Cognitive impairment among children at-risk for schizophrenia

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A R T I C L E   I N F O

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A B S T R A C T

Adults with schizophrenia present cognitive impairments, as do individuals at ultra-high risk for the disorder, youth with relatives with schizophrenia spectrum disorders, and children with antecedents of the disorder. The present study aimed to determine if impairments in childhood differed depending on the definition of risk and/or on the degree of relatedness to an affected individual, and if impairments were explained by IQ. Four groups of children aged 9–12 years were studied: (1) 13 children with ≥1 first-degree or ≥2 second-degree affected relatives (high familial loading: FHxH); (2) 14 with ≥1 affected second-degree relative (lower familial loading: FHxL); (3) 32 with well-replicated antecedents of schizophrenia (ASz); and (4) 45 typically-developing (TD) children with neither a positive family history nor antecedents. Compared to TD children, both FHxH and ASz children exhibited significantly poorer verbal comprehension, scholastic achievement, and verbal memory, while FHxL children additionally displayed significantly lower full-scale IQ, and verbal memory and executive function impairments. After adjusting statistical analyses for IQ, group differences were attenuated. Relative to TD children, FHxL children showed no significant differences in performance. The results imply that impairments in verbal comprehension, scholastic achievement, and verbal working memory may index vulnerability for schizophrenia among children with affected relatives with the disorder and among those with multiple antecedents of the disorder who have no affected relatives. More accurate identification of children at-risk for schizophrenia and the specific deficits that they present provides opportunities for interventions such as cognitive remediation that may impact the development of the illness.

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impairments on measures of IQ, attention, memory, and executive functioning (for review: Reichenberg and Harvey, 2007). The deficits are, however, less pronounced than those presented by schizophrenia patients. Low IQ and deficits in specific cognitive functions have also been reported among non-ill first and/or second-degree relatives aged less than 30 years (for review: Agnew-Blais and Seidman, 2013) and among children/adolescents with an ill parent (for reviews of the extensive early literature on these studies, see: Agnew-Blais and Seidman, 2013; Erlenmeyer-Kimling, 2000; Kremen et al., 1994; Niemi et al., 2003). Findings from these prospective longitudinal studies of offspring of parents with schizophrenia indicate that low IQ, poor scholastic achievement, verbal ability, attention, verbal memory, and working memory assessed during childhood are associated with later development of schizophrenia (Erlenmeyer-Kimling et al., 2000; Sorensen et al., 2006; Seidman et al., 2013).

Evidence indicates that among non-ill adult relatives of individuals with schizophrenia, the degree of neurocognitive impairment is associated with familial loading for the disorder: the higher the genetic loading, the greater the level of impairment on neurocognitive measures (Faraone et al., 2000; Gur et al., 2007; Tsuang et al., 2006; Tuulio-Henriksson et al., 2003; Zilles et al., 2009). Similarly, among youth aged 10–25 years with a positive family history, those with an affected first-degree relative showed greater impairment than those with an affected second-degree relative (Keshavan et al., 2010).

Neurocognitive impairments are also observed among individuals meeting ultra-high-risk (UHR) criteria for psychosis (i.e., either attenuated psychotic symptoms, brief, limited intermittent psychotic symptoms, or genetic risk [family history] plus functional decline). Help-seeking UHR youth present poorer verbal memory, processing speed, attention, working memory, and executive functioning than healthy comparison groups (for reviews: Addington and Barbato, 2012; Furas-Poli et al., 2012). The magnitude of these neurocognitive impairments appear to be as severe as those reported among individuals with a family history of schizophrenia (FHX) (Agnew-Blais and Seidman, 2013).

To date, three studies have directly compared performance of FHX and UHR individuals on a comprehensive neurocognitive test battery (Mukkala et al., 2011; Myles-Worsley et al., 2007; Seidman et al., 2010). Seidman and colleagues reported specific impairments on measures of verbal comprehension, processing speed, and verbal fluency among the FHX group (both first and second-degree relatives) compared to healthy individuals, while those meeting UHR criteria performed more poorly than the comparison group on tests of processing speed, verbal learning, and memory. Direct comparisons of performance revealed significant differences between FHX and UHR youth only on tests of verbal memory, with UHR individuals exhibiting significantly greater impairment (Seidman et al., 2010). Another investigation found that among youth aged 14–19 years, those with at least one first- or two second-degree affected relatives with the disorder displayed impaired verbal memory, verbal working memory, attention, and motor function, while those meeting UHR criteria were impaired on spatial working memory and perceptual organisation only (Myles-Worsley et al., 2007). By contrast, a recent study reported no differences in neurocognitive functioning between young adult offspring of parents with schizophrenia and UHR individuals relative to a healthy comparison group (Mukkala et al., 2011).

Thus, both FHX and UHR individuals show evidence of impairments in cognitive functioning relative to healthy individuals. Moreover, cognitive impairments are present prior to the typical age of onset of schizophrenia, suggesting that neurocognitive impairments index vulnerability for schizophrenia. Examining neurocognitive functioning among children presenting antecedents of schizophrenia could provide important information about alternative trajectories of risk for illness than that conferred by family history of illness. Based on this approach, one recent study reported that young adolescents with psychotic-like experiences (PLEs) at clinical interview displayed slower processing speed and poorer non-verbal working memory relative to healthy adolescents without PLEs (Kelleher et al., 2012).

Extending this strategy, our group developed an alternative, novel approach which uses multiple well-replicated risk markers for later development of schizophrenia. A large community sample of children aged 9–12 years and their primary caregiver completed questionnaires in order to identify children presenting a triad of antecedents of schizophrenia (ASz) (Laurens et al., 2007, 2011), incorporating: (1) PLEs; (2) social, emotional, and/or behavioural problems in the clinical range; and (3) early speech and/or motor developmental delays/abnormalities. Previous investigations have shown that ASz children, compared to typically-developing children, are characterised by features qualitatively similar to those observed among adults with schizophrenia, including: (1) poorer performance on standardised intelligence and neuropsychological tests of executive function and memory (Cullen et al., 2010); (2) poorer facial emotion recognition (Dickson et al., in press); (3) elevated levels of social withdrawal (Matheson et al., 2013); (4) dyskinetic movement abnormalities (MacManus et al., 2012); and (5) reduction in the amplitude of the error-related negativity event-related potential component generated in the anterior cingulate that indexes internal monitoring of behaviour (Laurens et al., 2010); and (6) structural brain abnormalities encompassing the temporal lobe (Cullen et al., 2013).

Thus, preliminary evidence indicates that, like individuals with a first-degree affected relative, children presenting antecedents of schizophrenia display neurocognitive impairment. It is not known, however, whether these impairments tap corresponding domains of similar severity, nor whether these impairments represent difficulties in specific cognitive domains or a general cognitive deficit represented by lower than average IQ. Further, among those who are at risk by virtue of family history, the severity and breadth of impairments vary by closeness of the affected relatives but could differ by age. These differences, if confirmed, may index differences in specific aetiological factors.

The present study examined neurocognitive impairments in children defined as being at-risk for schizophrenia either by the presence of affected relatives or by the presence of multiple antecedents of the disorder. The aims were to determine whether impairments differed depending on the definition of risk and/or on the degree of relatedness to an affected individual. We also sought to explore the extent to which impairments were explained by IQ. We therefore compared performance on a broad array of neurocognitive tests among four groups of children aged 9–12 years, namely those with (1) at least one first-degree or two second-degree affected relatives (i.e., high family loading: FHXH); (2) one affected second-degree relative (i.e., lower family loading: FHXS); (3) no affected relatives; and (4) typically-developing (TD) children. We anticipated that all three high-risk groups of children, FHXH, FHXS, and ASz, would display poorer neurocognitive performance in IQ, scholastic achievement, memory, and executive function than TD children, and that the specific impairments would differ across the risk groups (Myles-Worsley et al., 2007; Seidman et al., 2010). We also expected that children with a higher degree of family loading for schizophrenia (FHXH) would exhibit more severe neurocognitive impairments than those in whom the degree of family loading was presumed to be lower (FHXS). The study also determined the extent to which IQ explains differences in neurocognitive performance among children defined as FHXH, FHXS, and ASz.
1. Method

1.1. Sample

One hundred and four children aged 9–12 years were recruited via two methods described following. Children recruited into the study had never experienced a psychotic episode or taken antipsychotic medication, and none presented with a neurological disorder, learning difficulties (IQ < 70), or a diagnosis of autism or Asperger’s disorder.

Ethical approval of the study was obtained from the Joint South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry Research Ethics Committee. Children provided written assent and caregivers provided written consent for participation in the study.

Recruitment of ASz and TD children: Children from 73 primary schools in greater London and their primary caregivers completed questionnaires designed to assess replicated antecedents of schizophrenia that have been described previously (Laurens et al., 2007, 2011). Children presenting antecedents of schizophrenia (ASz) met three criteria: (1) a child-reported “certainly-true” response on at least one of nine PLE items assessing hallucination- and delusion-like experiences (Laurens et al., 2012); (2) a score in the clinical range (approximately top tenth percentile of U.K. population norms) on the child-reported emotional symptoms scale or the caregiver-reported conduct problems, hyperactivity-inattention, or peer relationship problems scales of the Strengths and Difficulties Questionnaire (Goodman, 2001); and (3) a caregiver-report of a delay/abnormality in motor and/or speech development (Laurens et al., 2007). In contrast, TD children were defined as those who presented none of the three ASz criteria nor had a first-, second-, or third-degree relative with a schizophrenia spectrum disorder, as confirmed using the Family Interview for Genetic Studies which was completed with the child’s primary caregiver (FIGS: Maxwell, 1992).

In total, 1504 children and caregivers completed screening questionnaires. Among these, 9.4% of children met ASz triad criteria, and 22.9% of children did not present with any of the antecedents of schizophrenia. Half of these families (50.2%) indicated a willingness to be contacted for further research, of whom 145 were subsequently invited to participate in a research study that included neurocognitive assessments. Thirteen of these potential participants were excluded: four with insufficient English to complete assessments, three with neurological disorder, and six with a diagnosis of autism or Asperger’s disorder. Of the 54 ASz and 78 TD children invited, 32 (59%) and 45 (58%) participated, respectively. There were no differences observed in the prevalence of ASz triad components among ASz and TD children who participated and who did not participate in the present study, with a single exception. Proportionately fewer of the ASz children in the present study than those who completed only the screening questionnaire obtained SDQ scores for emotional symptoms in the clinical range.

Recruitment of FHx children. To identify children with a family history of schizophrenia or schizoaffective disorder, the screening questionnaire included items assessing family mental health problems. Approximately 2.1% of the 1504 caregivers completing questionnaires indicated that their child had a relative with a schizophrenia spectrum disorder. Additionally, some children aged 9–12 years were recruited as relatives of patients receiving treatment within the South London and Maudsley National Health Service Foundation Trust. One third (36%) of FHx families recruited either through schools or as relatives of patients declined to participate after initial contact. Just over half of the 27 participating FHx children were recruited via schools (56%) and the remainder through contacts with patients.

FHx children had at least one first- or second-degree relative with schizophrenia (n = 25) or schizoaffective disorder (n = 2), confirmed by the FIGS (Maxwell, 1992). Initially, a genetic liability score was computed based on the degree of relatedness and the number of affected relatives (Campbell et al., 2010). With the exception of two children with two affected second-degree family members, the results showed a bimodal distribution distinguishing FHx children with and without a first-degree affected relative. A previous study detected no differences in neurocognitive impairment between adolescents with an affected parent and those with two affected second-degree relatives with schizophrenia (Myles-Worsley et al., 2007). Consequently, FHx children were divided into two groups. The high familial loading for schizophrenia (FHxH) group was defined to include children with one first-degree and one second-degree relative (n = 4), one first-degree relative only (n = 7), or two second-degree relatives (n = 2) with schizophrenia or schizoaffective disorder. The low familial-loading group (FHxL) included children with one second-degree relative with the disorder.

The final sample comprised four groups: 13 FHxH, 14 FHxL, 32 ASz, and 45 TD children. One FHxH child and four FHxL children also met ASz criteria, but were retained in their respective FHx groups. Table 1 presents demographic comparisons of the four groups. Groups were similar as to age at the time of neurocognitive assessment, handedness, and the proportion of males, but differed as to self-ascribed ethnicity, and parents’ occupational status.

1.2. Procedure

Eligible children and their primary caregivers were invited to participate in a research study that incorporated a battery of neurocognitive assessments in addition to biological and psychosocial measures.

1.3. Neurocognitive assessments

A brief description of each neurocognitive measure comprising the test battery is provided in Table 2, with subtests spanning the neurocognitive domains of general intelligence (IQ), scholastic achievement, memory, and executive function (EF).

Each neurocognitive subtest provided standardised scores based on manual-reported, age-adjusted normative data; only the WIAT-II UK provided norms for samples of children from the UK. Scores for each subtest were converted into standardised z-scores based on TD group (risk group mean minus TD mean, divided by the TD standard deviation), so that the TD group had a mean of 0 and a standard deviation of 1.

1.4. Statistical analyses

Univariate ANOVA and chi-square tests were used to compare groups on demographic variables. The distributions of raw scores and standardised z-scores were assessed for normality and outliers. Scores on the scholastic achievement domain for two TD children diagnosed with dyslexia were excluded, as was the perceptual reasoning score of one ASz child with a diagnosis of dyspraxia. To compare scores on the neurocognitive tests of the four groups, analysis of covariance (ANCOVA) tests were conducted adjusting for ethnicity and parents’ occupational status, with post-hoc Bonferroni–Hochberg correction applied (Hochberg, 1988). The size of the group differences is expressed as Cohen’s d effect sizes (Cohen, 1988). To explore the role of general intellectual ability on specific domains of neurocognitive performance, ANCOVA analyses were repeated with the inclusion of full-scale IQ as an additional covariate.
2. Results

2.1. Group comparisons of neurocognitive performance

Standardised z-scores calculated for each task and for each risk group relative to the TD group are presented in Figs. 1 and 2. FHxH children exhibited neurocognitive impairments on all measures except visual memory, while ASz children performed at an intermediate level relative to the FHxL and FHxH groups. Neurocognitive performance of FHx children in all domains except visual memory fell between that of ASz and TD groups.

Tables 3 and 4 present mean scores for performance of each group on the neurocognitive tests, the results of ANCOVAs adjusting for ethnicity and parents’ occupation, and the significant post-hoc group comparisons. Significant overall group differences were obtained for full-scale IQ, verbal comprehension, scholastic achievement, verbal memory, verbal working memory, EF – category switching accuracy, and EF – inhibition/switching.

Post-hoc group comparisons with corrections for multiple testing indicated that FHxH children obtained significantly lower visual memory scores than FHxH children (p = 0.01). On the EF-inhibition/switching subtest, FHxH performed significantly more poorly compared to the FHxL (p = 0.02) and TD groups (p = 0.007).

3. Discussion

The present study examined neurocognitive functioning of three groups of children aged 9–12 years putatively at-risk for schizophrenia, relative to TD peers. FHxH children exhibited lower full scale IQ, verbal IQ, and perceptual reasoning scores, and poorer scholastic achievement, verbal memory, verbal working memory, category switching and inhibition/switching. FHxH children showed no significant differences to TD children, and ASz children presented significantly lower verbal comprehension, and poorer scholastic achievement and verbal working memory. Scores obtained by the FHxH and ASz children were similar on all tests except EF-category switching accuracy, where FHxH children demonstrated more a prominent impairment. These results imply that, by late childhood, children with one first-degree or two second-degree relatives with schizophrenia, and children presenting well-replicated antecedents of schizophrenia, are characterised by cognitive impairment.

Deficits in verbal comprehension, verbal working memory, and scholastic achievement were observed among both FHxH and ASz children compared to the TD children. Poor verbal comprehension and verbal working memory have been identified consistently in children and youth with a first-degree relative with schizophrenia who have not yet passed through the age-range of risk for the disorder (Agnew-Blais and Seidman, 2013) and among UHR adolescents and young adults (Addington and Barbaro, 2012; Fusar-Poli et al., 2012). These specific cognitive impairments may represent generalised risk markers for later psychosis that span genetic (i.e., individuals with a first-degree affected relatives) and clinical high-risk groups. The poor verbal abilities observed among both FHxH and ASz children are in keeping with a previous investigation suggesting that verbal abilities may be one of the first cognitive processes to show impairment in children who subsequently develop schizophrenia (Reichenberg et al., 2010).

The extent to which poor school performance is associated with later schizophrenia is currently unclear (Dickson et al., 2012).
Among 16 year old offspring of adults with schizophrenia, two studies have reported an association between poor scholastic achievement based on end of year school assessment and family history of schizophrenia (Forsyth et al., 2013; Jundong et al., 2012), while there are no investigations of scholastic achievement among UHR individuals. Recent evidence supports an association between low scholastic performance and PLEs during childhood (Bartels-Velthuis et al., 2011; Hameed et al., 2013).

Meta-analyses indicate that lower than average IQ characterises children and adolescents who subsequently develop schizophrenia (Dickson et al., 2012; Woodberry et al., 2008). Consistent with this finding, the results of the present study demonstrated that inclusion of full-scale IQ as a covariate in analyses of specific neurocognitive domains attenuated group differences, suggesting that specific cognitive impairments in FHx and ASz children were partly attributable to differences in general intellectual ability. However, adjusting for IQ in statistical analyses may lead to an underestimation of specific neurocognitive deficits, since some aspects of cognitive ability are correlated with IQ (MacCabe et al., 2012).

The current findings demonstrate that children with differing profiles of risk for schizophrenia exhibit different degrees of neurocognitive impairment; those with a higher familial loading for schizophrenia were more cognitively impaired than children with lower familial loading, and children presenting with antecedents of schizophrenia. These results extend previous findings of greater neurocognitive impairment among youth with a first-degree compared to second-degree relative with schizophrenia (Keshavan et al., 2010) to children assessed well before the typical period of risk for development of the disorder.

FHx children, relative to TD children, additionally showed poor verbal memory, which is among the most robust impairment observed among children and young adults with affected first-degree relatives with schizophrenia and UHR individuals.

Table 2
Details of cognitive assessments.

<table>
<thead>
<tr>
<th>Cognitive measure</th>
<th>Test description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intelligence</strong> (Wechsler Abbreviated Scale of Intelligence; WASI, Wechsler, 1999)</td>
<td></td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td></td>
</tr>
<tr>
<td>- Vocabulary</td>
<td>Define orally and visually presented words</td>
</tr>
<tr>
<td>- Similarities</td>
<td>Identify similarities between pairs of words</td>
</tr>
<tr>
<td>Perceptual Reasoning</td>
<td></td>
</tr>
<tr>
<td>- Block Design</td>
<td>Replicate geometric patterns using two-coloured cubes within a specified time limit</td>
</tr>
<tr>
<td>- Matrix Reasoning</td>
<td>Choose one shape from five to complete a pattern</td>
</tr>
<tr>
<td><strong>Scholastic Achievement</strong> (Wechsler Individual Achievement Test; WIAT-II UK, Wechsler, 2005)</td>
<td></td>
</tr>
<tr>
<td>- Word Reading</td>
<td>Read aloud a word list</td>
</tr>
<tr>
<td>- Numerical Operations</td>
<td>Complete mathematical problems</td>
</tr>
<tr>
<td>- Spelling</td>
<td>Write verbally presented words</td>
</tr>
<tr>
<td><strong>Memory</strong> (Wide Range Assessment of Learning and Memory; WRAML2, Sheslow and Adams, 2003)</td>
<td></td>
</tr>
<tr>
<td>Verbal Memory</td>
<td></td>
</tr>
<tr>
<td>- Story Memory</td>
<td>Immediate recall of details from two short stories read aloud</td>
</tr>
<tr>
<td>- Verbal Learning</td>
<td>Immediate free recall of word list (four trials)</td>
</tr>
<tr>
<td>Visual Memory</td>
<td></td>
</tr>
<tr>
<td>- Design Memory</td>
<td>Immediate recall of five geometric designs</td>
</tr>
<tr>
<td>- Picture Memory</td>
<td>Identify differences between four similar pairs of pictures</td>
</tr>
<tr>
<td>- Verbal Working Memory</td>
<td>Immediate recall of word lists by animal and non-animal categories</td>
</tr>
<tr>
<td><strong>Executive Functioning</strong> (Delis-Kaplan Executive Function System; D-KEFS, Delis et al, 2001)</td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td></td>
</tr>
<tr>
<td>- Letter Fluency</td>
<td>Generate words beginning with F, A, and S in 60 s</td>
</tr>
<tr>
<td>- Category Fluency</td>
<td>Generate animals and boys’ names in 60 s</td>
</tr>
<tr>
<td>- Category Switching Accuracy</td>
<td>Alternately generate words from fruits and furniture categories in 60 s</td>
</tr>
<tr>
<td>Colour Word interference</td>
<td></td>
</tr>
<tr>
<td>- Inhibition</td>
<td>Name ink colour of colour words printed in different colour ink (Stroop, 1933)</td>
</tr>
<tr>
<td>- Inhibition/Switching</td>
<td>As for Inhibition subtest; or, reading colour word (ignore printed ink colour)</td>
</tr>
<tr>
<td>Towers Tests</td>
<td></td>
</tr>
<tr>
<td>- Towers Test Achievement score</td>
<td>Build towers using one to five disks in the fewest possible number of moves</td>
</tr>
</tbody>
</table>

Notes: FIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ; SA = scholastic achievement domain score; FHxH = children with high familial loading for schizophrenia; FHxL = children with low familial loading; ASz = children presenting with multiple antecedents of schizophrenia; and TD = typically-developing children without antecedents or family history of schizophrenia.

Fig. 1. Group z-scores of intelligence and scholastic achievement scores standardised to the typically-developing group mean.

Fig. 2. Group z-scores of memory and executive functioning scores standardised to the typically-developing group mean.
Comparisons of general intelligence and scholastic achievement of children with high familial loading for schizophrenia (FHxH), children with low familial loading (FHxL), children with antecedents of schizophrenia (ASz), and typically-developing children without antecedents or family history of schizophrenia (TD).

### Table 3

<table>
<thead>
<tr>
<th>Subtest variable</th>
<th>FHxH (n = 13)</th>
<th>FHxL (n = 14)</th>
<th>ASz (n = 32)</th>
<th>TD (n = 45)</th>
<th>ANCOVA adjusted for ethnicity and parents’ occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F (df); p; Significant post-hoc tests, Cohen’s d</td>
</tr>
<tr>
<td>Full scale IQ</td>
<td>92.8 (13.7)</td>
<td>107.4 (14.3)</td>
<td>103.1 (11.8)</td>
<td>114.9 (15.0)</td>
<td>4.2 (3,98); 0.008; FHxH &lt; TD, d = 1.1</td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td>93.3 (10.8)</td>
<td>109.1 (14.2)</td>
<td>101.9 (12.3)</td>
<td>113.9 (14.6)</td>
<td>4.7 (3,98); 0.004; FHxH &lt; TD, d = 1.3; ASz &lt; TD, d = 0.9</td>
</tr>
<tr>
<td>Perceptual Reasoning</td>
<td>93.8 (17.0)</td>
<td>103.5 (12.7)</td>
<td>102.6 (13.5)</td>
<td>112.2 (15.4)</td>
<td>2.6 (3,97); 0.06; FHxH &lt; TD, d = 1.2</td>
</tr>
<tr>
<td>Scholastic Achievement</td>
<td>89.6 (12.3)</td>
<td>102.7 (8.3)</td>
<td>94.9 (12.0)</td>
<td>104.4 (11.0)</td>
<td>4.5 (3,93); 0.006; FHxH &lt; TD, d = 1.3; ASz &lt; TD, d = 0.8; FHxH &lt; FHxL; d = 1.3</td>
</tr>
</tbody>
</table>

Notes. Information on scholastic achievement was not available for 2 ASz participants. ANCOVA statistics include F statistic, degrees-of-freedom, and p-value, and are adjusted for ethnicity and parents’ occupation. Only post-hoc tests that were significant after Bonferroni–Hochberg corrections for multiple testing are reported.

(Addington and Barbato, 2012; Agnew-Blais and Seidman, 2013; Fusar-Poli et al., 2012). Importantly, verbal memory deficits predict conversion to later psychosis among young offspring of individuals with schizophrenia and UHR youth (Brewer et al., 2005; Erlenmeyer-Kimling et al., 2000; Lencz et al., 2006; Simon et al., 2012; Woodberry et al., 2010). Previous investigations directly comparing neurocognition in adolescents and young adults with first/second degree FHx relatives and UHR individuals observed verbal memory impairments in the FHx group (Myles-Worsley et al., 2007) or the UHR group only (Seidman et al., 2010). Methodological differences between studies make results hard to aggregate; however, our findings, and those of a recent review of cognitive impairment among first-degree family members of affected individuals aged 30 years and younger (Agnew-Blais and Seidman, 2013), indicate that poor verbal memory may represent a possible genetic vulnerability indicator for schizophrenia.

Further, FHxH children displayed impairment in additional cognitive domains that were not observed in FHxL or ASz groups. Relative to the TD group, FHxH children performed more poorly on two EF tasks, category switching accuracy and inhibition/switching, indicating reduced cognitive flexibility. These findings are consistent with the poor cognitive flexibility widely observed among first-degree relatives of individuals who have yet to pass the age-range of risk typically associated with the disorder (Agnew-Blais and Seidman, 2013).

Our previous investigation based on a smaller sample of ASz and TD children indicated lower full-scale IQ, verbal memory, working memory, and EF – inhibition scores in ASz children relative to TD children (Cullen et al., 2010). The differences in results obtained across studies might be due to the small sample in the previous investigation or inclusion in that ASz group of three children with a positive family history of schizophrenia (two FHxH and one FHxL).

Moreover, in the present study, unlike the previous one, group comparisons controlled for ethnicity and parents’ occupation. The prevalence of schizophrenia is higher among people of low socioeconomic status and of African-Caribbean and black African ethnicity living in the UK (Fearon et al., 2006; Tandon et al., 2008). Similarly, the prevalence ASz is higher among children of African-Caribbean and black African origin, than among white British children, living in the UK (Laurens et al., 2011, 2008).

Strengths of the present study include the novel comparison of three groups at-risk for schizophrenia based on differing vulnerability profiles, the examination of children prior to the age typically associated with onset of the prodrome, and the broad array of neurocognitive tests employed. The small sample size may have limited our ability to detect neurocognitive impairments of small effect, and prohibited further examination of the role of confounding variables such as ethnicity in explaining group differences. Nonetheless, already in childhood, those with a first degree or two second-degree relatives with schizophrenia showed impairment across a range of cognitive domains consistent with several reviews of cognitive functioning in FHx adolescents and young adults (Agnew-Blais and Seidman, 2013; Erlenmeyer-Kimling, 2000; Niemi et al., 2003). While indexing family history

### Table 4

Comparisons of general intelligence and scholastic achievement of children with high familial loading for schizophrenia (FHxH), children with low familial loading (FHxL), children with antecedents of schizophrenia (ASz), and typically-developing children without antecedents or family history of schizophrenia (TD).

<table>
<thead>
<tr>
<th>Subtest variable</th>
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<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>F (df); p; Significant post-hoc tests, Cohen’s d</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>17.2 (5.1)</td>
<td>21.6 (3.6)</td>
<td>21.7 (4.6)</td>
<td>23.9 (4.8)</td>
<td>3.1 (3,97); 0.03; FHxH &lt; TD, d = 0.9</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>18.8 (5.0)</td>
<td>15.5 (5.6)</td>
<td>16.7 (4.7)</td>
<td>18.8 (3.5)</td>
<td>2.5 (3,97); 0.06</td>
</tr>
<tr>
<td>Verbal Working Memory</td>
<td>9.1 (2.4)</td>
<td>10.0 (2.0)</td>
<td>9.7 (2.2)</td>
<td>11.5 (2.5)</td>
<td>3.8 (3,96); 0.01; FHxH &lt; TD, d = 1.0; ASz &lt; TD, d = 0.7</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>10.2 (2.4)</td>
<td>11.5 (3.6)</td>
<td>10.5 (3.2)</td>
<td>11.5 (2.6)</td>
<td>1.5 (3,97); 0.22</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>11.4 (2.2)</td>
<td>12.0 (3.4)</td>
<td>12.2 (2.9)</td>
<td>12.8 (2.8)</td>
<td>0.1 (3,96); 0.93</td>
</tr>
<tr>
<td>Category Switching Accuracy</td>
<td>7.2 (3.4)</td>
<td>10.4 (1.5)</td>
<td>10.2 (2.9)</td>
<td>11.2 (2.8)</td>
<td>4.4 (3,97); 0.01; FHxH &lt; TD, d = 1.4; FHxH &lt; ASz, d = 1.0; FHxH &lt; FHxL, d = 1.3</td>
</tr>
<tr>
<td>Colour Word Interference</td>
<td>9.1 (3.5)</td>
<td>10.6 (1.7)</td>
<td>10.7 (2.3)</td>
<td>11.7 (2.3)</td>
<td>1.5 (3,96); 0.22</td>
</tr>
<tr>
<td>Inhibition/switching</td>
<td>8.8 (2.5)</td>
<td>11.1 (2.2)</td>
<td>10.5 (2.8)</td>
<td>11.2 (2.0)</td>
<td>2.9 (3,96); 0.04; FHxH &lt; TD, d = 1.2</td>
</tr>
<tr>
<td>Towers Test</td>
<td>10.3 (2.3)</td>
<td>10.8 (1.8)</td>
<td>10.6 (2.4)</td>
<td>11.2 (2.6)</td>
<td>0.2 (3,95); 0.90</td>
</tr>
</tbody>
</table>

Notes: Data were missing for memory, verbal working memory, and executive functioning for 1 ASz participant, category fluency for 1 FHxH participant, inhibition/switching for 1 TD participant, and achievement score on the Towers test for 1 ASz and TD participant.

Scores for inhibition from 1 FHxH participant were excluded as an outlier. ANCOVA statistics include F statistic, degrees-of-freedom, and p-value. Only post-hoc tests that were significant after Bonferroni–Hochberg corrections for multiple testing are reported.
as a continuous measure may theoretically provide more statistical power for detecting associations between liability and neurocognitive impairment, a categorical approach to indexing genetic liability identified two groups of children at-risk, and yielded similar results to a previous study that used both categorical and continuous definitions of family risk and identified similar neurocognitive impairments among non-ill relatives (Byrne et al., 2003).

Both children with a first-degree relative or two second-degree relatives with schizophrenia and those presenting a triad of antecedents showed impairments on neurocognitive tests relative to TD children. The impairments were explained largely by differences in IQ. By contrast, the performance of children with one second-degree affected relative on these tests was similar to that of TD children. If replicated, these findings may provide clues for identifying distinct aetiological factors active within each risk group, though verbal comprehension, scholastic achievement, and verbal working memory domains may confer generalised risk for psychosis across at-risk groups. Intervening to improve cognitive performance in children at risk for schizophrenia might alter the course of the developing illness. For example, among children with deficits in working memory, a learning-based intervention has been shown to largely eliminate the deficit (Holmes et al., 2009). Evaluating such interventions with different risk groups of children may further understanding of the aetiology of schizophrenia and identify strategies to increase resilience.

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Contributors

KRL and SH designed the study, and KRL and RGM selected the neurocognitive measures. HD and AEC completed the neuropsychological assessments. HD conducted the literature search, statistical analyses, and wrote the initial draft of manuscript. AR and DDC provided statistical/analytical advice. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare no conflict of interest.

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