Journal of Affective Disorders 332 (2023) 318–326

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Working memory heterogeneity from age 7 to 11 in children at familial high risk of schizophrenia or bipolar disorder– The Danish High Risk and Resilience Study

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ARTICLE INFO

Keywords:
Working memory
Heterogeneity
Familial high risk
Schizophrenia
Bipolar disorder

ABSTRACT

Background: Despite the genetic overlap between bipolar disorder and schizophrenia, working memory impairments are mainly found in children of parents with schizophrenia. However, working memory impairments are characterized by substantial heterogeneity, and it is unknown how this heterogeneity develops over time. We used a data-driven approach to assess working memory heterogeneity and longitudinal stability in children at familial high risk of schizophrenia (FHR-SZ) or bipolar disorder (FHR-BP).

Methods: Based on the performances on four working memory tasks by 319 children (FHR-SZ, N = 202, FHR-BP, N = 118) measured at age 7 and 11, latent profile transition analysis was used to test for the presence of subgroups, and the stability of subgroup membership over time. Population-based controls (VIA 7, N = 200, VIA 11, N = 173) were included as a reference group. The working memory subgroups were compared based on caregiver- and teacher ratings of everyday working memory function, and dimensional psychopathology.

Results: A model with three subgroups characterized by different levels of working memory function (an impaired subgroup, a mixed subgroup, and an above average subgroup) best fitted the data. The impaired subgroup had the highest ratings of everyday working memory impairments and psychopathology. Overall, 98 % (N = 314) stayed in the same subgroup from age 7 to 11.

Conclusion: Persistent working memory impairments are present in a subset of children at FHR-SZ and FHR-BP throughout middle childhood. Attention should be given to these children, as working memory impairments influence daily life, and may serve as a vulnerability marker of transition to severe mental illness.

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https://doi.org/10.1016/j.jad.2023.04.011
Received 30 August 2022; Received in revised form 30 March 2023; Accepted 7 April 2023
Available online 12 April 2023
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1. Introduction

Schizophrenia and bipolar disorder are severe mental disorders with high heritability (Gottesman et al., 2010; Wray and Gottesman, 2012), and a substantial genetic overlap (The International Schizophrenia Consortium et al., 2009; Craddock et al., 2006). Working memory impairments are well-established in individuals diagnosed with schizophrenia, and to a lesser degree in individuals with bipolar disorder (Bortolato et al., 2015; Soraggi-Frez et al., 2017). Due to heritability, relatives of individuals with schizophrenia or bipolar disorder have an increased risk of being diagnosed with the same or another severe mental disorder (Rasic et al., 2013). As working memory is proposed as one cognitive function, that is associated with an increased risk of transitioning to psychosis (Reichenberg et al., 2010; Seidman et al., 2013) studying working memory in children of parents with these disorders represents a unique opportunity to gain knowledge about working memory impairments as a potential vulnerability marker of severe mental disorders.

Working memory is an essential cognitive function, including verbal and spatial short-term storages, as well as a central executive component that enables manipulation of the stored material (Baddeley, 2003). Working memory is important to everyday life and is predictive of academic performance and social learning (Eriksson et al., 2015; Park and Gooding, 2014). The development of working memory is characterized by a continuous increase in ability, and full working memory capacity is expected to be reached in late adolescence/early adulthood (Eriksson et al., 2015). In individuals who are later diagnosed with psychosis, working memory development has been characterized by a lag when compared to controls (Mollon et al., 2018; Reichenberg et al., 2010). While working memory impairments in schizophrenia and bipolar disorder have been found to include verbal as well as spatial modalities (Forbes et al., 2008; Soraggi-Frez et al., 2017), it has been suggested that premorbid neurocognitive impairments may be more pronounced in spatial modalities. Yet, different study methodologies limit what can be concluded as to whether verbal and spatial premorbid neurocognitive impairments are equally affected (Mollon and Reichenberg, 2018).

Working memory impairments are well-established in first-degree relatives and offspring of individuals with schizophrenia (Agnew-Blais and Seidman, 2013; De la Serna et al., 2020; Diwadkar et al., 2011), but not in relatives of individuals with bipolar disorder (Arts et al., 2007; Bora and Özerdem, 2017), nor in children and adolescents of parents with bipolar disorder (De la Serna et al., 2020; Diwadkar et al., 2011). A two-year follow-up study of children between ages 6 to 17 years found developmental stability in working memory function in children at familial high risk of schizophrenia or bipolar and concluded that the early impairments seen in children at familial high risk of schizophrenia remained stable over time (De la Serna et al., 2020). These findings are in line with previous results from the cohort included in the present study (The Danish High Risk and Resilience Study - VIA), where children at familial high risk of schizophrenia (FHR-SZ), but not children at familial high risk of bipolar disorder (FHR-BP), showed stable working memory impairments from age 7 to 11 (Knudsen et al., 2022). However, these results were based on group-level analyses, which might mask individual differences in working memory function - with some children experiencing serious problems, while others have little or no problems.

Recently, person-centered approaches focusing on the heterogeneity of cognitive abilities in schizophrenia and bipolar disorder have emerged (Bechi et al., 2019; Bora, 2016; Carruthers et al., 2019; Green et al., 2019; Lim et al., 2021; Lima et al., 2019; Russo et al., 2017; Van Rheenen et al., 2017; Vaskinn et al., 2020). These studies have typically identified three (sometimes four) subgroups with distinct cognitive characteristics in or across schizophrenia and bipolar disorder: A relatively intact subgroup, an intermediate/mixed subgroup (sometimes split into two subgroups), and a globally impaired subgroup. A somewhat similar pattern has been reported in offspring of parents with schizophrenia or bipolar disorder (Bora et al., 2019; Valli et al., 2021), as well as in two previous studies conducted on the Danish High Risk and Resilience Study-cohort (Hemager et al., 2022; Knudsen et al., 2023). Intriguingly, these studies have shown that a subgroup of children and adolescents of parents with bipolar disorder do display working memory impairments, which demonstrates that the findings of intact working memory function in first-degree relatives of bipolar disorder may be concealed when doing analyses on a group-level (Arts et al., 2007; Bora and Özerdem, 2017). The majority of previous studies assessing neurocognitive heterogeneity in children at familial high risk of schizophrenia or bipolar disorder have been cross-sectional. As such, it remains unclear whether the established heterogeneity remains stable over time, which is important in the understanding of potential developmental trajectories. Further, these studies have in common that they have all examined working memory as part of a larger neurocognitive assessment, encompassing several neurocognitive domains at once (and not just working memory). Thus, it remains unknown whether similar heterogeneity applies when generating subgroups based on tasks targeting working memory function alone, which limits our understanding of the selectivity of neurocognitive heterogeneity (Carruthers et al., 2019).

1.1. Present study – objective and hypotheses

The objectives of the present study were twofold: First, at a cross-sectional level, we wanted to test for the presence of different working memory subgroups (based on four working memory tasks) and compare the subgroups based on caregiver and teacher ratings of everyday working memory ability and caregiver ratings of dimensional psychopathology. Second, taking a longitudinal perspective, we aimed to examine the transition between subgroups from age 7 to 11 and to explore the characteristics of those who remain in the same subgroup at both assessment times (i.e., 'stayers') and those who change subgroup membership from the first to the second assessment (i.e., 'movers'). Based on previous person-centered analyses, we expected to find three subgroups, characterized by different levels of working memory function. We also expected a higher representation of children at FHR-SZ in the most impaired subgroup compared to children at FHR-BP, while we expected a higher representation of children at FHR-BP in the least impaired subgroup compared to children at FHR-SZ. Based on previous studies of working memory development in individuals at risk of severe mental disorders, we hypothesized that most children would stay in the same subgroup over time whereas a subset of children would transition into a subgroup characterized by more working memory impairments (i.e., developmental lag).

2. Methods

This study is part of The Danish High Risk and Resilience Study – VIA, a longitudinal and nationwide cohort study of 522 children of parents with a diagnosis of schizophrenia, bipolar disorder, or neither of these disorders. The VIA study is detailed in Thorup et al. (2018) and Thorup et al. (2015), but will briefly be outlined below.

2.1. Participants

The participants in this study were 202 children at FHR-SZ and 120 children at FHR-BP identified through the Danish Civil Registration System (Pedersen et al., 2006) and The Danish Psychiatric Central Research Register (Mors et al., 2011). A population-based control group (PBC, N = 200) was included for comparison purposes. PBC was matched with children at FHR-SZ based on age, sex, and municipality. Children at FHR-BP were not matched but did not differ from the two other groups concerning age or sex distribution. All children were assessed at age 7 (i.e., the VIA 7 study), and again at age 11 (i.e., the VIA 11 study). At age 11, the retention rate was 89 % (465 children: FHR-SZ, N = 179, FHR-BP, N = 105, PBC, N = 181). Children were assessed with

neuropsychological tests, administered in quiet and structured surroundings either at a research facility or in the homes of the participants, by trained research nurses, psychologists, and medical doctors. Primary caregivers (defined as an adult living with the child, who knew the child very well at the time of assessment), and teachers (pointed out by the primary caregiver as the ones who had the closest relation to the child in the school setting) completed questionnaires about the child. All participants received written and/or oral information about the study before giving written consent to participate. The study was approved by the Danish Data Protection Agency and by the National Committee on Health Research Ethics (H-16043682).

2.2. Measures

All measures, chosen based on age-appropriateness and their previous use in research as well as clinical practice, were administered at both time points (i.e., at age 7 and 11). The data in the VIA 11 study were collected using REDcap (Harris et al., 2019; Harris et al., 2009).

2.3. Working memory tasks

Working memory tasks targeting verbal working memory were the Letter-Number Sequencing and the Arithmetic subtests from the Wechsler Intelligence Scale for Children (WISC IV, Wechsler, 2003) where higher scores represent better function. Working memory tasks targeting spatial working memory were Spatial Working Memory (SWM) and Spatial Span (SSP) from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Sahakian and Owen, 1992) where lower total errors on the SWM and longer span lengths of the SSP represent better function.

2.4. Questionnaires

The Working Memory subscale of The Behavior Rating Inventory of Executive Function (BRIEF, Gioia et al., 2010) completed by the primary caregiver and the teacher, independently, was used to assess the child's everyday working memory function. The subscale consists of 10 items (response categories: never (=1), sometimes (=2), and often (=3)) with higher scores indicating more perceived working memory impairments in the child. The total score on the Child Behavior Checklist School-Age version (CBCL, Achenbach and Rescorla, 2000) completed by the primary caregiver was used to assess the level of dimensional psychopathology in the child. Higher scores on the CBCL indicate more emotional and behavioral problems.

2.5. Data analyses

2.5.1. Data preparation

Outliers were recoded as missing (<0.5 %). In order to keep the original variation, all indicators were analyzed using raw scores (Johnson, 2021).

2.5.2. Latent profile transition analyses

The latent profile transition analysis (LPTA) had two steps: First, latent profile analyses were conducted based on scores from the SSP, the SWM, the Letter-Number Sequencing, and the Arithmetic tasks. The latent profile analyses were conducted independently at each wave (age 7 and 11) and across children at FHR-SZ and FHR-BP. Models with one to six profiles (i.e., number of possible subgroups) were run with all cross-class variances constrained to be equal, and within-class residual covariances not permitted. The estimator was Maximum Robust Likelihood, and to avoid solutions due to local maxima, 2500 sets of starting values were used initially, and 250 final stage optimizations. The best loglikelihood value was replicated. Fit statistics were applied to determine which model fitted the data best, including Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and adjusted Lo-Mendell-Rubin test (LMR-A). Entropy was also considered. Lower values on AIC and BIC indicate better model fit, but if the values continue to decrease when adding additional subgroups, the point of the largest decrease should be located to identify the model with the best fit (see recommendations by Johnson, 2021; Spurk et al., 2020). The LMR-A test compared the model to the neighboring model, and a non-significant *p*-value indicates that the model with one less subgroup should be accepted (Johnson, 2021). With regard to entropy, there is no clear recommendation for a cut-off, but an entropy above 0.60–0.80 has been suggested as appropriate (Spurk et al., 2020). To avoid over-extraction, the number of individuals across subgroups was also considered in the evaluation of the models (Berlin et al., 2014; Ram and Grimm, 2009).

Second, a transition analysis was conducted, in which the models that had the best fit in the preceding latent profile analyses were linked together. As such, the number of subgroups was pre-specified in the transition analysis, whereupon the LPTA provided information on most likely subgroup membership, estimations of mean and standard errors of the input variables for each profile, as well as the probability of transitioning between subgroups over time. Due to the development in working memory capacity as children grow older, it was not possible to test for measurement invariance over time using the traditional methods, since they assume equality in means over time (Johnson, 2021; Morin et al., 2016). Missing data were handled according to the full information maximum likelihood (Johnson, 2021).

2.5.3. Post-hoc analyses

For illustrative purposes, the estimated means of each subgroup were compared to the observed means of the PBC using independent *t*-tests. In Fig. 1, the scores were standardized using z-scores based on the mean and standard deviation of the PBC. Chi-square tests of independence or one-way ANOVAs were conducted to compare the distribution of age, sex, and high risk status, as well as the child's total score on the CBCL and the BRIEF working memory scale. An alpha level of 0.05 was used for all analyses. Multiple comparisons were adjusted using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) with a false-discovery rate of 5 %. Latent profile- and latent transition analyses were conducted using MPlus version 8.7 (Muthén and Muthén, 1998-2017), and the remaining analyses were conducted *using STATA version 16* (StataCorp, 2019).

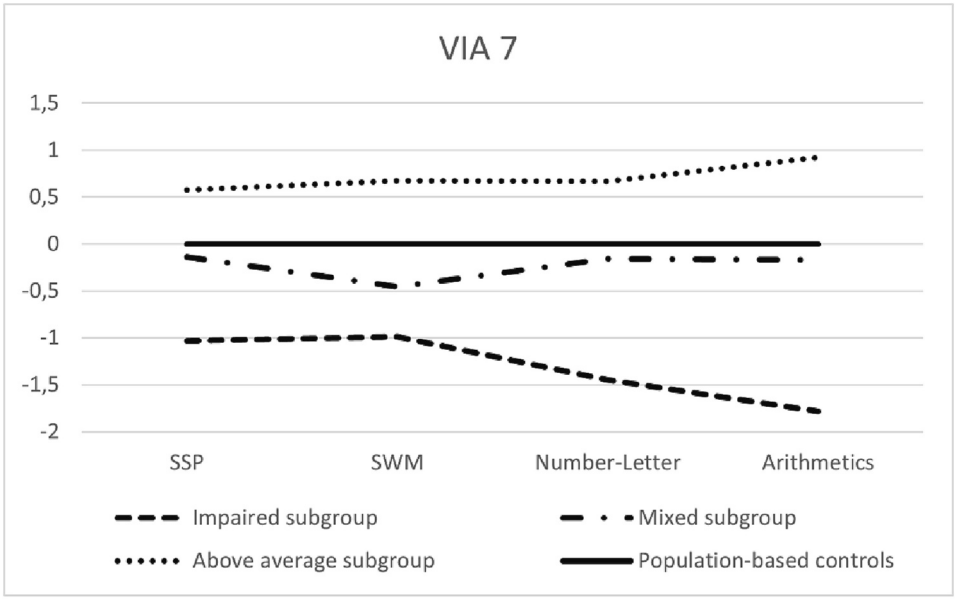
3. Results

In total, 317 (FHR-SZ, N = 199, FHR-BP, N = 118) children completed at least one of the working memory tasks at age 7 (Letter-Number sequencing, N = 313; Arithmetic, N = 313; SWM, N = 312; SSP, N = 312), and 271 children (FHR-SZ, N = 168, FHR-BP, N = 103) at age 11 (Letter-Number sequencing, N = 261; Arithmetic, N = 261; SWM, N = 266; SSP, N = 266). Based on the full information maximum likelihood estimation where data points are estimated using the available data from each time point, data on 319 children (FHR-SZ, N = 202, FHR-BP, N = 118) was used in the LPTA. Drop-out analyses are reported elsewhere (Knudsen et al., 2022).

3.1. Latent profile transition analysis

Fit statistics are detailed in Table 1. Based on the performance of children at FHR-SZ and FHR-BP on the four working memory tasks, a three-subgroup solution had a significant LMR-A at both time points. Further, the largest drop in AIC and BIC was observed when moving from a two- to a three-subgroup solution, and the entropy values of the three-subgroup solution were above 0.70. Finally, the three subgroups included a substantial number of participants. Based on this, and taking parsimony into consideration, a model with three subgroups was considered the 'best' model at both time points.

Subgroup 1 (VIA 7, N = 71; VIA 11, N = 76) was characterized by the lowest scores on all working memory measures. Consequently, this



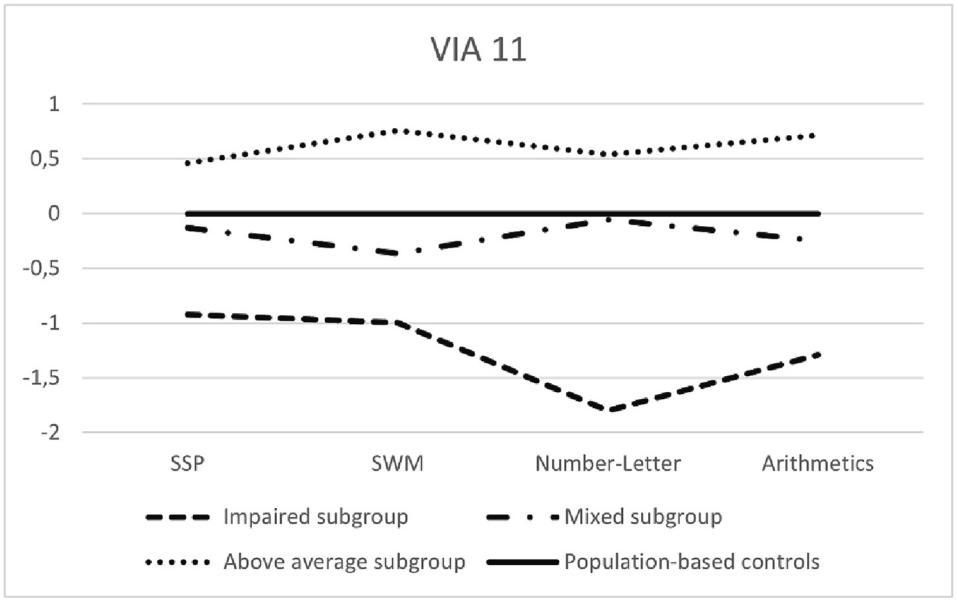


Fig. 1. Standardized scores on working memory tasks by working memory subgroups compared to population-based controls - age 7 and 11.
Note: SSP = Spatial Span (span length). SWM = Spatial Working Memory (total errors), Number-Letter = Number-Letter sequencing (total score), Arithmetics (total score). Subgroups based on latent profile transition analyses of working memory scores by 319 children at familial high risk of schizophrenia (N = 201) or bipolar disorder (N = 118). In this figure, scores were standardized using the mean and SD from the population-based controls (VIA 7, N = 200; VIA 11, N = 173).

Table 1
Latent profile analyses – cross-sectional fit statistics (age 7 and 11).

	No of profiles	AIC	BIC	Entropy	LMR-A	LMR-A *p*-value
VIA 7	1	6963.93	6994.01	–	–	–
Latent profile analysis N = 317	2	6725,84	6774.70	0.814	239.769	$p < .0001$
	3	6672.28	6739.94	0.722	61.429	$p = .0050$
	4	6653.41	6739.86	0.787	27.901	$p = .2825$
	5	6644.11	6749.35	0.811	18.653	$p = .4098$
	6	6635.56	6759.60	0.838	17.924	$p = .0347$
VIA 11	1	5969.05	5997.86	–	–	–
Latent profile analysis N = 271	2	5803.01	5849.83	0.858	169.973	$p = .0013$
	3	5747.85	5812.69	0.707	62.912	$p = .0209$
	4	5729.68	5812.53	0.701	27.196	$p = .3231$
	5	5721.94	5822.80	0.734	17.128	$p = .5527$
	6	5710.35	5829.22	0.785	20.850	$p = .0735$

Note: AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; LMR-A: Lo-Mendell-Rubin Adjusted Likelihood-Ratio Test. Fit statistics from latent profile analyses across children at familial high risk of schizophrenia (age 7, N = 199, age 11, N = 168) or bipolar disorder (age 7, N = 118, age 11, N = 103), using the performance on four working memory tasks as indicators.

subgroup was labeled 'the impaired subgroup'. Subgroup 2 (VIA 7, N = 153; VIA 11, N = 148) was characterized by low scores on some of the working memory measures (at age 7: SWM, at age 11: SWM, and Arithmetic), and was labeled 'the mixed subgroup'. Subgroup 3 (VIA 7, N = 95; VIA 11, N = 95) was characterized by the highest scores on all working memory measures and labeled 'the above average subgroup'. These labels were also supported by raw-score comparisons with population-based controls (see Supplementary Table 1), and for ease of interpretation, the standardized scores on each working memory task are visualized in Fig. 1.

As described above, it was not possible to test for measurement invariance. However, the similar number of profiles at each wave, and the similarities in terms of the degree of impairment/no impairment over time (see Fig. 1), suggest that the three subgroups at age 11 are an expression of a continuation of the three subgroups at age 7, with a change in means due to development in working memory capacity over time. As such, the three subgroups were considered to remain stable over time, which makes it possible to draw conclusions regarding the possible movers and stayers between subgroups from age 7 to 11. The results of the transition analysis showed that 98 % of the children (N = 314) stayed in the same subgroup over time (see Table 2). All children in the impaired subgroup and the above average subgroup at age 7 were in the equivalent subgroup at age 11, whereas five children (FHR-SZ, N = 3; FHR-BP, N = 2) transitioned from the mixed subgroup at age 7 to the impaired subgroup at age 11.

3.2. Subgroup characteristics

The characteristics of the three subgroups are depicted in Table 3. At age 7 and 11 there were no significant differences in the distribution of sex or age across the three subgroups. At both time points, there were significantly more children at FHR-SZ (26–28 %) in the impaired subgroup compared to children at FHR-BP (16–17 %), and more children at FHR-BP (37 %) in the above-average subgroup compared to children at FHR-SZ (25 %) (see Fig. 2). Caregiver and teacher ratings on the BRIEF working memory subscale did significantly differentiate between the three subgroups, with the impaired subgroups having the highest ratings of everyday working memory impairments, the above-average subgroup having the lowest ratings, and the mixed subgroup intermediate between the two. Likewise, all subgroups differed significantly on levels of dimensional psychopathology (as measured by the CBCL), with the impaired subgroup having the highest levels, and the above average subgroup having the lowest levels of psychopathology.

4. Discussion

In this study, LPTA was used to investigate working memory heterogeneity from age 7 to 11 across children at FHR-SZ or FHR-BP. We found three subgroups characterized by different levels of working memory function at both age 7 and 11, that is an impaired subgroup, a mixed subgroup, and an above average subgroup. Ratings of everyday working memory impairments and dimensional psychopathology were higher for children in the impaired subgroup. From age 7 to 11, almost all children remained in their respective working memory subgroup, suggesting that the heterogeneity in working memory is characterized by developmental stability in middle childhood.

Table 2
Transition probabilities between working memory subgroups from age 7 to 11.

VIA 7 subgroups	VIA 11 subgroups					
	Impaired subgroup		Mixed subgroup		Above average subgroup	
	N	*prob (95 % CI)*	N	*prob (95 % CI)*	N	*prob (95 % CI)*
Impaired subgroup	71	1.00 (1.00; 1.00)	0	0.00 (0.00; 0.00)	0	0.00 (0.00; 0.00)
Mixed subgroup	5	0.06 (0.01; 0.25)	148	0.95 (0.72; 0.99)	0	0.00 (0.00; 0.00)
Above average subgroup	0	0.00 (0.00; 0.00)	0	0.00 (0.00; 0.00)	95	1.00 (1.00; 1.00)

Note: prob.: probability of being classified into a subgroup at age 11 (i.e., VIA 11) based on subgroup-membership at age 7 (i.e., VIA 7). Transition probabilities from a latent profile transition analysis across children at familial high risk of schizophrenia (N = 202) or bipolar disorder (N = 118) at age 7 and 11, using the performance on working memory tasks as indicators.

Table 3
Characteristics of working memory subgroups at age 7 and 11 in children at familial high risk of schizophrenia or bipolar disorder.

	Impaired subgroup	Mixed subgroup	Above-average subgroup	Overall comparison *p*-value	
VIA 7, total n = 319	n = 71	n = 153	n = 95		
Female (%)	30 (42.25 %)	71 (46.41 %)	47 (49.47 %)	.6532[b]	
Age, mean (SD)	7.84 (0.25)	7.84 (0.21)	7.87 (0.18)	.5587[a]	
FHR-SZ (%)	53 (26.37 %)	97 (48.26 %)	51 (25.37 %)	**.0215**[b]	
FHR-BP (%)	18 (15.25 %)	56 (47.46 %)	44 (37.29 %)		
CBCL total score, mean (SD)	31.97 (22.59)	24.78 (20.08)	22.78 (19.11)	**.0138**[a]	1 > 2 > 3
Caregiver, BRIEF-WM total score, mean (SD)	18.81 (5.09)	16.64 (4.66)	14.50 (3.86)	**<.0001**[a]	1 > 2 > 3
Teacher BRIEF-WM total score, mean (SD)	18.73 (5.52)	16.04 (5.42)	12.97 (4.04)	**<.0001**[a]	1 > 2 > 3
VIA 11. total n = 319	n = 76	n = 148	n = 95		
Female (%)	33 (43.42 %)	68 (45.95 %)	47 (49.47 %)	.7246[b]	
Age, mean (SD)	11.94 (0.29)	11.95 (0.24)	11.96 (0.24)	.9025[a]	
FHR-SZ (%)	56 (27.86 %)	94 (46.77 %)	51 (25.37 %)	**.0263**[b]	
FHR-BP (%)	20 (16.95 %)	54 (45.76 %)	44 (37.29 %)		
CBCL total score, mean (SD)	33.95 (22.45)	20.76 (19.61)	17.85 (18.30)	**<.0001**[a]	1 > 2 > 3
Caregiver BRIEF-WM total score, mean (SD)	19.71 (5.23)	15.95 (4.98)	14.05 (3.44)	**<.0001**[a]	1 > 2 > 3
Teacher BRIEF-WM, total score, mean (SD)	19.44 (5.61)	15.08 (5.34)	11.75 (2.60)	**<.0001**[a]	1 > 2 > 3

Note: BRIEF-WM: the Behavior Rating Inventory of Executive Function – working memory subscale. FHR-SZ: Familial high risk of schizophrenia. FHR-BP: Familial high risk of bipolar disorder. CBCL: Child Behavior Checklist.
Multiple comparisons were adjusted for using the Benjamini-Hochberg procedure, with a false-discovery rate of 5 %. *p*-Values marked with bold were considered statistically significant.
[a] One-way ANOVA.
[b] Chi-square test.

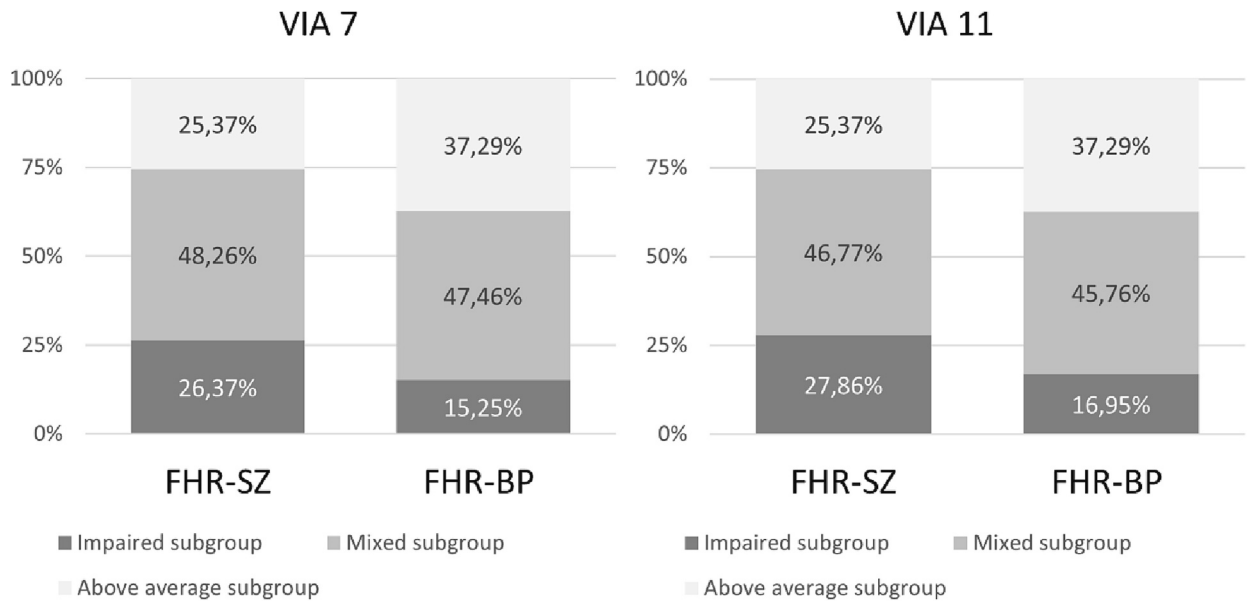


Fig. 2. Distribution of children at familial high risk of schizophrenia or bipolar disorder in the working memory subgroups - age 7 and age 11.
Note: FHR-SZ = Familial high risk of schizophrenia. FHR-BP = Familial high risk of bipolar disorder. The working memory subgroups are based on a latent profile transition analysis of 319 children at FHR-SZ (N = 201) and children at FHR-BP (N = 118).

4.1. Movers and stayers

The LPTA showed that 98 % of the children at FHR-SZ or FHR-BP stayed in the same working memory subgroup from age 7 to 11. These findings are in line with results from previous group-level analyses of stability in the development of working memory performance in children aged 6–17 years at familial high risk of schizophrenia or bipolar disorder (De la Serna et al., 2020) and a recent follow-up study from this cohort (Knudsen et al., 2022). In contrast, previous studies of premorbid characteristics of individuals transitioning to psychosis have found evidence of a developmental lag in working memory performance throughout childhood and adolescence (Mollon et al., 2018; Reichenberg et al., 2010). However, while these studies focused on individuals who all conversed to psychosis, a familial high risk study design, as is employed in the present study, assesses an at-risk sample where it is not expected that most children will convert to psychosis. Because of the low number of children (2 %) who moved between subgroups in the present study, it was not possible to determine their characteristics, but as they all transitioned to a subgroup characterized by poorer working memory function, it could suggest that some children become increasingly impaired with time. Studies (using larger samples) should further investigate whether there is a subgroup of children who show increasing working memory impairments over time and whether these children are more vulnerable to conversion to psychosis. Overall, the findings from the current study support the presence and stability of working memory heterogeneity in children at FHR-SZ and FHR-BP. As working memory impairments are associated with lower academic and social functioning (Eriksson et al., 2015; Park and Gooding, 2014), these findings further suggest that early identification of the subgroup with widespread working memory impairment is important.

4.2. Familial high risk children in the subgroups

As expected, we found a higher prevalence of children at FHR-SZ in the impaired subgroup, and a higher prevalence of FHR-BP in the above average subgroup, suggesting that more children at FHR-SZ exhibit widespread working memory impairments. We did not find evidence of a subgroup of children with impairments limited to tests primarily targeting spatial or verbal abilities. Until now, no studies have investigated heterogeneity based on working memory tasks alone (and thus assessed heterogeneity within working memory function), but the model of three subgroups with different degrees of working memory function is in line with previous studies assessing heterogeneity based on multiple neurocognitive domains (Bora et al., 2019; Hemager et al., 2022; Knudsen et al., 2023; Valli et al., 2021). These findings suggest that the heterogeneity when assessing working memory alone follows the heterogeneity when assessing multiple neurocognitive functions, which could imply that the neurocognitive heterogeneity seen in children at FHR-SZ or FHR-BP relies on a single underlying cognitive factor (Carruthers et al., 2019).

Our findings indicate considerable heterogeneity in working memory function in children at FHR-SZ at age 7 and 11 and illustrate that the working memory function in children at FHR-SZ varies between significant and widespread impairments to above average working memory function. This demonstrates, that even though working memory impairments have consistently been established in children and relatives of individuals with schizophrenia (Agnew-Blais and Seidman, 2013; De la Serna et al., 2020), the differences found at a group level may be driven by a subset of impaired individuals. Further, the findings that many children at FHR-SZ do not display working memory impairments, should be emphasized to reduce stigma and increase nuanced information about mental vulnerability.

As mentioned, previous group-level studies have not found evidence of working memory impairments in children and youth of parents with bipolar disorder (De la Serna et al., 2020; Diwadkar et al., 2011), including findings from the present cohort (Hemager et al., 2018; Knudsen et al., 2022). However, our results show that around 15–17 % of the children at FHR-BP were in the impaired subgroup, which shows that a substantial subset of children at FHR-BP does display significant working memory impairments. This finding aligns with cross-sectional studies assessing neurocognitive heterogeneity in children and youth aged 6–17 years at familial high risk of bipolar disorder, where a similar percentage are characterized by significant neurocognitive impairment (Bora et al., 2019; Valli et al., 2021). Likewise, a cross-sectional study assessing neurocognitive heterogeneity in this cohort, found that 20 % of 7-year-old children at FHR-BP were in a subgroup characterized by neurocognitive impairments (including working memory function) (Hemager et al., 2022). It has been suggested that the challenge of

establishing premorbid cognitive characteristics of bipolar disorder may in part be due to the disorder's vast heterogeneity (Olvet et al., 2013; Russo et al., 2017). For instance, it has been proposed that premorbid neurocognitive deficits may represent a neurodevelopmental subtype of bipolar disorder (Kloiber et al., 2020). Also, children of parents with bipolar disorder who are lithium non-responders have been found to have more early antecedents, including neurocognitive impairments (Duffy et al., 2007; Duffy et al., 2014). Thus, the explanation for a subset of children at FHR-BP exhibiting widespread working memory impairments and others exhibiting no impairments may be associated with distinct subtypes of bipolar disorder. Further, neurocognitive impairments in patients with bipolar disorder or schizophrenia have been found to be better predicted by a history of psychosis rather than diagnostic category (Simonsen et al., 2011). Since conversion to illness in familial high-risk populations is not specific to parental diagnosis (Paccalet et al., 2016; Rasic et al., 2013), another possible interpretation of our findings is that working memory impairments serve as a transdiagnostic vulnerability marker of psychosis. This understanding is supported by a study of brain activity during working memory tasks, where patients with schizophrenia and psychotic bipolar disorder showed similar deficits in the regions that underlie working memory (Huang et al., 2019). In conclusion, the findings from this study align with previous studies assessing neurocognitive heterogeneity and support the idea that working memory impairments are present in a subset of children at FHR-BP.

4.3. Caregiver and teacher ratings

Overall, the parent and teacher ratings of everyday working memory function supported the results from the LPTA, as the children in the impaired working memory subgroup had higher ratings of working memory impairments compared to the children in subgroups characterized by less or no impairments. This finding was consistent across raters and at both waves of assessment. This suggests that overall, and taking heterogeneity into consideration, the ratings of everyday working memory ability follow the working memory capacity as assessed by working memory tests, and thus lend support to the interpretation of the data-driven subgroups. The results from the LPTA were also supported by the caregiver ratings of psychopathology in the child, as the impaired subgroup had significantly higher levels of psychopathology than the subgroups with less or no impairments (again this result was evident both at age 7 and 11). As working memory impairments have been suggested to be vulnerability markers of transition to psychosis (Reichenberg et al., 2010; Seidman et al., 2013), the individuals in the impaired subgroup may represent a subset of children at familial high risk, that have an increased risk of getting a diagnosis themselves. Future follow-up assessments of this cohort will make it possible to employ follow-back analyses regarding working memory function and later development of severe mental illness.

5. Strengths and limitations

This study had several strengths. Not only is it the first study to examine heterogeneity within the domain of working memory (based purely on working memory tasks) in children at FHR-SZ or FHR-BP, but also the first to use a longitudinal design when doing so. Further strengths include the use of LPTA, which has several advantages, including formal criteria with which to evaluate model fit, and thereby minimize subjectivity bias (Vermunt and Magidson, 2002). Additionally, working memory was assessed using multiple and validated neurocognitive tests, and parent and teacher ratings were included to support the findings. Finally, the sample was large and consisted of same-aged children. The limitations include the lack of additional time points, which could have strengthened conclusions regarding transition patterns, as well as the fact that data-driven methodology relies on the validity of the indicators (Carruthers et al., 2019), and thus the inclusion of other working memory tasks could have resulted in slightly different subgroups.

6. Conclusion

Working memory in children at familial high risk of schizophrenia or bipolar disorder is characterized by considerable heterogeneity, and this heterogeneity remains stable throughout middle childhood. Children with pronounced working memory impairments have higher levels of dimensional psychopathology and are rated as having more everyday problems with working memory by caregivers and teachers. As working memory impairments may be a vulnerability marker of transition to psychosis as well as have a substantial impact on daily life, future studies and clinical practice should aim to identify the subset of children at familial high risk, who do exhibit significant working memory impairments.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.04.011.

Funding statement

The study was supported by the Lundbeck Initiative for Integrative Psychiatric Research (iPSYCH, grant number: R155-2014-1724), the Tryg Foundation, the Innovation Fund Denmark (grant number: 6152-00002B), the Mental Health Services of the Capital Region of Denmark, Aarhus University, the Independent Research Fund Denmark (grant number: 9039-00220B), and the Beatrice Surovell Haskell Fund for Child Mental Health Research of Copenhagen (grant number: 11531). The authors declare no conflicts of interest.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the participants for taking their time to participate in our study, and J. Ohland, A.M. Bundsgaard, H.B Stadsgaard, L. Carmichael, M. Birk, M. Melau, M. Wilms, N. L. Steffensen, S. B. Rohd, Å.K. Prøsch, D. L. Gantriis, D.V. Ellersgaard, and C.J. Christiani, for their contribution to the data collection.

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