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Dissociable impairments of verbal learning differentiate childhood risk profiles for schizophrenia

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ABSTRACT

Poor verbal learning and memory function is well-documented among individuals with schizophrenia and those at clinical high-risk for psychosis. This study aimed to identify these impairments among children aged 9–12 years with different schizophrenia risk profiles (family history or antecedents of schizophrenia, each of higher$^{[H]}$ or lower$^{[L]}$ risk load) relative to typically developing peers. These three groups were recruited via community-screening, and differentiated for analysis into: typically developing children (TD = 45); children who had 1 first- or ≥2 second-degree affected relatives (FHx^H = 16) or one second-degree relative (FHx^L = 15); and children presenting multiple replicated antecedents of schizophrenia whose clinical symptoms persisted at 2- and/or 4-year follow-up (ASz^H = 16) or remitted during follow-up (ASz^L = 16). Verbal learning/memory measures assessed at baseline (age 9–12 years) included: (i) total recall; (ii) trial 1 recall; (iii) learning score; (iv) intrusions; (v) total words lost; and (vi) serial position patterns. Analyses of variance indicated that FHx^H and ASz^H youth demonstrated impaired total recall compared to TD and ASz^L children and lost significantly more words between trials than TD and FHx^L children. Learning score was impaired among both FHx^H and FHx^L relative to TD and ASz^L children. Thus, among putatively at-risk children, total words recalled and lost distinguished those with higher risk load (by family history or persistent antecedent symptomology), whereas learning score indexed familial vulnerability. Follow-up of the sample is needed to determine the capacity of verbal learning deficits to predict later illness and provide a potential avenue for early remediation to improve clinical or functional outcomes.

1. Introduction

Cognitive deficits that precede a diagnosis of schizophrenia may represent a stable indicator of disease vulnerability and an important target for preventative intervention (Cannon et al., 2000a; Eastvold et al., 2007; Sheffield et al., 2018). Verbal learning/memory impairment is among the most replicated and severe of the cognitive deficits exhibited by help-seeking youth at clinical high-risk (CHR) for psychosis and by patients at their first-episode of psychosis (Catalan et al., 2021; Mesholam-Gately et al., 2009), and extends beyond the generalised cognitive impairment indexed by IQ (Dickinson et al., 2008; Seidman et al., 2016). Verbal learning may represent an endophenotype or genetic marker for psychosis (Wang et al., 2022), with genetic high-risk studies of adolescent and young adult relatives of schizophrenia patients revealing similarly poor verbal learning compared to healthy controls (Agnew-Blais and Seidman, 2013), including early deficits among young offspring of patients (mean age 12.7 years) (Ozan et al., 2010). Meta-analyses demonstrate verbal learning impairments of moderate magnitude for both youth with genetic (familial) and clinical (CHR) risk presentations (Bora et al., 2014), but a study comparing the independent effects of genetic and clinical (i.e., symptomatic) risk identified more pronounced cognitive deficits among adolescents aged 14–19 years with genetic risk than among symptomatic CHR youth without family history (Myles-Worsley et al., 2007). The genetic vulnerability might be titrated by degree of relatedness, with greater cognitive impairments noted among first-degree relatives of

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schizophrenia patients aged 10–25 years than among second-degree relatives (Keshavan et al., 2010).

As verbal learning demonstrates utility as an independent predictor of psychosis transition among CHR individuals (Addington et al., 2017; Carrión et al., 2018; Seabury and Cannon, 2020), exploring the presence of these deficits in younger samples may improve early detection initiatives. Determining whether premorbid verbal learning deficits are specific to at-risk children with high familial loading, or are present also among children with lower familial loading or a symptomatic risk profile for schizophrenia, may help inform early remediation strategies to improve clinical and functional outcomes (Glenthøj et al., 2017). The London Child Health and Development Study (CHADS) has investigated cognitive functioning among children identified via community screening at 9–12 years of age as being putatively at risk of illness based on either a family history of schizophrenia (FHx) or the presence of a triad of replicated developmental antecedents of schizophrenia (ASz), relative to typically developing (TD) peers (Laurens and Cullen, 2016). The triad of antecedents included psychotic-like experiences (PLEs), internalising and/or externalising psychopathology, and speech and/or motor development delays or abnormalities. Children with family history had first- or second-degree relatives with schizophrenia/schizoaffective disorder. A previous cross-sectional investigation of this sample (Dickson et al., 2014) identified impaired performance on a composite verbal memory index that included both verbal word-list learning and story memory. This impairment was specific to children with high familial loading (i.e., those with at least one first- or two second-degree affected relatives) relative to TD peers; it was not observed among children with lower familial loading (i.e., with a single second-degree affected relative only) or among ASz children. However, use of a composite index might obscure variable disruptions across verbal memory functions, and thereby restrict capacity to guide early targeted cognitive remediation and refined risk detection (Cirillo and Seidman, 2003). Accordingly, the present study sought to examine dissociable indices of verbal learning performance on a list learning task, encompassing both encoding and consolidation processes, among children with different profiles of risk for schizophrenia, to characterise specific and/or common verbal learning impairments across these risk profiles during a putative premorbid phase of schizophrenia.

The lack of impairment observed previously on the composite verbal memory index among ASz children relative to their TD peers (Dickson et al., 2014) might also signify heterogeneity of risk within this group, related to the persistence versus transience of their symptoms into adolescence. Persistence of PLEs and internalising/externalising psychopathology during adolescence has been associated with increased risk for adverse mental health outcomes including psychosis (Colman et al., 2007; Dominguez et al., 2011; Kalman et al., 2019; Kim-Cohen et al., 2003). Longitudinal follow-up of the CHADS sample allowed for novel comparison of whether verbal learning performance that was assessed between the ages of 9–12 years may differ among ASz children whose internalising/externalising psychopathology and PLE symptoms later remit versus persist during adolescence (Laurens et al., 2020).

Notwithstanding the lack of impairment observed previously for ASz relative to TD children on the composite verbal learning measure, in the context of the broader literature indicating verbal list learning deficits among CHR youth, we hypothesised that children demonstrating any profile of risk for schizophrenia (i.e., family history or antecedents) would demonstrate impairments of verbal learning/memory, spanning both encoding and consolidation processes, relative to their TD peers at age 9–12 years. We further predicted that such deficits would be greater among those with a higher risk loading (by familial history [FHx^H] or persistence of symptoms into adolescence [ASz^H]), than among children with lower risk loading (by family history [FHx^L] or remission of symptoms in adolescence [ASz^L]).

2. Method

2.1. Participants

Children aged 9–12 years displaying the antecedent triad (ASz) and typically developing children (TD) were identified by questionnaire-based screening of a community sample attending primary (elementary) school in Greater London, United Kingdom (Laurens and Cullen, 2016). Questionnaires were completed by children at school, and at home by the child's primary caregiver. FHx children were recruited via either the school-based questionnaire administration (by caregiver report of family history of mental illness; with diagnoses later confirmed using the Family Interview for Genetic Studies [FIGS]; Maxwell, 1992) or as relatives of patients with schizophrenia/schizoaffective disorder who were receiving treatment within the South London and Maudsley National Health Service Foundation Trust (patients with a relative aged 9–12 years were identified by medical record review and the families approached via the patient's care worker). FHx^H children were those with at least one first- or two second-degree affected relatives with schizophrenia/schizoaffective disorder, and FHx^L were those with one second-degree relative only.[1] For all children, affected relatives came from the same parental line.

TD children presented none of the triad of antecedents and had no family history of schizophrenia in first-, second-, or third-degree relatives (confirmed using the FIGS). ASz children were those reporting: (i) at least one child-reported "certainly true" response on the 9-item Psychotic-Like Experiences Questionnaire for Children (PLEQ-C; Gutteridge et al., 2020; Laurens et al., 2007, 2012); (ii) a score in the clinical range (approximately top tenth centile on UK population norms) of the child-reported Emotional Symptoms, and/or caregiver-reported Conduct Problems, Hyperactivity-Inattention, or Peer Relationship Problems subscales of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001); *and* (iii) a caregiver-reported delay/abnormality in speech and/or motor development (Laurens et al., 2007). ASz children who continued to demonstrate PLEs and SDQ psychopathology at questionnaire reassessments completed approximately 2 and 4 years after the initial screening formed the persistent group (ASz^H), while ASz children whose symptoms remitted following screening formed the remitting group (ASz^L). Specifically, ASz^H children were those who, at either follow-up assessment, presented a score in the clinical range, by child or caregiver report, on any of the four SDQ psychopathology subscales *and* at least one child-reported "somewhat true" or "certainly true" response on the PLEQ-C.

From 1343 children and caregivers who completed questionnaire screening via schools, 9.5% of the children ($n = 128$) met ASz criteria and 22.5% ($n = 302$) met TD criteria. Among 1204 children who were screened for family history by questionnaire, 2.8% ($n = 34$) had a relative with schizophrenia/schizoaffective disorder, and 36 FHx children were identified via medical record review. From 182 families invited to participate in the baseline research assessment (58 ASz, 43 FHx, 81 TD), 40.7% declined. The 108 participants who completed the verbal learning assessment comprised 45 TD, 16 ASz^H, 16 ASz^L, 16

[1] Genetic liability scores, based on the degree of relatedness and the number of affected relatives (Campbell et al., 2010), differentiated children with and without first-degree affected relatives, with the exception of two children with two affected second-degree relatives whose liability scores were intermediate between those groups (Dickson et al., 2014). The FHx^H group thus included 8 children with one first-degree affected relative only (6 of whom had relatives in the maternal line), 6 children with one first- and one second-degree relative (all in the maternal line), and 2 children with two second-degree relatives and multiple affected relatives of more distal relation (1 in the maternal line). The FHx^L group included 13 children with one second-degree affected relative only (8 in the maternal line) and 2 with one second- and one third-degree relative (both in the paternal line).

FHx^H, and 15 FHx^L. Six children meeting both FHx and ASz criteria were assigned to FHx groups, including 2 FHx^H (one of whom was ASz^H) and 4 FHx^L (three of whom were ASz^H). All children were educated in English, and fluent speakers of English.

2.2. Procedure

The study received ethical approval from the Joint South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry Research Ethics Committee. Written informed assent and consent for participation was obtained from children and caregivers, respectively.

Children completed the verbal learning assessment at age 9–12 years as part of a larger battery of neurocognitive and other assessments. The derivation of the ASz^H versus ASz^L groups used PLEQ-C and SDQ data from reassessments completed with participants approximately 2 and 4 years later.

2.3. Measures

Age of the child on the date of neuropsychological assessment was computed as a continuous variable. Caregivers reported participants' gender, ethnicity, and parental socioeconomic status (highest occupation of either parent, according to the UK National Statistics Socioeconomic Classification [Office of National Statistics, 2010]). Ethnicity was dichotomized for analyses as white versus other, and socioeconomic status coded into three levels of Social Class: (i) professional occupations; (ii) managerial and technical occupations; and (iii) skilled and unskilled manual occupations and unemployed.

Verbal learning was assessed using the word-list learning task from the Wide Range Assessment of Memory and Learning version 2 (Sheslow and Adams, 2003). This task tests the immediate recall of a list of 16 common, single syllable words, presented in four trials using a consistent order of presentation. Six outcome measures (detailed in Table 1) were computed: (i) *total recall*; (ii) *trial 1 recall*; (iii) *learning score*; (iv) *intrusions*; (v) *total words lost*; and (vi) *serial position patterns*. Full-scale IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), representing the sum of standardised scores obtained on four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning.

Table 1
Verbal learning outcome measures.

Measure	Description
Total recall	Total number (sum) of words recalled correctly across the four trials, excluding intrusions and repetitions (score range: 0–64).[a]
Trial 1	Sum of words recalled correctly immediately following the participant's first exposure to the word list (score range: 0–16).[a]
Learning score	The difference between the number of words recalled at trial 4 and the number of words recalled at trial 1 (score range: 0–16).[a]
Intrusions	The frequency with which the participant provided a word that was not on the list, summed across all trials (1 through 4).[a]
Total words lost	The number of times the participant failed to recall a word on a trial that they had recalled on the previous trial.[b]
Serial position patterns	The pattern of recall across words within the list, represented by the total number of words recalled correctly in each quartile of the presented list (first, second, third, and fourth quartiles), summed across the four trials (score range: 0–16 within each quartile).[c]

[a] Measure derived from the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2; Sheslow and Adams, 2003).

[b] Derived from a measure of *words omitted* by Blachstein and Vakil (2016).

[c] Replicates the division of words on the California Verbal Learning Test (CVLT; Delis et al., 1987) by Pflueger et al. (2018).

2.4. Statistical analyses

Analyses were conducted using the Statistical Package for Social Sciences (version 27.0). Univariate analyses of variance (ANOVA) and chi-square/Fisher's Exact tests of independence were used to identify group differences (FHx^H, FHx^L, ASz^H, ASx^L, TD) on demographic indices. Separate one-way between-subjects ANOVAs were conducted on the first five verbal learning indices. Where the omnibus test indicated a significant group effect, Fisher Least Significant Difference (LSD) bootstrapped (bias-corrected and accelerated: BCa) post hoc comparisons were applied to identify between-group differences. To compare the five groups on the effect of word list position (by quartiles), a mixed repeated-measures ANOVA was conducted, employing bootstrapped (BCa) LSD post hoc analyses to follow-up quartile effects.

To control the risk of type 1 error across the six ANOVAs conducted, we adopted a Bonferroni adjusted omnibus alpha of <0.014, which accounted for a mean correlation of 0.3 between measures (Supplementary Table S1; https://www.quantitativeskills.com/sisa/calculations/bonfer.htm). The magnitude of between-group differences were characterised using Cohen's *d* effect size (small 0.20, medium 0.50, large 0.80) and partial eta-squared (small 0.01, medium 0.06, large 0.14) (Cohen, 1988).

To remove the potential confounding effects of demographic factors in the relationship of participant group with the outcomes, analyses were repeated with the inclusion, as a covariate, of any demographic factor that related significantly both to group assignment and to the outcome.

Correlation analyses were conducted within each group to characterise associations between total recall (the verbal learning measure most commonly employed with schizophrenia and high-risk samples) and the other verbal learning measures. Further, because controlling IQ in studies of schizophrenia (or schizophrenia risk) potentially removes from the data a feature of the core pathophysiology of this illness (Meehl, 1971), our primary analyses were conducted without covarying IQ. Instead, correlations between IQ and verbal learning indices were examined within each group to determine whether specific deficits in verbal learning were independent of a generalised cognitive deficit. Secondary analyses, repeating the primary analyses with IQ as a covariate, are reported in Supplementary materials.

3. Results

Table 2 presents the demographic characteristics of the five groups (FHx^H; FHx^L; ASz^H; ASz^L; TD). No significant differences were identified between these groups on age, sex, or social class. Groups differed significantly on ethnicity and full-scale IQ, with TD children more likely to be white than all other groups, and both ASz groups more likely to be white than the FHx groups. TD children demonstrated significantly higher IQ scores than all risk groups, while FHx^H children demonstrated significantly poorer IQ performance than all other risk groups.

Table 3 presents the results of the one-way ANOVAs evaluating differences among the five groups on the first five verbal learning measures. Significant main effects of group status were observed on three measures, namely total recall and learning score (encoding) and total words lost (consolidation). Bootstrapped (BCa) LSD post hoc comparisons revealed distinct between-group differences across the three indices, though on all three measures, poorest performance was consistently by the FHx^H group.[2]

With respect to performance of the various risk groups relative to TD

[2] As a sensitivity test, analyses were repeated with the family history groups instead differentiated according to the presence of a first-degree affected relative. That is, the two children with two second-degree affected relatives were reassigned to the FHx^L group. Omnibus findings were the same, and the magnitude of post hoc effects changed minimally.

Table 2
Demographic indices for participant groups.

	FHx^H (n = 16)	FHx^L (n = 15)	ASz^H (n = 16)	ASz^L (n = 16)	TD (n = 45)	Statistic
	n	*n*	*n*	*n*	*n*	
Sex (male)	9 (56)	5 (33)	11 (69)	10 (63)	21 (47)	$\chi^2(4)$ = 5.23, p = .265
Ethnicity						*Fisher's Exact Test*, p < .001
White	3 (19)	3 (20)	7 (44)	8 (50)	33 (73)	
Other	13 (81)	12 (80)	9 (56)	8 (50)	12 (27)	
Social class[a]						*Fisher's Exact Test*, p = .147
Professional	2 (13)	5 (36)	3 (20)	4 (25)	21 (47)	
Managerial/ technical	6 (40)	7 (50)	9 (60)	8 (50)	18 (40)	
Skilled/ unskilled/ unemployed	7 (47)	2 (14)	3 (20)	4 (25)	6 (13)	
Full-scale IQ	92 (14)	106 (15)	105 (13)	102 (11)	115 (15)	$F(4,102)$ = 8.36, p < .001[b] TD > FHx^H, d = 1.62 TD > FHx^L, d = 0.65 TD > ASz^H, d = 0.74 TD > ASz^L, d = 0.90 FHx^H < ASz^H, d = −0.88 FHx^H < FHx^L, d = −0.98 FHx^H < ASz^L, d = −0.72
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age at assessment (years)	10y,11 m (14 m)	11y,2 m (13 m)	10y,9 m (9 m)	10y,11 m (11 m)	11y,0 m (10 m)	$F(4,101)$ = 0.40, p = .812

Note: Cohen's d: small 0.20, medium 0.50, large 0.80.
n = number of participants, sd = Standard Deviation, y = years, m = months, FHx^H = high family loading, FHx^L = low family loading, ASz^H = continuing antecedent symptoms, ASz^L = discontinuing antecedent symptoms, TD = typically developing.
[a] Social class based on highest occupational level of either parent.
[b] With significant post-hoc bootstrap tests (bias-corrected and accelerated).

children on these three indices, FHx^H and ASz^H children recalled fewer words in total and lost significantly more words between trials, while FHx^H and FHx^L children learned significantly fewer words between trials 1 and 4. The performance of ASz^L children did not differ from TD children on any measure.

Among the risk groups, the FHx^H group recalled significantly fewer words in total than all other groups and lost significantly more words between trials than both FHx^L and ASz^L children. FHx^H and FHx^L both learned significantly fewer words between trial 1 and trial 4 than ASz^L children. ASz^H recalled significantly fewer words in total than ASz^L children, and lost significantly more words between trials than FHx^L. Detail on all post hoc comparison results is provided in Supplementary Table S2.

The repeated-measures mixed design ANOVA, employing Greenhouse-Geisser correction, revealed a significant and large main effect for quartile position, $F(2.93,302.06) = 42.30$, $p < .001$, $\eta_p^2 = 0.29$, but no significant interaction between group and quartile, $F(11.73,302.06) = 1.03$, $p = .421$, $\eta_p^2 = 0.04$. Bootstrapped (BCa) post hoc comparisons revealed significant differences in performance between all quartiles except the second and third (Fig. 1), with words in the first quartile recalled most frequently, followed by those in the fourth.

Ethnicity was significantly associated with total recall, trial 1, and intrusion measures, but re-analysis of these outcomes with ethnicity as a covariate revealed unchanged results.

Within the TD group, total recall correlated significantly with three of the four other verbal learning indices, excepting learning score (Supplementary Table S1). In contrast, for the risk groups, consistent correlations were observed only between total recall and trial 1 score. Full-scale IQ correlated with selected measures only, most prominently with total recall (Supplementary Table S3), where the maximal correlation (Pearson's $r = 0.55$) was apparent in the TD group. Correlations between IQ and verbal learning measures were predominantly non-significant among the risk groups.

In supplementary analyses controlling for IQ, all findings became non-significant at the Bonferroni adjusted omnibus alpha (<0.014; see Supplementary Table S4).

4. Discussion

This study of verbal learning/memory among children aged 9–12 years identified different patterns of impairment according to risk profile and learning measure. Cognitive function among ASz children distinguished those whose symptoms persisted (ASz^H) verses remitted (ASz^L) during follow-up: the ASz^L group showed no learning deficits relative to their TD peers, whereas ASz^H children showed deficits of total recall and total words lost (i.e., encoding and consolidation) relative to TD. Among children with a higher degree of familial loading for schizophrenia (FHx^H), deficits relative to both TD and ASz^L peers encompassed total recall, learning score, and total words lost. Children with a lower familial loading (FHx^L) evidenced limited impairment of encoding only, specific to learning score, relative to both TD and ASz^L children. Thus, total words recalled and lost distinguished those with higher risk load (either by family history or persistent antecedent symptomology, though total recall deficits were more pronounced in FHx^H than in ASz^H children), whereas FHx children, irrespective of risk load, demonstrated impairment in learning between trials 1 and 4.

These findings suggest a more nuanced picture, dependent on risk profile and learning measure, than that described previously in a cross-sectional study of adolescents aged 14–19 years (mean ~ 17 years), where poorer neurocognitive functioning differentiated those with genetic risk from those with clinical (symptomatic) risk (Myles-Worsley et al., 2007), and studies indicating greater cognitive impairment among young first-degree than second-degree relatives of schizophrenia patients (Dickson et al., 2014; Keshavan et al., 2010). In the present study, FHx^H children evidenced the greatest magnitude of impairment relative to TD children on each of the three verbal learning indices for which significant group differences were identified, but only on total recall did their performance differ significantly from that of ASz^H children. Both of the high-risk profiles (FHx^H and ASz^H) showed encoding and consolidation deficits relative to TD children. On total recall, the large effect size demonstrated for FHx^H (Cohen's d −1.39) and moderate effect size for ASz^H (Cohen's d −0.65) relative to TD children ranged up to the magnitude of group differences revealed by meta-analyses comparing

Table 3
Comparison of group performance on verbal learning measures.

	FHx^H ($n = 16$)	FHx^L ($n = 15$)	ASz^H ($n = 16$)	ASz^L ($n = 16$)	TD ($n = 45$)	ANOVA			
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F (4, 103)	p	η_p^2	Significant post-hoc tests (BCa), Cohen's d
Total recall	26.50 (9.46)	35.07 (7.94)	32.69 (10.40)	38.81 (7.10)	38.09 (7.59)	6.84	<0.001	0.21	$FHx^H < TD$, $d = -1.39$ $FHx^H < ASz^L$, $d = -1.48$ $FHx^H < FHx^L$, $d = -1.03$ $FHx^H < ASz^H$, $d = -0.74$ $ASz^H < TD$, $d = -0.65$ $ASz^H < ASz^L$, $d = -0.74$
Trial 1	4.81 (1.97)	6.47 (2.13)	5.69 (2.24)	5.94 (1.77)	6.13 (1.73)	1.85	0.126	0.07	
Learning score	3.38 (3.30)	3.80 (2.76)	4.88 (2.80)	6.31 (2.18)	5.96 (2.58)	4.44	0.002	0.15	$FHx^H < TD$, $d = -0.95$ $FHx^H < ASz^L$, $d = -1.09$ $FHx^L < TD$, $d = -0.80$ $FHx^L < ASz^L$, $d = -0.93$
Intrusions	2.88 (3.30)	3.00 (2.70)	1.50 (2.10)	1.31 (2.02)	1.76 (2.39)	1.66	0.166	0.06	
Total words lost	6.75 (2.77)	4.13 (0.74)	6.38 (3.30)	5.00 (2.76)	4.60 (2.29)	3.85	0.006	0.13	$FHx^H > TD$, $d = 0.87$ $FHx^H > ASz^L$, $d = 0.71$ $FHx^H > FHx^L$, $d = 1.06$ $ASz^H > TD$, $d = 0.72$ $ASz^H > FHx^L$, $d = 0.91$

Note. n = number of participants, M = mean, SD = standard deviation, FHx^H = high family loading, FHx^L = low family loading, ASz^H = continuing antecedent symptoms, ASz^L = discontinuing antecedent symptoms, TD = typically developing; BCa = bootstrap bias-corrected and accelerated tests; η_p^2: small 0.01, medium 0.06, large 0.14; Cohen's d: small 0.20, medium 0.50, large 0.80.

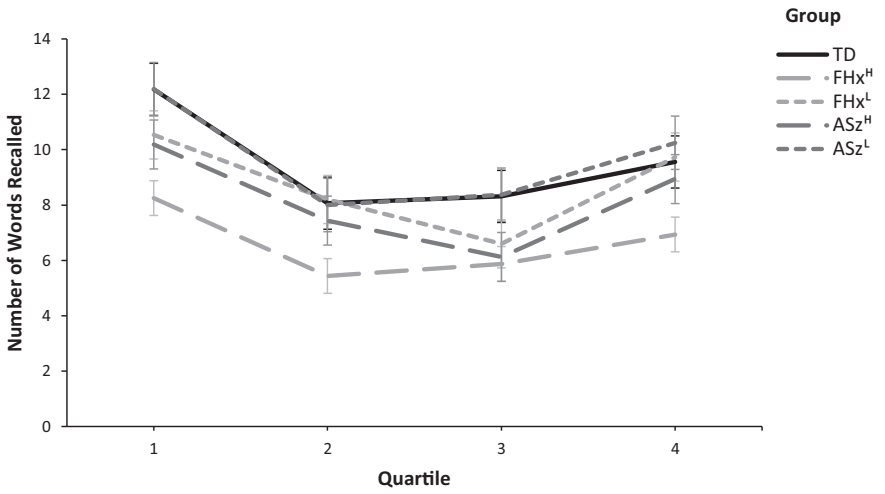

Fig. 1. Mean recall (and standard error) by participant group across the four quartiles of the word list.
Note. Error bars represent 1 standard error; TD = typically developing, FHx^H = high family loading, FHx^L = low family loading, ASz^H = continuing antecedent symptoms, ASz^L = discontinuing antecedent symptoms.

healthy controls against patients with chronic schizophrenia (Cohen's d −1.41) (Heinrichs and Zakzanis, 1998), first-episode patients (Cohen's d −1.20) (Mesholam-Gately et al., 2009), and clinical high-risk individuals (Hedges' g −0.50 to −0.86) (Catalan et al., 2021). Thus, the recall deficit observed in those later phases of illness was also present by middle childhood and (along with the words lost index) demarcated a high degree of vulnerability (genetic or clinical) for this disorder.

Differentiation of ASz children into those whose antecedent symptomology persisted (ASz^H) versus remitted (ASz^L) subsequent to the verbal learning assessment appears to account for important heterogeneity in performance among children assessed while symptomatic at age 9–12 years, with early learning deficits specific to ASz^H. The hypothesised differentiation of FHx children by degree of familial loading ($FHx^H > FHx^L$) was true of the total recall and total words lost indices specifically, but not learning score (a separate measure of encoding). All children with a family history of schizophrenia (both FHx^H and FHx^L) displayed impaired performance on this latter index relative to both TD and ASz^L children. Impaired learning scores among FHx children may reflect inherited abnormalities within hippocampal structures that are common among relatives of patients with schizophrenia (Keshavan et al., 2002), yet appear to be unrelated to psychotic symptoms (Lawrie et al., 2001). As such, poor learning scores may reflect a cognitive vulnerability among relatives that may not necessarily index likelihood of progression to psychosis.

Group differences were not detected on immediate recall on the first list learning trial, intrusion errors, or serial position patterns of learning, suggesting potential specificity in the encoding and consolidation processes that are disrupted during middle childhood in at-risk children. Similarly intact serial position patterns have been reported among first-episode patients and clinical high-risk youth (Pflueger et al., 2018). However, a larger sample might have revealed subtle differences in group performance on immediate recall and/or intrusion errors. Significantly poorer immediate recall (on trial 1) compared to controls has been observed among chronic schizophrenia and CHR patients (Frommann et al., 2011; Laes and Sponheim, 2006), and Cannon et al. (2000b) identified frequent intrusion errors among unaffected adult twins (mean age ~ 49 years) of schizophrenia patients who had passed beyond the age of maximal risk for psychosis. Immediate verbal recall

may lack equivalent sensitivity for distinguishing schizophrenia risk during middle childhood. Future studies in larger samples might examine whether immediate recall deficits emerge more prominently closer to illness onset, and whether intrusion errors may relate to genetic risk for schizophrenia but not risk for transition to psychosis.

Covarying IQ nullified differences between groups on verbal learning indices, masking the capacity of verbal learning indices to demarcate differential impairments across risk profiles in the context of this general cognitive impairment common to all risk groups. The different patterns of verbal learning impairments across risk profiles indicate that verbal learning might index susceptibility to illness more sensitively than general cognitive impairment during middle childhood, and distinguish risk of symptom continuation among children presenting antecedents in a way that general cognitive impairment (IQ) does not.

The findings of the present study must be interpreted in light of various limitations. Despite the utility of using multiple indices to distinguish different profiles of impairment according to risk type (family history vs. antecedents) and degree (higher vs. lower risk loading), the verbal learning task employed is unavoidably multidimensional and performance relies, to an extent, on other cognitive processes such as attention, processing speed, working memory, motivation, and language comprehension (Cirillo and Seidman, 2003; Dickinson and Gold, 2008). We note also that the standardised IQ scores reported reflect population norms derived on a U.S. sample rather than a U.K. population; thus, the reported scores provide a useful means to compare performance within this sample, but may not accurately index IQ scores of the sample relative to the U.K. population. As discussed, the small participant group sizes may have limited our capacity to detect subtle between-group differences on several learning indices. The study also could not demarcate deficits in children meeting both FHx and ASz criteria (children at familial risk whom are also demonstrating the three antecedents), given their small number ($n = 6$). These children were assigned to FHx groups on the basis that family history is the most replicated risk factor for schizophrenia; consequently, the ASz groups did not represent all children presenting the antecedents of schizophrenia. It would be interesting to examine whether the presence of antecedents among children with family history explains variation within this group in a different manner to degree of relatedness, but this additional analysis was not pursued in the context of our small group sizes and multiple tests. We also acknowledge that internalising and externalising psychopathology (Copeland et al., 2009), PLEs (Fisher et al., 2013), and neurocognitive impairments (Bora and Özerdem, 2017) are antecedents for a broad range of adult psychopathology. Accordingly, ASz children may progress to schizophrenia, other psychoses, or other psychiatric disorders, while others (particularly ASz^{L}) are likely to experience no adult disorder. Further follow-up of the sample is needed to establish the predictive utility of these verbal learning impairments for later illness outcomes. We also did not consider other influential factors, such as trauma, other adversities, and drug exposure, which may contribute to the development of schizophrenia differently for children with genetic versus clinical risk profiles (Murray et al., 2017). Owing to the small sample size, in concert with the number of groups and analyses performed, replication in a larger sample is needed to validate these findings.

This study identified impairments of verbal learning/memory during middle childhood among putatively at-risk children that varied according to risk profile and learning measure. Verbal learning deficits have demonstrated potential as a candidate marker of risk for transition to psychosis among CHR youth (Addington et al., 2017; Carrión et al., 2018; Seabury and Cannon, 2020). Further follow-up in this sample may help elucidate the utility of childhood verbal learning deficits to predict eventual psychosis and improve early detection initiatives. Given impaired verbal learning is associated with poorer functioning (Bora et al., 2014) and more rapid transition to illness (Seidman et al., 2010), targeting verbal learning may prove pertinent to early intervention initiatives beginning in childhood. Cognitive remediation training programs impart modest improvements in psychosocial functioning (Lee et al., 2013) and verbal learning and memory among patients with schizophrenia (Revell et al., 2015; Wykes et al., 2011) and CHR individuals (Glenthøj et al., 2017). Earlier intervention while the brain is still undergoing significant maturation might facilitate longer term benefits and increase the likelihood that skills may be transferred to other settings.

CRediT authorship contribution statement

Author KRL designed the study. Author EJC managed the literature searches and statistical analyses. Authors AEC and HD collected, entered, and cleaned data. Author EJC wrote the first draft of the manuscript, and author KRL provided critical revision. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

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