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Symptom Dimensions and Subgroups in Childhood-onset Schizophrenia

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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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Contributors: Dr. Rapoport designed the study and wrote the protocol. Ms. Zhou and Dr. Liu performed the statistical analysis. Dr. Dickinson provided statistical advice and assisted in data interpretation. Mr. Gochman managed the data and contributed to data interpretation. Ms. Craddock performed literature review, interpreted the data, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Keywords

subgroups; symptomatology; childhood-onset schizophrenia; symptom dimensions

1.1 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, 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, 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, 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.

1.2 Materials and Methods

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).

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.

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.

Statistical analysis

In order to assess the compatibility of the SAPS and SANS data with adult dimension models, confirmatory factor analysis (CFA) was performed using the robust maximum likelihood procedure to test and compare pre-existing symptom dimensions. Data was compared to 5 models, compiled by Dollfus and Everitt, 1998, including two, three, and four factor solutions (originally described by Andreasen, 1995; Peralta et al., 1994). This set of models was selected because it contained solutions reflective of commonly reported themes and allowed us to compare our CFA results directly to AOS findings.

All analyses were performed using R version 3.2.3 (R Core Team, 2014). CFA was performed using the 'lavaan' package (Rosseel, 2012). The fit of the model was evaluated using common goodness-of-fit measures (Jackson et al., 2009), including chi-square (χ^2) test, comparative fit index (CFI), Tucker Lewis index (TLI), goodness of fit index (GFI) and the Root Mean Square Error of Approximation (RMSEA). Based on previous literature, χ^2 statistic with a probability of occurrence > 0.05 , CFI, TLI, and GFI values > 0.95 , and RMSEA < 0.05 indicated a good fit (Barrett, 2007; Hu and Bentler, 1999; Kline, 2010).

K-means cluster analysis was performed using each patient's dimension score from the best fitting dimension solution, as assessed by CFA. Cluster number was determined based on elbow criterion, variance explained, average silhouette value, and practical considerations. R packages 'stats' and 'cluster' were used (Machler et al., 2017).

Demographic and clinical data, which were external to the cluster analysis, were compared between groups. For categorical variables, group differences were assessed using chi-square and Fisher's exact tests. For continuous variables, Levine's test (α level=0.05) was used to determine whether group variances were equal. When variances were equal, one-way ANOVA were conducted, otherwise Welch's ANOVA was used. When appropriate, post hoc tests (Tukey or Games Howell) were performed using 'userfriendlyscience' package (Peters, n.d.). After Bonferroni correction for multiple comparisons, $p < 3.57E-03$ (0.05/14) was considered statistically significant.

1.3 Results

Of the five SAPS/SANS models, a two-factor solution (Andreasen, 1995) containing positive and negative dimensions was determined to best fit the COS data ($\chi^2_{(19)}=21.6$, $p=0.307$, CFI:0.989, TLI:0.983, GFI:0.987, RMSE:3.38E-02). A three-factor solution, including positive, negative, and disorganized dimensions, was a less optimal fit ($\chi^2_{(16)}=27.2$, $p=0.039$, CFI:0.955, TLI:0.921, GFI:0.984, RMSE:7.69E-02). None of the remaining models met any of the criteria for a good model besides GFI (Dollfus, 1998).

K-means cluster analysis was performed using patients' scores on the positive and negative dimensions from the best fitting model from the CFA. According to elbow criterion, the average silhouette values (2-cluster: 0.42, 3-cluster: 0.41), and variance explained (2-cluster: 47.13%, 3-cluster: 66.42%), both 2 or 3 cluster solutions were possible solutions. We preferred the 3-cluster solution because of the greater variance explained and because it aligned better with our clinical experience of the affected individuals. The three groups had:

low scores on both dimensions (n=37), high negative scores with low positive scores (n=33), and high scores on both dimensions (n=55), herein referred to as low mixed, high negative, and high mixed respectively (Figure 1).

The Andreasen 2-factor model includes all the SAPS global ratings within the positive dimension, but excluded the alogia, intimacy and closeness, and relationship SANS global ratings from the negative dimension. Thus, SANS scores were compared between groups to compare the two measures of negative symptoms. SANS scores differed ($p=3.80E-27$), as high negative and high mixed had significantly higher scores than low mixed ($p=8.29E-14$, $p=6.59E-14$).

Comparison of the groups' demographic and clinical information revealed no differences in demographics or CNV status, but showed variance in clinical scores between groups (Table 2). Full scale IQ differed between groups ($p=1.97E-03$), as low mixed had a significantly higher score (88.34 ± 18.37) than high mixed (75.54 ± 14.19) ($p=1.50E-03$) (Figure 2). Additionally, although the significance of pairwise comparisons did not survive correction, onset age differed between groups ($p=3.09E-03$), as high negative had a later onset (10.75 ± 1.57 years) compared to low and high mixed (9.18 ± 2.19 , 9.89 ± 1.99 years). The prevalence of behavior disorder comorbidities, including attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD), also differed between groups ($p=2.35E-03$) (Table 3). Although the significance of pairwise comparison did not survive correction, low mixed had a higher prevalence (41.94%) than high mixed (8.89%) and high negative (18.52%). Finally, groups' CGAS scores differed ($p=4.85E-09$), as low mixed had significantly higher scores (40.49 ± 10.31) than high mixed (26.71 ± 9.17) ($p=2.13E-09$), while high negative had an intermediate score (33.13 ± 9.76) (Table 2).

1.4 Discussion

CFA revealed that a two-factor solution, comprised of a positive and negative dimension, best fit COS clinical data. Although the three-factor solution, which included an additional disorganized dimension, had been found to fit AOS data better in two previous studies (Andreasen, 1995; Dollfus and Everitt, 1998), it provided a less optimal fit for the COS sample. Consistent with our findings, limited studies in EOS generally report positive and negative dimensions, with some reporting additional factors, although notably not disorganized ones (Banaschewski et al., 2000; Bunk et al., 1999; Maziade et al., 1996a; McClellan et al., 2002). This distinction may reflect the scarcity of COS/EOS studies, but might also suggest that disorganized symptoms are less independent and more closely tied to other positive symptoms in earlier onset schizophrenia samples compared to AOS. Interestingly, both studies examining dimension stability in EOS found that the configuration of EOS symptom factors more closely approximated AOS findings when EOS patients were re-tested in adulthood (Bunk et al., 1999; Maziade et al., 1996a), consistent with other reports of an orderly developmental progression between COS/EOS and AOS (Frangou, 2010; Ordonez et al., 2015). Overall, our CFA results were consistent with the limited EOS literature and overlapped with AOS studies in finding positive and negative dimensions, but differed in the lack of a disorganized dimension.

Our cluster analysis identified high negative, high mixed, and low mixed symptom groups. This was highly consistent with the other SAPS/SANS studies, which found the same 3 groups, although the exact dimensions and symptoms included, particularly in the positive dimension, varied (Dollfus et al., 1996; Jackson et al., 1989; Lastra et al., 2000; Morrison et al., 1990; Williams, 1996). Several studies found additional groups including a high positive group and a mid-level mixed symptom group (Dollfus et al., 1996; Lastra et al., 2000; Williams, 1996). Studies using PANSS data commonly identify negative and low symptom groups too, but are otherwise difficult to compare because of the greater representation of non-psychotic psychopathology on that scale (Dickinson, 2017; Dollfus and Petit, 1995). Nevertheless, our groups reflect the general themes found in AOS studies, particularly those using SAPS and SANS.

Group comparisons of demographic and clinical data provided insight into the characteristics of each patient group. There were no differences in demographics or CNV status. The difference in SANS scores paralleled group differences in the negative dimension scores, demonstrating the patients' factor scores reflected the core negative symptoms included in the negative dimension and that their SANS scores were not greatly influenced by alogia, intimacy and closeness, and relationship global ratings. As high mixed was the largest group (n=55), the most common symptomatology profile in the NIMH cohort consisted of high levels of both positive and negative symptoms. The subgroup proportions may have been affected by selection and referral bias, but the large size of the high mixed group also likely reflects the generally severe nature of COS.

There was also a group difference in full scale IQ, which was driven by the significant difference between the high (88.34 ± 18.37) and low (75.54 ± 14.19) scores of low and high mixed groups respectively. High negative also had a low score (78.55 ± 16.90), although it was not significantly different from either other group. AOS subgrouping studies reported less cognitive deficit in low symptom groups, matching the high score of our low mixed group (Dickinson, 2017; Jackson et al., 1989; Williams, 1996). In AOS literature, severe cognitive deficits are primarily associated with negative symptoms (Gold et al., 1999; Hartmann-Riemer et al., 2015), a trend reflected in the low scores of our high negative and high mixed groups, both of which experience severe negative symptoms.

Additionally, onset age differed between groups. Although the pairwise comparison did not survive correction, high negative was older (10.75 ± 1.57) than low and high mixed at illness onset (9.18 ± 2.19 & 9.89 ± 1.99), perhaps suggesting a longer more insidious path to onset for this subgroup. Conversely to our results, severe symptoms, especially negative ones, are associated with earlier onset age in AOS (Clemmensen et al., 2012; Guerra et al., 2002; Kao and Liu, 2010). However, onset age comparison of AOS and COS is confounded given the early and compressed nature of COS onset.

Although pairwise comparison does not survive correction, the prevalence of externalizing disorders, including ADHD, ODD, and/or CD, also varied by group. Low mixed had the highest prevalence (41.94%), while high mixed had the lowest (8.89%). High negative had an intermediate prevalence (18.52%). There is evidence of overlap between the risk factors, genetics, and symptoms of ADHD and schizophrenia, including high rates of ADHD in the

COS general population that is thought to reflect the neurodevelopmental origin of schizophrenia (Barr, 2001; Owen et al., 2011; Ross et al., 2006). Yet, there is little research comparing schizophrenic patients with and without these disorders. Consistent with our findings, one AOS study reported a group of patients with severe attention deficit and lower schizophrenia symptoms than other AOS patients (Bellak, 1985). The connection between symptom severity and these disorders is novel in COS; thus, this finding may provide further insight into additional deficits commonly experienced by COS patients, particularly those with relatively lower levels of positive and negative symptoms. Interestingly, one EOS cluster analysis found a group like our low mixed with highly prevalent ADHD, ODD, and/or CD co-morbidity and a young onset age (Jerrell et al., 2017). All these findings reflect the complex relationship among neurodevelopmental disorders, including schizophrenia, which is not yet fully understood.

Finally, global functioning differed between groups. Low mixed had significantly higher CGAS scores than high mixed. High negative also had a low score, although it was not significant from either of the other groups. These results are consistent with adult literature that typically associates low symptom burden with reduced functional impairment, and severe negative symptoms, found in both our high mixed and high negative groups, with the greater impairment (Diaz-Caneja et al., 2015; Dickinson, 2017; Hawk et al., 1975; Startup et al., 2002). In the COS sample, a mixed positive and negative symptom profile showed the worst functioning. This finding reflects the relative impact of symptom type on ability to function in COS, suggesting psychotic symptomatology and cognitive impairment are more closely related to functioning than the externalizing symptoms or co-morbidities prominent in the low mixed group. Thus, similarly to adults, a combination of low IQ and psychotic symptoms is most toxic for global functioning.

This study has several limitations. The NIMH cohort, although the largest available COS sample, represents a severely ill population and is small due to disease rarity; thus, there are unknown referral and selection biases. Methodologically, some have criticized using cluster analysis for subgroup formation because results vary by method and can be unstable (Kessler, 2002; Marquand et al., 2016). To address the former, methods from AOS studies were replicated as closely as possible and only general thematic comparisons were made. Unfortunately, precise comparison to AOS was still challenging due to illness severity of the COS cohort, variety of items included in dimensions, the rarity of similar analyses, and the prevalence of PANSS use over SAPS/SANS in other studies. Longitudinal analysis to address instability was outside the scope of this paper; however, future studies using latent class growth analysis could address this concern and assess if COS symptomatology, like in EOS, shifts closer to AOS as patients age. Additionally, the significance of several of our results did not survive correction, likely due to the large number of comparisons and contributed to by the small sample size in this study. These findings were included and discussed because they neared significance and aided in investigating distinctions between groups; nevertheless, it is important to note their lack of statistical significance makes these findings less certain and increases the possibility of conflicting results in future COS studies.

In conclusion, we found COS clinical data were well described by positive and negative dimensions, which were used to form three distinct subgroups that differed in clinically

meaningful ways. To our knowledge, this is the first study reporting CFA and subgroups in a purely COS population. The dimension findings were consistent with EOS and some AOS studies, although the lack of disorganized dimension was different from most AOS literature. Despite this difference, our subgroups had similar defining characteristics with the few comparable AOS studies. Additionally, the differences between our groups reflected general themes often seen in AOS research, including the influence of symptom severity and type on IQ and global functioning. The main exception was onset age findings that showed opposite trends to AOS. Importantly, our analysis both confirmed the typical severe and impaired characterization of COS, but also revealed the presence of other groups with distinct symptomatology and deficits. Overall, these subgroups and dimensions offer additional nuance in characterizing the NIMH COS population and, for the most part, support the continuity of COS, EOS, and AOS in terms of symptomatology.

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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

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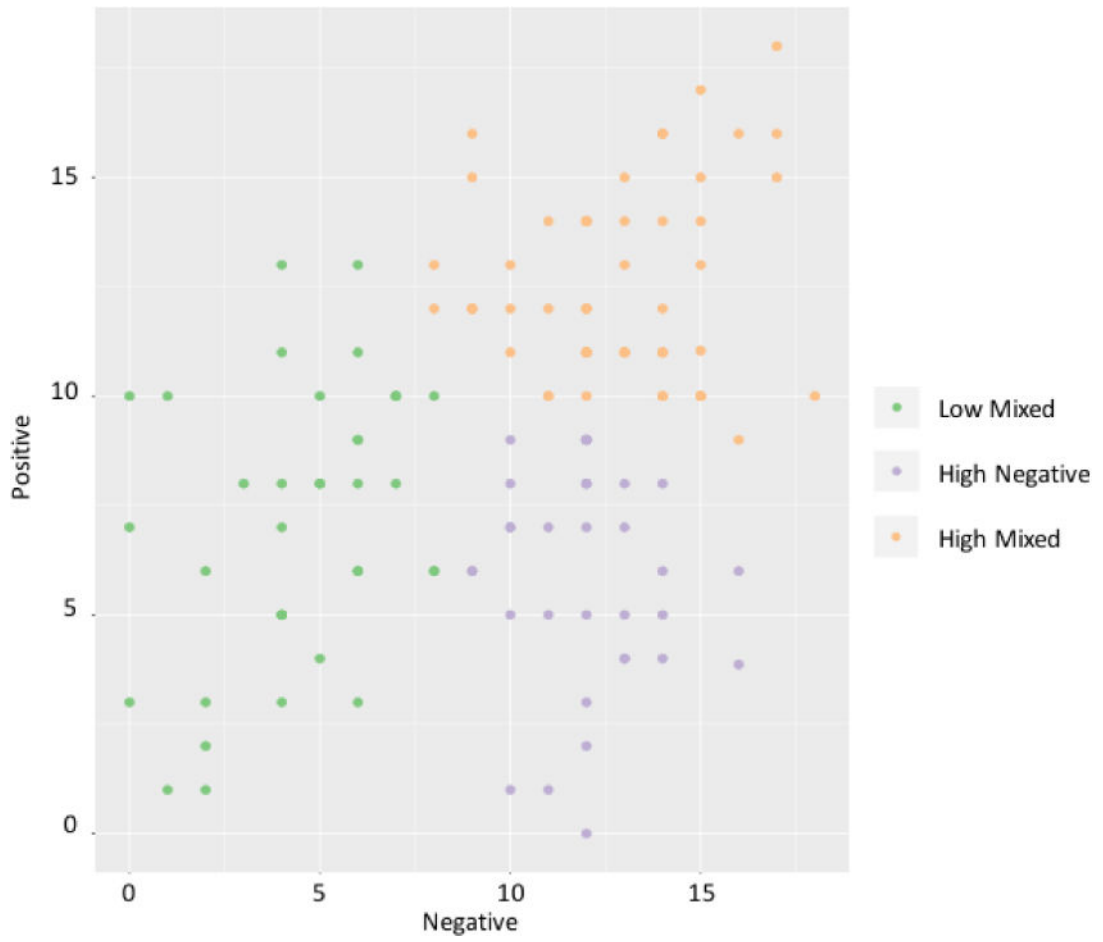


Figure 1. Three patient groups derived from K-means cluster analysis of positive and negative dimension scores.

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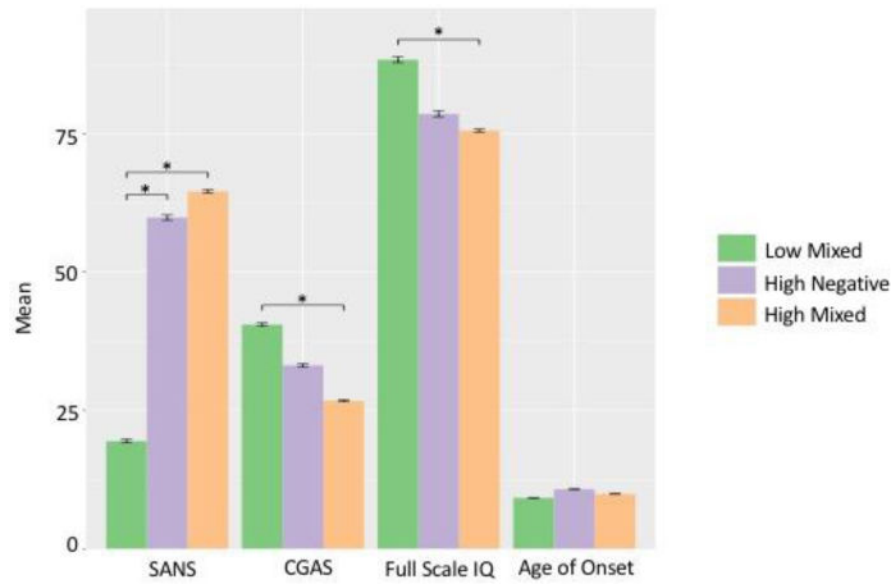


Figure 2. Group comparison of clinical rating scale scores. *Indicates significance in post-hoc test after Bonferroni correction ($p < 3.57E-03$). Bars show standard error. SANS: Scale for the Assessment of Negative Symptoms. CGAS: Children's Global Assessment Scale.

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

Comparison of demographics, clinical information, and clinical rating scores between groups. Bold values indicate significant results after Bonferroni correction ($p < 3.57E-03$).

Table 2

	N	Low Mixed		High Negative		High Mixed		Statistic	P Value
		n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD		
Female	125	16	43.24	16	48.49	28	50.91	$\chi^2_{(2)}=0.53$	7.69E-01
SES	123	62.68	25.87	57.13	28.27	59.02	31.27	$F_{(2,120)}=0.34$	7.15E-01
Race									
Caucasian	125	26	70.27	17	51.52	25	45.45	Fisher Exact Test	1.32E-01
African American		7	18.92	14	42.42	18	32.73		
Asian		1	2.70	1	3.03	4	7.27		
Others		3	8.11	1	3.03	8	14.55		
Age of Onset	124	9.18	2.19	10.75	1.57	9.89	1.99	$F_{(2,74)}=6.25$	3.09E-03
Age at Rating	121	13.22	3.11	14.16	2.07	12.88	2.63	$F_{(2,118)}=2.36$	9.91E-02
CNV	125	5	13.51	4	12.12	8	14.545	$\chi^2_{(2)}=0.10$	9.50E-01
Negative Dimension	125	4.46	2.33	12.00	1.75	12.78	2.41	$F_{(2,122)}=170.14$	5.11E-36
Positive Dimension	125	7.11	3.20	5.81	2.51	12.49	2.17	$F_{(2,67)}=96.22$	1.86E-20
SANS	125	19.43	11.88	59.83	15.46	64.54	17.29	$F_{(2,122)}=104.36$	3.80E-27
SAPS	125	27.82	15.27	23.14	11.63	49.78	14.21	$F_{(2,122)}=47.41$	5.82E-16
CGAS	124	40.49	10.31	33.13	9.76	26.71	9.17	$F_{(2,121)}=22.52$	4.85E-09
Full Scale IQ	114	88.34	18.37	78.55	16.90	75.54	14.19	$F_{(2,111)}=6.59$	1.97E-03

Comparison of co-morbidities between groups. Affect, anxiety, and behavior disorders were current disorders measured using the Kiddie Schedule for Affective Disorders and Schizophrenia at time of admission. Affect disorders included Depression and Mania. Anxiety disorders included Separation Anxiety Disorder, Generalized Anxiety Disorder, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Panic Disorder, Agoraphobia, Specific Phobia, and Social Phobia. Behavior Disorders included Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, and Conduct Disorder. Bold values indicate significant results after Bonferroni correction ($p < 3.57E-03$).

Table 3

N	Low Mixed		High Negative		High Mixed		Statistic	P Value	
	n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD			
PDD	119	8	22.22	6	20.00	6	11.321	$\text{Chi}^2_{(2)}=2.11$	3.47E-01
ASQ score	117	9.92	9.05	10.32	9.41	7.46	6.43	$F_{(2,114)}=1.55$	2.17E-01
K-SADS Disorders									
Affect disorders	103	7	22.58	4	14.82	6	13.33	$\text{Chi}^2_{(2)}=1.21$	5.45E-01
Anxiety disorder	104	13	40.63	5	18.52	18	40.00	$\text{Chi}^2_{(2)}=4.18$	1.24E-01
Behavior disorders	103	13	41.94	5	18.52	4	8.89	$\text{Chi}^2_{(2)}=12.11$	2.35E-03