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Abnormal involuntary movements are linked to psychosis-risk in children and adolescents: Results of a population-based study

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ABSTRACT

Background: Altered motor behavior has consistently been reported in medication-naive adult patients with schizophrenia and first episode psychosis and adults at clinical high risk for psychosis (CHR). This study is the first to evaluate the prevalence of abnormal involuntary movements in a community sample of children and adolescents with and without CHR.
Methods: We examined CHR in 102 children and adolescents aged 8–17 years from the general population of the Canton Bern. Attenuated and brief intermittent psychotic symptoms, as well as basic symptoms, were assessed using the Structured Interview for Psychosis Risk Syndromes and the Schizophrenia Proneness Instrument, Child & Youth Version. Motor symptoms were assessed using the Abnormal Involuntary Movement Scale (AIMS). Additionally, psychosocial functioning, a neurocognitive test battery, and DSM-IV Axis I disorders were examined.
Results: Eleven (10.8%) participants met CHR criteria, 13 (12.7%, 5 with and 8 without CHR) met criteria for increased abnormal involuntary movements (AIMS ≥ 2). Both AIMS total scores and the percentage of children with AIMS ≥ 2 were significantly higher in the CHR group. Psychosocial functioning was reduced in subjects with abnormal involuntary movements, and movement abnormalities were linked to deficits in attention and perception but not to the presence of non-psychotic mental disorders.
Conclusions: Our findings suggest that abnormal involuntary movements are linked to psychosis risk in children and adolescents from the general population. Thus, abnormal involuntary movements might represent an additional useful and easily accessible predictor of psychosis.

1. Introduction

Psychoses have repeatedly been shown to lead to enormous disability and cost. The lifetime prevalence rate of all psychoses is estimated at 3–3.5% with a peak of first onset between the ages of 20 to 25, and an annual incidence of 0.035% (Kirkbride et al., 2006; Perala et al., 2007); 10 to 15% have an onset before the age of 18. Currently, early detection of and intervention in persons with initial signs of emerging psychosis is regarded as a promising strategy to reduce the burden of this disease (WHO, 2004). To this aim, two complementary sets of clinical high risk (CHR) criteria were developed on predominately adult samples: (1) "ultra-high risk" criteria (UHR) (McGlashan et al., 2010; Yung et al., 1996; Yung et al., 1998) including attenuated and brief intermittent psychotic symptoms and a combination of genetic risk factors and a recent significant functional decline; and (2) the basic symptom criteria (BS) "cognitive-perceptive basic symptoms" (COPER) (Klosterkotter et al., 2001) and "cognitive disturbances" (COGDIS) (Schultze-Lutter and Koch, 2010; Schultze-Lutter et al., 2012). Yet, recent studies indicate that CHR criteria may be less predictive of psychosis conversion in children and adolescents (Cornblatt et al., 2015; Schimmelmann et al., 2015; Schultze-Lutter et al., 2015), thus making the search for additional predictors to improve prognostic accuracy even more imperative in children and adolescents.

Altered motor behavior has consistently been reported in the schizophrenia literature (Bleuler, 1911; Kahlbaum, 1874; Kraepelin, 1899), including a wide range of motor symptoms. These comprehensive clinical descriptions were later neglected when scientific attention shifted to antipsychotic-related motor symptoms. The importance of motor symptoms has recently been rediscovered as symptoms were found in never-medicated patients (Cunningham Owens and Johnstone, 1980; Fenton et al., 1994; Walther and Strik, 2012) and first episode psychosis (Walther et al., 2014b). Movement patterns were predictive of the severity of positive symptoms, disorganization, and agitation in schizophrenia (Walther et al., 2014a). Furthermore, neuroimaging data demonstrated alterations in the human motor system in schizophrenia

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(Bracht et al., 2013; Walther et al., 2011). Among schizophrenia-related motor symptoms, abnormal involuntary movements have frequently been investigated (Pappa and Dazzan, 2009; Whitty et al., 2009). When these motor abnormalities occur prior to antipsychotic exposure, they are considered "Spontaneous Movement Abnormalities", including dyskinesia and Parkinsonism (Pappa and Dazzan, 2009); presently we will use the term "Abnormal Involuntary Movements" (AIM). AIM comprise abnormal, involuntary, repetitive movements of the orofacial, limb, trunk, and respiratory musculature (Waddington, 1989) and have been detected in healthy relatives of patients with schizophrenia (Koning et al., 2010; Mittal et al., 2007b), as well as in help-seeking adolescents fulfilling UHR criteria (Mittal et al., 2008). In fact, several studies on UHR adolescents suggested that AIM were predictive of conversion (Callaway et al., 2014; Mittal et al., 2007a). Furthermore, in retrospective studies of schizophrenia patients, motor abnormalities could be traced into childhood (Walker et al., 1994), and in young offspring of schizophrenia patients, deficits in gross motor skills were reported to be predictive of schizophrenia-related psychoses in adulthood (Erlenmeyer-Kimling et al., 2000). Recent studies indicated that AIM in CHR reflect striatal pathology (Dean and Mittal, 2015) and are associated with poorer psychosocial (Mittal et al., 2011) and cognitive functioning (Howes et al., 2009; Mittal et al., 2010).

However, the association of abnormal involuntary movements and CHR in psychosis has not been investigated in population-based samples of children and adolescents from the community. With respect to both CHR and AIM status, selected samples of help-seeking persons must be assumed a non-representative minority of the CHR/AIM population. In contrast, population based epidemiological studies additionally provide information on non-help-seeking individuals, which might be of particular value for the development of effective preventive strategies.

Therefore, we tested whether the frequency of AIM differs in children and adolescents from the community with and without CHR to develop psychosis. Moreover, we investigated whether AIM were associated with disturbances in social functioning, cognition or psychopathology beyond the CHR state.

2. Materials and methods

2.1. Sample

The sample was part of the Binational Evaluation of At-Risk Symptoms in Children and Adolescents, BEARS-Kid study (Schimmelmann et al., 2015). Stratified sampling by sex (1:1) was used to randomly select potential participants aged 8–17 years from approximately 384,000 persons of this age group included in the obligatory population register of Canton Bern, Switzerland. The local ethics committee approved the study. Written informed assent/consent was provided by participants and their parents. Eligibility criteria included appropriate age, an available telephone number, and main residence in Canton Bern (i.e., a valid address and not being abroad during the assessment period). Participants were sent an information letter and subsequently contacted by telephone; if agreeing to participate, invited for an interview at our premises or their home. At first face-to-face contact written informed consent was secured. Interviews were discontinued if respondents had a lifetime diagnosis of psychosis or insufficient German, French, or English language skills. Within 33 months (09/2011 to 05/2014), 41.5% of eligible subjects agreed to participate. Participants and non-participants did not differ in age, gender, and nationality. Main reasons for refusal to participate were lack of interest in the topic or lack of time.

2.2. Assessment

A CHR state was defined either by the presence of UHR or BS criteria. For UHR criteria, the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan et al., 2010) was used to assess current presence of attenuated psychotic symptoms (APS; any SIPS positive P item with a score between 3 and 5), brief intermittent psychotic symptoms (BIPS; any SIPS P item with a score of 6), genetic risk and functional decline (GRFD), and the related criteria requirements concerning onset/worsening (onset or worsening within the past 12 months for APS; level of psychotic intensity reached within the past 3 months for BLIPS) and frequency (at least weekly presence in the past month for APS; at least several minutes per day at a frequency of at least once per month for BIPS). Nonperceptive (P1, P2, P3, and P5) and perceptive (P4) APS/BIPS were also distinguished. For BS criteria, the Schizophrenia Proneness Instrument, Child & Youth Version (SPI-CY) (Schultze-Lutter and Koch, 2010) was used for the evaluation of the 14 BS included in COPER and COGDIS. Interviewers received an intensive 3-month training prior to the start of the study. Further, weekly supervision of symptom ratings was provided by two of the authors (F.S.-L. and C.M.).

AIM were assessed using the Abnormal Involuntary Movement Scale (AIMS, Supplement Table S1) (Guy, 1976). The AIMS was originally constructed to assess severity of AIM in tardive dyskinesia. Facial, oral, extremity, and trunk movements are rated on 7 items. In our non-clinical community sample, we used a liberal, lowered threshold for presence of AIM of ≥2 for AIMS total score. A total score of 2 implies either one item rated as "mild," or two items rated as "minimal." Two raters performed all AIMS assessments. These raters were trained and instructed with videos and live interviews by S.W. to ensure high data quality. Rater trainings were repeated once a year. Administration was conducted in a standard setting. The investigation strictly followed the AIMS examination procedure (for details see the Supplement). Interrater reliability met a Kappa of 0.74.

Symptom-independent current global level of psychosocial functioning was estimated using the Social and Occupational Functioning Assessment Scale (SOFAS) (APA, 1994). The Mini-International Neuropsychiatric Interview for Children and Adolescents (Sheehan et al., 1998) was used to assess mental disorders according to DSM-IV (APA, 1994) criteria and to exclude psychotic individuals. Interviewers were equally trained and supervised on these instruments as on the SIPS and SPI-CY assessments.

With regard to neurocognitive domains frequently reported to be impaired in CHR states and linked to conversion, verbal memory and learning were examined with the German version of the Auditory Verbal Learning Test (AVLT) (Helmstaedter et al., 2001), spatial working memory with the Subject-Ordered Pointing Task (SOPT) (Petrides and Milner, 1982), verbal fluency with the Regensburg Word Fluency Test (RWT) (Aschenbrenner et al., 2000), and processing speed with the Digit Symbol Test (DST) (Petermann and Petermann, 2010) and the Trail-Making Test, Part A (TMT-A) (Reitan, 1971). Part B of the TMT was used to assess set-switching as one subdomain of executive functions, and premorbid verbal intelligence was assessed with the Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn, 2007). Percentiles on age-adjusted norms were used. The order of assessment was as follows: sociodemographic variables, motor examination, psychopathology, and cognitive tests. This procedure ensured that AIMS ratings were made blind to the clinical status of the subjects.

2.3. Statistics

Using SPSS 21.0, frequencies and percentages were compared by chi-square tests, means of normally distributed interval data by two-sample *t*-tests, and non-normally distributed interval or ordinal data by Mann-Whitney *U* tests. Statistical distribution was examined with Kolmogorov-Smirnov tests, and statistical outliers (±2 SD) were excluded from the final analysis. Binary logistic regression analyses were performed both forward and backward to assess effects of psychopathology (i.e., the 19 SIPS items) on AIM. To observe the suggested event: predictor ratio of 5:1 (Vittinghoff and McCulloch, 2007), the most promising predictors according to their level of significance were initially selected by Mann-Whitney *U* tests. The goodness-of-fit (GoF)

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