Chapter

Clinical and Biological Overlap between Schizophrenia, Autism Spectrum Disorder, and Trauma and Stress-Related Disorders: The Three-Tree Model of SCZ-ASD-TSRD

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Abstract

There is significant overlap in the clinical and neurobiological profiles of schizophrenia (SCZ), autism spectrum disorder (ASD), and trauma- and stress-related disorders (TSRDs); moreover, they often co-occur as comorbid disorders. Although current international classification criteria and those in the psychiatry/psychology field recognize such comorbidities, the assessment and treatment of these patients are provided as independent disorders. In this chapter, we summarize the current understanding of the attributes shared by the three disorders and discuss the possible contributors to the development of SCZ, ASD, and TSRD, which include environmental, genetic, and biological factors. We also propose a three-tree model that represents the clinical and biological relationships among the three diseases as a new perspective for assessing and treating these disorders. A comprehensive understanding of these disorders will enable improvements in medical care for patients with these illnesses.

Keywords: schizophrenia, autism spectrum disorder, trauma- and stress-related disorders, adverse childhood experiences, psychiatric disorder

1. Introduction

Schizophrenia (SCZ) is a severe chronic neuropsychiatric disorder characterized by a mixture of positive and negative symptoms. Positive symptoms reflect cognitive excesses or errors (e.g. delusions, hallucinations, and disorganized behaviors), whereas negative symptoms reflect a decrease or absence of normal behaviors (e.g. avoidance, loss of pleasure, and asociality) and expressions (e.g. insensitive emotions and alogia) that depend on motivation and interest [1]. Patients with SCZ are usually

treated with antipsychotic medications; however, approximately 30% of cases are unresponsive to drug treatment and are referred to as having treatment-resistant SCZ (TRS) [2]. Owing to these distinctive clinical aspects of the chronic and severe disease course, SCZ is considered a global burden [3].

Several psychiatric disorders present with similar clinical symptoms to those of SCZ, and the differentiation and comorbidity of these disorders with SCZ is a common clinical problem. Autism spectrum disorder (ASD) is a neurodevelopmental disorder, and core symptoms include impairments in social interactions and communication and the presence of restricted and repetitive behaviors [4]. Notably, it has recently become widely recognized in clinical practice that some of the symptoms of SCZ (especially negative symptoms) and ASD share similarities [4]. Trauma- and stress-related disorders (TSRDs) are a group of emotional and behavioral problems that result from childhood trauma and stress experiences, which have also received attention as disorders that exhibit symptoms similar to those of SCZ, especially the positive symptoms of SCZ [5]. Traumatic and stressful experiences that cause TSRD include exposure to physical and emotional violence and distress, such as abuse and neglect.

It is well established that SCZ, ASD, and TSRD often co-occur as comorbid disorders. Such comorbidities are recognized in international classification criteria for psychiatric disorders, such as the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) and the International Classification of Diseases, 11th Revision (ICD-11) [6, 7]; moreover, the comorbidity of these disorders is widely recognized by professionals in the clinical psychiatry field (e.g. psychiatrists and clinical psychologists). However, the assessment and treatment of patients with these disorders are independent of each other, and the importance of comprehensively understanding and assessing these disorders is not widely recognized. The purpose of this chapter is to summarize recent research findings on the clinical, epidemiological, and biological correlates of SCZ, ASD, and TSRD and provide new perspectives on providing better medical care for patients with SCZ.

2. History of the debate on the relationship between SCZ, ASD, and childhood living environment

The term SCZ was first coined by Eugen Bleuler in 1908 and stems from the Greek words "schizo" (split) and "phren" (mind) [8]. Bleuler categorized the clinical symptoms of SCZ into basic, primary, and secondary symptoms. The basic symptoms are known as the famous Bleuler's four As: alogia, autism, ambivalence, and affect blunting [9]. Schneider's 1939 proposal of "first-rank symptoms" (FRSs) was incorporated into the SCZ section of the DSM-III and has greatly influenced the diagnostic approaches for SCZ for several decades [10].

In 1943, Leo Kanner reported detailed observations on 11 cases of children with "autistic disturbances of emotional contact" [11], who were described as having "infantile autism," based on the symptoms of "autism" that Bleuler had previously described as typical symptoms of adult patients with SCZ. Kanner also described "autism" as independent of SCZ and explained that autism is not a precursor to SCZ and that autism symptoms are evident immediately after birth or in early childhood [10]. However, during this time, "infancy autism" was generally considered the earliest form of childhood SCZ; that is, a subtype of SCZ. In the late 1960s, Rutter introduced the notion that infancy autism is a developmental disorder rather than

SCZ by questioning the view that infancy autism and SCZ are the same disorder given their differences, such as the age of onset [12, 13]. Wing defined impairments in interpersonal interactions as impairments in interpersonal cognition, interpersonal communication, and interpersonal imagination and understanding, and referred to these symptoms as a continuum of autistic traits [14]. Wing broadened Kanner and Rutter's concepts of autism to include a wider range of symptoms [15], which subsequently became the basis for the current definition of ASD and, in turn, contributed to the development of a more comprehensive disease concept of neurodevelopmental disorders. Therefore, since the disease concept was established, it was assumed that ASD symptoms would overlap with those of SCZ.

The association between SCZ and ASD and an inappropriate nurturing environment was discussed during the early stage of establishing the disease concepts of ASD and SCZ. As early as 1943, Leo Kanner reported that mothers of autistic children lacked warmth and affection [11]. This theory that parenting attitudes lead to the development of ASD and SCZ in children is known as the "refrigerator mother" theory and was aggressively adopted by the medical community around 1950 as a label for parents of children diagnosed with autism and SCZ. However, this theory was largely refuted in the mid-1960s, and most medical professionals no longer accept this theory today. Nevertheless, extensive research on the relationship between child maltreatment (including all types of abuse and neglect of children by parents, caregivers, or other persons in custodial roles) and ASD/SCZ is ongoing, and various new findings have renewed the outdated and prejudiced "refrigerator mother" theory.

3. Clinical overlap between ASD and SCZ

Recent reports have indicated that a family history of psychiatric disorders, including SCZ, is not uncommon in families with ASD patients. In fact, 63% of ASD patients have a family history of some form of psychiatric disorder; moreover, a family history of SCZ is associated with a 2.1-fold increase in the odds ratio (ORs) for a child developing ASD [16]. Parental SCZ has been shown to be associated with an increased risk of ASD in Swedish nationals (OR = 2.9, 95% confidence interval [CI] = 2.5–3.4) and Stockholm County cohorts (OR = 2.9, 95% CI = 2.0–4.1). Similarly, an increased risk of ASD has been reported in Swedish nationals (OR = 2.6, 95% CI = 2.0–3.2) and Israeli conscript cohorts (OR = 12.1, 95% CI = 4.5–32) who have a peer with ASD [17]. It is estimated that up to 34.8% of ASD patients will be diagnosed with a psychiatric disorder in their lifetime and between 3.6% and 60% will develop SCZ [18]. Patients with ASD show deficits in social-emotional reciprocity and engagement, which include lack of emotional empathy, lack of social activity, lack of nonverbal communication, and reduced spontaneous communication and conversation [19], and clinically distinguishing between these behavioral characteristics of ASD and the negative symptoms of SCZ (which may include impairments in social communication and social and emotional interactions) is often difficult; indeed, in some cases, there is a comorbidity of the two disorders [20]. Furthermore, some patients with ASD have additional symptoms that are suggestive of comorbid psychotic disorders [21]. For example, ASD patients often present with symptoms related to language abnormalities, such as echolalia and abnormal intonation, atypical social behaviors (e.g. exaggerated gestures and facial expressions), inappropriate sociability, sensory sensitivity, repetitive hand and body movements, adherence to routinized behaviors, and stereotyped and repetitive behaviors (e.g. restricted interests), and

adherence to identity [19], and differentiating between these characteristic behaviors of ASD patients and positive symptoms in SCZ is often challenging [21].

4. Clinical overlap between SCZ and TSRD

Adverse traumatic experiences, such as discrimination, social-environmental adversity, bullying, migration, and childhood trauma, can all be risk factors for mental illness, and the development of SCZ is no exception [22]. In a meta-analysis of studies published between 1806 and March 1, 2013, childhood trauma experiences were found to contribute to the development of SCZ with ORs ranging from 2.01 to 4.15 [23]. Another meta-analysis of studies published between July 2016 and July 2021 similarly found that childhood adversity experiences played a role in the development of SCZ [8]. In contrast, a systematic review published in 2012 on SCZ and adverse traumatic experiences showed that patients with psychosis were 2.72 times more likely than controls to be exposed to childhood adversity [24]. Whether childhood adversity experiences lead to the development of psychiatric disorders has been shown to be influenced by the timing and type of trauma. The probability of developing SCZ was high for those who had been exposed to several types of childhood adversity: sexual abuse (OR = 2.38, 95% CI = 1.98–2.87), physical abuse (OR = 2.95, 95% CI = 2.25–3.88), and psychological abuse (OR = 3.40, 95% CI = 2.06–5.62) [24]. There were also significant differences between all types of childhood adversity and psychiatric disorders, except parental death [24]. A review that assessed self-reported childhood experiences of SCZ patients indicated that 26% had been sexually abused, 39% had been physically abused, and 34% had been psychologically abused [25]. Additionally, it has been reported that even a single experience of sexual abuse specifically increases the probability of developing and severity of SCZ [26, 27].

Childhood trauma experiences are also associated with the degree of symptoms, with higher levels of trauma being associated with more positive symptoms, depressive symptoms, and lower levels of cognitive functioning. Childhood trauma experiences are associated more with positive symptoms, such as hallucinations and delusions, than with negative symptoms [5]. Childhood trauma induces dissociation, where stronger childhood trauma experiences are reflected by higher scores on the Dissociative Experiences Scale (DES), which measures dissociation. Positive symptoms have also been shown to correlate positively with DES scores in SCZ patients [28]. Indeed, some researchers have proposed the idea that symptoms such as hallucinations and delusions reflect a personal perception of intrusion that leads to a sense of hopelessness [5]. Furthermore, it is worth noting that the direction of Schneider's first-class symptoms, which were historically considered important symptoms of SCZ, are more common in patients with dissociative identity disorder than in those with SCZ [29]. These reports provide a valuable perspective on the importance of differentiating dissociative symptoms from the positive symptoms of SCZ. It is also of clinical importance to note that patients with both psychotic disorders and a history of childhood maltreatment have higher rates of hospitalization because of symptoms, more persistent and earlier onset of psychosis, more severe episodes, higher rates of treatment failure, and a higher risk of suicide and substance abuse [30].

As described earlier, there is accumulating evidence of a close relationship between TRS and SCZ at both diagnostic and symptomatic levels. Therefore, the importance of assessment and treatment approaches for psychotic patients who consider the presence of adverse traumatic experiences should be emphasized.

5. Clinical overlap between ASD and TSRD

Empirical research on the effects of adverse trauma in ASD patients is surprisingly limited. Mandell et al. found that out of 156 children with ASD, 18.5% had been physically abused, 16.6% had been sexually abused, and physically and sexually abused children were more likely than non-abused children to engage in sexual and abusive behaviors [31]. It was also reported in a sample of children and adolescents with ASD that 26% had a history of trauma [32]. Furthermore, a significant proportion of children with a history of institutional rearing or severe neglect exhibit autism-like patterns (quasi-autism), and a quarter of these quasi-autistic children show core features of autism that improve by the age of 11 years [33].

Therefore, in light of these reports, those performing medical assessments of children with ASD-like behavioral characteristics should consider that individuals who are not biologically vulnerable because of abuse or neglect may also exhibit autism-like symptoms and characteristics.

6. Biological mechanisms common to SCZ, ASD, and TSRD: genetic and other biological factors

In recent years, the relationship and overlap between functional psychiatric disorders (e.g. SCZ and bipolar disorder) and neurodevelopmental disorders have been reported; moreover, the idea that these disorders are a series of spectrums caused by genetic and environmental factors has been discussed [34, 35]. Recent genomic analyses support the biological association between functional psychiatric disorders and neurodevelopmental disorders, and the same genetic variant is often reported to be a risk factor for various psychiatric and neurodevelopmental disorders. Recurrent microdeletions and microduplications in a 600-kb genomic region of chromosome 16p11.2 have been implicated in childhood-onset developmental disorders, and a meta-analysis of multiple psychiatric datasets identified a significant association between 16p11.2 duplication and SCZ, bipolar disorder, and ASD [36]. The Cross-Disorder Group of the Psychiatric Genomics Consortium performed a meta-analysis of genome-wide association studies (GWASs) of five psychiatric disorders (ASD, attention-deficit hyperactivity disorder [ADHD], bipolar disorder, major depression, and SCZ) to identify specific disease-related variants common to these disorders. In the primary analysis, they found that single-nucleotide polymorphisms (SNPs) at four loci surpassed the cutoff for genome-wide significance ($p < 5 \times 10^{-8}$): regions on chromosomes 3p21 and 10q24 and SNPs within two L-type voltage-gated calcium channel subunits, CACNA1C and CACNB2 [37]. Another GWAS meta-analysis of SCZ, bipolar disorder, ASD, ADHD, and depression also reported significant enrichment of overlapping genes among different disorders [38]. The polygenic risk score (PRS) for common variants can be used to determine shared genetic risk among different disorders. The PRS in GWAS for multiple psychiatric disorders reports a strong correlation between SCZ and bipolar disorder and a weak yet significant correlation between SCZ and ASD [39].

In summary, reports suggesting a genetic link between functional psychiatric disorders, including SCZ, and neurodevelopmental disorders, including ASD, have been increasing annually. In recent years, SCZ has been considered a developmental risk factor model that encompasses both biological and social risk factors, rather than a simple neurodevelopmental disorder [40]. Interestingly, it has been reported that the

molecular genetic risk state for SCZ shows an additive interaction with exposure to certain environmental factors (e.g. regular cannabis use or childhood adversity) [41]. Thus, it has been suggested that not only genetic factors but also numerous environmental factors increase the risk of developing SCZ. How does a traumatic experience affect the brain and lead to the development of SCZ?

When the body is stressed, the hypothalamus-pituitary-adrenal (HPA) axis responds, and child abuse survivors have been shown to possess an overreactive HPA system [42]. Functional changes in the HPA axis may alter many neurobiological elements, such as neurotransmitter function (e.g. dopamine), physiological responses via the autonomic nervous system, and structural and functional neural changes, all of which may increase vulnerability to the development of psychosis [43]. In addition, recent research on the association between childhood trauma and psychotic symptoms suggests immune system dysregulation as a biological mediator. A meta-analysis of recent traumatic experiences and immune system biomarkers revealed that individuals exposed to childhood trauma have significantly higher baseline peripheral blood C-reactive protein, interleukin (IL)-6, and tumor necrosis factor (TNF)-α. Furthermore, a subgroup analysis of patients who had been exposed to specific types of trauma (i.e. sexual, physical, and emotional abuse) showed that each type impacted single inflammatory markers differently. Notably, these results indicated that childhood trauma contributes to inflammatory conditions in adulthood and that the inflammatory profile is dependent on the type of trauma [44]. It has also been reported that only SCZ patients who had experienced childhood trauma had elevated levels of TNF-α and IL-6, whereas those who had not experienced trauma had cytokine levels similar to those of controls [45]. Additionally, all patients with first-episode SCZ had higher cytokine levels than controls. However, patients who have experienced childhood trauma have also been shown to have higher serum TNF-α levels than those who have not [46]. There have also been reports of increased messenger RNA expression of cytokine genes in the lymphocytes of SCZ patients [47], which may be due to epigenetic mechanisms that underlie the relationship between SCZ and childhood stress [48, 49]. Although very few studies have directly analyzed this association between childhood stress and epigenetic changes and schizophrenia at this time, epigenetic abnormalities in specific genetic loci, such as abnormal methylation of the glucocorticoid receptor 1 (GR-1) gene and long interspersed nucleotide element-1 (LINE-1), have been reported [50, 51].

7. Discussion

This chapter provided an overview of the comorbidities and clinical similarities between SCZ, ASD, and TSRD, as well as recent genetic and biological studies. Currently, SCZ, ASD, and TSRD are defined independently on the basis of their core concepts and symptoms in diagnostic and classification systems for mental disorders, such as the ICD-11 and DSM-5. However, recent studies have suggested that their clinical manifestations are similar and share several aspects in the context of their pathogeneses, as if they were three adjacent trees (**Figure 1**). Given these common clinical and biological aspects shared by these three disorders, the question of how psychiatric professionals should comprehend and assess these disorders remains.

To address this question, the issues around comorbidity among the disorders must be organized. The term "comorbidity" is typically used to describe conditions that simultaneously meet the multiple definitions of mental illness. Comorbidity

is conventionally used to signify "coexisting" or "cooccurring" illnesses. However, some have argued that the definition of "comorbidity" is still immature [52]. Meghani et al. organized the concept of "comorbidity" as follows: 1) concurrent

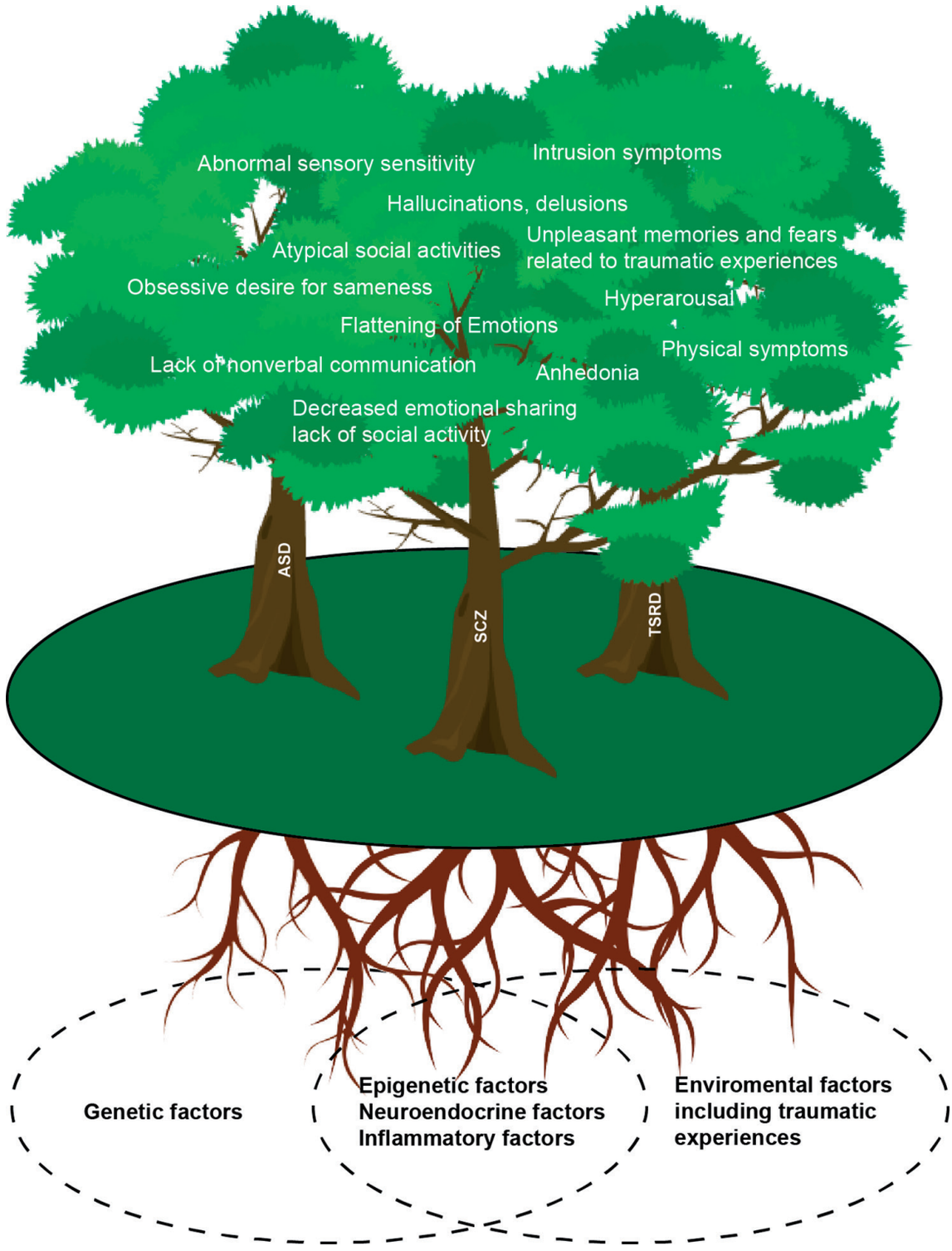

Figure 1.
The three-tree model of SCZ-ASD-TSRD. This figure represents the clinical and biological relationships among the three diseases discussed in this chapter (SCZ, ASD, and TSRD) as three trees. Although the core concepts of each disease (the tree trunk) are independent, the clinically observed symptoms (the tree crown) are shared, and the diseases share common genetic and environmental factors (including adverse traumatic experiences) that contribute to the development of the diseases. SCZ: schizophrenia, ASD: autism spectrum disorder, TSRD: trauma- and stress-related disorders.

(no "known" relationship); 2) antecedent-consequent or complicating morbidity; 3) reciprocal morbidity; 4) principal/causal morbidity (major underlying mechanism responsible for multiple diseases); and 5) latent-manifest morbidity (assumed consequent disease may have been developing slowly below the threshold level for clinical diagnosis). Of these, 1) is defined as "coexisting diseases" or "multimorbidity," and the others are defined as "cooccurring/co-dependent diseases" or "comorbidity" [52, 53]. As discussed in this chapter, there is accumulating evidence for comorbidity at both diagnostic and symptomatic levels for the three diseases; however, there remains a lack of studies that directly and empirically examine the causal relationships or mechanisms of interaction among the three diseases. Therefore, further empirical studies on the comorbidity of these diseases are essential.

In addition, recent genetic and biological analyses have provided extensive evidence for a common biological background for these diseases. This suggests that SCZ, ASD, and TSRD are not biologically independent, despite each having been given a clinically independent diagnostic category. The National Institute of Mental Health has proposed the Research Domain Criteria (RDoC) initiative to conceptualize symptoms within and across different disorders [54, 55] aimed at introducing a novel classification system that incorporates the interrelationship between the clinical phenotype of psychopathology and its underlying biological pathophysiology by dimensionally assessing and matching symptoms to several biological hierarchies, such as genetic, molecular, cellular, and neural circuitries [54, 55]. The RDoC is unique in that it explicitly focuses on the complex overlapping multidimensionality of psychiatric disorders, which allows research to be conducted without the need to consider comorbidities among disorders. In the future, research generated by the RDoC project will enable better characterization of the multidimensionality of SCZ, ASD, and TSRD and provide a basis for comprehensively understanding the three disorders.

In addition, it is worth emphasizing the utility of understanding and evaluating these three diseases comprehensively rather than as separate diseases, from the perspective of both basic and biological research, as well as clinically. For example, higher levels of dissociation have been reported in patients with TRS than in patients who are more sensitive to pharmacotherapy [56]. Furthermore, the degree of social cognitive dysfunction and autistic features in TRS patients may be similar to that in ASD patients; indeed, similarities between TRS and ASD have been reported [57]. Thus, a comprehensive assessment of ASD symptoms and traumatic experiences for patients with TRS may assist in the treatment of TRS patients. Specifically, it may be useful to assess ASD tendencies in TRS patients using standardized scales (e.g. the Autism Diagnostic Interview-Revised [ADI-R] or Autism Diagnostic Observation Schedule Second Edition [ADOS-2]) [58, 59] and traumatic experiences using structured interview (e.g. Clinician-Administered PTSD Scale for DSM-5 [CAPS-5]) [60]. In cases in whom ASD is determined to be a comorbid illness, therapeutic interventions similar to those for ASD may be effective, such as environmental adjustments that take into account communication style, lifestyle, sensory oversensitivity, under-registration, avoidance, immersion, applied behavior analysis (ABA)-based behavioral therapy, operant conditioning based on learning theory, Treatment and Education of Autistic and related Communication-handicapped Children (TEACCH), and other treatment strategies [61, 62]. Similarly, treatment strategies for TRS with comorbid TSRD may include trauma-informed care and cognitive behavioral therapy targeting the traumatic experience, which is similar to treatments for TSRD [63–65].

8. Conclusion

This chapter provided an overview of recent research findings on the clinical and biological overlap of SCZ, ASD, and TSRD. Comprehensive understanding and assessment of these disorders will not only prevent the inability to "see the forest for the trees" and provide better assessment for patients but also offer opportunities for physicians and researchers in this field to deepen their understanding of these disorders.

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Conflict of interest

The authors declare no conflict of interest.

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