The Neurodevelopmental Theory of Schizophrenia: Evidence from Studies of Early Onset Cases

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ABSTRACT

The neurodevelopmental theory of schizophrenia has been of great importance focusing most etiologic research over the past two decades. We review research on the neurodevelopmental aspects of Early Onset Schizophrenia, a rare and severe form of schizophrenia in which onset occurs during childhood or adolescence. Developmental, cognitive, genetic and brain imaging findings are outlined and discussed in relation to the neurodevelopmental theory. The main limitations of the theory are presented, and future conceptualizations are formulated.

INTRODUCTION

Schizophrenia is a clinical syndrome with peak onset in late adolescence or early adulthood, whose symptoms are manifest in multiple domains of behavior. Although delusions and hallucinations are the hallmark of psychosis patients also present with impairments in social communication, as well as motor, volitional and emotional abnormalities. While some patients only experience one acute psychotic episode, for a majority the condition is considered lifelong, with episodes of illness followed by periods of remission (1).

A neurodevelopmental etiologic theory of schizophrenia has been influential during the past decades. According to this theory there is deviance in early brain development whose full adverse consequences emerge only in adolescence or early adulthood (2-4). Considerable research has focused on the brain changes and behavioral abnormalities that precede onset of illness as indicators of abnormal development in an effort to identify possible risk markers and biological mechanisms underlying psychosis.

EARLY ONSET SCHIZOPHRENIA

Early Onset Schizophrenia (EOS) is a rare and severe form of schizophrenia in which onset occurs during childhood (COS) or adolescence (AdOS) up to the age of 17 years. Only around 4% of schizophrenia patients will experience an early onset (5). Longitudinal studies have shown diagnostic stability to be high in EOS at around 80-90% (6, 7). Studies investigating prognosis in this group used a range of variables to assess outcome; typical indicators include presence of symptoms, length of remission, number and duration of hospitalizations, educational and occupational impairment and social disability. Evidence from studies that followed up EOS patients over 40 years confirm that outcome on such measures is consistently worse for EOS compared to adult-onset schizophrenia (AOS) (7-9), with some evidence that COS, with an onset before age 12, is associated with the worst clinical and psychosocial outcomes (10). EOS is clinically and neurobiologically continuous with AOS, but is associated with greater neurodevelopmental deviance early in life (11, 12). EOS could therefore provide an opportunity to learn more about the neurodevelopmental aspects of schizophrenia.

This paper presents a selective overview of research on the neurodevelopmental aspects of EOS: namely, premorbid development, cognitive function, genetics and neurobiology. Particular attention is given to research on developmental delay and impairment in the areas of motor, social and language function.

METHODOLOGICAL CONSIDERATIONS

Table 1 presents a summary of studies of early development in EOS. Because EOS is rare, true prospective data

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collection is practically impossible. Therefore, as can be seen in the table, assessments of premorbid functioning are generally made retrospectively using self- and/ or parental recall, or school and medical records review. Popular instruments for assessing premorbid function are the Premorbid Adjustment Scale (PAS) (13), and Child Behavior Checklist (CBCL) (14). Although these instruments have been shown to be reliable and valid in measuring premorbid functioning (15), studies should be viewed and interpreted in light of this limitation.

COGNITIVE DEVELOPMENT IN EOS

Motor Impairments: Delayed motor milestones, poor coordination and repetitive movements are widely reported in EOS and appear to be more frequent the earlier the age of onset. Watkins et al. (16) reported that 64% of their COS sample had motor delays and difficulties, including delayed milestones and poor coordination. Alaghband-Rad et al. (17) found that 35% of their COS sample were delayed in walking. This figure is comparable to the finding of Hollis (18), who used subjects from the Maudsley Case Register in his study, and reported that 33% of the COS group also showed this delay, with 31% of the whole EOS sample exhibiting stereotyped movements and coordination problems premorbidly. Nicolson et al. (19) reported that 57% of cohort of COS recruited by the National Institute of Mental Health (NIMH), showed delayed motor milestones as well as abnormal repetitive movements. Schothorst et al. (20) found that 35% of a group consisting of AdOS cases and adolescent onset affective psychosis cases showed delayed motor development and poor coordination. Vourdas et al. (11) tested EOS subjects recruited for the Maudlsey Early Onset Schizophrenia Study and reported much lower rates of motor delay, specifically delayed walking, in an EOS group, at only 3%. However, they suggest that this discrepancy may have occurred because their sample consisted mainly of AdOS cases and only included a single measure of motor development.

Speech and Language Impairment: Delayed speech production and childhood problems with receptive and expressive language appear to be common in schizophrenia and have been found in major cohort studies of AOS (21-23). Watkins et al. (16) found that 55% of COS cases had deficits in speech development or no speech prior to 30 months. Similarly, Alaghband-Rad et al. (17) reported that 43% of their COS sample showed delayed sentence production. Hollis (18) found that his COS group was more likely to have premorbid speech and language impairment than an AdOS group, and this difference was accounted for by impairments in language production and perception, which were apparent only in the COS group. Nicolson et al. (19) found that 55% of their COS sample had premorbid speech and language impairment, including problems with receptive and expressive language as well as delayed speech milestones. In addition, COS patients with speech and language problems had greater familial loading for Schizophrenia Spectrum Disorders (SSD). Vourdas et al. (11) found that 19.4% of their EOS group showed language impairments consisting of delayed speech and difficulties with reading and spelling.

Social Functioning: Abnormal social behavior including isolation and social withdrawal are often reported in pre-schizophrenic children and adolescents. Kolvin et al. (24) reported that 87% of parents of EOS children reported "odd or unusual" behavior in their children prior to illness, mainly shyness or introversion. Watkins et al. (16) found that 82% of their COS sample were socially impaired in early childhood. Hollis (18) found that 30% of his Maudsley Case Register AdOS sample and 50% of his COS sample showed social impairments premorbidly compared to non-psychotic psychiatric controls. Two studies that did not use the PAS but assessed similar items related to social adaptation found comparable results. Nicolson et al. (19) reported that 55% of their COS sample had deviant social development including abnormal peer relationships, isolation and social disinhibition. Finally, the degree of impairment in social interaction is moderated by gender and age of onset. Vourdas et al. (11) found that their EOS and AOS groups were similar premorbidly in terms of social adjustment measured by the PAS; however, EOS males showed more deviant social behavior in adolescence than AOS males. In addition, early developmental abnormalities including motor, speech and language deficits were associated with more problems in premorbid social functioning during adolescence.

Premorbid social deficits may be greater for patients with EOS compared to early onset cases of other mental disorders. Asarnow and Ben-Meir (25) found that a COS sample had worse PAS scores than a group with childhood onset depression, particularly for items relating to social behavior and adaptation. Similarly, Werry et al. (26) found that 54% of EOS cases in their study had

Table 1. *Studies on Early Development in Early-Onset Schizophrenia*

Author	Sample	Method	Results	Comment
Alaghband-Rad et al. (1995)	COS cases with onset up to 12 years (N=12).	Psychological, school and medical records of premorbid history.	43% showed delayed sentence production, not related to IQ. 35% had delayed motor milestones.	36% of sample showed evidence of PDD and all were part of a trial for nonresponders to neuroleptics, so this group represented more severe cases.
Asarnow & Ben-Meir (1988)	Children aged 7 to 13 years with COS or childhood onset depression (N= 66).	School, hospital and family records of premorbid history and Premorbid Adjustment Scale (PAS).	COS group had worse PAS scores, particularly for items related to social behavior and adaptation.	
Hollis (1995)	COS group (N=18, onset 7 to 13 years); AdOS group (N=43, onset 14 to 17 years); non-psychotic psychiatric controls (N=61).	Checklist of premorbid function administered at time of admission.	COS group more likely to have premorbid speech and language impairment than AdOS group. 33% of AdOS group and 28% of COS group showed impaired motor development, and 30% of the AdOS group and 50% of COS group showed social impairments compared to controls.	Difference between AdOS and COS in language was accounted for by language production and perception disorders, which were not apparent in the AdOS group.
Kolvin et al. (1971)	Patients with infantile psychosis (< 3 years at diagnosis; N=41) and later onset psychosis (aged 5 to 15 years at onset; N=33).	Parental report	87% of parents of later onset cases reported odd or unusual behavior in their children before illness. This was mainly shyness and introversion. 46% of this group had not produced three word phrases by age 3 years. 17% of this group exhibited motor abnormalities.	An early study that aimed to differentiate infantile psychosis from late onset childhood psychosis. Motor abnormalities consisted of repetitive movements of the whole body, particularly hands and fingers.
McClellan et al. (2003)	EOS group (N=27); BD group (N=22); psychosis NOS group (N=20).	Compared premorbid histories using PAS based on information obtained at admission into study combined with medical records and parental interviews.	Only 13% of EOS and NOS group considered "normal" before onset of illness. EOS cases more globally impaired and socially withdrawn than those with BD. Sociability scale of the PAS was only significant predictor between BD and EOS, with greater introversion predictive of schizophrenia.	
Muratori et al. (2005)	EOS group, healthy control group and psychiatric control group (anorexics) N=23 for each group.	Maternal report using the Child Behavior Checklist. Focus on social and behavioral problems up to 11 years of age.	At age 2-3 years, significant difference on all scales compared to healthy controls but not anorexic controls. At age 4-11 years higher mean scores on all scales compared to healthy controls and higher scores than anorexic group on social, thought and attentions problems and school competencies. Social problems relate to shyness, underactivity and hypersensitivity.	Chose anorexics as a control group because this disease is considered developmental in origin.
Nicolson et al. (2000)	COS patients N=49	Examined case histories and used parental recall for missing information.	55% had speech and language impairment premorbidly, including problems with receptive and expressive language and delayed milestones. 57% had motor impairment premorbidly consisting of delayed milestones, abnormal repetitive movement, poor coordination. 55% had deviant social development including abnormal peer relationships, isolation and social disinhibition.	More boys than girls had premorbid motor problems. Patients with speech and language problems had greater familial loading for SSD.
Schothorst et al. (2006)	EOS group (onset aged 12-18, N=36); Affective psychosis group (N=40) including BD, depression with psychotic symptoms and schizoaffective disorder.	Reviewed medical records.	No difference between subgroups in premorbid function. 35% of all patients showed problems in motor development, particularly coordination, 67% showed social problems, particularly isolation and withdrawal	

Table 1. *Studies on Early Development in Early-Onset Schizophrenia*

Author	Sample	Method	Results	Comment
Vourdas et al. (2003)	EOS group (onset before 18th birthday, N=40); AOS group (N=54); Healthy control group (N=40).	Maternal interviews and PAS	EOS and AOS groups the same for premorbid social adjustment. EOS males showed more deviant social behavior in adolescence than AOS males. EOS cases had delayed milestones compared to control groups, in speech development, with more reading and spelling difficulties. 19.4% of EOS group showed language impairments. 3% of sample was delayed in walking. In 20% of EOS cases, delay in some area was sufficiently pronounced to warrant professional help (10 times higher than healthy controls).	Low rate of motor impairment compared to other studies could be due to older onset and/or not including wider range of motor behaviors.
Walker et al. (1994)	Pre-schizophrenic children and healthy siblings, pre-affective disorder children and their healthy siblings, healthy control children.	Researchers watched home movies of all subjects.	Higher rate of neuromotor abnormalities in pre-schizophrenic children compared to all other groups during first two years of life. Abnormalities were mainly on left side, including choreoathetoid movements and posturing of the upper limbs.	AOS cases
Watkins et al. (1988)	Children with COS (onset before 10th year; N=18). One third of this sample had autistic symptoms early in childhood.	Child Behavior Checklist Symptoms rated at four time points from 0 to 12 years for each case, based on school and medical records.	For the COS cases without history of autism: 55% had deficits in language development or no language prior to 30 months. 64% had motor problems before the 6th year consisting of delayed milestones and poor coordination. 82% were socially impaired in early childhood.	
Werry et al. (1991)	EOS group (N=30) with mix of COS and AdOS cases. Group of patients diagnosed with psychosis during childhood or adolescence but later confirmed to have BD (N=23).	Medical records, parental and patient interviews.	54% of schizophrenics had moderate to severely abnormal personalities, compared to 26% of mood disorder cases. The personality type ascribed to schizophrenic patients tended to be "odd" (30%) whereas most bipolar cases were described as "normal" (52%).	Main motivation for study was to examine stability of diagnosis over time rather than detailed exploration of premorbid history.

moderate to severely abnormal personalities premorbidly, compared to 26% of a group who were diagnosed with psychosis but later had this diagnosis changed to bipolar disorder. The personality traits ascribed to EOS patients tended to be "odd," whereas most bipolar disorder cases were described as "normal" premorbidly. McClellan et al. (27) reported that only 13% of EOS and psychosis not otherwise specified (psychosis NOS) cases were considered "normal" before onset of illness. They also found that the sociability scale of the PAS was the only significant variable that distinguished between later bipolar disorder and EOS, with greater introversion predictive of later schizophrenia. Muratori et al. (28) used the CBCL to examine social and behavioral problems in an EOS group compared to both healthy controls and a psychiatric control group with anorexia. They found evidence of behavioral problems in both psychiatric groups at age 2 to 3 years, but by age 4 to 11 years, the EOS group had worse scores on all CBCL

scales compared to control groups, encompassing social, thought and attention problems as well as school competencies. The social problems were related to shyness, underactivity and hypersensitivity. However, there is at least one contradictory report by Schothorst et al. (20) who found that 67% of their AdOS and affective psychosis patients showed social problems premorbidly, particularly isolation and withdrawal.

Intellectual ability: Several studies examined childhood and adolescence intellectual functioning (IQ) in individuals who later were diagnosed with schizophrenia (predominantly Adult-Onset). Jones et al. (21) examined educational assessments conducted at ages 8, 11 and 15 in the 1946 British birth cohort, and found that low scores were a risk factor for adult schizophrenia. Cannon et al. (23) used standard age-appropriate intelligence scales to assess cognitive development in the Dunedin birth cohort at ages 3, 5, 7, 9 and 11. Individuals who later developed schizophreniform disorder performed

more poorly than both healthy controls and psychiatric controls at all five assessments, suggesting that persistently low scores in premorbid cognitive testing have some specificity for schizophrenia. Studies of conscripts (29-31) have also demonstrated that, as a group, future schizophrenia patients have lower IQ scores than controls. Gochman et al. (32) in a 13-year follow-up study of COS cases, reported that COS cases had lower IQ scores before diagnosis, as well as a decline in general intellectual function that was not associated with a particular developmental period but occurred, on average, in the two years preceding and following the onset of psychosis and remained stable thereafter.

STRUCTURAL NEUROIMAGING FINDINGS IN EOS

Findings from structural MRI studies in AOS show increased volume of the lateral ventricles (33), and slightly decreased overall brain, gray and white matter volumes (34, 35). A recent meta-analysis suggests that the left medial temporal lobe and left superior temporal gyrus (STG) are key regions of reduced volume (35). Volume decreases are found in numerous other regions, including the hippocampus and amygdala (36), frontal lobes (37) and a relatively modest reduction in thalamic size (38).

Studies of COS have also found gray matter reduction and ventricular enlargement (39, 40) as well as reduced overall cerebral volume (41). However, in contrast to AOS, findings with regard to temporal lobe structures and hippocampal volume are mixed, suggesting that volume reduction in these regions may be moderated by age of onset and illness duration. Hippocampal volumes in EOS cases may be comparable to healthy individuals in childhood and early adolescence (42, 43) with progressive volume decreases occurring as patients approach adulthood (39). With regards to other temporal lobe structures, one study found evidence of reduced volume of the right STG in EOS (43); others reported no difference between COS patients and controls in temporal lobe structures (41, 42), and another study reported increased volume of the right posterior STG (44). An intriguing finding of EOS studies to date is the apparent importance of parietal lobe integrity and connectivity for schizophrenia. Thompson et al. (45) reported that the earliest deficits in NIMH COS were seen in parietal gray matter. In a new cohort of EOS patients, recruited at the Maudsley Hospital, diffusion tensor imaging (DTI) revealed abnormalities in parietal white matter compared to healthy controls (46), supporting the

above finding that parietal abnormalities may play an early role in the pathophysiology of schizophrenia.

Thompson et al. (45) followed 12 COS patients and matched controls over a five-year period during adolescence in order to investigate deficits related to disease progression during this stage of development. They report a dynamic wave of gray matter loss in the COS group beginning in the parietal association cortex that progressed anteriorly into the dorsolateral prefrontal cortex and temporal lobes, including STG. However, the pattern of change over time was diverse for different brain regions. A more recent study of the NIMH COS sample initially tested by Thompson et al. found dorsal to ventral frontal reductions in gray matter, which the authors interpret as an exaggeration of normal adolescent gray matter loss (47). Greenstein et al. (48) found that as COS patients approached adulthood, cortical gray matter development in the parietal cortex appeared to normalize, and volume deficits were mainly found in frontal and temporal regions, consistent with findings in AOS and providing further evidence for continuity between COS and AOS.

GENETICS AND EOS

Schizophrenia is known to be highly heritable (49). The concordance rate for monozygotic twins is higher than for same-sex dizygotic twins (50), suggesting that both genetic and environmental factors shape the developmental path leading to illness. While there are numerous susceptibility genes for schizophrenia, it is still unclear which of these genes are clinically relevant, and many genes may be of general importance for neurodevelopment and thus implicated in a wide range of neurodevelopmental disorders (51). In addition, genes may have different developmental effects at different points in time; only by studying the effect of the various candidate genes at different time points during the lifespan will more precise neurodevelopmental genetic models for schizophrenia emerge. Several of the genes conferring risk for schizophrenia have been examined in COS in terms of their association with various phenotypic measures (51). These genes are briefly discussed below.

GENES RELATED TO NEURODEVELOPMENT AND EOS

Two important general findings have emerged from the NIMH COS studies. First, that familial risk for

Schizophrenia Spectrum Disorders is higher for COS than AOS groups (52), suggesting that risk genes in this group may exert a greater effect on neurodevelopmental processes. Second, that risk genes for autism were not contributing to risk for schizohrenia in the COS group, despite high rates of Pervasive Developmental Disorders in this sample, suggesting that these genes cannot be seen as general risk factors for the neurodevelopmental problems in COS (53).

The 2q31.1 gene GAD1 is implicated in cortical, thalamic, cerebellar and hippocampal development. In the NIMH COS sample it was associated with greater frontal gray matter loss in adolescence and more severe deficits in smooth pursuit eye tracking (54). Specifically, six single nucleotide polymorphisms (SNPs) were associated with an increased rate of frontal gray matter loss over time and a different SNP was associated with eye-tracking dysfunction and worse scores on a measure of premorbid function which included social, speech and motor delays.

Addington et al. (55) investigated the two overlapping genes G72/G30 on 13q33.2. SNPs at the G72/G30 locus were associated with both bipolar illness and schizophrenia, suggesting that G72/G30 is a susceptibility locus for both illnesses. In addition, G72/G30 was specifically associated with later age of onset and better premorbid development, shown by better scores on the Autism Screening Questionnaire. They suggest that G72/G30 may act later than other risk factors in their sample, given its association with longer normal development prior to illness.

The 8p12 gene NRG-1 regulates aspects of neural development and synaptic plasticity and is associated with abnormal brain development in schizophrenia (56). In the COS group, the risk allele at 420M9-139 was associated with poorer premorbid social functioning (early childhood social withdrawal and poor peer relationships, measured by the PAS) and a different pattern of brain volume changes than healthy controls (56). The key finding was that risk allele carriers in the COS group had greater gray matter volumes during childhood but a steeper rate of decline of these volumes during adolescence.

The 6p22.3 gene DTNBP1 is involved in multiple neuronal functions, suggesting that it may play an important role in the pathophysiology of schizophrenia (51). In the COS group, it was associated with poor premorbid functioning; specifically, four adjacent SNPs of this gene were associated with worse PAS scores (12).

SUMMARY OF FINDINGS IN EOS

Although methodologies and sample sizes vary considerably between studies, collectively the evidence confirms that significant premorbid delay and impairment occur (and often co-occur) in EOS in the areas of motor, language and social development. Studies of EOS thus clearly support a neurodevelopmental theory for schizophrenia.

These often subtle developmental deficits show some specificity for schizophrenia and are considered to reflect early neurodevelopmental processes that may already be acting to predispose the child to later psychotic illness (51). In particular, speech and language delays and deficits are observed in many EOS cases and may be an early sign of a neurodevelopmental pathway to schizophrenia (52). Genetic factors, broadly associated with schizophrenia, are also associated with EOS, suggesting common genetic contribution across psychosis phenotypes. Risk genes potentially express their effects on both brain development, and cognitive/behavioral developmental characteristics.

CONCLUSIONS AND FURTHER DIRECTIONS

For more than two decades, the neurodevelopmental theory has been the prevailing explanatory theory for the etiology of schizophrenia. In its simplest form this theory posits that schizophrenia is the behavioral outcome of an aberration in neurodevelopmental processes that begins long before the onset of clinical symptoms and is caused by a combination of environmental and genetic factors (51).

Attempts to provide a more specific conceptualization of the neurodevelopmental hypothesis contrasted those favoring an early (pre- or perinatal), "static" brain lesion theory (4), and those advocating a late adolescent disturbance in brain maturation (2). However, subsequent research, including brain imaging studies that reveal a pattern of progressive changes both for early onset as well as chronic adult patients, indicated that the pathophysiological processes involved in schizophrenia need not be restricted to the pre- or perinatal period (51).

It is becoming increasingly evident that risk genes for schizophrenia have multiple actions and variable expression at different developmental stages and different brain regions (51). This suggests that genetic factors model the brain across the lifespan, and therefore distinctions between early and late theories and between

neurodevelopmental and neurodegenerative hypotheses may be outdated (51). Furthermore, despite the wealth of evidence on premorbid function and brain changes, no unitary neurodevelopmental account of these early subtle impairments currently exists, and more research is needed to try and link the behavioral and neurobiological aspects of aberrant neurodevelopment to the characteristic symptomatology in schizophrenia.

The variable expression and actions of genes may allow associating specific genetic factors with specific aspects of neurodevelopment. As discussed previously in this article, the gene dysbindin (DTNBP1), a schizophrenia susceptibility gene, has been also associated with poor premorbid functioning in COS (12), supporting the hypothesis that this (and possibly other schizophrenia susceptibility genes) also contribute to early neurodevelopmental impairment. This is only one example how susceptibility genes for psychosis also affect neurodevelopment and behavior. There are also clear hypotheses of how and when various etiological genetic factors might interact with early and later onset environmental risk measures (57, 58). Thus, two main lines of evidence will likely contribute to the development of more specific etiological models for schizophrenia: The study of single gene effects on brain and behavior, and the study of gene environment interactions.

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