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Systematic meta-analysis of childhood social withdrawal in schizophrenia, and comparison with data from at-risk children aged 9–14 years

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ABSTRACT

Social withdrawal is a robust childhood risk factor for later schizophrenia. The aims of this paper were to assess the evidence for childhood social withdrawal among adults with schizophrenia and, comparatively, in children aged 9–14 years who are putatively at-risk of developing schizophrenia. We conducted a meta-analysis, including cohort and case-control studies reporting social withdrawal measured by the Child Behavior Checklist (CBCL) in adults with schizophrenia vs. controls. Further, an experimental study compared CBCL withdrawal scores from typically-developing children with scores from two groups of putatively at-risk children: (i) children displaying a triad of replicated antecedents for schizophrenia, and (ii) children with at least one first- or second-degree relative with schizophrenia or schizoaffective disorder. Six studies met inclusion criteria for the meta-analysis ($N = 3828$), which demonstrated a large effect of increased childhood social withdrawal in adults with schizophrenia (standardized mean difference [SMD] score = 1.035, 95% CI = 0.304–1.766, $p = 0.006$), with no indication of publication bias, but considerable heterogeneity ($I^2 = 91\%$). Results from the experimental study also indicated a large effect of increased social withdrawal in children displaying the antecedent triad (SMD = 0.743, $p = 0.001$), and a weaker effect in children with a family history of schizophrenia (SMD = 0.442, $p = 0.051$). Childhood social withdrawal may constitute a vulnerability marker for schizophrenia in the presence of other antecedents and/or genetic risk factors for schizophrenia.

1. Introduction

Social functioning is an important predictor of functional outcome in schizophrenia. Social skills competency among affected individuals is associated with better role functioning in the community, and predicts vocational functioning independently of cognitive ability (Dickinson et al., 2007). It is also modifiable, with evidence showing a significant benefit of social skills training for improving social interactions, community functioning, and general psychopathology in people with schizophrenia (Pfammatter et al., 2006; Kurtz and Mueser, 2008). Deficits in social functioning may constitute a relatively stable marker of vulnerability to psychosis (Cannon et al., 2007), and social withdrawal in particular is considered a robust childhood risk factor for schizophrenia (Olin et al., 1995; Cannon et al., 2001; Miller et al., 2002; Johnstone et al., 2005). Social withdrawal is proposed to contribute to the development of other symptoms, including hallucinations and delusions that carry social valence, as high levels of social withdrawal in vulnerable individuals can lead to attribution of false social meaning (Hoffman, 2007). Evidence from longitudinal studies has shown that social withdrawal is modifiable in shy children, particularly with parental encouragement (Kagan et al., 1987, 1989). The modifiability of social withdrawal among children who later develop schizophrenia is yet to be determined.

A recent systematic review of prospective investigations of birth cohorts and of high-risk cohorts of youth with a family history of schizophrenia, as well as follow-back case-control studies of individuals with schizophrenia, compared premorbid social

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withdrawal among youth who later developed schizophrenia and youth who did not (Tarbox and Pogue-Geile, 2008). The review combined data from diverse measures to provide a broadly-defined index of social withdrawal and internalizing behaviour, and suggested an increasing magnitude of association between social withdrawal and schizophrenia with age. In early-middle childhood (ages 4–9 years) the association was modest, but social withdrawal constituted a more sensitive predictor of schizophrenia among older children (by age 11) and even more so in adolescence (ages 13–17 years). However, the relationship between adolescent withdrawal and later schizophrenia was of smaller magnitude in two high-risk cohorts (Carter et al., 2002; Schiffman et al., 2004) relative to birth cohort and case-control investigations, implying that withdrawal may be a less sensitive and specific predictor of schizophrenia among individuals with a family history of the disorder than among the general population.

Recognizing and intervening with children at risk of developing schizophrenia offers the potential to prevent or minimize deviant development and resulting disability (Laurens et al., 2011). While family history of schizophrenia constitutes a robust indicator of vulnerability to the illness, almost two thirds of affected individuals have no first- or second-degree relative with the disorder (Gottesman and Erlenmeyer-Kimling, 2001). Therefore, we developed a complementary method of screening community samples of children aged 9–12 years to identify putatively at-risk individuals on the basis of a triad of replicated antecedents of schizophrenia (Laurens et al., 2007). The triad of antecedents incorporates: (i) caregiver-reported speech and/or motor development lags or problems, (ii) child-reported psychotic-like experiences (Laurens et al., 2011), and (iii) child-reported social, emotional, and/or behavioural problems. Longitudinal follow-up of the children is necessary to determine the specificity and sensitivity with which the antecedent triad predicts later schizophrenia, but preliminary investigations indicate that children presenting the triad show similar brain function abnormalities to patients with schizophrenia on event-related potential recordings, even during preserved task performance (Laurens et al., 2010). They are also characterized by abnormalities in grey and white matter volumes within the temporal lobes (Cullen et al., 2013). The children show involuntary dyskinetic movement abnormalities of the face and upper body (MacManus et al., 2012), which are consistent with childhood motor dysfunctions reported in patients with schizophrenia (Dickson et al., 2012). They are less able to accurately recognize facial emotions (Dickson et al., 2013), and show poorer intellectual and cognitive function on standardized neuropsychological tests relative to their typically-developing peers (Cullen et al., 2010).

The present study included two components. Firstly, to quantify the magnitude of childhood social withdrawal among individuals who later developed schizophrenia, we conducted a meta-analysis of cohort and case-control studies that used a standardized and validated instrument to measure social withdrawal (Achenbach, 1991). Subsequently, we employed this same measure of withdrawal to quantify the magnitude of social withdrawal reported by the primary caregivers of children aged 9–14 years, separately for two groups of at-risk children relative to typically-developing (TD) peers. These were: (i) children presenting the triad of antecedents of schizophrenia (ASz) and (ii) children with a family history of schizophrenia (FHx), having at least one first- or second-degree relative with schizophrenia/schizoaffective disorder. We anticipated that the meta-analysis would demonstrate significantly elevated ratings of childhood social withdrawal on the standardized and validated measure among individuals who later developed schizophrenia relative to comparison participants; and further, that both groups of high-risk children would present greater social withdrawal than their typically-developing low-risk peers.

2. Materials and methods

2.1. Meta-analysis

2.1.1. Literature search

2.1.1.1. Inclusion/exclusion criteria. We included cohort and case-control studies reporting childhood (<18 years) social withdrawal data from the Withdrawn subscale of the Child Behavior Checklist [CBCL; (Achenbach, 1991)] in people with a diagnosis of a schizophrenia spectrum disorder (i.e., schizophrenia, schizoaffective disorder, schizophreniform disorder, or non-affective psychosis) relative to healthy controls or other comparison groups. The decision to include or exclude studies was conducted independently by two of the authors (S.M. and A.S.), with disagreements resolved by discussion.

2.1.1.2. Search strategy. Medline and Embase were searched in July 2012. The search strategy was designed to be sensitive while retaining acceptable specificity. The search terms were: exp Schizophrenia, schizophreni$.tw, non-affective psychosis.tw, Child Behaviour Checklist.tw, Child Behavior Checklist.tw, and CBCL.tw. Handsearching of reference lists of included reviews was also conducted.

2.1.2. Quality assessment

Quality assessments were completed independently by two authors (S.M. and A.S.), with disagreements settled by discussion. The quality of reporting was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, which outlines a preferred way to report observational studies (http://www.strobe-statement.org).

2.1.3. Data extraction and statistical analysis

All data extraction was completed independently by two of the authors (S.M. and A.S). The following variables were extracted: (1) CBCL Withdrawn scale means and standard deviations (SDs); (2) study design, age range covered by the CBCL assessment, and method of CBCL administration; and (3) sample characteristics including age and sex. Where multiple age ranges for CBCL assessment were reported in a study, we selected the age ranges that most closely aligned with the experimental sample of 9–14 year-olds. For example, Rossi et al. (2000), reported CBCL Withdrawn scale means and standard deviations for five age groups; under 3 years, 4–7 years, 8–11 years, 12–15 years, and 16–18 years. As our experimental study included children aged between 9 and 14 years, we pooled the means and standard deviations from age groups 8 to 11 years and 12 to 15 years only for the meta-analysis, and excluded the data from the other three age groupings.

Comprehensive Meta-Analysis software [CMA V2; (Borenstein et al., 2005)] was used to conduct the meta-analysis. We report standardized mean differences scores (SMDs, or d) and their 95% confidence intervals (CIs): SMDs allow pooling of CBCL scores that may have been reported differently across studies, such as raw scores and standardized scores. A SMD <0.4 represents a small effect, around 0.5 a medium effect, and >0.8 represents a large effect (Cochrane, 2008). A random effects model was used as heterogeneity across study results was expected. The I^2 statistic indexes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error, and is interpreted as low (≤25%), medium (~50%), and high (≥75%) (Higgins et al., 2003). Publication bias was assessed using classic fail-safe N which indicates the number of studies with null results needed to change the observed p-value to ≥alpha (0.05).