

Autism Spectrum Disorder and Schizophrenia: Do They Overlap?

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ABSTRACT: *Starting from Kanner's description of autism, suggesting a similarity with schizophrenia, the question of comorbid association or phenotypic variations between autism and schizophrenia has been raised many times. These disorders are currently conceptualized as distinct illnesses. However, in the last years, the possible overlap between the two disorders has been investigated under several aspects: environmental risks factors, alterations in neural development, genetics, neural anatomy, neurocognitive and social cognitive impairment. Several studies underline the possibility that autism spectrum disorder and schizophrenia share at least some pathogenetic mechanisms and that similar alterations in brain developmental pathways might underline part of the phenotypic spectrum of these disorders. This review briefly summarizes the commonalities and overlapping features between autism spectrum disorder and schizophrenia. Exploring the commonalities between autism spectrum disorder and schizophrenia could provide new insight to better understand the etiology, pathophysiology, treatment, and prevention of these disorders.*

Key words: *Autism spectrum disorder, Schizophrenia, Neurodevelopmental disorders, Comorbidity, Diagnosis*

INTRODUCTION

Schizophrenia and autism spectrum disorder (ASD) are currently conceptualized as distinct disorders. In the current DSM-5 (APA, 2013) criteria, schizophrenia is defined as a neuropsychiatric disorder that begins at a predictable stage of development, i.e., late adolescence and early adulthood and is characterized by delusions, hallucinations, disorganized speech and behaviour and other symptoms that cause social or occupational dysfunctions. On the other hand, ASD is included in the neurodevelopmental disorders and is characterized by a spectrum of abnormal behaviours that include: persistent deficits in social communication and interaction across multiple contexts and restricted and repetitive patterns of behaviours, interests or activities. Etiologically, both disorders seem to involve a genetic predisposition that may be triggered by environmental factors (van Loo & Martens, 2007). However, the relationship between these two heterogeneous disorders has been revisited in recent years due to repeated observations that they share phenotypic and genotypic expression, putting into question the nature and extent of their commonalities (Chisholm, Lin, Abu-Akel & Wood, 2015).

Historical and Nosographic Background

To depict the historical background of the distinction between the two syndromes, it is necessary to go back to 1943, when Kanner described for the first time autism, characterized by emotional disturbances resulting from early attachment experiences, and considered it nosologically related to schizophrenia (Kanner, 1943). In the 60's and 70's researchers on autism led to a clearer definition of the framework with respect to other psychiatric disorders and particularly schizophrenia, showing that the two disorders are different in terms of age of onset, family history, clinical manifestations and outcome (Starling & Dosssetor, 2009). Looking at the classification of autism in the Diagnostic and Statistical Manual of Mental Disorders (DSM), it appears that in the first edition (DSM-I;

APA, 1952) the diagnosis of autism did not exist and children with autistic symptoms were classified with a diagnosis of "schizophrenic reaction, childhood type". Even in the DSM-II (APA, 1968), autism was not included as a separate diagnostic category: children who showed autistic, atypical and introverted behaviours, were diagnosed as affected by "schizophrenia, childhood type". As a result of clinical, familiar and follow-up trials, in the DSM-III (APA, 1980) autism was classified as a separate diagnostic category. Initially the diagnosis concerned "infantile autism", but then, in the DSM-III-R (APA, 1987), it was changed into "autistic disorder". Then, the DSM-III-R, the DSM-IV (APA, 1994) and the DSM-IV-TR (APA, 2000) introduced the category of "pervasive developmental disorders" and its different subtypes. This trend was then adopted also by the ICD-10 (International Classification of Diseases - Tenth Revision, WHO, 1992), in the chapter "Global changes of psychological development." In the transition between DSM-IV-TR and DSM-5, however, there has been an important changing of the concept of autism (Volkmar & McPartland, 2014). While the DSM-IV outlines a categorical model, the DSM-5 refers to autism as a spectrum ("autism spectrum disorder"), with changes in the everyday functioning involving minor or major levels of assistance. Finally, the DSM-5 renames the autistic disorder as "autism spectrum disorder" and puts it among the "neurodevelopmental disorders".

The three fundamental aspects of the DSM IV-TR for the diagnosis of "autistic disorder", i.e., qualitative impairment of social interaction, qualitative impairment in communication, patterns of behaviour, restricted, repetitive and stereotyped interests and activities, in the DSM-5 are grouped in two: persistent deficit in communication and social interaction in different contexts, not justified by a global developmental delay; and repetitive behaviours and restricted interests and abnormal response to sensory stimuli. Moreover, in the DSM-5 the symptoms do not necessarily have to be present in early childhood, but they can show up even later, in circumstances where the social needs and demands exceed the limited capacities of the subject (Volkmar a& McPartland, 2014).

The ASD, initially considered a form of psychotic disorder of

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childhood, was thus subsequently differentiated from psychosis and it has acquired a nosographic autonomy in the context of the so-called "neurodevelopmental disorders". However, even if the diagnostic boundaries between autism and schizophrenia seem to have become more pronounced over the years, the conception of two clearly separated disorders has been challenged by the idea and evidence that there are a spectrum of autistic disorders and a spectrum of schizophrenic disorders, with possible areas of continuity and overlap (King & Lord, 2011; Unenge Hallerback, Lugnegård & Gillberg, 2012). In particular, an increasing number of genetic and brain imaging studies has strengthened the hypothesis that there may be a connection between the two spectra, not only at a clinical level, but also at a pathophysiological and etiopathogenetic level (de Lacy & King, 2013; Wilson et al., 2014).

ASD and Schizophrenia: Overlapping Areas

Schizophrenia and ASD are both considered neurodevelopmental disorders resulting from atypical neural development due to a variety of causes (Owen, O'Donovan, Thapar & Craddock, 2011). Starting from Kanner's description of autism, suggesting a similarity with schizophrenia, the question of comorbid association or phenotypic variations between autism and schizophrenia has been raised many times. Recent research has called into question the dichotomic separation of these two diseases (King & Lord, 2011) and several studies have highlighted the overlap of autistic and schizophrenic symptoms in different clinical populations (Skokauskas & Gallagher, 2010). Below we will show a brief review of the main interconnections between autism and schizophrenia.

Environmental Risk Factors

The possible overlap between the two disorders has been investigated under several aspects, starting from environmental risk factors: an advanced paternal age, some early fetal injury indicators, such as prenatal viral infections, or immune activation during pregnancy have been associated with both diseases (Hamlyn, Duhig, McGrath & Scott, 2013; Hommer & Swedo, 2015; Winter et al., 2008).

Genetic Risk Factors

Genetic studies have shown numerous direct and indirect links between ASD and schizophrenia (Wang, Jeffries & Wang, 2015). ASD and schizophrenia rates of heritability are both estimated to be high, around 50-80% (Cardno & Gottesman, 2000). Furthermore, recent genetic data, have shown common genetic risk loci associated with both conditions, including a set of copy number variations (CNVs) and specific genes as CNTNAP2 and NRXN1 (Craddock & Owen, 2010). Moreover, epigenetic effects have been reported to contribute to abnormalities of brain cytoarchitecture that have been related to both schizophrenia and ASD (de Lacy & King, 2013).

Neurobiological Features

There are many studies that identify common alterations in neural development as a possible pathophysiological link between the two disorders, and could be the basis of a phenotype characterized by cognitive impairment and negative symptoms, common to both disorders (de Lacy & King, 2013; Waltereit, Banaschewski, Meyer-Lindenberg & Poustka, 2014).

Brain Imaging

Neuroimaging studies are investigating the hypothesis that there is a relationship between the two disorders also at the anatomical substrate level (Baribeau & Anagnostou, 2013). Patients with ASD show abnormal development of brain regions also implicated in schizophrenia, such as striatum and frontal lobe; furthermore, a reduction of gray matter volume in the limbic-striatal-thalamic circuit (right posterior cingulate, right parahippocampal gyrus,

putamen, left insula and thalamus) is present in both disorders (Toal et al., 2009). These shared structural abnormalities might partially explain the clinical and physiopathological overlaps of ADS and schizophrenia (Cheung et al., 2010).

Clinical Features

Many studies focused on the presence of schizophrenia spectrum disorders in patients with ASD (King & Lord, 2011). In particular, negative symptoms and disorganization have been reported both in adults and in adolescents with ASD (Konstantareas & Hewitt, 2001). Follow-up studies show that a significant proportion of children diagnosed as ASD develops schizophrenia spectrum disorders later in life, with a conversion rate of 34.8% (Mouridsen, Rich & Isager, 2008). On the other hand, several studies have focused on the presence of high levels of autistic traits in patients with schizophrenia spectrum disorders (Bender, 1970; Esterberg et al., 2008; Sheitman, Kraus, Bodfish & Carmel, 2004). In the wider available study involving 101 children and adolescents with childhood onset schizophrenia (COS) (younger than 13), a total of 28% of cases of comorbidity with ASD was reported (Rapoport et al., 2009). Thus, it was emphasized that adolescents with childhood history of ASD could show psychotic symptoms in adolescence and adolescents who had childhood or early-onset schizophrenia could express clear and persistent autistic traits. Moreover, it is difficult, based on the DSM-5 criteria, to differentiate ASD from COS that has not yet developed delusions, hallucinations or disorganized speech. Some authors have hypothesized that many cases of ASD and COS are part of the same spectrum disorder. The relationship may be so close that a subset of cases of ASD and schizophrenia spectrum disorders are indistinguishable, especially in childhood cases of schizophrenia, in which delusions, hallucinations or disorganized speech have not yet appeared (Ross, 2014).

Social Cognition

Recent studies have identified the presence of similar deficits of the mirror neuron system in ASD and schizophrenia (King & Lord, 2011). Such dysfunctions seem to be the basis of the deficits of social cognition, of affective-emotional domains, of deficits in empathy, and difficulties in the identification with the others, which characterize both disorders. ASD and schizophrenia are both characterized by impairments in social and non social cognition (Abdi & Sharma, 2004). In this regard, a recent study underlines similarities in social and non social cognitive impairment in adults with ASD or schizophrenia, with particularly marked deficits in speed of processing and emotion recognition (Eack et al., 2013). Other studies have shown that also deficits in Theory of Mind (ToM) are not specific for ASD, but are present also in people with schizophrenia (Bora, Yucel & Pantelis, 2009).

Conclusions and Future Directions

These findings raise the possibility that ASD and schizophrenia share at least some pathogenetic mechanisms and that similar alterations in brain developmental pathways might underline the phenotypic spectrum of these disorders. Exploring the commonalities between ASD and schizophrenia could provide new insights to better understand their etiology, pathophysiology, treatment, and prevention. In this respect, some nuclear symptoms present in both disorders, such as negative symptoms and social withdrawal, cognitive and social cognition deficits, could be a primary target of treatment. It is currently well known that, although antipsychotics have been shown to be effective in reducing positive symptoms, they are not effective on other important clinical features of schizophrenia, such as negative symptoms and cognitive dysfunction, which are associated with functional outcome (Owen, Sawa & Mortensen, 2016), and may be shared with ASD. Several studies have clearly demonstrated the effectiveness of cognitive

remediation in schizophrenia (Cavallaro et al., 2009; Vita et al., 2011; Wykes et al., 2011). Future research should therefore consider the symptomatological areas shared between ASD and schizophrenia as specific targets of treatment and should assess the effectiveness of cognitive remediation also in patients with ASD and evaluate whether it is especially effective on this shared clinical dimension. Starting from this example, the recommendations for future research may be extended to all of the overlapping features. As a matter of fact, the identification of overlapping areas between the two disorders, regarding clinical, pathophysiological and etiopathogenetic aspects, it is crucial in addressing future research: currently, for patients with ASD, followed by children and adolescent's services who are taking cared by adult services, there is indeed a shortage of tools that respond to their needs for care. Identify overlapping areas with other neurodevelopmental disorders, in particular with schizophrenic spectrum disorders, could be a good starting point for further research aimed at developing and evaluating the effectiveness of new procedures and therapeutic tools.

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