a subtle but distinct pattern of cortical GM gain in left temporal cortex and loss in right temporal and bilateral subgenual cingulate cortices; pattern that has no overlap with that seen for COS (Gogtay et al., 2007a, 2007b). These observations point towards diagnostic specificity of the GM findings in COS (Gogtay et al., 2004a, b, 2007a, 2007b). It is difficult to study the effects of medications on GM development in COS. This is partly because it is practically not possible to obtain medication naïve COS patients, and majority of the COS cases are already heavily medication exposed prior to coming to the NIMH due to the severity of the phenotype. However, the lack of overlap in GM deficit pattern between COS and 'rule out' subjects (both MDI as well as bipolar subjects that had similar medication exposure at initial time point) suggests that GM changes are less likely due to medication effects, at least at first scan. These studies still do not address the effects of medications on 'longitudinal' GM trajectories. A recent analyses comparing GM development between COS subjects treated with clozapine and those with olanzapine showed no differences in GM trajectories (Mattai et al.). Further studies are needed correlating medication exposure as a continuous measure with brain development, or on unmedicated subjects to address this question.

2.6. Trajectories as endophenotypes? Genotype imaging interactions in schizophrenia

Schizophrenia is a heritable disorder and GM abnormalities in schizophrenia may be, at least in part, familial/trait markers (Weinberger and McClure, 2002; Cannon et al., 2003; Gilbert et al., 2003; Yucel et al., 2003). We have extended this question in our studies to ask whether GM 'trajectories', rather than deficits are endophenotypes, indicting dysregulation of

development as the crucial defect (e.g. see Crespi et al., 2010). We have been examining brain development for healthy COS full siblings.

Longitudinal GM findings in 52 healthy full siblings of COS patients showed initial cortical GM deficits which, not only did not progress during adolescence (unlike their COS probands) but normalized by age 20. The early GM loss in siblings was most prominent in prefrontal and temporal cortices (see Fig. 3) as has been seen for COS probands, but unlike the pattern seen in probands, healthy siblings showed minimal parietal GM loss only at much younger ages. A recent analysis using 47 non-overlapping healthy siblings matched with 48 non-overlapping healthy controls, replicated these findings (Dr. Mattai, unpublished data). Several inferences can be drawn from these findings. First, the pattern of ‘improving GM deficits’ and the localization to ‘pre-frontal and superior temporal areas’ in both COS probands and siblings point towards overall similarities in the patterns of GM development in both groups where healthy siblings show a more time limited ‘shift to the left’ compared to the COS probands (earlier deficits which are corrected before adulthood). Second, this points to protective/restitutive factors in sibling brain development, which could relate to functional outcome (Gogtay et al., 2007a, 2007b). Finally, absence of parietal deficits in healthy siblings may indicate that parietal deficits require a non-genetic trigger as supported by twin studies of adult onset cases (Cannon et al., 2002) (Fig. 4).

These studies suggest a two-hit (diathesis-stress) model, in which posterior parietal brain regions appear vulnerable to environmental triggers, and after psychosis onset, the trajectory of deficits proceeds to frontal regions where a genetic liability for deficits has been found leading to deficits in executive function and working memory (Cannon et al., 2002).

Other evidence for GM trajectories as intermediate phenotypes comes from the studies of individual susceptibility gene alleles and GM development in COS. Candidate genes for schizophrenia are increasingly being related to disturbed pre and postnatal brain maturation (Jaaro-Peled et al., 2009), and there is growing knowledge about the complex transcriptional and molecular underpinning of human brain development (Johnson et al., 2009). Genetic studies of COS patients have to date shown some relationships between anatomic brain trajectories and candidate genes for schizophrenia (Addington et al., 2004, 2007).

2.7. White matter changes in COS

The profound GM loss in COS could in theory be only a perceived loss resulting from the encroachment of continued white matter growth, a process that extends through at least the 4th decade (Benes, 1993; Benes et al., 1994; Sowell et al., 1999). New findings using tensor-based morphometry (TBM) showed that COS patients actually had up to 2% slower WM growth rates per year than healthy controls ($p = 0.02$, all p -values corrected), with greater effect sizes in the right hemisphere ($p = 0.006$) (Gogtay et al., 2008); thus progressive GM deficits seen in COS do not appear secondary to WM growth (Gogtay et al., 2008).

2.8. Deeper cortical structures and cerebellum in COS

Deeper cortical structures and cerebellum remain relatively less explored in schizophrenia, probably due to methodological inconsistencies, and mostly cross-sectional data resulting in inconsistent findings. However, some consistencies have emerged over the years such as loss

of volume in hippocampus and other medial lobe structures (Shenton et al., 2001; Pantelis et al., 2005). As studies begin to explore cortical circuitries (e.g. fronto-striatal, fronto-thalamic, etc.) relevant to schizophrenia, it becomes important to study the development of deeper cortical structures, which may then allow further correlational analyses of structures involved in specific neurocircuitries.

We have recently used automated free surfer methodology on a large datasets consisting of 89 COS probands (198 scans), 78 healthy siblings (172 scans) and 79 matched controls (198 scans) to see the longitudinal hippocampal development. Here, the COS subjects show a significant but *fixed* hippocampal volume deficit. In contrast, the healthy siblings did not differ from controls. The fixed hippocampus deficit in COS thus appears to be a *state* (not a *trait*) marker (Mattai et al., in press).

Cerebellar abnormalities have also been reported in AOS but again the results have been inconsistent (Weinberger et al., 1980; Reyes and Gordon, 1981; Lohr and Jeste, 1986; Supprian et al., 2000). Studies have reported reduced (Volz et al., 2000; Ichimiya et al., 2001; Loeber et al., 2001) (Rossi et al., 1993; Nopoulos et al., 1999), increased (Levitt et al., 1999) as well as unchanged (Andreasen et al., 1994; Flaum et al., 1995; Keshavan et al., 1998) (Mathew and Partain, 1985; Uematsu and Kaiya, 1989; Aylward et al., 1994) cerebellar hemispheric and vermal volumes. There have been only two longitudinal studies so far; DeLisi et al. (1997) reported right cerebellar volume reduction in patients with AOS and our previous study on 50 COS patients reported progressive loss of total cerebellar volume ($n = 50$) (Keller et al., 2003).

We have recently revisited the cerebellar development in COS with a newer method to measure cerebellar lobes and vermis (Pierson et al., 2002). In this study with 94 COS subjects (208 scans), 86 healthy siblings (171 scans) and 110 matched healthy controls (270 scans), both COS and healthy siblings show a progressively declining total cerebellar volume trajectory compared to healthy controls. However, when the data are examined cross-sectionally at adult ages (20 and higher), the volume differences are significant only at trend level, suggesting a weaker overall effect especially in later (adult) ages. However, the overlapping ‘trajectories’ of total and some sub regional cerebellar measurements between COS probands and siblings, may suggest endophenotypic nature of some of the sub regional cerebellar development which needs to be explored further (Greenstein et al., submitted).

2.9. Genetic studies

While rare copy number variants (CNVs) have been found to be increased for our COS population (Walsh et al., 2008), only two variants (16p11.2 and 22q11) have shown a unique anatomic brain profile (Usiskin et al., 1999; McCarthy et al., 2009). Recently, genome wide expression analyses of brain tissue from varied post-natal ages indicated that schizophrenia susceptibility genes are over represented during frontal cortical development (Webster et al., in press, 2010; Choi et al., 2009; Harris et al., 2009; Wong et al., 2009). However, given the large number of weak genetic and environmental risk factors and increasing evidence for the dimensional nature of psychosis (Polanczyk et al., 2010), it seems more and more likely that schizophrenia represents a continuum of risk involving many factors. For example a recent population study found a 9-fold risk of schizophrenia if the presence of a parent with

psychosis was combined with maternal depression during pregnancy (Maki et al., 2010). Other studies have documented other gene-environmental interactions such as that between genetic risk and urban birth (van Os et al., 2004).

2.10. Dysconnectivity in COS

The findings of WM growth abnormalities also support the recent notion that schizophrenia could be a disorder of dysconnectivity; either structural or functional (Stephan et al., 2006; Cheung et al., 2008). In particular abnormalities in functional connectivity are postulated to be important pathophysiologic mechanism underlying schizophrenia (Lim et al., 1999; Lawrie et al., 2002; Konrad and Winterer, 2007). Impaired hippocampal-prefrontal synchrony was recently documented in a genetic mouse model (22q11 deletion) for schizophrenia (Sigurdsson et al., 2010) and similar evidence is merging for cerebello-frontal (Kanaan et al., 2009), or fronto-temporal (Allen et al., in press; Crossley et al., 2009) dysconnectivity.

Novel methodologies now make it possible to test the dysconnectivity models in schizophrenia. Structural dysconnectivity can be studied with diffusion tensor imaging (DTI) or tensor based morphometry (TBM). Functional connectivity can be explored using either task based functional imaging, default (resting state) network functional analyses, or with correlational analyses such as studying the small world network properties. Several recent studies using these methodologies provide evidence for a disturbed functional organization in various neurocircuitries in schizophrenia and correlation with psychotic symptoms (Garrity et al., 2007; Harrison et al., 2007; Zhou et al., 2007; Calhoun et al., 2009; Whitfield-Gabrieli et al., 2009). fMRI studies are difficult to carry out in most of our COS subjects due to the severity of their illness, which makes it hard for them to participate in any tasks. However, default network studies, which do not require task participation from probands, and studies in healthy siblings are still possible to explore the connectivity in COS. Preliminary analyses using graph theory for the whole-brain resting state fMRI networks shows the breakdown of functional communities in COS. Networks in COS subjects ($n = 19$) are less modular, less small world, and more random compared to matched healthy controls ($n = 13$) (Alexander-Bloch et al., in press).

3. Summary

The unique prospective study of what is now over 100 childhood onset schizophrenia probands and their healthy full siblings, has revealed a variety of developmental abnormalities. The probands show progressive loss of gray matter, delayed/disrupted WM growth, and a progressive decline in cerebellar volume, all of which have some parallels in the siblings. In siblings, however, normalization of early regional cortical GM abnormalities suggests the role of restitutive/protective factors. In contrast the static hippocampal volume loss across the age span in COS is not shared by their healthy siblings and thus appears to be state specific.

As is always true for anatomic imaging studies we can only speculate about these changes and our data probably raise more (provocative) questions for future research than they answer. In addition, our focus has been largely on anatomic development as the only

consistent measure across a more than 20-year age span. Further all our studies to-date have been done on the 1.5 T magnet, which has imposed limitations on the scan resolution and inability to perform more state of the art methodologies such as high resolution DTI, the scanner and imaging parameter, but the consistency of scanning parameters over 20 years has been uniquely advantageous.

It is widely accepted that schizophrenia is a neurodevelopmental disorder but we have a wealth of non-exclusive neurodevelopmental models. Since anatomic MRI gives no hint of the underlying cellular basis for these changes, there remains a great need to correlate imaging findings with *in vivo* brain changes and a primate study might address this. Our data imply abnormalities in timing of development (e.g. evidence for *shift to the left* for cortical thinning during adolescence, or age dependent *normalization* of sibling cortical deficits, etc.), which may be influenced by genetic or environmental (e.g. medications) factors that remain yet to be identified. The widespread nature of the anatomic deficits, throughout the cortex, white matter, deeper nuclei and cerebellum points to a diffuse interconnected abnormality in the development of many cortical circuits, which need to be analyzed. Analyses including resting state fMRI and small world network properties are ongoing in our program.

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A. Parietal-Frontal Progression of GM Loss During Adolescence

B. The GM loss Declines and is Circumscribed to Prefrontal and Temporal Cortices By Age 24

C. Regions where GM loss *normalizes* in COS by Age 24 (converging trajectories between COS and NV) **Fig. 1.**

Pattern of progression of cortical GM loss in COS. The top panel (A) shows the pattern of cortical GM loss in COS during ages 12–16. The sequence depicts p-maps across age, across entire brain surface comparing GM density at each cortical point between 12 COS children and 12 matched healthy controls repeatedly scanned between ages 12 through 16. Most significant GM loss (pink color) is visualized as a dynamic wave in the parieto-frontal direction across adolescence. The middle panel (B) shows this pattern extended up to age 24 (only shown on the right side) where the GM loss appears to decline with age and gets circumscribed to prefrontal and temporal cortices. The lower panel (C) shows areas where cortical GM loss ‘normalizes’ with age in COS; parietal and prefrontal areas showing normalization across the age range. These findings were replicated recently by using a non-overlapping sample of COS subjects and matched controls (Dr. Greenstein, unpublished data). (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)

Fig. 2.

Diagnostic specificity of GM changes in COS. Panel A shows the parieto-frontal pattern of cortical GM loss in COS as shown in Fig. 1 earlier. Panel B shows subtle GM changes in pediatric onset psychotic bipolar I children compared with matched healthy controls. The maps are ratio maps color-coded to depict whether bipolar children have growth (yellow to orange), loss (blue to aqua) or same (green) amount of cortical GM compared to their matched controls. The patterns between COS and bipolar are non-overlapping with psychotic bipolar I subjects showing gain in temporal cortices post-onset. Panel C shows percent change in GM volume over 2-year period in matched groups of patients with atypical psychosis (MDI; blue), COS (red), and healthy control (yellow). The MDI and NV groups show no significant change over two-year period while COS shows significant GM loss. These findings, in addition to supporting the diagnostic specificity, also suggest that the GM changes in COS are unlikely to be due to medications at least at the initial scan. (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)

Fig. 3.

Cortical GM deficits in healthy full siblings of COS. Panel A shows progression of cortical GM deficits in healthy siblings of COS patients across age. The results, published in 2007, showed early prefrontal and temporal deficits in healthy sibling compared to controls, which normalized by the time the siblings were 18 years old.

Fig. 4.

White Matter growth abnormalities in COS. Comparison of 12 COS subjects with matched controls, scanned repeatedly across ages 12 through 16 showed that the WM growth was delayed for COS compared to healthy controls. Panel (A) shows absolute difference in growth rates between COS and healthy controls, while panel (B) shows significance maps for the growth difference in panel (A).