

Differential Neurodevelopmental Trajectories in Patients With Early-Onset Bipolar and Schizophrenia Disorders

Celso Arango^{*,1,2}, David Fraguas¹, and Mara Parellada¹

¹Child and Adolescent Psychiatry Department, Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine, Universidad Complutense, CIBERSAM, Madrid, Spain; ²Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland, School of Medicine, Baltimore, MD

*To whom correspondence should be addressed; Hospital General Universitario Gregorio Marañón, Ibiza 43, 28009 Madrid, Spain; tel: 34-914265006; fax: 34-91426004, e-mail: carango@mprc.umaryland.edu

Schizophrenia and bipolar disorders share not only clinical features but also some risk factors such as genetic markers and childhood adversity, while other risk factors such as urbanicity and obstetric complications seem to be specific to schizophrenia. An intriguing question is whether the well-established abnormal neurodevelopment present in many children and adolescents who eventually develop schizophrenia is also present in bipolar patients. The literature on adult bipolar patients is controversial. We report data on a subgroup of patients with pediatric-onset psychotic bipolar disorder who seem to share some developmental trajectories with patients with early-onset schizophrenia. These early-onset psychotic bipolar patients have low intelligence quotient, more neurological signs, reduced frontal gray matter at the time of their first psychotic episode, and greater brain changes than healthy controls in a pattern similar to early-onset schizophrenia cases. However, patients with early-onset schizophrenia seem to have more social impairment, developmental abnormalities (eg, language problems), and lower academic achievement in childhood than early-onset bipolar patients. We suggest that some of these abnormal developmental trajectories are more related to the phenotypic features (eg, early-onset psychotic symptoms) of these 2 syndromes than to categorically defined Diagnostic and Statistical Manual of Mental Disorders disorders.

Key words: neurodevelopment/cognition/neuroimaging/psychosis/differential diagnosis/premorbidity/impairment/neurodegeneration

Introduction

In 1987, two of the most prominent schizophrenia researchers in recent times, Daniel Weinberger and Robin Murray, posited the neurodevelopmental hypothesis of schizophrenia.^{1,2} In brief, the theory postulated

that the consequences of genetic predisposition and early adverse events, such as insults during gestation, would be latent throughout the first 2 decades of life and would only manifest as psychosis in early adulthood when normative maturational changes “unmask” an earlier insult. This hypothesis had been postulated some years earlier by John Strauss and William Carpenter: “The various biological, psychological, and social factors in schizophrenia and its treatment require a framework for organizing information and understanding. The interactive developmental systems model emphasizes both the interaction of many factors and the evolution of their impact over time. Although the model is tentative and incomplete, it provides a basis for organizing the complexities involved in schizophrenic disorders.”³ Of course others had previously paved the way for the neurodevelopmental hypothesis. For instance, Feinberg had also suggested that exaggerated synaptic regression (“pruning”) in adolescence may underlie schizophrenia.⁴ Even earlier, Barbara Fish suggested that schizophrenia might be a consequence of a congenital inherited neurointegrative defect that she referred to as “pandysmaturation” or “pandevolutionary retardation.”⁵ And if we go back even farther, as much as 2000 years ago, we read in the Yellow Emperor’s Classic of Internal Medicine that mental disorders result from a bad scare to the mother when she was pregnant.⁶

Much less attention has been paid to the study of bipolar disorder as a neurodevelopmental disorder. As a tribute to William Carpenter, who illuminated the research by our group, we will review the evidence gathered in recent years on the developmental trajectories of those individuals who eventually develop early-onset schizophrenia or bipolar disorder, with particular emphasis on bipolar disorder with psychotic symptoms.

Bipolar Disorder and Schizophrenia: More in Common Than Supposed

In addition to symptomatic overlap, particularly in acute episodes and with regard to psychotic symptoms, schizophrenia and bipolar disorder share many associated features and risk factors. The age of onset for schizophrenia and bipolar disorder is similar, although it may be earlier for bipolar disorder if first depressive episodes are included.^{7–10} In both disorders, males seem to have an earlier age of onset. Both conditions respond to some common treatments such as dopamine blockers. Other similarities and differences between the 2 disorders are reviewed in [table 1](#).

There is vast literature supporting that aberrant developmental processes occurring during fetal, childhood, or adolescent periods are related to an increased risk of developing schizophrenia.^{5,11–14} The major question addressed in this article is whether, in addition to the commonalities in clinical features and risk factors (genetic and environmental) between schizophrenia and bipolar disorder (with psychotic symptoms), these 2 syndromes share abnormal brain development trajectories. Indirect ways of assessing abnormal neurodevelopment are cognitive performance, early functionality, and adjustment to the environment, as well as brain structural deviances from healthy subjects during development. We will focus mainly on 2 special groups of patients with these syndromes: those with early-onset schizophrenia and those with early-onset bipolar disorder with psychotic symptoms. We define early-onset as any case where the first psychotic episode (not just symptoms) appears before the age of 18.

Cognitive Impairment During Development in Schizophrenia and Bipolar Disorder

The evidence for an abnormal cognitive performance during development in schizophrenia is overwhelming and beyond dispute. In a systematic metareview, the strongest evidence among the putative antecedents in schizophrenia was for motor dysfunction and low intelligence quotient (IQ).¹⁵ Low IQ at age 7 has been significantly associated with genetic vulnerability to psychoses, in particular with schizophrenia.¹⁶ On the contrary, there is evidence to support that better than normal school performance is associated with adult bipolar disorder. In a cohort study including longitudinal data from over 900 000 individuals in Sweden, individuals with excellent school performance were almost 4 times more likely to develop bipolar disorder in adulthood than those with average grades.¹⁷ However, individuals at the low end of the school grade distribution also had a significantly higher risk for bipolar disorder. Those in the lowest grade category were about twice as likely to develop bipolar disorder as the average grade group. In the same sample, above-average grades

were associated with a decreased risk for schizophrenia.¹⁸ In the Dunedin cohort study, children who developed schizophrenia in adulthood had cognitive impairment and that was not the case for bipolar patients ($n = 20$).¹⁹ In a more recent analysis of the same cohort, while lower childhood IQ was associated with increased risk of developing schizophrenia spectrum disorder, depression, and adult anxiety at age 32, a higher childhood IQ predicted increased risk of mania ($n = 8$) at the same age.²⁰ In an independent sample, although a lower IQ at age 8 was a better predictor of nonclinical psychotic symptoms at age 12, very high IQ was also related to psychosis.²¹

At the time of the first psychotic episode in adults, patients with schizophrenia seem to have widespread cognitive impairment compared with controls, while patients with bipolar disorder have much less impairment apparently mainly in scores on tests assessing delayed verbal memory and category fluency.²² It is noteworthy that onset of a first psychotic episode, whether of schizophrenia or mania, is in many cases coincident in time with cognitive maturation of the prefrontal and parietal cortices.

In our studies in children and adolescents with a first psychotic episode, we see cognitive impairment that does not distinguish between those with schizophrenia and bipolar disorder, with both groups scoring worse than healthy controls in all assessed cognitive domains.^{23,24}

The discrepancy between the data showing cognitive impairment in bipolar disorder and close relatives^{25–28} and the better premorbid cognitive functioning and scholastic performance in longitudinal studies in subjects who end up having adult bipolar disorder could be due to sample selection bias, medication, drug use, cognitive decline prior to the first psychotic episode, or other confounding factors. Reading difficulties and scholastic underachievement, however, seem to be more specific to early-onset schizophrenia than early-onset bipolar I disorder.²⁹

Neurological signs (NS), which are neurological abnormalities in sensory and motor performance, are not specific to schizophrenia as they are also present in bipolar disorder,³⁰ in early-onset psychoses independently of whether the individuals later develop schizophrenia or bipolar disorder,³¹ and in subjects with an at-risk mental state for psychosis.³² NS are also more prevalent in early-onset cases of both schizophrenia and bipolar disorder than in healthy controls.³³

Premorbid Functioning and Developmental Impairments Other Than General Cognition

In addition to premorbid developmental impairments (language, reading, motor development) being described both in adult-³⁴ and childhood-onset schizophrenia,^{34,35} the level of functioning prior to the first psychotic episode, also known as premorbid adjustment, has also been the focus of much attention in the past. Lower levels of functioning have been described in adult-onset,^{36–39}

Table 1. Bipolar Disorder and Schizophrenia: More in Common Than Supposed (Common Features Between Bipolar Disorder and Schizophrenia)

Genetics ^a	Individual genes: <i>AKT1</i> , <i>DISC1/DISC 2</i> , <i>Dysbindin</i> , <i>NOS1</i> , <i>GRM4</i> , <i>G30/G72</i> , <i>NRG1</i> , <i>MIR137</i> . ^{79,81-83} Loci (GWAS): <i>CACNA1C</i> , <i>ANKK3</i> , <i>ITIH3-ITIH4</i> region. ^{80,81} Linkage “hot-spots”: 18p11, 22q11, 13q32, 10p14, and 1q32. ⁸³ CNVs are found in excess in schizophrenia, but not in BD. ⁷⁶
Developmental abnormalities	Rates of developmental abnormalities (language abnormalities such as articulation abnormalities, language delay, and receptive-expressive language dysfunctions, as well as motor impairments such as delayed motor milestones, clumsiness, and poor coordination) are not significantly different between schizophrenia and bipolar patients. ⁵⁰ Some developmental problems such as reading or writing difficulties seem to be more common in early-onset cases of schizophrenia than bipolar disorder. ²⁹ Between childhood and early adolescence, both schizophrenia and bipolar patients show a greater decline in academic adjustment than healthy controls, more specifically in adaptation to school. ⁵⁰ However, lifelong academic underachievement was greater and started earlier in an early-onset schizophrenia group than in an early-onset bipolar disorder group. ²⁹
Antioxidant status	First-episode early-onset psychosis patients have been shown to have low antioxidant status, with no differences between schizophrenia and bipolar patients; however, only those with schizophrenia have lower glutathione at baseline. ⁷⁴ Decreased glutathione levels during the first psychotic episode were related to greater loss of cortical gray matter 2 years later in patients with first-episode early-onset psychosis. ⁸⁴
Neuroimaging	Lateral ventricle volumes are enlarged in both schizophrenia and BD, although this is more pronounced in schizophrenia than in BD. ^{63,64} GM reductions are less marked in subjects with BD than in those with schizophrenia. ^{61,64} In general, cortical and limbic GM abnormalities (such as hippocampus volume) are more pronounced in schizophrenia. ^{63,64} However, there are notably overlapping abnormalities in the paralimbic regions. ⁶⁴ Studies in children and adolescents with a first psychotic episode show that most volume abnormalities, including thinner frontal cortical thickness or increased intracranial CSF, are common to bipolar and schizophrenia patients, although they seem to be quantitatively larger in those developing schizophrenia vs bipolar type I. ^{51,67,69,70} In early-onset psychosis, progressive brain volume changes (mainly reduction in frontal GM volume) seem to be more marked in those who develop schizophrenia than in those who develop other diagnoses. ⁵² However, it is not clear to what extent this larger reduction is a reflection of the different diagnosis or a severity marker. ⁵²
NS	NS are present in both schizophrenia and BD. ³⁰
Insight	Chronic impaired insight characterizes those patients with a diagnosis of schizophrenia but not so much those with BD. ⁸⁵
Environmental factors	Childhood adversity seems to increase the risk for both schizophrenia and affective psychosis. ⁸⁶ Cannabis use has also been related to increased risk of schizophrenia and other psychoses ^{87,88} or BD. ^{89,90} Schizophrenia has been related to prenatal infection, prenatal famine, prenatal micronutrient deficiency (eg, vitamin D, iron, folate), prenatal psychological stress, and other prenatal complications (antepartum hemorrhage, gestational diabetes, rhesus incompatibility, or preeclampsia). ⁹¹ However, the association between BD and pre- and perinatal complications is controversial. ⁹²⁻⁹⁴ Migration has also been a replicated risk factor for schizophrenia, ⁹⁵ while its effect on BD is controversial. ⁹⁶ Urbanicity has repeatedly been found to be a risk factor for schizophrenia, but could be a protective factor for affective psychosis. ⁹⁷ Obstetric complications have also been a replicated risk factor for schizophrenia ¹⁵ that does not seem to increase the risk for BD. ⁹⁴
Premorbid developmental impairments	Premorbid developmental impairments (language, reading, motor development) have been described both in adult- ³⁴ and childhood-onset schizophrenia. ^{34,35} The relationship between premorbid adjustment and BD is more controversial in early-onset cases, although there seems to be an association between poor premorbid functioning and severe forms of the disorder. ⁴⁷⁻⁴⁹
Cognitive function	Neuropsychological impairment may be considered an intermediate phenotype, which is present and familial in schizophrenia and BD, but more severe in schizophrenia than in bipolar patients. ⁹⁸ Cognitive impairment seems to remain similar during the first 2 years after the first psychotic episode in both bipolar and schizophrenia patients. ²³

Note: BD, bipolar disorder; CSF, cerebrospinal fluid; CNVs, copy number variants; GM, gray matter; GWAS, genome-wide association studies; NS, neurological signs (abnormalities in sensory and motor performance).

^aData on genetics show only some common genes as examples of genetic overlapping between schizophrenia and bipolar disorder.⁷⁹⁻⁸²

and childhood- and adolescent-onset schizophrenia.^{35,40} Early-onset cases of schizophrenia seem to have a worse premorbid adjustment compared with adult-onset cases. The relationship between premorbid adjustment and bipolar disorder is more controversial. Premorbid impairments,^{41,42} normal premorbid adjustment,⁴³⁻⁴⁵ and better than normal^{36,37,46} premorbid adjustment have been reported in the past. There seems to be an association between poor premorbid functioning and severe forms of the disorder.⁴⁷⁻⁴⁹ Inclusion of different types of bipolar disorder (eg, type I/II), age of onset, and patients with or without psychosis are factors that could account for the differences in bipolar studies. The need is there to further study developmental antecedents of nonpsychotic bipolar patients.

In our studies with children and adolescents with a first psychotic episode, we see that schizophrenia patients show not only more social impairment in childhood than healthy controls but also more social impairment than early cases of bipolar disorder.⁵⁰ The rates of language abnormalities (such as articulation abnormalities, language delay, and receptive-expressive language dysfunctions) were higher in schizophrenia than in healthy controls, although there were no significant differences between schizophrenia and bipolar patients.⁵⁰ Some developmental problems such as reading or writing difficulties and scholastic underachievement seem to be more common in early-onset cases of schizophrenia than bipolar disorder.²⁹ Late in development (between childhood and early adolescence), both schizophrenia and bipolar patients have shown a greater decline in academic adjustment than healthy controls, more specifically in adaptation to school.⁵⁰ This academic decline at the beginning of adolescence may be a vulnerability marker for transition to general psychosis, more than a specific marker for schizophrenia. To what extent this academic underachievement and adaptation to school are markers of severity within psychosis or specifically related to a diagnostic entity is in need of further research.

Brain Abnormalities in Imaging Studies

Magnetic resonance imaging evidence indicates that schizophrenia is associated with changes in brain volume that predate the onset of the clinical syndrome.⁵¹⁻⁵⁴ Although neuroimaging studies have shown a different pattern in childhood and early adolescence-onset schizophrenia compared with late adolescence-onset and adult-onset (“back-to-front” tissue loss with early parietal gray matter [GM] loss followed by frontal and temporal GM loss in childhood-onset vs GM loss mostly in prefrontal and temporal cortices in adult-onset), there is a tendency to resemble the pattern seen in adult-onset as children become young adults.^{55,56} Furthermore, neuroimaging studies in childhood-onset schizophrenia (COS) have reported some results consistent with the adult-onset

schizophrenia literature, ie, increased lateral ventricular volume, decreased total and regional cortical GM volumes, decreased hippocampal and amygdala volumes, and increased basal ganglia volumes that progressed during adolescence.^{57,58} In addition, prospective studies of nonpsychotic full siblings of patients with COS have shown a pattern of reduced prefrontal and temporal GM volume in childhood that appears to normalize by the time the subjects reach late adolescence.^{59,60}

But do subjects with bipolar disorder undergo the same brain changes as those with schizophrenia? Brain alterations seem to be more marked in adult cases of schizophrenia than adult cases of bipolar disorder.^{61,62} Three meta-analyses have compared structural brain volumes in adult subjects with schizophrenia and bipolar disorder.^{61,63,64} Lateral ventricle volumes were enlarged in both disorders, although more pronounced in schizophrenia than in bipolar disorder.^{63,64} GM reductions were less marked in subjects with bipolar disorder than in those with schizophrenia.^{61,64} In general, cortical and limbic GM abnormalities (such as hippocampus volume) were more pronounced in schizophrenia.^{63,64} However, there were notably overlapping abnormalities in the paralimbic regions.⁶⁴ On the other hand, a recent study conducted in twin pairs have found smaller white matter volume and common areas of thinner cortex (thinner parahippocampus, thinner right orbitofrontal cortex, and thicker temporoparietal and left superior motor cortices) in both disorders, suggesting that these share genetic factors.⁶⁵

With respect to studies specifically comparing brain volumetric differences in young people with schizophrenia or bipolar disorder, although the first cross-sectional studies comparing brain volumes between adolescent schizophrenia and bipolar disorder did not find significant differences,⁶⁶ recent research involving cortical brain volume differences in these populations have found lower volumes in the schizophrenia group.^{67,68}

In our studies in children and adolescents with a first psychotic episode, we see that most volume abnormalities, including thinner frontal cortical thickness or increased intracranial cerebrospinal fluid (CSF), are common to bipolar and schizophrenia patients, although they seem to be quantitatively larger in those developing schizophrenia vs bipolar type I.^{51,67,69,70} In our samples, no significant differences between different psychotic diagnostic subgroups (eg, schizophrenia vs bipolar) appear in any region⁷¹ at the time of the first psychotic episode, although schizophrenia patients significantly differ from healthy controls in different brain regions (bipolar patients differ significantly from controls only in larger total CSF volumes). Differences seem to be more quantitative than qualitative, with bipolar patients in between healthy controls and schizophrenia patients.⁵² As some of these brain abnormalities seem to predict outcome, they may be more a marker of severity than disorder specific.

Early-onset bipolar patients with psychotic symptoms seem to have baseline structural abnormalities that probably represent deviant developmental processes, but progression of these has not been demonstrated to the same extent. Differential treatment with antipsychotics and/or other psychotropics in terms of doses and duration may account for volumetric differences between different disorders^{25,26}.

What Happens After a First Psychotic Episode in Children and Adolescents?

Studies in patients with COS show that they have significantly greater total, frontal, temporal, and parietal GM loss than those with childhood-onset atypical psychoses or healthy control groups.⁷² On the other hand, young patients with psychosis not otherwise specified showed some areas of temporal and prefrontal deficits, although more subtle compared with the extensive bilateral cortical deficits seen in COS.⁷³ In fact, adolescents with early-onset schizophrenia-spectrum disorders have GM deficits compared with healthy controls and adolescents with early-onset psychotic mood disorders.⁶⁸ Altogether, these results suggest that progressive brain changes may be diagnosis related, although alternative explanations (eg, medication, stress, disease severity) cannot be ruled out.

In our own sample, progressive changes (mainly reduction in frontal GM volume) seem to be more marked in those who develop schizophrenia than in those who develop other diagnosis.⁵² However, it is not clear to what extent this larger reduction is a reflection of the different diagnosis or a severity marker, as larger reductions in GM volume were related to more days in the hospital and less improvement in negative symptoms, with schizophrenia patients showing a worse outcome in those measures.⁵² In line with the possibility that patients with psychosis have a particularly degenerative or deteriorating outcome, first-episode early-onset psychosis patients have been shown to have low antioxidant status, with no differences between schizophrenia and bipolar patients; however only those with schizophrenia have lower glutathione at baseline.⁷⁴

In terms of cognition, the impairment seems to remain similar during the first 2 years after the first psychotic episode in bipolar and schizophrenia patients,²³ with cognitive reserve (composed of an estimation of premorbid IQ and a measure of educational-occupational levels and lifetime leisure-social activities) predicting long-term working memory and attention.⁷⁵

Discussion

While for schizophrenia, whether early- or adult-onset, abnormal brain development is uncontroversial, the same may not be the case in early-onset or adult-onset bipolar disorder. In adult studies that include both bipolar I and

II disorders, cognitive impairments and brain structural abnormalities do not seem to be present in the early stages as they are in schizophrenia or early-onset bipolar disorder⁷⁶. However, in our studies in early-onset cases of bipolar disorder with psychotic symptoms, we do not see any differences between these patients and those with early-onset schizophrenia with respect to cognitive impairment, premorbid adjustment (other than social or life time underachievement), or most of the brain structural abnormalities assessed (although they are not as marked in the group of bipolar patients). Bipolar patients with an early-onset disorder with psychotic symptoms, like the ones included in our samples, seem to have cognitive impairment and neurodevelopmental deviance. On the other hand, late-onset bipolar disorder has been associated with high scholastic achievement and more preserved neurodevelopment. Lower cognitive functioning may be a significant risk factor for earlier onset of bipolar disorder. However, it may not be a significant determinant of the overall incidence of bipolar disorder, as the percentage of bipolar patients with early-onset disorder with psychotic symptoms is in the minority.

Longitudinal studies assessing large cohorts of subjects from inception will shed light on the extent of the relationship between brain developmental trajectories and psychiatric diagnoses as we have conceptualized them. In the future, we should also assess whether brain trajectories are more related to functional and prognostic outcomes than diagnosis. Stratifying patients in an objective, quantitative way according to clinical and functional outcomes may generate patient clusters that are not only more clinically meaningful but also closer to brain developmental trajectories. In fact, depression with psychotic symptoms seems to be more closely aligned with schizophrenia than has been considered previously.⁷⁷

It has been previously hypothesized that certain genes involved in neuroplasticity and neurodevelopment predict liability to a continuum of serious mental illnesses.^{78–81} Those subjects who are additionally neurodevelopmentally compromised express schizophrenic symptoms, while their cognitively unimpaired counterparts present a bipolar picture.⁷⁶ Or, from a dimensional perspective, schizophrenia could be considered one consequence of a failure to reach the final state of cortical maturation, resulting in retention of an immature cortex.¹¹ Subjects with bipolar disorder would have a not so immature cortex, but they also would have some degree of inadequate maturation of the cortex. Naturally, all those genes may interact epistatically and respond to environmental change.⁵

It seems important to take an approach based on dimensional space rather than categorical distinctions. Bipolar disorder and schizophrenia are not homogeneous diseases. In contrast, they seem to be syndromes that include different kinds of diseases. From this perspective, it is quite difficult to find specific neurodevelopment trajectories for nonspecific clinical categories.

Conclusions

Evidence suggests that, at least in schizophrenia, early insults to the brain produce dynamic alterations rather than static ones in brain ontogeny that manifest through deviant neurodevelopmental trajectories well before the onset of psychotic symptoms. This seems to also be the case, although to a lesser extent, in a subgroup of bipolar psychotic patients with an earlier age of onset. At least in early-onset cases, neurodevelopmental trajectories seem to be different between bipolar and schizophrenia cases at a quantitative rather than qualitative level. To what extent these trajectories are a risk for psychosis rather than for the actual definition of these 2 syndromes is a question that has not yet been solved. The progressive brain changes that take place after the first psychotic episode seem to be different, more marked in schizophrenia, and dependent on the number of episodes. In any event, as there are no genes coding for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) disorders, there are also no developmental trajectories typical for these 2 categorical entities. It seems more reasonable to search for abnormal trajectories that correlate with different clinical phenotypes such as early-onset psychosis than with an arbitrarily defined diagnosis.

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