

Schizophrenia and Autism—Related Disorders

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The clinical connections between schizophrenia (SCZ) and autism spectrum disorder (ASD) have long been recognized. More than a century ago, Bleuler ascribed 4 primary symptoms to the group of disorders he termed “schizophrenia”: autism (turning inward to oneself), ambivalence, affective disturbance, and loosening of associations.¹ In 1933, Potter described childhood SCZ as including: (1) loss of interest in the environment; (2) dereistic thinking; (3) thought disturbance; (4) difficulties with emotional rapport; (5) decreased or distorted affect; and (6) behavioral alterations, such as markedly increased or decreased activity, perseveration, or stereotypies.^{2,3} A decade later, when Leo Kanner published his seminal case series, “Autistic disturbances of affective contact,”⁴ the 11 youth he described were thought by many to be suffering from infantile psychosis. Presenting with social detachment, absence of communicative language, behavioral rigidity, and an interest in objects over people, these children shared many of the symptoms outlined by Potter—an apparent lack of interest in the environment, difficulties with emotional rapport, decreased affect and abnormal behaviors, including perseverations and stereotypies. However, Kanner’s cohort differed in one notable way—all had symptom onset within the first 2 years of life.⁵ This difference in illness onset and course ultimately proved to be the key factor supporting the differentiation of ASD from childhood SCZ, a conceptual shift that occurred gradually over a period of several decades. The demarcation was clarified in the 1980 publication of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM III), which noted that the lack of psychotic symptoms and prominence of social deficits clearly distinguished ASD from SCZ.⁶ Thus, ASD moved out from under the umbrella of psychotic disorders and began to be considered as a separate entity.

Although DSM-5 maintains nosologic separation of ASD and SCZ, comparison of the diagnostic criteria for the 2 disorders shows that they have marked similarities in clinical presentation. ASD is defined by 2 major criteria: (1) persistent deficits in social communication, social interactions, social-emotional reciprocity, and communicative behaviors and (2) restricted, repetitive patterns of behavior, interests or activities, which include

stereotyped or repetitive movements, behavioral rigidity, odd or intense interests, and abnormally high or low reactivity to sensory stimuli.⁷ The DSM-5 diagnostic criteria for SCZ require at least 2 of the following symptoms be present: hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and/or negative symptoms.⁷ Although hallucinations, delusions, and thought (speech) disorder are essential features of SCZ (and are not present in ASD), the negative symptoms are often more impairing, pervasive, and treatment resistant.⁸ These negative symptoms, which include asociality, alogia, and low levels of emotional expression (also an indicator of impaired nonverbal communication) can be construed more broadly as deficits in social communication and motivation. Thus, the negative symptoms of SCZ share many features in common with the social deficits of ASD. Similarly, grossly disorganized or abnormal motor behavior as described in SCZ includes a number of signs and symptoms consistent with those of ASD Criterion B, such as repeated stereotyped movements, echolalia, unpredictable agitation, and decreased interaction with or interest in one’s environment.

Given the shared clinical manifestations of SCZ and ASD, it is not surprising that the 2 disorders co-occur frequently. Nearly 30% of youth diagnosed with childhood onset SCZ in a large NIH cohort had co-morbid ASD,⁹ and both epidemiologic and retrospective clinical studies suggest an association between ASD diagnosis or childhood autistic traits and later psychotic experiences.^{10,11} Similar patterns of cognitive deficits have also been noted. For example, studies designed to assess systems for social processes demonstrate that facial recognition and emotion processing are impaired in SCZ¹² as well as in ASD.¹³ Further, both groups have been shown to have deficits in social cueing associated with eye gaze, as well as in performance on theory of mind tasks.^{14–17} Meta-analyses of SCZ reports suggests that deficits are correlated with negative symptoms and disorganization.^{18,19}

Autism and SCZ also appear to share biological underpinnings that may begin very early in neural development. Whole exome sequencing analyses implicate ASD and SCZ risk genes in the development of deep layer cortical projection neurons in the prefrontal and primary motor-somatosensory cortical

(ASD) and dorsolateral and ventrolateral prefrontal cortical (SCZ) regions, respectively.²⁰ A number of neurodevelopmental disorders with known genetic defects are associated with high rates of both ASD and SCZ, including 22q11.2 Deletion Syndrome, Shank3 mutations, and duplications at the Williams Syndrome locus (7q11.23), among others.^{20–22} Epigenetic effects and alterations in copy number variants have been reported to contribute to abnormalities of cerebral cytoarchitecture that have been related to SCZ and ASD.¹¹ In addition, environmental factors, such as advanced paternal age and maternal infection/immune activation during pregnancy, have been reported to increase risk of both ASD and SCZ.^{23,24}

In 1955, Eisenberg and Kanner wrote that early infantile autism was a “total psychobiological disorder,” and suggested that it was “probably related generically” to SCZ.⁵ After more than 5 decades of research and clinical experience, we are beginning to appreciate the veracity of their prediction, and to understand the nature of this relationship. Exploring commonalities between SCZ and ASD, while appreciating salient differences between the 2 disorders, should provide new insights into their etiology, pathophysiology, treatment, and prevention. To forward these efforts, the Schizophrenia Bulletin will provide occasional special features giving emphasis to key similarities and differences between SCZ and ASD and also welcomes high quality reports addressing these issues.

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