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# Heritability of Memory Functions and Related Brain Volumes: A Schizophrenia Spectrum Study of 214 Twins

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**Background:** Memory performance is heritable and shares partial genetic etiology with schizophrenia. How the genetic overlap between memory and schizophrenia is related to intelligence (IQ) and brain volumes has not been formally tested using twin modeling. **Methods:** A total of 214 twins were recruited nationwide by utilization of the Danish registers, including monozygotic and dizygotic twin pairs concordant or discordant for a schizophrenia spectrum disorder and healthy control pairs. Memory/IQ assessments and MRI scans were performed and structural equation modeling was applied to examine the genetic and environmental effects and to quantify associations with schizophrenia liability. **Results:** Significant heritability estimates were found for verbal, visual and working memory. Verbal and visual memory were associated with schizophrenia, and for visual memory the association was due to overlapping genetics. IQ was highly heritable, but only performance IQ was associated with schizophrenia. Genetic factors also contributed to total brain, right superior frontal, left rostral middle frontal and hippocampal volumes. Smaller total brain and hippocampal volumes were associated with schizophrenia, and for the left hippocampus this association was due to overlapping genetic factors. All 3 memory measures were associated with IQ, but only visual memory was associated with total brain and hippocampal volumes. **Discussion:** Specific memory measures and brain volumes

were moderately heritable and showed overlap with schizophrenia liability, suggesting partially shared etiological influences. Our findings further suggest that factors impacting IQ also influence memory, whereas memory impairments and brain volume abnormalities appear to represent separate pathological processes in the pathway to schizophrenia.

**Key words:** Heritability, twin-study, cognition, memory, brain volumes, psychosis

## Introduction

Impaired memory functioning is a robust finding in patients with schizophrenia,<sup>1,2</sup> and has also been demonstrated in antipsychotic-naïve patients.<sup>3</sup> Moreover, memory impairments have been observed in individuals at ultra-high risk, who later transition to psychosis,<sup>4-6</sup> and in unaffected family members of patients with schizophrenia.<sup>7</sup> Deficient verbal memory is also among the best predictors of poor functional outcome.<sup>8,9</sup> Deficits have been documented for immediate and delayed recall of both verbal and visual materials.<sup>10,11</sup> Memory functioning has been found to be heritable, with small contributions from common environmental factors for some measures.<sup>12</sup>

Two previous twin studies reported a significant genetic overlap between schizophrenia and memory measured by selected subtests from the Wechsler Memory Scale, suggesting that shared genes may regulate the development of memory deficits and schizophrenia risk.<sup>13,14</sup>

One potential factor that could impact the relationship between memory and schizophrenia is intelligence, a highly heritable trait genetically associated with the illness.<sup>15,16</sup> We previously demonstrated that performance intelligence, but not verbal intelligence influenced some associations between specific cognitive functions and schizophrenia liability.<sup>17</sup> On the other hand, evidence also suggests that memory impairments in schizophrenia are not fully attributable to effects of intelligence.<sup>18–20</sup>

Neuroimaging studies of normal memory functioning have implicated interactions between the prefrontal and middle temporal lobe, including the hippocampus,<sup>21</sup> but specific components of memory performance may depend on different underlying neural systems. For example, impaired consolidation of episodic memory has been linked to the hippocampal network,<sup>22</sup> whereas frontal regions may be more involved in executive control of memory processes and working memory.<sup>23</sup> Altered gray matter in frontal regions has been reported in patients with schizophrenia and to a lesser extent in their unaffected siblings.<sup>24–27</sup> Hippocampal volume reduction is also a very consistent finding in patients with schizophrenia,<sup>28</sup> and has been demonstrated across illness stages.<sup>29–31</sup> Moreover, smaller hippocampal volumes are among the most profound brain abnormalities observed in non-affected relatives of patients with schizophrenia.<sup>32</sup> In the general population, twin studies have consistently demonstrated genetic influences on brain volumes with high heritability estimates observed for total brain, frontal and temporal volumes, while more moderate heritability estimates have been found for hippocampus.<sup>33,34</sup> However, evidence from studies using schizophrenia samples suggests that hippocampal volumes and frontal gray matter may be more susceptible to environmental effects in patients and their unaffected relatives.<sup>35–38</sup>

Previous studies have reported significant correlations between memory performance and brain structure in patients with schizophrenia,<sup>18,39,40</sup> for both frontal regions<sup>41,42</sup> and hippocampus.<sup>43–45</sup> These findings suggest that abnormal brain morphology and impaired memory may be intertwined in the pathophysiology of schizophrenia. However, it is currently unknown whether genetic or environmental factors influence the co-occurrence of memory deficits and brain abnormalities. To the best of our knowledge, no previous twin study has examined how brain structure relates to the genetic relationship between memory and schizophrenia. It is therefore unknown whether the same underlying etiological processes lead to memory deficits and brain volume abnormalities in

schizophrenia. A better understanding of the genetic and environmental underpinnings of cognition, related brain structure and the relationship with schizophrenia risk may increase our understanding of the etiology of the illness.

The primary aim of the study was to examine the heritability of (verbal, visual, and working) memory and (genetic or environmental) associations with schizophrenia liability. As a secondary aim, we examined the heritability of intelligence/brain volumes and their (genetic or environmental) associations with memory and schizophrenia liability.

## Methods

Data were obtained from 214 individuals as part of the Vulnerability Indicators of Psychosis (VIP) study. This cohort has been described in more details previously.<sup>46,47</sup> Informed consent was obtained from all participants. The study was approved by The Danish Health and Medicines Authority, The Danish National Committee on Health Research Ethics (H-2-2010-128), and The Danish Data Protection Agency (2010-41-5468).

### Participants

All monozygotic (MZ) and dizygotic (DZ) twin pairs in Denmark concordant or discordant for a diagnosis in the schizophrenia spectrum were identified by linking The Danish Twin Register<sup>48</sup> with The Danish Psychiatric Central Research Register.<sup>49</sup> The identified study population of proband pairs was constrained to include twin pairs aged 18–60 years, where both twins were alive and residing in Denmark. All MZ proband pairs were invited to participate in clinical examinations, while DZ proband pairs and healthy control (HC) pairs were recruited subsequently and matched on age and gender to the included MZ proband pairs. Thirty-two complete MZ proband pairs, 22 complete DZ proband pairs, 29 complete MZ HC pairs and 20 complete DZ HC pairs participated in this study. In addition, 8 twins from proband pairs participated without their sibling (singletons) (MZ patient = 1, MZ co twin = 1, DZ patient = 3, DZ co twin = 3), resulting in a final sample size of 214 individuals. All DZ proband pairs were discordant for the disorder, while 5 of the complete MZ proband pairs were concordant as well as one singleton MZ twin (twin diagnosis obtained from the registers) ([table 1](#)).

Register diagnoses were verified using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview<sup>50</sup> according to ICD-10 criteria. The project diagnosis was used in cases of discrepancy between the register and project diagnosis. Zygosity status was confirmed by blood samples (PsychCHIP v.1-1, Illumina). Register information was used in 17 cases where DNA samples were not available (MZ proband = 8, DZ proband = 5, DZ HC = 4).

**Table 1.** Demographic and Clinical Variables

	Patients ( <i>N</i> = 63)	MZ Co-twins ( <i>N</i> = 28)	DZ Co-twins ( <i>N</i> = 25)	HC ( <i>N</i> = 98)	Statistical Test
Age, years; mean (SD)	41.10 (10.62)	39.25 (10.99)	41.76 (10.20)	40.64 (15.85)	$F(3, 210) = 0.30, P = .827$
Sex					
Females; <i>N</i> (%)	29 (46.0%)	13 (46.4%)	14 (56.0%)	48 (49.0%)	$\chi^2(3) = .773, P = .856$
Males; <i>N</i> (%)	34 (54.0%)	15 (53.6%)	11 (44.0%)	50 (51.0%)	
Years of education; mean (SD)	13.11 (2.69)	13.73 (3.19)	14.26 (3.87)	15.85 (2.78)	$F(3, 200) = 11.45, P < .001$
ICD-10 F2x Diagnosis; <i>N</i>	63	0	0	0	
Schizophrenia	38				
Schizotypal disorder	11				
Acute/transient psychotic	9				
Schizoaffective	4				
Unspec. non-org. psychosis	1				
Con-/discordant <i>N</i>	11/52	-	-	-	
Age at first F2x diagnosis; mean (SD)	26.88 (7.33)	-	-	-	
Years since first F2x diagnosis; mean (SD)	14.69 (8.96)	-	-	-	
Antipsychotic treatment; <i>N</i> (%)	39 (61.9%)	-	-	-	

Note: MZ, Monozygotic; DZ, Dizygotic. For the concordant proband pairs, both twins are included in the patient group.

Exclusion criteria for the present study included serious physical illness, pregnancy, serious head trauma (resulting in loss of consciousness >5 minutes as verified in medical records), and drugs/alcohol addiction. For HC pairs no diagnosis of major psychosis in first-degree relatives was allowed.

### Memory and IQ Assessments

Memory was examined using the list learning task from the Brief Assessment of Cognition in Schizophrenia (BACS),<sup>51</sup> 15 word pairs,<sup>52</sup> Rey Complex Figure Test (RCFT),<sup>53</sup> and 2 subtests from the Cambridge Automated Neuropsychological Test battery (CANTAB): Spatial Span (SSP) and Spatial Working memory (SWM)<sup>54,55</sup> (see [supplementary materials](#) for detailed descriptions of the tasks). To reduce the number of variables, factor scores were created for the memory measures using SPSS (version 24). First, z-scores were calculated based on the mean and standard deviation of one twin from each HC pair (the first-born twin). We used data from one twin only because data from 2 twins in a twin pair are not independent. Including both healthy control twins would potentially capture the same overall variance in creation of factors scores, and hereby influence heritability estimates. A principal component analysis (PCA) with varimax rotation using z-scores resulted in 3 memory factors, ie, verbal memory (BACS total recall + error scores from 15 WP), visual memory (RCFT copy, immediate recall, and recognition + SSP span length and number of attempts), and working memory (SWM between errors and strategy).

Intelligence (IQ) was estimated using 4 subtests (matrix reasoning, block design, vocabulary and similarities) from The Wechsler Adult Intelligence Scale (WAIS-III)<sup>56</sup> and the Danish version of the National Adult Reading Test.<sup>57,58</sup> Based on a separate PCA using the same approach as above, IQ was divided into verbal and performance IQ. The IQ and CANTAB data from this cohort has been previously published.<sup>17</sup>

### MRI Image Acquisition

Structural brain scans were conducted on a Philips 3.0 T Achieva whole-body MRI scanner (Philips Healthcare, Best, The Netherlands) with a 32-channel SENSE Head Coil (Invivo) and obtained with a T1-weighted sequence. The scanner was upgraded approximately halfway through inclusion. Structural images were processed using FreeSurfer (version 5.3) (<http://surfer.nmr.mgh.harvard.edu/fswiki/>). Quality control was performed on all scans blinded to group status according to the ENIGMA guidelines (protocol 2.0) (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>). We included regions relevant to memory functioning based on earlier findings in the literature.<sup>18,21,40</sup> The Desikan-Killiany atlas was used to extract the volumes of bilateral hippocampi, superior, rostral and caudal middle frontal cortices as well as the intracranial (ICV) and total brain volume.<sup>59</sup> Of the 214 participants, 10 did not have an MRI scan (MZ patients *N* = 7, DZ patients *N* = 1, MZ co-twins *N* = 2).

### Statistical Analyses

**Preparing for Model Fitting.** Outliers more than 3 SD from the mean were removed before model fitting for

the applied memory measures and brain volumes. To test for possible effects of a scanner upgrade, prior to genetic modeling, we corrected the brain volumes, by computing residuals of a linear model that included a 0/1 covariate for scanner update. This did not change the findings so in what follows, we present results without the scanner upgrade correction. For completeness, we analyzed both the cognitive components and individual outcome measures. The error scores from 15 word pairs were highly skewed with a substantial proportion of participants making zero mistakes. The error scores were therefore divided into 4 categories before model fitting: the first containing everyone with zero mistakes and the remaining 3 categories divided into approximately equal-sized groups. For some measures, data was only available from one member of a twin pair, but all available data was included in the analyses to increase power and to get a better estimate of group means and variances.

*Genetic Model Fitting.* Twin modeling utilizes the fact the MZ twins share (almost) 100% of their segregating genes, while DZ twins share 50% (on average). Thus, if the covariance of a given trait is stronger in MZ twins compared to DZ twins, genetic factors are assumed to influence the trait. On the other hand, if MZ and DZ twins resemble each other to a similar extent, common environmental factors are thought to influence the trait. The variance that is not shared between MZ twins is attributed to unique environmental effects.

This was quantified using structural equation modeling (SEM) in the OpenMx software (2.9.6) installed on the R platform (3.3.2). SEM allows for an estimation of additive genetic effects (A), common (shared) environmental effects (C), and unique environmental effects (+ measurement error) (E) on a given trait, by modeling latent factors for A, C, and E, assuming A correlate 1 in MZ pairs, and 0.5 in DZ pairs, C correlate 1 for both zygositys, and E is independent by definition. SEM uses maximum likelihood estimation to compare the observed covariance matrix with the covariance matrix predicted by the model. Significance of variance components was based on comparing the full model with the model in which the variance component was constrained at zero. Minus 2 times the difference in the log-likelihood of these models is distributed as a 50:50 mixture of a Chi-square distribution with zero and one degree of freedom, respectively<sup>60</sup> (please see [supplementary materials](#) for the equations applied and illustrations). Age and sex were included as covariates on the mean for the memory traits and brain measures.

*Modelling Schizophrenia Liability.* For schizophrenia, a threshold model was assumed, in which the risk of schizophrenia is normally distributed, and the disorder only occurs when a certain threshold is exceeded. Because this

was not a population-based study, the critical threshold and heritability for schizophrenia was not estimated. The liability threshold was fixed in correspondence with an overall population prevalence of 1.85%. The heritability of a schizophrenia spectrum disorder was fixed at 73% and unique environmental influences at 27%, based on a recent population-based study from our group using the Danish registers.<sup>61</sup>

*Modelling Genetic Associations Between Traits.* A bivariate model was applied to examine potential associations between schizophrenia liability and other traits. The proportion of the correlation explained by genetic, shared environmental and unique environmental factors can be estimated by comparing cross-twin cross-trait correlations in MZ and DZ twins. Larger MZ cross-correlations than DZ correlations indicate a genetic factor that influences both schizophrenia liability and the other trait (eg, memory or brain volume). Because the applied estimates for schizophrenia did not show a significant C-component, correlations with schizophrenia liability cannot be due to common environmental factors and thus not modeled. The  $R_a$  and  $R_c$  were combined with the observed heritability estimates to calculate the part of the phenotypic correlation ( $R_{ph}$ ) due to genetics ( $R_{ph-a}$ ) and unique environmental effects ( $R_{ph-e}$ )<sup>16</sup> ([supplementary figure 1](#)).

Finally, we also examined associations between the memory components and brain volumes. Only brain measures showing an association with schizophrenia were included in this model. Additionally, based on our previous finding that some associations between specific cognitive components and schizophrenia may be driven by performance IQ, we also examined the covariance between memory and IQ. We estimated these association in a trivariate model including schizophrenia to account for the fact that these associations were estimated in a schizophrenia cohort. Similar to the bivariate case, these associations can be split into genetic and environmental parts.

## Results

**Table 1** shows the demographic and clinical variables for patients, their unaffected co-twins and HC's. There were no significant group differences in age or distribution of the sexes, but there was a significant difference in years of education between groups. [Supplementary tables S1 and S2](#) show the average memory performance and brain volumes for the 4 groups and the number of participants included for each measure.

### *Heritability of Memory and Associations With Schizophrenia Liability*

The genetic and environmental influences on memory performance and associations with schizophrenia liability

**Table 2.** Genetic, Common, and Unique Environmental Influences on Memory and Associations With Schizophrenia Liability

	A [CI]	C [CI]	E [CI]	$R_{ph}$ [CI]	$R_{pha}$ [CI]	$R_{phe}$ [CI]
<b>Verbal memory</b>	<b>0.48</b> [0.17–0.62]	0.00 [0.00–0.27]	<b>0.52</b> [0.38–0.68]	<b>-0.15</b> [-0.29 to -0.01]	-0.09 [-0.24–0.06]	-0.06 [-0.16–0.04]
BACS memory total	<b>0.55</b> [0.17–0.66]	0.00 [0.00–0.34]	<b>0.45</b> [0.34–0.60]	-0.13 [-0.25–0.01]	-0.08 [-0.22–0.06]	-0.04 [-0.13–0.05]
15 WP errors first trial	<b>0.30</b> [0.01–0.50]	0.00 [0.00–0.50]	<b>0.70</b> [0.50–0.92]	<b>0.20</b> [0.06–0.34]	0.13 [-0.03–0.28]	0.08 [-0.04–0.20]
15 WP immediate recall	<b>0.30</b> [0.01–0.50]	0.00 [0.00–0.34]	<b>0.70</b> [0.50–0.93]	<b>0.17</b> [0.03–0.31]	0.11 [-0.06–0.26]	0.07 [-0.06–0.19]
15 WP delayed recall	<b>0.52</b> [0.21–0.68]	0.00 [0.00–0.23]	<b>0.48</b> [0.32–0.69]	<b>0.20</b> [0.05–0.34]	0.10 [-0.07–0.26]	0.10 [-0.01–0.21]
<b>Visual memory</b>	<b>0.21</b> [0.01–0.51]	0.15 [0.00–0.42]	<b>0.64</b> [0.49–0.81]	<b>-0.28</b> [-0.40 to -0.14]	<b>-0.20</b> [-0.35 to -0.05]	-0.07 [-0.18–0.03]
RCFT copy	0.04 [0.00–0.39]	0.19 [0.00–0.35]	<b>0.77</b> [0.61–0.95]	<b>-0.26</b> [-0.37 to -0.14]	<b>-0.17</b> [-0.30 to -0.02]	-0.09 [-0.20–0.02]
RCFT immediate recall	<b>0.58</b> [0.34–0.70]	0.00 [0.00–0.19]	<b>0.42</b> [0.30–0.57]	<b>-0.31</b> [-0.43 to -0.18]	<b>-0.25</b> [-0.39 to -0.11]	-0.06 [-0.14–0.02]
RCFT recognition	0.12 [0.00–0.46]	0.15 [0.00–0.38]	<b>0.73</b> [0.54–0.92]	<b>-0.17</b> [-0.30 to -0.04]	<b>-0.10</b> [-0.25–0.05]	-0.07 [-0.18–0.05]
SSP span length	<b>0.12</b> [0.02–0.56]	0.30 [0.00–0.48]	<b>0.58</b> [0.43–0.74]	<b>-0.29</b> [-0.41 to -0.15]	<b>-0.24</b> [-0.38 to -0.08]	-0.05 [-0.15–0.05]
SSP no. of attempts	<b>0.50</b> [0.03–0.65]	0.02 [0.00–0.43]	<b>0.48</b> [0.35–0.66]	<b>0.29</b> [0.15–0.41]	<b>0.20</b> [0.05–0.34]	0.09 [-0.01–0.18]
<b>Working memory</b>	<b>0.58</b> [0.09–0.69]	0.00 [0.00–0.43]	<b>0.42</b> [0.31–0.57]	-0.14 [-0.27–0.00]	-0.09 [-0.24–0.06]	-0.04 [-0.13–0.05]
SWM strategy	<b>0.58</b> [0.25–0.70]	0.00 [0.00–0.28]	<b>0.42</b> [0.30–0.57]	<b>0.18</b> [0.04–0.31]	<b>0.17</b> [0.02–0.31]	0.01 [-0.07–0.10]
SWM between search errors	<b>0.59</b> [0.34–0.70]	0.00 [0.00–0.21]	<b>0.41</b> [0.30–0.56]	<b>0.25</b> [0.11–0.37]	<b>0.16</b> [0.01–0.31]	0.08 [-0.00–0.17]

*Note:* Numbers represent the estimated effects of A, additive genetic factors/heritability; C, common environmental factors; E, unique environmental factors;  $R_{ph}$ , Phenotypic association;  $R_{pha}$ , association due to genetic factors;  $R_{phe}$ , association due to unique environmental factors. Confidence intervals are presented in brackets.  $X^2$  tests based on the  $-2 \log$  likelihood difference for the  $P$ -values were used to determine significance. Significant effects displayed in bold, E includes measurement error and is significant by default. Verbal memory (BACS total recall + all error scores from 15 word pairs [WP]), Visual memory (Rey Complex Figure Test [RCFT] copy, immediate recall, and recognition + Spatial Span [SSP] span length and number of attempts) and Working memory (Spatial Working Memory [SWM] between errors and strategy). For BACS memory total, RCFT copy, immediate recall and recognition and SSP span length, higher scores represent better performance and a negative association with schizophrenia indicates that better performance is associated with lower liability. For 15 WP, SSP no. of attempts, SWM strategy and between search errors higher scores represent poorer performance, and therefore a positive association with schizophrenia indicates that better performance is associated with lower liability. For the memory components, scores from 15 WP, SSP no. of attempts, SWM strategy, and between search errors were inverted.

are presented in [table 2](#). Genetic factors significantly influenced all 3 memory factors, with working memory showing the highest heritability estimate followed by verbal and then visual memory.

Both verbal and visual memory were negatively associated with schizophrenia liability, indicating that a poorer performance in these measures is associated with a higher disease liability. For visual memory, the association was due to overlapping genetic factors. Even though the individual outcome measures included in working memory, ie, SWM strategy and between search errors, were significantly associated with schizophrenia liability separately, the estimate for the working memory component did not reach significance.

#### *Heritability of IQ/Brain Volumes and Associations With Schizophrenia Liability*

[Table 3](#) shows the genetic and environmental influences on IQ and the included brain volumes and associations with schizophrenia liability. Both verbal and performance IQ were highly heritable, but only performance IQ was associated with schizophrenia. ICV, total brain, right superior frontal, left rostral middle frontal and hippocampus volumes (right and left) were significantly heritable. In addition, common environmental factors also significantly influenced ICV, total brain, right hippocampus, rostral middle frontal volumes (right and left) and right caudal middle frontal. Left superior frontal and left caudal middle frontal volumes were only explained by unique environmental factors. Total brain and hippocampus volumes were associated with schizophrenia, and for the left hippocampus this association was due to overlapping genetics.

#### *Associations Between Memory and IQ/Brain Volumes in Schizophrenia*

Finally, we examined potential associations between the 3 memory factors and IQ/brain volumes ([figure 1](#)). Verbal and working memory were significantly associated with both verbal and performance IQ, whereas visual memory only correlated with performance IQ. For the associations between verbal memory and IQ (both verbal and performance) we observed a significant genetic contribution. The same was the case for the association between working memory and verbal IQ.

Of the included brain volumes, only total brain and hippocampal volumes were significantly associated with schizophrenia liability ([table 3](#)), so these were included in the final analyses. Visual memory was significantly associated with total brain and right hippocampus volume. We did not have the power to separate these into genetic or environmental contributions. When controlling for total brain volume, the association with hippocampus was no longer significant. Verbal and working memory were

not associated with either total brain or hippocampal volumes.

## Discussion

The first aim of this study was to examine genetic and environmental influences on memory performance and associations with schizophrenia liability. All 3 memory factors were significantly heritable with moderate estimates, further confirming the important role of genetic factors in memory.<sup>12</sup> Both verbal and visual memory were negatively associated with schizophrenia liability, consistent with previous twin studies.<sup>13,14</sup> For visual memory, the covariance with schizophrenia could be explained by overlapping genetic factors. The association between working memory and schizophrenia did not reach significance; however, the individual measures comprising the working memory factor score, ie, SWM strategy and between search errors, were both significantly associated with schizophrenia liability. Further, these associations had a significant genetic contribution. The associations between the memory components and schizophrenia were negative, indicating that a lower memory performance is associated with a higher disease liability. These results contribute to our understanding of the processes underlying the co-occurrence of cognitive deficits and psychosis,<sup>62</sup> by demonstrating a partially shared etiology, consistent across different types of memory. The significant genetic contributions to the majority of these associations suggest that an overlapping set of genes regulate the development of memory and schizophrenia risk, which may partly explain why many patients with schizophrenia experience memory problems. Nevertheless, the genetic correlations were small, and thus the memory deficits do not simply arise from schizophrenia liability nor can schizophrenia derive from the presumed common factors alone, including neural change, leading to memory deficits.

Although the observed estimates of the genetic effects on memory were lower than the estimated heritability of 79% for schizophrenia,<sup>61</sup> the heritable memory measures showing genetic associations with schizophrenia liability could represent endophenotypes for the disorder.<sup>14,63,64</sup> It may not be feasible to identify an endophenotype that is more heritable than schizophrenia itself, and another potentially useful strategy would be to identify a collection of endophenotypes that additively resemble the heritability of schizophrenia.<sup>65,66</sup> Through this approach, the complexity of the phenotypic presentation of schizophrenia is reduced, by focusing on specific aspects of the illness, and hereby delineating the entire heritability of schizophrenia into components with specific underlying neurobiology.

The second aim of the study was to examine the heritability of IQ/brain volumes and their influence on the relationship between memory and schizophrenia. We included

**Table 3.** Genetic, Common, and Unique Environmental Influences on Brain Volumes and IQ and Associations With Schizophrenia Liability

	A [CI]	C [CI]	E [CI]	$R_{ph}$ [CI]	$R_{ph-a}$ [CI]	$R_{ph-e}$ [CI]
Intracranial volume	<b>0.26</b> [0.09–0.52]	<b>0.62</b> [0.41–0.78]	<b>0.12</b> [0.08–0.18]	-0.06 [-0.17–0.06]	-0.02 [-0.16–0.11]	-0.04 [-0.09–0.01]
Total brain volume	<b>0.32</b> [0.15–0.49]	<b>0.55</b> [0.40–0.72]	<b>0.13</b> [0.09–0.17]	<b>-0.15</b> [-0.27 to -0.04]	-0.09 [-0.21–0.04]	<b>-0.07</b> [-0.11 to -0.02]
Hippocampus volume L	<b>0.45</b> [0.14–0.81]	0.32 [0.00–0.61]	<b>0.23</b> [0.16–0.33]	<b>-0.23</b> [-0.36 to -0.09]	<b>-0.20</b> [-0.34 to -0.05]	-0.03 [-0.10–0.04]
Hippocampus volume R	<b>0.23</b> [0.01–0.53]	<b>0.56</b> [0.26–0.76]	<b>0.21</b> [0.15–0.29]	<b>-0.17</b> [-0.29 to -0.03]	-0.14 [-0.28–0.01]	-0.03 [-0.08–0.03]
Superior frontal volume L	0.35 [0.00–0.76]	0.35 [0.00–0.65]	<b>0.30</b> [0.21–0.41]	-0.09 [-0.23–0.04]	-0.02 [-0.17–0.12]	-0.07 [-0.15–0.00]
Superior frontal volume R	<b>0.49</b> [0.16–0.82]	0.28 [0.00–0.52]	<b>0.24</b> [0.17–0.33]	-0.12 [-0.25–0.01]	-0.04 [-0.18–0.10]	<b>-0.08</b> [-0.14 to -0.02]
Rostral middle frontal volume L	<b>0.42</b> [0.05–0.78]	<b>0.46</b> [0.07–0.61]	<b>0.36</b> [0.28–0.49]	-0.09 [-0.23–0.05]	0.02 [-0.13–0.17]	<b>-0.11</b> [-0.19 to -0.04]
Rostral middle frontal volume R	0.18 [0.00–0.61]	<b>0.46</b> [0.07–0.69]	<b>0.36</b> [0.25–0.47]	-0.03 [-0.15–0.10]	0.01 [-0.11–0.14]	-0.04 [-0.12–0.03]
Caudal middle frontal volume L	0.36 [0.00–0.70]	0.25 [0.00–0.59]	<b>0.40</b> [0.29–0.53]	0.01 [-0.12–0.14]	0.10 [-0.05–0.23]	<b>-0.09</b> [-0.18 to -0.01]
Caudal middle frontal volume R	0.15 [0.00–0.60]	<b>0.34</b> [0.19–0.51]	<b>0.50</b> [0.38–0.65]	0.04 [-0.08–0.17]	0.14 [-0.01–0.29]	-0.10 [-0.19–0.00]
Verbal IQ	<b>0.86</b> [0.53–0.90]	0.00 [0.00–0.33]	<b>0.14</b> [0.10–0.19]	-0.04 [-0.18–0.10]	0.01 [-0.14–0.15]	-0.05 [-0.10–0.01]
Performance IQ	<b>0.53</b> [0.14–0.78]	0.17 [0.00–0.53]	<b>0.30</b> [0.22–0.41]	<b>-0.23</b> [-0.36 to -0.10]	<b>-0.18</b> [-0.32 to -0.03]	-0.05 [-0.13–0.02]

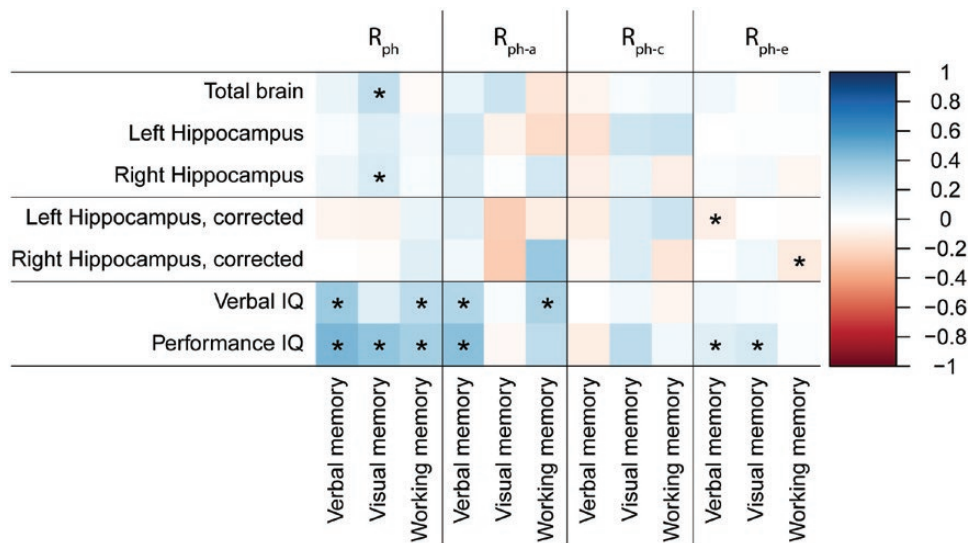
Note: Numbers represent the estimated effects of A, additive genetic factors/heritability; C, common environmental factors; E, unique environmental factors;  $R_{ph}$ , Phenotypic association;  $R_{ph-a}$ , association due to genetic factors;  $R_{ph-e}$ , association due to unique environmental factors. Confidence intervals are presented in brackets.  $X^2$  tests based on the  $-2$  log likelihood difference for the  $P$ -values were used to determine significance. Significant effects displayed in bold; E includes measurement error and is significant by default.

brain volumes showing an association with schizophrenia liability as well as verbal and performance IQ. For IQ we found high heritability estimates consistent with existing literature,<sup>12,67</sup> but only performance IQ was significantly associated with schizophrenia liability (see ref.<sup>17</sup> for an expanded discussion of these findings). All 3 memory factors, verbal, visual, and working memory, were significantly associated with performance IQ, and both verbal and working memory were also associated with verbal IQ. The associations between verbal memory and both verbal and performance IQ and between working memory and verbal IQ were due to overlapping genetic factors. These findings suggest that factors influencing IQ, also influence some aspects of memory in schizophrenia.

For brain volumes, we observed significant heritability estimates for total brain, right superior frontal, left rostral middle frontal, and hippocampal (left and right) volumes, in line with previous research demonstrating genetic influences on brain volumes.<sup>33,34</sup> Based on the literature in healthy individuals, one might expect a low contribution of common environmental effects to brain volumes. However, in this schizophrenia cohort, we also observed moderate contributions from common environmental factors for several measures, ie, total brain, right hippocampus, rostral middle frontal (left and right), and right caudal middle frontal volumes. Lower heritability and higher contributions of common environment has been observed in schizophrenia samples before<sup>35</sup> and might be related to household-related factors such as childhood trauma or substance abuse, both of which have been found to increase the risk for schizophrenia.<sup>68,69</sup>

None of the included frontal measures were significantly associated with schizophrenia liability. To the best of our knowledge, no previous twin study has investigated volumes of specific frontal subregions in schizophrenia patients. Hulshoff Pol et al<sup>70</sup> reported a thinner right orbitofrontal superior cortex with higher schizophrenia liability when measuring cortical thickness in twins. However, Van Haren et al<sup>71</sup> reported no significant association between total frontal cortical gray matter and schizophrenia liability, which is in accordance with our findings. For total brain volume we observed a significant association with schizophrenia liability, consistent with previous reports.<sup>35,71,72</sup> Moreover, in our study hippocampal volumes were associated with schizophrenia, in line with previous findings,<sup>35,36</sup> although a lack of an association has also been reported.<sup>72</sup> In our study, the association between left hippocampus and schizophrenia was due to overlapping genetic factors, indicating a differential role of the 2 hemispheres in the genetic origins of schizophrenia. Several previous studies have indicated the importance of left hippocampus in schizophrenia, especially in the early phases of the disease.<sup>30,73–76</sup>

Finally, when examining associations between memory and brain volumes, only visual memory was significantly associated with total brain and the right hippocampus.



**Fig. 1.** Associations between memory and brain volume/IQ. *Note:*  $X^2$  tests based on the  $-2 \log$  likelihood difference for the  $P$ -values were used to determine significance. Stars represent significant associations.  $R_{ph}$ , Phenotypic association;  $R_{ph-a}$ , association due to genetic effects;  $R_{ph-c}$ , association due to common environmental effects;  $R_{ph-e}$ , association due to unique environmental effects. TB corrected, Corrected for total brain volume on an individual level.

When controlling for total brain volume, the association with hippocampus disappeared, suggesting a more global effect. We did not observe any associations between the brain measures chosen and verbal or working memory. The phenotypic associations are indications of potential common etiological influences between the 2 traits. It may be the case that both memory and brain volumes are abnormal in schizophrenia, but that these abnormalities are caused by distinct genetic and/or environmental factors.<sup>62</sup> Our findings suggest that visual memory impairments may be influenced by the same underlying factors as total brain and hippocampus volumes in schizophrenia, whereas deficits in verbal memory/working memory, and brain abnormalities may represent separate processes in the pathway to schizophrenia.

One possible limitation of this study is that twin pairs were specifically selected based on a schizophrenia spectrum diagnosis, and therefore model parameters for schizophrenia were not directly assessed. However, we applied estimates from a very recent Danish population-based study of which our sample is a subset.<sup>61</sup> Another potential limitation concerns the number of participants included. Even though we took advantage of the Danish registers to identify eligible participants, the number of twin pairs concordant or discordant for a schizophrenia spectrum diagnosis is relatively sparse. This, in combination with the fact that the patient group is often difficult to recruit, especially for a study with such a comprehensive examination program, resulted in a relatively small sample size for genetic twin modeling, which raises concerns about power issues. Finally, the current sample size did not allow us to explore potential gene-environment interactions that likely exist.

In sum, verbal, visual, and working memory were heritable, providing further evidence of the importance of genetics in memory functioning. Moreover, most memory measures showed genetic overlap with schizophrenia liability, indicating a partially overlapping etiology. Our findings further suggest that the same factors involved in the development of IQ also influence memory functioning.

Total brain, right superior frontal, left rostral middle frontal and hippocampal volumes were also heritable, but only total brain and hippocampal volumes were associated with disease. Finally, visual memory was associated with total brain and hippocampus, indicating an overlap in the underlying processes, whereas verbal/working memory impairments and brain abnormalities seem to represent separate pathological processes in the pathway to schizophrenia.

### Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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