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Symptom dimensions and subgroups in childhood-onset schizophrenia

Kirsten E.S. Craddock [a], Xueping Zhou [a], Siyuan Liu [a,*], Peter Gochman [a], Dwight Dickinson [b], Judith L. Rapoport [a]

[a] Child Psychiatry Branch, Intramural Research Program, National Institute of Mental Health, NIH, 10 Center Drive, Bldg. 10- Rm. 4N244, Bethesda, MD 20814, United States
[b] Clinical and Translational Neuroscience Branch, Intramural Research Program, National Institute of Mental Health, NIH, 10 Center Drive, Bldg. 10- Rm. 3C115, Bethesda, MD 20814, United States

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ABSTRACT

Objective: This study investigated symptom dimensions and subgroups in the National Institute of Mental Health (NIMH) childhood-onset schizophrenia (COS) cohort and their similarities to adult-onset schizophrenia (AOS) literature.
Method: Scores from the Scales for the Assessment of Positive and Negative Symptoms (SAPS & SANS) from 125 COS patients were assessed for fit with previously established symptom dimensions from AOS literature using confirmatory factor analysis (CFA). K-means cluster analysis of each individual's scores on the best fitting set of dimensions was used to form patient clusters, which were then compared using demographic and clinical data.
Results: CFA showed the SAPS & SANS data was well suited to a 2-dimension solution, including positive and negative dimensions, out of five well established models. Cluster analysis identified three patient groups characterized by different dimension scores: (1) low scores on both dimensions, (2) high negative, low positive scores, and (3) high scores on both dimensions. These groups had different Full scale IQ, Children's Global Assessment Scale (CGAS) scores, ages of onset, and prevalence of some co-morbid behavior disorders (all $p < 3.57E-03$).
Conclusion: Our analysis found distinct symptom-based subgroups within the NIMH COS cohort using an established AOS symptom structure. These findings confirm the heterogeneity of COS and were generally consistent with AOS literature.

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1. Introduction

Methods of categorizing the symptoms of schizophrenia and subgrouping schizophrenic patients into homogenous groups have long been studied (Adityanjee et al., 1999; Crow, 1985). More recently, research has shifted from rigid categories towards symptom dimensions and novel subtyping methods to better define and treat this heterogeneous disease (Andreasen and Carpenter, 1993; Bleich-Cohen et al., 2014; Carpenter et al., 1988; Harvey et al., 2016; Reininghaus et al., 2013). Childhood-onset schizophrenia (COS), defined by onset before the 13th birthday, is a rare and more severe version of the adult disorder in which symptom dimensions and subtypes have not been examined (Nicolson and Rapoport, 1999).

There is some consensus in adult-onset schizophrenia (AOS) regarding the broad themes of schizophrenia symptom dimensions, with many studies reporting at least a positive, negative, and disorganized dimension (Dazzi et al., 2016; Peralta and Cuesta, 2001; von Knorring and Lindstrom, 1992; Wallwork et al., 2012). Scale for the Assessment of Positive and Negative Symptoms (SAPS & SANS) studies find between 2 and 4, but commonly three, dimensions (Andreasen, 1995; Crow, 1985; Cuesta et al., 1994; Lewine et al., 1983; Mortimer et al., 1990; Peralta et al., 1994; Peralta and Cuesta, 2001), while studies using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987; Wallwork et al., 2012) or the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) most commonly identify 4 or 5-factor solutions (Dazzi et al., 2016; Mueser et al., 1997; Salokangas et al., 2002; Wallwork et al., 2012). Notably, despite common themes, the items included and variance explained differed between studies, even those using the same scales (Dollfus and Everitt, 1998; Peralta et al., 1994; Peralta and Cuesta, 2001; Potuzak et al., 2012). In studies with additional factors, paranoid, depressive, and hostile/excitement factors were often reported (Peralta and Cuesta, 2001; Wallwork et al., 2012). Studies investigating symptom dimensions are valuable as they provide insight into schizophrenia symptomatology and offer novel framework to explore the relationship between symptoms and clinical, biological,

Abbreviations: ASD, Autism Spectrum Disorders; ASQ, the Autism Screening Questionnaire; AOS, Adult onset schizophrenia; ADHD, Attention Deficit Hyperactivity Disorder; BPRS, Brief Psychiatric Rating Scale; COS, Childhood onset schizophrenia; CGAS, Children's Global Assessment Scale; CD, Conduct Disorder; CFA, Confirmatory Factor Analysis; CFI, Comparative Fit Index; CNVs, Copy Number Variants; EOS, Early onset schizophrenia; GFI, Goodness of Fit Index; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; NIMH, National Institute of Mental Health; ODD, Oppositional Defiant Disorder; PDD, Pervasive Developmental Disorder; PANSS, Positive and Negative Symptom Scale; RMSEA, Root Mean Square Error of Approximation; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; TLI, Tucker Lewis index.

* Corresponding author at: 10 Center Drive, Bldg. 10- Rm. 4N244, Bethesda, MD 20814, United States.
E-mail address: siyuan.liu@nih.gov (S. Liu).

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and treatment data (Colasanti et al., 2010; Collin et al., 2012; Docherty et al., 2015; Salokangas et al., 2002; Viher et al., 2016).

Very few studies have examined symptom dimension in early-onset schizophrenia (EOS), defined as onset before 18 (Banaschewski et al., 2000; Bunk et al., 1999; Maziade et al., 1996b, 1996a; McClellan et al., 2002). Generally, these studies reported positive and negative dimensions, with some including two or three additional factors, although a disorganization dimension was not consistently reported. Two studies examined the stability of EOS dimensions over time and found that although EOS results were relatively similar to adult onset schizophrenia (AOS) findings, the dimensions more closely resembled AOS studies when EOS patients were re-examined in adulthood (Bunk et al., 1999; Maziade et al., 1996a). These studies suggest that while the general themes of dimensions are similar between EOS and AOS, there are differences, mainly less clarity regarding a disorganized dimension.

Recent studies in adults have also investigated novel methods of subtyping schizophrenia, including groups based on imaging (Bleich-Cohen et al., 2014), cognitive (Rangel et al., 2015), biological (Chien et al., 2015), genetic (Boks et al., 2008), and symptom data (Voineskos et al., 2013) to better understand the heterogeneous disease. One method for investigating symptom based groups is through cluster analysis of clinical scale scores or subscale scores (Dickinson et al., 2017; Dollfus et al., 1996; Lastra et al., 2000; Morrison et al., 1990). Studies using SAPS, SANS, or PANSS show some consistency in the broad themes of subgroups, often deriving a "deficit" or severe negative symptom group, a low symptom group, and other groups with mixed negative and positive symptoms (Dollfus et al., 1996; Jackson et al., 1989; Lastra et al., 2000; Morrison et al., 1990; Williams, 1996). Fewer studies have additionally identified groups specifically characterized by positive symptoms (Lastra et al., 2000) or disorganized symptoms (Dollfus et al., 1996). Although diagnostic subtypes are no longer used, new approaches to subtyping offer means of attacking the heterogeneity of schizophrenia and may reveal differences relevant to treatment response, clinical outcomes, and novel targeted treatment (Boks et al., 2008; Carpenter et al., 1988; Chien et al., 2015; Rangel et al., 2015; Villar-Menendez et al., 2014).

Although a few studies have investigated categorical subtypes beyond the classic diagnostic subtypes in EOS (Bellgrove et al., 2006; Eggers et al., 1999; Reddy et al., 1996), none have done so in COS. Notably, one study using cluster analysis of EOS Medicaid claims found two older patient groups, one with more mood dysregulation comorbidities, the other lacking co-morbidities, along with an especially early diagnosis group with higher rates of developmental delays and behavioral co-morbidities (Jerrell et al., 2017). The latter group likely includes COS patients, but these findings provide no further nuance about this population.

To more precisely characterize COS, in the current study, we explore both symptom dimensions and symptom-driven subgroups in the largest known sample of COS patients. Specifically, we examined the fit of SAPS and SANS data with previously established AOS symptom dimensions and then used the best fitting dimensions to form symptom based subgroups. We then compared demographic, clinical, cognitive, and genetic data across the resulting groups. COS has been shown to be mainly continuous with AOS (Jacobsen and Rapoport, 1998; Ordonez et al., 2015) and thus we expected our results to parallel adult research. Nevertheless, given the variation in the adult literature, the slight distinctions noted in EOS literature, and the association between earlier onset and more severe symptoms, cognitive impairment, premorbid disability, and poorer outcomes (Luoma et al., 2008; Ropcke and Eggers, 2005), we also sought to characterize any differences between COS and AOS in symptom dimensions and subtypes.

2. Materials and methods

2.1. Sample

Patients were recruited nationally as part of a COS longitudinal study at the National Institute of Mental Health (NIMH). Selection and exclusion criteria have been described previously (Gordon et al., 1994). Briefly, participants were screened by phone, assessed during an outpatient visit, and admitted if history and screening interviews suggested a probable COS diagnosis. Child psychiatrists made a final diagnosis after an inpatient observation of up to three months, including a medication washout, using DSM-III R/DSM-IV criteria. Exclusion criteria were IQ under 70 before COS onset, neurological or medical illness, or substance abuse. Onset age was determined by child psychiatrist as the onset of impairing schizophrenic symptoms based on medical records and parent interview. Data from 125 COS patients were used in this study (Table 1).

2.2. Neuropsychological and clinical measures

At admission, the clinical team conducted structured, including SAPS, SANS, the BPRS, and Children's Global Assessment Scale (CGAS), and unstructured clinical interviews with patients and their parents. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers et al., 1985) was used to determine co-morbid diagnoses, except Pervasive Developmental Disorder (PDD)/Autism Spectrum Disorders (ASD), which involved a psychiatrist evaluation (see Sporn et al., 2004) and the Autism Screening Questionnaire (ASQ) (Berument et al., 1999). Average age at initial rating was 13.3 ± 2.7 years.

During inpatient stay and/or at follow up, trained research staff tested participants using the most recent Wechsler Intelligence Scale for their age. Due to the longitudinal nature of the study and the variety of testing ages, tests included the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Abbreviated Scale of Intelligence First Edition (WASI)/second edition (WASI-II), or Wechsler Intelligence Scale for Children-Revised (WISC-R)/third edition (WISC-III) (Wechsler, 1974, 1981, 1991, 1999, 2011). In cases with multiple scores, the highest score was used because symptom severity can impact testing. Average testing age was 15.4 ± 3.1 years.

2.3. Genetic data

Genomic DNA from purification of peripheral blood leukocytes was used to identify genetic abnormalities for all patients. Samples were screened using array based single-nucleotide polymorphism genotyping, as extensively described elsewhere (Ahn et al., 2014). Forty-six rare copy number variants (CNVs) associated with risk for development of AOS, intellectual disability, autism, and/or epilepsy were investigated. Previous studies showed the NIMH COS cohort had far higher rates of these disease-related CNVs than controls and AOS patient populations (Ahn et al., 2014). In this study, patients were categorized as carriers or non-carriers of these CNVs.

Table 1
Demographic and clinical characteristics of the childhood-onset schizophrenia patient cohort.

	N	n/mean	%/SD
Female	125	60	48.00
Race	125		
Caucasian		68	54.40
African American		39	31.20
Asian		6	4.80
Other		12	9.60
SES	123	59.63	28.81
Age Of Onset	124	9.90	2.03
Age At Rating	121	13.32	2.68
SAPS	125	36.25	18.41
SANS	125	49.94	25.12
CGAS	124	32.48	11.24
Full scale IQ	114	80.16	16.99

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