

Neurobiology of Schizophrenia Spectrum Disorders

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The *schizophrenia spectrum disorders* are a group of psychiatric diagnoses that share several clinical features, typically involving reality distortion. Each is considered a *disorder*, diagnosed with a distinct set of diagnostic criteria. *Spectrum* conveys the idea that they are somehow similar to each other. Such similarity could be defined on purely clinical grounds or at the level of disease mechanism and aetiology. It is this tension of distinctiveness and similarity that makes the scientific study of the schizophrenia spectrum disorders challenging.

The concept of the schizophrenia spectrum can be traced back to Bleuler and his book *Dementia Praecox or the Group of Schizophrenias*.¹ The *schizophrenias* are characterised by significant heterogeneity of signs and symptoms, disease course and outcome. This gives rise to various clinical subtypes and to variants defined by a shorter duration of illness. Most importantly, the outcome of the *schizophrenias* ranges from long-term disability to full remission. As a result, the current version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR)² recognises 5 subtypes of schizophrenia (i.e., catatonic, disorganized, paranoid-hallucinatory, undifferentiated and residual), 2 forms of schizophrenia with shorter duration (i.e., schizophreniform disorder and brief psychotic disorder), 2 delusional disorders (i.e., delusional disorder and shared psychotic disorder), and 3 personality disorders with features that resemble schizophrenia (i.e., schizotypal, paranoid, and schizoid personality disorder). In addition, 3 diagnoses capture psychotic patients with significant mood symptoms – one with an emphasis on psychosis (schizoaffective disorder) and two with an emphasis on mood symptoms (psychotic bipolar disorder and psychotic depression).

How can we test the hypothesis that these 15 diagnoses identify distinct disorders? Most importantly for clinicians, a prediction of illness course and outcome would support the validity of the diagnoses. While there is evidence for a gradient of dysfunction (with schizophrenia having the greatest and personality disorder the smallest burden of disability),³ there remains substantial variability within each diagnostic group. For example, some patients with schizophrenia respond poorly to all available treatments

and have a poor outcome, while others respond well to treatment, some with full remission of all symptoms and full recovery to the premorbid level of functioning.⁴ This significantly limits the usefulness of our diagnostic labels and raises concern about the stigmatisation of a person who will recover from a bout of psychosis. This has led some to argue for the removal of the diagnosis of schizophrenia altogether.⁵

The neurobiological exploration of schizophrenia spectrum disorders is relevant in this debate. Neuroscientific data could support our current nosology, if they confirmed that patients within the same diagnostic group share similar disease mechanism and aetiology. It would be even more compelling if patients in different diagnostic groups could be separated based on disease mechanism and aetiology. If the diagnostic categories represented biological entities, then validators such as allelic variation, gene expression, brain structure or cognitive function would converge on the same diagnoses and separate different diagnoses. There is now considerable doubt that neurobiological validators do indeed converge on the same diagnosis. At the same time, several lines of evidence support the distinction of schizophrenia spectrum disorders along a dimensional continuum.

The holy grail in this debate is the separation of schizophrenia and psychotic bipolar disorder by genetic risk and neural mechanism. Kraepelin argued strongly for such a categorical distinction. He asserted that there is a diagnostic neuropathology of schizophrenia and no neural substrate for manic-depressive illness (bipolar disorder). This position is now untenable. First, several risk genes, originally identified in schizophrenia cohorts, are now also linked to an increased risk for bipolar disorder. Compelling examples are Neuregulin-1 (NRG1) and DISC1.⁶ Second, neurobiological findings such as an abnormal function of cortical interneurons have been reported for cohorts of schizophrenia and bipolar subjects alike.^{7,8} However, a recent meta-analysis of structural imaging studies in bipolar disorder concluded that brain volume changes are less significant and less localised when compared to studies of subjects with schizophrenia.⁹ While the debate about the categorical distinction of schizophrenia and bipolar disorder

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is ongoing, some have asked for the removal of the Kraepelinian dichotomy from our diagnostic system.¹⁰ What does this mean for the other schizophrenia spectrum disorders?

The diagnosis schizoaffective disorder lives in the borderland between schizophrenia and mood disorder. Kasanin¹¹ introduced the diagnosis to capture a milder form of schizophrenia, associated with better outcome. But the current version of the DSM conceptualises it as schizophrenia with prominent mood symptoms, with no *a priori* distinction of disease course or outcome. Despite the low reliability of the diagnosis,¹² many researchers have compared the genetics and neurobiology of schizophrenia and schizoaffective disorder. Recent reviews of this literature^{13–16} have questioned the validity of the diagnosis, but continued to recommend a diagnostic separation along the continuum from psychosis to mood disorder.

Another dimension of the schizophrenia spectrum is subjects who have mild, subsyndromal features of schizophrenia. Two groups have attracted considerable interest, i.e., subjects with schizotypal personality disorder and first-degree relatives of patients with schizophrenia. Both groups can be studied without the confound of long-term treatment with psychotropic medication. Furthermore, the study of relatives allows us to explore how genetic risk factors affect the neural substrate of psychosis. The preliminary conclusion from the studies of schizotypal personality disorder is that some regions (e.g., medial temporal lobe) are similarly affected, whereas others (e.g., prefrontal cortex) are more severely affected in schizophrenia.¹⁷

It will be important to determine how the different diagnostic validators are related to each other. For example, are aetiological validators (e.g., risk allele or environmental risk factor) consistently coupled to brain-based validators (e.g., regional brain volume or cognitive function)? Such associations would greatly enhance our understanding of disease pathways – from genetic and environmental risks via neural mechanisms to the behavioural syndrome.

Schizophrenia spectrum disorders are the result of a categorical diagnostic system. Future research needs to go beyond this nosology. Ultimately, studies of the neurobiology of schizophrenia spectrum disorders have to focus on the prediction of risk and the development of new treatments. The identification of shared mechanisms of disease can provide biological markers for improved diagnosis. With such markers in hand, we can develop the ideal strategy for the prevention and early treatment of schizophrenia spectrum disorders: screening for subjects

who are at increased risk, early identification of subjects who will progress to psychosis and selection of the appropriate intervention. The intervention and treatment will take into consideration the specific disease mechanism identified for the individual person. This will replace our academic debate about nosology and classification systems with real improvement of mental healthcare.

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