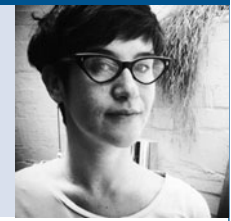


Editorial

Uncovering neurodevelopmental features in bipolar affective disorder

Isabel Valli, Chiara Fabbri and Allan H. Young

**Summary**

Schizophrenia and bipolar disorder are genetically related and their clinical features overlap. Schizophrenia is conceptualised as a neurodevelopmental disorder but the evidence for bipolar disorder is less clear. Cluster-analytic approaches reveal different cognitive profiles within bipolar disorder, possibly reflective of differing neurodevelopmental loads, which are also suggested by recent genetic and neuroimaging studies. Such studies suggest the potential utility of further clinical subcategories in bipolar disorder based on neurodevelopmental load.

Declaration of interest

None.

Keywords

Bipolar affective disorders; psychotic disorders; schizophrenia; aetiology; developmental disorders.

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Background

Schizophrenia and bipolar disorder have historically been considered different entities but they co-segregate in families and genetic studies provide increasing evidence that they share risk alleles.¹ Biological and clinical evidence of shared pathophysiology among major psychiatric disorders promoted the development of dimensional classifications such as the Research Domain Criteria. However, although schizophrenia shows neuropsychological and biological features of a neurodevelopmental disorder, the evidence for bipolar disorder is less clear.²

Neurodevelopmental disorders are characterised by early brain abnormalities resulting from the impact of genetic and environmental factors on neurodevelopment. Such abnormalities increase the risk for the disorder, but overt symptoms may not become clinically manifest until a specific phase of development when the involved brain regions reach functional maturity. However, subtle manifestations of pathology can be identified before clinical onset, presenting as delayed psychomotor milestones, neurological soft signs, abnormalities in sensory integration and deficits in several cognitive domains. These are associated with a variable degree of abnormalities observed in measures of brain morphology and connectivity.²

Epidemiological, neuropsychological and neuroimaging evidence

Obstetric complications are one of the perinatal factors most strongly associated with schizophrenia, whereas evidence of their role in bipolar disorder is inconclusive.² Some studies reported higher incidence and others no difference for people with bipolar

disorder relative to healthy controls.² Mixed evidence also emerged from studies in offspring who are at high risk for bipolar disorder,² although higher incidence was reported in a recent study – the first to include a comparison with healthy controls.

Cognitive impairments are one of the core clinical dimensions of schizophrenia. They are present premorbidly and are reliable predictors of long-term outcome.³ Because of the distributed topography of their functional imaging correlates, these impairments are thought to be a result of connectivity pathology sustained by neuronal cell migratory abnormalities which are neurodevelopmental in origin.⁴ Deficits span across all neurocognitive domains, with the most significant impairments identified for executive function, verbal learning and processing speed.³ The same cognitive domains are the most impaired in bipolar disorder both in euthymic and symptomatic phases, with most of the evidence suggesting a similar pattern but milder overall severity compared with schizophrenia.³ However, a different longitudinal trajectory seems to characterise cognitive deficits in the two disorders: in schizophrenia both retrospective reviews of patients' academic records and prospective studies showed premorbid general intellectual deficits, whereas the limited studies available in bipolar disorder mainly reported good academic achievement in the years preceding illness onset. But more recent studies suggest that examining population mean cognitive function may have masked increased risk at the extreme ends of premorbid scholastic achievement. Thus in more recent studies both poor and excellent school performance were associated with increased risk of later developing bipolar disorder, suggesting that the time frame of emergence of cognitive dysfunction may not be uniform and may perhaps precede illness onset in those who underperform. Studies in high-risk cohorts robustly support the premorbid emergence of widespread cognitive impairment in schizophrenia.² Evidence in cohorts at high risk for bipolar disorder is less conclusive, with some studies reporting impairments and others no differences compared with healthy controls.² However, a recent meta-analysis identified a modest yet significant underperforming of youths at familial risk for bipolar disorder; this was considered to support the role of neurodevelopmental abnormalities in bipolar disorder. The milder severity compared with populations at high risk for schizophrenia may reflect a less pronounced developmental load in bipolar disorder or result from possible dilution effects. In line with clustering analysis studies that have identified different cognitive profiles within bipolar disorder,³ the results appear consistent with the existence of a bipolar disorder subgroup with deficient premorbid cognitive function.

Neurological soft signs have been robustly identified in schizophrenia⁴ but inconsistently in bipolar disorder.² However, a recent meta-analysis demonstrated a robust increase in bipolar disorder, only moderately less severe than that observed in schizophrenia, and their presence has been identified in offspring at high risk for bipolar disorder.

In schizophrenia early signs of brain pathology manifest as structural brain abnormalities already present at illness onset.² These are also observed in individuals at risk of developing the disorder,² with a similar distribution yet milder severity compared with those observed at first episode. Findings are more heterogeneous in bipolar disorder but meta-analytic evidence indicates that structural brain abnormalities are also present in patients with first episode bipolar disorder, although deficits in grey matter volume appear less pronounced compared with schizophrenia.² Morphological brain abnormalities have also been described in cohorts at high risk for bipolar disorder, yet findings have been more inconsistent compared with the evidence in populations at high risk for schizophrenia.²

Categorical and dimensional contributions to classification

Neurodevelopmental mechanisms are therefore either less pronounced in bipolar disorder than in schizophrenia or only pertain to a subgroup of people with bipolar disorder. The Research Domain Criteria approach proposes cognitive function as a transdiagnostic domain to evaluate pathogenetic mechanisms of psychiatric disorders. The use of data clustering rather than diagnostic categories demonstrated that cognitive functioning across patients with schizophrenia and bipolar disorder appeared distributed – albeit not evenly – over different clusters, ranging from no impairment to global and severe.³ People with schizophrenia were disproportionately more represented in the global impairment cluster, whereas people with bipolar disorder were less frequently characterised by widespread cognitive dysfunction.³ This evidence raises the question of whether more severe cognitive dysfunction in bipolar disorder is associated with a clinical picture closer to schizophrenia. A recent meta-analysis examined cognitive dysfunction between potential bipolar disorder subtypes. Bipolar disorder type I significantly underperformed bipolar disorder type II across most domains, as did bipolar disorder with a history of psychosis relative to bipolar disorder without psychosis. Cognitive differences between the groups were reported to be significant yet modest, hence raising questions about cognitive heterogeneity within bipolar disorder being discriminatory between bipolar disorder clinical subtypes.

Molecular imaging studies in schizophrenia have consistently shown increased striatal dopamine synthesis capacity.⁵ This was not observed in acute mania without psychosis.⁵ However, a recent study in bipolar disorder with psychosis revealed an increase in dopamine synthesis capacity similar to that observed in schizophrenia.⁵

Further evidence regarding features potentially discriminating between bipolar disorder with psychosis and bipolar disorder without psychosis derives from polygenic risk score (PRS) analysis of common variants. Using this method, extensive genetic sharing has been observed between schizophrenia and bipolar disorder, but this is paired with growing evidence that differences between the two disorders also have a genetic basis.¹ However, a significant increase in schizophrenia PRS was observed for bipolar disorder with psychosis compared with bipolar disorder without psychosis¹ and was associated with earlier age at onset.¹

The conceptualisation of cross-disorder risk has recently been expanded beyond schizophrenia and bipolar disorder as



population studies have also examined intellectual disability, autistic spectrum disorders and attention-deficit hyperactivity disorder.⁴ For these disorders a gradient of neurodevelopmental pathology has been suggested, indexed by mutational load and cognitive impairment, with intellectual disability at the most affected end of the spectrum and bipolar disorder at the other end.⁴ Different clinical pictures, rather than representing discrete constructs, are considered to lie on a continuum reflecting the severity and time frame of the insult on the affected underlying brain circuitry.⁴

PRS analyses capture common genetic variants but do not identify more rare ones, such as copy number variants (CNVs). The latter were reported to be distributed along a gradient of frequency from autistic spectrum disorders and intellectual disability at one end and bipolar disorder at the other end of the spectrum.⁴ Large CNVs are significantly less strongly associated with bipolar disorder relative to schizophrenia but some evidence, albeit not definitive, suggests that they are particularly enriched among people with bipolar disorder that have early onset and greater cognitive impairment.⁴ This is in line with the idea of a broad neurodevelopmental gradient but also highlights the known heterogeneity within bipolar disorder, again likely reflective of a greater neurodevelopmental load in a subgroup of people with bipolar disorder.

Conclusions

Consistent with the idea of a neurodevelopmental continuum, evidence suggests that at least a subgroup of people with bipolar disorder demonstrate early cognitive impairment, documented premorbidly and associated with a higher burden of large CNVs.⁴ It is currently unclear whether early features of a neurodevelopmental disorder are associated with a specific bipolar disorder phenotype in adulthood. We might hypothesise that individuals with a more pronounced set of childhood developmental features are more likely to develop bipolar disorder with psychotic symptoms and a neurobiology closer to schizophrenia, in line with molecular imaging and genetic findings. Work on transdiagnostic dimensions highlights neurodevelopmental continuity between previously distinct constructs, with intellectual disability at one end of the spectrum and bipolar disorder at the other end. This work might also lead to identifying more homogenous and valid subcategories within the currently broadly defined disorders. This appears to be a critical step in bringing diagnostics closer to the underlying biological mechanisms.

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Poem

The last sigh

By Ethan Taylor

Bedridden, laden with fears
 those sorrowful tears
 are helpless to cleanse,
 the infirm gravely yield
 to the pernicious will
 of disease.

Seeking
 reassurance
 one lifts his eyes
 to examine the familiar
 faces which surround
 his dying frame.

Disheartened,
 he sees mirrored
 in fretful stares
 the distress
 in which he
 is bathed.

Refuge,
 he sees well,
 is not to be found
 in the regretful eyes
 of the beloved.
 Nor can it lie
 in the kind hollows
 of consolation.

In
 isolation
 he is condemned
 to lie; absent
 are those estranged
 faces, ever distant
 as they gather
 to witness
 the last sigh.

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