THINKING THROUGH THE SCHIZOPHRENIA SPECTRUM: NOSOLOGICAL SCENARIOS AND PERSPECTIVES BEYOND PSYCHOSIS

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THINKING THROUGH THE SCHIZOPHRENIA SPECTRUM: NOSOLOGICAL SCENARIOS AND PERSPECTIVES BEYOND PSYCHOSIS

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EDITORIAL
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Editorial: Thinking Through the Schizophrenia Spectrum: Nosological Scenarios and Perspectives Beyond Psychosis

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Keywords: schizophrenia, psychosis spectrum, nosology, endophenotype, neurodevelopment

Editorial on the Research Topic

Thinking Through the Schizophrenia Spectrum: Nosological Scenarios and Perspectives Beyond Psychosis

The concept of schizophrenia remains a matter of enduring debate, although often limited to the psycho-behavioral surface of its descriptive criteria. This Research Topic integrates such debate providing a set of different state of the art perspectives on the challenges surrounding the schizophrenia concept.

In contemporary research, the notion of a broad psychotic spectrum, within which schizophrenia loses its nosological boundaries and dissolves, has gained once again a certain momentum. Proponents of this view argue that this concept is better supported by genetic, neurobiological, and neurodevelopmental data than the traditional categorically defined diagnoses. Others, however, defend the concept of schizophrenia or schizophrenia spectrum and continue the search for its essence that will allow demarcation of schizophrenia from other forms of psychosis. From yet other points of view, the Research Domain of Criteria (RDoC) and the Hierarchical Taxonomy of Psychopathology (HiTOP) address the general validity crisis of current nosography and explore new possible nosological horizons. This Research Topic aimed at an overview of possible nosological scenarios for schizophrenia and its spectrum disorders.

Consistent with the RDoC approach, Cuthbert and Morris, in their perspective article, argue that genomic data provide increasing support for the concept of systematic, trans-diagnostic components of neurodevelopmental and genomic spectra. In this view, the neurodevelopmental gradient is not simply a matter of cognitive performance, but a result of multiple functional domains, whose combinations comprise potentially significant clinical phenotypes with schizophrenia representing one segment of multiple broader spectra.

From the perspective of HiTOP, Cowan and Mittal, in their brief research report article, present a transdiagnostic dimensional analysis of psychiatric comorbidity in a Clinical High Risk (CHR) sample. They found that, although the CHR group presented more positive symptoms compared to healthy controls, the negative symptom factor was much more strongly linked than the other factors to impaired cognition, impaired social and role functioning, and risk of transition to psychosis This finding suggests that negative symptoms may be more specific of the progression toward psychosis in the broader spectrum of subthreshold positive psychopathology.

In their original research article, Pontillo et al. found that in children and adolescents

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with early and very early onset schizophrenia, the presence or absence of neurodevelopmental disturbances or difficulties differentiated the characteristics of psychotic onset. In fact, in the presence of neurodevelopmental dysfunctions, the onset occurs earlier and was associated with more severe functional impairment, positive and disorganized symptoms. By contrast, in children and adolescents without neurodevelopmental disorders or difficulties, the psychotic onset was later and associated with negative symptoms.

Collectively, these papers explore the relationship between neurodevelopmental disorders and schizophrenia through analysis of psychopathological trajectories and clinical pathways of childhood neuropsychiatric disorders.

Exploring new potential phenotypes and endophenotypes, was another aim of the Research Topic, and it was addressed by Gao et al. In their original research article, patients with schizophrenia showed an association between cognitive dysfunction and increased regional homogeneity values (ReHo), an index of neural activity, in prefrontal regions including the right rectus gyrus, inferior frontal gyrus/insula, the lower right and left insula, interestingly, all in the limbic area. Furthermore, ReHo values in the right inferior frontal gyrus/insula were correlated with negative symptoms and verbal learning tasks. The combined increases of ReHo values in the left inferior frontal gyrus/insula with the right gyrus rectus may be an underlying biomarker differentiating patients with schizophrenia from healthy controls.

Bleuler, who coined the schizophrenia concept, considered formal thought disorders ("disturbances of association"), and ego-disorders as fundamental symptoms of schizophrenia. In contemporary psychopathological research, ego-disorders have been re-conceptualized and systematically assessed under the notion of self-disorders. The novelty of the original research paper by Nordgaard et al. is the finding of a close relationship between formal thought disorders and self-disorders—a finding that further reinforces the notion of self-disorders as a unifying, psychopathological core beneath the apparently heterogeneous symptoms of schizophrenia spectrum disorders.

Consistently, through the novel theoretical approach of shared intentionality, Salice and Henriksen, in their Hypothesis and Theory Article, aimed to differentiate the sources of social difficulties in schizophrenia spectrum disorder and severe autism spectrum disorder. They proposed a distinction between two kinds of shared intentionality—joint- and we-intentionality—and argue that we-intentionality may be affected in schizophrenia, whereas both joint- and we-intentionality are impaired in autism. They argue that the qualitatively distinct social difficulties are linked to the disorders' different psychopathological cores. Trait-like self-disorders may affect the psychological preconditions for we-intentionality, whereas the psychological preconditions for both forms of shared intentionality are impeded by problems with the ability to "be moved" by others' intentions, perspective-taking, and mind-reading in autism.

The complex relationship between formal thought disorders, self-disorders, negative symptoms, and social cognition may be reflected in a specific phenotype, which, in part, concerns dis-sociality and detachment from the common sensical world. This phenotype is reflected in the classical phenomenon of schizophrenic autism, which Bleuler also originally described as a fundamental symptom of schizophrenia. In their original research article, Palumbo et al. proposed a novel scale, viz. the Autism Rating Scale (ARS), to detect and measure the phenomenon of schizophrenic autism. Their article explored the psychometric properties of the ARS and furthermore found that scorings on the ARS differentiated patients with schizophrenia and bipolar disorder.

Finally, in their opinion article, Guloksuz and van Os provocatively restate their belief in the death of schizophrenia concept and in the promise of the wider psychosis spectrum concept. They summarize shortcomings to the schizophrenia concept (e.g., lack of etiological and phenotypic specificity as well as its stigmatizing connotations such as chronicity and deterioration) and highlight the benefits of the psychosis spectrum concept in conjunction with clinical characterization.

Overall, we hope that this Research Topic dedicated to the nosological promise and perils of the Schizophrenia Spectrum concept will contribute to further advancements in the field.

AUTHOR CONTRIBUTIONS

AC, MH, and AR contributed equally to drafting the Editorial and revising it critically. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Enhanced Prefrontal Regional Homogeneity and Its Correlations With Cognitive Dysfunction/ Psychopathology in Patients With First-Diagnosed and Drug-Naive Schizophrenia

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Background: Schizophrenia, regarded as a neurodevelopmental disorder, is characterized by positive symptoms, negative symptoms, and cognitive dysfunction. Investigating the spontaneous brain activity in patients with schizophrenia can help us understand the underlying pathophysiologic mechanism of schizophrenia. However, results concerning abnormal neural activities and their correlations with cognitive dysfunction/psychopathology of patients with schizophrenia were inconsistent.

Methods: We recruited 57 first-diagnosed and drug-naive patients with schizophrenia and 50 matched healthy controls underwent magnetic resonance imaging. The Positive and Negative Syndrome Scale (PANSS) and the MATRICS Consensus Cognitive Battery were used to assess the psychopathology/cognitive dysfunction. Regional homogeneity (ReHo) was used to explore neural activities. Correlation analyses were calculated between abnormal ReHo values and PANSS scores/standardized cognitive scores. Lastly, support vector machine analyses were conducted to evaluate the accuracy of abnormal ReHo values in distinguishing patients with schizophrenia from healthy controls.

Results: Patients with schizophrenia showed cognitive dysfunction, and increased ReHo values in the right gyrus rectus, right inferior frontal gyrus/insula and left inferior frontal gyrus/insula compared with those of healthy controls. The ReHo values in the right inferior frontal gyrus/insula were positively correlated with negative symptom scores and negatively correlated with Hopkins verbal learning test-revised/verbal learning. Our results showed that the combination of increased ReHo values in the left inferior frontal gyrus/insula and right gyrus rectus had 78.5% (84/107) accuracy, 85.96% (49/57) sensitivity, and 70.00% specificity, which were higher than other combinations.

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Conclusions: Hyperactivities were primarily located in the prefrontal regions, and increased ReHo values in the right inferior frontal gyrus/insula might reflect the severity of negative symptoms and verbal learning abilities. The combined increases of ReHo values in these regions might be an underlying biomarker in differentiating patients with schizophrenia from healthy controls.

Keywords: schizophrenia, regional homogeneity (ReHo), cognitive dysfunction, support vector machine analysis, prefrontal

INTRODUCTION

Schizophrenia, a psychiatric syndrome affecting 0.6% of the population in China, is characterized by positive symptoms (hallucination, delusions, and disorganization symptoms), negative symptoms (hypobulia, anhedonia, affective blunting, social withdrawal, and alogia), and cognitive dysfunction (processing speed, attention/vigilance, working memory, etc.) (1, 2), however, its etiology is still unclear, and diagnosis primarily relies on psychopathology. To date, schizophrenia is regarded as a neurodevelopmental disorder, and its symptoms occur spontaneously. Therefore, investigating spontaneous brain activities in patients with schizophrenia can help us understand the potential pathophysiologic mechanism of schizophrenia (3).

Resting-state functional magnetic resonance imaging (MRI), as a non-invasive examination, has been applied to explore the neural activity by recording signals dependent on blood oxygenation levels. Several studies have focused on functional connectivity (FC) analyses and revealed that subjects with a high risk of schizophrenia and first-episode schizophrenia showed a shared aberrant FC in the prefrontal cortex (PFC); those findings have indicated that abnormalities occur before disease onset, and abnormal neural activities in this region may be a trait alteration of schizophrenia (4, 5). In addition, a review has demonstrated that abnormal connections are found in patients with schizophrenia between the PFC and other regions, such as the basal ganglia, temporal regions, parietal regions, hippocampus, and default mode network; dysconnectivity between regions is associated with cognitive dysfunction and psychopathology (6). However, studies on FC have investigated "distinct" brain areas and hardly reflected "local" synchronization (3). In contrast to traditional FC, local FC based on neurodevelopment can be used to measure the functional interactions or synchronization of neighboring voxels. Local FC also affects remote FC and whole brain dynamics, highlighting the importance of exploring local FC (7–10).

Regional homogeneity (ReHo) can be used to measure the similarity or synchronism of the time series within neighboring voxels and reflect the coordination of regional neural activities. Increased and decreased ReHo values represent abnormal neural activities (11). According to previous studies on subjects with a high risk of schizophrenia (12, 13), first-episode adolescent-onset drug-naïve schizophrenia (14, 15), first-episode drug-naïve schizophrenia (16), chronic schizophrenia (17), and treatment-resistant schizophrenia (18), abnormal ReHo may be a good biomarker to distinguish patients with schizophrenia from healthy controls with increased or decreased ReHo values in different regions. However, previous results were inconsistent. Moreover, abnormal neural activities are associated with clinical symptoms and cognitive dysfunction, and ReHo may be used to evaluate the severity of clinical symptoms and cognitive dysfunction. With regard to clinical symptoms, abnormal ReHo values in several brain regions of patients with schizophrenia are positively/negatively/not associated with the Positive and Negative Syndrome Scale (PANSS) total score, positive factor, disorganized/concrete factor, excited factor and depressed factor (14–16, 19). In term of cognitive dysfunction, a study on subjects with a genetically high risk of schizophrenia has demonstrated that delayed recall is negatively associated with decreased ReHo values in the right superior frontal gyrus. Uncoupled relationships in patients with schizophrenia between abnormal ReHo values in several regions and attention impairments are found (20). Fluency scores and stroop color-word test scores are related to abnormal ReHo values (14, 15). These findings have suggested that investigating the spontaneous brain activities and their relationships with cognitive dysfunction/psychopathology in patients with schizophrenia can help us understand the potential pathophysiologic mechanism of schizophrenia.

In our study, we hypothesized that abnormal neural activities could be found regionally in the PFC, and these abnormities could reflect the severity of cognitive dysfunction and psychopathology. We might offer insights into the pathophysiologic mechanism of schizophrenia and develop a biomarker to distinguish patients with schizophrenia from healthy controls. First-diagnosed and drug-naïve patients with schizophrenia were recruited to explore the ReHo values in the whole brain and its correlations with cognitive dysfunction/psychopathology and to eliminate the interference of an antipsychotic drug. Computer-based analysis was conducted to re-evaluate the diagnosis of schizophrenia by using ReHo values. Support vector machine (SVM) analyses, an optimized classification method, is applied to classify and diagnose the disease (21). Therefore, using SVM to calculate the accuracy of abnormal ReHo values could help us distinguish patients with schizophrenia from healthy controls.

METHODS

Subjects

For patients with schizophrenia, 60 right-handed inpatients with schizophrenia were recruited from Affiliated Nanjing Brain Hospital, Nanjing Medical University, from April 2018 to

December 2019. Schizophrenia was co-diagnosed by two chief psychiatrists in accordance with the International Classification of Diseases, 10th Revision (ICD-10: F20) using the MINI-International Neuropsychiatric Interview for ICD-10 diagnoses. The severity of symptoms and cognitive dysfunction were assessed with the PANSS (22) and MATRICS Consensus Cognitive Battery (MCCB) (23, 24), respectively, in the first interview. Moreover, the Annett Hand Preference Questionnaire was utilized to assess right-handedness. Patients were eligible if they met the following inclusion criteria: (1) patients aged at 16–60 years, (2) patients satisfying met the ICD-10 criteria for schizophrenia and PANSS total score of $\geq$60, and (3) first-time diagnosed and drug-naïve (without any psychiatric treatment). Patients were excluded if they satisfied the following exclusion criteria: (1) patients with organic disorders, psychoactive substances, mood disorder, transient psychotic disorder, and intellectual disability; (2) patients who could not perform a MRI scan, and patients with other brain diseases, such as brain tumors, intra-abscesses, and cerebral infarction; (3) patients who used psychiatric medication ever.

For the healthy controls, 52 right-handed healthy controls were recruited from the community via advertisement. The inclusion criteria were as follow: (1) race, sex, age, and matched patient groups; (2) no mental disorders that met the ICD-10 diagnosis using the MINI-International Neuropsychiatric Interview at present or in the past; and (3) negative family history of mental disorders. The exclusion criteria were as follows: (1) history of severe somatic diseases; (2) cannot perform an MRI or other brain diseases (such as cerebral infarction, brain tumors, demyelinating lesions, and brain abscesses); (3) intellectual disability, IQ <70; and (4) history of alcohol and drug abuse.

This study was approved by the local ethics committee of the Affiliated Nanjing Brain Hospital, Nanjing Medical University (2017-KY017). All the participants and their legal guardians were informed about the procedures with written informed consent.

Data Acquisition

The demographic and clinical characteristics of the subjects were collected during the first interview. The raw scores of MCCB were standardized with the MCCB software (2014 The Regents of the University of California and SIStat, Version: 3.9.2) mainly in terms of age, sex, and education (25). All the participants were examined with a 3.0T Siemens MRI scanner (Verio, Siemens Medical System) at Affiliated Nanjing Brain Hospital, Nanjing Medical University. Pre-cautions and a birdcage head coil with foam padding were given to all the participants in case of head movement. The scanning parameters were as follows: repetition time (TR) = 2,000 ms; echo time (TE) = 30 ms; FOV = 220 × 220 mm; flip angle = 90°; matrix size = 64 × 64; slice thickness = 4 mm; Gap = 0.6 mm; layers = 33; and time point = 240.

ReHo Data Processing

Image data were processed using SPM12 (SPM12, Wellcome Department of Imaging Neuro-science, London, UK) and REST (http://resting-fmri.sourceforge.net). Image pre-processing was conducted as follows: (1) except the first 10 time points, (2) slice timing, (3) head motion correction: we excluded the subjects whose maximum displacement of head movement exceeded 2.0 mm in x, y, or z direction or 2° of angular motion and calculated framewise displacement (FD) for each subject and used the mean FD as a covariate in group comparisons, what's more, aggressive head motions (the time points with FD >0.2 mm) were removed to reduce the effect of head motion, (4) spatial normalization, (5) linear trend removing, and bandpass filtering: several sources of spurious variance were then removed from the data using linear regression, including Friston-24 head motion parameters, white matter signal, and cerebrospinal fluid. The data were temporally band-pass filtered (0.01–0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noise.

Regional homogeneity analysis was conducted with the REST software (11). Kendall's coefficient of concordance (KCC) was determined to measure the similarity and consistency of one voxel with those of its nearest neighbors (26 voxels). The KCC map of the whole brain of each participant was calculated. The KCC of each voxel was divided by the average KCC of the whole brain to reduce the individual difference in the whole brain signal. Then, the average KCC of the brain of each participant was obtained, and it corresponded to the average ReHo brain map. Moreover, the averaged ReHo maps were smoothened with a Gaussian kernel of 4 mm full-width at half-maximum to reduce the spatial noise.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for Social Science version 24.0 (SPSS 24.0). Age, education, and cognitive scores were evaluated with two-sample *t*-tests between patients with schizophrenia and healthy controls; sex distributions were examined with a Chi-square test. Voxel-based comparisons of the whole-brain ReHo maps with two-sample *t*-tests involving age, sex, years of education, and FD as covariates were performed with the REST software. The Gaussian random field theory was applied to correct for multiple comparisons at $p < 0.05$ by using the REST software (voxel significance: $p < 0.001$, cluster significance: $p < 0.05$).

The ReHo values of the abnormal brain region were extracted as regions of interest. Furthermore, partial correlation analyses on age, sex, illness duration, time of onset, years of education, and FD as covariates were calculated between abnormal ReHo values and standardized cognitive scores/PANSS scores.

SVM Analyses

The method of SVM was designed to find the optimal line or surface with the largest interval through an appropriate kernel function to measure the data. This method was widely applied to classify and diagnose the disease (21). SVM was conducted to examine the possibility of abnormal ReHo values in brain regions and to distinguish patients with schizophrenia from healthy controls by using the LIBSVM software package (http://www.csie.ntu.edu.tw/~cjlin/libsvm/) (26). Regarded abnormal ReHo values of brain regions as features, we used the grid search

method and Gaussian radial basis function kernels to optimize the parameters, and then the "leave-one-out" cross-validation method was used to calculated the best sensitivity and specificity, finally, permutation test was applied to test the significance of accuracy.

TABLE 1 | Demographic and clinical characteristics of the participants.

Variables		Patients with schizophrenia ($n = 57$)	Healthy controls ($n = 50$)	p
Age (years)		31.63 ± 11.43	28.38 ± 6.87	0.074
Sex (male/female)		20/37	23/27	0.323
Years of education (years)		12.86 ± 3.42	15.64 ± 2.26	<0.05
Illness duration (years)		2.52 ± 2.72		
TMT-A		36.47 ± 12.71	42.90 ± 9.85	<0.05
BACS-SC		35.23 ± 12.89	45.34 ± 9.29	<0.05
HVLT-R		37.67 ± 13.66	44.52 ± 7.51	<0.05
WMS-III SS		32.51 ± 12.32	34.28 ± 11.22	0.441
NAB Mazes		38.84 ± 10.78	45.44 ± 9.91	<0.05
BVMT-R		42.05 ± 11.61	47.16 ± 9.50	<0.05
Fluency		43.72 ± 11.37	48.76 ± 7.95	<0.05
MSCEIT/Managing Emotions		33.14 ± 8.15	35.32 ± 6.49	0.132
CPT-IP		38.19 ± 13.61	45.56 ± 9.69	<0.05
Speed of processing		34.70 ± 12.12	44.28 ± 9.10	<0.05
Attention/Vigilance		38.19 ± 13.61	45.56 ± 9.69	<0.05
Working Memory		32.51 ± 12.32	34.28 ± 11.22	0.441
Verbal Learning		37.67 ± 13.66	44.52 ± 7.51	<0.05
Visual Learning		42.05 ± 11.61	47.16 ± 9.50	<0.05
Reasoning and Problem Solving		38.84 ± 10.78	45.44 ± 9.91	<0.05
Social Cognition		33.14 ± 8.15	35.32 ± 6.49	0.132
Overall Composite		28.47 ± 13.45	37.60 ± 9.19	<0.05
PANSS	Positive	26.39 ± 4.85		
	Negative	20.68 ± 6.89		
	General	44.79 ± 7.41		
	Total	91.84 ± 14.16		

TMT-A, trail making test part A; BACS-SC, brief assessment of cognition in schizophrenia-symbol coding; HVLT-R, Hopkins verbal learning test-revised; WMS-III SS, Wechsler Memory Scale-III Spatial Span; NAB-Mazes, neuropsychological assessment battery-mazes; BVMT-R, brief visuospatial memory test-revised; MSCEIT, Mayer-Salovey- Caruso Emotional Intelligence Test/Managing Emotions; CPT-IP, continuous performance test-identical pair; PANSS, positive and negative syndrome scale.

RESULTS

Demographic and Clinical Characteristics of the Participants

We recruited 60 inpatients and 52 healthy controls, but only 57 inpatients and 50 healthy controls were enrolled because of the excessive head movement of the three patients with schizophrenia and two healthy controls. The characteristics of the participants are described in **Table 1**. No difference in age and sex was found between the two groups. The years of education of healthy controls were longer than those of patients with schizophrenia. With regard to the cognitive scores, no difference was found in Wechsler Memory Scale-III Spatial Span, Mayer-Salovey-Caruso Emotional Intelligence Test/Managing Emotions, Working Memory, and Social Cognition between the two groups. However, other cognitive scores were worse in patients with schizophrenia than in healthy controls.

ReHo Analysis: Differences Between the Patients With Schizophrenia and Healthy Controls

Patients with schizophrenia showed increased ReHo values in the right gyrus rectus, right inferior frontal gyrus/insula, and left inferior frontal gyrus/insula compared with those of the healthy controls, and no decreased ReHo values in the brain region (**Table 2**, **Figure 1**).

Correlation Analysis: Relationship Between the Abnormal ReHo Values and Clinical Characteristics

In patients with schizophrenia, the ReHo values in the right inferior frontal gyrus/insula were significantly and positively correlated with the negative symptom scores ($r = 0.319$, $p = 0.023 < 0.05$). The ReHo values in the right inferior frontal gyrus/insula were negatively correlated with Hopkins verbal learning test-revised (HVLT-R)/verbal learning ($r = -0.342$, $p = 0.014 < 0.05$). No difference was observed after being corrected by multiple comparisons. On the contrary, no relationship was found between ReHo values and cognition scores in healthy controls (**Table 3**).

TABLE 2 | Abnormal ReHo values in the brain region between patients with schizophrenia and healthy controls.

Cluster location	Peak (MNI)			Number of voxels	*T value**
	x	y	z		
Right Gyrus Rectus	24	45	−21	25	3.8188
Right Inferior Frontal Gyrus/Insula	42	30	12	64	3.8489
Left Inferior Frontal Gyrus/Insula	−39	12	12	23	4.1425

**A positive t value represents an increased ReHo values.*
MNI, Montreal Neurological Institute; ReHo, regional homogeneity.

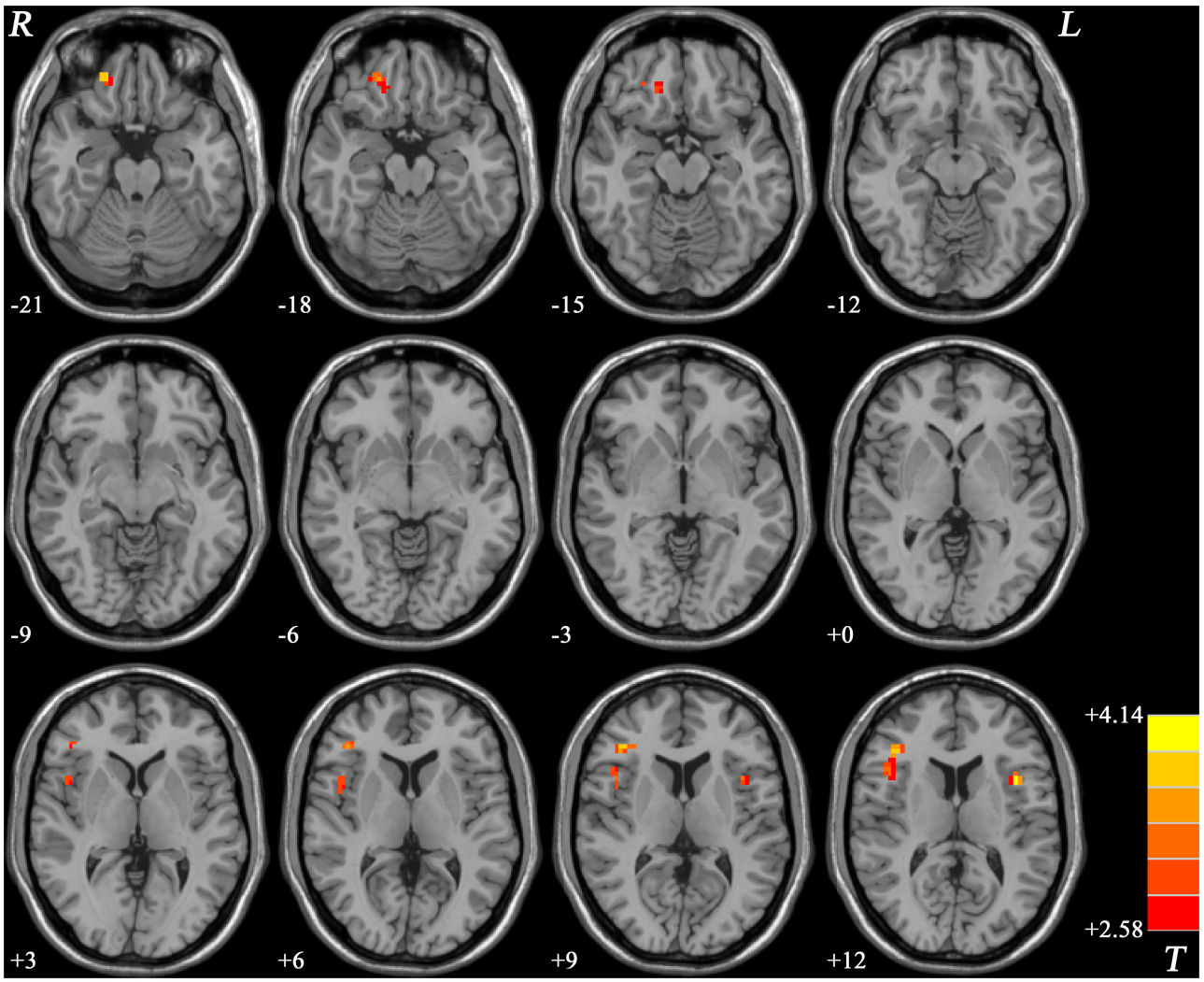

FIGURE 1 | ReHo values difference between patients with schizophrenia and healthy controls. R, right; L, left; ReHo, regional homogeneity.

TABLE 3 | Relationship between abnormal ReHo values and clinical characteristics.

	Right inferior frontal gyrus/insula (schizophrenia)		Right inferior frontal gyrus/insula (healthy controls)	
	p	r	*p*	r
HVLT-R	0.014	−0.342	0.277	0.164
Verbal Learning	0.014	−0.342	0.277	0.164
Negative scores	0.023	0.319	/	/

HVLT-R, Hopkins verbal learning test-revised.

SVM Analyses: Identifying Potential Imaging Biomarkers of Schizophrenia

As shown in **Figures 2**, **3**, SVM was used to explore whether abnormal ReHo values could distinguish patients with schizophrenia from healthy controls with high optimal sensitivity and specificity. The accuracy of each abnormal ReHo value was too low to distinguish patients with schizophrenia from healthy controls. Therefore, each abnormality was coupled, and the accuracy of each combination was calculated (**Figure 2**). Our results indicated that the combination of increased ReHo values in the left inferior frontal gyrus/insula with the right gyrus rectus had 78.5% (84/107) accuracy, 85.96% (49/57) sensitivity, and 70.00% specificity, which were higher than those of other combinations.

DISCUSSION

As shown in our results, the ReHo values in the right gyrus rectus, right inferior frontal gyrus/insula, and left inferior frontal gyrus/insula increased compared with those of the healthy controls, and all these regions existed in the PFC.

However, no decreased ReHo values in the brain regions were found. ReHo could be used to measure the similarity or synchronism of the time series within neighboring voxels and reflect the coordination of regional neural activities. An increased ReHo represented the enhanced neural activity coordination and reflected the abnormal regulation of emotion and behavior. The decreased ReHo indicates uncoordinated movement and disconnection within local neurons in the brain (11). Cognitive dysfunction, including overall composite, speed of processing, attention/vigilance, verbal learning, visual learning, reasoning, and problem solving, was observed in patients with schizophrenia compared with those of the healthy controls. The results indicated that ReHo in the right inferior frontal gyrus/insula was positively correlated with negative symptom scores and negatively correlated with Hopkins verbal learning test-revised/verbal learning, but no difference was found after values were corrected via multiple comparisons. On the contrary, this relationship was not found in the healthy controls.

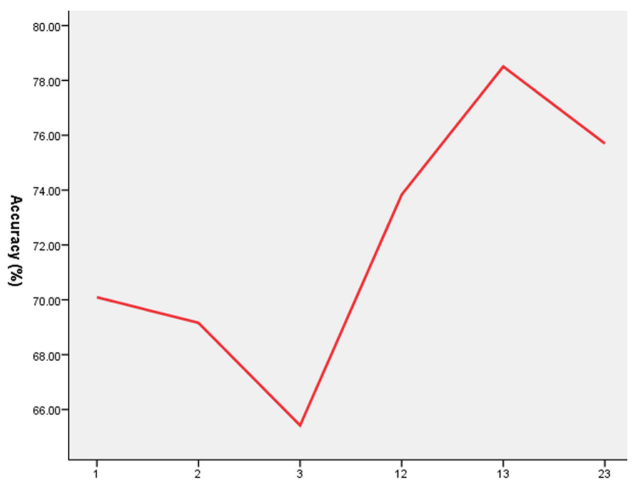

FIGURE 2 | The accuracy of each abnormal ReHo value combination. 1 = Left Inferior Frontal Gyrus/Insula, 2 = Right Inferior Frontal Gyrus/Insula, 3 = Right Gyrus Rectus, ReHo, regional homogeneity.

The prefrontal cortex, which was divided into the dorsolateral PFC (DLPFC), ventrolateral prefrontal cortex (VLPFC), anterior prefrontal cortex, medial prefrontal cortex (MPFC), and orbital PFC (OPFC), plays a crucial role in the cognitive process (particularly in working memory, salience detection, attention, and social cognition) (27) and psychopathology (such as auditory verbal hallucination) (28). A previous review showed an abnormal FC between the PFC and the basal ganglia/temporal regions/parietal regions/hippocampus/default mode network associated with cognition and psychopathology (6). Our results indicated that abnormal ReHo was primarily distributed over the PFC, including the right gyrus rectus (located in OPFC), bilateral inferior frontal gyrus/insula (located in VLPFC), and associated with negative symptom scores in the PANSS and verbal learning ability. Increased ReHo values represented enhanced neural activities coordination in the PFC, supporting that regional abnormalities might affect the remote functional connection and result in cognitive impairment and psychopathology. According to the dopamine hypothesis on schizophrenia, a decrease in dopamine levels in the VLPFC and OPFC is associated with cognitive deficits and negative symptoms (29, 30), which supported our results. Research indicated that ReHo has neurobiological relationship with structural, developmental and neurocognitive (31). In the term of structural MRI, previous studies showed that the gray matter reduction of the PFC is related to prospection impairments in patients with schizophrenia (32). For the functional MRI, increased ReHo values were in the PFC, which is distributed over the DLPFC

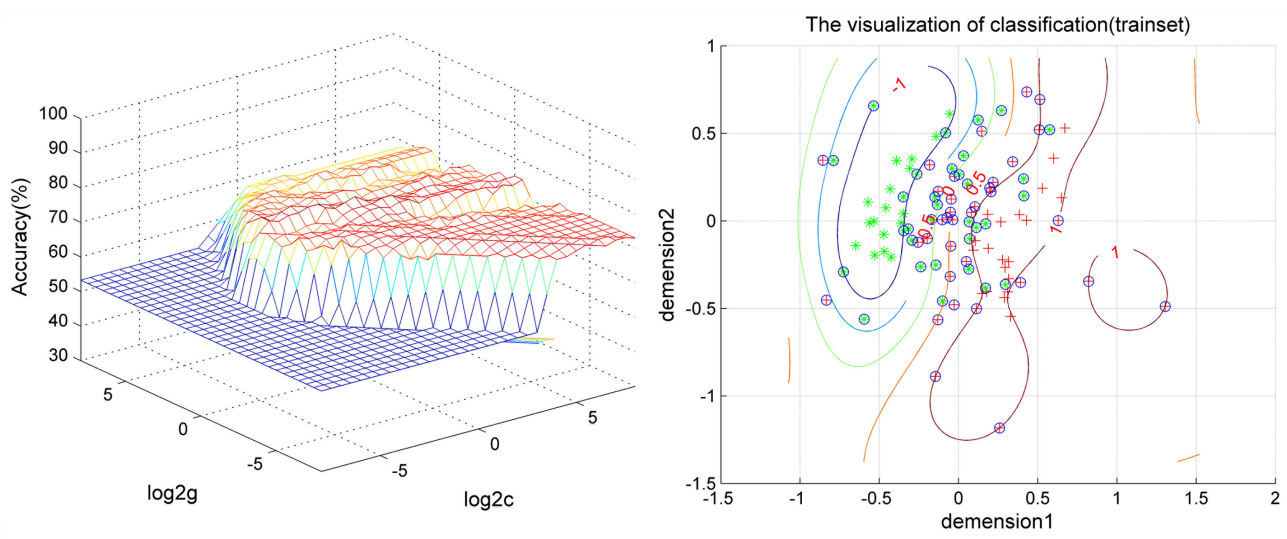

FIGURE 3 | Visualization of the SVM results for distinguishing patients from controls using the combination of ReHo values in the left inferior frontal gyrus/insula and right gyrus rectus. SVM, support vector machine; ReHo, regional homogeneity.

(19, 28), and MPFC (15, 33), but the parts of the PFC are inconsistent with our results, and those differences may be caused by the type of patients with schizophrenia, the size of sample, the condition of medication, the standard of assessment. In addition to cross-sectional studies, one 8-week follow-up study regarding emotional processing showed that the activation of the VLPFC normalizes after olanzapine treatment (34). Consequently, these findings supported our results that abnormal activities existed in the PFC and possessed the relationship with cognition and psychopathology, further suggesting that abnormal activities in PFC may contribute to the pathophysiology and cognitive impairment in schizophrenia.

To our knowledge, the right gyrus rectus is part of the OPFC and involved in the prefrontal association integration. Todd Lencz et al. (35) emphasized that the rs1344706 polymorphism in ZNF804A (a candidate gene of schizophrenia) may alter neuroanatomical (including the gyrus rectus) and neurocognitive phenotypes; besides, a post-mortem brain mRNA study has revealed that somatostatin mRNA+ cell density of the gyrus rectus layer II is lower in patients with schizophrenia than in healthy controls, which may give rise to the reduced gray matter volume (36). Furthermore, the gray matter volume in the right gyrus rectus decreased in the groups of subjects with an ultrahigh risk of psychosis (37) and first-episode schizophrenia (38, 39). In addition, the gray matter volume of the gyrus rectus are negatively related to the positive scale of PANSS (particularly in delusion scores, suspiciousness/persecution scores, conceptual disorganization scores, grandiosity scores, and hostility scores) in patients with schizophrenia (40). Abnormalities in the right gyrus rectus may occur at the early stage with genetic pre-disposition. Moreover, structural abnormalities affected functional activities in this region. In functional MRI, abnormal FC was found between the cingulate gyrus and gyrus rectus in early-onset schizophrenia (41). Meanwhile, our research indicated that the ReHo in the right gyrus rectus of patients with schizophrenia increased compared with that of the healthy controls; therefore, this damaged region might explain the abnormal FC. Although no association with cognition and psychopathology was found, exploring abnormal neural activities could help us to reveal the mechanism of schizophrenia.

The inferior frontal gyrus/insula possesses core roles in the salience network as well as the cognitive task control network, which is distributed over the VLPFC. In our study, ReHo in the bilateral inferior frontal gyrus/insula increased, but the left frontal gyrus/insula was more severe than the right side. Zhu et al. (42) found that the decreased parameter of asymmetry in the right inferior frontal gyrus/insula, may account for asymmetrical changes in the abnormal ReHo values of this area. Previous studies confirmed that variation in rs1344706 encoding ZNF804A affects structural brain alteration in the inferior frontal (43) and insula (44). Schizophrenia and their unaffected siblings showed the amplitude of low-frequency fluctuation abnormalities in the inferior fronto-insular gyrus and compared it with that of healthy controls (45). Consequently, structural and functional brain abnormalities in inferior frontal gyrus/insula have genetic pre-dispositions, which suggest that functional brain abnormalities in inferior frontal gyrus/insula may be occurred before the onset of disease, and further support neurodevelopmental hypothesis. Moreover, in our study, the ReHo in the right inferior frontal gyrus/insula was positively related to negative symptom scores and negatively associated with HVLT-R scores/verbal learning abilities. However, this relationship was hardly found in healthy controls; therefore, these abnormalities of clinical phenotype might be triggered by increased ReHo values in this region, which might be associated with the enhanced neural activity coordination. This result indicated that ReHo in this area might reflect the severity of negative symptoms and verbal learning abilities. In adolescent-onset patients with schizophrenia, one study showed that the increased FC strength in the right inferior frontal gyrus/insula is related to the general psychopathology scores of PANSS (46). Differences in these results might be caused by various MRI methods and different samples/types/states of patients with schizophrenia (43–45). Furthermore, our results revealed that abnormal neural activities occurred in the inferior frontal gyrus/insula; similarly, Leslie K. Jacobsen et al. (47) found that the glucose metabolic rate in the inferior frontal gyrus/insula of adolescents with childhood-onset schizophrenia increased. Above all the studies implied that abnormalities in the inferior frontal gyrus/insula might be a potential neurophysiological endophenotype of schizophrenia.

In our study, the accuracy of each abnormal ReHo value in the bilateral inferior frontal gyrus/insula or right gyrus rectus was too low to discriminate patients with schizophrenia from healthy controls; this phenomenon may be related to deficits in these regions that may not be specific to schizophrenia (48, 49). Furthermore, coupling each abnormal ReHo value in the regions and using the method of SVM, we found that the combination of increased ReHo values in the left inferior frontal gyrus/insula with the right gyrus rectus had 78.5% (84/107) accuracy, 85.96% (49/57) sensitivity, and 70.00% specificity compared with those of the other combinations. This result might help us distinguish patients with schizophrenia from healthy controls.

A few limitations were found in our study except the sample size and the age range. First, our research was a cross-sectional study. A longitudinal study might help us detect the stability of ReHo and the neural activities of the regions. Therefore, research methods should be optimized, different approaches may be considered to obtain different results, multimodal MRI should be applied to distinguish patients with schizophrenia from healthy controls.

Despite limitations, our study emphasized that hyperactivities were primarily located in the prefrontal regions, including the right gyrus rectus, right inferior frontal gyrus/insula, and left inferior frontal gyrus/insula. Abnormal ReHo values in the right inferior frontal gyrus/insula might reflect the severity of negative symptoms and verbal learning abilities. The combined increases of ReHo values in the left inferior frontal gyrus/insula with the right gyrus rectus might be an underlying biomarker in differentiating patients with schizophrenia from healthy controls.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the local ethics committee of the Affiliated Nanjing Brain Hospital, Nanjing Medical University (2017-KY017). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

NZ and XX designed this research. XX, SG, YM, JW, YG, SN, SL, RZ, and JS collected the imaging data and clinical information. The PANSS scales were evaluated by SG and the MCCB scales were evaluated by SG, YM, JW, and YG. XX and SG analyzed the imaging data. SG wrote the first draft of this manuscript. All authors reviewed and approved the final manuscript.

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BRIEF RESEARCH REPORT
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Transdiagnostic Dimensions of Psychiatric Comorbidity in Individuals at Clinical High Risk for Psychosis: A Preliminary Study Informed by HiTOP

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Background: Although psychiatric comorbidity is the norm among individuals at clinical high risk for psychotic disorders (CHR), research has yet to examine transdiagnostic dimensional models of comorbidity in this critical population.

Methods: This study analyzed quantitative measures of eleven psychiatric syndromes in a group at CHR ($n = 71$) and a matched healthy comparison group ($n = 73$) to determine these syndromes' dimensional structure and relationships to cognition, functioning, and risk of conversion to psychotic disorders.

Results: Relative to the comparison group, the CHR group was elevated on all eleven psychiatric syndromes. Exploratory factor analysis found three psychopathology dimensions: internalizing, negative symptoms, and positive symptoms. Depression cross-loaded onto the internalizing and negative symptom dimensions. Hypomania loaded positively on positive symptoms but negatively on negative symptoms. The negative symptom factor was associated with poorer cognition and functioning and a higher risk of conversion to psychosis.

Conclusions: These dimensions align with internalizing, detachment, and thought disorder, three of the five spectra in higher-order models such as the Hierarchical Taxonomy of Psychopathology (HiTOP). In the CHR state, detachment appears to be particularly insidious and predictive of psychosis. Further research is required to distinguish depression and hypomania from attenuated psychotic symptoms in this population.

Keywords: clinical high risk (CHR) for psychosis, comorbidity, factor analysis, detachment, internalizing, positive symptoms of psychosis, negative symptoms of psychosis, hierarchical taxonomy of psychopathology (HiTOP)

INTRODUCTION

Psychiatric comorbidity presents an enduring puzzle in schizophrenia. Most people diagnosed with schizophrenia also qualify for at least one other DSM diagnosis, most commonly mood, anxiety, and substance use disorders (1). Comorbidity rates are as high or higher among individuals at clinical high risk for psychotic disorders (CHR), that is, individuals without a current psychotic disorder who show elevated risk for psychosis based on attenuated psychotic symptoms, brief intermittent psychotic symptoms, or genetic risk and functional decline (2). Seventy to eighty percent of individuals in CHR studies tend to meet criteria for at least one lifetime non-psychotic DSM disorder (3–7). However, research has yet to apply transdiagnostic dimensional models of comorbidity in this critical population.

Conceptually, how can researchers and clinicians make sense of populations in which most individuals meet diagnostic criteria for multiple psychiatric disorders? The comorbidity puzzle has generated considerable debate about overlap between disorders and relationships between normative variation and psychopathology (8–10). Widely used diagnostic systems (DSM-5 and ICD-10) present two solutions: (a) diagnose multiple co-occurring, putatively independent disorders (meeting the traditional definition of comorbidity); or (b) diagnose hierarchically, such that one diagnosis can take precedence over or subsume the symptoms of another. For instance, DSM-5 and ICD-10 describe anxiety and depression as possible features of schizophrenia in addition to symptoms of co-occurring disorders (11, 12). There are advantages to both approaches, with the independent-disorders approach prioritizing full information and the hierarchical approach prioritizing parsimony.

Recently, an alternative transdiagnostic framework has emerged which models symptoms as correlated indicators of latent dimensions (8, 13–15). For instance, a latent internalizing dimension could be expressed in one case as social anxiety symptoms, in another case as social anxiety and obsessive-compulsive symptoms, and in a third case as social anxiety and panic symptoms. Multivariate dimensional models allow symptoms to be understood at multiple levels of analysis, providing both parsimony at broader levels of analysis (e.g., latent psychopathology dimensions) and full information at specific levels of analysis (e.g., manifest psychiatric syndromes). This hierarchical dimensional approach has been codified in the Hierarchical Taxonomy of Psychopathology (HiTOP), which links broad spectra (e.g., internalizing) to specific syndromes (e.g., social anxiety) through descending levels of specificity (15)[1].

Dimensional models are widely used in schizophrenia research, most notably in the classic distinction between positive and negative symptom dimensions (16). Indeed, symptom dimensions have consistently outperformed categorical diagnoses in explaining clinical outcomes in individuals with psychotic diagnoses (16, 17). Recent research shows that a thought disorder/positive symptom dimension is clearly distinct from a detachment/negative symptom dimension; both dimensions can be further subdivided; and both dimensions relate to normative and abnormal personality processes (18–25). Most of this work has focused on the structure of psychotic symptoms, and less is known about how these symptoms fit within broader transdiagnostic models of psychopathology such as HiTOP (15).

Transdiagnostic models are increasingly relevant as psychosis research focuses on the CHR state, aiming to identify early risk indicators, understand the pathogenesis of psychotic disorders, and develop early interventions (26). Only 10–30% of CHR individuals go on to develop a psychotic disorder (26, 27), but the remaining 70–90%, traditionally classified as "nonconverters," show persistent cognitive and functional impairment (28) and high rates of nonpsychotic disorders (5). Many researchers now adopt a clinical staging framework which models the CHR state as a transdiagnostic indicator of pooled risk for multiple disorder phenotypes (29, 30). Dimensional models can be important tools in understanding transdiagnostic elements of the CHR state: they can clarify the conceptual status of psychiatric comorbidity; use all the data at our disposal to improve prediction of psychotic disorders; and deepen our understanding of nonconverters who may instead develop chronic nonpsychotic pathology.

This preliminary study presents a transdiagnostic dimensional analysis of psychiatric comorbidity in a CHR sample. We carried out a secondary analysis of an extant dataset in which we identified continuous self-report and interview measures of eleven psychiatric syndromes covering positive symptoms, negative symptoms, internalizing, externalizing, and hypomania. We examined latent dimensions through exploratory factor analysis. Although this research was primarily exploratory, we hypothesized that the dimensions would reflect two or more of the five spectra identified in HiTOP research (detachment, thought disorder, internalizing, disinhibited externalizing, and antagonistic externalizing). We then examined the dimensions' clinical utility by analyzing their relationships to cognition, social and role functioning, and risk of conversion to a psychotic disorder. We hypothesized that psychotic dimensions would outperform nonpsychotic dimensions in predicting conversion risk, but that psychotic and nonpsychotic dimensions may both impair cognition and functioning.

METHODS AND MATERIALS

Participants

Participants were 71 help-seeking community participants who qualified for a CHR syndrome as defined by the Structured Interview for Psychosis-Risk Syndromes (2), and 73 matched healthy comparison participants (HC). Participants were recruited at a university research clinic specializing in

[1] "Syndrome" and "disorder" have slightly different meanings in this literature. "Syndrome" refers to an empirical group of symptoms/traits which cluster together. Traditionally, "disorder" refers not only to a psychiatric syndrome but also to specific diagnostic criteria, prevalence, course, subtypes, specifiers, and putative mechanisms (11, 15). Because these concepts are closely related, the study of syndromes can greatly enhance our understanding of traditional disorders. In this paper, we refer to our main variables as syndromes because they are defined psychometrically rather than diagnostically (15).

psychosis-risk in a midsize Western American city, through community professional referrals, newspaper, transit, and Craigslist ads, and e-mail postings. Participants in the CHR group were referred or self-referred based on unusual experiences such as suspiciousness, social withdrawal, or "mind tricks," and distress associated with these experiences.

The CHR group was 39% ($n = 28$) female; 68% (31) White, 15% (11) Hispanic, and 17% (12) other race; with a mean age of 18.7 (SD = 1.8); a mean of 12.4 (SD = 1.8) years of education; and a median family income of $60,000–$99,999. Psychiatric prescriptions rates were 12 (17%) participants prescribed stimulant medication, 11 (15%) SSRIs, 8 (11%) antipsychotics, 8 (11%) other antidepressants, and 7 (10%) mood stabilizers. Comorbid DSM-IV-TR Axis I disorders included 21 mood disorders (29%), 6 posttraumatic stress disorder (8%), 6 obsessive compulsive disorder (8%), 25 other anxiety disorders (34%), 7 attention-deficit/hyperactivity disorder (10%), and 1 eating disorder (1%). Six participants (8.5%) converted to a confirmed psychotic disorder within 24 months: these included 2 diagnoses of psychotic disorder NOS, 1 schizophrenia, 1 schizophreniform, 1 bipolar disorder with psychotic features, and 1 brief psychotic disorder.

The HC group was 56% (32) female; 63% (33) White, 19% (14) Hispanic, and 18% (13) other race; with a mean age of 18.2 (SD = 2.6); a mean of 12.3 (SD = 2.5) years of education; and a median family income of $60,000–$99,999.

Procedures

Participants completed clinical interviews, self-report instruments, and cognitive testing as part of a baseline assessment battery for an observational study of psychosis risk in a university research clinic. Baseline assessments were conducted over multiple days as needed to manage participant fatigue. Clinical interviews were conducted by graduate students and post-doctoral researchers with multiple years of clinical experience who were blind to participants' self-report scores. Participants were followed naturalistically for 24 months, with follow up assessments of diagnostic status conducted at 12 and 24 months. This study was observational, and participants received treatment as usual during this time from any pre-existing community providers. Participants were not enrolled in any treatment studies during this time. All procedures were approved by the university Institutional Review Board and all participants provided written informed consent.

Measures

CHR status was assessed by the Structured Interview for Psychosis-Risk Syndromes (SIPS) (2). Psychiatric syndromes were measured by interview and self-report instruments. The broader study included a range of measures intended to capture theoretically relevant variables to psychosis, adolescent and young adult development, risk, and resilience. The authors evaluated all measures in the broader study to assess their suitability for a transdiagnostic dimensional analysis, prioritizing fit within generally accepted psychiatric syndromes based on available validity data for each scale. For instance, the Self-Rating Anxiety Scale (SAS) (34) was administered to participants, but it was not included because it primarily measures nonspecific somatic symptoms of anxiety. By contrast, the Beck Anxiety Inventory (BAI) (35) was included because multiple studies have reported that it is most closely tied to panic symptomatology (36, 37). All measures matching a given syndrome were included. When multiple measures were available for a given syndrome, all measures were included, and their mean standardized score was used as the syndrome score.

Full details including descriptive statistics for all measures are included in the **Supplementary Material**. Positive symptoms were assessed by the positive subscale of the SIPS, as well as the Prodromal Questionnaire-Brief (PQB) (38), the Launey-Slade Hallucination-Proneness Scale (LSHS) (39), and the positive subscale of the Community Assessment of Psychic Experiences (CAPE) (40). Negative symptoms were assessed by the negative symptom subscale of the SIPS. To achieve more equal weighting of psychotic and nonpsychotic symptoms in the factor analysis, we divided psychotic symptoms into multiple theoretically and empirically grounded symptom groups: positive-perceptual, positive-nonperceptual, negative-emotion, and negative-volition (19, 32, 41–43). See **Supplementary Material 1.2** for details.

Depression was assessed by the Beck Depression Inventory (BDI-II) (44). Generalized anxiety was assessed by the generalized anxiety subscale of the Revised Screen for Child Anxiety Related Disorders (SCARED-R) (45). Social anxiety was assessed by the Social Interaction Anxiety Scale (SIAS) (46) and the social anxiety subscale of the SCARED-R. Panic was assessed by the Beck Anxiety Inventory (BAI) (35) and the panic subscale of the SCARED-R. Hypomania was assessed by the Hypomanic Personality Scale (HPS) (47) and the Responses to Positive Affect scale (RPA) (33). Substance abuse was assessed during the clinical interview as the frequency of the participant's most frequently used substance, and the impairment associated with the participant's most impairing substance. The antisocial behavior syndrome included measures of impulsivity and conduct problems. Impulsivity was assessed by the Positive Urgency Measure (PUM) (48). Conduct problems were assessed by the mean scores on the "anger," "hate," and "contempt" items of the Modified Differential Emotions Scale (mDES) (49); and by the occurrence of antisocial life events within the past year, assessed by a modified version of the Peri Life Events Scale (LE) (31)[2].

Cognition was assessed by the composite score on the MATRICS Consensus Cognitive Battery (MCCB) (50). Psychosocial functioning was assessed by the Social and Role scales of the Global Functioning Scales (GFS) (51). Risk of conversion to psychosis was assessed in two ways. Cross-sectionally, we calculated baseline risk scores following the North American Prodromal Longitudinal Study procedure (52). This formula uses specific age, positive symptoms, social functioning, and cognition variables to estimate a risk for conversion within 24 months. Longitudinally, we compared baseline symptom scores in participants who converted to a confirmed psychotic disorder within 24 months vs. those who did not convert to a psychotic disorder.

[2]See **Supplemental Material 1.1** for details on antisocial life events.

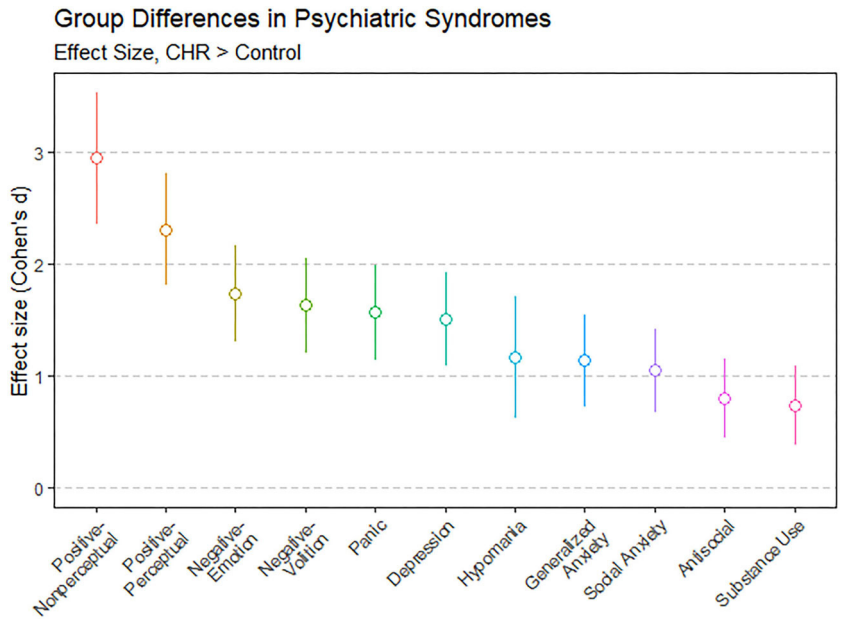

FIGURE 1 | Group differences between individuals at clinical high risk for psychosis (CHR; $n = 71$) and matched control participants ($n = 73$) showed that CHR participants scored significantly higher on all psychiatric syndromes. Group differences for each syndrome are shown as effect sizes in Cohen's d: $d = 0$ would indicate that CHR and control means were the same, $d = 1$ would indicate that the CHR mean was 1 standard deviation above the control mean, and so on. Error bars show 95% confidence intervals. Two-tailed t-tests confirmed that all effects were significant, *FDR-corrected* $p < 0.001$.

Data Analysis

Analyses were carried out in *R* version 3.6.1 (53). Baseline demographic differences between groups were compared by *chi*-squared tests (categorical data) and two-tailed independent samples t-tests with effect sizes expressed as Cohen's d (continuous data). Symptom variables were standardized to the HC participants mean and standard deviation, so that 0 indicates the HC mean and units are HC standard deviations. This allows all variables to be interpreted in the common metric of "standard deviations above/below local community norms." Syndrome scores were calculated as the mean of standardized variables within each syndrome. We examined group differences between CHR and HC groups on syndrome scores using two-sample t-tests with effect sizes expressed as Cohen's d.

Syndrome scores were then entered into an exploratory factor analysis with minimum residual estimation and oblimin rotation, which allowed for correlated factors. The number of factors was determined by parallel analysis, which compares the eigenvalues of factors in observed data to the eigenvalues of factors in simulated random data with the same number of participants and items. To avoid overfactoring, factors were considered significant if their eigenvalues exceeded the 95th percentile of randomly simulated eigenvalues. Missing data were imputed as the median.

Factor scores were saved and compared to external clinical validators (cognition, functioning, and risk scores) by Pearson correlations. Finally, t-tests examined group differences in factor scores between participants who converted to a confirmed psychotic disorder vs. those who did not convert. All p-values were corrected for multiple comparisons using FDR-correction.

RESULTS

CHR Scored Higher on All Syndromes

Tests of group differences (two-tailed t-tests for continuous variables and chi-squared tests for categorical variables) found no significant group differences on demographic variables. As shown in **Supplemental Table 1**, CHR and HC groups differed on all other variables (all $ps < 0.01$) except antisocial life events ($p = 0.060$) and cognition ($p = 0.510$). For all syndromes, mean scores were higher in the CHR group than the HC group. Group differences in syndrome scores were confirmed by two-tailed t-tests, which found all FDR-corrected p-values < 0.001. **Figure 1** shows effect sizes of these group differences. Effect sizes were large, ranging from $d = 0.73$ (substance use) to $d = 2.94$ (nonperceptual positive symptoms). Effect sizes were largest for positive symptoms, followed by negative symptoms, and then by other comorbid psychiatric syndromes.

Internalizing, Negative, and Positive Psychopathology Dimensions

To examine the latent structure of syndrome scores, we carried out an exploratory factor analysis with oblique (oblimin) rotation. Parallel analysis indicated that three factors were optimal. As shown in **Table 1**, the three factors explained 51% of the item-level variance. Factor 1 (Internalizing) was characterized by panic, generalized anxiety, and social anxiety. Factor 2 (Negative symptoms) was characterized by avolitional and impaired emotion negative symptoms. Factor 3 (Positive symptoms) was characterized by perceptual and nonperceptual

TABLE 1 | Exploratory factor analysis of psychiatric syndromes in CHR group.

Item	Factor 1 (Internalizing)	Factor 2 (Negative)	Factor 3 (Positive)	Item communality	Item complexity
Panic	**0.86**	−0.12	0.07	0.68	1.1
Generalized anxiety	**0.82**	0.06	−0.06	0.69	1.0
Social anxiety	**0.53**	0.29	0.00	0.47	1.6
Negative—Volition	−0.03	**0.83**	−0.02	0.67	1.0
Negative—Emotion	−0.01	**0.78**	0.10	0.65	1.0
Depression	**0.37**	**0.48**	0.10	0.52	2.0
Positive—Non-perceptual	−0.07	0.05	**0.94**	0.88	1.0
Positive—Perceptual	0.16	0.00	**0.78**	0.69	1.1
Hypomania	−0.07	**−0.37**	**0.40**	0.24	2.1
Substance use	−0.12	−0.14	0.19	0.06	2.6
Antisocial behavior	0.22	−0.17	0.10	0.06	2.3
SS Loadings	1.98	1.89	1.74		
Proportion of variance	0.18	0.17	0.16		
Cumulative variance	0.18	0.35	0.51		
Factor intercorrelations					
Factor 2	0.32				
Factor 3	0.24	0.24			

Bold indicates absolute factor loadings > 0.30. CHR, Clinical High Risk.

positive symptoms. Factor intercorrelations were positive and in the small to moderate range (*r*s = 0.24–0.32).

Depression cross-loaded on the Internalizing and Negative dimensions. Hypomania cross-loaded on the Negative and Positive dimensions, with a negative loading on the Negative dimension. In other words, hypomania was associated with higher positive symptoms but lower negative symptoms. Substance use and antisocial behavior did not load onto any factors, nor did they form a separate externalizing factor. In fact, substance use and antisocial behavior were uncorrelated ($r = -0.11$, $p = 0.37$).

One possible concern with this factor analysis is its relatively low subject to item ratio (6.45:1). As a test of robustness, we dropped the substance use and antisocial behavior syndromes (due to item communalities < 0.20) and re-ran the factor analysis. This analysis, which had a somewhat higher subject to item ratio (7.89:1), found substantively identical results.

Dimensions' Impact on Cognition, Functioning, and Conversion Risk

Did psychopathology dimensions relate to cognition and functioning? As shown in **Table 2**, the negative symptom dimension moderately correlated with impaired cognition, $r_{(66)} = -0.34$, *FDR-corrected* $p = 0.008$, and strongly correlated with impaired social, $r_{(70)} = -0.74$, *FDR-corrected* $p < 0.001$, and role functioning, $r_{(70)} = -0.64$, *FDR-corrected* $p < 0.001$. The positive symptom dimension marginally correlated with intact cognition, $r_{(66)} = 0.21$, *FDR-corrected* $p = 0.079$. The internalizing dimension did not correlate with cognition or functioning, all FDR-corrected *p*-values > 0.250.

TABLE 2 | Psychopathology factors and clinical variables in CHR group: Pearson correlations with 95% confidence intervals.

	Factor 1 (Internalizing)	Factor 2 (Negative)	Factor 3 (Positive)
Cognitive function	−0.13 [−0.35, 0.12]	−0.34** [−0.54, −0.11]	0.23† [−0.01, 0.45]
Social function	−0.15 [−0.37, 0.09]	−0.74*** [−0.83, −0.61]	−0.21 [−0.42, 0.03]
Role function	−0.13 [−0.35, 0.11]	−0.64*** [−0.76, −0.47]	−0.09 [−0.32, 0.14]
Conversion risk score	0.22† [−0.02, 0.44]	0.54*** [0.35, 0.69]	0.27* [0.03, 0.48]

Cognition assessed by the composite score on the MATRICS Consensus Cognitive Battery. Functioning assessed by the Global Functioning Scales. Conversion risk score calculated by the NAPLS formula.

†*FDR-corrected p < 0.10; *FDR-corrected p < 0.05; **FDR-corrected p < 0.01; ***FDR-corrected p < 0.001.*

Did dimensions predict risk of conversion to psychosis? We addressed this question in two ways. First, we calculated a risk score from participants' baseline data, following the NAPLS risk calculation formula (52). As shown in **Table 2**, the negative symptom dimension strongly correlated with risk scores, $r_{(65)} = 0.54$, *FDR-corrected* $p < 0.001$, the positive symptom dimension moderately correlated with risk scores, $r_{(65)} = 0.27$, *FDR-corrected* $p = 0.044$, and the internalizing dimension marginally correlated with risk scores, $r_{(65)} = 0.22$, *FDR-corrected* $p = 0.099$.

Second, as shown in **Figure 2**, we compared baseline symptom dimensions in CHR participants who converted to a confirmed

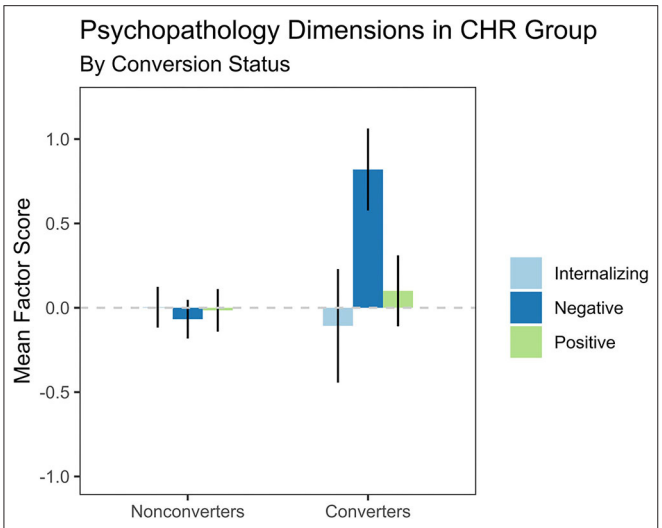

FIGURE 2 | The Negative Symptoms dimension predicted conversion to psychosis in individuals at clinical high risk for psychosis (CHR). Participants who converted to a psychotic disorder within 24 months ($n = 6$) reported higher scores at baseline on Negative Symptoms, $t_{(7.43)} = 3.30$, *FDR-corrected* $p = 0.036$, $d = 1.00$, and no significant difference on Internalizing, $t_{(6.36)} = -0.31$, *FDR-corrected* $p = 0.767$, $d = -0.12$, or Positive Symptoms, $t_{(9.15)} = 0.47$, *FDR-corrected* $p = 0.767$, $d = 0.12$, compared to participants who did not convert to a psychotic disorder ($n = 65$). Error bars indicate the standard error of the mean.

psychotic disorder within 24 months ($n = 6$) vs. other participants ($n = 65$). Despite the very small sample size, converters were elevated on the negative symptom dimension at baseline compared to nonconverters, with a large effect size, $t_{(7.43)} = 3.30$, *FDR-corrected* $p = 0.036$, $d = 1.00$. The other two dimensions did not differentiate converters from nonconverters, FDR-corrected p-values > 0.750.

DISCUSSION

This is the first study to model psychiatric comorbidity in a CHR sample in a transdiagnostic dimensional framework. The CHR state is increasingly understood as a transdiagnostic construct in clinical staging models (29, 30). Conceptually, a transdiagnostic dimensional approach is a natural fit to capture this complexity. Practically, a transdiagnostic dimensional approach can generate novel and clinically useful insights into the relationships between apparently diverse forms of psychopathology in the CHR state.

We identified eleven psychiatric syndromes in an extant dataset, including four psychotic syndromes and seven nonpsychotic syndromes. The CHR group was most elevated (compared to matched healthy controls) on positive symptoms, followed by negative symptoms, then by internalizing syndromes and hypomania, and finally by externalizing syndromes. All group differences were highly significant, and, notably, the CHR group differed from controls by more than one standard deviation on all syndromes except antisocial behavior and substance use. Individuals at CHR tended to report broad, distressing, and impactful symptoms, both psychotic and nonpsychotic.

Could latent dimensions make sense of this comorbidity picture? An exploratory factor analysis found that three dimensions accounted for a majority of the variance in syndrome scores. The first dimension captured both fearful (panic, social anxiety) and distressed (generalized anxiety, depression) internalizing. The second dimension captured primarily negative symptoms, and the third dimension captured primarily positive symptoms. As predicted by hierarchical models such as HiTOP, the three dimensions corresponded to three higher-order psychopathology spectra (internalizing, detachment, and thought disorder) and positively correlated with one another with small to medium effect sizes ($r = 0.24$–0.32).

The negative symptom factor was much more strongly linked than the other factors to impaired cognition, impaired social and role functioning, and risk of conversion to psychosis. In fact, the only significant correlation for another factor was between positive symptoms and the conversion risk score. This correlation is slightly dubious because the NAPLS risk score includes two positive SIPS items in its risk calculation formula, which makes the positive symptom and risk score variables slightly statistically dependent. Moreover, despite the very small sample size of converters, the negative symptoms factor prospectively predicted conversion while the positive symptoms factor did not. Multiple studies have shown that negative symptoms are predictive of conversion to psychosis (54–56). The current study strengthens those findings. The approach in this study—exploratory modeling of multivariate dimensions—is novel, and it is noteworthy that this analysis confirmed the importance of negative symptoms. This effect seems to be robust to very different statistical methodologies.

Moreover, several nuances of the factor structure provide novel insights into comorbidity in the CHR state. Help-seeking individuals meeting CHR criteria have been described as "a troubled group presenting with many comorbid problems" (5), and it is critical to understand how these problems interact to predict which individuals will go on to develop psychotic disorders and which will go on to develop chronic nonpsychotic disorders. The current study found several novel insights into CHR comorbidity: depression and hypomania were hybrid constructs, and externalizing syndromes (substance use and antisocial behavior) failed to load on any factors.

Depression was a hybrid construct, loading onto both internalizing and negative symptoms. The detachment and internalizing spectra are generally found to be distinct in adult clinical populations (15); however, multiple studies have found considerable overlap between depression and negative symptoms in CHR samples (57–59). Incipient negative symptoms can closely resemble internalizing symptoms, and depressed mood is often one of the earliest observable signs of a high risk syndrome (29, 60). The current study adds to this body of research by showing that, even at the level of broad dimensions, self-reported depression can indicate internalizing, detachment, or both. Notably, this finding was specific to depression; self-reported measures of generalized anxiety, social anxiety, and panic were clearly

separate from negative symptoms. One practical implication concerns research which statistically controls for depression when studying negative symptoms [e.g., (61)]. If depression and negative symptoms partly form a common psychopathology factor, then statistically controlling for depression will reduce the effects of negative symptoms in unpredictable ways. Further research is required to determine the dividing lines, if any, between depression and negative symptoms in the CHR state.

Hypomania was another hybrid construct, as a component of higher positive symptoms but lower negative symptoms. There is some debate about transdiagnostic relationships between mania, thought disorder, and internalizing: is mania a component of internalizing, a component of thought disorder, a blend of both, or a separate dimension entirely (15, 20, 22, 23, 62)? This study suggests a somewhat novel placement of (hypo)mania in the CHR state, as a component of thought disorder that in some way protects against detachment. Perhaps individuals who tend toward mania and grandiosity would experience lower-intensity psychotic-like experiences as being highly salient, meaningful, and personally significant—for example, as evidence that the individual has been chosen for a special purpose by a higher power. These individuals might report significant positive symptoms, without attendant negative symptoms. Crucially, because the negative symptom dimension was most associated with risk of psychotic disorders, a hypomanic-positive symptom presentation with low negative symptoms would be less likely to indicate an incipient psychotic disorder. This intriguing possibility warrants follow-up research examining (hypo)mania's prognostic role in the CHR state.

Externalizing syndromes—substance use and antisocial behavior—did not load onto any of the three factors. Nor did they form an externalizing factor—in fact, they were uncorrelated ($r = -0.11$, $p = 0.37$). This negative result is difficult to interpret, given that the quality of the variables was generally poorest for these syndromes. The CHR state has not traditionally been associated with externalizing and, like most CHR studies, the broader study from which these data were drawn did not focus on externalizing. It may be worth attending more to externalizing in CHR studies. A recent review has shown that childhood antisocial and aggressive behavior predicts later psychotic symptoms, suggesting that there may be an unrecognized link between externalizing and the CHR state (63). Future research taking a transdiagnostic dimensional approach in the CHR state would be enhanced by more complete assessment of externalizing syndromes.

We consider this study to be preliminary because of two notable limitations. First, the study was limited by sample size. The subject to item ratio was less than ideal for factor analysis. A supplemental analysis improved the subject to item ratio by dropping the substance use and antisocial behavior syndromes and found similar results; nevertheless, the sample size could have caused misclassifications in the factor solution. The sample size of converters was also very small ($n = 6$) in the prospective analysis of conversion risk (**Figure 2**), and these results are speculative. It would be valuable to examine the transdiagnostic structure of psychopathology in larger CHR samples, particularly as CHR samples may contain individuals in multiple clinical stages of disorder pathogenesis, in which symptoms may exhibit different latent structures (29). Future research would be particularly valuable to comparing transdiagnostic structure between clinical stages. Second, the study was limited in its coverage of externalizing and personality. The HiTOP model posits that psychopathology spectra correspond to normative and pathological personality dimensions (15, 20, 25), but we were unable to validate factors with respect to personality because the dataset contained no personality measures. Future research on transdiagnostic dimensional models of psychopathology in the CHR state could build on these preliminary findings by including larger sample sizes and more comprehensive assessment including measures of externalizing and personality traits. Other potential limitations include possible effects of participant fatigue and treatment by community healthcare providers. Ultimately, no one factor solution is ever definitive, and our goal in presenting this study is to stimulate further research with other datasets—which will have their own strengths and weaknesses—to continue defining the dimensional contours of comorbidity in CHR populations.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Dataset not publicly available due to sensitivity of the clinical data and risks of deidentification. Requests to access these datasets should be directed to Henry R. Cowan, hrcowan@u.northwestern.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Colorado-Boulder Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HC contributed to study design, data analysis, and manuscript writing. VM contributed to study design, data collection, and manuscript writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.614710/full#supplementary-material

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Autism Rating Scale: A New Tool for Characterizing the Schizophrenia Phenotype

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Social dysfunctions (SD) are frequently observed in subjects with schizophrenia. Some of these dysfunctions are also observed in other neuropsychiatric disorders such as autism spectrum disorders (ASD), major depression, bipolar disorder, or Alzheimer disease. Recently, a characterization of a specific type of SD in schizophrenia has been proposed, with the concept of dis-sociality, which form the core aspect of "Schizophrenic Autism" (SA). The present study aimed to explore the presence in people with schizophrenia of SA, independent of other autistic traits, which can be often found in schizophrenia and other neurodevelopmental disorders. We used a structured interview—the Autism Rating Scale (ARS), an instrument devised to detect and measure SA. Fifty-one outpatients affected by schizophrenia (26 remitted, SCZ-r) and 28 affected by bipolar disorder type 1, with psychotic features, in the euthymic phase (BD-e) were recruited. Before assessing the specificity for schizophrenia of SA, we tested the internal consistency, the convergent and divergent validity of the ARS in the schizophrenia sample. Specificity was assessed by examining potential differences in ARS scores between SCZ-r and BD-e subjects. ARS showed good internal consistency, as well as convergent and divergent validity. ARS items were more frequently of moderate severity in SCZ-r than in BD-e subjects. This scale can contribute to establish more precise phenomenal boundaries between schizophrenia and bipolar disorder, and opens up the possibility of identifying a different type of SD in schizophrenia, independent of autistic traits and negative symptoms, which might benefit from different treatments.

Keywords: social dysfunction, schizophrenic autism, schizophrenia, remitted schizophrenia, autistic traits, euthymic bipolar disorder

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INTRODUCTION

DSM-5 (1) defines Social Dysfunction (SD)—within the diagnostic criteria for schizophrenia—as an impairment of social functioning (e.g., interpersonal relationships) and, when the onset of the disorder occurs in adolescence, as the impossibility to reach the expected levels of interpersonal functioning. This conceptualization of SD has three main limitations: (1) it endorses a strictly behavioral-functionalist perspective in which deficits in social behavior are emphasized; (2) these deficits are mainly defined and assessed in terms of quantitative reduction in performance; and (3) the current concept encompasses the real-life functioning domain of impairment, i.e., reduction of

social contacts, which might be the consequence of stigmatization (2, 3). Due to these limitations, it is difficult to differentiate SD as a specific dimension of schizophrenia psychopathology from SD in general, or SD that merely emerges in the face of adversities. Several studies on SD in schizophrenia reflect these limitations, as they do not investigate the personal level of experience in the affected subjects. There is a need, therefore, to develop tools assessing the experiential dimension of SD in people with schizophrenia.

Phenomenological Perspective on Autism in Schizophrenia

Lately, a phenomenological characterization of Social Dysfunction (SD) in schizophrenia has been introduced, with the concept of dis-sociality (4–6). The concept emphasized the subjective alteration of social competence by going beyond the behavioral-functionalist perspective. It reflects a disturbance of participation in social life related to phenomena defining the "Schizophrenic Autism" (SA).

The concept of SA refers to a detachment from reality associated with a rich fantasy life (7) and includes several symptoms and signs, such as emotional indifference, rigid attitude and behavior, dereistic, and overinclusive thinking. The number and variety of included features illustrates the difficulty in defining autism, and reflects the fact that none of these features is in itself sufficient to "diagnose" SA (7, 8). Recently, clinical phenomenologists resumed the construct of SA building on and extending the conceptualizations of Minkowski and Blankenburg. Minkowski et al. (9) assumed that autism is the primary, fundamental disorder in schizophrenia, i.e., a trait alteration from which other psychopathological features of the syndrome originate. He defined autism as the loss of vital contact with reality, an impairment in the capacity to adjust and modify one's own behavior in a contextually relevant manner. Blankenburg (10) characterized autism as a crisis of "common sense", i.e., the lack of the ability to comprehend "the rules of the game" of human behavior (e.g., the background of tacit knowledge shared by a social group). Common sense is not intended as a body of objective knowledge, but as a natural attitude that underlies the ability to be attuned to the world as it appears in everyday experience. From this perspective, the fundamental anomaly is in the pre-conceptual and pre-cognitive appraisal of social situations (11).

The essential feature of the SA is a qualitative impairment of spontaneous and intuitive participation in social life, referred to as dis-sociality (12). Dis-sociality embraces negative (disturbances of social attunement, detachment form social standards, social shared knowledge, and principles of causality) and positive features (a peculiar set of values), both contributing to the impairment of patients' social attitude (13).

In recent years, research has investigated the relationships between autism spectrum disorders (ASD) and other psychiatric conditions, such as schizophrenia and bipolar disorder (14, 15). In a recent meta-analysis (15), Lai et al. note that schizophrenia and bipolar disorder co-occur in 4% and 5% of cases of ASD, respectively. Several studies have investigated sub-threshold ASD in bipolar disorder and schizophrenia (16–19). Dell'Osso et al. (19) note that ∼43% of the sample of subjects with bipolar disorder have clinically significant autistic traits. Studies carried out on samples of patients with schizophrenia, using the PANSS Autism Severity Score (PAUSS), report that a large portion of patients with schizophrenia (40–50%) has clinically significant ASD (16, 17). These data are in line with the hypothesis that autism, schizophrenia, and bipolar disorder may have a common etiology, although they show different psychopathological phenomena (18, 20, 21).

Unlike the ASD traits that can co-occur in different psychiatric diseases, SA is believed to identify characteristic symptoms of schizophrenia. The assessment of ASD and SA is also different: while ASD rating scales mainly evaluate behavior through observation, SA investigation considers exclusively the subjective experience of social life.

Study Aims

The present study aimed to explore the prevalence of SA in people with schizophrenia and in those with bipolar disorder-type I with psychotic features in a euthymic phase, and to demonstrate its specificity for schizophrenia. We used a structured interview—the Autism Rating Scale (ARS) (11, 22), specifically developed to measure SA. The focus is on persons' experience of social interaction, i.e., their own description about emotional attunement/disattunement, self-other demarcation/non-demarcation, emotion recognition/non-recognition, emotional/cognitive attitude toward others, endorsement/refusal of social norms. A secondary aim of the study was to assess the independence of SA from ASD traits, as measured by the PAUSS, in subjects with schizophrenia.

METHODS

Study Participants

Fifty-one outpatients affected by schizophrenia (SCZ), and 28 euthymic outpatients with bipolar disorder-type I with psychotic features (BD-e) who experienced one or more recent episodes of depression or mania with psychotic features were recruited from those regularly attending the outpatient unit for psychotic or mood disorders of the Department of Psychiatry of the University of Campania "Luigi Vanvitelli" and consecutively seen from January 2016 to May 2017, who accepted to participate in the study. Inclusion criteria were: (a) diagnosis of SCZ or BD-Type I, according to DSM-IV criteria, confirmed by the Structured Clinical Interview for DSM-IV - Patient Version (SCID - IP); (b) sufficient motivation, introspective skills, and appropriate language skills to participate in the interview, evaluated on the referring psychiatrist clinical impression. Exclusion criteria were: (a) neurological diseases; (b) history of alcoholism or substance abuse; (d) intellectual disability; (e) changes in antipsychotic medication or hospitalization within 3 months prior to the inclusion in the study. For bipolar patients, euthymia was defined as remission of the mood episode and psychotic symptoms for at least 4 weeks at the time of the evaluation.

TABLE 1 | List and description of the ARS domains.

ARS domains	Items (N)	Description
Hypo-Attunement	3	The immediate feeling of reduced attunement, i.e., emotional contact with other persons. The pervasive feeling of inexplicability /incomprehensibility of people's behavior and social situations.
Invasiveness	3	Feeling oppressed and invaded by the others, from without.
Emotional flooding	2	Feeling oppressed and submerged from within by paroxysms of one's emotions and bodily sensations evoked by interpersonal contacts.
Algorithmic conception of sociality	3	The conceptual, analytic, hyper-cognitive, hyper-rationalist, hyper-reflective stance toward sociality. Patients may endorse a mechanistic, strategic and in some way "mathematisable" (as in a chess game) conceptualization of interpersonal transactions in everyday life.
Antithetical attitude toward sociality	3	Feeling to be vulnerable to the influx coming from the external world and claim one's independence as the most important value.
Idionomia	2	Idionomia is characterized by an existential re-orientation driven by the exaltation of one's own principles, interrogations, or world-view. This exalted existential standpoint does not allow integration or compromise with the other's point of view or with common sense.

The study was approved by the Ethics Committee of the University of Campania Hospital and all patients signed an informed consent before being included in the study.

Instruments

All study participants were assessed by the following instruments:

1) The Italian version of the ARS to assess SA (22). The scale explores the subjective experience of inter-personal relationships, contacts and social situations of people with schizophrenia in their daily life in the last 3 months. It investigates all kinds of real-life situations (e.g., home, work, school, leisure, friendship, etc.), including behavioral aspects (e.g., diminished social interests, interactions, reduced interpersonal involvement, etc.). The ARS includes 16 distinctive items grouped in 6 dimensions: Hypo-Attunement, Invasiveness, Emotional flooding, Algorithmic conception of sociality, Antithetical attitude toward sociality and Idionomia [further information on dimensions in (11)]. Severity is scored on a scale from 1 to 7 (higher scores correspond to greater severity) by taking into account frequency, intensity of subjective arousal or distress, level of impairment, and possibility to cope. The interview takes 30–60 min. In **Table 1** the 6 ARS dimensions are shortly described.
2) The Positive And Negative Syndrome Scale (PANSS) is a 30-item clinical scale which evaluates general psychopathology, positive and negative symptoms (23). Each item is rated on a 7-point symptom severity scale, ranging from 1 (absent) to 7 (extremely severe). In this study, ratings on PANSS items were summed to calculate positive and disorganization dimensions of schizophrenia symptomatology, according to the consensus factor model by Wallwork et al. (24).
3) The PANSS autism severity score (PAUSS) is a scale composed by 8 PANSS items, covering the three main specific autism symptom clusters, summed up as follows: (a) difficulties in social interaction: item 1 ("blunted affect"), 3 ("poor rapport"), and 4 ("social withdrawal") of the PANSS negative subscale; (b) difficulties in communication: items 5 ("difficulties in abstract thinking") and 6 ("lack of spontaneity and flow of conversation") of the PANSS negative subscale; (c) limited, repetitive and stereotypic patterns of behavior: items 5 ("mannerism") and 15 ("preoccupation") of the PANSS general subscale and item 7 of the PANSS negative subscale ("stereotyped thinking") (16). Each PAUSS item, according to PANSS, is rated on a 7-point scale and a total score is derived by summing all 8 items (range: 8–56) with higher scores indicating more severe autistic features.
4) The Brief Negative Symptom Scale (BNSS) was administered to evaluate the severity of the negative symptoms: it consists of 13 items organized in 6 sub-scales: anhedonia, distress, asociality, avolition, blunted affect, and alogia. All the items are rated on a 7-point scale (0–6), with a total scores ranging from 0 to 78. For all items in the 6 domains, the highest score is associated with the greatest severity of symptoms, while for the distress item the highest score is associated with the greatest reduction or absence of negative emotions. The total score of the BNSS is calculated by summing the ratings from all the items except for the item "distress"; the scores of the subscales are calculated by summing the scores of the items that the subscale includes. The Italian version of the scale was validated as part of the Italian Network for Research on Psychoses activities (25).

Training of Evaluators and Assessment of Inter-rater Reliability

The assessment was conducted by three residents in Psychiatry properly trained for the administration of the instruments. Both for the PANSS and BNSS the three evaluators achieved a certificated training. The training for the administration of the ARS was conducted by one of the authors of the instrument (MB) and an excellent agreement was observed among raters (intraclass correlation coefficient ranging from 0.74 and 0.96). Further information on the procedure of the training and inter-rater reliability analysis can be found in Ballerini et al. (22).

Statistical Analysis

All statistical analyses described below were conducted using IBM SPSS Statistics Version 22. The significance level for all statistical comparisons was set at $p < 0.05$.

Before assessing the specificity for schizophrenia of the observed SA and the degree of its association with ASD traits as

assessed by the PAUSS in subjects with schizophrenia, we tested the internal consistency and the convergent validity of the ARS.

Internal Consistency

The ARS internal consistency was evaluated using Cronbach's Alpha in the SCZ sample.

Convergent Validity

In the SCZ sample, ARS convergent validity was assessed by examining its correlations (both total and dimension scores) with the PANSS positive and disorganization dimensions, as well as with the BNSS total score and dimensions. A Bonferroni correction for multiple comparisons was applied to control for type 1 error.

Divergent Validity

In the SCZ sample, ARS divergent validity was assessed by examining its correlations (both total and dimension scores) with the PAUSS total and item scores. A Bonferroni correction for multiple comparisons was applied to control for type 1 error.

Specificity

The specificity was analyzed by comparing the frequency and severity of the ARS dimensions between SCZ with remitted (r) positive symptoms (SCZ-r) [according to the severity criteria proposed by (26)] and BD-e. The choice of identifying SCZ-r patients and comparing them exclusively to BD-e is due to the need to minimize the clinical differences between the two groups of subjects (i.e., mood symptoms and positive psychotic symptoms). This allows comparing the frequency and severity of ARS dimensions between the two groups of subjects that do not differ with respect to other clinical characteristics. A one-way analysis of variance (ANOVA) was used to test differences between SCZ-r and BD-e with respect to age, education and duration of illness. The two clinical populations were also compared for sex distribution by the $\chi 2$ test.

In order to assess differences in the frequency of symptoms, the number of symptoms of at least mild severity (i.e., with a score ≥ 3) was computed in both groups. Subsequently, the data obtained were compared by the $\chi 2$ test.

Differences in symptom severity between the two patient groups were tested using a multivariate analysis of variance (MANOVA), with dimensions of the ARS (Hypo-Attunement, Invasiveness, Emotional flooding, Algorithmic conception of sociality, Antithetical attitude toward sociality and Idionomia) as within-subject factors, and diagnosis as between subject factor (SCZ-r and BD-e). Follow-up univariate ANOVAs for investigation of simple effects were carried out only when significant group main effects or interactions were found in the MANOVA.

RESULTS

Socio-Demographic and Clinical Characteristics

The SCZ group was composed by 51 subjects, 33 (64.7%) males, with a mean age of 40.33 (SD ± 10.82), mean education of 13,57 (SD ± 3.05) years and mean illness duration of 17.8 (SD ± 9.96) years.

TABLE 2 | Characteristics of the study groups.

	SCZ $n = 51$	SCZ-r $n = 26$	BD-e $n = 28$
Males (%)	64.7	50	57.14
Age (mean yrs ± SD)	40.33 ± 10.82	37.19 ± 11.63	41.29 ± 9.39
Education (yrs mean ± SD)	13.57 ± 3.05	14.19 ± 3.02	13.25 ± 5.07
Illness Duration (yrs mean ± SD)	17.8 ± 9.96	14.15 ± 9.99	16.29 ± 10.9
Antipsychotic therapy			
Typical antipsychotics % (N/Total)	17.65 (9/51)	19.23 (5/26)	10.71 (3/28)
Atypical antipsychotics % (N/Total)	64.71 (33/51)	73.07 (19/26)	85.71 (24/28)
Typical and Atypical antipsychotics % (N/Total)	17.65 (9/51)	7.69 (2/26)	0 (0/28)
No antipsychotic treatment	0 (0/51)	0 (0/51)	3.57 (1/28)
Chlorpromazine – equivalent daily dose – median (Range)	400 mg (125–1,200)	400 mg (125–1,200)	300 mg (0–800)

SCZ, Subjects affected by schizophrenia; SCZ-r, Subjects affected by schizophrenia with remitted positive symptoms; BD-e, Subjects affected by bipolar disorder-type I with psychotic features during a euthymic phase.

Twenty-six out of 51 SCZ met the remission criteria. No statistically significant difference was found between the SCZ-r group and BD group for gender distribution ($\chi^2 = 0.28$; $p = 0.60$), age ($F = 2.04$; $p = 0.16$), education ($F = 0.67$; $p = 0.41$), and duration of illness ($F = 0.56$; $p = 0.46$). Medication, socio-demographic, and clinical characteristics of the study groups are illustrated in **Table 2**.

Internal Consistency

The internal consistency of the ARS was very high ($\alpha = 0.850$) suggesting excellent psychometric properties.

Convergent Validity

The ARS total score was significantly correlated with the positive dimension of the PANSS ($r = 0.50$, $p < 0.01$). The ARS dimensions *Invasiveness*, *Algorithmic conception of sociality,* and *Idionomia* were moderately correlated with the PANSS Positive dimension (**Table 3**). The ARS total score had no correlation with negative symptoms ($r = -0.040$, $p > 0.2$), assessed by BNSS; the ARS dimension *Antithetic attitude toward sociality* had a moderate positive correlation with the BNSS total score, due to the correlation with the subscales *Asociality* and *Avolition*, while the ARS dimension *Invasiveness* had a moderate negative correlation with the BNSS total score, due to the negative correlation with the two subscales *Alogia* and *Blunted affect* (**Table 3**).

Divergent Validity

The ARS total score had no correlation with autistic features calculated by PAUSS total score ($r = 0.095$, $p > 0.2$); the ARS dimension *Invasiveness* had a moderate inverse correlation with *Blunted affect*, *Social withdrawal,* and *Lack*

TABLE 3 | Correlations of Autism Rating Scale total and dimensions scores with other psychopathological dimensions.

Other Psychopathological dimensions	Autism Rating Scale						
	Hypo-attunement	Invasiveness	Cenesthopatic/ emotional flooding	Algorithmic conception of sociality	Antithetical attitude toward sociality	Idionomia	ARS total
BNSS anhedonia	0.136	−0.287	−0.070	0.096	0.369	−0.120	0.051
BNSS distress	0.004	−0.234	−0.066	−0.013	0.177	−0.196	0.061
BNSS asociality	0.056	−0.183	−0.109	−0.051	0.413**	−0.209	0.003
BNSS avolition	0.085	−0.159	−0.073	−0.023	0.425**	−0.236	0.032
BNSS blunted affect	−0.068	−0.304*	−0.173	−0.050	0.140	−0.243	−0.146
BNSS Alogia	0.095	−0.383**	−0.122	0.064	0.139	−0.095	−0.062
BNSS total score	0.058	−0.319*	−0.131	0.008	0.330*	−0.217	−0.040
PANSS pos	0.200	0.569**	0.250	0.349*	0.247	0.474**	0.504*
PANSS dis	−0.052	−0.050	0.021	0.183	−0.132	0.253	0.104

*BNSS, Brief Negative Symptom Scale; PANSS pos, Positive and Negative Syndrome Scale, positive dimension; PANSS dis, Positive and Negative Syndrome Scale, disorganization dimension. *p < 0.05; **p < 0.01.*

TABLE 4 | Correlation coefficients between Autism Rating Scale and PANSS autism severity score (PAUSS).

PAUSS	Autism Rating Scale						
	Hypo-attunement	Invasiveness	Cenesthopatic/ emotional flooding	Algorithmic conception of sociality	Antithetic attitude toward sociality	Idionomia	Total
Blunted affect	0.039	**−0.332**	−0.164	−0.008	0.267	−0.143	−0.067
Poor rapport	0.136	−0.144	−0.018	0.101	0.123	0.067	0.063
Social withdrawal	0.026	**−0.470**	−0.166	−0.054	**0.288**	−0.193	−0.128
Difficulties in abstract thinking	−0.060	−0.106	0.198	0.050	−0.008	0.032	0.011
Lack of spontaneity	0.118	**−0.343**	−0.155	0.173	0.158	0.077	0.015
Stereotyped thinking	0.150	−0.141	0.028	0.234	0.092	0.268	0.132
Mannerism	0.142	−0.008	0.049	0.094	**0.276**	0.108	0.159
Preoccupation	0.215	**0.314**	**0.411**	**0.335**	0.090	**0.316**	**0.398**
Total	0.133	−0.242	0.018	0.164	0.230	0.088	0.095

In bold correlations with a significance level of p < 0.05.

of spontaneity, and the dimension *Antithetic attitude toward sociality* had a low correlation with the PANSS items *Social withdrawal* and *Mannerism*. Only the PAUSS item *Preoccupation* showed moderate correlations with several ARS dimension, except *Hypo-attunement* and *Antithetic attitude toward sociality* (**Table 4**).

Specificity

Frequency of Symptoms

The frequency of ARS dimensions showing at least mild severity (i.e., ≥3) (**Figure 1**) was higher in the SCZ-r than in BD-e sample, except for *Idionomia* dimension (frequency: 65.38% in the SCZ-r sample compared to 42.9% in the BD-e sample, $p = 0.09$). All dimensions had at least mild severity in over 65% of subjects with SCZ-r.

Severity of Symptoms

MANOVA showed an interaction group x dimensions ($F = 10.61$, $p < 0.0001$). ARS mean scores were significantly higher in patients with SCZ-r than in those with BD-e on all dimensions (**Table 5**).

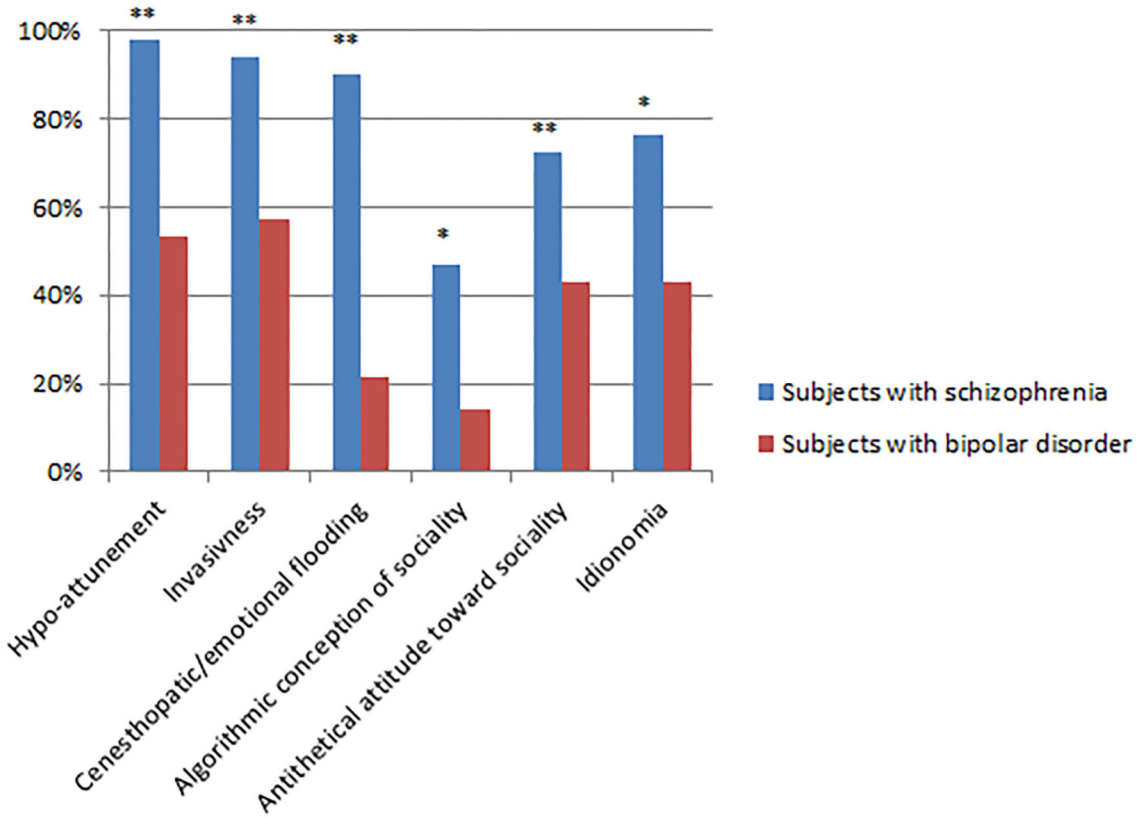

FIGURE 1 | Frequency (%) of ARS dimensions of at least mild severity (≥3); *$p < 0.05$, **$p < 0.01$.

TABLE 5 | Severity of the Autism Rating Scale (ARS) scores in the two patient groups.

ARS	SCZ-r ($N = 26$)		BD-e ($N = 28$)		p
	Mean ± SD	Range	Mean ± SD	Range	
Hypo-attunement	11.69 ± 3.31	5–19	4.61 ± 1.66	3–9	0.0001
Invasiveness	10.58 ± 4.74	3–19	5.07 ± 1.98	3–10	0.0001
Cenesthopatic/ emotional flooding	7.04 ± 2.58	2–11	3.00 ± 1.51	2–8	0.0001
Algorithmic conception of sociality	7.88 ± 4.79	3–17	3.68 ± 1.02	3–6	0.0001
Antithetical attitude toward sociality	8.38 ± 3.88	3–17	4.18 ± 1.41	3–9	0.0001
Idionomia	5.85 ± 3.56	2–13	3.57 ± 2.00	2–8	0.01
ARS global score	51.42 ± 16.37	25–80	24.11 ± 6.41	17–41	0.000000001

SCZ-r, Subjects affected by schizophrenia with remitted positive symptoms; BD-e, Subjects affected by bipolar disorder-type I with psychotic features during a euthymic phase; SD, Standard Deviation.

DISCUSSION

Schizophrenic Autism as Assessed by the ARS

The ARS (11, 22) contributed to a detailed characterization of social experiences of SCZ. It documents impairments of the intuitive, pre-reflexive grip on social situations *(Hypo-attunement*), fears of *invasion/violation* of one's own personal space and of being *submerged by own's emotions* when facing other people. Anomalies of intuitive attunement with others may be compensated by the attempt to make sense of the others' behavior and grasp the meaning of social interactions through a hyper-cognitive stance (*Algorithmic conception of sociality*).

Also, the ARS contributes to characterize the patients' social attitude, i.e., their reflexive and deliberate motivation of their asociality and social withdrawal, linking their behavior to a peculiar set of values (12, 27) whose principal features are the refusal of common-sense knowledge and the devaluation

of interpersonal bonds (*Antagonomia*), the endorsement of an idealistic quasi-utopian humanitarism *(Abstract idealization*) and the exaltation of idiosyncratic principles and rules, all detached from the values, standards, and symbols characterizing their socio-cultural context (*Idionomia*).

The ARS focuses on these characteristics of SA organizing them in six domains: *Hypo-attunement*, *Invasiveness*, *Emotional flooding*, *Algorithmic conception of sociality*, *Antithetical conception of sociality*, and *Idionomia*. The internal consistency proved to be excellent (Cronbach' alpha 0.850). These findings demonstrate that the ARS is suitable for clinical assessment and research purposes.

Convergent Validity

The convergent validity was evaluated in the total sample of SCZ. The ARS total score was correlated with the PANSS positive subscale, and this effect was largely due to *invasiveness*, *algorithmic conception of sociality* and *idionomia*. All these phenomena contribute to the unusual behaviors occurring in schizophrenia, being connected to the fragility of ego boundaries, a peculiar way to understand others and social situations, and to a radical breakdown of common sense (12, 27).

Antithetical attitude toward sociality (*antagonomia and abstract idealization*) was correlated with BNSS "avolition" and "asociality," suggesting that a peculiar set of values may contribute to negative symptomatology.

The only aspect that was not associated with either positive or negative symptomatology was *Hypo-attunement*. Hypo-attunement refers to a particular impairment of social cognition (SC), distinct from the impairment of the ability to process social information and from the theory of mind (28). Attunement is the pre-reflexive entanglement between a person and a context of worldly significance based on inter-emotionality and inter-corporeality (8). Robust meta-analyses have documented impairment of the other components of SC in people with schizophrenia (29, 30). Relations between SC and negative symptomatology is debated: Sergi et al. (31) described SC as an independent construct, weakly related with negative symptoms; however, more recent studies have reported either the absence of correlation (32, 33), or moderate correlations (34–36). The presence of different components of SC and the use of diverse instruments to assess SC abilities may account for discrepancies of correlations between SC and negative symptoms. *Hypo-attunement,* as measured by the ARS, implements the assessment of the non-strictly "cognitive" component of SC, which seems independent of the negative symptomatology.

Degree of Overlap and Divergence of SA and ASD

The ARS total score does not correlate significantly with the PAUSS total score. The reason for this is that the two scales are based on different constructs of "autism" and therefore explore different phenomena.

PAUSS is a scale validated in relation to *Autism Diagnostic Observation Schedule*, a semi-structured scale used for diagnostic purposes in ASD (16). PAUSS is therefore able to grasp some aspects related to ASD in different samples of subjects, including SCZ (16, 17).

In contrast, ARS has been developed to capture core characteristics of SA as it is defined in the phenomenological tradition (see *Introduction*) in SCZ. There is a substantial difference between the characteristics of ASD and the concept of SA. The ARS explores the *experiential* dimension of SA aiming to answer the question "What is it like to be with schizophrenia in the social world"? The PAUSS, on the other hand, assesses *behavior* on the basis of *observation* (as for instance is the case for the "interpersonal behavior" items where the interviewer must measure the patient level of "immersion in himself" during the interview), whereas the ARS measures the patients' micro-narratives related to their mental states including their feelings and distressing experiences.

The lack of correlation between the total ARS score and the total PAUSS score therefore indicates that there might be two different profiles of the complex phenomenon called "autism" in SCZ. The PANSS items included in the PAUSS are from the negative symptom subscale and general symptomatology. The ARS does not exclusively capture the aspects linked to the negative symptoms of schizophrenia and in fact correlates significantly with positive symptoms. The results of the correlation between the individual ARS domains and the PAUSS items are not surprising. The *Invasiveness* domain, that is positively correlated with the PANSS positive dimension, showed a negative correlation with the BNSS and PAUSS items investigating negative symptoms. In line with the latter finding, the *Antithetical attitude toward sociality* domain was positively correlated to some items of the BNSS and also slightly correlated to some PAUSS items.

Finally, the correlations between several ARS dimensions and the item "Preoccupation" of the PAUSS are expected. In fact, this PAUSS item investigates patient's interpersonal behavior, in particular the absorption with self-generated experiences, based on what can be observed by the interviewer from an external perspective. ARS investigates interpersonal behavior from the first-person perspective, that is, starting from the patient's subjective experience. It is therefore possible that PANSS "Preoccupation" and different dimensions of the ARS correlate because they investigate similar aspects from different perspectives.

Specificity

In this study, the specificity of the scale has been assessed matching the SCZ-r patients with the sample of BD patients. This strategy has been adopted a) to remove the possible confounding effect of higher scores on positive symptoms, with the aim to put in evidence possible vulnerability, trait-like characteristics able to differentiate the two clinical populations. Trait-like characteristics (37) are evident "prior to, during, and following periods of clinical symptom exacerbations," and are thought to reflect the core process of the disease and to be closely related to an "intermediate phenotype" (38).

The ARS mean total score robustly discriminated SCZ-r from BD subjects; if replicated, the phenomenon of SA, as measured by the ARS, might represent a characteristic *pheno-phenotype* or

experiential phenotype (39) of schizophrenia and, possibly, of the whole schizophrenia spectrum disorders.

According to these findings, specific trait-like anomalous experiences can discriminate schizophrenia from bipolar disorder.

In our study, not only the ARS total score, but also all its constitutive domains demonstrated diagnostic specificity. SCZ-r obtained higher scores than BD in each ARS domains, with the partial exception of *Idionomia*. The percent of patients who reported a score of at least mild on the ARS items was significantly higher in the SCZ-r sample than in the BD sample. The strongest significance was found for *Hypo-attunement* and *Emotional flooding*, but also *Invasiveness*, *Algorithmic conception of sociality,* and *Antithetical attitude toward sociality* resulted significant, documenting specific anomalies of intuitive self-other attunement, fears of violation of one's self from outside and of being submerged by own's emotions from within when facing other people, the attempt to grasp the meaning of social interactions through a hyper-cognitive stance and the refusal of common-sense knowledge and of interpersonal bonds. Only the frequency of *Idionomia* did not discriminate SCZ from BD. The result is not surprising: in fact to assess idionomia (22) the interviewer investigates the patients' charismatic orientation (i.e., the certainty to have a special gift or power) with questions like "Did you happen to receive something like a very particular revelation or profound illumination?" or "Did you notice that you have particular characteristics or faculties that other people do not have?" These ideas, which may or may not crystallize in true grandiose delusions, may be present both in schizophrenia and in bipolar disorders (40–42). In our sample, however, the clinical severity of this experience appears to be greater in SCZ-r, although the frequency does not differ significantly.

CONCLUSIONS

Schizophrenia is a complex condition that defies simple description. In addition to psychotic symptoms and the diagnostic criteria identified by the DSMs, the schizophrenia phenotype is also characterized by anomalous subjective experiences that need to be documented and measured through reliable and valid assessment tools.

SA is regarded by phenomenological psychopathology as a hallmark of schizophrenia: patients display a marked tendency toward the constitution of a private world detached from attunement, harmony, and vital contact with social world and the tendency to escape into a private world that is sometimes filled by an efflorescent imaginative inner life, and others haunted by odd and aloof simulacres. The main limit of the phenomenological literature, however, is the lack of valid instruments to collect reliable data. Our findings demonstrate that the ARS represents a valid instrument to capture the experiential phenotype of dis-sociality, distinct from the negative domain of asociality and from other autistic traits. ARS might measure a specific social dysfunction, characterized by anomalies of the pre-reflexive attunement, with profound disorganization of the basic structure of the social life in schizophrenia, which accounts for the bizarreness and detachment from common sense of the affected subjects (27). The scale should now be used in larger sample studies to investigate more specifically whether this type of social dysfunction has different correlates than the autistic traits and the negative domain of asociality. In particular, it should be investigated if ARS indices have any association with deficits of social and non-social cognition, known to be associated with the autistic traits in schizophrenia [e.g., theory of mind impairment and neurocognitive deficits, (43)], as well as with the lack of motivation subtending asociality in schizophrenia (44).

Furthermore, the validity of the scale should be tested longitudinally in subjects characterized by primary negative symptoms (deficit schizophrenia) which do not remit over time and are characterized by a severe impairment of real-life interpersonal relationships (45). The cross-sectional design of our study clearly prevents further inference on this point and represents a limitation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Campania Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DP, AM, GS, MB, and SG designed the experiments. DP and AM analyzed the data. DP, GS, and AM wrote the manuscript in consultation with GG, MB, PL, and SG. All authors contributed to the article and approved the submitted version.

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Disturbances of Shared Intentionality in Schizophrenia and Autism

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Schizophrenia and autism are today considered complex spectrum disorders characterized by difficulties in social behavior. Drawing on recent advances in collective or shared intentionality studies, we present a novel theoretical approach to these social difficulties by exploring them from the angle of shared intentionality. We begin by describing two forms of shared intentionality: joint intentionality and we-intentionality. Joint intentionality crucially relies on the agents' mentalizing abilities such as mind reading and the ability to factor in (or "to be moved" by) their partner's intentions in deliberation and action planning. By contrast, we-intentionality relies on the agents' capacity to understand themselves as group members and to adopt the group's perspective. In schizophrenia spectrum disorders, we propose that joint intentionality remains unaffected, but we-intentionality may be impaired. In severe autism spectrum disorder (i.e., infantile autism), we propose that both forms of shared intentionality are impaired. We suggest that the source of the problems affecting we-intentionality in schizophrenia spectrum disorders lies primarily in trait-like, anomalous self-experiences. In severe autism spectrum disorder, we suggest that problems with mind reading, the ability to "be moved" by others' intentions, and with the capacity for perspective-taking impede both forms of shared intentionality.

Keywords: anomalous self-experience, autism spectrum disorder, group identification, mind reading, perspective-taking, schizophrenia, self-disorders, shared intentionality

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INTRODUCTION

In the last decades, collective or shared intentionality has attracted rapidly growing attention in many research communities. Shared intentionality can be described as the power of the mind to share mental states like emotions, intentions, and beliefs with others [see (1)]. Philosophers and empirical researchers have argued that this capacity is of paramount importance for characteristically human forms of social life, because it appears to underlie key social phenomena, including communication (2), cooperation (3), group and corporate agency (4), the constitution of institutional facts (5), human moral psychology (6), and collective responsibility (7). By uncovering how pervasive shared intentionality is in human life, this wealth of insights also supports the prediction that disturbances of this capacity will reflect noticeable changes in human sociality.

This prediction delivers the background motivation of this paper, whose principal aim is to shed new light on the nature of aberrant social behavior in schizophrenia spectrum disorders (i.e., schizophrenia and schizotypal disorder, hereafter "SSD") and autism spectrum disorder ("ASD"). The social behavior in these disorders has been a subject of intense research for decades [see (8, 9)], typically associating such behavior with various forms of neurocognitive and social cognitive deficits. Previous studies have generally not explored aberrant social behavior from the perspective of shared intentionality except for some sporadic contributions [these include (10–13)][1]. We suggest that recent advances in studies on shared intentionality may offer a new framework for understanding the characteristic impairments of sociality in SSD and ASD and for illuminating crucial differences in social impairments in these diagnostic groups. Furthermore, appreciating the specific nature of these impairments in the two disorders may enable us to better comprehend the features of shared intentionality that are required for it to function unproblematically.

The paper is organized as follows. In Joint and We-Intentionality and Their Core Features section, we develop a conceptual framework for thinking about shared intentionality. We claim that shared intentionality comes in at least two forms, which we label "joint intentionality" and "we-intentionality," and that they have different core features and psychological preconditions. In short, joint intentionality requires mentalizing abilities such as mind reading and the ability to be "moved" by the intention of another agent (Joint Intentionality section). By contrast, we-intentionality crucially hinges on group identification, which is the capacity to acquire a self-understanding as group member and to adopt the group's perspective (We-Intentionality section).

In Schizophrenia Spectrum Disorders section, we advance theses partially already defended in previous work (10), which specifically concerned sociality in schizophrenia[2]. We present reasons for thinking that, of the two forms of shared intentionality identified in Joint and We-Intentionality and Their Core Features section, only one of them seems to be impaired in SSD. Whereas, joint intentionality does not appear to be affected in SSD, we suggest that we-intentionality can, in fact, be impaired in SSD (Social Behavior in Schizophrenia Spectrum Disorders section). We propose that the difficulties of we-intentionality are linked to the presence of non-psychotic, anomalous self-experiences (or "self-disorders"), which contemporary research documents hyper-aggregate in SSD but not in other mental disorders [see (14)], and which can be considered to be trait-like features of SSD, antedating psychosis and persisting after remission from a frank psychotic episode (15, 16). We propose that the anomalous self-experiences may hamper the process of group identification, thereby potentially impairing the formation and maintenance of we-intentionality (Frailty of We-Intentionality in Schizophrenia Spectrum Disorders section).

In Autism Spectrum Disorder section, we look into ASD by zooming in on the severe end of the spectrum [what in *International Classification of Diseases*, Tenth Revision (ICD-10) is termed "infantile autism"]. It is therefore important to highlight already now that our account, by exclusively focusing on the severe end of the spectrum, deliberately leaves aside milder cases of autism (i.e., Asperger's syndrome) and so-called high-functioning autism. After some general considerations concerning sociality in severe ASD (Social Behavior in Severe Autism Spectrum Disorder section), we present the hypothesis that, in severe ASD, both forms of shared intentionality are disrupted (Joint Intentionality in Severe Autism Spectrum Disorder section). We argue that the problems with mentalizing abilities and the capacity for perspective-taking, which the current literature has already acknowledged as a qualifying trait of severe ASD, have negative repercussions for initiating interactions based on both joint intentionality and we-intentionality (We-Intentionality in Severe Autism Spectrum Disorder section)[3].

Before approaching the notion of shared intentionality, one last remark is in order: part of the motivation for this project stems from a general absence of empirical research around shared intentionality in SSD and severe ASD. Against this backdrop, the following sections try to break new ground by offering a novel theoretical or conceptual account of the disturbances of shared intentionality in the two syndromes. Evidently, there is no available experimental design to test our account or empirical evidence to validate or falsify it. Yet we draw on both classic and contemporary research to get to the psychopathological core of the two syndromes and develop our account. The hope is that this paper may contribute to open a line of research on shared intentionality in psychopathology in which the basic hypotheses of the presented account may be tested.

[1]Two comments are in order. The first is that, although closely related, social cognition and shared intentionality are conceptually distinct capacities: whereas the first capacity is about understanding others' mental states, the second capacity (esp. when it narrowly refers to shared *intentions qua* conative states, see the next section) concerns the *motivation* to engage in pro-social behavior and collaborative actions with others (12). The debate on shared intentions has been sparked almost 30 years ago by the insight that the second capacity does not boil down to the first [see (1)]. The second comment is that, of course, we do not mean to imply that other psychiatric disorders (e.g., organic or affective psychosis, personality disorders, or social anxiety) are not confronted with problems of sociality and that an investigation into shared intentionality could not shed light to these disorders, too [see (13)].

[2]Although the current paper builds upon Salice and Henriksen (10), it also substantially advances and, in certain cases, rectifies the view we develop there. In addition to including infantile autism in the account, the current paper offers a more precise analysis of shared intentionality. As the next sections show, this analysis relies on a refined understanding of group identification (as an umbrella term that encompasses two different processes: self-transformation and the adoption of the group's perspective) and on an equally refined understanding of what it means to factor in another's intention (or "to be moved by" that intention) in deliberation. Also, the current analysis does not any longer hinge on a taxonomy of groups.

[3]Note that we do not argue that the factors, which we discuss in this paper, are the only ones that may affect shared intentionality in ASD and SSD. For example, based on the idea that awareness of others' mental states does not rely only on mentalizing capacities but is also related to intersubjectively constituted embodied attunement, Fuchs (11) has argued that a disorder at the level of "pre-reflective embodied relationship of self and other" may be a cause of disruption for intersubjectivity in the two syndromes.

JOINT AND WE-INTENTIONALITY AND THEIR CORE FEATURES

Philosophy of mind usually distinguishes among a general and a specific meaning of the term "intentionality." When used in the general sense, intentionality is a property of mental states: a mental state qualifies as intentional if it is about an object or a fact in the world (17). On this understanding, shared intentionality refers to the power to share mental states that are intentional. Accordingly, investigating the ways in which, say, perceptions, emotions, or beliefs are shared among several individuals is part and parcel of the investigation into this power[4].

When used in the specific sense, intentionality is a property of actions: an action is intentional if it is performed upon a conative state like an intention (20). On this second understanding of "intentionality," shared intentionality narrowly refers to the power of sharing states of a conative kind and, especially, intentions. Although an exhaustive assessment of impaired sociality in SSD and ASD demands investigations of how sharing of cognitive or emotive states is affected in the two conditions, the present paper will exclusively focus on the "specific" sense of "shared intentionality" as the capacity to share conative attitudes and, more specifically, intentions. However, it should be noted already now that an explanation of this capacity will not exclusively appeal to conative states and attitudes. Rather, as it will turn out, sharing intentions relies on a host of psychological preconditions that also include cognitive and emotional states.

To intuitively corroborate what is meant by the expression "shared intention," imagine two individuals walking down the street (21). For our purposes, this scenario can play out in two different ways. First, the two individuals may be performing *distinct* actions in strategic equilibrium. Here, each individual monitors what the other is doing in order to avoid disruption in one's course of action, e.g., accidentally stepping on the other's foot. Second, the individuals may be performing an action *together*. It has been convincingly argued [e.g., by (21–24)] that what distinguishes the first scenario from the second is the fact that the individuals, in the latter, walk together because they *have jointly decided to walk together* or, to put this another way, because they *share the intention of walking together*. A large part of the current debate concerns what, exactly, it means for several individuals to "share" intentions. Recently, one view is gaining significant traction in the literature. According to this view, "sharing" does not point to just one thing, as it were; rather, there are different ways in which mental states like intentions can be shared [authors endorsing this idea include (3, 25, 26), among others]. In the following, we develop a conceptual framework that aims at capturing two different ways of sharing intentions [see (10, 27, 28)].

Joint Intentionality

We call the first form of sharing "joint intentionality." In joint intentionality, agents pursue individual goals that happen to overlap, where a goal is the state of affairs that an agent is committed to bring about. For example, imagine that I intend to write a paper and you intend to write a paper as well. In this case, our individual goals (to write a paper) can be said to overlap [at least to a certain extent, see (29)]. Suppose that I become aware of your intention and you of mine: assuming some favorable circumstances (we esteem each other, or we have complementary expertise, etc., the details are irrelevant for our purposes), this may motivate me to form the intention to write the paper together with you on condition that you, too, intend to do so. So I decide to write the paper together with you, "partly because" you, too, have the intention of writing a paper with me (24). But also, I form the intention in "accordance with" yours, where accordance is required to exclude cases of exploitation or coercion, in which I use you as a mere social tool or against your own interests (24). Thus, we propose the following two psychological preconditions for intentions to be "shared" in a way leading to a jointly intentional activity: (1) I am aware that you have a mental state, which qualifies as an intention ("mind reading"), and (2) this intention of yours figures in my pool of motivations in a particular way; i.e., for our intentions to lead to intentional joint action, your intention must "move" me in the sense that I factor in your intention in my deliberation and action planning by forming my participatory intention "in accordance" with, and "partly because" of, yours. When individual intentions—i.e., intentions that are held from the agents' individual perspectives and are the endpoint of a deliberative process aimed at solving a practical problem that each of the individual agents is confronted with—are formed this in specific way, they may be called "participatory intentions." To put this differently, two or more individuals engage in joint intentionality when each of them forms participatory intentions.

Once participatory intentions are in place, a further requirement for them to lead to intentional joint action is shared deliberation about the plan and the distribution of labor. To elaborate on the example, either concomitant or expected deliberation about—and subsequent agreement on—which part of the paper will be written by whom is part and parcel of what it means for you and me to decide to write a paper together (24). This implies that the interactants put themselves under the pressure of assigning roles and statuses based on their specific features, expertise, and capabilities (30, 31). Of course, such pressure may be minimal (or practically inexistent) in very simple interactions where the course of action is evident to the agents, but it can also peak in case of complex interactions where the agents' stakes are very high. Importantly, the rules based on which such roles and statuses are assigned (as well as the agents' intentions that initiate the joint action) will typically be formulated in an explicit way, which secures common knowledge about them among participants. Usually, common knowledge is described as a set of recursive beliefs that range over others' (recursive) beliefs. On this view, a proposition p is common knowledge in a population n, if everybody in n knows (and, thus, believes) p, everybody in n knows (and, thus, believes) that everybody in n knows (and, thus, believes) p, etc.

To be sure, it is very much debated in the literature whether common knowledge is indeed required by joint intentionality and how the notion ought to be understood (32–34). Yet many

[4]On shared beliefs, see the classical work by Gilbert (18). For recent work on shared emotions, see von Scheve and Salmela (19).

prominent accounts concur that common knowledge indeed is an important feature of joint intentionality, which is required to make all parties informed about the fulfillment of the above-described psychological preconditions [see (23, 25, 35, 36)].

Another characteristic of joint intentionality should not go unnoticed: the intentions had by the individuals come in the "I-form" [or "I-mode," see (25)]. In other words, individuals form and maintain intentions from their own *individual* perspective[5]. Basically, this means that an interaction steered by joint intentionality is initiated by intentions, which the agents form on the basis of *individual* reasons and motives (in the example at stake: your and my individual intention of writing a paper) and which they entertain from their *individual* perspectives. Another way of putting this is that, in joint intentionality, agents have the unilateral power to break apart the shared intention by a simple change of mind—if an alternative emerges, which is more appealing to the individual, this individual is free to give up on his or her intention and pursue another option [(35), p. 79]. This is also why agents operating on the basis of joint intentionality often monitor each other with circumspection—one agent is motivated to invest efforts in the joint activity only as long as, and to the extent to which, the other agent, too, invests resources in the activity (thereby signaling that they remain committed to their individual goal) and vice versa.

We-Intentionality

Things look differently if one turns to "we-intentionality." Here, individuals occupy mental states in the "we-form" [or "we-mode," see (25)], which are poised to be reported by employing the first-personal plural pronoun ("we intend …"). For example, imagine that some friends decide to cook dinner together by each of them forming an intention of the form "we intend to cook dinner." In this case, the goal is *not* shared *distributively* as in joint intentionality, where the individual goals happen to overlap. Rather, in we-intentionality, the goal is understood as a group's goal, which all group members, *collectively*, are committed to bring about. Differently put, each individual forms a we-intention that aims at a goal, which is framed as collective or as a group's goal and the achievement of which the individuals are committed to. Importantly, because of this commitment to the achievement of the group's goal, agents do not have unilateral power to dissolve their we-intentions—if one individual considers giving up on the joint action, some form of permission for doing so should be sought in the other parties (35)[6].

Engaging in we-intentionality appears to require at least two elements. The first is that individuals must be able to answer the question "Who am I?" by saying: "I am one of us" (39). More specifically, they must be able to understand themselves as group members. This self-understanding as a group member elicits a subjective sense of group membership (39), belongingness (40), or we-ness (41), which transforms the agent's self-experience into a self-experience as a group member, thereby delivering the motivation to form and entertain we-intentions. In other words, insofar as agents see themselves as group members, they are motivated to act as such[7].

The second requirement of we-intentionality is that agents must be able to answer the question "What should we do?" by referring to the group's goals or preferences (42): "we intend to φ." This presupposes the capacity to take the group's perspective or the "we-perspective" (43–45) and, thereby, to frame the world from the perspective of one's group[8]. Adopting this perspective also provides the agents with "group nous" (48) or "group ethos" (25), i.e., with practical knowledge on how to plan their conduct and to efficiently adapt it to the group's goal.

We subsume the process of acquiring a self-understanding as group member and the capacity to adopt the group's perspective under the umbrella term of "group identification" [(27); see also (49, 50)]. We will elaborate on the issue of group identification in the next sections, but it should be emphasized already now that group identification may happen even in the absence of previous interaction among the agents. Given certain conditions, to which we come back especially in Frailty of We-Intentionality in Schizophrenia Spectrum Disorders section, total strangers may group identify and, thereby, acquire the disposition to collaborate. This may suggest that the difference between joint and we-intentionality does not hinge on pre-existing relations among the involved individuals—both forms of shared intentionality may build upon previously existing relations, but both could also be activated even in the absence of those relations[9].

[5]Perhaps not surprisingly, not everybody agrees on this point. For instance, Searle (22) and Wilby (37) argue that for individual intentions to steer a joint action, they must be held by the agents from the group's perspective (they are "we-intentions"). Despite substantial differences, the account of we-intentionality, which we develop in *We-Intentionality* section, broadly aligns with this approach. However, one bone of contention is whether we-intentionality is the *only* psychological power that can steer a joint action, and this is what we deny (as this section on joint intentionality illustrates).

[6]This seems clear enough in large groups, but what about in small dyads? Would not a change of mind in one of the two parties necessitate a change of mind in the other and, therefore, the collapse of the joint activity? In actual practice, this might well be the case, but this possibility still remains contingent on the following, namely, that members are licensed to do so only under the understanding that both of them have reneged on the commitment toward their goal. Often, that understanding remains tacit, but this is simply because the members typically know each other well and consider this procedure for dissolving the commitment permissible [see on this in (38)].

[7]Note that this does not exclude the possibility for individuals to contribute to a group's goal for other reasons as well (e.g., conformism and reputation management).

[8]One behavioral outcome of the adoption of the group's perspective is the so-called "black sheep effect," which can be detected already at the age of three (46) but manifests itself in its mature form from the age of eight (47). This effect is evident in the way in which loyalty or disloyalty to a group is assessed: loyal behavior of in-group members is praised more than a similar behavior by out-group members; and deviant, or disloyal, behavior of in-group members is punished more severely than a similar behavior by out-group members. Importantly, since the tokens of behaviors that are assessed do not differ in their properties, there is nothing that makes these tokens of behaviors intrinsically better or worse. This illustrates that, when the perspective of the group is factored in, the assessment of the behavior in question diverges: a loyal action toward group G is assessed as more praiseworthy than loyal actions toward other groups only from G's perspective. Conversely, it is only from G's perspective that a deviant action toward G is punished more harshly than deviant actions toward other groups.

[9]On this note, it might be important to remark that we-intentionality has the disposition to sediment and to solidify through time, enabling the existence of large groups animated by a sense of cohesion that is sustained by a shared social identity (3, 51).

There are important differences between interactions based on joint intentionality and interactions based on we-intentionality. First, when steered by we-intentionality, the whole interaction assumes a spontaneous character—the other does not need to be monitored constantly but is *trusted* to deliver the contribution to the joint activity because the other, as oneself, is framed as an in-group member [see (52)]. This is a form of trust described in social psychology under the label of "depersonalized trust," where it designates a trust that is "extended to any member of the ingroup whether personally related or not" [(53), p. 433] just in virtue of the fact that the other has been framed as an in-group member. In addition, in these interactions, the agents are not under the relentless pressure of deliberating about the plans: things can be done the way "we" do, by substantially relying on shared *common sense*[10]. Obviously, this does not imply that agents will not scrutinize, revise, or reassess the group's plan at any point in time where this may be required. Shared deliberation about means and distribution of labor is and remains in the service of shared agency, but the pressure on the agents to engage in action planning is arguably more limited than in joint intentionality scenarios.

The discussion of these two forms of sharing is not meant to be exhaustive and leaves open several important questions such as whether these two forms of shared intentions are distinct in kind (or just in degree of, e.g., cognitive complexity), which form is ontogenetically and phylogenetically more primitive[11], whether there are yet other forms of shared intentions, and whether sharing of beliefs and emotions operates in the same way as sharing of intentions. These questions already show that we are not proposing a "one-fit-all" account of shared intentionality. However, we do suggest that this conceptualization of shared intentionality and especially the description of the main features and psychological preconditions of joint and we-intentionality (as summarized in **Tables 1**, **2**) may be a valuable theoretical framework for understanding the impairment of sociality in SSD and severe ASD.

Before approaching how shared intentionality is disrupted in SSD and ASD, it is important to add a few further details to this picture to avoid potential misunderstandings. *First*, talking of we-intentionality in the context of this paper is talking of intentions had by individual agents, who have group identified, and where group identification is a psychological process that elicits as *subjective* sense of group memberships (i.e., one frames oneself as an in-group member). While one can speculate that an *objective* sense of group memberships (i.e., the social fact that an individual belongs to a certain group) must be related to a subjective sense of group memberships, our paper is entirely focused on those joint actions that are enabled by a subjective sense of group membership. *Second*, our paper takes shared agency in informal and small-scale groups as its main explanandum and remains largely silent on agency in large and institutionalized groups, and on their relation to shared intentionality. However, it should be noted that we do not see any straightforward relation between informal, small-scale groups and joint intentionality, on the one hand, or between large, institutionalized groups and we-intentionality, on the other. Just as we-intentionality can be activated in dyadic joint action, so can joint intentionality be activated in large-scale corporate agency. So, for instance, it could be that an individual agent's goal and a group's goal overlap—in this case, the individual agent may form a participatory intention with another agent in the sense of joint intentionality (it just so happens that the other agent is a group agent). *Third*, because factors like trust, collective goals, and the group's perspective are inherent in we-intentionality, and because they enable, regiment, and sustain joint activities, we-intentionality can steer activities that do not require plans, rules, structure, norms, etc. (which, however, is not to say that we-intentionality cannot also steer activities that are planned, structured, normed, etc.). By contrast, precisely because joint-intentionality lacks those factors, it is conducive to activities that require plans, rules, and structure.

SCHIZOPHRENIA SPECTRUM DISORDERS

The contemporary diagnostic manuals, i.e., ICD-10 (60) and *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) (61), define schizophrenia as a psychotic disorder, characterized by delusions, hallucinations, catatonia, severe formal thought disorders (e.g., incoherence), and negative symptoms (e.g., decreased emotional expressivity). Schizotypal disorder is defined slightly differently in the two manuals: ICD-10 lists it immediately after schizophrenia [(60), p. 95], whereas DSM-5 lists it among the personality disorders [(61), p. 655]. However, there is general agreement that schizotypal disorder is a part of the schizophrenia spectrum [(61), p. 90].

These manuals also acknowledge interpersonal difficulties that may accompany schizophrenia, e.g., impoverished interpersonal relations [(61), p. 99] and social withdrawal or lowered social performance as a result of negative symptoms [(60), p. 88]. DSM-5 describes schizotypal disorder as a "pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships" [(61), p. 655]. In addition, "lack of close friends or confidants other than first-degree relatives" forms a diagnostic criterion; ICD-10 lists "poor rapport with others and a tendency to socially withdraw" as a criterion. Classical accounts of SSD [e.g., (57, 62–64)] emphasize that interpersonal difficulties are not some additional or marginal aspect, e.g., mere sequela of psychosis, paranoid ideation, or suspiciousness, but an integral, often persistent part of SSD.

In the following, when we explore aberrant social behavior in schizophrenia, we will therefore not zoom in on abnormalities of behavior that primarily co-occur with psychotic or near-psychotic episodes [e.g., walking naked in the streets, mutism,

[10]By "common sense," we understand the body of "hinges propositions" (54) that enable our (individual or collective) agency in a shared world. These are propositions that "stand fast" for the agents and deliver their "primitive certainties." Accordingly, Wittgenstein's hinge propositions are to some extent similar to Searle's "background capacities" [(55), p. 175–96], which are not really beliefs but rather ways of behaving that manifest that something has been taken for granted [(56), p. 112–13]. In the psychiatric literature, Blankenburg (57, 58) has offered a detailed account of loss of common sense as a central feature of schizophrenia.

[11]Although it exceeds the purposes of this paper to elaborate on this, it merits attention that one of us has argued that we-intentionality developmentally precedes joint intentionality [see (27, 28, 38, 59); for a similar view, see (41)].

TABLE 1 | Core features of joint and we-intentionality.

	Goals	Perspective	Interpersonal stance
Joint intentionality	Individual	Individual perspective	Circumspection
We-intentionality	Collective	Group's perspective	Trust

TABLE 2 | Psychological preconditions of joint and we-intentionality.

	Psychological preconditions	
Joint intentionality		Mentalizing abilities
	Mind reading	"Being moved" by the other's intention
We-intentionality		Group identification
	Self-transformation	Adoption of the group's perspective

or the so-called "crazy actions"; (65–72)], which in themselves reflect a dislocation from the shared-social world. Rather, we will key in on more pervasive and persistent interpersonal difficulties that regularly are found in SSD, and which classical psychopathologists associated with the Bleulerian concept of *schizophrenic autism* [see (62), p. 63ff], which should not be conflated with the notion of autism that arose from the work of Kanner (73) and Asperger (74), and which has formed the basis of the concept of ASD (see Social Behavior in Severe Autism Spectrum Disorder section).

Social Behavior in Schizophrenia Spectrum Disorders

When approaching the topic of sociality in schizophrenia, one is likely to encounter the following puzzle. On the one hand, patients with SSD often report continuous difficulties in establishing and maintaining social relations with others, and frequently these difficulties are a source of loneliness and isolation. On the other hand, patients may simultaneously report that they really enjoy and often participate in various forms of social interactions. What is puzzling is of course not that patients participate in all kinds of social interactions, despite the difficulties they may experience, but that some of these social interactions apparently are experienced as easy and enjoyable, whereas other interactions are experienced as almost intolerable. Yet it remains unclear what constitutes this significant difference. How can we explain this puzzle?

In previous work (10), we have described, based on anecdotal clinical experience over many years, that social activities such as karate, ballet, board games, live action role-playing, and massively multiplayer online game (MMOG) often seem to be experienced as quite unproblematic. By contrast, other activities such as spontaneous or informal social interactions or establishing and maintaining close friendships over an extended period of time often are experienced as difficult. A few examples from patients with SSD may help illustrate our points.

One patient, who regularly isolated himself for months, participated in a weeklong live role-playing game with many people he had never met before. He said, "There I could be myself in a way I haven't been able to since high school. When I play, I am 'in character' in a world, where B necessarily follows from A. It's a universe that you control yourself and unlike the real world, there's always a reason for what's happening" (75). A recovered patient, now working as a teacher, felt most interpersonal exchange, apart from that she had with her intimates, deeply uncomfortable. However, her professional life provided her with an important exception. She said, "I was surprised at how well it went (…) I think it's because I have a foundation in talking about professional stuff and the students don't expect that you small-talk a whole lot with them (…) There I'm playing a part, I have a certain role, I kind of have a function" (75). Another patient, a nursing student, describes how she avoids spending time with her colleagues during breaks, because the small talk makes her uncomfortable. Instead, she prefers to be around patients. She said, "I think I might have a bit more energy when I'm wearing my uniform (…) Then I have a part to play. Then I have to be a nursing student and I know what to say and what not to say (…) It's kind of like there are more written rules on how to behave, and that's more difficult when you're just being yourself." In her spare time, she reports being involved in eight groups of friends that all are organized around discrete activities. She said, "Compared with many of my friends who just get together without doing anything, I'm like (…) there needs to be some kind of point in meeting up or a kind of purpose." For her, one such purpose was badminton—"Then there's badminton, and it's from seven to nine, and that's it, then it's over" (76).

We have suggested that one answer to the question of the puzzling social behavior in SSD may be that some of these activities predominantly correlate with joint intentionality, whereas others predominantly correlate with we-intentionality[12]. In our view, the hypothesis that best coheres with the observations about social behavior is that patients with SSD regularly may find interaction based on we-intentionality difficult, whereas they typically do not encounter problems with joint intentionality. As we have argued in Joint Intentionality section, it is usual for interactions steered by joint intentionality to have quite neatly defined roles, to be structured (some of these interactions are ritualized), and to rely on a set of explicitly formulated rules. These features of social interaction based on joint intentionality are vividly described in the examples above. We have argued that these features evoke a sort of tranquilizing effect insofar as they contribute to make the activities and the social context in which they occur predictable, reliable, and essentially safe. Differently put, the uneasiness, confusion, and pervasive anxiety that many patients with SSD may experience in social situations are counteracted or balanced by these features as they enable participants to know *what* to do, *how* to do it, and *when* to do it [(10), p. 160]. Further studies into the social life world of patients with schizophrenia indicate that

[12]We write "predominantly" because the kind of activity at stake *per se* is not revelatory of the kind of shared intentionality that steers it. One and the same activity (e.g., karate, writing a paper, or cooking dinner) can be engaged in by joint intentionality or we-intentionality. What matters is how the agents frame the activity and, in particular, whether the activity's goal is shared distributively or collectively. We come back to this point below.

patients may, in fact, adopt joint intentionality in social contexts and relationships, where one perhaps would expect to find we-intentionality (75, 76). For example, patients may actively employ various "compensatory strategies" to navigate the social world, e.g., imposing a spatiotemporal structure on social interactions (that typically would not necessarily possess such a structure) and seeking out or preferring activities marked by a clear distribution of social roles and rules (75). In our experience, patients do not regard such compensatory strategies as constraints ideally to be overcome but rather as a structure on which their involvement with the social world hinges (75). In other words, such compensatory strategies, which, at least to some extent, exploit the resources of joint intentionality, seem to help patients live a social life, stabilize the conditions, and promote recovery [see (77)].

At this stage, it is important to note that the observations about the predilections of ritualized and structured joint activities in SSD could be claimed to be compatible with the possibility that the patients do activate we-intentionality when interacting. As we have suggested above, the correlation between joint intentionality and a structured form of agency is merely stronger in joint intentionality, but this does not exclude the possibility of rigidly structured interactions, which are steered by we-intentionality. So what does support the hypothesis that, in SSD, we-intentionality (but not joint intentionality) is disrupted?

The prevailing view in the literature is that impaired social functioning in schizophrenia is caused by social cognitive or neurocognitive deficits, which have been found to explain 20–60% of the variance of social functional outcome in schizophrenia (78). Thus, a considerable proportion of the variance remains unexplained, motivating a continued search for other relevant factors or mediators. Our suggestion is that the fairly specific psychopathological profile of SSD, viz., the aggregation of anomalous self-experiences in SSD, is a key source of these patients' difficulties in the interpersonal domain and, more specifically, that the aggregation of anomalous self-experiences exerts friction on the process of group identification, which, as described above, is a psychological precondition for activating and maintaining we-intentionality. In order to better explain our claim, we will, therefore, explore in some detail the notions of group identification and anomalous self-experience. We start with group identification and then discuss how certain anomalous self-experiences may destabilize this mental process.

In We-Intentionality section, we have introduced "group identification" as an umbrella term for two different processes. On the one hand, transformation in self-experience enables the formation of we-intentions. On the other, the adoption of the group's perspective, understood as a specific process of perspective-taking, delivers information to the agent about the group's preference or goal by instructing him or her on how to act based on the expectations and predictions of how the group will act. We will postpone a more thorough discussion of this second aspect of group identification till we turn to severe ASD (see We-Intentionality in Severe Autism Spectrum Disorder section). For now, we focus on the transformation in self-experience.

Such transformation of self-experience can be triggered quite easily as experiments conducted since the early 70s on the so-called minimal group paradigm illustrate [see (79, 80)]. This branch of research also shows that several conditions need to be fulfilled for a self-conception as "group member" to be acquired. What then are these conditions? First, the individual should be aware of what has been labeled "group cues" (49), which include having common interests, sharing a common fate, facing a competing group, and using we-language [(43); we return to these cues in We-Intentionality in Severe Autism Spectrum Disorder section, where we shall discuss a particularly important cue, namely, joint attention].

For now, it suffices to state that when a subject perceives these group cues, they can trigger two interrelated consequences. The first is "self-categorization," which conduces subjects to see themselves as saliently similar to the others (those who, say, have the same preferences, exemplify the same properties, or are in the same life condition, etc.). The second is what social psychologists call "depersonalization," which is described as "a shift toward the perception of self as an interchangeable exemplar of some social category and away from the perception of self as a unique person defined by individual differences from others" [(39), p. 50]. Because the term "depersonalization" also denotes both a psychiatric symptom and a disorder [(61), p. 302ff], we will refrain from using this term and instead use the term "de-individuation" to avoid potential confusions.

From the perspective of social psychology research, the ultimate effect of self-categorization and de-individuation is the acquisition of a self-understanding as group member or a "social self" (81). By conceiving of myself as member of a group (to which you, too, belong), I am moved to behave as a group member[13].

Frailty of We-Intentionality in Schizophrenia Spectrum Disorders

Let us now explore how various anomalous self-experiences may counteract group identification and, more specifically, the interrelated process of self-categorization and de-individuation.

It is important to keep in mind that anomalous self-experiences are not discrete, atomic-like symptoms but mutually implicative aspects of the psychopathological *Gestalt* of the schizophrenia spectrum (85, 86). Empirical studies have documented that, on average, patients with SSD have ∼20 anomalous self-experiences, and this is significantly more than what has been found in all other mental disorders (66–72, 87, 88). Overall, the empirical studies on anomalous self-experiences seem to support the idea that the basic disturbance in schizophrenia spectrum disorders is a disorder of ipseity or minimal self (14, 89–91)].

[13]What sort of representation is the social self, viz., this peculiar understanding of oneself as a group member? In related work (27), we have argued that this is neither a doxastic state (like beliefs and perceptions) nor a conative state (like intentions and desires). Understanding oneself as a group member, in the sense at stake here, is to be in a state that at once describes the subject as a group member and motivates her to act as such. In the literature, different authors have labeled states as these differently: "Pushmi-Pullyu Representations" (82), "Aliefs" (83), or "Interested Participatory Representations" (84).

In the following, when we address a few singular anomalous self-experiences and discuss how they individually may impede self-categorization and de-individuation, this is done strictly for expository purposes. Other anomalous self-experiences may impede these processes as well (e.g., thought pressure, ambivalence, inability to distinguish modalities of intentionality, diminished sense of being present in the world, and quasi-solipsistic experiences), but they will not be explored here. Furthermore, we are not ruling out the roles that deficits in theory of mind, neurocognition, or social cognition may have on group identification, and we have no reason to believe that such roles should somehow be inconsistent with the role that we here ascribe to anomalous self-experiences—e.g., one study found that patients with first-episode schizophrenia under-interpreted social cues and over-interpreted non-social cues (92). There is a long tradition of research on theory of mind deficits in schizophrenia (93). While such deficits perhaps also may exert friction on the process of group identification and thus we-intentionality, these deficits do generally not appear to be so severe that they hamper the psychological preconditions for joint intentionality in SSD (we discuss this issue in the end of Joint Intentionality in Severe Autism Spectrum Disorder section).

In the following, we first summarize a few anomalous self-experiences and the process they may impact before subsequently exploring these issues in further detail. In our view, self-categorization by which subjects perceive themselves as saliently similar to others is often destabilized by a feeling of being different from others (*Anderssein*) and problems involving common sense problems.

First, "Anderssein" refers to enduring and pervasive feelings, which usually have been present since childhood or early adolescence, of being different from others or simply "wrong" as some patients put it [(14), p. 253]. In short, it is a profound feeling of inner and existential alienation. Nagai has aptly stressed the difficulty in understanding this feeling of being different in schizophrenia [(94), p. 497]. Usually, when we speak of differences, we presuppose a shared domain in which such differences occur and are measurable against each other. But in the case of "Anderssein" in schizophrenia, Nagai suggests that there is no such shared domain and that we are instead faced with a non-objectifying, contentless feeling of difference [(94), p. 497f]. In other words, we are dealing with a global feeling of difference that often resists verbalization and precedes thematization, i.e., finding out "what" is different. Nonetheless, patients often search for and find some explanation for their pervasive feelings of difference (e.g., "it's my low self-esteem" or "I am an introvert"), but when explored in depth, such explanations usually do not fully exhaust their profound feeling of difference, which often appears to be rooted in a much deeper sense of "being ontologically different" [(14), p. 253]. While many patients struggle to convey the quality of this feeling of difference, others are able to express it in quite illustrative ways. For instance, one patient said, "I looked just like every other child, but inside I was different. It is as if I am another creature that somehow ended up inside a human body" [(95), p. 436]. Another patient said, "I've always felt as if others could almost smell that I was different. They could simply feel that I was a different animal in the herd. I always felt like a giraffe among rhinos" (75). Yet another patient described how he already from childhood felt lonely, insecure, and different from others. At one point, he asked his mother if he was robot because, as he said, "I felt like I was a machine … if one could remove the face, then I thought there would be a machine inside or perhaps some other creature" [(96), p. 180]. In our view, such profound feelings of *ontological dissimilarity* may impede recognition of more *mundane similarities* (e.g., similar taste in music) or make such similarities appear superficial or arbitrary, thereby impeding self-categorization and, thus, group identification [(10), p. 162f].

Second, feelings of being different from others often go hand in hand with various problems of common sense [(57, 58), p. 307f]. The heart of common sense problems appears to be a failing of automatic, pre-reflective attunement in the person's self-, other-, and world-relation [(14), p. 253]. Common sense problems often manifest as an inability to simply take for granted what others consider obvious or matter of fact. One patient offers a vivid description of how she experienced these issues—she said,

> I have always struggled to understand why people didn't take life more seriously. I mean, "How can you just walk around, be named 'Angie,' buy butter, and take riding lessons?" Every morning, when I wake up, I realize like for the first time that this is the real reality, that we are all going to die, that we don't know why we are here, that nothing makes sense … This is one of the reasons why I feel different from others. They walk around and talk on their phone, plan what they want to do … It puzzles me that I haven't gotten used to it. Everyday I realize that the sky is just above us, right … infinity is so near, we don't know why we are here, and we will all die … It hurts me that it is so easy and natural for the rest of the world. They don't even think about it [(95), p. 267].

Another patient reported that she often pondered questions such as "why a table is called a table or why humans only have two arms instead of four or why the arms aren't placed lower to the ground, which would make it easier to pick up things" [(96), p. 180]. As Stanghellini (97) has argued, the crisis of common sense in schizophrenia does not only concern subject–object relations but crucially also the subject–subject attunement. This was also the case for this particular patient—she said, "I speculate a lot on why people do what they do? I often don't get it" [(96), p. 180]. As the examples indicate, common sense problems are typically associated with tendencies to hyper-reflect about oneself, others, or objects in the environment, often in an attempt to decode their meaning. In our view, common sense problems and hyper-reflection may impede recognition of group cues, e.g., by disallowing relevant properties to stand out as salient in social contexts. The prediction that these considerations justify is that, again, this particular anomalous self-experience may impede self-categorization.

Next, we suggest that the process of de-individuation by which subjects deemphasize individual differences in favor of properties that are shared with others is destabilized by experiences of hyper-reflection/self-monitoring and transitivism.

First, as implied above, the objects of hyper-reflection may not only be others or objects in the environment but also aspects of oneself. For example, one patient reported that his central

problem concerned difficulties with engaging and remaining in relationships with others [(98), p. 206–208]. Starting a conversation was very difficult for him, and, at one point in his life, he stopped communicating with others altogether. He feels that "starting a conversation with someone implies taking over responsibility for the relationship, especially for the next step. Because he feels paralyzed at the same time, he doesn't dare to even start a conversation. The scenarios, which are constructed in his head before any relationship even takes place, completely block him" [(98), p. 207]. Similarly, other patients report that they, before starting a conversation with someone, prepare themselves minutely by imagining and playing out all possible routes the conversation may take (99). In other cases, hyper-reflection may lead to excessive forms of self-monitoring that are operative alongside the subject's engagement with others. For example, one patient reported how this made social interactions difficult for her:

> I always feel that it is like enormously feigned when I have some social interaction. It feels false, like I can't react naturally or sincerely like everyone else … I have the experience that there are two of me: the one that interacts with someone and then there is the real me, who sits there behind. For example, "I sense that the one I'm talking to finds my statement a little transgressive, so I add a little humor here to establish an ironic distance. That may perhaps … yes, that worked well …" And I do it, like, simultaneously. I don't feel present at all [(95), p. 267].

In our view, the self-involvement that is at stake in such experiences of hyper-reflection and self-monitoring may not only render fluid, spontaneous interactions with others difficult but also impede the subject from de-emphasizing individual differences as required in de-individuation.

Second, transitivism (sometimes also referred to as "demarcation problems" or "problems with ego-boundaries") denotes a group of experiences that are characterized by permeability of the me/not-me boundary. According to Schneider, most of the first-rank symptoms of schizophrenia (e.g., thought insertion, withdrawal or broadcasting, and other passivity phenomena) fundamentally involve transitivism—a "loss of the very contours of the self" [(100), p. 134; see also (101)]. Experiences of transitivism are frequently reported in SSD. For example, patients may describe experiences of being somehow "mixed up" with another person, not knowing what side of the mirror they are on, or more pervasive experiences of being "too open" or "without any barriers" (102). One patient reported being very anxious among others, whom she felt "can see through me and see all the bad things I have done in my life" [(96), p. 180]. Parnas and Handest (103) offer another illustrative vignette:

> A young man was frequently confused in a conversation, being unable to distinguish between himself and his interlocutor. He tended to lose the sense of whose thoughts originated in whom, and felt "as if" his interlocutor somehow "invaded him," an experience that shattered his identity and was intensely anxiety provoking. When walking on the street, he scrupulously avoided glancing at his mirror image in the windowpanes of the shops, because he felt uncertain on which side he actually was. He used to wear a wide and tight belt in order to feel "more whole and demarcated" [(103), p. 130].

In our view, experiences of transitivism, which usually are experienced as very disturbing, may also affect the process of de-individuation. It seems at least possible that patients who already feel vulnerably transparent and too open may want to resist de-emphasizing individual differences.

One could question whether the non-psychotic anomalous self-experience, which we have described here, in and of themselves also could impact joint intentionality. In our view, this is not the case. Although patients often feel different from others, joint intentionality, unlike we-intentionality, does not hinge on group identification. Patients also often report problems with common sense (e.g., a failing grasp of the implicit rules of social interaction), regularly accompanied by hyper-reflection. However, such confusion in social interaction is largely bypassed in joint intentionally, which typically has a well-defined goal and rely on explicitly formulated rules and roles, securing common knowledge among the participants. With regard to transitivism, it is important to emphasize that although patients, in certain situations, may feel "as if" others, merely by looking at them, can know what they are thinking, they actually know that this is not the case (as implied in the conditional "as if"). In other words, the ego-boundaries, though sometimes felt as frail or permeable, are not dissolved. Thus, it does not follow that the patients' capacities for being aware of others' intentions and forming participatory intentions to, say, write a paper together or play badminton necessarily would be compromised by this group of anomalous self-experiences.

To briefly summarize, this section sought to explain the aberrant social behavior in SSD by claiming that we-intentionality is fragile, whereas joint intentionality remains unaffected. Moreover, we have argued that group identification is a psychological precondition of we-intentionality and that group identification—and more specifically the interrelated process of self-categorization and de-individuation—can be destabilized by various anomalous self-experiences, which then render we-intentionality fragile. In this regard, disturbances of sociality can be seen as an integral part of the schizophrenia spectrum, as originally pinpointed by classical psychopathologists.

AUTISM SPECTRUM DISORDER

Before describing autism and assessing the functioning of shared intentionality in ASD, it is important to emphasize that our previous description of the two forms of shared intentionality and their psychological preconditions was framed from a developmentally advanced perspective. Turning now to developmental psychology and psychopathology, and more specifically to the case of autism in young children and toddlers, one should bear in mind that, as Hobson repeatedly has stressed (104, 105), what appears to be, from a developmentally advanced perspective, relatively distinct capacities (e.g., thinking, feeling, and willing) may *not* be clearly distinct capacities in infancy and early childhood. Moreover, these very capacities may *themselves*

be achieved and relatively separated from each other on the basis of a complex social-emotional developmental process.

This observation also pertains to our own account of shared intentionality: some of the psychological preconditions, which we have described, are of course not available capacities in infancy and early childhood [see (27)]. Rather, they emerge fairly late in psychological development and thus arguably hinge on other, more basic factors. This is why, when exploring shared intentionality in children with severe ASD, we will not, as in the case of schizophrenia, assume the psychological preconditions are available and then explore ways in which they may be affected. Rather, we will key in on certain fundamental issues that seem to impede the emergence of the psychological preconditions for joint and we-intentionality in severe autism.

We now turn to how autism is defined in the diagnostic manuals. DSM-5 and ICD-10 concur in describing autism as a pervasive developmental disorder, which is characterized by deficits in social communication, in social interaction across multiple contexts (verbal, emotional, etc.), in restricted and often repetitive behavior, and in a limited range of interests. While ICD-10 (60) distinguishes between infantile autism (F84), atypical autism (F84.1), and Asperger's syndrome (F84.5), DSM-5 has replaced the diagnoses of autistic disorder and Asperger's disorder from DSM-IV-TR (106) with the diagnosis of ASD, and a similar nosological change will occur in ICD-11. ICD-10 states that some deficits in the above-mentioned domains of development are manifest before 36 months for infantile autism [(60), p. 253; (107), p. 147], and DSM-5 states that symptoms of ASD typically are recognized between 12 and 24 months [(61), p. 55]. Asperger's syndrome is defined by "the same kind of qualitative abnormalities of reciprocal social interaction that typify autism," together with limited interests and restricted behaviors, but without clinically significant delays in cognitive development or retardation of language [(60), p. 258f; cf. (106), p. 80]. In the following, we will focus on social behavior in the severe end of ASD and explore it from the perspective of shared intentionality.

Social Behavior in Severe Autism Spectrum Disorder

Aberrant social behavior has always been considered as a hallmark of autism. The current diagnostic criteria reflect some aspects of this social behavior, but they also, inevitably, ignore other aspects and qualities of such behavior. A few clinical examples, offered in the foundational texts on infantile autism by Kanner (73) and Asperger (74), may serve to illustrate characteristic forms of disturbed sociality in autism and help us key in on some of the central features. Despite the fact that almost 70 years has passed since the publication of these foundational texts, their clinical observations remain valid for infantile autism—even though they do not apply to what is nowadays defined as "Asperger's syndrome," "high-functioning autism," or the full spectrum of ASD. This gives us an opportunity to reinforce that our account aims at covering *severe* forms of autism, i.e., infantile autism, but does not apply to milder form of ASD. Our approach to aberrant social behavior in severe ASD further draws on the existing literature [e.g., (104, 105, 108)], and it supplements this extensive body of knowledge by addressing the topic from the perspective of shared intentionality.

In his original study, Kanner (73) described the case of a 4.5-year-old boy, Charles N., whose mother expressed her chief complaint as follows, "The thing that upsets me the most is that I can't reach my baby" [(73), p. 235]. She described her child as detached and as living "in a world of his own where he cannot be reached. No sense of relationships to persons." She also said, "When he is with other people, he doesn't look up at them. Last July, we had a group of people. When Charles came in, it was just like a foal who'd been let out of an enclosure. He did not pay attention to them but their presence was felt (…) At school, he never envelops himself in a group, he is detached from the rest of the children, except when he is in the assembly; if there is music, he will go to the front row and sing" [(73), p. 236]. Charles N. displayed many of the signs that came to define the concept of autism such as repetitive behaviors or stereotypies (e.g., spinning toys for hours), preferring aloneness, avoiding eye contact, abnormalities of communicative exchange (e.g., echolalia, not responding to his own name, and reversing personal pronouns), restricted interests, and insistence on sameness in his routines.

These characteristic autistic features made the interpersonal relation between Charles and his mother very difficult, leading her to describe him as "unreachable" and "inaccessible." In his concluding remarks, Kanner keyed in on this specific aspect of autism: "The outstanding, 'pathognomonic,' fundamental disorder is the children's *inability to relate themselves* in the ordinary way to people and situations from the beginning of life" [(73), p. 242]. He further stated: "The children's *relation to people* is altogether different" [(73), p. 246], exemplifying it with (i) avoiding eye contact; (ii) not paying attention to other people present; (iii) not clearly registering persons coming and going; (iv) if an adult intruded in the child's game by hindering access to a desired object, the child would struggle with the obstructing hand or foot as a detached object, but would not attend the person, whose hand or foot it was; and (v) for the 6- to 8-year-olds, not playing *with* other children or participating in groups (though sometimes playing in the periphery of a group *alongside* other children), etc. [(73), p. 246–250]. Finally, Kanner famously concluded, "We must, then, assume that these children have come into the world with innate inability to form the usual, biologically provided affective contact with people, just as other children come into the world with innate physical or intellectual hand[i]caps" [(73), p. 250]. Notably, Kanner also emphasized some of the children's remarkable memory and good vocabulary.

The following year, Asperger published his study on "autistic psychopathy" in children (1944/1991), which bore strong resemblances to Kanner's study. Asperger also described autistic children's marked difficulties in social interaction, avoidance of eye contact, inability to play with other children or participate in groups, obsessive-like behaviors (close to what Kanner called "insistence on sameness"), hypersensitivity to sensuous stimuli, motorically clumsiness, stereotypic activities, and positive aspects of "autistic intelligence." Asperger suggested that autism can

occur at all levels of intellectual ability [(109), p. 58f, 74], and he argued that autistic features were visible early in development and temporally persistent: "From the second year of life we find already the characteristic features which remain unmistakably and constant throughout the whole lifespan" [(109), p. 67][14]. He concluded, "the essential abnormality in autism is a disturbance in the lively relationship with the whole environment," and this disturbance "explains all peculiarities shown by autistic individuals" [(109), p. 74]. A few pages later, he specified his claim as follows: "It has been my aim to show that the fundamental disorder of autistic individuals is the limitation of their social relationships" [(109), p. 77], and he argued that a "distinctive emotional defect" may be "an ultimate cause for their social disturbance" [(109), p. 80], which he then described as "a genuine defect in their understanding of the other person" [(109), p. 81].

Many of the clinical observations in these foundational texts have since been empirically corroborated and extensively elaborated. An important point, which is mostly implicit in these texts, however, is that children with severe ASD are not without communicative interests, though they communicate and interact less and differently than children without ASD or even with milder forms of ASD. They are also not insensitive to or unaffected by the presence of others (112). Furthermore, studies have dismissed the idea that autistic children and their mothers, despite the distress, cannot form secure attachments [e.g., (113, 114)], which seemed to be implied in Kanner's case of Charles N.

However, to sum up, following Kanner's and Asperger's insights, the essential problem in severe autism concerns *relating* to or *understanding* other persons *as* persons.[15] As one autistic adult put it:

> I really didn't know there were other people until I was seven years old … I then suddenly realized that there were people. But not like you do. I still have to remind myself that there are people … I never could have a friend. I really don't know what to do with other people, really [(116), p. 388; cited in (104), p. 3].

A 22-year-old autistic individual (Tony W.) who had been diagnosed with infantile autism nearly two decades prior offered the following description (text as in original):

> I dont or didnt trust anybody but my self – that still (is) a problem today. And (I) was and still (am) verry insucure! I was very cold Harted too. I(t) was impossible for me to Give and Receive love from anybody. I often Repulse it by turning people off. Thats is still a problem today and relating to other people. I liked things over people and didnt care about People at all (…) My problems havn't changed at ALL from early childhood [(117), p. 50, 52].

Apart from highlighting forms of sociality that may appear strange for people without autism (e.g., the *realizing* that there are others, having to *remind* oneself that there are people or *turning people off*), the descriptions also illustrate the autistic individuals' partial awareness of their own difficulties in relating to other persons.

Joint Intentionality in Severe Autism Spectrum Disorder

Let us start with an investigation into the relation between severe ASD and joint intentionality. The first precondition for joint intentionality concerns mind reading abilities, which enable the subjects to become aware of the other agents' intentions and also to establish common knowledge among them about the fulfillment of the various requirements (where common knowledge is generally understood as a set of recursive beliefs ranging over others' beliefs about one's beliefs, etc.). The second precondition is that the subject should "be moved" by the other's intention in the sense of being willing to consider it and factor it in in her own deliberation and action planning. Remember that, in joint intentionality, the individual decides to act together with the other "partly because" of but also in "accordance with" the other's intention (24). Are these psychological preconditions met in severe ASD?

Let us now have a look at the first precondition and, in particular, with the capacity of tracking other agents' intentions. There is consensus in the literature that children with ASD are able to understand goal-directed actions [(118), p. 63, (105, 119)]. What remains a matter of debate is whether these patients are fully able to ascribe conative attitudes like intentions to others. First, it is controversial whether understanding goal-directed actions in young children amounts to understanding that a certain behavior is steered by a certain mental *attitude* (120, 121). Second, even granting the first point, it is unclear whether the kind of conative attitudes that children (with or without ASD) are able to understand is that of *intention*—in contradistinction to other kinds of conative states like wishes or desires[16].

Regardless of how these issues will be settled, experimental studies have long demonstrated that children with severe autism show deficits in theory of mind and, therefore, have problems in forming beliefs about others' mental states (which, by extension, implies problems in establishing common knowledge with others). In a seminal study, Baron-Cohen et al. (108) demonstrated that children with autism have difficulties discriminating another's (false) belief about a situation from their own (correct) belief about it. Using Wimmer and Perner's

[14] Asperger claimed that social adaption and integration in adulthood are to some extent possible but depend especially on the individual's intelligence. Concerning the differential–diagnostic boundaries between autism and schizophrenia, which today has become a topic of debate [e.g., (88, 110, 111)], Asperger, like Kanner, argued that they were distinct conditions, and Asperger explicitly denied the possibility that childhood autism could be a precursor for schizophrenia [(109), p. 86; cf. (73)].

[15] Kanner's and Asperger's attempts to articulate the generative disorder of autism in terms of "disturbance of affective contact" or "emotional defect" have since been challenged, especially by cognitive or meta-cognitive accounts [e.g., (108)]. Hobson's account, as we shall see later, can also be viewed as challenging the "affective" accounts of Kanner and Asperger as well as the more "cognitive" accounts insofar as he locates the systemic disorder in a basic form of relatedness that is irreducibly cognitive/conative/affective in nature [(105), p. 7, 131f]. For a brief overview of positions, see Trevarthen et al. [(115), p. 123–126].

[16] On the distinction between these conative states, see Bratman (122). On children's understanding of various kinds of conative states, see Astington (123) and Perner (124).

design (125), Baron-Cohen, Leslie, and Frith introduced two doll protagonists, Sally and Anne. Sally had a basket and Anne had a box. Sally then placed a marble in her basket and left the scene. Anne now took the marble out of Sally's basket and hid the marble in her own box. Sally then entered the scene, and the child was asked the critical question "where will Sally look for her marble?" The authors examined children with infantile autism, children with Down's syndrome, and normally developing children; and they found that children with Down's syndrome and normally developing children scored similarly, where 86% and 85%, respectively, passed the test. By contrast, 80% of the children with autism failed the test—they all "incorrectly" pointed to the actual position of the marble. According to the authors, the children with infantile autism did not appreciate the difference between their own knowledge of the event and the knowledge that could be attributed to the doll [(108), p. 43]. Since the children with Down's syndrome, who had lower intellectual ability than the children with autism, performed well on test, failing the test could not be explained as a mere sequela of intellectual disability.

Interestingly, the authors described what they were testing as a "*conceptual* perspective-taking skill," contrasting it with more traditional testing of "*perceptual* perspective-taking" such as "line of sight" or "three mountains" (where the child is confronted with the task of telling what can be seen from another, visual point of view [(108), p. 43f.]). Such tasks, they argue, may be solved solely by using visuo-spatial skills [e.g., (126)] and thus do not require attributing mental states to others. Finally, the authors refer to a study by Hobson (127), demonstrating that children with severe autism were no more impaired in *perceptual* perspective-taking tasks with doll protagonists than normally developing children matched on intellectual ability. Baron-Cohen, Leslie, and Frith conclude that the identified problem in the conceptual perspective-taking skill constitutes a specific cognitive deficit in ASD. In the following, we return to and dig deeper into this critical issue of conceptual perspective-taking in infantile autism.

For now, it suffices to state that literature on theory of mind, which covers more features than attributing false beliefs to others, show that individuals with severe autism typically have theory of mind deficits (128) and are impaired in the intuitive understanding that other people have mental states [(129), p. 283], or, as we put it earlier, in understanding persons *as* persons. This is sufficient for us to make the claim that individuals with severe ASD are likely to have difficulties fulfilling the first psychological precondition for joint intentionality. They encounter problems in tracking other intentions and in forming the recursive beliefs required for common knowledge.

What about the second precondition, i.e., the disposition to consider the other's intention and factor it in in the right way in one's conduct? In this respect, an important study by Hobson and Lee (130) has unveiled the difficulties for children with severe ASD precisely to be moved "according to" another's attitude. The study compared the way in which children with and without ASD acted after observing non-symbolic and non-conventional goal-directed actions performed by the experimenter by adopting different (and often idiosyncratic) styles of actions. Interestingly, children without ASD attempted to achieve the goal precisely by adopting the style or mode of action of the experimenter, i.e., by selective imitation[17]. According to the experimenters, this shows that the children without ASD were able to register and assimilate "another person's bodily anchored psychological stance (whether in feeling or action or some other way of relating to the world), in such a way that the stance becomes a potential way of the observer relating to the world from his or her own position" [(131), p. 411]. By contrast, children with ASD

> were not moved to adopt the orientation of the person they were watching. They did not adopt the style with which the experimenter executed the actions, [. . .] they were perfectly able to perceive and copy the strategies by which he achieved the goals in each demonstration. So they were able to learn something from watching what the experimenter did. They were also motivated to use what they had learned when their own turn came round. Yet what they learned seemed to be available from their position as a kind of detached observer of actions and goals. They were not "moved" [(132), p. 200].

Hobson's conclusion is reminiscent of Asperger's observation that children with autism have "an inability to learn from adults in conventional ways. Instead, the autistic individual needs to create everything out of his own thought and experience" [(109), p. 56]. It is crucial here to note that Hobson is using the expression "being moved" in a developmentally more primary sense than we have done so far. In our conceptual framework, "being moved" refers strictly to "being moved by the other's *intention*." By contrast, what Hobson is arguing here is that children with infantile autism have a *relative* decreased propensity to identify with others' bodily anchored attitudes toward objects or events in the world, whereby children are rarely emotionally drawn or "moved" to assume the others' psychological attitude and, eventually, to acquire it as a potential attitude for themselves [(104, 105), p. 14–28, 131–140][18]. It is plausible to conjecture that it is precisely because children with autism have a relative decreased propensity to identify with others that they also have difficulties factoring in the other's intentions when deliberating on how to pursue their own goal. Since the children rarely are "moved" in Hobson's sense of the term, they are also seldomly "moved" in the other sense that applies to the formation of participatory intentions.

[17] For instance, the "rolling policeman" is "a 10 cm high plastic toy policeman that stood on wheels. When the policeman was pushed down from above, a spring mechanism operated so that the policeman moved forward across the table under his own steam. The two styles that [the experimenter] used in operating the rolling policeman were as follows. In one case [the experimenter] cocked back his right hand and depressed the head of the policeman with the front of his wrist: in the other case he extended his index and middle finger, and used these to press down on the head" [(130), p. 655]. Whereas children without autism largely imitated the styles of the experimenter after observing them, the vast majority of autistic children did not imitate properly by activating the mechanism in any of the two styles but just used the palm of their hand to press on the head.

[18] Hobson employs the notion of identification in a technical sense, which should not be confounded with the other technical concept of group identification we discussed above (to mark Hobson's specific notion, we hyphenate, as he does, the notion of "identifying-with").

If these observations are correct, then they indicate that individuals with severe ASD have problems with fulfilling both psychological preconditions of joint intentionality[19]. First, they have difficulties in tracking other intentions and establishing common knowledge with others. Second, they also have difficulties in forming participatory intentions "partly because" of and in "accordance with" the other's intention.

Before proceeding to the next section on we-intentionality in ASD, we would like to tackle a potential objection concerning our claims about the relation of joint intentionality and ASD, on the one hand, and joint intentionality and SSD, on the other. The reservation is this: the alleged difference we draw between the two disorders vis-à-vis joint intentionality (which has been claimed to be problematic in ASD, but unproblematic in SSD) is unsubstantiated because the same problems with theory of mind observed in ASD, and detrimental to joint intentionality, can also be observed in SSD. And this should indicate the existence of problems with joint intentionality in SSD, too (contrary to our claim).

As a reply to this objection, we offer the following considerations. As noted earlier, our account targets only severe ASD. We are aware of some findings from literature on milder forms of ASD, e.g., ascertaining that theory of mind deficits do not generally apply to persons with high-functioning autism (134). Other studies, comparing schizophrenia and ASD, have reported fairly similar theory of mind deficits in the two syndromes [e.g., (9, 135, 136)]. However, two observations are here in order. First, the empirical study by Pinkham et al. (9) and the majority of studies, examined in the meta-analysis by Chung et al. (135) and in the review and meta-analysis by Bliksted et al. (136), only included persons with ASD with an IQ $>$ 70. Thus, as clearly pointed out by both Chung et al. [(135), p. 611] and Bliksted et al. [(136), p. 25), their findings are not generalizable to more severe ASD or to persons with severe ASD and intellectual disability. Second, the finding of comparable theory of mind deficits in schizophrenia and ASD also reflects the applied theory of mind tests. Notably, Doody et al. (137) applied the Sally-Anne test (a so-called first-order theory of mind test) to different patient groups, including schizophrenia. Not a single patient with schizophrenia ($n = 28$) failed the Sally-Anne test. Some problems were, however, observed in an additional second-order theory of mind test in patients with schizophrenia as well as in other diagnostic groups. This finding is echoed in a conclusion of a review on theory of mind deficits in schizophrenia, which states that understanding of first-order theory of mind problems is relatively preserved in schizophrenia (138). In our paper, we focus solely on infantile autism, and thus, given the observations above, the findings of comparable theory of mind deficits in high-functioning ASD (with IQ $>$ 70) and SSD do not contradict our conclusions that joint intentionality is impaired in severe ASD but not in SSD.

[19]Let us emphasize again that our considerations only apply to severe autism. In fact, it has been suggested that Asperger patients may be able to engage in activities steered by joint intentionality (133).

We-Intentionality in Severe Autism Spectrum Disorder

Turning now our attention to we-intentionality, the analysis will mainly focus on certain characteristic difficulties that seem to impede the emergence of the two psychological preconditions that enable group identification and thus this form of shared intentionality. These are the capacity to understand oneself as a group member (i.e., "transformation in self-experience") and the ability to adopt the group's perspective (or we-perspective). Earlier, we have argued that the process of transformation in self-experience is initiated by the perception of group cues in the environment, which then triggers self-categorization and de-individuation (see **Figure 1**). Our discussion starts with the limited efficacy that group cues have in triggering group identification in subjects with ASD. We then move to transformation in self-experience, where we assess major difficulties that counteract especially self-categorization. We end with some speculative thoughts on why the adoption of the group perspective is impaired in the disorder.

As we have seen, some of the cues identified in social psychology research include sharing common interests or a common fate, facing a competing group, and using we-language. However, not all cues are equiprimordial from a developmental perspective, and one might doubt whether children of very young age are able to encode the properties at the basis of these cues. Yet at the same time, research into the early development of joint action has convincingly shown that children from the age of 18 to 24 months can engage in joint actions (139–142). Given the cognitive demandingness of joint intentionality (34, 143), it has been suggested that the joint actions in 18–24 months young children most likely are steered by some form of we-intentionality [see (27, 49)][20].

So what can facilitate we-intentionality in children of 18–24 months of age? One proposition that has been put forward [see (27, 34)] is that triadic joint attention may well play the required role here. To participate in an episode of triadic joint attention may sustain self-categorization because it is integral to the qualitative or phenomenal character of joint attention (i.e., to how joint attention is lived through by the subjects) that the participants see themselves as *co-attenders* and, arguably, that they are aware of sharing certain salient similarities. At this early stage of development, attending to the same object and perhaps with the same attitude, e.g., curiosity, is a sufficient salient similarity.

If triadic joint attention is relevant to we-intentionality, then difficulties with we-intentionality should be also expected in severe ASD, given that impairment in joint attention is a robust and predictively powerful indicator of severe ASD in

[20]One argument supporting this claim is that, in children, the ability to engage in joint action emerges earlier than the development of mindreading abilities. Passing the false belief test, e.g., the Sally-Anne test, at the age of 4 has traditionally been considered the first reliable mark of theory of mind abilities (125, 144, 145). While some theory of mind tests [so-called "spontaneous-response" (146) or "indirect" tests (147) in contrast to classical "elicited-response" tests like the Sally-Anne test] predate the emergence of these abilities to 2.5 years of age (148), if not even to 13 months of age (146), they still do not align with the developmental emergence of joint actions.

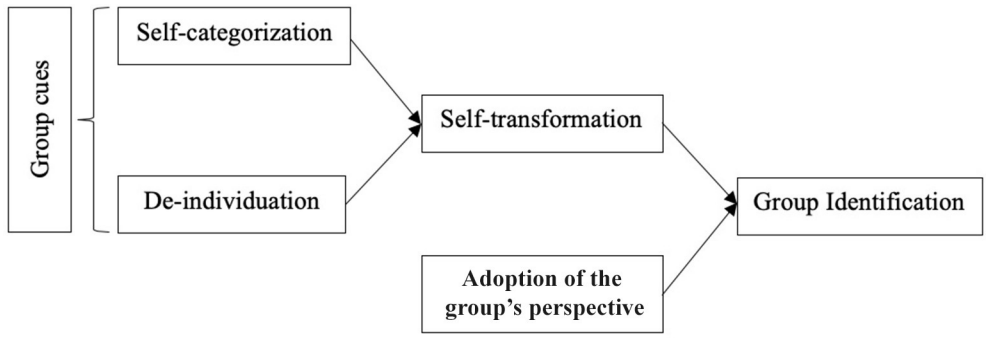

FIGURE 1 | Group identification.

young children (149)—as Trevarthen and his colleagues put it with regard to joint attention, here "autistic children appear characteristically impaired" [(115), p. 123][21]. Accordingly, one group cue, which is particularly important from a developmental perspective, seems to be ineffective in triggering group identification in ASD.

But why is the ability to jointly attend to something problematic in ASD, and what evidence is there to support the claim that group identification and, specifically, transformation in self-experience are impaired in severe ASD? These questions are not unrelated, and, to answer them, we turn to Hobson's account of triadic joint attention, which he subsumes under the heading of "the relatedness triangle" (104). According to Hobson, triadic joint attention is not just a matter of two individuals, e.g., a child and a caregiver, attending to the same object in the world. In addition to relating to the object, the child also relates (i) to the caregiver, who reciprocally relates to the child, and (ii) to the caregiver's bodily expressed attitude or perspective on the object in the world. By socially and emotionally relating to the caregiver's bodily anchored and expressed attitude or perspective on an object in the world (e.g., a caregiver's curiosity toward a new toy), the child's own attitude or perspective on the object is potentially shaped or modified (e.g., the child's attitude may switch from feelings of uncertainty to curiosity toward the new toy).

More specifically, a significant developmental process is instigated when the child "moves to the position of the other," thereby assimilating or assuming the bodily expressed attitude of the other and acquiring it as a potential attitude for itself [(104, 105), p. 14–28, 131–140]. As already noted, Hobson designates the crux of this developmental process with the concept of "identifying-with." Most importantly, he distinguishes between different levels of identifying-with [(105), p. 17, 135], which roughly may be divided into two: first, a superficial form of identifying-with the other, enabling one to imitate or copy the other's goal-directed behavior; and second, a deeper form of identifying-with the other in which one is emotionally drawn or "moved" to assume the other's bodily anchored psychological attitude or perspective, enabling one's own attitude or perspective to be configured according to what is perceived in the other (e.g., the beforementioned shift from uncertainty to curiosity toward a new toy). According to Hobson, it is pivotal for the emerging social understanding that the infant "registers this shift *as* a shift across perspectives, not merely as a change in the meaning of objects at the focus of referencing" [(105), p. 137]. In other words, the deeper form of identifying-with is quintessentially person-centered [(105), p. 138], which means that the infant experiences the shift in her own attitude toward the object or event as mediated by another person. In this process, the child is "lifted out of her own stance and (…) drawn into adopting another perspective" [(151), p. 106, 108]. By repeatedly engaging in triadic joint attention and by shifting between self/other perspectives based on the deeper form of identifying-with, the child gradually comes to understand not only that there are different perspectives on the same objects and that she herself can be an object of another's perspective but also, eventually, that persons are sources of perspectives and that she herself is a person with a perspective [(105), p. 106]. Leaving other details of Hobson's account aside, one can conclude that, on that view, triadic joint attention, based on the deeper form of identifying-with the other, is crucial for coming to understand others *as* persons as well as oneself *as* a person.

Where does this leave us in the case of severe ASD? According to Hobson, children with infantile autism manifest a "negative image" of triadic joint attention (or the relatedness triangle)—as he puts it, "It is especially when a normal child would be attending to, registering, evaluating, and identifying with the *subjective orientation* of another person, that the autistic child is the most abnormal" [(104), p. 197]. Said another way, children with severe ASD are typically not impaired when it comes to the superficial form of identifying-with the other. However, when it comes to the developmentally crucial, deeper form of identifying-with others, children with severe ASD are markedly impaired [(105), p. 14–28, 131–140]. On Hobson's account, this decreased propensity to identify with others—this relative impairment in the capacity to be "emotionally moved" to assume the other's

[21] This point will not apply to patients with high-functioning autism of whom it has been ascertained that they may point to social interaction as one of their favorite activities [e.g., see (150)].

subjective attitude or perspective and acquire it as a potential perspective for oneself—is *the* generative disorder in infantile autism or, as he also puts it, "what makes autism autism" [(105), p. 131].

This fundamental disorder reverberates in other aspects of sociality: it is well-known that infants with severe ASD regularly not raise their arms to be picked up, have decreased eye contact, have impoverished proto-declarative pointing[22], have a failing grasp of others' use of proto-declarative pointing, often do not participate in turn-taking with adults, and rarely show objects to others, etc. Their social impairments are also mirrored later in life. In a series of experimental studies of social emotions, Hobson et al. (105) found important group differences between children and adolescents with severe autism, and children and adolescents with developmental delays and learning disabilities (without autism). For example, children and adolescents with severe autism were less likely to manifest person-focused social emotions such as shame and guilt and their manifestation of these emotions were atypical—e.g., they rarely reported feeling guilty for hurting someone but rather guilty for breaking a rule. Furthermore, children and adolescents with severe autism frequently described and expressed pride but, again, in an atypical, non-person-focused manner than the developmentally delayed control group—children and adolescents with autism expressed pride over their own achievements but appeared indifferent when praised for their achievements by others. In another study, Lee and Hobson (153) examined self-concepts in adolescents with autism and a matched control group with intellectual disability and found notable group differences with regard to social self-statements in terms of *quantity* (adolescents with autism produced less social self-statements, e.g., about helping others or being bullied) and *quality* [not a single adolescent with autism referred to a friend (whereas 70% of those without autism did) or to being a member of a social group]. In brief, children with severe ASD have basic problems in relating to others—problems that cannot be explained merely by intellectual disability—and these problems predate and most likely also constrain and structure the development of a range of other capacities, including social emotions and what Baron-Cohen and colleagues called "conceptual perspective-taking."

Returning now to the psychological preconditions of group identification, we suggest that the fundamental problems involved in conceptual perspective-taking in severe ASD hampers these very preconditions of we-intentionality. We first look into difficulties related to self-transformation and, specifically, self-categorization before turning our attention to the adoption of the group's perspective.

To start with self-categorization, this process, as we saw, leads to a self-perception as an individual saliently similar to others. It thus presupposes the possibility to relate to oneself in a specific way which, importantly, takes others into consideration. I should have a, however rudimentary, sense of myself but also of others as minded beings (like me) to become aware of significant similarities between us (154). If impairments in triadic joint attention, grounded in a decreased propensity for deeply identifying-with others and subsequent problems in conceptual perspective-taking, etc., entail fundamental problems in relating to others and oneself *as* persons, then these very same problems will also affect the process of self-categorization and, consequently, of self-transformation. Our interim conclusion, thus, is that self-transformation is impaired in ASD.

Finally, the last precondition for we-intentionality is the ability to adopt the group's perspective. Philosophical research has argued that adopting the group's perspective could be described as a form of perspective-taking (27, 155). In the adoption of the group's perspective, just as in other forms of perspective-taking, the subject adopts the perspective of another agent; it just is that, here, the perspective that the agent adopts is the perspective of a group agent and not that of another individual. Although, to the best of our knowledge, there are no empirical studies yet to support this conjecture, it seems reasonable to suggest that, if children with severe ASD have fundamental problems with adopting the perspective of others (conceptual perspective-taking), then those very same problems with perspective-taking may also affect the capacity to adopt the group's perspective and to factor it in in deliberation and action planning.

We conclude that both joint intentionality and we-intentionality are impaired in severe ASD, since the psychological preconditions of these forms of shared intentionality appear not to be met.

CONCLUSIONS

We have proposed that shared intentionality comes in at least two different forms, namely, joint intentionality and we-intentionality, and we have suggested that these two forms require different psychological preconditions to be established and maintained. In joint intentionality, the agents' motivation and perspective are *individual*, and for them to lead to joint action, they must be accompanied by robust mentalizing abilities. By contrast, in we-intentionality, the agents act on collective motivation and perspective, as they must be able to adopt the group perspective and act in accordance with the group's preferences and goals.

With regard to joint intentionality, we have argued that it is impaired in severe ASD but not in SSD and that the impairment in severe ASD may be caused by problems with mind reading and with the ability to "be moved" by others' intentions. With regard to we-intentionality, we have argued that the presence of various, trait-like anomalous self-experiences may exert friction on the psychological preconditions for self-transformation and thus render we-intentionality fragile in SSD. In severe ASD, by contrast, we have argued that fundamental problems involved in perspective-taking seem to violate the psychological preconditions for group identification and thus we-intentionality. Although we-intentionality appears to be

[22]Goodhart and Baron-Cohen define proto-declarative pointing as "pointing to comment or remark on the world to another person, to share interest or attention about an object, as an end it itself" [(152), p. 226]. Proto-declarative pointing is distinguished from proto-imperative pointing, which is pointing "to use another person to obtain an object" (152).

affected in both SSD and ASD, the root problems are different, linked to the disorders' specific psychopathological cores, and result in qualitatively distinct difficulties in this domain of social interaction.

Our analysis of disturbed shared intentionality in SSD and ASD also made it clear that the psychological preconditions for joint intentionality and we-intentionality, which we described from a developmentally advanced perspective (see **Table 2**), are, in fact, not able to fully account for these two forms of shared intentionality. In these analyses, it became evident that for these psychological preconditions to work, other and developmentally more primary factors need to be in place. For example, for group cues to bring about self-transformation and, eventually, group identification, a certain sense of oneself as a *person*, of others as *persons*, of groups as consisting of *persons*, and not least the basic capacity to be "emotionally moved" by others, is indeed required.

Finally, it of course merits attention that the hypotheses that we have put forth here concerning disturbances of these two forms of shared intentionality require empirical corroboration before any definitive conclusions can be drawn on these complex matters.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made an equal, substantial, direct and intellectual contribution to the work, and approved it for publication.

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Evolving Concepts of the Schizophrenia Spectrum: A Research Domain Criteria Perspective

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Several trends intersecting over the past two decades have generated increasing debate as to how the concepts of schizophrenia, the schizophrenia spectrum, and the psychotic disorders spectrum should be regarded. These trends are reflected in various areas of research such as genomics, neuroimaging, and data-driven computational studies of multiple response systems. Growing evidence suggests that schizophrenia represents a broad and heterogenous syndrome, rather than a specific disease entity, that is part of a multi-faceted psychosis spectrum. Progress in explicating these various developments has been hampered by the dependence upon sets of symptoms and signs for determining a diagnosis, and by the reliance on traditional diagnostic categories in reviewing clinical research grants. To address these concerns, the U.S. National Institute of Mental Health initiated the Research Domain Criteria (RDoC) project, a translational research program that calls for studies designed in terms of empirically-based functions (such as cognitive control or reward learning) rather than diagnostic groups. RDoC is a research framework rather than an alternative diagnostic system, intended to provide data that can inform future nosological manuals. This commentary includes a brief summary of RDoC as it pertains to schizophrenia and psychotic spectra, examples of recent data that highlight the utility of the approach, and conclusions regarding the implications for evolving conceptualizations of serious mental illness.

Keywords: psychiatric diagnosis, psychiatric nosology, research domain criteria, psychopathology, schizophrenia spectrum, psychosis spectrum

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INTRODUCTION

The concept of schizophrenia (SZ) has elicited continual debate since the first descriptions of psychosis appeared in the middle of the nineteenth century. The nature of the concept has fluctuated across the years according to the views of the scientific zeitgeist and various schools of psychopathology, but has always persevered in one form or another (1). Within the last decade, however, advances in multiple areas of science—genomics, neuroimaging, cognitive science, and epidemiology—have begun to challenge classic conceptions of schizophrenia (2, 3).

Progress in expanding these various developments has been hampered by two major obstacles. First, disorders continue to be defined almost exclusively by sets of symptoms and signs; however, the relationships between diagnostic categories and biological or behavioral measures have proven to be modest and inconsistent, frustrating both a more comprehensive understanding of disorders and the development of more effective treatments (4). Second, research on mental disorders has been constrained by the persistence in grant review committees of a de facto requirement that

hypotheses will embody DSM/ICD categories as their scientific focus, thus foiling applications proposing alternative approaches.

To address these problems, the US National Institute of Health (NIMH) initiated the Research Domain Criteria (RDoC) project in 2009 "to develop, for research purposes, new ways of [studying] mental disorders based on dimensions of observable behavior and neurobiological measures" (5). RDoC was conceived as an experimental framework to support research in psychopathology organized around basic functional domains such as cognition, motivation, and motor activity, most of which are pertinent to multiple disorders as currently defined (and may partially account for the extensive co-morbidity in current disorders).

The various elements of the RDoC framework have been described in detail elsewhere (5–7) and are briefly summarized here. RDoC is intended as an explicitly translational program: The focus is on fundamental operations of adaptive behavioral/cognitive and brain functioning (e.g., working memory, fear behavior), and psychopathology is viewed in terms of dysregulation in these systems rather than starting with clinical syndromes and trying to determine their source. A core desideratum of RDoC is to study entire dimensions of functioning from the normal range to increasingly abnormal extents, and no specific cutpoints for disorders are specified in order to encourage studies of transitions from normality to degrees of pathology. To foster such analyses, RDoC calls for study designs that include a broader range of "healthy controls," patients with mild/subsyndromal psychopathology, and unaffected relatives of probands.

The basic dimensions of RDoC are organized in six superordinate domains of functioning (negative valence, positive valence, cognition, social processes, arousal/regulatory systems, and sensorimotor systems). Each domain contains multiple constructs, which—central to the entire framework—are defined jointly by data for a behavioral or cognitive/affective function, evidence for a neural circuit or system that plays a primary role in implementing the function, and relevance to psychopathology (8).

The domains and constructs were defined in a series of workshops attended by experts in both basic and clinical research. This process was essential for two reasons. First, it is important to communicate to the field well-validated constructs from the basic behavioral neuroscience literature that have demonstrated promise for understanding psychopathology. Second (and less evident), it is critical to provide clear guidelines for grant review. Just as established criteria for defining patient groups contributed significantly to the DSM's hegemony in study sections, examples of domains and constructs are essential to serve as standards for both applicants and reviewers in submitting and evaluating RDoC applications. Since RDoC is an experimental framework, applicants are not required to use one of the current constructs, and no claim is made that the current list of constructs is complete; in fact, a major goal of the program is to encourage research that establishes new constructs or domains, based on the premise that promoting diversity of ideas in research is the best way forward (Note that NIMH accepts DSM-oriented grant applications as always, although applicants are encouraged to address pertinent heterogeneity).

In keeping with the basic-to-clinical translational approach, RDoC focuses on relatively specific aspects of disordered functioning rather than syndromal categories. Study designs might include patients from one or more DSM/ICD categories, analyzing dimensions or subgroups in the full sample or examining selected subjects with particular characteristics (e.g., cognitive control or reward-related deficits). Participants in transdiagnostic studies are typically drawn from related areas of psychopathology, such as mood/anxiety disorders or psychotic disorders (plus comparison participants appropriate for exploring dimensions of functioning). An important emphasis concerns individual differences in psychopathology, given the heterogeneity that is now recognized for all syndromal disorders. Studies that include multiple domains/constructs are encouraged, such as the relationship of threat to attention or reward-related activity to social processes. RDoC-related research further advocates the use of multiple classes of measurement, ranging from genomics and circuit measures to behavioral and self-report, in order to seek an integrative understanding of brain-behavior relationships as they relate to particular functions.

RDoC AND THE PSYCHOTIC SPECTRUM

The RDoC program has consistently emphasized its agnostic position with respect to disorders as defined in the DSM/ICD system: The goal is to stimulate research that can inform revisions to future diagnostic manuals, however similar or divergent to current disorders and their definitions. Recent developments in the field demonstrate novel conceptions across the entire range of psychopathology, employing various types of dimensions, clusters, and hierarchical approaches that align with the RDoC approach (9).

Research focused on psychotic disorders amply reflects this trend (10). As one expert recently explained in a publication for psychiatric professionals, "Over the last decade or so, our field has experienced a radical shift in our understanding of schizophrenia and other serious psychotic disorders, such as schizoaffective disorder and bipolar disorder with psychosis. …. Accumulating evidence indicates that psychotic disorders constitute syndromes rather than diseases *per se*. … Patients with different clinical diagnostic phenotypes … can show similar underlying patterns of cognitive dysfunction and neurobiological abnormalities" (11). Space allows only a small number of papers to be cited here as examples of RDoC approaches in the psychotic spectrum [which are treated more comprehensively in a recent chapter; (7)].

Transdiagnostic Findings

The current interest in a schizophrenia or psychotic disorders spectrum is consistent with the kinds of trans-diagnostic mechanisms that RDoC prioritizes. There are multiple types of relevant research designs. These include overlaps between traditional diagnostic classes, such as SZ and bipolar Type 1 disorder (BPD), that are frequently used when it is difficult to

examine disorder subtypes or dimensions due to the nature of measurement (as in GWAS studies). A second type of design involves transdiagnostic dimensions or gradients; these differ from the prior design in that the analyses focus on how functional domains are arrayed along one or more dimensions across two or more disorders. Finally, cluster or similar analyses use data-driven techniques to reveal groupings that cut across traditional disorder categories.

Psychiatric genetics has provided increasing support for systematically related trans-diagnostic mechanisms as sample sizes grow. Comparisons of GWAS data across disorders have shown results that are consistent with a recently-posited gradient of neurodevelopmental syndromes ordered by the extent of neurodevelopmental impairment (from most to least: intellectual disability, ASD, ADHD, SZ, schizoaffective disorder (SZ-A), BPD, major depressive disorder [MDD]; (2, 12)). Larger coheritabilities were observed for disorder pairs that were closer on the spectrum; e.g., SZ-BPD and BPD-MDD were larger than SZ-ASD or BPD-ADHD (13).

More elaborated data emerged from a study comparing eight disorders in a larger sample, resulting in three clusters of disorders based on shared loci—mood and psychotic disorders (SZ, BPD, and MDD), early-onset neurodevelopmental disorders, and compulsive behaviors (14). As the authors concluded, "… these results indicate a substantial pairwise genetic correlation between multiple disorders along with a higher-level genetic structure that point to broader domains underlying genetic risk to psychopathology. These findings are at odds with the classical, categorical classification of mental disorder." (14, p. 1475).

A second aspect of trans-diagnostic comparisons involves dimensions that cut across disorders. For example, a recent study from the CNTRACS group employed multiple measures of performance that tapped distinct aspects of cognition (cognitive control, episodic memory, and visual perception) in a large sample consisting of individuals diagnosed with SZ, BPD, or SZ-A (15). A latent profile analysis returned a solution with three trans-diagnostic clusters of high ability (mostly indistinct from control subjects), medium performance, and low performance. The proportions of patients from the three diagnostic groups were distributed across the three ability clusters, indicating that the latter were not simply proxies for diagnosis. Confirmatory factor analysis was consistent with the presence of an underlying one-dimensional structure across the three cognitive profiles, suggesting a shared mechanism not related to diagnostic classes *per se*.

Moving toward multi-measure studies that are compatible with the RDoC approach, computational analyses that identify transdiagnostic clusters of patients illustrate the potential of empirically-derived phenotypes that align with particular biological and behavioral functions. In the exemplary B-SNIP study (Bipolar & Schizophrenia Network on Intermediate Phenotypes), investigators recruited a large sample of patients (SZ, SZ-A, or BPD with psychosis) and acquired a wide range of biological, behavioral, and clinical measures (16). A cluster analysis of factor scores from cognitive and electrophysiological measures grouped patients into three "biotypes" that cut across DSM disorder categories (as in the previous example). The first two biotypes were characterized by impaired cognitive functioning (slightly more severe in Biotype 1) but divergent sensorimotor reactivity (event-related potential responses related to simple stimuli) that was markedly blunted in Biotype 1 and hyper-responsive in Biotype 2; both measures for the third biotype were only slightly different from healthy controls. The biotypes were validated by several different measures not used in the cluster analysis, including gray matter loss as assessed by voxel-based morphometry. This study demonstrated that deriving transdiagnostic clusters based on a combination of behavioral and psychophysiological functions (cognition and perception), consistent with an RDoC approach, have promise in determining data-driven clinical phenotypes with more validity than traditional disorder classes.

Dimensionality

RDoC emphasizes the gamut of normal-to-abnormal functioning. This aspect can be considered both in terms of cross-sectional and longitudinal studies. The latter, in this context, include trajectories of neurodevelopment from conception to risk states and overt psychopathology.

Cross-sectional discussions of psychosis dimensionality date back nearly as far as the concept of schizophrenia itself, with unresolved discussions as to whether the clinical phenomena represent one or more clinical categories, one or more dimensions, or some combination (17, 18). More recently, extensive analyses have been adduced to support replacing the schizophrenia concept with a broader "psychosis spectrum" (19) that reflects a continuous dimension of psychosis proneness from normal to abnormal (20), although also allowing for a continuous psychometric spectrum that contains one or more latent categorical structures (21).

This type of normal-to-abnormal dimensional viewpoint comports with the RDoC framework. At the same time, another RDoC principle is to remain agnostic (as with the DSM) and eschew a priori conclusions regarding the number and composition of dimensions and their clinical significance. One of the hurdles that RDoC was created to address concerns the often-modest relationships among the presence/severity of clinical symptoms and various other measures, such as cognitive tests or brain circuit activity. As noted in a recent paper on RDoC and psychosis, "… one must empirically test whether dimensionality of a symptom indicates dimensionality of a mechanism" [(7), p. 32]. In short, the field is just starting to make progress in unpacking the relationships within and across multiple neurocognitive functions, multiple kinds of symptoms, and multiple neurobiological and genetic measures—compounded by the complexities of intermixed clusters and dimensions (22). In spite of the daunting challenges, the evidence is already strong that the field is moving in positive directions.

Neurodevelopmental Studies

RDoC places a high priority on neurodevelopmental trajectories. While the clinical high-risk state (CHR) state for psychosis is perhaps the most thoroughly researched example of a trajectory leading toward disorder (23), more recent studies

have expanded the scope of neurodevelopment and functions consistent with RDoC principles. For instance, a recent study followed an unselected sample of children from age 8 to late adolescence, collecting a large number of measures including neurocognitive tests and symptoms; children who developed psychotic symptoms later in adolescence were on average 1–2 years behind typically-developing children in cognitive growth, suggesting that early cognitive impairment could be a marker for psychosis risk and that growth charting may be an opportunity for early detection and prevention (24). Another group has independently begun to implement this concept with a developmental battery of "gamified" tasks (running on a mobile e-platform) that assesses six cognitive domains in young children in India as a first step to developing normative growth curves (25).

Such promising programs are only the tip of the iceberg for neurodevelopmental studies involving RDoC (which comprise nearly half of RDoC-themed translational grants funded by NIMH). An equally important issue concerns the need to explicate neurodevelopmental changes from birth to adulthood – addressing both substantive and psychometric issues of identifying and assessing functions that emerge at various points in development, as well as relating growth trajectories to the complex effects of multiple environmental influences (26, 27).

SUMMARY

It is a stimulating time for research on mental disorders. The field is burgeoning with intriguing new results and new ideas – sparked by developments in genomics, neuroimaging, behavioral science, computational approaches, and many other disciplines. The RDoC initiative has been a part of this contemporary zeitgeist, enabling conversations about innovative approaches to psychopathology (28–30) and supporting research projects that represent new avenues for future directions (31–33).

These developments have accelerated progress regarding the schizophrenia (or more broadly, the psychotic) spectrum. Genomic data provide increasing support for the concept of systematic transdiagnostic components of neurodevelopmental spectra (2, 12). In this view, schizophrenia represents not so much a distinct disease as one segment of multiple broader spectra. However, the evidence is also clear that a neurodevelopmental gradient is not simply a matter of performance as assessed by the usual cognitive test batteries; it is important to consider multiple functional domains whose combinations comprise potentially significant clinical phenotypes, e.g., biotypes defined by both cognitive performance and sensorimotor reactivity (16).

A further aspect of the emerging literature, consistent with the RDoC approach, concerns various gradients from normal to abnormal functioning and how these relate to illness and dysfunction. It is now evident that some types of functional impairments are not necessarily tied to manifest clinical features. As two examples, both the B-SNIP and CNTRACS studies (summarized above) reported that patients in one of the three clusters, in spite of meeting criteria for SZ, BPD, or SZ-A, were characterized by functional performance in cognition and perception that was modestly to indistinguishably different from healthy controls (15, 16). A necessary agenda for future research is to unravel the complex relationships among the extent of such factors as genetic load, functional impairments, and clinical symptoms.

The current status of evidence about the psychotic disorders spectrum raises significant questions regarding both near-term implications for research on clinical assessment and services, and long-term directions for scientific priorities and perspectives. With respect to clinical practice, the DSM/ICD nosology continues to dominate procedures for diagnosis and treatment. However, there is increasing attention to transdiagnostic approaches for diagnosis and treatment that build upon awareness of heterogeneity and clinicians' wisdom that many (if not most) treatment plans are focused on specific problems (e.g., sleep, attention, interpersonal relationships) irrespective of formal diagnosis (34, 35), and at least one case report specifically cites the use of a transdiagnostic, RDoC approach (36). Further, some clinical programs have explicitly adopted a transdiagnostic process for assessment and treatment of first-episode psychosis in recognition of the change in diagnosis across time in many patients (37).

Regarding scientifically-driven changes in nosology, there appears to be a clear consensus that traditional disorder classes in this spectrum need to be revamped, and dozens of promising genetic, circuit-based, and behavioral findings provide clues to future classification systems. However, the nature and extent of potential changes to nosology remain far from clear, as different measurement classes and analytical techniques have yet to coalesce. There also remains the question of the granularity of concepts and measurement that are optimal for clinical use; these concerns apply across all areas—e.g., the number and combinations of specific gene abnormalities for molecularly based therapies; the count and locations of voxel-based structural abnormalities (38); or whether cognitive difficulties are best addressed at the level of broad test batteries, intermediate functional domains (e.g., executive function), or more specific operations (e.g., working memory).

A key question concerns the routes by which research advances can be implemented in diagnostic and treatment practice. Alterations to formal nosological criteria are not likely to be made soon, given conservative approaches to change in diagnostic manuals. Revisions based upon neuroscience and/or systematic behavioral data are yet more difficult to envision since they would involve an overhaul of the long-established reliance on symptoms and signs for diagnosis.

However, it is possible that rapid change may be recognized in other ways. Regulatory agencies, e.g., are well aware of the need for improved treatments and the potential for groupings and/or dimensions that manifest within or across traditional diagnostic categories. For instance, in 2016 the US Food and Drug Administration (FDA) promulgated an innovative new Drug Development Tool (DDT) Qualification program created to evaluate and approve (Qualify) such tools as "a biomarker used for clinical trial enrichment" [e.g., approval of the N170 event-related potential as a biomarker for social processing in ASD (39)] "… and a clinical outcome assessment used to evaluate clinical

benefit…" (40). Further, the tools are developed in a "context of use" that represents "the manner and purpose of use for a DDT," i.e., essentially the specific impairment to be addressed (40). Such developments could lead directly to innovative practices that advance treatment while suggesting new conceptions of clinical phenotypes that are validated inherently by their use in patient care.

CONCLUSION

In sum, the notion of a psychotic spectrum is evolving rapidly, but schizophrenia—as broad concept or specific diagnostic category—remains a core aspect of contemporary psychopathology. Both general and specialty journals continue to publish large numbers of papers devoted directly to SZ, reflecting widespread support from multiple funding agencies across the world. In September, 2020 the National Institutes of Health announced the AMP-SCZ initiative (Accelerating Medicines Partnership-Schizophrenia), bringing together NIH, the US FDA, and multiple non-profit and private organizations to seek biomarkers for the diverse array of clinical trajectories and adverse outcomes observed in individuals identified as at elevated risk of psychosis. Accordingly, there seems to be little doubt that SZ will remain a central concept in mental disorders for some time to come (41). While future directions remain difficult to predict given the nascent state of the research, novel research frameworks seem likely to foster the continued expansion of research designs and integrative science—and, in turn, to stimulate more precise thinking about the nosology of SZ and the psychosis spectrum.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

BC and SM contributed equally to the overall outline and scope of the manuscript. BC wrote the first draft. SM contributed extensive comments and edits that resulted in the final version. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Formal Thought Disorder and Self-Disorder: An Empirical Study

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Background: Formal thought disorder was constitutively linked to the original concept of schizophrenia and has since been one of central features supporting its diagnosis. Bleuler considered formal thought disorder as a fundamental symptom of schizophrenia among other fundamental symptoms, including ego disorders. The contemporary concept of self-disorder represents a more developed, nuanced, and systematic approach to disturbances of self-experience than the Bleulerian concept of ego disorders. As fundamental symptoms, on Bleuler's account, are persistently present in every case, an association between these symptoms could be expected. The purpose of this study was to examine the association between self-disorder and formal thought disorder.

Methods: A sample of 94 diagnostically heterogeneous patients was examined for formal thought disorder using clinical rating and a proverb test. The proverb test was analyzed for two different aspects of formal thought disorder: literal responses and bizarre responses. The sample was comprehensively assessed for psychopathology, including self-disorder as measured with the Examination of Anomalous Self-Experience scale.

Results: The patients, who provided bizarre responses, had a higher level of self-disorder, more negative symptoms, lower level of social functioning, and lower level of intelligence. Bizarre answers aggregated in patients diagnosed within the schizophrenia spectrum compared with patients outside the schizophrenia spectrum. We found moderate correlations between the two measures of formal thought disorder (clinically rated and bizarre responses) and self-disorder (0.454 [$p < 0.01$] and 0.328 [$p < 0.01$]). Literal responses did not differ between diagnostic groups and also did not correlate with bizarre responses. Specificity of bizarre responses for a diagnosis within schizophrenia spectrum was 86.89%, whereas sensitivity was 40.85%.

Conclusion: The close relation between formal thought disorder and self-disorder further adds to the notion of self-disorder as a unifying psychopathological core beneath the apparently heterogeneous symptoms of schizophrenia.

Keywords: schizophrenia, schizotypy, proverb, bizarre, literal, self-disorder, formal thought disorder

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INTRODUCTION

Formal thought disorder was constitutive for the creation of the concept of schizophrenia. Kraepelin (1) used the term "Zerfahrenheit," which is sometimes translated into "incoherence," but which also refers to more subtle distortions of meaning in the patient's speech (2). Bleuler also used this term, but he introduced the general notion of "loosening of associations" as a fundamental symptom of schizophrenia (3). On his account, the fundamental symptoms were specific for the diagnosis of schizophrenia. Formal thought disorder has been subsequently included in most definitions of schizophrenia, although with permutations of its characteristic features and severity. Importantly, the notion of formal thought disorder must be distinguished from the broad Anglo-Saxon concept of "thought disorder." The latter term is more inclusive and refers to a variety of disturbance of thought, including disorders of thought content such as delusions.

In current literature, it is frequent to use the term "speech disorder." Obviously, we only have access to the patients' thought processes through their expressions, in speech, writing, or behavior [e.g., "unsinnige Handlungen" (4, 5)]. *Formal* thought disorder refers to disturbances in the structure (or *form*) of thinking, e.g., the boundaries of concept formation, semantic disturbances (such as neologisms), or disturbances in the transitions between thought segments (6, 7). Although formal thought disorder is expressed through the patient's speech, it is often difficult to detect disorder of thinking, if the patient's responses are brief or laconic or in interviews with a high degree of structure. It is a well-established clinical observation that the more structured the conversation is, the less prominent the manifestation of the patient's formal thought disorder will be (6). Thus, there are basically two approaches to detect and measure formal thought disorder. One, used in all clinical assessments, is simply the rating of disorder manifest in the patient's speech. Nancy Andreasen has published a detailed scale of "thought, language, and communication disorder" (8) that can be used for this approach. Another approach is based in the tradition of psychological projective tests such as object sorting test or Rorschach (e.g., Holzman's Thought Disorder Index) (9). Another possible test, which is one we also used in the current study, is the proverb test in which the patient is presented with a number of different proverbs, which he then must explain the meaning of (see below) (10).

Studies of formal thought disorder have shown that formal thought disorder may be considered a marker of illness severity. Basic demographics do not seem to be related to the presence of formal thought disorder, whereas the level of intelligence has been related to bizarre thinking. Studies examining the association between social functioning and formal thought disorder have shown ambiguous results (7, 11).

As already mentioned, Bleuler considered formal thought disorder as a fundamental symptom of schizophrenia related to other fundamental symptoms such as ego disorders. However, in modern literature, the relationship between disturbances of self-experience and formal thought disorder has not been probably explored except from theoretical suggestions (12, 13). [For details of self-disorder, see, e.g., (14, 15)]. In the current study, we were interested in the following questions:

1) How is self-disorder as measured by the Examination of Anomalous Self-Experience (EASE) (16) related to clinically rated formal thought disorder and formal thought disorder rated through proverb test?
2) How is formal thought disorder related to other canonical dimensions of schizophrenia (positive and negative symptoms) as well as to social functioning?

MATERIALS AND METHODS

Sample

The original sample comprised the first 100 admissions, diagnostically heterogeneous patients aged between 18 and 65 years. The sample comprised the consecutive first admissions to the Psychiatric Center Hvidovre (a psychiatric inpatient facility of the University of Copenhagen) that provides psychiatric service to a population of 150,000 in one particular catchment area of the City of Copenhagen (there are no private inpatient psychiatric facilities in Denmark). The patients were included over a period of 18 months independently of their clinical diagnosis at admission. All consecutive first admissions were screened for eligibility. If there were more eligible patients than it was possible to examine within the pragmatic constraints of the project, the youngest patient was always selected. The patients participated on the condition of informed consent, and a relevant medical ethical committee approved the study.

The patients had to be in a condition in which they could tolerate a lengthy interview, because one of the goals of the primary study was to assess the adequacy of different psychopathological interviews (17). This led to exclusion of aggressive, agitated, or severely psychotic patients, who were not able to collaborate. Additional exclusion criteria comprised primary or clinically dominating substance use, history of brain injury, and organic brain disorder. Involuntarily admitted or legal patients were also excluded. Moreover, all participants had to have an intelligence level within the normal range as measured by the Intelligenz-Struktur Test 2000 R (18). All patients were asked to do a proverb test, but four patients declined. After inclusion in the project, two patients later withdrew their consent to the research project. Thus, a total of 94 patients took the proverb test.

Assessments

Formal thought disorder was assessed using a proverb test consisting of 11 proverbs. The test was chosen as it is easy to administer, not too time consuming, and it is a commonly used test for rating bizarre responses (19, 20). We analyzed the proverbs for (1) literalness and (2) bizarreness, as these are two commonly agreed aspects of formal thought disorder (21). For literalness, we followed the scoring manual by Hertler et al. (22). Based on selected keywords in the proverbs, it was assessed whether these keywords were attributed literalness. We only looked for presence or absence of literalness. To illustrate the test: the proverb "a thief believes everybody steals" means

that one ascribes to others one's own flawed or weak mindset or habit. Here are two examples of responses that were rated for literalness: "if you yourself are a thief, you assume that all people are thieves too," and "people who break the law believe that it is normal."

For rating bizarreness, we constructed a simple scoring system for bizarre answers inspired by Exner's comprehensive system for scoring the Rorschach (23), more specifically, the DV (Deviant Response) score. Again, we only looked for presence or absence of bizarre response. We rated answers as bizarre; if they were idiosyncratic; if the rater was unable, or found it difficult, to grasp the meaning of the answer; or if there was a private use of terms or expressions in which the meaning may be clear, but the expression itself is unusual. The rating was done jointly and based on clinical judgment in the same way as one would approach the scoring of DV in a Rorschach protocol. Here are a few examples of responses, which we rated bizarre in the present sample: Asked to explain the meaning of the proverb "don't cry over spilt milk," which means that there is no reason to get upset over something that have already occurred and that cannot be changed, one patient responded, "One should not get upset. To have courage or to get courage." Another example, asked to explain the meaning the proverb "many a mickle makes a muckle," which means that lots of small amounts can be accumulated to large amount, one patient responded, "that means that you have to stay young."

Raters of Formal Thought Disorder

All ratings of formal thought disorder (i.e., literal and bizarre responses to the proverbs) were done by two psychologists (MBP and MGJ), both of which have vast clinical experience and extensive training and experience with the use of the Rorschach test. Both raters were blinded to diagnosis, any kind of psychopathological information, and level of functioning of the patients.

Psychopathology and Diagnosis

All patients were thoroughly assessed for psychopathology and diagnosed by JN and JP. The interviews were split over two to three sessions, and the total duration of the interviews was 3–6 h. The interview was carried out by an experienced psychiatrist and expert in the use and teaching of the EASE (16) (JN). The interviews were conducted in a semistructured, conversational style, including a thorough psychosocial history, a description of the illness evolution, the Operational Criteria Checklist (OPCRIT) (24) expanded with additional items from the Schedule for Affective Disorders and Schizophrenia (SADS) (25), the Examination of Anomalous Self-Experiences (EASE) (16), the perceptual section from the Bonn Scale for the Assessment of Basic Symptoms (BSABS) (26), and of abnormal expressive features (27). The proverb test was administered after completed interviews. All interviews were videotaped.

The present study used lifetime *International Classification of Diseases, 10th Revision* (*ICD-10*) diagnoses based on all available, diagnostically relevant information (interview videos, notes, information from the hospital charts, which also contained second informant descriptions of the illness' symptoms and their evolution). Self-disorder was assessed using the EASE and rated on a lifetime basis as present or absent. We constructed a "positive symptom scale" (including psychotic symptoms) and a "negative symptom scale" (including negative symptoms) by adding items selected from the interview schedule in order to obtain the measures of the canonical dimensions of schizophrenic symptomatology. **Table 1** shows the composition and Cronbach α's of the positive and negative symptoms scales in addition to a scale of items targeting clinically rated formal thought disorder.

The variable "social and professional difficulties" was created by summing two items from the interview checklist: "social difficulties" (which covered difficulties in personal relationships as measured by <2 close relations) and "professional difficulties" (which covered difficulties in maintaining jobs or education within the last year); maximal score was 2.

Ethics

All patients participated upon written consent. The study was approved by the Danish Data Protection Agency. According to Danish legislation, approval from The Danish National Committee on Health Research Ethics is not required for interview studies of this kind. The study adhered to the ethical principles laid down by the Helsinki Declaration.

Statistical Analysis

We analyzed the sample divided into two groups: one group, consisting of patients who provided at least one bizarre response, and another group of patients, who did not provide any bizarre response.

Subsequently, we did some extra analyses with the sample divided into two diagnostic groups: schizophrenia spectrum disorders (i.e., schizophrenia, other non-affective psychoses, and schizotypy) and non-schizophrenia spectrum disorders (including bipolar disorder, major depression, personality disorder, anxiety, and adjustment disorder).

We tested for equality of means by t test when normally distributed and Mann–Whitney U test when not. Correlations were tested with Spearman ρ. For these analyses, we used

TABLE 1 | Psychopathological scales.

Positive symptom scale	Negative symptom scale
Hallucinations	Disturbance of volition, avolition, inertia
Delusions	Apathy
Persecutory delusions	Social withdrawal
Delusional grandiosity	Anergy
	Alogia, poverty of speech
Chronbach $\alpha = 0.710$	Cronbach $\alpha = 0.721$
Clinically rated formal thought disorder	
Incoherence	
Tendency to idiosyncratic or bizarre communication	
Rapport compromised by formal thought disorder	
Tangentiality	
Illogical thinking	
Cronbach $\alpha = 0.709$	

TABLE 2 | Sample description, psychopathology, and diagnostic groups.

	Bizarre response	Non-bizarre response	Statistics
n	32	62	
Gender (male/female)	11/21	20/42	*T* test $p = 0.838$
Mean age	27.1 (sd = 7.7)	28.0 (sd = 9.9)	*T* test $p = 0.640$
Social and professional difficulties, mean	1.50 (sd = 2.35)	0.50 (sd = 0.64)	Mann–Whitney $p = 0.003$
Literal answers to proverbs	0.5 (sd = 0.508)	0.32 (sd = 0.471)	*T* test $p = 0.096$
Positive symptoms, mean	4.25 (sd = 0.68)	3.10 (sd = 3.99)	Mann–Whitney $p = 0.078$
Negative symptoms, mean	2.00 (sd = 1.50)	1.29 (sd = 1.50)	Mann–Whitney $p = 0.022$
Clinically assessed formal thought disorder, mean	2.22 (sd = 2.2)	0.74 (sd = 1.33)	Mann–Whitney $p = 0.000$
Total EASE score, mean	19.56 (sd = 7.93)	13.81 (sd = 8.90)	Mann–Whitney $p = 0.002$
Intelligence level (max is 80), mean	32.35 (sd = 10.91)	39.24 (sd = 12.52)	*T* test $p = 0.011$
Diagnostic group			
Schizophrenia	18	25	
Schizotypal disorder	11	17	
Other mental illness	3	20	
	Schizophrenia spectrum disorders	**All other disorders**	**Statistics**
n	71	23	
At least one literal answer (*n*)	27 (38%)	9 (39%)	$\chi^2 = 0.009$ ($p = 0.925$)
At least one bizarre answer (*n*)	29 (41%)	3 (13%)	$\chi^2 = 5.788$ ($p = 0.016$)

The sample is divided in two different ways.
sd, standard deviation.

SPSS version 26. Specificity and sensitivity were calculated using Medcalc's diagnostic test calculator (28).

RESULTS

Literal Responses

Table 2 shows that the number of patients with literal responses did not differ between the two groups (bizarre responses vs. no bizarre responses). When dividing the sample into two groups depending on diagnosis, i.e., schizophrenia spectrum disorders vs. all other disorders, we found no significant differences between the groups for literal responses. Looking at the whole sample, we did not find any significant correlation between self-disorder and literal responses to the proverbs.

Bizarre Responses

Table 2 shows significant differences between the group with bizarre responses and the group with no bizarre responses in regard to self-disorder, negative symptoms, clinically rated formal thought disorder, social and professional difficulties, and level of intelligence. We tested if intelligence was a mediating factor for the effect of self-disorder on bizarre responses by linear regression and found that it was not. Self-disorder and level of intelligence were independently contributing to bizarre responses.

The correlations between bizarre responses and other variables are displayed in **Table 3**. The correlation between self-disorder (mean EASE score) and bizarre responses was moderate ($\rho = 0.328$, $p < 0.01$). Bizarre responses significantly aggregated in the schizophrenia spectrum disorders group.

Schizophrenia Spectrum Disorders vs. All Other Diagnoses

At the bottom of **Table 2**, it can be seen that 29 of 71 patients within the schizophrenia spectrum gave at least one bizarre response to the proverbs. By contrast, only three patients with a diagnosis outside the schizophrenia spectrum gave a bizarre response.

Finally, we found that the specificity of bizarre responses for schizophrenia spectrum diagnoses was 86.89%, whereas the sensitivity was 40.85% (**Table 4**).

DISCUSSION

This is the first study to systematically examine the relation between formal thought disorder and self-disorder. We found a highly significant, moderate correlation between bizarre responses and self-disorder. The correlation between bizarre answers and negative symptoms as well as clinically rated formal thought disorder was significant, whereas the correlation between bizarre answers and positive symptoms was not. Moreover, we found significantly more difficulties in social and occupational functioning in the group of patients who had given a bizarre response. These findings point to bizarre responses tapping into something central for schizophrenia spectrum disorders (i.e., schizophrenia, other non-affective psychoses, and schizotypy).

Literal responses did not relate significantly with any of the examined variables and did not differ between the diagnostic groups. Literal and bizarre responses did not correlate with

TABLE 3 | Correlation matrix Spearman ρ.

	Bizarre responses	Literal responses	Positive symptoms	Clinically rated formal thought disorders	Negative symptoms	EASE total score	Level of intelligence
Bizarre responses	—						
Literal responses	0.178	—					
Positive symptoms	0.181	0.107	—				
Clinically rated formal thought disorder	0.398**	0.136	0.310**	—			
Negative symptoms	0.222*	−0.002	0.378**	0.230*	—		
EASE total score	0.328**	0.153	0.317**	0.454**	0.489**	—	
Level on intelligence	−0.265*	−0.177	−0.294**	−0.142	0.005	−0.040	—

***Correlation is significant at the 0.01 level (two-tailed).*
**Correlation is significant at the 0.05 level (two-tailed).*

TABLE 4 | Diagnostic sensitivity and specificity of bizarre responses for a schizophrenia spectrum disorder.

	Value	95% confidence interval
Sensitivity	40.85%	29.32–53.16%
Specificity	86.89%	66.41–97.22%
Positive likelihood ratio	3.13	1.05–9.33
Negative likelihood ratio	0.68	0.53–0.87
Positive predictive value	90.38%	75.92–96.55%
Negative predictive value	32.89%	27.62–38.61%
Accuracy	52.37%	41.81–62.78%

each other and appear to reflect different dimensions. These findings are in line with previous studies, which have shown that the formal thought disorder of idiosyncratic verbalizations, autistic logic, and absurd thinking are more characteristic of schizophrenia (9, 29–31).

The specificity of bizarre answers for a diagnosis within schizophrenia spectrum disorders was high, suggesting that the presence of formal thought disorder should prompt clinicians to suspect or at least examine if the patient may fulfill the criteria for a schizophrenia spectrum disorder. Conversely, the absence of formal thought disorder cannot rule out schizophrenia spectrum disorders, as a considerable proportion of these patients did not offer bizarre responses. However, it should be emphasized that these figures should be taken with caution because the confidence intervals in **Table 4** vary considerably, and schizophrenia spectrum diagnoses are partly dependent on the presence of formal thought disorder.

From a theoretical point of view, the association between expressive features (formal thought disorder) and subjective experiences (e.g., self-disorder) is perhaps not so surprising. In general, formal thought disorders are typically conceived as a disturbance in the individual's capacity of producing and expressing thoughts in terms of semantics or relations between semantic units. Alternatively, formal thought disorder can be seen as the individual's ability to draw upon the intersubjective resources that help structure our thinking and expression (note that these two views are not mutually exclusive). In the latter view, we have to distinguish, in the terms of Merleau-Ponty, between "le langue" and "la parole" (32). The former is a historically and socially determining intersubjective matrix that dictates or influences our conceptual/cognitive abilities. "Le langue" is this matrix, whereas "la parole" is the individual's thinking and speech. In Merleau-Ponty's view, cognition is therefore heavily dependent on perception and embodied interaction in the social world, in agreement with earlier views of Vygotski (33). In the case of schizophrenia, it has repeatedly been emphasized that consciousness here entails a sort of disintegration. Kraepelin considered the disintegration as a product of weakened center of self-consciousness (Ich-Bewusstsein) (34). Famously, Bleuler introduced the concept of "loosening of associations" as an instance of a general tendency of splitting (Spaltung). Unfortunately, Bleuler's view was often understood as a sort of mechanical deficit in associative mechanisms. Bleuler himself, however, saw this splitting as a lack of hierarchy in the goal-directedness or intentionality. As an example of this intentionality, he mentions a peasant, whose overarching goal is to maximize the productivity of his land. Other activities such as sowing or plowing are subordinate activities to his primary goal. The peasant may do other things such as eating or sleeping, but the overarching goal is always tacitly present in his mind and structures his behavior. Thus, Bleuler saw the splitting and loosening of associations as an expression of diminished intentional directedness of consciousness. He ascribed this deficiency to a disorder of the ego and its activity (3). In the psychoanalytic literature of ego psychology, disorder of thinking was also considered as an expression of the pathology of the self (35).

Viewed from the perspective of the EASE-based self-disorder research, we can point to the following aspects of the link between self-disorder and formal thought disorder. First, self-disorder implies a weakened intersubjective attachment (a disorder of "common sense"), a tendency to solipsistic experiences and generally unstable self-awareness leading to a confusion between modalities of intentionality (14, 16, 36). Self-disorder may also imply a range of preverbal experiences, which may be quite unique and unusual and create a difficulty for conceptualization and verbalization, perhaps prompting the patient to use private or idiosyncratic formulations to articulate prereflectively altered self-experience. Finally, patients with schizophrenia spectrum

disorder often seem to exist in different and sometimes competing ontological frameworks, one reflecting our natural attitude and one more private where the laws of causality and non-contradiction do not exist (37–39).

In this study, we approached the issue of self-disorder from a different perspective than that of diagnoses, as the purpose was to explore the association between formal thought disorder and self-disorder. Our findings seem to converge around central phenomena of schizophrenia spectrum disorders, including self-disorder. From our own and others' studies, we know that self-disorder constitutes a trait phenomenon that is present before the full symptomatology of schizophrenia manifests (40–44), suggesting that self-disorder constitutes a basic framework within which the heterogeneous symptoms associated with schizophrenia may be unified and to some extent understood.

In the diagnostic systems of *ICD-10* and *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, formal thought disorder is defined at a quite severe level; perhaps leading to more subtle manifestations of formal thought disorder tends to be overlooked. Our findings point to the importance of paying close attention to potential formal thought disorder in the clinical encounter. Additionally, clinicians must be aware that interviews with a high degree of structure can impede formal thought disorder from materializing, and obviously assessments using self-rating scales do not allow for tracking formal thought disorder.

The major limitation to the study is the relatively small sample size. However, studies with such comprehensive assessment of psychopathology are very time consuming, making it difficult to obtain larger samples. Moreover, it should be mentioned that the translation of formally disturbed responses from Danish to English has built-in difficulties, and it is likely that some of the disturbed answers have lost some relevant aspects in the translation.

DATA AVAILABILITY STATEMENT

The datasets generated for this article are not readily available because it contains sensitive personal information. Requests to access the datasets should be directed to Julie_nordgaard@dadlnet.dk.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JN and JP designed the study and JN collected the data. MG-J and MB-P did the analyses. JN wrote the first draft of the manuscript. All authors contributed to the final manuscript.

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OPINION
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En attendant Godot: Waiting for the Funeral of "Schizophrenia" and the Baby Shower of the Psychosis Spectrum

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"Wax on, wax off."
From the movie The Karate Kid, 1984

INTRODUCTION

The debate on the concept of schizophrenia is alive and kicking (1) because the concept of schizophrenia is dead and decaying (2). Despite continual demands for reconceptualization proposed by highly influential academics, heated discussions during the revision processes of DSM and ICD, and attacks from every angle, the concept of schizophrenia, as we know it, has managed to "make a goal-line stand" every time. These discussions over decades have failed to go beyond merely stimulating exchanges between scholars that resulted in minor revisions only. We—like the two characters in *En attendant Godot*—are still waiting for a meaningful action toward reconceptualization that probably will never come. In this brief viewpoint, we will attempt to summarize the shortcomings of the schizophrenia concept and reiterate our understanding of psychosis spectrum disorder—hopefully, once and for all.

THE ILLUSION OF ETIOLOGICAL SPECIFICITY

The evidence thus far suggests that the etiology of mental disorders consists of multicausal, interdependent, interacting, and non-specific factors contributing to largely shared behavioral, social, and biological mechanisms (3). Schizophrenia is no exception.

Environmental factors, as part of a dynamic network (so-called exposome), associated with schizophrenia, are interdependent and causally and non-causally related to almost all psychiatric phenotypes (4). In the general population, environmental exposures, such as cannabis use and childhood adversity, are not only directly associated with psychotic experiences but also interact with multidimensional psychopathology and family history of affective disorders to increase psychosis expression: the so-called affective pathway to psychosis (5–7).

Genome-wide association studies (GWAS) consistently demonstrate that schizophrenia is genetically correlated with various psychiatric disorders, in particular bipolar disorder (8, 9). Similarly, polygenic liability score for schizophrenia is non-specifically associated with subclinical multidimensional phenotypes, including cognitive and affective domains (10–13), as well as broad mental and physical health outcomes in the general population (14).

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Based on the findings showing phenomenological, cognitive, genetic, molecular, and electrophysiological similarities between schizophrenia and bipolar disorder (15), we have argued that schizophrenia, schizoaffective disorder, and bipolar disorder may be different phenotypic presentations of a largely shared pathoetiology with diverse outcome trajectories (2). Multiple sclerosis is a well-known example of substantial phenotypic and clinical heterogeneity that stems from a shared pathoetiology. With the analogy of multiple sclerosis, these different diagnostic categories might be different types of a shared disease process with varying outcomes and phenotypical representations, suggestive of a unitary model of psychosis instead of discrete entities such that: brief psychotic disorder ∼ clinically isolated syndrome; bipolar disorder ∼ relapsing-remitting type; schizoaffective disorder ∼ secondary progressive type; schizophrenia ∼ primary progressive type. In light of accumulating evidence, we contemplate that psychosis spectrum disorder, a superordinate level category, would likely encompass bipolar disorder, at least in clinical research practice that we already observe in contemporary first episode psychosis studies. However, more transdiagnostic research is needed to confirm this proposition. Furthermore, we wish to clarify that this unitary framework should not be interpreted as against the possibility of distinct subtypes. We envision this unitary approach will set the ideal stage to think beyond the borders of traditional categories in the pursuit of improved taxonomy and may eventually lead to more precise classification.

THE ILLUSION OF DISCRETE ENTITY

The current taxonomy implies that schizophrenia represents a point of rarity, a discrete disease phenotype with well-defined boundaries. However, converging evidence suggests that psychosis expression, including positive, negative, and cognitive symptoms, represents an etiologically, phenomenologically, and temporally continuous phenotype across the general population, with prevalence rates varying between 5% (interview-rated) and 8% (self-report) (16, 17).

In the temporal domain, subclinical psychosis expression is associated with subsequent clinical psychotic disorders and non-psychotic disorders (18) and functional impairment, serving as a general severity indicator for broad psychopathology (17).

Recent findings from GWAS provide support to the liability-threshold model, first postulated by Gottesman and Shields more than 50 years ago (19). According to this model, which is fully compatible with the psychosis continuum concept, each individual has quantifiable (environmental and genetic) liability for schizophrenia to varying degrees but develops schizophrenia only when the combined liability exceeds the threshold on the continuum. Conforming to the psychosis continuum model, polygenic risk score for schizophrenia is associated with psychotic experiences in the general population (13). Furthermore, recent evidence lends support for a shared genetic liability between schizophrenia and psychotic experience (20). Environmental factors associated with schizophrenia—childhood trauma, cannabis use, urban environment—are likewise strongly associated with psychotic experiences at the population level (21). Furthermore, recent studies suggest that genetic liability for schizophrenia interact with environmental exposure to increase psychosis expression and comorbid psychopathology (22, 23).

THE ILLUSION OF PHENOTYPIC SPECIFICITY

Per definition of current classifications, schizophrenia represents a true distinct disease entity, of which the boundaries are clearly defined. This implication of rarity has reassured the implicit confidence of "schizo"-prism that the origins of the prodrome can logically be traced back using the same operational criteria, with a particular emphasis on positive psychotic subclinical symptoms. This unfounded confidence has led to the birth of the "clinical high risk" concept (24). However, it appears that the predictive performance of the clinical high risk is low, with only around 15% transitioning to clinical psychosis over a 3-year period in the help-seeking population (25). The fixation on psychosis—disregarding early expression of non-specific symptoms—comes at the expense of the multidimensional nature of psychopathology. However, it is well-established that non-psychotic psychopathology, such as anxiety, depressed mood, sleep disturbance, motivational impairment, social and neurocognitive alterations, precede early stages of psychotic disorders—so called heterotypic continuity.

In fact, the population-based estimates clearly show that even though the psychosis high-risk state displays a high relative risk for subsequent clinical psychosis outcome, the incidence of clinical psychosis outcome in the general population is largely attributable to non-psychotic mental disorder categories (i.e., mood, anxiety, alcohol, and drug use disorders) (18). These findings show that targeted "clinical high risk" early intervention model based on the schizophrenia concept can yield minimal benefit at the expense of major resource for case-finding, considering the scarcity of the psychosis high-risk state in the population (24, 26).

THE ILLUSION OF POOR OUTCOME

Per definition, schizophrenia is associated with chronicity, deterioration, and poor outcome—as reflected by psychiatrists' perception of schizophrenia: "Persons that turn out 'normal' again a few years later, I am forced to consider that I was mistaken about a schizophrenia early diagnosis" (27); "Good prognosis 'schizophrenia' is not mild schizophrenia, but a different illness" (28). In fact, studies show that a major challenge for improving the outcome of schizophrenia is paradoxically the narrow definition of neo-Kraepelinian schizophrenia, first introduced in DSM-III (29, 30).

Furthermore, accumulating evidence shows that early studies conducted mainly in inpatient units and tertiary specialized centers typically collect severity- and chronicity-enriched samples of patients with poor outcome and therefore are subject to systematic selection bias that is known as Berkson's bias

(31). In this regard, early studies of enriched samples overlook patients with better outcome and those recovered or displayed an improved course of illness and thereby no longer meeting the criteria for schizophrenia diagnosis. Findings from the contemporary studies, particularly those from the follow-up of patients with first episode psychosis in early intervention services, demonstrate that better outcomes are achievable (32). The 10-year follow-up of the Scandinavian TIPS Early Detection in Psychosis Study demonstrated that the recovery percentage was significantly higher in early-detection patients than those in the usual-detection area (30.7 vs. 15.1%) (33).

THE ILLUSION OF CLINICAL UTILITY

Psychiatry has disproportionately and erroneously placed too much emphasis on the clinical utility of diagnoses (34). As discussed above, schizophrenia diagnosis does not provide testable theories about the pathoetiology, treatment planning, or management but only "moves the goalpost" with the claim of predicting the course, which in reality comes with the ingrained chronicity and deterioration into the definition of schizophrenia.

Schizophrenia diagnosis has largely been deemed fairly stable and definitive, but mental health care professionals report that inaccurate and controversial diagnosis of schizophrenia in their clinical practice takes place frequently (35). Accordingly, the results of a WHO survey demonstrate that clinicians rate the ease of use and goodness of fit of schizophrenia no higher than other diagnoses, such as depressive and bipolar disorders (36).

SOLUTIONS FOR ILLUSIONS

There is a growing dissatisfaction with the notion of reifying psychiatric diagnostic categories as discrete entities. Research in search of the origins of schizophrenia has yielded neither actionable nor tangible evidence to improve our understanding. Several frameworks alternative to categorical conceptualization have been introduced particularly for research purposes: the US National Institute of Mental Health (NIMH) initiated Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP). Although the multidimensional assessment of schizophrenia was introduced in Section III of DSM−5 as "emerging measures" and the wording was revised slightly as "schizophrenia spectrum disorder," these changes had minimal impact on our use of schizophrenia in clinical practice.

It is clear that we need more—much more—evidence to propose drastic changes in the nosology of mental disorders including schizophrenia. Therefore, instead of a "grand idea," we propose a modest solution to pave the way for better conceptualization and improving clinical practice by emphasizing the importance of clinical characterization over diagnostic reductionism (37, 38). To encourage clinicians and researchers to think outside the borders of schizophrenia, we embrace a trans-syndromal framework of mental suffering yet retain an "umbrella" syndrome category (psychosis spectrum disorder) to satisfy clinical practice conventions (2). In fact, we propose the following framework: *psychosis spectrum* + *clinical characterization* (38). The use of "psychosis spectrum," while nomothetic, deliberately refers to something so broad and non-specific that it only makes sense if it is accompanied by an idiographic personal characterization. As the word "schizophrenia" has indelible negative connotations and implicit support for discrete entity, renaming is essential to enable seeing without the imaginary boundaries of current schizophrenia concept (39).

META-SOLUTIONS FOR DENIAL: FROM REPUDIATION TO TAKING RESPONSIBILITY

It is clear that the time for the funeral of schizophrenia was yesterday; nevertheless, we remain in the denial stage. Why is this so?

About three decades ago, Mary Boyle wrote her seminal work on schizophrenia as a "scientific delusion" (40). Many authors have since delivered similar cogent, scientific, clinical, ethical, and public health arguments for abandoning the schizophrenia concept (41–45)—yet nothing has changed. It is well-known that a switch in terminology can result in a disease being perceived as more serious and more likely to be a rare condition (46). Therefore, in medicine, changes in terminology are readily applied in response to social or ethical demands. Erectile Dysfunction, Myocardial Infarction, Alzheimer's disease and Down's syndrome are but a few examples. Such changes reflect the advent of the "moral era" of medicine and health care (47), in which the focus is not on narrow medical outcomes *per se* but on the degree to which they add value to highly personal life goals of the patient. Patients, professionals, and institutions therefore should learn to work together to "co-create" a terminology to suit the needs of the individual and society within the space of the inevitable scientific uncertainty surrounding the condition in question. Arguably, no area of medicine presents with more moral dilemmas as the practice of calling mental variation "things"—for example, "schizophrenia"—particularly, if accompanied by scientifically unfounded conviction that the "thing" is a nosological entity and is embedded exclusively in the brain. The bearer of an experience that falls within this nosological entity, for example, a person hearing voices, likely will have difficulties making himself "heard," because the mental health professional—and society in line with him—hears a symptom of a distinct brain disease. This phenomenon is called "epistemic injustice" and arguably represents one of the most important dilemmas to solve, should psychiatry wish to enter the moral era of medicine (48). Put simply, premature conclusions based on inconclusive science have real consequences that can result in epistemic injustice, and the use of the term "schizophrenia" has all the hallmarks of this. The degree to which psychiatry remains tone deaf to the issue of epistemic injustice inherent to schizo-labeling, matches with the evident loss of societal support for psychiatry as a science (49). Psychiatry, unlike oncology for example, receives cogent and well-organized critical feedback from many sources, including *Mad in America* and the *Hearing Voices Movement*. Instead of ignoring these sources of critical review, psychiatry could actively engage with them and co-create solutions, particularly

for pressing problems like the language and the concepts we use to describe mental variation.

In conclusion, there is ample reason for psychiatry to consider the issue of management of diversity with the gravity it deserves. Instead of letting the field become increasingly imprudent to diversity, we can choose innovation that befits the moral era of medicine, and grow out of our self-imposed state of non-responsiveness to embrace diversity in a fashion that fits science and avoids epistemic injustice.

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Neurodevelopmental Trajectories and Clinical Profiles in a Sample of Children and Adolescents With Early- and Very-Early-Onset Schizophrenia

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Schizophrenia before the age of 18 years is usually divided into two categories. Early-onset schizophrenia (EOS) presents between the ages of 13 and 17 years, whereas very-early-onset schizophrenia (VEOS) presents at or before the age of 12 years. Previous studies have found that neurodevelopmental difficulties in social, motor, and linguistic domains are commonly observed in VEOS/EOS patients. Recent research has also shown a high prevalence of neurodevelopmental disorders (e.g., intellectual disability, communication disorders, autism spectrum disorder, neurodevelopmental motor disorders) in VEOS/EOS patients, indicating genetic overlap between these conditions. These findings lend support to the neurodevelopmental continuum model, which holds that childhood neurodevelopmental disorders and difficulties and psychiatric disorders (e.g., schizophrenia) fall on an etiological and neurodevelopmental continuum, and should not be considered discrete entities. Based on this literature, in this study we focused on the overlap between neurodevelopmental disorders and schizophrenia investigating, in a large sample ($N = 230$) of VEOS/EOS children and adolescents, the clinical differences, at the onset of psychosis, between VEOS/EOS with neurodevelopmental disorder or neurodevelopmental difficulties and VEOS/EOS with no diagnosed neurodevelopmental disorder or neurodevelopmental difficulties. The findings showed that, in children and adolescents with a neurodevelopmental disorder or neurodevelopmental difficulties, psychosis onset occurred at an earlier age, was associated with more severe functional impairment (e.g., global, social, role), and was characterized by positive symptoms (e.g., grandiose ideas, perceptual abnormalities, disorganized communication) and disorganized symptoms (e.g., odd behavior or appearance, bizarre thinking). Instead, in children and adolescents without a neurodevelopmental disorder or neurodevelopmental difficulties, psychosis onset was mainly characterized by negative symptomatology (e.g., social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness). Given these differences, the presence of a neurodevelopmental disorder or neurodevelopmental difficulties should be carefully investigated and integrated early into the assessment and treatment plan for VEOS/EOS patients.

Keywords: schizophrenia, neurodevelopmental disorders, early onset psychosis, children, adolescents

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INTRODUCTION

Among children, schizophrenia is a rare neuropsychiatric disorder. The best prevalence estimates for schizophrenia in patients younger than 15 years is 0.05%, and only 2% of adult patients are estimated to have experienced the onset of their psychosis before the age of 13 years. According to the data and criteria provided by the National Institute of Mental Health (NIMH), in childhood and adolescence, two types of schizophrenia are commonly described, depending on the age of onset: early-onset schizophrenia (EOS), which presents between the ages of 13 and 17 years; and very-early-onset schizophrenia (VEOS), which presents at or before the age of 12 years. Although they are less common than adult-onset schizophrenia (AOS, presenting from the age of 17 years), VEOS and EOS tend to be more severe and disabling (1, 2). Concerning their clinical profile, both show higher rates of auditory hallucinations (3), negative symptoms, and bizarre behavior (4), as well as more severe neurocognitive difficulties (5), relative to AOS. Evidence of more severe neurocognitive difficulties among VEOS/EOS patients has been provided by anatomical brain MRI studies showing a greater progressive loss of cortical gray matter (6, 7) and progressive increases in ventricular volume (7) over time. In addition, compared with AOS patients, VEOS/EOS patients usually experience a longer duration of untreated psychosis (DUP) (8), worse outcomes (9), and more premorbid neurodevelopmental disorders (1).

Previous studies (10) have shown that premorbid neurodevelopmental difficulties are frequently present in children and adolescents who develop schizophrenia, especially those who experience an early onset of psychotic symptoms (e.g., VEOS patients). Within the NIMH cohort, Driver et al. (1, 11) observed that 67% of VEOS patients registered premorbid social, motor, language, and learning difficulties. This finding supports the results obtained by the same research group on a cohort of 118 participants with childhood-onset schizophrenia (11), of whom 55% ($n = 65$) showed premorbid academic difficulties, 72% ($n = 85$) had premorbid social difficulties, and 44% ($n = 52$) had premorbid motor difficulties; in addition, 20% ($n = 24$) screened positive for a pervasive developmental disorder (e.g., autism, Asperger syndrome) according to DSM-IV-TR criteria. Building on these findings, other longitudinal studies (12) have shown an overlap between early autistic symptoms and psychotic symptoms during childhood and adolescence. Specifically, in one study, 20–50% of VEOS participants were found to meet the criteria for premorbid autism spectrum disorder, according to DSM-5 criteria. Finally, some studies (11, 13, 14) have found the outcome and prognosis of VEOS/EOS patients to be positively correlated with the presence and severity of premorbid difficulties. Kincaid et al. (15) reported that VEOS/EOS patients with autistic features had higher symptom severity and poorer long-term outcomes compared with VEOS/EOS patients without autistic symptoms. Overall, these findings lend support to the neurodevelopmental continuum model, which holds that childhood neurodevelopmental difficulties and psychiatric disorders (e.g., schizophrenia) fall on an etiological and neurodevelopmental continuum, and should not be considered discrete entities (16). Recent studies (16, 17) have indicated a genetic overlap between schizophrenia and other syndromes that commonly arise during the developmental period. In the DSM-5, these syndromes are classified as "neurodevelopmental disorders," and include intellectual disability (ID), communication disorders (CDs), autism spectrum disorder (ASD), neurodevelopmental motor disorders (including tic disorders), and specific learning disorders (SLDs).

Over the years, many empirical studies have shown that childhood neurodevelopmental disorders such as ID, ASD, and ADHD share specific genetic risk alleles, both with each other and with psychiatric disorders, particularly schizophrenia (16, 18). For example, Singh et al. (17) found that copy number variants associated with ID were significantly enriched in individuals with schizophrenia, concluding that many additional ID-related variants may be a risk factor for schizophrenia. Further support for this theory is provided by studies showing that individuals with ID have higher rates of schizophrenia than the general population (19, 20). More recently, Stanfield et al. (21) confirmed the relationship between ID and risk for psychotic positive symptoms in a large sample of adolescents ($N = 168$).

In addition, neuroimaging studies (22) on brain alteration in VEOS/EOS patients have found less intracranial, hippocampal, and amygdala volume and higher caudate, pallidum, and lateral ventricle volume compared with healthy controls. This result is relatively consistent with data reported for adult psychosis patients (23), with the exception of the lower intracranial volume (ICV). This lower ICV in VEOS/EOS patients, compared with adult psychosis patients, suggests more severe disruption of brain neurodevelopment and at an earlier age. Of note, previous studies have found lower ICV in children and adolescents with attention deficit hyperactivity disorder (ADHD) (24) and higher ICV in patients with ASD (22), highlighting the importance of considering ICV in neurodevelopmental disorder imaging studies. In addition, both children and adolescents with ADHD and adults suffering from schizophrenia and bipolar disorder have been found to have lower hippocampal volume (25, 26). Thus, lower hippocampal volume could be a feature of several neurodevelopment disorders, reflecting both shared and distinct illness mechanisms. Overall, these results provide further support for the neurodevelopmental continuum model, which considers neurodevelopmental disorders and psychiatric disorders (e.g., schizophrenia) diverse outcomes on the range of disrupted or deviant brain development (27).

However, most of the studies cited so far consider small samples of VEOS/EOS and do not deepen the differences in the clinical presentation of psychosis between VEOS/EOS with a neurodevelopmental disorder or neurodevelopmental difficulties and VEOS/EOS without a neurodevelopmental disorder or neurodevelopmental difficulties.

Studying clinical differences at the onset of psychosis in these clinical populations could allow us to better understand the overlap between neurodevelopmental disorders and schizophrenia, and thereby improve the diagnostic and treatment process. For example, previous studies (15) suggest that a longer duration of illness is associated with poorer

long-term outcomes and higher symptom severity in VEOS/EOS with neurodevelopmental disorders or neurodevelopmental difficulties (i.e., autistic features). Therefore, an early screening of psychosis in children and adolescents with neurodevelopmental difficulties or diagnosed neurodevelopmental disorder could allow starting earlier both psychological and pharmacological treatments and possibly modify the clinical outcome. On this basis, the present study aimed to investigate, in a large sample ($N = 230$) of VEOS/EOS, the clinical differences, at the onset of psychosis, between VEOS/EOS with neurodevelopmental difficulties or diagnosed neurodevelopmental disorder as proposed in DSM-5 (ID, CDs, ASD, neurodevelopmental motor disorders, and SLDs) and VEOS/EOS with no diagnosed neurodevelopmental disorder or neurodevelopmental difficulties. In particular, we have focused on the age of psychosis onset, clinical profile at the onset of psychosis (e.g., positive, negative, disorganized, and general symptoms), and functional impairment at the onset of psychosis.

MATERIALS AND METHODS

Participants and Procedure

The study participants were 230 children and adolescents who had been consecutively admitted to the Child and Adolescent Neuropsychiatry Unit of the Clinical and Research Hospital Bambino Gesù of Rome with a recent onset of psychosis between January 2018 and January 2020.

In particular, participants had been admitted to a specialized clinical service for clinical high risk and VEOS/EOS children and adolescents. We admitted help-seeking children and adolescents with a suspected prodromal condition or suspected presence of frank psychosis symptoms. At intake, a multi-specialized clinical team of child neuropsychiatrists and psychologists trained in developmental neuropsychology and psychopathology administered clinical evaluations based on present, past symptomatology, and neurodevelopmental history. This allows investigating the psychotic symptoms for which evaluation is required and the possible presence of a previous diagnosis of neurodevelopmental disorders or neurodevelopmental difficulties.

The single inclusion criterion was the presence of any schizophrenia spectrum disorder (according to the DSM-5) (28). The exclusion criteria were a past diagnosis of a psychotic disorder, the presence of a traumatic brain injury or neurological disorder, and current or previous drug or alcohol abuse. The participation rate was 77% of all consecutively admitted children and adolescents. Fifty-four patients (23%) were excluded on the basis of the exclusion criteria. None of the eligible patients refused to participate. The final sample was composed of 176 children and adolescents (67 female, 109 male). Patients experienced an onset of psychosis between the ages of 7 and 18 years ($M = 14.69$ years; $SD = 2.19$ years; median = 15 years).

All participants and their parents/legal guardians provided written informed assent and consent.

For all participants, the presence of a neurodevelopmental disorder or neurodevelopmental difficulties was ascertained from retrospective anamnestic data.

TABLE 1 | Frequency and percentage of neurodevelopmental disorder (group 1) and neurodevelopmental difficulties (group 2).

Variables	Group 1 *N* (%)	Group 2 *N* (%)
Neurodevelopmental disorder according to DSM-5		
Intellectual disabilities	25 (38)	
Communication disorders	12 (18)	
Autism spectrum disorder	7 (11)	
Attention-deficit/hyperactivity disorder	21 (32)	
Specific learning disorder	18 (28)	
Motor disorders	6 (9)	
Neurodevelopmental difficulties		
Difficulties in psychomotor development: - *Unsupported sitting >8 months* - *Walking >18 months*		9 (24)
Language difficulties: - *First word >24 months* - *First 2/3 word phrases >36 months*		15 (39)
Reading/writing difficulties: - *School or parent report confirmed reading, writing, and calculation difficulties*		9 (24)
Social difficulties: - *Lack of reciprocal social communication* - *Failure to regulate gaze, facial expression, posture* - *Lack of imaginative or imitative play* - *Failure to make friends and share interests*		22 (58)

Table 1 presents the clinical criteria used to determine neurodevelopmental difficulties.

As result, participants were divided into the following groups:

- Group 1: VEOS/EOS patients with a diagnosed neurodevelopmental disorder [e.g., ID, CD, ASD, neurodevelopmental motor disorder (including tic disorder), SLD] before the onset of psychosis;
- Group 2: VEOS/EOS patients with neurodevelopmental difficulties (i.e., motor, linguistic, social difficulties) but no diagnosed neurodevelopmental disorder (28) before the onset of psychosis; and
- Group 3: VEOS/EOS patients with no diagnosed neurodevelopmental disorder or neurodevelopmental difficulties before the onset of psychosis.

Clinical Assessment

Clinical assessment was conducted on the entire sample ($N = 230$) by a neuropsychiatrist and two psychologists. All the clinicians had been trained in the application of structured and semi-structured neuropsychiatric and psychopathological diagnostic tools, and were specialized in the evaluation of psychotic symptoms in children and adolescents, with and without a comorbid neurodevelopmental disorder.

Mental disorders were assessed using the Schedule for Affective Disorders and Schizophrenia for School Aged Children

Present and Lifetime Version DSM-5 (K-SADS-PL DSM-5). K-SADS-PL DSM-5 investigates the possible presence of psychopathological disorders according to DSM-5 (including schizophrenia spectrum disorders) (29). The K-SADS-PL DSM-5, as proposed in the instrument manual by Kaufman et al. (29), provides as a source of information not only the child/adolescent but also the parent. In addition, for some particular cases (i.e., ID), the parent is considered the main source of information with respect to the child.

Psychotic symptoms were indexed using the Structured Interview for Psychosis-Risk Syndrome (SIPS/SOPS) (30). The SIPS/SOPS measures four symptom dimensions: *positive symptoms* (i.e., unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiose ideas, perceptual abnormalities/hallucinations, disorganized communication), *negative symptoms* (i.e., social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, occupational functioning), *disorganized symptoms* (i.e., odd behavior or appearance, bizarre thinking, trouble with focus and attention, impairment in personal hygiene), and *general symptoms* (i.e., sleep disturbance, dysphoric mood, motor disturbances, impaired tolerance to normal stress). These dimensions are assessed according to the presence, duration, and severity of specific experiences and behaviors, with each item rated on a scale of 0 (*symptom absent*) to 6 (*extreme* symptom intensity, or *psychotic* for the Positive Symptom items).

SIPS/SOPS interviews were conducted by clinical psychologists and neuropsychiatrists trained by the main author of the factor-structure analysis study on the Italian version of the Scale of Prodromal Symptoms (SOPS) in comparison with the English version (31).

For children under the age of 13 years and for children and adolescents with ID, the K-SADS PL DSM-5 and the SIPS/SOPS interviews consult both the child and the parents. According to procedure used in previous studies (19, 21, 32, 33), K-SADS-PL DSM-5 and SIPS/SOPS interviews were completed face to face with children and adolescents with IDs supported by their caregiver or another appropriate person. Information was also collected from relatives separately.

Level of global functioning (referring to family, school, and social domains) was measured with the Childhood Global Assessment Scale (34). This scale assesses functional impairment due to neuropsychiatric disorders and produces a score ranging from 1 (*constant supervision*) to 100 (*functioning above the norm in all areas*). Social and role functioning were assessed using the Global Functioning: Social Scale (GF: Social) (35) and the Global Functioning: Role Scale (GF: Role) (36) to obtain differential measures of functioning. GF: Social investigated the quantity and the quality of peer relationship, involvement with family members, and level of peer conflict. GF: Role investigated the level of performance in school, work, or at home. These scales are based on 10 criteria of functioning, assessed from 1 (*extreme social isolation* or *role impairment*, respectively) to 10 (*higher interpersonal* and *role functioning*, reflectively). Both scales provide indications of current functioning, lowest functioning in the past year, and highest functioning in the past year.

Neurocognitive functioning (IQ) was measured with the Wechsler Intelligence Scales (WISC-IV: Wechsler Intelligence Scale for Children; WAIS-IV: Wechsler Adult Intelligence Scale) (37, 38).

Finally, we documented the presence of substance use and diagnosed psychosis in patients' first- and second-degree relatives.

Statistical Analyses

Statistical analyses were performed with Stata for Windows (StataCorp LLC, College Station, Texas; version 13.0 released in 2013). One-way analyses of variance (*F*-tests or ANOVAs) were used to test the independence between continuous response variables and the categorical explanatory variable (group variable). Row scores for each measure were considered.

Post-hoc analyses were performed to determine Bonferroni CIs (95%) and establish differences between means. Associations between group, sex, and type of substance use (i.e., nicotine, alcohol, cannabis) were examined using χ^2-tests.

RESULTS

Sample Characteristics

The final sample ($N = 176$; mean age of psychosis onset = 14.69 years, $SD = 2.19$; male: $n = 109$, 62%) was divided into three groups. Group 1 was composed of 65 (37%) VEOS/EOS subjects (male: $n = 43$; 66%) with a diagnosed neurodevelopmental disorder. Group 2 consisted of 38 (22%) VEOS/EOS subjects (male: $n = 25$; 66%) with neurodevelopment difficulties.

Finally, group 3 included 73 (41%) VEOS/EOS subjects (male: $n = 41$; 56%) with neither neurodevelopment difficulties nor a diagnosed neurodevelopmental disorder.

There were no significant differences in sex (Pearson $\chi^2 = 1.7612$, $p = 0.415$) between groups (total sample: 62% male).

Table 1 reports the percentage frequency of neurodevelopmental disorders in group 1 and neurodevelopmental difficulties in group 2.

Table 2 reports the frequency and percentage frequency of diagnosed schizophrenia spectrum disorders and a family history of psychiatric illness and/or substance use, for each group.

No significant differences were found in substance use (Pearson $\chi^2 = 2.6666$, $p = 0.615$) between groups.

Comparison Between Groups

Age of Psychosis Onset, Number of Hospitalizations, IQ, and Functioning

As shown in **Table 3**, significant differences between three groups were found in age of psychosis onset [$F_{(2, 173)} = 6.70$, $p = 0.0016$]. Bonferroni *post-hoc* analyses showed that groups 1 and 2 presented a younger age of psychosis onset than group 3 (Gr1 vs. Gr2: $p = 1.000$; Gr1 vs. Gr3: $p = 0.002$; Gr2 vs. Gr3: $p = 0.046$).

Regarding number of hospitalizations, no significant differences were found between groups [$F_{(2, 173)} = 0.62$, $p = 0.5387$].

IQ significantly differed between groups [$F_{(2, 173)} = 17.19$, $p = 0.000$]. Bonferroni *post-hoc* analyses showed that group 1 had

TABLE 2 | Socio-demographic and clinical data scores separately for three groups.

Variables	Group 1 *N* (%)	Group 2 *N* (%)	Group 3 *N* (%)	Statistics
Male gender	43 (66)	25 (66)	41 (56)	$\chi^2 = 1.7612$ $p = 0.415$
Nicotine use	1 (2)	1 (3)	5 (7)	$\chi^2 = 2.6666$ $p = 0.615$
Alcohol use	0 (0)	0 (0)	3 (4)	
Cannabis use	9 (14)	3 (8)	17 (23)	
First-degree relative with psychotic disorder	1 (2)	4 (11)	1 (2)	
Second-degree relative with psychotic disorder	5 (8)	5 (13)	5 (7)	
Schizophrenia spectrum disorders according to DSM-5				
Delusional disorder	0 (0)	0 (0)	3 (4)	
Brief psychotic disorder	20 (31)	8 (21)	21 (29)	
Schizophreniform disorder	10 (15)	5 (13)	22 (30)	
Schizophrenia	32 (49)	24 (63)	21 (29)	
Schizoaffective disorder	3 (5)	1 (3)	6 (8)	

TABLE 3 | Group differences on age of psychotic onset, number of hospitalizations, IQ, and functioning.

Variables	Group 1 Mean (*SD*)	Group 2 Mean (*SD*)	Group 3 Mean (*SD*)	*F*	*p*-value
Age of psychosis onset (years)	14.12 (2.54)	14.34 (2.25)	15.38 (1.58)	6.70	0.0016*
Number of hospitalizations	1.31 (1.58)	1.71 (3.10)	1.37 (0.99)	0.62	0.5387
IQ	75.81 (18.90)	88.18 (11.09)	90.21 (12.83)	17.19	0.0000**
C-GAS	40.83 (7.67)	40.34 (6.35)	45.72 (6.37)	11.69	0.0000**
GF: Role	3.16 (0.83)	3.18 (0.69)	3.67 (0.68)	9.40	0.0001**
GF: Social	3.16 (0.83)	3.18 (0.69)	3.67 (0.68)	9.40	0.0001**

*$p \leq 0.005$ and **$p \leq 0.0001$.
IQ, intelligence quotient; C-GAS, Children's Global Assessment Scale; GF: Social, Global Functioning: Social Scale; GF: Role, Global Functioning: Role Scale.

lower scores than groups 2 and 3 (Gr1 vs. Gr2: $p = 0.000$; Gr1 vs. Gr3: $p = 0.000$; Gr2 vs. Gr3: $p = 1.000$).

There were also significant differences between groups with respect to global, social, and role functioning.

Bonferroni *post-hoc* analyses showed that groups 1 and 2 presented with significantly worse global functioning measured by C-GAS [$F_{(2, 173)} = 11.69$, $p = 0.000$] compared with group 3 (Gr1 vs. Gr2: $p = 1.000$; Gr1 vs. Gr3: $p = 0.000$; Gr2 vs. Gr3: $p = 0.000$). With respect to GF-Role and GF-Social, similar results were found, with groups 1 and 2 presenting significant social and role impairment [$F_{(2, 173)} = 9.40$, $p = 0.0001$] relative to group 3 (Gr1 vs. Gr2: $p = 1.000$; Gr1 vs. Gr3: $p = 0.000$; Gr2 vs. Gr3: $p = 0.004$).

These significant group differences in global [$F_{(2, 173)} = 13.71$, $p = 0.000$], role [$F_{(2, 173)} = 10.30$, $p = 0.0001$], and social [$F_{(2, 173)} = 10.30$, $p = 0.0001$] functioning were maintained when covariate IQ was added. Significant group differences in global [$F_{(2, 173)} = 8.12$, $p = 0.0004$], role [$F_{(2, 173)} = 5.35$, $p = 0.0055$], and social [$F_{(2, 173)} = 5.35$, $p = 0.0055$] functioning were also maintained when the covariate number of diagnoses was added.

SIPS/SOPS Psychotic Symptoms Dimensions

Table 4 reports significant group differences for each SIPS/SOPS symptom dimension.

Positive Symptoms

Significant group differences were found in grandiose ideas [$F_{(2, 173)} = 3.91$, $p = 0.0218$], perceptual abnormalities/hallucinations [$F_{(2, 173)} = 3.79$, $p = 0.0245$], and disorganized communication [$F_{(2, 173)} = 2.98$, $p = 0.0496$]. Bonferroni *post-hoc* analyses were conducted; comparisons of all groups were made. Regarding grandiose ideas, group 1 reported major mean score compared with group 3 (Gr1 vs. Gr3: $p = 0.050$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 1.000$; Gr2 vs. Gr3: $p = 0.066$). Concerning perceptual abnormalities/hallucinations, group 1 reported major score compared with group 3 (Gr1 vs. Gr3: $p = 0.025$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 1.000$; Gr2 vs. Gr3: $p = 0.285$). Finally, with respect to disorganized communication, group 1 reported major score compared with group 3 (Gr1 vs. Gr3: $p = 0.049$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 0.302$; Gr2 vs. Gr3: $p = 1.000$).

No significant group differences were found in unusual thought content/delusional ideas [$F_{(2, 173)} = 0.79$, $p = 0.4573$] or suspiciousness/persecutory ideas [$F_{(2, 173)} = 0.64$, $p = 0.5279$]. Globally, no significant differences were found in regards to the SIPS total score for positive symptoms [$F_{(2, 173)} = 2.68$, $p = 0.0711$].

TABLE 4 | Group differences on SIPS/SOPS.

Variables	Group 1 Mean (*SD*)	Group 2 Mean (*SD*)	Group 3 Mean (*SD*)	*F*	*p*-value
SIPS positive items					
P1: Unusual thought content/delusional ideas	5.18 (1.43)	5.23 (1.34)	5.45 (1.16)	0.79	0.4573
P2: Suspiciousness/persecutory ideas	4.35 (1.97)	4.39 (1.79)	4.69 (1.91)	0.64	0.5279
P3: Grandiose ideas	2.03 (1.80)	2.13 (1.72)	1.34 (1.60)	3.91	0.0218*
P4: Perceptual abnormalities/hallucinations	4.81 (1.75)	4.57 (1.60)	3.91 (2.28)	3.79	0.0245*
P5: Disorganized communication	4.55 (1.40)	3.94 (1.94)	3.83 (2.02)	2.98	0.0496*
SIPS positive total score	20.93 (3.62)	20.28 (4.59)	19.24 (4.72)	2.68	0.0711
SIPS negative items					
N1: Social anhedonia	4.29 (1.68)	4.89 (1.68)	5.31 (1.43)	7.18	0.0010*
N2: Avolition	3.92 (1.73)	3.52 (2.12)	4.80 (1.34)	8.70	0.0003*
N3: Expression of emotion	3.46 (1.59)	4.26 (1.40)	5.00 (1.36)	19.05	0.0000**
N4: Experience of emotions and self	3.12 (1.70)	4.00 (1.33)	4.90 (1.39)	24.14	0.0000**
N5: Ideational richness	3.60 (1.59)	4.84 (1.28)	4.49 (1.39)	10.69	0.0000**
N6: Occupational functioning	5.41 (1.05)	5.78 (0.47)	5.52 (1.24)	1.53	0.2194
SIPS Negative total score	23.81 (6.99)	27.31 (5.46)	30.04 (7.02)	14.82	0.0000**
SIPS disorganized items					
D1: Odd behavior or appearance	4.70 (1.53)	4.39 (1.51)	3.87 (1.97)	4.04	0.0193*
D2: Bizarre thinking	4.92 (1.58)	4.73 (1.68)	4.02 (2.16)	4.30	0.0150*
D3: Trouble with focus and attention	3.81 (1.50)	4.10 (1.20)	3.60 (1.70)	1.35	0.2621
D4: Impairment in personal hygiene	3.43 (1.66)	3.50 (1.79)	2.93 (1.58)	2.15	0.1196
SIPS Disorganized total score	18.87 (3.74)	16.73 (4.58)	14.43 (5.20)	5.81	0.0036*
SIPS general items					
G1: Sleep disturbance	3.93 (1.88)	4.36 (1.73)	4.56 (1.78)	2.08	0.1284
G2: Dysphoric mood	4.52 (1.64)	4.78 (1.59)	4.76 (1.64)	0.49	0.6154
G3: Motor disturbances	2.55 (1.87)	2.78 (1.86)	2.83 (1.91)	0.41	0.6614
G4: Impaired tolerance to normal stress	4.29 (1.89)	4.84 (1.76)	4.31 (1.77)	1.31	0.2726
SIPS general total score	15.30 (4.78)	16.78 (4.21)	16.47 (5.00)	1.53	0.2199

*$p \leq 0.05$ and **$p \leq 0.0001$.
SIPS, Structured Interview for Psychosis-Risk Syndrome.

Negative Symptoms

With respect to negative symptoms, significant group differences were found in social anhedonia [$F_{(2, 173)} = 7.18$, $p = 0.0010$], avolition [$F_{(2, 173)} = 8.70$, $p = 0.0003$], expression of emotion [$F_{(2, 173)} = 19.05$, $p = 0.0000$], experience of emotions and self [$F_{(2, 173)} = 24.14$, $p = 0.0000$], and ideational richness [$F_{(2, 173)} = 10.69$, $p = 0.0000$]. Bonferroni *post-hoc* analyses were conducted; comparisons of all groups were made. Concerning social anhedonia, group 3 reported major score compared with group 1 (Gr1 vs. Gr3: $p = 0.001$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 0.193$; Gr2 vs. Gr3: $p = 0.560$). Regarding avolition, group 3 reported major score compared with groups 1 and 2 (Gr1 vs. Gr3: $p = 0.007$; Gr2 vs. Gr3: $p = 0.001$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 0.746$). With respect to expression of emotion, group 3 reported major score compared with groups 1 and 2 (Gr1 vs. Gr2: $p = 0.024$; Gr1 vs. Gr3: $p = 0.000$; Gr2 vs. Gr3: $p = 0.038$). Also, in experience of emotions and self, group 3 reported major score compared with groups 1 and 2 (Gr1 vs. Gr2: $p = 0.014$; Gr1 vs. Gr3: $p = 0.000$; Gr2 vs. Gr3: $p = 0.009$).

Finally, regarding ideational richness, group 3 reported major score compared with group 1 (Gr1 vs. Gr3: $p = 0.001$). Also, group 2 reported major score compared with group 1 (Gr1 vs. Gr2: $p = 0.000$). Other comparison was not significant (Gr2 vs. Gr3: $p = 0.694$). No significant group differences were found with respect to occupational functioning [$F_{(2, 173)} = 1.53$, $p = 0.2194$].

Globally, significant differences were found for the SIPS total score for negative symptoms [$F_{(2, 173)} = 14.82$, $p = 0.0000$] with group 3 reporting major score compared with group 1 (Gr1 vs. Gr3: $p = 0.000$). Also, groups 1 and 2 differed significantly (Gr1 vs. Gr2: $p = 0.034$). All other comparisons were not significant (Gr2 vs. Gr3: $p = 0.131$).

Disorganized Symptoms

Significant group differences were found with respect to odd behavior or appearance [$F_{(2, 173)} = 4.04$, $p = 0.0193$], and bizarre thinking [$F_{(2, 173)} = 4.30$, $p = 0.0150$].

Bonferroni *post-hoc* analyses were conducted; comparisons of all groups were made.

Specifically, group 1 reported major score in odd behavior or appearance compared with group 3 (Gr1 vs. Gr3: $p = 0.016$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 1.000$; Gr2 vs. Gr3: $p = 0.409$). Also, group 1 reported major score in bizarre thinking compared with group 3 (Gr1 vs. Gr3: $p = 0.017$).

All other comparisons were not significant (Gr1 vs. Gr2: $p = 1.000$; Gr2 vs. Gr3: $p = 0.178$).

No significant group differences were found with respect to trouble with focus and attention [$F_{(2, 173)} = 1.35$, $p = 0.2621$], or impairment in personal hygiene [$F_{(2, 173)} = 2.15$, $p = 0.1196$]. Overall, significant group differences were found in the SIPS total score for disorganized symptoms [$F_{(2, 173)} = 5.81$, $p = 0.0036$]. In particular, group 1 reported major total score compared with groups 2 and 3 (Gr1 vs. Gr3: $p = 0.006$; Gr2 vs. Gr3: $p = 0.039$). All other comparisons were not significant (Gr1 vs. Gr2: $p = 1.000$).

General Symptoms

No significant group differences were found with respect to sleep disturbance [$F_{(2, 173)} = 2.08$, $p = 0.1284$], dysphoric mood [$F_{(2, 173)} = 0.49$, $p = 0.6154$], motor disturbances [$F_{(2, 173)} = 0.41$, $p = 0.6614$], or impaired tolerance to normal stress [$F_{(2, 173)} = 1.31$, $p = 0.2726$]. Overall, there were no significant group differences in the SIPS total score for general symptoms [$F_{(2, 173)} = 1.53$, $p = 0.2199$].

DISCUSSION

The main aim of the present study was to explore, in a large sample of VEOS/EOS, the clinical differences, at the onset of psychosis, between VEOS/EOS with neurodevelopmental difficulties or diagnosed neurodevelopmental disorder as proposed in DSM-5 (ID, CDs, ASD, neurodevelopmental motor disorders, and SLDs) and VEOS/EOS with no diagnosed neurodevelopmental disorder or neurodevelopmental difficulties.

We have focused on the age of psychosis onset, clinical profile at the onset of psychosis (e.g., positive, negative, disorganized, and general symptoms), and functional impairment at the onset of psychosis.

The first finding suggested that neurodevelopmental disorders may be common in our sample VEOS/EOS children and adolescents. Indeed, in our large sample ($N = 176$), 65 (37%) participants had a diagnosed neurodevelopmental disorder. Most frequently, the diagnoses were for ID ($n = 25$; 38%) and ADHD ($n = 21$; 32%). This finding is consistent with the results of previous studies showing that ID is common in individuals who develop schizophrenia (19, 32). Also, a history of ADHD symptoms is common in children and adolescents who develop schizophrenia (39), and ADHD is diagnosed in a high proportion of children at genetic risk for schizophrenia (40).

In addition, 22% of our participants had neurodevelopmental difficulties (e.g., motor, social, linguistic difficulties) that did not meet the criteria for a frank neurodevelopmental disorder. Specifically, 58% showed social difficulties, 39% showed language difficulties, 24% showed psychomotor difficulties, and 24% showed learning difficulties. These results are consistent with previous research finding that motor, linguistic, and social difficulties are present in children and adolescents who develop schizophrenia (1, 11).

Concerning the age of psychosis onset, in our sample, children and adolescents with a diagnosed neurodevelopmental disorder or neurodevelopmental difficulties showed an earlier onset of psychosis compared with participants with no neurodevelopmental diagnosis or difficulties. This result also aligns with the previous studies (10, 14, 41–43), which reported an association between earlier psychosis onset and the presence of language, motor, and social difficulties. For example, Petruzzelli et al. (44) found early onset of schizophrenia in 36 patients (age range: 7–17 years), of whom 70.6% presented neurodevelopmental difficulties, as well as difficulties in school learning or difficulties in sphincter control (enuresis).

Regarding clinical profile at the onset of psychosis, based on the SIPS/SOPS domains, we distinguished between positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. Regarding positive symptoms, VEOS/EOS patients with a diagnosed neurodevelopmental disorder scored higher on grandiose ideas, perceptual abnormalities/hallucinations, and disorganized communication than VEOS/EOS patients with neurodevelopmental difficulties and VEOS/EOS patients with neither a neurodevelopmental disorder nor neurodevelopmental difficulties. The same pattern was found for disorganized symptoms, with VEOS/EOS patients with a diagnosed neurodevelopmental disorder scoring higher in odd behavior or appearance and bizarre thinking.

Regarding negative symptoms, VEOS/EOS patients with neither a neurodevelopmental disorder nor neurodevelopmental difficulties scored higher on social anhedonia, avolition, expression of emotion, experience of emotions and self, and ideational richness, relative to VEOS/EOS patients with a neurodevelopmental disorder or neurodevelopmental difficulties. Regarding general symptoms, we found no significant differences between groups.

Finally, regarding functional impairment at the onset of psychosis, in our sample, VEOS/EOS patients with a neurodevelopmental disorder or neurodevelopmental difficulties reported major global functional impairment, whereas VEOS/EOS patients without these two conditions did not. To understand the effect of neurodevelopmental disorders and difficulties on functioning in our VEOS/EOS sample, we also investigated two specific functioning domains: role and social. Both of these domains were found to be more compromised in VEOS/EOS patients with a neurodevelopmental disorder or neurodevelopmental difficulties than in VEOS/EOS patients with neither of these two conditions. We examined the relationship between neurodevelopmental disorders and difficulties and global, social, and role functioning, controlling for IQ (in the subgroup with neurodevelopmental disorders we included patients with ID) and number of neuropsychiatric disorders (neurodevelopmental disorders plus VEOS/EOS). The results showed that the poorer global, social, and role functioning of VEOS/EOS patients with a neurodevelopmental disorder or neurodevelopmental difficulties was not affected by any of these variables. In other words, neurodevelopmental disorders and difficulties tended to determine poorer global, social, and role functioning, regardless of cognitive functioning and the number of neuropsychiatric disorders.

Overall, based on our findings, we propose that the clinical picture of VEOS/EOS patients may differ at the onset of psychosis

according to the presence (or lack) of a neurodevelopmental disorder or neurodevelopmental difficulties. In more detail, in children and adolescents with a neurodevelopmental disorder or neurodevelopmental difficulties, psychosis onset tends to occur at an earlier age and is associated with more severe (global, social, and role) functional impairment. In addition, in these patients, the onset of psychosis is likely to be characterized by positive symptoms (e.g., grandiose ideas, perceptual abnormalities, disorganized communication) and disorganized symptoms (e.g., odd behavior or appearance, bizarre thinking). Instead, in children and adolescents without a neurodevelopmental disorder or neurodevelopmental difficulties, the onset of psychosis is likely to be characterized by negative symptomatology (e.g., social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness). These results should be replicated in future studies, with caution, to gain further information on the clinical and neurodevelopmental profiles of children and adolescents with suspected VEOS/EOS. Such research is essential for the early recognition of symptoms at the onset of psychosis and the preparation of a therapeutic program tailored to each patient.

The present research was the first study to explore the differences on clinical presentation of psychosis between VEOS/EOS with a neurodevelopmental disorder or neurodevelopmental difficulties and VEOS/EOS without a neurodevelopmental disorder or neurodevelopmental difficulties. Among the strengths that can be considered are the size of the sample and the age range (7–18 years) adequately representative of the developmental age. The research also considered a rich neurodevelopmental profile—considering both neurodevelopmental disorders (according to the DSM-5) and neurodevelopmental difficulties—and assessed psychotic symptoms (e.g., SIPS/SOPS) and level of functioning (e.g., GF: Role, GF: Social) at the onset of psychosis using semi-structured interviews. The study has several limitations. The first relates to the high prevalence of ID in the group with a neurodevelopmental disorder. This may have overestimated the presence of psychotic positive symptoms in this group. The second relates to the lack of data analysis about patients' pharmacological or psychosocial treatment before the onset of psychosis. The third relates to the lack, in the literature, of standardized structured or semi-structured interviews that can be used for the assessment of psychotic symptoms in children and adolescents with IDs. Future research should examine this aspect through longitudinal studies focused on the clinical overlap between neurodevelopmental disorders, neurodevelopmental difficulties, and VEOS/EOS.

DATA AVAILABILITY STATEMENT

The study data are not available due to ethical concerns. Patient privacy and security are protected, according to the ethical rules of our institutions and their restriction on data sharing.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Children Hospital Bambino Gesù. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MP and RA conceived the research study. MCT and MLP collected data. MP and MCT contributed to the data analysis/interpretation. MP, MCT, FC, and MLP contributed to the writing of the article. MP, RA, and SV critically reviewed the final draft of the article. All authors contributed to the article and approved the submitted version.

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