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Impairments in verbal and spatial working memory as a predictor of psychopathology in offspring of patients with schizophrenia or bipolar disorder

Master thesis Neuropsychology

Utrecht University

Author: Saline van de Veen
Student number: 5720737
Email: s.w.vandeveen@students.uu.nl

Supervisor(s): Drs. M. Engel, Utrecht University
Drs. N. Setiaman, UMC Utrecht
Prof. dr. N. E. M. van Haren, Erasmus MC Rotterdam

Abstract

Schizophrenia offspring (SZo) and bipolar disorder offspring (BDo) are at an increased risk for developing psychopathology. To recognize at-risk individuals early, more insight into the vulnerability markers of both disorders is needed. Research suggests that verbal and spatial working memory could be cognitive markers for developing schizophrenia or bipolar disorder. The current study investigated whether SZo and BDo differed in verbal and spatial working memory compared to healthy controls (HCo). In addition, it was examined whether verbal and spatial working memory performance could serve as a predictor for (sub)clinical psychotic, depressive or manic symptoms. This study was part of the longitudinal Dutch Bipolar and Schizophrenia Offspring Study (DBSOS). At baseline, the sample included 200 subjects (age *M*=13.10; *SD*=2.42). The Backward Digit Span and Spatial Temporal Span measured verbal and spatial working memory at baseline and follow-up. The Comprehensive Assessment of At-Risk Mental States (CAARMS) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) were administered at follow-up, to measure the presence of psychotic, depressive and manic symptoms. Results revealed no significant differences in verbal and spatial working memory between SZo, BDo, and HCo. In addition, only manic symptoms could be predicted by spatial working memory performance. The findings implicate that these possible cognitive markers of bipolar disorder and schizophrenia are not visible at an early age. Future research should explore the presence of working memory difference at a later stadium of the disorders.

Keywords: verbal working memory, spatial working memory, schizophrenia offspring, bipolar offspring.

Introduction

Schizophrenia and bipolar disorder are both severe and chronic psychiatric disorders, that causes impairments in social, emotional and cognitive functioning (American Psychiatric Association, 2013). Schizophrenia patients are recognized by three distinguishable types of symptoms; positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. affective flattening and apathy) and disorganization symptoms (e.g. disorganized speech and abnormal motor behavior) (American Psychiatric Association, 2013). The lifetime prevalence of schizophrenia is estimated between 0.3% and 0.7%, (McGrath, Saha, Chant & Welham, 2008). Patients diagnosed with bipolar disorder are characterized by the occurrence of one or more manic episodes, often alternated with major depressive episodes or euthymic periods (American Psychiatric Association, 2013). The prevalence of bipolar disorder is comparable to schizophrenia, with a lifetime prevalence of 0.6 % (Merikangas et al., 2007).

Schizophrenia and bipolar disorder are defined as two unique disorders, but they also show some overlap in symptoms. For instance, depressive symptoms are often reported in schizophrenia patients, while psychotic symptoms are common during manic episodes in bipolar patients (Murray et al., 2004). In addition, similarities between the disorders are also found in common susceptibility genes, high heritability, and age of onset (Craddock & Owen, 2010; American Psychiatric Association, 2013). Patients with schizophrenia and bipolar disorder are mostly diagnosed at late adolescence or early adulthood. However, several studies suggest that the first symptoms are visible a couple of years before the diagnosis (Duffy, 2009; Fusar-Poli et al., 2012).

Despite the evidence for the early impairments, it is still unclear how schizophrenia and bipolar disorder develop over time (Duffy, Malhi & Grof, 2017; Thorup et al., 2015). Since early interventions could reduce the risk of a disorder to further develop, it is crucial that at-risk individuals are identified on time (Rasic et al., 2013). Early identification is more effective when there is more clarity about the vulnerability markers of schizophrenia and bipolar disorder. To gain more insight into these vulnerability markers, the current study will investigate the offspring of patients with schizophrenia (SZo) or bipolar disorder (BDo). Given the high heritability of schizophrenia and bipolar disorder, studying offspring is considered a reliable method for investigating vulnerability factors (de la Serna et al., 2016). Since the overlap in the disorders

makes differential diagnoses in at-risk individuals challenging, it is adequate to include both offspring groups in one study.

Earlier studies on vulnerability factors in schizophrenia and bipolar disorder patients have suggested that disturbances in cognitive functioning potentially could serve as a predictor for the onset of the disorders (Snitz, MacDonald III & Carter, 2005). This is suggested because previous studies revealed that cognitive deficits existed before the illness onset of both disorders (Nuechterlein, Ventura, Subotnik & Bartzokis, 2014; Robinson & Ferrier, 2006). A cognitive function that often is reported as impaired in these patients is the working memory (Park & Gooding, 2014; Bortolato, Miskowiak, Köhler, Vieta & Carvalho, 2015). Working memory is known as a brain system that provides temporary storage and manipulation of the information necessary for complex cognitive tasks (Baddeley, 1992). It develops in a relatively long period of time, and is at its optimal level around the age of 18 (Waber et al., 2007). Studies on working memory often distinguish between two types of working memory, verbal and spatial. Verbal working memory includes the temporary storage of verbal information (e.g. letters and numbers), while spatial working memory includes the temporary storage of spatial information (e.g. spatial relation between objects).

Previous studies on vulnerability factors in BDo and SZo showed that working memory problems reported in schizophrenia and bipolar disorder patients were also found in their offspring (Diwadkar et al., 2011, de la Serna et al., 2016). The review of Balanzá-Martínez et al. (2008) reported verbal working memory impairments in unaffected relatives of bipolar patients, compared to healthy controls (HCo). Additionally, impairments in verbal working memory are also reported in studies on twins and unaffected schizophrenia relatives (Park & Gooding, 2014). Spatial working memory deficits have been consistently observed in SZo (Glahn et al., 2003; Barrantes-Vidal et al., 2007; Diwadkar et al., 2011), however results regarding BDo are inconsistent. In the review of Park and Gooding (2014) there were some studies in which spatial working memory impairments were found in BDo, however others did not found these deficits. In general, impairments are most prominent reported in SZo. BDo show the same deficits, but less severe.

Taken together, the existing literature suggests that verbal and spatial working memory both could be cognitive markers in schizophrenia and bipolar disorder. However, due to the inconsistency in results, previous studies advise to include both offspring groups in a

longitudinal study (Diwadkar et al., 2011; Thorup et al., 2015). Using a longitudinal design provides the opportunity to study the onset and course of working memory deficits. In addition, it could be investigated if working memory performance could predict (sub)clinical symptoms. In this way, more insight into valuable cognitive markers and early differential symptoms in SZo and BDo will be obtained.

In order to gain this insight, the current study will investigate BDo, SZo, and HCo in a longitudinal study. The study will include a baseline (T1) and a follow-up around 4 years later (T2). To investigate if verbal and spatial working memory could serve as a predictor for the development of schizophrenia or bipolar disorder, both functions will be measured at T1 and T2. (Sub)clinical depressive, manic and psychotic symptoms will also be measured at T1 and T2, in order to examine the presence of one of the disorders.

From previous studies it is known that working memory develops until late adolescence, therefore it is expected that the verbal and spatial working memory performance will improve between T1 and T2, in all offspring groups. In addition, it is expected that SZo will perform lower on verbal and spatial working memory, compared to BDo and HCo, while BDo are expected to perform lower on spatial and verbal working memory compared to Co.

Since previous findings have suggested that verbal and spatial working memory could be a predictor for the development of psychopathology it is hypothesized that the verbal and spatial working memory performance at baseline, is negatively correlated with subclinical depressive, manic and psychotic symptoms at T2.

Methods

The current study is part of the Dutch Bipolar and Schizophrenia Offspring Study (DBSOS) which is carried out at the department of Psychiatry in UMC Utrecht. DBSOS is a longitudinal study which aims is to find possible risk and resilience factors for the development of schizophrenia and bipolar disorder.

Ethics statement

The DBSOS is approved by the Medical Ethical Test Commission of the University Medical Center Utrecht (UMCU). All participants and their parents signed an informed consent form before taking part in the study. The parents signed for own participation, but also for approval of the participation of their child. When participants outreached the age of 18, approval of the parents was no longer required.

Participants

At the first assessment (T1), the final sample consisted of 200 participants, aged between 8 and 18 years (M=13.10; SD=2.42). The sample consisted of three groups; 59 offspring of schizophrenia patients (SZo), 88 offspring of bipolar disorder patients (BDo) and 53 offspring of parents without psychotic or severe mood disorders (HCo). At the second assessment (T2), the final sample consisted of 143 participants (M=17.31; SD=2.66), including 38 SZo, 73 BDo, and 32 HCo.

The participants in the SZo and BDo groups had at least one parent or two second-degree relatives with schizophrenia or bipolar disorder. Participants in the HCo group were only included when they had no psychiatric history, did not use psychotropic medication, and had no first or second-degree relatives with a mood or psychotic disorder. Inclusion criteria that applied for all participants were: Dutch-speaking, no serious medical history, and IQ > 70.

The descriptive statistics of the demographic variables sex, age and IQ for the offspring groups are summarized in Table 1. The groups differed significantly from each other, on sex and IQ.

Table 1. *Descriptive Statistics per Offspring Group.*

	SZo	**BDo**	**HCo**	**Total**	**Test statistics**		**Pairwise Comparison**		
							SZo vs BDo	SZo vs HCo	BDo vs HCo
N	26	60	29	115					
Sex female (%)	20 (76.92)	32 (53.33)	11 (37.93)	63 (54.78)	$\chi 2$=8.52	***p*= .01***			
Age in years T1 (*SD*)	12.76 (2.54)	13.58 (2.46)	12.82 (2.17)	13.21 (2.42)	*F*=1.54	*p*= .22	*p*= .45	*p*=1.00	*p*= .50
Age in years T2 (*SD*)	16.87 (2.94)	17.67 (2.64)	16.93 (2.64)	17.31 (2.71)	*F*=1.17	*p*= .32	*p*= .62	*p*=1.00	*p*= .68
IQ T1 (*SD*)	104.00 (18.77)	105.36 (18.77)	118.72 (11.18)	108.48 (18.06)	*F*=7.01	***p*= .01***	*p*=1.00	***p*= .01***	***p*= .01***
IQ T2 (*SD*)	103.42 (18.78)	102.34 (15.05)	113.72 (12.60)	105.51 (16.04)	*F*=5.57	***p*=.01***	*p*=1.00	***p*= .05***	***p*= .01***

Note. * is significant effect (*p*<.05). SZo = offspring of patients with schizophrenia. BDo = offspring of patients with bipolar disorder. HCo = offspring of parent without a mood or psychiatric disorder . N = number of participants. SD = standard deviation

Procedure and instruments

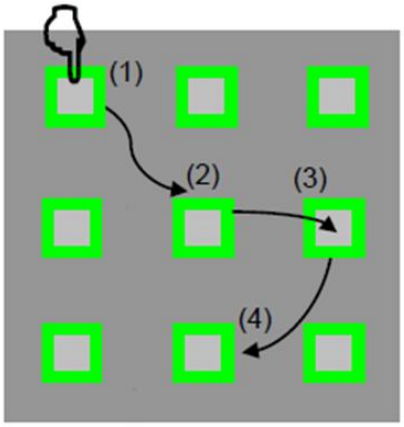
The current study consists of two measuring moments. The first measuring moment (T1) started in 2010 until 2015. Around four years after T1 the participants were invited for the second measuring moment (T2). Each measuring moment consist of two testing days, in which neuropsychological tests, interviews, surveys, MRI-scans and blood samples were administered for the DBSOS study. The measurements that are relevant for the current study are described below.

Verbal working memory. The subtest Backward Digit span from the Wechsler Intelligence Scale For Children (WISC III) is used to measure verbal working memory. In this test, the instructor reads a series of digits at a rate of 1 digit per second. Afterwards, the participant is asked to recall the series of digits in a reverse order, after hearing them once. Every trial consisted of two attempts with an equal number of digits. The test started with two digits, with an increasing load as long as the participant was able to recall them in one of the two attempts. When the participant was not able to recall the series of digits in both attempts, the test was aborted. The outcome measure was the number of digits that the participant was able to

recall, in which the higher score means the better the verbal working memory. The Backward Digit span has a high construct validity and is therefore a good test to measure verbal working memory (Kaufman, Raiford & Coalson, 2015; Wechsler, 1997).

Spatial working memory. The subtest Spatial Temporal Span backward (STS-part 2) of the 'Amsterdamse Neuropsychologische Taken' (ANT), is used to measure spatial working memory (Sonneville, 2008). This test is conducted on a HP Laptop: EliteBook 755 G3, 14 Inch).

During the task, the participant is placed behind the laptop on a distance of 30-50 cm from the screen. Beforehand, the participants were instructed to remember in which order different squares were highlighted. When the test started, nine squares were presented in a three-by-three matrix on the computer screen. A hand animation pointed out the pattern that needed to be remembered by the participant (See Figure 1).



Figuur 1. Spatial temporal span task, with an example of a trial. Copied and adapted from Amsterdamse Neuropsychologische Taken; gebruikshandleiding (p. 100) by L. Sonneville, 2015.

After the sequence was presented, the participant had to click on the same squares in reverse order (Huizinga, Baeyens & Burack, 2018). The test consisted of multiple trials, with different patterns in each trial. The length of the sequence to remember increased as long as the participant was able to recall it. The participants had two attempts for each sequence with the same length. When two sequences of the same length were both executed incorrectly, the task was automatically finished. The outcome measure in this test was the number of squares that were correctly recalled. The higher the score means the better the spatial working memory (Laan,

2013). The validity, sensitivity and reliability of the STS are evaluated as high by research of Sonneville (2015).

Depressive and manic symptoms. Subclinical depressive and manic symptoms were measured with the Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL). The K-SADS is a semi-structured interview which is based on the DSM IV diagnoses (Kaufman et al., 1996). The interview is intended for children and adolescents between the age of 6 and 18 years.

The K-SADS consists of five diagnostic categories: Affective Disorders, Psychotic Disorders, Anxiety Disorders, Behavioral Disorders, Substance Abuse and Other Disorders. In order to measure the variables depressive and manic symptoms, only the category Affective Disorders will be used in the current study. The categories are divided into two parts: a screening and supplement questions. Questions from the supplement were only asked, if participants reached the threshold score on the screening. This did not account for the supplements of affective and psychotic disorders, which were administered at all times.

The interview was conducted in all participants and in one of their parents. The parent that reported on their child could be the affected or the non-affected parents. The interviews were done separately, so the responses of both informants could be evaluated in a combined score. The scores ranged from 0 (no information), 1 (not present), 2 (mild) to 3 (severe). In order to ensure continuity in assessing subclinical symptoms, the interview was also conducted in participants who outreached the age of 18. The parents' score was no longer included in participants from the age of 20. In the current study, the combined scores of all symptoms were used as the outcome measure. The validity and reliability of the K-SADS is supported by multiple studies (Kaufman et al., 1997; Lauth et al., 2010).

Psychotic symptoms. The presence of subclinical psychotic symptoms was measured with the Comprehensive Assessment of At-Risk Mental States (CAARMS). The CAARMS is a semi-structured interview, designed to measure the presence of possible psychopathology in young people who are at risk of developing a psychosis (Yung et al., 2006). The age criteria of this interview is 15 years, which means that no data of this interview is available of participants below this age.

Since in the current study the psychotic symptoms are of interest, only the first subscale of the CAARMS was used. This subscale measures positive symptoms, and consist of the items

unusual thoughts, non-bizarre ideas, perception disorders and disoriented speech. For each item, a score from 0 (Never present) to 6 (Severe and Psychotic) was given, to indicate the severity of each symptom. In addition, the frequency, duration, and the degree of distress were scored. Lastly, the influence of possible substance use on the presence of symptoms was checked. To draw conclusions from this interview, the total sum score of the severity of symptoms was used as outcome measure of this interview. The higher the total sum score means the more severe the (sub)clinical psychotic symptoms are present. No cut off score was used. In the study of Yung et al. (2005), the validity and the reliability of the CAARMS was evaluated as good.

Data inspection

The data obtained from the tests and interviews were analyzed by the use of the Statistical Package for the Social Sciences (IBM SPSS Statistics 25). Before the analyses were performed, the assumptions of all analyses were checked. During the check, it appeared that the assumption of normality was violated for all outcome variables. However, the tests that will be used in this study are considered robust tests against violation of the normality (Schmider et al., 2010; Levy, 1980; Williams, Grajales & Kurkiewicz, 2013). In the regression analyses, it appears that the assumption of outliers was violated (Mahalanobis distance exceeded critical χ^2). Within this dataset, the presence of outliers means a high score on (sub) clinical symptoms. Because these symptoms are of interest in this study, no correction for extreme outliers was performed. Furthermore, all assumptions were met unless stated otherwise.

Covariates. In the data analysis, a number of variables were included as a covariate. First, the continuous variable IQ was included as a covariate in the analyses in which working memory was the outcome measure, because the study by Shelton et al. (2009) showed that there is a relationship between IQ and the performance on the working memory tasks. In addition, results from the demographic statistics revealed a significant difference between the offspring groups regarding IQ. In order to prevent the studied effect from being caused by the difference in IQ, the current study corrected for this by including IQ as a covariate.

Second, the continuous variable age was included as a covariate in all analyses. Since the expression of subclinical symptoms in schizophrenia and bipolar disorder patients mostly occurs in early adulthood, it was expected that the age of the participants will play an important role in

the outcomes (Welham, Thomis & McGrath, 2004). Furthermore, research has shown that working memory develops until late adolescence (Scherf, Sweeney & Luna, 2006). For this reason, it was seen reasonable to include the variable age as a covariate.

Lastly, the variables subclinical symptoms at T1 were included as covariates in the analyses in which subclinical symptoms at T2 were analyzed. In the current study it is investigated if verbal and spatial working memory could predict psychopathology in SZo and BDo. When symptoms were already present at T1, no valid conclusions can be drawn about the causal relationship between working memory and subclinical symptoms. Consequently, subclinical symptoms at T1 were included as covariate in the appropriate analyses.

Analyses

Demographics After the data inspection, it is investigated if the offspring groups differed on age, sex, and IQ at baseline and follow-up. One-Way analysis of variance (ANOVAs) were performed ($\alpha < .05$) to examine the continuous variables (IQ and age) independent and a Chi-Square Test of Independence was performed ($\alpha < .05$) to examine the dichotomous variable sex.

Verbal working memory. In order to measure whether there are differences in performance on verbal working memory between the groups (SZo, BDo and HCo), a one way ANOVA ($\alpha < .05$) was used. Subsequently, a one way ANCOVA was used to control for covariates, IQ and age. Both analyses were performed with verbal working memory as dependent variable and groups as independent variable. A Repeated Measures ANCOVA was used to investigate how the verbal working memory performance improved over time. In this analyses was verbal working memory the dependent variable and groups the independent variable. Age and IQ were added as covariates. In cases of statistical significance, pairwise mean comparisons were carried out with Gabriel's correction.

Spatial working memory. To examine if the groups differed in spatial working memory performance, again a one way ANOVA and ANCOVA ($\alpha < .05$), with covariates IQ and age, were used. Spatial working memory was in these analyses the dependent variable and groups was the independent variable. Consequently, a Repeated Measures ANOVA ($\alpha < .05$) was used to investigate how spatial working memory performance improved over time. In this analyses was spatial working memory the dependent variable and groups the independent variable. Age

and IQ were added as covariates. In cases of statistical significance, pairwise mean comparisons were carried out with Gabriel's correction.

Influence psychopathology. A Multiple Regression ($\alpha < .05$) was used to investigate if there was a correlation between working memory (verbal and spatial) at T1 and (sub)clinical symptoms (depressive, manic or psychotic) at T2. In the analyses, the performance on verbal and spatial memory were independent variables, and the depressive, manic and psychotic subclinical symptoms were the dependent variables. The variables age and (sub)clinical symptoms at T1 were included as covariates in this analysis. If the results were significant a stepwise entry method was used, otherwise the variables were analyzed simultaneously.

Results

Verbal working memory over time

Mauchly's Test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 1.000$, $p < .0005$, and therefore, a Greenhouse-Geisser correction was used. After accounting for the effects of the covariates, the Repeated Measures ANCOVA revealed that there was no significant main effect of time. This indicates that the verbal working memory performance remained stable over time in all groups.

Verbal working memory

The ANOVA analyses indicated that the verbal working memory performance was not significantly different between the offspring groups at both measuring moments. Additionally, the ANCOVA, in which the covariates were included (age and IQ) did not change the results, F (2, 196) = .17, p = .84. See Table 2 for the descriptive statistics of the verbal working memory performance for all groups.

Table 2. *Descriptive Statistics (M, SD) of Verbal Working Memory T1 and T2 (one-way ANOVA).*

	SZo	**BDo**	**HCo**	**Total**	**Test statistics**	
N	46	76	40	162		
VWM T1	4.41	4.62	4.58	4.55	*F*=1.24	*p*= .29
(*SD*)	(1.11)	(1.11)	(1.28)	(1.15)		
N	46	76	40	162	*F*=.47	*p*= .63
VWM T2	5.04	5.05	5.50	5.16		
(*SD*)	(1.37)	(1.37)	(1.62)	(1.44)		
Time	*F*= .16	*p*= .69				
Time * Groups	*F*= .57	*p*= .57				
Groups (T1 and T2)	*F*= .32	*p*= .73				

Note. * is significant effect (*p*<.05). SZo = offspring of patients with schizophrenia. BDo = offspring of patients with bipolar disorder. HCo = offspring of parent without a mood or psychiatric disorder . N = number of participants. SD = standard deviation

Spatial working memory over time

Mauchly's Test indicated that the assumption of sphericity had been violated, $\chi^2(2) = 1.000$, $p < .0005$, and therefore, a Greenhouse-Geisser correction was used. After accounting for the effects of the covariates, the Repeated Measures ANCOVA revealed a significant main effect of time, indicating that the spatial working memory positively changed over time in all groups.

Spatial working memory

An one-way ANOVA revealed a statistically significant effect, indicating that the spatial working memory performance at T1 is significantly different in the offspring groups. A Post hoc analyses with Gabriel's (using an α of .05) revealed that HCo and BDo had significantly higher spatial working memory scores than SZo. However, the ANCOVA with covariates (age and IQ) no longer reached significance $F(2, 191) = 2.10$, $p = .13$. In addition, no significant spatial working memory differences were found at T2. See Table 3 for the descriptive of the spatial working memory performance for all groups.

Table 3. *Descriptive Statistics (M, SD) of Spatial Working Memory T1 and T2 (one-way ANOVA).*

	SZo	**BDo**	**HCo**	**Total**	**Test statistics**		**Pairwise Comparison**		
							SZo vs BDo	SZo vs HCo	BDo vs HCo
N	36	70	30	136					
SWM T1	6.49	7.14	7.27	7.05	*F*=7.38	***p* <.01***	*d*= .36	*d*=.53	*p*= .23
(*SD*)	(1.24)	(1.18)	(1.26)	(1.23)					
N	36	70	30	136	*F*=2.27	*p*=0.11			
SWM T2	7.42	7.47	7.90	7.55					
(*SD*)	(1.38)	(1.09)	(.92)	(1.15)					
Time	*F*= 4.33	***p*= .04***							
Time * Groups	*F*= .81	*p*= .45							
Groups (T1 and T2)	*F*= .47	*p*= .73							

Note. * is significant effect ($p<.05$). SZo = offspring of patients with schizophrenia. BDo = offspring of patients with bipolar disorder. HCo = offspring of parent without a mood or psychiatric disorder . N = number of participants. SD = standard deviation

Working memory and depressive symptoms

In this model, all predictors accounted for 31% of the variability in depressive symptoms at T2, adjusted R^2 = .29, F(4, 121) = 13.219, p < .001. However, looking at the explained variances of the variables verbal and spatial working memory, revealed that both predictors were non-significant. This result indicates that verbal and spatial working memory at T1 did not predict depressive symptoms at T2. The total significant effect of the predictors, can be explained by the significant predictor depressive symptoms at T1. Unstandardised (*B*) and standardized (β) regression coefficients, squared semi partial correlations (sr^2), and p-values for each predictor in the regression model are reported in Table 4.

Table 4. *Descriptives for each Predictor a Regression Model Predicting Depressive Symptoms.*

Variable	*B [95% CI]*	β	sr^2	*p*
VWM T1	-.65 [-2.02, .72]	-.08	.01	.35
SWM T1	-.30 [-1.75, 1.15]	-.04	< .01*	.68
Age	-.16 [-.83, .51]	-.04	.00	.64
Depr. Symptoms (T1)	.70 [.50, .90]	.55	.28	< .01*

Note. N = 122 CI = confidence interval B= Unstandardized Regression Coefficients β = Standardized Regression Coefficients sr^2= Squared Semi- Partial Correlations.
* p < .05.

Working memory and manic symptoms

In combination, all predictors accounted for 40 % of the variability in manic symptoms at T2, adjusted R^2 = .38, F (4, 115) = 18.82, p < .01. When looking at the accounted variances of the individual predictors, it revealed that spatial working memory performance did significantly account for the observed variances. This result indicates that spatial working memory performance at T1 predicts manic symptoms at T2. In addition, results showed that verbal working memory was not a significant predictor. Unstandardised (*B*) and standardized (β) regression coefficients, squared semi partial correlations (sr^2), and p-values for each predictor in the regression model are reported in Table 5.

Tabel 5. *Descriptives for each Predictor a Regression Model Predicting Manic Symptoms.*

Variable	*B [95% CI]*	β	sr^2	*p*
VWM T1	-.21[-.54, .13]	-.10	.01	.22
SWM T1	-.43 [-.77, .09]	-.22	.03	.02*
Age	.24 [.07, .40]	-.25	.04	.01*
Manic Symptoms (T1)	.67 [.50, .84]	.57	.32	< .01*

Note. N = 122 CI = confidence interval B= Unstandardized Regression Coefficients β = Standardized Regression Coefficients sr^2= Squared Semi- Partial Correlations.
* $p < .05$.

Working memory and psychotic symptoms

In combination, all predictors accounted for 64 % of the variability in psychotic symptoms at T2, adjusted R^2 = .62, F (4, 67) = 28.34, $p < .001$. Interpreting the variables verbal working memory and spatial working memory, revealed no significant effects. This result indicates that both variables did not predict psychotic symptoms at T2. The significant effect of all predictors can be explained by the significant predictor psychotic symptoms at T1. Unstandardised (*B*) and standardized (β) regression coefficients, squared semi partial correlations (sr^2), and p-values for each predictor in the regression model are reported in Table 6

Tabel 6. *Descriptives for each Predictor a Regression Model Predicting Psychotic Symptoms.*

Variable	*B [95% CI]*	β	sr^2	*p*
VWM T1	-.05[-.29, .18]	-.04	.01	.64
SWM T1	.08 [-.17, .33]	-.06	.02	.54
Age	.03 [-.11, .16]	-.03	.01	.68
Psychotic Symptoms (T1)	.85 [.69, 1.01]	.80	.62	< .01*

Note. N = 122 CI = confidence interval B= Unstandardized Regression Coefficients β = Standardized Regression Coefficients sr^2= Squared Semi- Partial Correlations.
* $p < .05$.

Discussion

The current study aimed to investigate whether verbal and spatial working memory differs between offspring of patients with bipolar disorder (BDo), offspring of patients with schizophrenia (SZo), and healthy controls (HCo). In addition, it was investigated whether these differences were related to (sub)clinical symptoms (depressive, manic or psychotic) four years later. Since research has shown that symptoms of schizophrenia and bipolar disorder are present before illness onset, it is important to seek for early symptoms that could serve as vulnerability markers. In this way, at-risk individuals could be recognized, which could lead to early interventions and therefore better patient outcome (Rasic et al., 2013).

The results of this study were in contrast with the expectations. Primarily, no differences in verbal working memory over time were found. This result indicates that the offspring groups did not improve in verbal working memory over time. Although this is against the expectation, limitations regarding to follow-up times could be an explanation for this. Due to organizational factors there was a variety in follow-up times between the participants. Most participants have a follow-up time of around four years, but there are also participants that returned after two years. The study of Cockcroft (2015) showed that verbal working memory develops during adolescence with one capacity chunk in three years. This could indicate that for a considerable part of the participants the follow-up times were too short to observe a development.

In addition to the development over time, no difference in verbal working memory was found between the offspring groups. This result is not in line with previous studies, in which impairments in verbal working memory is reported in SZo and BDo (Balanzá-Martínez et al., 2008; Park & Gooding, 2014; de la Serna et al., 2014). An explanation for the contradictory in results could be the difference in the investigated samples. For example, in the study of de la Serna et al. (2014) it appears that in a considerable part of the BDo lifetime psychopathology was present. Since in the current study the BDo were less impaired, this could be the reason why fewer impairments in working memory were found compared. Another explanation could be the difference in used instruments. Because the studies of Balanzá-Martínez et al. (2008) and Park & Gooding (2014) have used other tests to measure verbal working memory, it could be that the Digit Span backwards is not suitable for distinguishing between SZo, BDo, and HCo.

For now, these results implicate that SZo and BDo in this sample (mean age T2 = 17.31)

do not show verbal working memory impairments compared to HCo. Nevertheless, it could be that the expected deficits will develop in the future of these individuals.

Results regarding spatial working memory revealed that the performance on spatial working memory improved over time. This is in line with the expectations and shows that spatial working memory is still in development until late adolescence (Waber et al., 2007). The results on group difference revealed that solely SZo showed difference in spatial working memory compared to BDo and HCo. This offspring group performed lower on spatial working memory tasks, while no difference was found between BDo and HCo. These results were partly in line with the hypotheses, in which lower spatial working memory was expected in SZo. On the other hand, was the absence of a spatial working memory difference between BDo and HCo unexpected.

Noteworthy, these group differences no longer reached significance when covariates age and IQ were added. After exploring the individual influences of the covariates, it revealed that the relation between IQ and groups could be concerning. This relation could mean that the effect of IQ overlaps with the effect of the offspring groups. In this situation, adding IQ as covariate reduced the studied effect because it explains some of the variances that would otherwise be attributable to the group differences (Field, 2013). Consequently, these results implicate that after correction for IQ, no difference in spatial working memory are present between SZo, BDo and HCo. This contradicts previous studies in which differences between the groups were consequently reported (Diwadkar et al., 2011, de la Serna et al., 2016). Methodological difference regarding used instruments and investigated samples could be an explanation for this. For now, it is important that these results are interpreted carefully. Since the groups differ in IQ, it is difficult to investigate the variables separately and determine if the studied difference fully can be explained by this covariate.

At last, the results of the current study showed that the working memory performance (spatial and verbal) at baseline was to a small extent related to (sub)clinical symptoms (depressive, manic and psychotic) at T2. Only spatial working memory performance at T1 could serve as a predictor for the onset of manic symptoms at T2. This is in line with the expectations, in which it was hypothesized that spatial working memory performance could predict (sub)clinical manic (Park & Gooding, 2014). Despite the inconsistencies in the existing literature, this result strengthens the value of spatial working memory as a predictor of bipolar

symptoms. This means that BDo that are at risk for developing manic symptoms could be recognized by spatial working memory performance. To enlarge the reliability and clinical relevance of this outcome, more studies with the same results are needed.

Based on previous research, it was also expected that verbal and spatial working memory could predict depressive and psychotic symptoms. However, this expectation was not supported by the results of this study. The age of the participants could be an explanation for this. According to American Psychiatric Association (2013), is the onset of both disorders mostly at the start of adulthood. Since the mean age of the participant is 17.31 at the follow-up, it is possible that the symptoms of interest had not yet expressed themselves.

To summarize, the results of the current study suggest that there are no differences in verbal and spatial working memory between SZo, BDo, and HCo However, considering the influence of IQ, it is important that these results are interpreted carefully. Moreover, the results showed that only spatial working memory developed positively over time, and could serve as a predictor for the development of manic symptoms at T2. It is important that the value spatial working memory as a cognitive marker is further investigated in future research. At last, verbal and spatial working memory at T1 could not serve as a valid predictor for the development of (sub)clinical depressive and psychotic symptoms at T2.

It should be noted that the current study has some limitations. Firstly, because of the relatively young age of the participants in this study, working memory deficits and symptoms that develop at a later age could not be investigated. In addition, since most of the participants signed up for this study on own initiative, it could be questioned if the investigated offspring groups are representative of the average patient groups. For instance, SZo and BDo might be motivated because they experience more impairments than other patients. Furthermore, the offspring groups have also a higher risk of developing psychopathology than the normal population. So findings cannot be generalized to (future) patients who have no affected relatives.

Despite the limitations, this study also had distinctive strengths compared to earlier studies. To our knowledge, this is the only study on verbal and spatial working memory that used a longitudinal design. Besides, the current study used a considerable sample size with different offspring groups (SZo and BDo) and a healthy control group (HCo).

Future research should follow up the current study, in which a third measuring moment (T3) will be included. In addition, it is important that the variable age will be included as a

variable of interest instead of a covariate. In this way, more information about the course, specific age stages and distinguish factors of both disorders will be provided .

Taken together, the findings of the current study implicates that difference in verbal and spatial working memory in SZo, BDo, and HCo are not visible at a early age. In this implication, the influence of IQ should be taken into account. Furthermore, this study found evidence for spatial working memory as predictor for manic symptoms. This evidence was not found for verbal and spatial working memory as predictors for depressive and psychotic symptoms. Future research is needed to explore the presence of working memory differences at a later stadium of the disorders. Hence, more information will be gained about working memory impairments as cognitive markers or otherwise just as consequences of schizophrenia and bipolar disorder.

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