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Developmental and symptom profiles in early-onset psychosis

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Abstract

Psychotic disorders in children are more heterogeneous than is captured by categorical diagnoses. In a new cohort of children and adolescents, we evaluated the relationships among age at onset (AAO), clinical symptoms and developmental impairments. Patients with schizophrenia and other “spectrum” psychotic diagnoses (N=88; AAO 6-17, mean 12.6) were evaluated with diagnostic interviews, a new clinical scale (Lifetime Dimensions of Psychosis Scale-Child and Adolescent), and neuropsychological and medical evaluations. Key findings were replicated in an adult cohort of 2 420 cases, including 127 with retrospective AAO<13. Factor and cluster analyses were carried out to identify clinical profiles. Five clinical factors were identified in each cohort: Positive, Bizarre Positive, Negative/Formal Thought Disorder, Depression and Mania. Earlier AAO predicted severity of bizarre positive symptoms in children and of bizarre and other symptoms in adults. Four clinical clusters in the child cohort were characterized by: more severe bizarre positive symptoms (N=31); negative symptoms (N=15); premorbid autism spectrum features and developmental delay (N=12); and depressive symptoms with heterogeneous diagnoses and mild positive/negative symptoms (N=25). Previous factor-analytic studies of childhood psychosis did not specifically consider bizarre positive symptoms. Here, bizarre positive symptoms emerged as clinical markers of severe, childhood-onset psychosis similar to adult schizophrenia. The four clusters are clinically meaningful and useful for treatment planning and potentially for biological research. Childhood-onset cases are rare and thus difficult to study, but additional, larger cohorts may be useful in dissecting the biological and developmental heterogeneity of psychotic disorders.

1. Introduction

Clinically significant psychotic disorders are rare in childhood. The best prevalence estimate for schizophrenia below age 15 is 0.05% (Kleinhaus et al., 2011), and 2% of adult cases have an estimated age at onset (AAO) below 13. (Schneider et al., 2015) The National Institute of Mental Health (NIMH) longitudinal study produced much of the available data, defining childhood onset schizophrenia (COS) by strict clinical criteria with AAO<13. (Ordonez et al., 2016; Rapoport et al., 2012) The low prevalence impedes recruitment of large cohorts. Early-onset cases have been useful models of many diseases. For example, in the NIMH COS cohort, repeated magnetic resonance imaging (MRI) demonstrated an increased rate of gray matter (GM) loss during adolescence and early adulthood, suggesting excessive synaptic pruning (Ordonez et al., 2016). Because similar GM reductions are seen in adult-onset schizophrenia, this suggests that the diseases mechanisms may be similar.

It is widely assumed that multiple pathophysiological mechanisms underlie susceptibility to schizophrenia, resulting in substantial clinical heterogeneity, but “subtypes” are difficult to define. The goal of this study was to use dimensional clinical ratings and developmental variables to characterize subgroups of early-onset schizophrenia spectrum psychoses, using a new child and adolescent version of the Lifetime Dimensions of Psychosis Scale (LDPS-CA). Cluster analysis of clinical and developmental variables identified four subgroups that are consistent with previous research. Analyses of adult LDPS data (Levinson et al., 2002) from a large adult schizophrenia cohort (Shi et al., 2009) yielded the same five-factor structure, and supported the finding in the child cohort of more severe bizarre positive symptoms in childhood-onset cases.

2. Methods

2.1 Recruitment and evaluation - child cohort. Subjects were recruited (10/2009-6/2016) from referrals (mostly in-patients) to the Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, with DSM-IV diagnoses of schizophrenia or another psychosis in the “schizophrenia spectrum” based on familial co-segregation with schizophrenia (Kendler et al., 1993a, b; Kendler et al., 1993c; Maier et al., 1993):

schizophreniform, schizoaffective or delusional disorder, brief psychotic episode, psychotic disorder not otherwise specified (NOS), or major depressive disorder with psychotic features. Exclusion criteria were: bipolar-I disorder; severe intellectual disability or autistic disorder; non-French speaking; or suspected alcohol or drug dependence or severe abuse. (Substantial overlap in common-variant heritability between schizophrenia and bipolar disorder was reported (Lee et al., 2013) after recruitment was well underway.) To focus on new onsets, we also excluded patients with previous antipsychotic treatment >two weeks or any previous mood stabilizer treatment.

If clinical screening suggested eligibility, parents/guardians were interviewed after giving written informed consent. The child gave written consent before interview.

Assessments included:

(i) Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994) (DIGS) 2.0 (French (Preisig et al., 1999)), administered by a child psychiatrist (MG, CL) after 3-6 weeks of treatment. Additional items covered variables from the universal French health record booklet of prenatal and pediatric visits (perinatal complications, Apgar scores, parental ages, milestones, special education, speech, language, occupational or physical therapy, psychotherapy, and any IQ testing). Previous test results were obtained where possible.

Ratings were based on child and parent interviews and clinical records.

(ii) Autism Diagnostic Interview-Revised (ADI-R), if language delay or atypical social behavior before age 3 was suspected.

(iii) Cognitive, speech/language, occupational or physical therapy evaluations where indicated.

(iv) Medical workup for suspected genetic, neurological or metabolic factors.

(v) LDPS-CA ratings (MG and/or CL) based on all information (see English and French versions in supplementary files). Symptoms were rated for lifetime duration and for severity during the worst two-week period. Severity ratings were analyzed here: 0=Absent; 1=Minimal, very mild or suspected symptoms; 2=Moderate, definite clinically significant;

3=Severe, clearly interferes with function or preoccupies; 4=Very severe, gross or nearly constant effect on function. Some items are rated present-absent. Domains retained from the adult version cover: positive (4 items), bizarre psychotic (4), negative (3), disorganized (2), mood and psychotic mood symptoms (4); deterioration; atypical features; quality of information; AAO and lifetime duration of psychotic and of mood syndromes; plus sub-items. Additional childhood domains include: catatonic symptoms (3 items); anxiety disorders (4); suicidality (1); comorbidity (premorbid childhood disorders, autism spectrum disorder features [4-point severity scale], delayed milestones, learning disorders and delays); medical history (perinatal and birth history, positive genetic tests; dysmorphic features, parents' ages at birth); and available IQ scores. LDPS-CA development is further discussed on page S15; supplementary files contain the full text (French and English). Inter-rater reliability was tested in 20 of these cases: both interviewers were present for the DIGS, independently reviewed all information and rated the LDPS-CA.

Five **summary developmental variables** were created (present-absent):

(i) Developmental signs (possible indications of *genetically-based* impairments in the absence of known environmental insults): congenital dysmorphic features, or birth weight less than 2 SD below the French male/female mean.

(ii) Pre-, peri- or neo-natal complications (potential *environmental* causes of impairment): gestational diabetes, maternal medication (e.g., antidepressants), preeclampsia or eclampsia, intrauterine bleeding, birth hypoxia, low Apgar scores, hyper-bilirubinemia, breech presentation, preterm pregnancies due to environmental risks, birth injury or trauma, possible infant malnutrition (e.g. vomiting or vitamin deficiency).

(iii) Any developmental delay: motor skills (not walking without support by 18 months); language skills (no two-word phrases by 24 months; no two-three-word sentences by 36 months; speech unintelligible; not following two-step commands); intellectual disability (IQ 50-70).

(iv) Verbal learning disability: dyslexia, dysphasia, dysorthographia.

(v) Non-verbal learning disability: dyspraxia, dysgraphia, dyscalculia.

2.2 Recruitment and evaluation - adult cohort. We analyzed LDPS data for European-ancestry cases from the MGS cohort (Shi et al., 2009) were recruited from diverse clinical settings. DSM-IV diagnoses and AAO were assigned by consensus of two doctoral-level diagnosticians based on DIGS2 interviews, interviewer's report, and available psychiatric records and family informant interviews. One diagnostician completed the adult LDPS. Cases had DSM-IV schizophrenia or schizoaffective disorder (meeting schizophrenia criterion A for 6 months). Analyses used 2 420 subjects with LDPS data, with AAO between 5-45 divided into ranges (5-12, 13-14, 15-17, 18-45; Ns=127, 114, 421, 1 758), to avoid over-reliance on retrospective estimates. Additional variables included DIGS lifetime visual hallucinations, and Schedule for the Assessment of Positive Symptoms (SAPS) and Schedule for the Assessment of Negative Symptoms (SANS) items (Andreasen, 1990) (rated at interview for the previous 30 days). Several childhood variables were extracted (see below).

2.3 Statistical analyses. Inter-rater reliability was tested for ordinal or continuous variables with intra-class correlation coefficients (two-way fixed effects model, see page S2 for discussion) and for categorical variables with Cohen's *kappa*.

Principal components factor analysis of the correlation matrix with Varimax (orthogonal) rotation was performed for each cohort on clinical variables (Table 2). (Oblimin [oblique] rotation produced the same factor structures and nearly identical loadings.) Appropriateness of cohorts for factor analysis was indicated by significant Bartlett's tests of global significance of each correlation matrix (adult: $X^2=7287.2$, 105 df, $p\sim 0$; child: $X^2=565.62$, 153 df, $p=1.46E-48$).

K-means cluster analyses of factor scores and developmental variables were performed (child cohort); larger Ns are preferred, but empirically the method can perform well with smaller samples. (Wharton, 1984)

Pearson or Spearman correlations were applied to continuous or ordinal data respectively, t-tests to two-group comparisons of continuous variables, and chi-square tests to categorical data.

In the adult cohort, to allow for nonlinear relationships between AAO and severity, severity ratings were entered as categorical dependent variables in multinomial logistic regressions (or binary logistic regression for present/absent items) to test their relationship to the four AAO ranges (N=2420); or to childhood (5-12) vs. adult-onset cases (18-45) (N=1 885).

Childhood-onset cases had earlier age at interview (AGEINT) (means 40.0 vs. 42.8, $t=2.44$, $df=137.7$, $p=0.016$) and longer duration of illness (YRSILL) (means 30.7 vs. 21.0, $t=-7.937$, $df=136.029$, $p=7 \times 10^{-13}$). To disentangle these effects, we collapsed 0 and 1 scores and used likelihood ratio tests to contrast scores for cases with AAO 5-12 vs. 18-45; e.g., to test the effect of AAO on hallucinations while accounting for YRSILL, we computed likelihood ratio chi-squares for multinomial logistic regression models (1) $HALL = \text{constant} + YRSILL$, and (2) $HALL = \text{constant} + YRSILL + CHILD1ADULT2$, and determined chi-square (df) by subtracting test2-test1. SAPS/SANS items were analyzed with chi-squares of severity (0-5 scale) x AAO range (four AAO ranges; or 5-12 vs. 18-45).

Analyses were performed using SYSTAT v13 (San Jose, CA, systat.com).

2.4 Ethics. All assessments were carried out with written informed consent consistent with the Helsinki Declaration of 1975, as revised in 2008: child cohort: protocol P080203, ID RCB2008-A00497-48, approved by Comité de Protection des Personnes, Hôpital Pitié-Salpêtrière, sponsored by Assistance Publique-Hôpitaux de Paris; MGS: IRB-approved protocols at each participating center (Shi et al., 2009).

3. Results

3.1 Characteristics of the child sample. Diagnoses of the 88 cases (*Table 1*) were schizophrenia (75%), schizoaffective disorder (6%), psychotic disorder NOS (9%) or other (10%). AAO varied from 6-17 years; 39 cases (44%) had AAO<13 (including 32 with

schizophrenia); and 67 (76%) below 15 (51 with schizophrenia). Consistent with previous research (Rapoport et al., 2012; Watkins et al., 1988), 74% had some developmental problem or learning disability; 62.5% had developmental delay and/or signs (26.1% both, 25% only signs, 11.4% only delay).

3.2 Inter-rater reliability (child cohort) (Table S1). For 26 ordinal variables (25 severity ratings on a scale of 1-4, and lifetime weeks of psychosis), average ICC was 0.802, with 17 values (65%) >0.8, and 24 values (92%) >0.628. Bizarre Behavior was a low outlier (ICC=0.436) and was omitted from the child cohort factor analysis. For 22 present/absent variables with adequate variability (one rater made the rarer rating $\geq 25\%$ of the time), kappa was ≥ 0.8 for 18%, ≥ 0.6 for 55%, and ≥ 0.4 for 82%, (mean 0.611). Non-paranoid, somatic and religious delusions and audible thoughts had kappa < 0.4. Dichotomous variables with low kappas were excluded from analyses.

3.3 Factor analyses. Table 2 shows factor analysis results for each cohort. For the child cohort, inclusion of factors with eigenvalues > 1 produced a readily interpretable five-factor solution and the most variance explained; six- and seven-factor solutions yielded single-variable factors. For MGS, five components with eigenvalues >1 were retained (see discussion of previous MGS results, page S15). Table 2 shows which variables were included in each analysis.

In both cohorts, a Bizarre Positive factor encompassed “first-rank” symptoms (control delusions; commentary or conversing hallucinations; thought insertion, withdrawal or broadcasting), while negative symptoms loaded with thought disorder. In children, the bizarre positive factor included severity of hallucinations and presence of visual hallucinations; in adults, hallucinations loaded more strongly on the Positive factor. The cohorts had similar symptom frequencies except for greater deterioration in adults (**Table 2**).

3.4 Bizarre positive symptoms/hallucinations and AAO (child cohort). AAO was negatively correlated with Bizarre Positive scores ($r=-0.338$, $p=0.0013$; **Figure 1**). This was significant in males ($r=-0.443$, $N=62$, $p=0.0003$; in females, $r=-0.184$, $N=26$, $p=0.37$); females

had higher scores than males ($t=3.90$, $df=54.99$, $p=0.0003$). For the five variables loading on the Bizarre Positive score, significant negative correlations were observed in males between AAO and commenting/conversing voices ($r_s=-0.403$, $N=62$, $p=0.0012$) and overall severity of hallucinations ($r_s=-0.375$, $p=0.0028$), with a trend for thought broadcasting/echo/audible thoughts ($r_s=-0.239$, $p=0.061$), but not control delusions ($r_s=-0.141$, $p=0.27$). SAPS visual hallucinations also predicted lower AAO in boys (mean AAO 11.3, $N=28$) vs. 13.4 ($N=34$) without VH ($t=2.925$, $df=49.94$, $p=0.005$); as did LDPS “non-affective verbal hallucinations spoken to the subject” (mean AAO 11.78, $N=44$; vs. 14.17, $N=18$ without NAVH, $t=3.099$, $df=32.33$, $p=0.004$).

3.5 Cluster analysis (child cohort). Initial solutions included a cluster of 5 subjects with high Mania and low Positive scores and only 2 schizophrenia diagnoses. Given that bipolar disorder was an exclusion criterion and the cluster was too small to make meaningful comparisons, these subjects were removed as outliers. For the remaining 83 subjects, the most parsimonious solution included four clusters (**Table 3**):

BIZPOS ($N=31$): higher *Bizarre Positive* scores; modestly higher *Mania* scores.

DEP ($N=25$): higher *Depression* and lower *Negative/FTD* scores.

NEG ($N=15$): higher *Negative/FTD* and lower *Depression* and *Bizarre Positive* scores.

ASD ($N=12$): highest *ASD symptom* scores, and the largest proportion with *developmental delay*.

The BIZPOS, DEP and NEG factor scores separated the first three clusters (**Table 3**). The breakdown of diagnoses in each cluster is shown in **Table S5**.

3.6 Symptoms and AAO in the adult cohort. **Figure 2** shows distributions of ratings by AAO range (see figure legend and **Table S2** for details). For all variables, COS cases (AAO 5-12) had the greatest severity or frequency. Early adolescent (14-15) onset cases were often intermediate. All items except commenting voices were significantly different across the ranges and for childhood vs. other cases. P-values <0.00001 were

observed across all ranges for deterioration, depression, hallucinations, poverty of speech and control delusions; and for childhood vs. other cases for deterioration, depression and hallucinations.

In the likelihood ratio tests of childhood- vs. adult-onset accounting for duration of illness, the most significant items were depression ($p=1 \times 10^{-6}$), poverty of speech ($p=5 \times 10^{-5}$) hallucinations ($p=0.00039$) and abnormal perception of thought (thought broadcasting, audible thoughts, thought echo) ($p=0.00045$). Four items lost significance (paranoia, formal thought disorder, deterioration and non-affective verbal hallucinations). After accounting for age at interview, p-values remained similar, with p-values $<10^{-6}$ for deterioration, depression, hallucinations, poverty of speech, delusions of control and abnormal perception of thought.

Interviewer SAPS/SANS ratings (**Table S3**) were significantly more severe across four AAO ranges and for childhood- vs. adult-onset for hallucinations, delusions, auditory hallucinations, visual hallucinations, voices commenting, voices conversing, and delusions of control. An increase in visual hallucinations was previously reported in COS. (David et al., 2011; Zalesky et al., 2015)

The MGS dataset contains limited childhood information (**Table S4**) and none about autistic features. Childhood-onset cases self-reported more learning disabilities or developmental delays, and received more consensus diagnoses of mild intellectual disability (moderate/severe ID was excluded). Those with ID (N=43) had *lower* LDPS severity ratings for hallucinations, delusions, first-rank symptoms, blunted affect and thought disorder.

4. Discussion

4.1 Consistency of clinical features of the child and adult cohorts. The NIMH COS studies suggest continuity of COS with adult schizophrenia in clinical features and structural brain changes, with greater clinical severity. (Rapoport and Gogtay, 2011) We support those conclusions with two new types of data. First, using lifetime (maximum) severity ratings from the same scale, we found virtually identical factor structures in our child cohort and a large adult cohort (except that severity of hallucinations loaded on the Bizarre

Positive factor in children vs. the Positive/Paranoid factor in adults; and deterioration was more common in adults and loaded on the Positive/Paranoid factor vs. the Negative/Disorganized factor in children). Secondly, in children, Bizarre Positive symptoms were negatively correlated with AAO. After controlling for illness duration, adults with estimated AAO<13 (COS) had significantly greater lifetime severity of first-rank symptoms as well as depression, poverty of speech, and hallucinations. After controlling for age at interview, deterioration was also more severe in COS. Consistency across these cohorts increases our confidence in the factor structure in the smaller child cohort.

4.2 Heterogeneity. In the child cohort, cluster analysis of these factor scores and developmental variables identified four profiles (and a fifth may have emerged if bipolar cases had been included):

Two profiles closely resembled adult schizophrenia. The BIZPOS cluster (35.2% of the cluster analysis cohort), had high Bizarre Positive symptoms (hallucinations and first-rank symptoms), low depressive symptoms, and variable severity of negative symptoms. The NEG cluster (17%) had high Negative/Formal Thought Disorder scores, usually with low Bizarre Positive and Depression scores. Positive and negative subgroups were observed in the NIMH COS cohort (Craddock et al., 2017), but bizarre positive symptoms were not studied (see below). These two clusters likely include most of the patients who progress to typical adult schizophrenia, with BIZPOS symptoms representing one marker of severe course (as seen also in early-onset adult cases).

The third (DEV) profile (14.5%) had elevated ASD symptoms, associated with developmental delay (67%), with schizophrenia diagnoses and mild psychotic and mood symptoms. Few children with “classical” autism meet criteria for schizophrenia (Cochran et al., 2013) (and we excluded patients with IQ<50, a common feature of severe classical autism). ASD diagnoses have been reported in COS, especially Pervasive Development Disorder Not Otherwise Specified (PDD-NOS). (Rapoport et al., 2009) This subgroup resembles Multiple Complex Developmental Disorder (MCDD) (Cochran et al., 2013),

characterized by impaired emotional regulation, social relationships and cognitive processing, and elevated risk of chronic psychosis. (Buitelaar and van der Gaag, 1998; Cochran et al., 2013; Towbin et al., 1993; Xavier et al., 2011) Rapoport's group reported that COS+PDD cases had greater gray matter loss but did not differ clinically from COS without PDD. (Sporn et al., 2004) Investigation of possible distinct etiologic factors in this group is impeded by the lack of premorbid developmental data in most large adult schizophrenia cohorts.

Finally, the DEP cluster (28.4%) had high Depressive factor scores including suicidal ideation, low Positive, Bizarre Positive and Negative scores, and diverse diagnoses (only 52% schizophrenia, **Table S5**). This is a heterogeneous group, probably including some of the NIMH Psychotic Disorder-NOS cases, which had a high rate (40%) of subsequent mood disorder diagnoses and sparing of gray matter (Rapoport and Gogtay, 2011), and some of the NIMH low-positive low-negative cases COS cases. (Craddock et al., 2017) McClellan et al. reported that 55% of 15 Psychotic Disorder-NOS children met PTSD criteria (McClellan et al., 2002) (we lack comparable data -- the DIGS does not probe PTSD) suggesting psychological trauma as a risk factor. Continuous re-thinking of diagnoses is particularly important in this subgroup.

We conceptualize these clusters as overlapping subgroups which may point to differences in their combinations of underlying susceptibility mechanisms, although their relationship to etiology remains unknown. Refinement of cluster definitions will require larger cohorts and longitudinal data. The four clusters correspond with our clinical experience. We agree with the suggestion that while categorical diagnoses are useful (if imperfect) predictors of course and medication response, evaluation of multiple clinical and developmental dimensions encourages and facilitates more highly individualized treatment. (Maj, 2018)

4.3 Reconsidering bizarre positive symptoms. Factor analyses produced Bizarre Positive symptom factors with high loadings for “first-rank” symptoms in both cohorts, plus severity of hallucinations in children. In the child cohort, higher Bizarre Positive scores were

a defining feature of the largest cluster, and were more prominent in patients with lower AAO (this was seen in boys, while girls had generally high scores, but our N of only 26 girls made it difficult to further dissect this sex difference). In adults, first-rank symptoms were among the more severe features in childhood-onset patients.

These findings have not been reported previously. Our study and the six previous factor-analytic studies of children and adolescents with psychotic disorders (Banaschewski et al., 2000; Bunk et al., 1999; Craddock et al., 2017; Maziade et al., 1996; McClellan et al., 2002; Rapado-Castro et al., 2010) (see **Table S6**) differed in sample sizes (40-125; ours is the third largest); diversity of diagnoses; number of cases with AAO<13 (5-125; ours is the second largest with N=39); rating scales (SAPS/SANS, Positive and Negative Symptom Scale [PANSS], Brief Psychiatric Rating Scale [BPRS]); and number of identified factors (2-5). No previous study entered bizarre positive symptoms into factor analyses: BPRS and PANSS do not rate them, and the other studies entered either eight SAPS/SANS domain scores or total positive and negative scores. We used three relevant LDPS items: control delusions (thought insertion, thought withdrawal, control of thoughts/actions); conversing, commenting or continuous hallucinations; and “abnormal perception of thought” (thought broadcasting, audible thoughts, thought echo), using DIGS interviews with multiple probes for each symptom. LDPS also makes *lifetime* severity ratings (the worst two-week period ever) based on all sources of information.

First-rank symptoms were previously considered characteristic of schizophrenia – as in the Research Diagnostic Criteria (Spitzer et al., 1975), DSM-III, -III-R and -IV. This was abandoned in DSM-V because these symptoms also occur in bipolar disorder. (Peralta and Cuesta, 1999) Additional evidence for genetic and biological relatedness of these disorders has been noted above. But the prognostic significance of *severe and persistent* first-rank symptoms has perhaps been too readily dismissed, regardless of diagnostic labels. Although first-rank symptoms are reported by a minority of psychotic bipolar patients, they are more frequent, severe, recurrent and persistent in schizophrenia. (Ihara et al., 2009; Rosen et al.,

2011; Soares-Weiser et al., 2015) The most relevant data come from a twenty-year study: in schizophrenia cases, hallucinations two years after onset predicted persistent or recurrent hallucinations and poor twenty-year recovery; and, comparing patients with and without first-rank symptoms at two years (seen in 45%), only 11% of the former group had one or more subsequent years of recovery, vs. 64% of the latter group. (Goghari et al., 2013) Further, over twenty years, 25% of 53 schizophrenia patients and *none* of 25 bipolar patients reported commenting/conversing voices at 3 or more of 6 follow-ups, and severity was greater in schizophrenia. (Rosen et al., 2011) Thus, severe bizarre positive symptoms may be markers of disease severity and chronicity and should be carefully measured in studies of psychotic disorders, including in children and adolescents.

4.4 Limitations. We recruited patients in a tertiary-care setting, which may be biased when compared with population-based sampling (but the latter is difficult for childhood-onset psychosis). Cases with bipolar psychosis patients were not studied. We lack longitudinal and biological data or uniform cognitive assessments; follow-up and neuroimaging studies are underway, along with expansion of the cohort. It was difficult to differentiate the effects of AAO vs. duration of illness because MGS cases had a narrow range of current ages (43 ± 11) so that duration was longer for COS (although for COS in the MGS cohort, duration was not correlated with hallucination severity; $r_s = 0.068$, $p=0.45$). Our N was small but was one of the largest to date, particularly for $AAO < 13$. The N of 88 may be considered small for K-means cluster analysis of 11 variables. The DIGS does not collect systematic data about childhood trauma, which could be useful in characterising the heterogeneous cluster of cases with increased depression. Childhood variables in the MGS dataset were inadequate for studying premorbid developmental features.

4.5 Conclusions. Using data from a new dimensional rating scale, we identified five clinical symptom factors in children and adolescents with schizophrenia spectrum psychoses. The original adult version of the same scale produced similar factors in a large, independent adult schizophrenia cohort. A cluster analysis of factor scores and

developmental features identified four clusters (profiles) that are consistent with previous evidence and with clinical experience. Bizarre positive symptoms (including, in the child cohort, first-rank symptoms and severity of hallucinations) were more severe in younger children, were characteristic of the largest cluster, and were associated with childhood onset in the adult cohort. These findings suggest that first-rank symptoms deserve further attention as markers of severity and chronicity of psychotic disorders.

The identification of clinically-meaningful clusters (profiles) of clinical and developmental variables underscores the value of using both categorical diagnoses and clinical symptom dimensions to characterize neuropsychiatric disorders. Dimensional approaches of increasing interest in psychiatry. (Kotov et al., 2017) Three studies found that premorbid functioning and course of illness were best predicted by combining diagnoses and dimensional ratings. (Allardyce et al., 2007; Demjaha et al., 2009; Dikeos et al., 2006) The Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) reported that diagnosis did not predict course or MRI variables as well as three “biotypes” defined by cognitive and psychophysiological markers (Clementz et al., 2016); but machine learning analysis demonstrated that adding both diagnoses and dimensional ratings improved cluster separation and prediction of social functioning, cortical thickness and smooth pursuit eye movement. (Mothi et al., 2018)

Patient care and biological research are both likely to benefit from the study of biomarkers and dimensional and categorical clinical measures in larger child/adolescent cohorts, if longitudinal follow-up can be accomplished in was the case in the NIMH cohort.

Supplementary information. LDPS_SupplementaryInformation.pdf includes 5 supplementary tables and author, acknowledgement and funding information for the MGS collaboration. Two additional supplementary files contain English and French versions of the LDPS-CA: LDPS-CA_English_v1.pdf and LDPS-CA_Francais_v1.pdf (Echelle d’Evaluation Dimensionnelle Diachronique des Psychoses chez l’Enfant et l’Adolescent). Note that clinical

data and biomaterials for the MGS cohort are available to qualified scientists
(nimhgenetics.org).

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Table 1: Demographics and diagnoses

| | Mean (SD) |
|------------------------------------------|-------------|
| Age at interview | 15.1 (2.5) |
| Age at onset – Psychosis | 12.6 (2.8) |
| Age at onset – Schizophrenia (N=70) | 13.6 (2.4) |
| Duration of psychosis (years) | 2.5 (1.9) |
| Duration of schizophrenia (years) (N=70) | 1.8 (1.4) |
| Age at first treatment | 13.9 (2.6) |
| Age at first hospitalization (N=75) | 14.3 (2.4) |
| | Male/Female |
| Sex | 62/26 |
| DSM-IV diagnosis | N(%) |
| Schizophrenia | 66 (75%) |
| Schizoaffective – Depressed | 4 (5%) |
| Schizoaffective – Bipolar | 1 (1%) |
| Psychotic disorder NOS | 8 (9%) |
| Other* | 9 (10%) |
| Developmental problems | |
| Developmental delay | 33 (38%) |
| Developmental signs | 45 (51%) |
| Verbal specific Learning Disability | 14 (16%) |
| Nonverbal specific Learning Disability | 30 (34%) |
| Any specific Learning Disability | 36 (41%) |
| Any of the above | 65 (74%) |

*Major Depressive Disorder with psychotic features 5; Brief Psychotic Disorder 3; Schizophreniform Disorder 1

Table 2: Factor analyses of psychotic and mood symptoms in the child and adult cohorts

| Variable | 1-BIZPOS | | 2-NEG/FTD | | 3-DEP | | 4-POS/PAR | | 5-MANIA | | Frequency* | |
|-----------------------------|----------|-------|-----------|-------|-------|-------|-----------|-------|---------|-------|------------|-------|
| | Child | Adult | Child | Adult | Child | Adult | Child | Adult | Child | Adult | Child | Adult |
| Hallucinations | 0.89 | 0.34 | 0.07 | 0.12 | 0.12 | 0.15 | -0.02 | 0.59 | 0.03 | -0.08 | 0.64 | 0.78 |
| Conversing/commenting | 0.84 | 0.70 | 0.11 | 0.01 | -0.02 | 0.21 | -0.02 | -0.03 | 0.12 | -0.11 | 0.58 | 0.41 |
| Control delusions | 0.75 | 0.71 | 0.09 | 0.03 | 0.08 | -0.07 | 0.07 | 0.16 | -0.22 | 0.14 | 0.52 | 0.34 |
| Visual hallucinations | 0.75 | | 0.04 | | -0.18 | | -0.02 | | 0.07 | | 0.51 | 0.48 |
| Thought broad/echo/audible | 0.43 | 0.75 | 0.08 | 0.01 | 0.18 | -0.03 | -0.11 | 0.13 | -0.28 | 0.04 | 0.19 | 0.26 |
| Poverty of speech | 0.09 | 0.04 | 0.85 | 0.80 | -0.09 | 0.12 | 0.05 | 0.04 | -0.03 | -0.03 | 0.33 | 0.26 |
| Blunted affect | -0.03 | -0.02 | 0.75 | 0.76 | 0.05 | 0.03 | 0.30 | 0.17 | -0.18 | -0.09 | 0.39 | 0.42 |
| Formal thought disorder | 0.06 | 0.06 | 0.74 | 0.43 | 0.12 | -0.40 | -0.24 | 0.31 | 0.29 | 0.32 | 0.40 | 0.46 |
| Social withdrawal | 0.01 | | 0.68 | | -0.06 | | 0.29 | | -0.27 | | 0.52 | |
| Deterioration | 0.20 | -0.02 | 0.63 | 0.34 | 0.02 | -0.04 | 0.07 | 0.57 | 0.12 | 0.07 | 0.19 | 0.84 |
| Bizarre behavior | | 0.12 | | 0.42 | | -0.35 | | 0.09 | | 0.39 | | 0.47 |
| Depressive psychotic themes | 0.09 | 0.07 | 0.00 | 0.13 | 0.78 | 0.76 | 0.26 | -0.02 | 0.16 | 0.19 | 0.27 | 0.12 |
| Suicidal ideation | 0.12 | | -0.17 | | 0.75 | | 0.03 | | -0.13 | | 0.28 | |
| Depression | -0.10 | 0.06 | 0.15 | -0.01 | 0.70 | 0.74 | 0.06 | 0.12 | -0.08 | 0.23 | 0.22 | 0.36 |
| Delusions of reference | -0.02 | | 0.10 | | 0.17 | | 0.79 | | 0.09 | | 0.31 | |
| Paranoia | -0.18 | 0.08 | 0.12 | -0.01 | 0.25 | 0.01 | 0.72 | 0.82 | -0.13 | 0.03 | 0.43 | 0.76 |
| Delusions | 0.20 | 0.07 | 0.21 | 0.08 | -0.09 | -0.02 | 0.65 | 0.86 | 0.42 | 0.10 | 0.68 | 0.88 |
| Mania | -0.42 | 0.02 | 0.03 | -0.05 | 0.13 | 0.20 | -0.07 | 0.05 | 0.76 | 0.83 | 0.01 | 0.16 |
| Manic psychotic themes | 0.26 | 0.00 | -0.08 | -0.04 | -0.23 | 0.21 | 0.27 | 0.02 | 0.56 | 0.82 | 0.01 | 0.08 |
| Eigenvalues | 3.2 | 1.7 | 2.8 | 1.6 | 1.9 | 1.6 | 2.0 | 2.3 | 1.5 | 1.7 | | |
| % Total variance explained | 17.8 | 11.3 | 15.8 | 10.7 | 10.8 | 10.5 | 11.0 | 15.2 | 8.1 | 11.6 | | |

For each factor, child (N=88) and adult (MGS) cohort (N=2 420) factor loadings are in the left and right columns respectively. Loadings >0.4 are shaded in dark (child) or light (adult) green; values <-0.4 are pink. Severity ratings (1-4) were entered for LDPS items; Visual Hallucinations was present/absent (from LDPS for child cohort; estimated from DIGS rating of "1" or SAPS rating of >1).

BIZPOS=Bizarre Positive; NEG/FTD=Negative/Formal Thought Disorder; DEP=Depressive; POS/PAR=Positive/Paranoid.

*Shown are proportions of subjects in each cohort with LDPS scores of >2 (where 2=minimal/questionable/very mild); or "present" for Visual Hallucinations as noted above.

Some items were available for only one cohort (see text).

Table 3:
Cluster analysis of clinical factors and childhood-specific variables (child cohort)

| Cluster | | | BIZPOS | DEP | NEG | DEV |
|---------------------------------------------|---------|--------------|---------------|---------------|---------------|---------------|
| N | 83 | | 31 (37.4%) | 25 (30.1%) | 15 (18.1%) | 12 (14.5%) |
| Variable | F-Ratio | P | Mean | Mean | Mean | Mean |
| Perinatal complications† | 1.499 | 0.221 | 0.29 | 0.08 | 0.13 | 0.17 |
| Developmental signs† | 2.567 | 0.060 | 0.58 | 0.32 | 0.73 | 0.58 |
| Conduct disorder† | 1.583 | 0.200 | 0.32 | 0.44 | 0.33 | 0.67 |
| Autism Spectrum Disorder symptom severity | 151.813 | 0E+00 | 0.07 | 0.08 | 0.20 | 2.58 |
| Any developmental delay† | 3.173 | 0.029 | 0.48 | 0.20 | 0.33 | 0.67 |
| Verbal specific learning disability† | 2.559 | 0.061 | 0.03 | 0.28 | 0.27 | 0.17 |
| Non-verbal specific learning disability† | 2.528 | 0.063 | 0.19 | 0.52 | 0.47 | 0.33 |
| Factor 1 – Bizarre Positive/Hallucinations | 17.894 | 6E-09 | 0.75 | -0.12 | -0.87 | 0.13 |
| Factor 2 – Negative/Formal Thought Disorder | 4.824 | 0.004 | -0.20 | -0.33 | 0.65 | 0.44 |
| Factor 3 – Depressive | 27.44 | 3E-12 | -0.35 | 0.95 | -0.99 | 0.01 |
| Factor 4 – Positive/Paranoid | 2.328 | 0.081 | 0.33 | -0.16 | 0.04 | -0.49 |
| Factor 5 – Mania | 8.332 | 7E-05 | 0.23 | -0.41 | -0.51 | -0.30 |
| Total | 12.384 | 0E+00 | | | | |
| Proportion schizophrenia diagnosis* | | 0.003 | 0.84 | 0.52 | 0.87 | 1.00 |
| Proportion female* | | n.s. | 0.42 | 0.32 | 0.13 | 0.17 |
| Age at onset mean±s.d.* | | n.s. | 12.6±3.0 | 12.3±3.1 | 13.2±2.4 | 11.2±2.1 |

Shown are results of K-means cluster analysis of clinical factor scores and developmental variables, after excluding 5 subjects who were assigned in an initial analysis to a cluster driven entirely by Mania factor scores (see text). † denotes binary variable (thus the mean=the proportion of cases with the characteristic). *Differences among clusters: Schizophrenia diagnosis: $\chi^2=14.071$, 3df, $p=0.003$; Sex: $\chi^2=5.138$, 3df, $p=0.162$; Age at onset: $F=1.250$, 3df, $p=0.297$. $df = 3,79$ for individual variables, $df=36,948$ in total. For variables that significantly differentiated among clusters, the most extreme values are shown in bold italics.

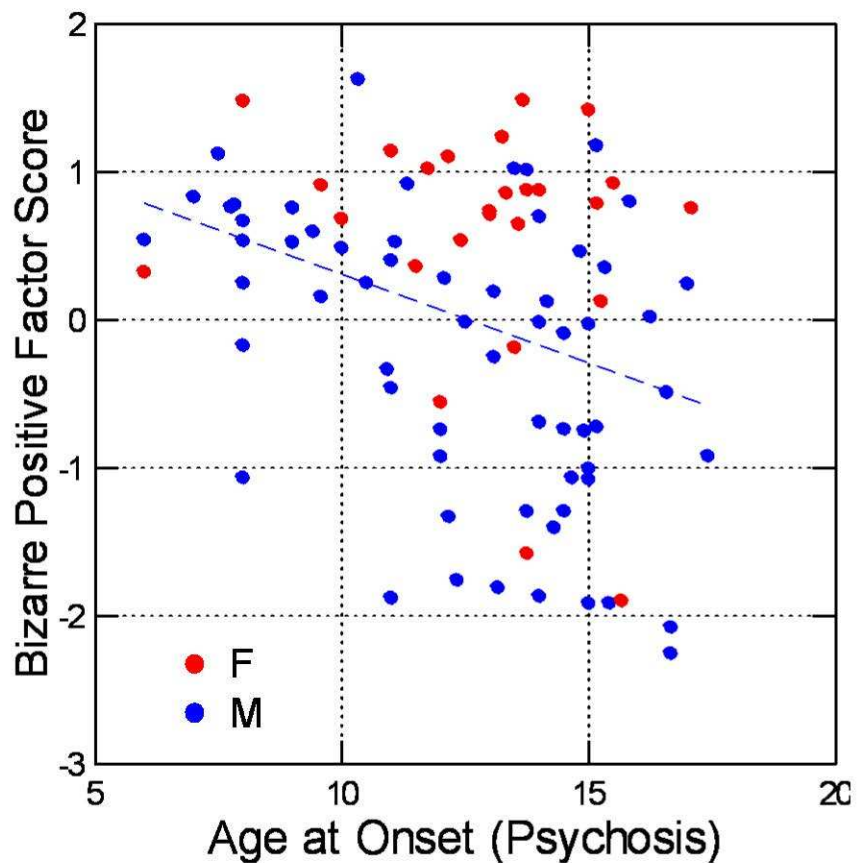


Figure 1: Bizarre positive symptoms and age at onset. Lower age at onset of psychosis predicted higher Bizarre Positive factor scores (red = females, blue = males; $r=-0.338$, $p=0.0013$; linear regression line is shown). The negative correlation was driven primarily by males who had a broader distribution of scores, whereas females had higher scores than males (see text).

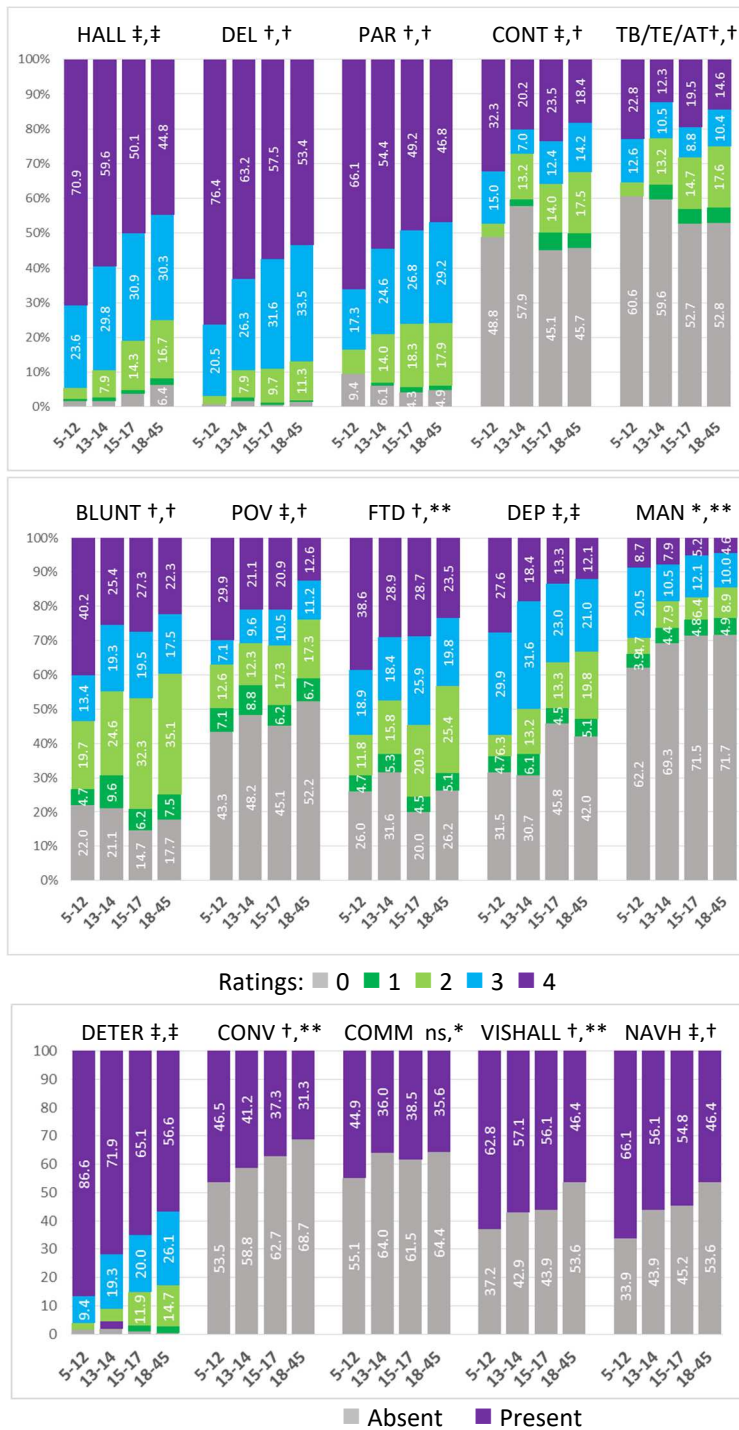


Figure 2: Symptom severity ratings across four AAO ranges. Each stacked bar shows % of MGS cases with each lifetime severity or present/absent rating, by AAO range: 5-12, 13-14, 15-17, 18-45 (Ns 127, 114, 421, 1 758). Symbols after each item name indicate statistical significance of X² tests of differences across (i) 4 AAO groups (df=12; df=3 for present-absent) and (ii) 5-12 vs. all others (df=4; df=1 for present-absent). ‡p<0.00001; †p<0.001; **p<0.01; *p<0.05. Abbreviations: HALL (hallucinations), DEL (delusions), PAR (paranoia), CONT (delusions of thoughts/actions being controlled), TB/TE/AT (thoughts perceived as broadcast, echoed or audible), BLUNT (blunted affect), POV (poverty of speech), FTD (formal thought disorder), DEP (depression), MAN (mania), DETER (overall functional deterioration), CONV (voices conversing), COMM (third-person "commenting" voices), VISHALL (visual hallucinations) and NAVH (non-affective verbal hallucinations spoken to the subject).

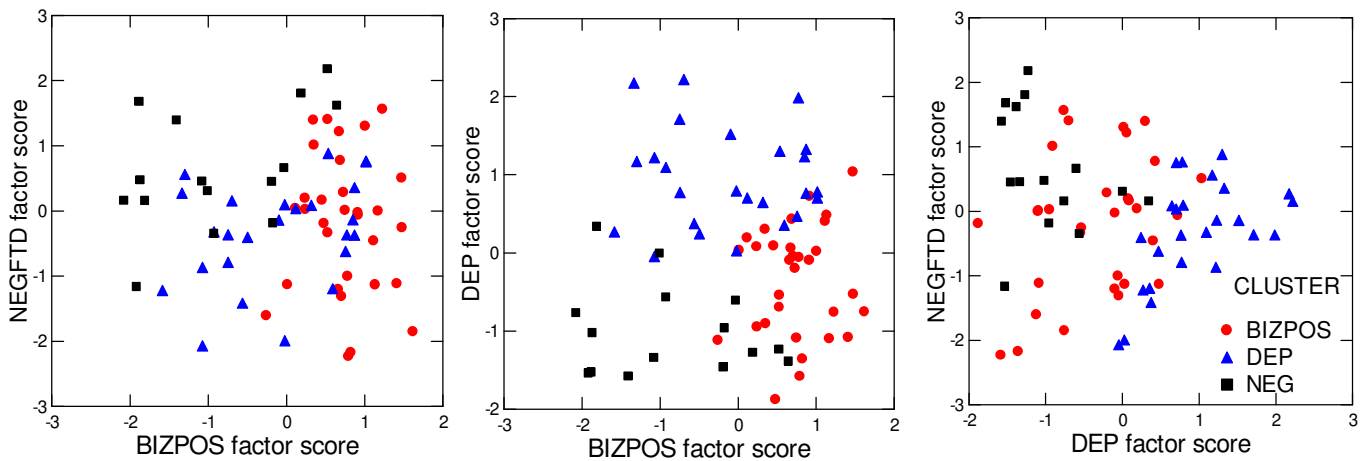


Figure 3: Separation of Bizarre Positive, Depressive and Negative clusters.

Three of the four clusters (**Table 3**) are separated primarily by three factor scores: The BIZPOS cluster (red circles) had uniformly high BIZPOS (left panel) and low DEP scores (middle and right), with mixed NEGFTD scores (left and right). The DEP cluster (blue triangles) had uniformly high DEP scores (middle and right) and mixed BIZPOS and NEG scores. The NEG cluster (black squares) had uniformly high NEGFTD (left and right) and generally low BIZPOS scores (left and middle).

The fourth (ASD) cluster was separated by high ASD scores and a high frequency of developmental delay (**Table 3**). (Note that 5 cases characterized by high mania scores and low frequency of schizophrenia diagnosis were excluded as outliers, see main text.) Note that Positive/Paranoid factor scores did not significantly separate the clusters.