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ORIGINAL ARTICLE

Genetic overlap between episodic memory deficits and schizophrenia: results from The Maudsley Twin Study

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Background. Visual and verbal episodic memory deficits are putative endophenotypes for schizophrenia; however, the extent of any genetic overlap of these with schizophrenia is unclear. In this study, we set out to quantify the genetic and environmental contributions to variance in visual and verbal memory performance, and to quantify their genetic relationship with schizophrenia.

Method. We applied bivariate genetic modelling to 280 twins in a classic twin study design, including monozygotic (MZ) and dizygotic (DZ) pairs concordant and discordant for schizophrenia, and healthy control twins. We assessed episodic memory using subtests of the Wechsler Memory Scale – Revised (WMS-R).

Results. Genetic influences (i.e. heritability) contributed significantly to variance in immediate recall of both verbal memory and visual learning, and the delayed recall of verbal and visual memory. Liability to schizophrenia was associated with memory impairment, with evidence of significant phenotypic correlations between all episodic memory measures and schizophrenia. Genetic factors were the main source of the phenotypic correlations for immediate recall of visual learning material; both immediate and delayed recall of verbal memory; and delayed recall of visual memory that, for example, shared genetic variance with schizophrenia, which accounted for 88% of the phenotypic correlation ($r_{ph} = 0.41$) between the two.

Conclusions. Verbal memory and visual learning and memory are moderately heritable, share a genetic overlap with schizophrenia and are valid endophenotypes for the condition. The inclusion of these endophenotypes in genetic association studies may improve the power to detect susceptibility genes for schizophrenia.

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Introduction

Endophenotypes could facilitate the endeavours of molecular geneticists to dissect the complex disease mechanisms of illnesses such as schizophrenia (Tan *et al*. 2008). Intermediate phenotypes or endophenotypes are discrete genetically determined disease-related phenotypes that gauge genetic predisposition (Gottesman & Gould, 2003). They may offer insights into the genetic transmission of psychiatric illness because they are more proximal to the gene effects than the heterogeneous and subjective symptoms that define clinical syndromes; and because of their quantitative and genetically simpler nature offer improved statistical power for genetic analyses (Cannon & Keller, 2006). Gottesman & Gould (2003) have suggested five criteria for the identification of endophenotypes: an endophenotype is associated with illness in the population; it is heritable; it is primarily state independent (manifests in an individual whether or not illness is active); within families, endophenotype and illness co-segregate; and it is found in non-affected family members at a higher rate than in the general population.

Neurocognitive impairments are putative endophenotypes, uncorrelated with illness subtype (Elvevag & Goldberg, 2000), show limited improvement from typical or atypical antipsychotics (Blyler &

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Gold, 2000), are present before clinical onset (Jones *et al*. 1994; Cannon *et al*. 2002), and persist throughout the course of illness (Heaton *et al*. 2001). Further support for neurocognitive endophenotypes has been suggested by genetic association studies, suggesting genetic effects linking both schizophrenia and episodic memory (Goldberg *et al*. 2003; Cannon *et al*. 2005; Prasad *et al*. 2005; Toulopoulou *et al*. 2006), such as the α_7 neural nicotinic acid receptor (CHRNA7) (Dempster *et al*. 2006). Deletion of a region of chromosome 15q13.3, which includes CHRNA7, is associated with schizophrenia (Stefansson *et al*. 2008).

Episodic memory (EM), together with deficits in attention and executive function, is among the most promising neurocognitive endophenotypic markers (Sitskoorn *et al*. 2004). Meta-analyses consistently report severe impairments in immediate and delayed verbal and non-verbal memory in patients (Heinrichs & Zakzanis, 1998; Aleman *et al*. 1999; Fioravanti *et al*. 2005; Dickinson *et al*. 2007). Cirillo & Seidman (2003) concluded that memory deficits are probably due to an encoding failure, with some evidence for mild but significantly impaired rate of forgetting.

The most compelling support for the validation of EM as a marker for schizophrenia has come from studies of unaffected relatives, where memory deficits are hypothetically determined by familial effects, attributable to either common environmental or genetic effects. Meta-analyses concur that unaffected relatives have moderate memory deficits with verbal material and mild to moderate with non-verbal material (for a review see Reichenberg & Harvey, 2007). Twin studies are now needed to confirm the heritability of EM and its genetic relationship with schizophrenia, as the earlier family studies could not discriminate between genetic and common environmental effects (Cannon, 2005). Studying monozygotic (MZ) and dizygotic (DZ) discordant pairs in a classic twin design offers a natural experiment to untangle these competing roles (Martin *et al*. 1997; Rijsdijk & Sham, 2002).

Very few twin studies have examined EM in schizophrenia (Goldberg *et al*. 1990, 1993; Cannon *et al*. 2000). Those that have formally quantified the heritability of EM in schizophrenia have tended to use the California Verbal Learning Test (CVLT), with small to moderate estimates (Tuulio-Henriksson *et al*. 2002; Glahn *et al*. 2007; Greenwood *et al*. 2007; Gur *et al*. 2007; Husted *et al*. 2009). Goldberg *et al*. (1993), studying MZ discordant pairs, found that the unaffected co-twins were also impaired on EM, in both immediate and delayed recall, and in verbal and non-verbal modalities. Cannon *et al*. (2000) used a broad neuropsychological battery and identified four tests, including verbal memory recall errors, to contribute to the discrimination of genetic loading for schizophrenia. However, to our knowledge no study has so far used formal genetic model fitting to investigate the heritability of EM and its genetic overlap with schizophrenia. We have used this model to quantify the heritability and genetic and environmental contributions to the covariation of schizophrenia and candidate endophenotypes, including intellectual functioning and working memory (Toulopoulou *et al*. 2007); brain volumes (Rijsdijk *et al*. 2005); and event-related potential components (Hall *et al*. 2007). Genetic modelling separates the covariance between two variables (e.g. schizophrenia and memory) into genetic and environmental components, indicating the degree to which the same genes influence the two traits, and the latter reflects the level to which their covariance is induced by the environment (Rijsdijk & Sham, 2002).

Our aim was to validate EM as a candidate endophenotype, specifically its heritability and the extent to which EM's dysfunction overlaps genetically with schizophrenia. We used regression analysis to test the hypothesis that (1) EM impairment in schizophrenia would be genetically influenced, with EM dysfunction increasing linearly with the degree of genetic loading for schizophrenia, such that an increased genetic risk for schizophrenia (in the healthy co-twins) predicts poor memory performance compared to controls; that is, patients < healthy co-twins < controls. We then used bivariate genetic modelling to quantify the genetic (i.e. heritability) and environmental contributions to variance on EM and also to estimate the genetic covariance between EM and liability to schizophrenia. We hypothesized that (2) EM would be moderately heritable; and (3) shared genetic influences would account for the majority of the covariance between EM and liability to schizophrenia. To investigate whether any covariance between memory and liability to schizophrenia was due to memory performance being an indicator of general intelligence, we also estimated the genetic covariance between intelligence and episodic memory.

Method

Participants

Twin patients were referred through National Health Service (NHS) treatment centres across the UK by their treating psychiatrists. The NHS cares for most patients with schizophrenia, and thus is a representative system from which to recruit. Control twins were recruited from the Institute of Psychiatry twin volunteer register and through newspaper advertisements. Exclusion criteria applied to all groups were: age under 18 years, a neurological disorder or a systemic illness with known neurological complications, any head

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injury associated with loss of consciousness for more than 1 minute, and current harmful substance use or dependency (within the past 12 months). No participants had a psychotic illness attributable to the use of illicit substances. All patients were clinically stable at the time of testing. All participants fulfilling study criteria provided written consent, which was approved by the UK Multicentre Research Ethics Committee.

Clinical assessment

DSM-IV diagnoses for all participants were made using the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (Spitzer & Endicott, 1978) and/or by the Structured Clinical Interview for DSM-IV (First *et al*. 1997), supplemented by medical notes where necessary. Patients' psychotic symptoms in the month before testing were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984*b*) and the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984*a*). Zygosity was confirmed by assessment of 12 highly polymorphic microsatellite markers and/or a standardized twin likeness questionnaire (Cohen *et al*. 1975).

In concordant pairs, both members fulfilled criteria for DSM-IV schizophrenia or schizo-affective disorder. In discordant pairs, one member met diagnostic criteria whereas the co-twin was free of any psychotic illness. In control pairs, both members had no personal or family history of psychosis or schizophrenia spectrum disorder (to second-degree relatives).

Neurocognitive assessments

We used selected measures from the UK version of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987) to assess modality-specific EM. Immediate and delayed versions of each subtest were administered. Specifically, verbal paired associates and logical memory were used to assess verbal learning and verbal memory respectively. Visual paired associates were used to evaluate visual learning and visual reproduction was selected to assess visual memory. Administration and scoring of the WMS-R was conducted in a standardized fashion. The Wechsler Adult Intelligence Scale version 3 was used as a measure of intelligence (full-scale IQ) (WAIS FSIQ; Wechsler, 1997).

Statistical analysis

Mean comparisons between patients, healthy co-twins and controls

We investigated whether patients and healthy co-twins performed significantly worse than controls on EM, and whether co-twins performed intermediate between patients and controls, using a regression analysis in Stata version 10 statistical software (Stata Corp., USA). Planned contrasts were performed to test our hypotheses by comparing MZ concordant patients, MZ discordant patients, and MZ discordant non-psychotic co-twins with MZ control twins. Similarly, affected and unaffected members of DZ discordant pairs were compared with DZ control twins. Age, years of education and sex were included as covariates.

Familial correlations violate the assumption of independence made in standard regression models. Generalized estimating equations (GEEs) were used to account for the lack of independence, specifically an exchangeable correlation structure was assumed to account for the within-family correlation. GEEs provide unbiased estimates of the marginal effects, even if the assumed correlation structure is misspecified (Hardin & Hilbe, 2003; Rabe-Hesketh & Skrondal, 2005). To safeguard against a possible misspecification in the variance/covariance matrix, we used robust Hubert White sandwich estimators to adjust standard errors, hence confidence intervals (CIs) and p values (Williams, 2000).

Genetic model fitting

Maximum-likelihood genetic model fitting was used to estimate the model parameters directly (additive genetic effects, A; common environmental effects shared between twins, C; and unique influences that twins do not share, E) from the observed raw MZ and DZ twin data. Using the program Mx (Neale, 1999), we applied liability threshold models that assume that the risk for schizophrenia is distributed normally and that the disorder occurs only when a certain threshold is exceeded. The partitioning of the correlation between schizophrenia and each cognitive measure into the different sources of covariation yields genetic (r_g), common environmental (r_c) and individual-specific environmental (r_e) correlations. As the r_g, r_c and r_e correlations do not take into account the heritability of either trait, it is possible for a large genetic correlation to in fact explain very little of the observed covariation between these two traits. Therefore, the model also combines the information from r_g, r_c and r_e with the heritabilities a^2, c^2 and e^2 of each trait to calculate that part of the phenotypic correlation (r_{ph}) due to genetic effects ($r_{ph\text{-}a}$) by $[\sqrt{(h^2_{Sz})} \times r_g \times \sqrt{(h^2_{memory})}]$, to common environment ($r_{ph\text{-}c}$) by $[\sqrt{(c^2_{Sz})} \times r_c \times \sqrt{(c^2_{memory})}]$ and to unique environment effects ($r_{ph\text{-}e}$) $[\sqrt{(e^2_{Sz})} \times r_e \times \sqrt{(e^2_{memory})}]$.

The model parameters for schizophrenia were fixed to the point estimates derived by meta-analysis

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Table 1. *Demographic characteristics for patients, well co-twins and controls (memory)*

	MZ CC ill ($n=50$)	MZ DC ill ($n=12$)	DZ DC ill ($n=12$)	MZ DC well ($n=13$)	DZ DC well ($n=13$)	MZ Control ($n=108$)	DZ Control ($n=72$)
Age range (years)	22–60	20–53	24–60	20–53	21–60	19–71	19–58
Age (years), mean (S.D.)	38.09 (9.87)	30.92 (10.11)	40.58 (11.48)	30.11 (10.14)	39.62 (11.64)	41.72 (12.78)	42.16 (11.12)
Sex, female, *n* (%)	10 (20)	3 (25)	3 (25)	3 (23.1)	7 (53.8)	80 (74.1)	62 (86.1)
Education, mean (S.D.)	12.78 (2.73)	12.58 (2.31)	14.75 (2.70)	12.92 (2.56)	15.15 (3.41)	13.74 (2.73)	14.65 (2.46)

CC, Concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic; S.D., standard deviation.

(Sullivan *et al*. 2003) as follows: $h^2=0.81$, $c^2=0.11$, $e^2=0.08$. In addition, the threshold on the liability to schizophrenia was fixed to a lifetime population prevalence of 1%. Before model fitting, the effects of age, sex and education on the neuropsychology variables were regressed out and ordinalized into five equal classes to facilitate raw ordinal data analysis in Mx. More information on this model can be found in the articles by Rijsdijk *et al*. (2005), Hall *et al*. (2007) and Toulopoulou *et al*. (2007).

The genetic overlap between intelligence and memory was also estimated using the above model; however, the model parameters did not need to be fixed as was the case for schizophrenia. This analysis was used to investigate whether EM is an indicator of general intelligence.

In some cases the second member of a twin pair did not complete the neuropsychology assessment due to attrition. However, data from one twin can still be used in regression analyses and in estimating variances in structural equation modelling. Therefore, to optimize the data set we included the first twin in our analyses.

Results

Demographic and clinical variables

Of the 297 participants (52 DZ pairs, 96 MZ pairs and one set of MZ triplets), 17 did not complete the neuropsychology assessment. When this occurred, their co-twin who did complete the assessment was retained in the analysis. The final sample of 280 included MZ concordant twins (22 twin pairs, one set of triplets and three patients whose co-twin did not complete the assessment), MZ discordant twins (12 pairs and one healthy co-twin), DZ discordant twins (10 pairs, two patients and three healthy co-twins), MZ controls (52 pairs and four co-twins) and DZ control (34 pairs and four co-twins). Table 1 displays the demographic data.

Among the 26 unaffected co-twins from the discordant pairs, 12 met criteria for historical DSM-IV Axis I diagnosis: one depression only, one depression and phobia, two depression and panic disorder, one depression, panic disorder and agoraphobia, one depression and generalized anxiety disorder, one depression, alcohol and substance misuse and obsessive–compulsive disorder (OCD), one drug-induced psychosis, one depression substance misuse and panic disorder, one a manic episode, panic disorder and OCD, one depression, panic disorder and generalized anxiety disorder, and one alcohol misuse only.

Among the 180 control twins, 13 individuals met criteria for historical DSM-IV Axis I diagnoses: eight depression only, one depression, mania, panic disorder and OCD, two depression, panic disorder, OCD and phobia, one panic disorder and generalized anxiety disorder, and one anorexia nervosa. None of the unaffected co-twins or controls were unwell at the time of testing, under medical supervision, or taking any psychotropic medication.

Results from the mean comparisons between patients, co-twins and controls

Summary statistics are presented in Table 2, and Table 3 presents the results of the GEE analyses. Group had a significant effect on all memory variables. MZ twin patients, concordant and discordant, performed worse than controls on every WMS-R measure. Importantly, the non-psychotic members of the MZ pairs discordant for schizophrenia also performed significantly worse than the control subjects on five of the WMS-R subtests. DZ patients performed worse than controls on four of the eight measures whereas their co-twins did not differ from controls on any of the measures. Both patients and unaffected co-twins performed significantly worse than controls on full-scale intelligence. All significant results remained significant after adjustment for multiple testing using the Simes method (1986).

Results from the bivariate twin modelling analysis

Heritability of EM

Table 4 shows the additive genetic effects (h^2), shared environmental effects (c^2) and unique environmental

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Table 2. *Summary statistics of means and standard deviations on WMS-R memory variables for patients, co-twins and controls*

	MZ CC twins with schizophrenia	MZ DC twins with schizophrenia	DZ DC twins with schizophrenia	MZ DC non-psychotic twins	DZ DC non-psychotic twins	MZ Control twins	DZ Control twins
Immediate recall							
Verbal Learning – Verbal paired associates	16.48 (4.76)	15.67 (3.85)	19.82 (3.95)	17.85 (4.62)	19.92 (3.20)	20.38 (3.33)	20.61 (3.44)
Visual Learning – Visual paired associates	9.08 (4.58)	10.42 (4.29)	14.30 (4.16)	12.08 (4.25)	15.25 (3.62)	15.34 (3.54)	15.54 (3.12)
Verbal Memory – Logical memory	18.14 (7.53)	14.58 (8.22)	20.00 (6.73)	17.54 (8.99)	24.69 (7.90)	27.36 (6.93)	27.47 (6.98)
Visual Memory – Visual reproduction	29.35 (9.62)	32.50 (5.25)	34.09 (5.86)	33.54 (6.36)	36.38 (3.91)	36.00 (4.93)	37.10 (3.33)
Delayed recall							
Verbal Learning – Verbal paired associates	6.88 (1.61)	6.50 (1.73)	7.27 (1.27)	6.85 (1.14)	7.54 (1.13)	7.54 (0.87)	7.83 (0.50)
Visual Learning – Visual paired associates	4.22 (1.75)	4.67 (1.56)	5.60 (1.26)	5.23 (1.30)	5.42 (1.16)	5.71 (0.84)	5.81 (0.60)
Verbal Memory – Logical memory	13.06 (7.59)	10.33 (6.49)	14.91 (5.05)	13.46 (7.24)	20.85 (8.56)	23.93 (8.37)	23.22 (7.19)
Visual Memory – Visual reproduction	23.52 (12.03)	28.33 (10.01)	24.55 (8.00)	27.92 (13.92)	32.23 (5.80)	33.34 (7.53)	33.97 (6.00)
General intelligence							
WAIS FSIQ	88.05 (14.51)	81.80 (20.61)	100.20 (12.79)	92.45 (15.27)	108.08 (13.57)	112.21 (15.27)	113.06 (12.31)

CC, Concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic; WMS-R, Wechsler Memory Scale – Revised; WAIS FSIQ, Wechsler Adult Intelligence Scale Full-Scale IQ.

effects (e^2) for WMS-R measures of EM. Genetic factors accounted for a significant proportion of total variance in four of the eight memory measures. Verbal memory recall demonstrated a moderate amount of variance due to genetic factors in both immediate ($h^2=0.45$) and delayed conditions ($h^2=0.41$), whereas immediate recall of visual learning ($h^2=0.31$) and delayed visual memory ($h^2=0.37$) were explained by small to moderate genetic influences. Shared environmental influences did not significantly account for inter-individual differences on any subtest. Unique environmental effects and error accounted for the remaining variances.

A, C and E overlap between episodic memory and schizophrenia

Significant phenotypic correlations (r_{ph}) suggested that increased liability to schizophrenia was associated with poorer performance on all the EM tests (see Table 5). Verbal memory delayed had the highest phenotypic correlation with schizophrenia ($r_{ph}=-0.48$), followed by visual learning immediate ($r_{ph}=-0.41$), verbal memory immediate ($r_{ph}=-0.40$) and visual memory delayed ($r_{ph}=-0.37$).

The extent to which two traits share genetic, common environmental and unique environmental effects is given by the correlations r_g, r_c and r_e respectively (Table 5). The same four subtests as above had significant genetic correlations (r_g) with schizophrenia, visual learning immediate recall ($r_g=-0.71$), and both verbal memory delayed ($r_g=-0.58$) and immediate recall ($r_g=-0.58$), and visual memory delayed ($r_g=-0.55$). No common environmental (r_c) or shared unique environment (r_e) correlations were significant.

The model also combines the information from r_g, r_c and r_e with the heritabilities of each trait to calculate that part of the phenotypic correlation (r_{ph}) due to genetic effects ($r_{ph\text{-}a}$), common environmental ($r_{ph\text{-}c}$) and unique environmental effects ($r_{ph\text{-}e}$).

Further examination of the four measures mentioned above revealed that 88% $[(r_{ph}-a/r_{ph})\times 100]$ of

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Table 3. *Age-, education- and gender-adjusted generalized estimator equations show the marginal mean differences of planned comparisons between groups on memory*

	MZ CC twins with schizophrenia *versus* MZ control twins mean difference (*p* value)	MZ DC twins with schizophrenia *versus* MZ control twins mean difference (*p* value)	Non-psychotic MZ DC twins *versus* MZ control twins mean difference (*p* value)	DZ DC twins with schizophrenia *versus* DZ control twins mean difference (*p* value)	Non-psychotic DZ DC twins *versus* DZ control twins mean difference (*p* value)	Non-psychotic MZ DC twins *versus* non-psychotic DZ DC twins mean difference (*p* value)
Immediate recall						
Verbal Learning – Verbal paired associates	−3.19 (<0.0005)	−4.88 (<0.0005)	−2.61 (0.038)	−0.18 (0.872)	−0.67 (0.531)	−1.79 (0.259)
Visual Learning – Visual paired associates	−5.59 (<0.0005)	−5.09 (<0.0005)	−3.35 (0.003)	−0.60 (0.653)	−0.17 (0.885)	−3.02 (0.049)
Verbal Memory – Logical memory	−8.53 (<0.0005)	−12.71 (<0.0005)	−9.54 (<0.0005)	−7.72 (<0.0005)	−3.27 (0.201)	−5.60 (0.087)
Visual Memory – Visual reproduction	−7.11 (0.001)	−4.86 (0.009)	−3.46 (0.101)	−3.43 (0.041)	−1.00 (0.457)	−3.44 (0.137)
Delayed recall						
Verbal Learning – Verbal paired associates	−0.59 (0.035)	−1.09 (0.033)	−0.76 (0.029)	−0.47 (0.189)	−0.30 (0.348)	−0.70 (0.135)
Visual Learning – Visual paired associates	−1.33 (<0.0005)	−1.06 (0.020)	−0.47 (0.197)	−0.16 (0.698)	−0.35 (0.369)	−0.16 (0.747)
Verbal Memory – Logical memory	−10.18 (<0.0005)	−13.23 (<0.0005)	−9.92 (<0.0005)	−8.47 (<0.0005)	−2.60 (0.347)	−5.90 (0.074)
Visual Memory – Visual reproduction	−10.25 (<0.0005)	−7.40 (0.017)	−6.76 (0.080)	−9.40 (<0.0005)	−1.66 (0.420)	−5.35 (0.197)
General intelligence						
WAIS FSIQ	−25.68 (<0.0005)	−29.30 (<0.0005)	−19.99 (<0.0005)	−18.72 (<0.0005)	−8.12 (0.034)	−11.43 (0.026)

CC, Concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic; WAIS FSIQ, Wechsler Adult Intelligence Scale Full-Scale IQ.
All significant results remain significant after Simes correction for multiple testing.

Table 4. *Additive genetic, common and specific environmental estimates (with 95% CI) of full ACE genetic model*

	A	C	E
Immediate recall			
Verbal Learning – Verbal paired associates	0.52 (0.00–0.69)	0.02 (0.00–0.50)	**0.45 (0.31–0.64)**
Visual Learning – Visual paired associates	**0.31 (0.01–0.62)**	0.15 (0.00–0.53)	**0.54 (0.38–0.73)**
Verbal Memory – Logical memory	**0.45 (0.02–0.63)**	0.02 (0.00–0.42)	**0.54 (0.37–0.74)**
Visual Memory – Visual reproduction	0.06 (0.00–0.66)	0.53 (0.00–0.68)	**0.41 (0.29–0.56)**
Delayed recall			
Verbal Learning – Verbal paired associates	0.39 (0.00–0.56)	0.00 (0.00–0.45)	**0.61 (0.44–0.81)**
Visual Learning – Visual paired associates	0.27 (0.00–0.65)	0.25 (0.00–0.60)	**0.48 (0.33–0.67)**
Verbal Memory – Logical memory	**0.41 (0.02–0.68)**	0.12 (0.00–0.52)	**0.47 (0.32–0.67)**
Visual Memory – Visual reproduction	**0.37 (0.01–0.76)**	0.28 (0.00–0.64)	**0.35 (0.24–0.50)**
Intelligence			
WAIS FSIQ	**0.63 (0.14–0.84)**	0.13 (0.00–0.57)	**0.24 (0.16–0.38)**

CI, Confidence interval; WAIS FSIQ, Wechsler Adult Intelligence Scale Full-Scale IQ.

Parameters for schizophrenia are fixed based on a prevalence of 1% and the following genetic model: $h^2=0.81$, $c^2=0.11$, $e^2=0.08$, where h^2, c^2 and e^2 indicate heritability, shared environment and non-shared environment respectively. CIs not including 0 indicate statistical significance, given in bold.

the phenotypic correlation between visual learning immediate and schizophrenia ($r_{ph}=-0.41$) was due to shared genetic influences ($r_{ph\text{-}a}=-0.36$); 88% of the phenotypic correlation with verbal memory immediate recall ($r_{ph}=-0.40$) was due to genetic overlap ($r_{ph\text{-}a}=-0.35$), whereas 69% for verbal memory delayed recall ($r_{ph}=-0.48$, $r_{ph\text{-}a}=-0.33$) and 81% of visual memory delayed ($r_{ph}=-0.37$, $r_{ph\text{-}a}=-0.30$) was due to the same shared genetic influences. The proportion of the phenotypic correlations due to shared unique environment or shared common environment was not significant for all subtests.

A, C and E overlap between EM and intelligence

As expected, significant phenotypic correlations were observed between intelligence and EM ranging from 0.39 to 0.62. However, no significant genetic correlations were observed, instead common environment correlations (r_c) and unique environment (r_e) correlations were significant. (See Supplementary Table 1, available online.)

Discussion

This study aimed to test the validity of EM as an endophenotype for schizophrenia. We first tested whether EM impairment increased linearly with level of genetic risk for schizophrenia to demonstrate that memory deficits are associated with the disorder's aetiological influences. MZ patients, whether concordant or discordant for schizophrenia, scored significantly lower than controls on all EM subtests, whereas DZ discordant patients performed worse than controls on only four of the EM subtests. No previous studies have found MZ and DZ patients to differ (Cannon, 2005). This finding is probably a power issue or due to our sampling method. Because of their high genetic risk (sharing all of their genes with their ill co-twins), non-psychotic MZ discordant co-twins should show a similar level of impairment as their ill co-twins, if memory impairment is indeed part of a genetic causal pathway. As we hypothesized, the non-psychotic MZ discordant co-twins performed very similarly to their ill co-twins.

We hypothesized that DZ co-twins would score intermediately between their ill co-twins and controls, as they share approximately half of their genes with their ill co-twin. DZ non-psychotic co-twins did not differ from controls, which could be anticipated given their ill co-twins' relatively good memory performance and their hypothesized intermediate status between patient and controls. Overall, the regression analysis suggested that higher genetic loading for schizophrenia predicts poorer memory performance.

Bivariate genetic modelling estimated that some EM measures were moderately heritable, a requirement of endophenotype validity (Cannon & Keller, 2006). The tests with the greatest proportion of variance due to genetic effects (i.e. the greatest heritability) were verbal memory (immediate and delayed), followed by immediate visual learning and delayed visual memory. Shared environment did not contribute significantly on any tests. The remainder of the variance on test performance was due to unique environmental effects and measurement error.

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Table 5. *The phenotypic correlations between schizophrenia and memory variables (r_{ph}), the decomposed sources of these correlations ($r_{ph\text{-}a}$, $r_{ph\text{-}c}$, $r_{ph\text{-}e}$) as predicted by the full ACE models and A, C and E correlation estimates (with 95% CI)*

	$r_{ph\text{-}a}$	$r_{ph\text{-}c}$	$r_{ph\text{-}e}$	r_{ph}	r_g	r_c	r_e
Immediate recall							
Verbal Learning – Verbal paired associates	−0.17 (−0.34 to 0.00)	−0.05 (−0.23 to 0.00)	−0.05 (−0.12 to 0.00)	**−0.26 (−0.38 to −0.14)**	−0.26 (−1.00 to 0.00)	−1.00 (1.00 to 0.00)	−0.24 (0.64 to 0.00)
Visual Learning – Visual paired associates	**−0.36 (−0.51 to −0.08)**	−0.05 (−0.24 to 0.00)	−0.01 (−0.10 to 0.00)	**−0.41 (−0.51 to−0.31)**	**−0.71 (−1.00 to −0.28)**	−0.39 (−1.00 to 0.00)	−0.04 (−0.46 to 0.00)
Verbal Memory – Logical memory	**−0.35 (−0.49 to −0.12)**	−0.04 (−0.22 to 0.00)	−0.02 (−0.12 to 0.00)	**−0.40 (−0.51 to −0.30)**	**−0.58 (−1.00 to −0.29)**	−1.00 (−1.00 to 0.00)	−0.07 (−0.55 to 0.00)
Visual Memory – Visual reproduction	−0.22 (0.36 to 0.00)	−0.03 (0.27 to 0.00)	−0.05 (−0.14 to 0.00)	**−0.30 (−0.41 to −0.18)**	−0.99 (−1.00 to 0.00)	−0.12 (−1.00 to 0.00)	−0.29 (−0.73 to 0.00)
Delayed recall							
Verbal Learning – Verbal paired associates	−0.22 (−0.33 to 0.00)	0.00 (−0.23 to 0.00)	0.00 (−0.08 to 0.00)	**−0.22 (−0.33 to −0.11)**	−0.39 (−1.00 to 0.00)	−1.00 (−1.00 to 0.00)	0.00 (−0.34 to 0.00)
Visual Learning – Visual paired associates	−0.04 (−0.31 to 0.00)	−0.17 (−0.26 to 0.00)	−0.04 (−0.12 to 0.00)	**−0.24 (−0.36 to −0.13)**	−0.09 (−1.00 to 0.00)	−1.00 (−1.00 to 0.00)	−0.19 (−0.59 to 0.00)
Verbal Memory – Logical memory	**−0.33 (−0.54 to −0.13)**	−0.11 (−0.24 to 0.00)	−0.04 (−0.13 to 0.00)	**−0.48 (−0.58 to −0.37)**	**−0.58 (−1.00 to −0.33)**	−0.93 (−1.00 to 0.00)	−0.21 (−0.64 to 0.00)
Visual Memory – Visual reproduction	**−0.30 (−0.41 to −0.03)**	0.00 (−0.23 to 0.00)	−0.06 (−0.13 to 0.00)	**−0.37 (−0.47 to −0.25)**	**−0.55 (−1.00 to −0.07)**	0.00 (−1.00 to 0.00)	−0.38 (−0.72 to 0.00)
Intelligence							
WAIS FSIQ	**−0.49 (−0.51 to −0.30)**	−0.12 (−0.25 to 0.00)	−0.03 (−0.09 to 0.00)	**−0.64 (−0.73 to −0.53)**	**−0.69 (−1.00 to −0.52)**	−1.00 (−1.00 to 0.00)	−0.18 (−0.63 to 0.00)

CI, Confidence interval; WAIS FSIQ, Wechsler Adult Intelligence Scale Full-Scale IQ.

$r_{ph\text{-}a}$, $r_{ph\text{-}c}$ and $r_{ph\text{-}e}$ indicate the phenotypic correlations due to additive genetic, shared environmental, and specific environmental influence respectively. r_{ph} indicates the total phenotypic correlation. r_g, r_c and r_e indicate the genetic, shared environmental, and specific environmental correlations respectively. The fixed genetic model for schizophrenia used the following parameters: $h^2 = 0.81$, $c^2 = 0.11$, $e^2 = 0.08$. The 95% CIs not including 0 indicate statistical significance, given in bold.

Our findings support the few studies that have estimated the heritability of EM from Wechsler memory scales. Husted *et al*. (2009) measured verbal and visual memory (but not visual or verbal learning) using the Wechsler Memory Scale, third edition (WMS-III), in multiplex families, and found immediate verbal memory ($h^2 = 0.49$) to be moderately heritable. Using sibling pairs that included discordant and control pairs, Chen *et al*. (2009) estimated the heritability of an EM composite score, which combined verbal memory and family pictures of the WMS-III and the CVLT, to be 0.57.

We used bivariate genetic modelling to formally quantify the hypothetical genetic relationship between EM deficits and schizophrenia. We found evidence of significant phenotypic correlations (r_{ph}) between the increased liability to schizophrenia and poorer performance on all the EM tests. We found significant genetic correlations (r_g) between schizophrenia and four tests: visual learning immediate recall ($r_g = -0.78$), both verbal memory delayed ($r_g = -0.58$) and immediate recall ($r_g = -0.58$), and delayed visual memory ($r_g = -0.55$). Although these moderate to strong genetic correlations suggest that a high proportion of the same genes are involved in both phenotypes, the statistic (r_g) does not consider the heritability of either trait. Partitioning the phenotypic correlation (r_{ph}) into the proportions due to genetic, shared environment and unique environment revealed that genetic influences were indeed responsible for the majority of the phenotypic correlations for these four subtests. For example, 88% of the phenotypic correlation between immediate visual learning and liability to schizophrenia ($r_{ph} = -0.41$) is due to shared genetic influences. We can conclude that verbal memory (immediate and delayed), immediate visual learning and delayed visual memory performance are heritable and share a substantial genetic overlap with schizophrenia. We have previously demonstrated that intelligence and its subcomponents, in particular working memory, are both heritable and share genetic variance with schizophrenia (Toulopoulou *et al*. 2007). These findings for episodic memory are unlikely to be caused by memory being correlated with general intelligence. Our analysis revealed no significant genetic correlation between memory and intelligence. These findings support the hypothesis that initial encoding of information is the core memory deficit in schizophrenia (Cirillo & Seidman, 2003). There is emerging evidence that genetic risk for schizophrenia is not disorder specific. For example, Genome-Wide Association Studies (GWAS) data show that many of the same risk variants are associated with bipolar disorder (O'Donovan *et al*. 2008) and a recent Swedish populations study shows the two disorders share a common genetic aetiology (Lichtenstein *et al*. 2009). The presence of memory deficits in other psychiatric and developmental disorders could be due to common genetic risk variants.

Limitations

There are several limitations to our study. First, the study was underpowered to detect shared common environmental effects; however, these are unlikely to be greater than the common environmental effects for schizophrenia, which are small. The heritability estimates of several subtests were moderate yet failed to reach significance, suggesting a lack of power. In addition, the large 95% CIs of the genetic correlations demonstrate that large twin samples are needed for bivariate genetic modelling studies. Second, although the classic twin design is a powerful method of determining the sources of phenotypic correlations, it is dependent on several assumptions, namely that: MZ and DZ twin pairs share their environments to the same extent; gene–environment correlations and interactions are minimal for the trait; twins are no different from the general population in terms of the trait; and matings in the population occur at random (no assortment). For a detailed review of the implications of the assumption, see Rijsdijk & Sham (2002). Genetic modelling of twin data is also subject to parameter indeterminacy (Keller & Coventry, 2005), whereby different combinations of the common environment/assortative mating and additive, dominant and epistatic genetic effects can lead to the same observed covariation between twin pairs. For example, intermediate levels of an endophenotype in DZ co-twins, that is between MZ co-twins and controls, may not be due to additive genetic effects, but alternatively could be due to non-additive genetic effects in combination with common environment (Keller & Coventry, 2005). Future studies can reduce this parameter indeterminacy, by also modelling the similarities among other family members, that is an extended twin-family design.

Finally, although the sample was recruited nationally, this is not a population-based study and therefore the heritability of schizophrenia could not be estimated. To account for this, our model parameters for schizophrenia were fixed to values estimated by a meta-analysis and the threshold to the population prevalence. Our results on the heritability of memory performance were compatible with those in healthy populations, supporting the findings of our study (Chen *et al*. 2009; Husted *et al*. 2009).

Conclusions

This is the first study to estimate the genetic overlap between learning and memory performance and

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liability to schizophrenia, using genetic modelling in the classic twin design. Verbal memory, visual memory and visual learning performance were moderately heritable and shared a substantial genetic overlap with schizophrenia. Although caution is needed because of our large CIs and relatively small sample, our findings nevertheless suggest that EM is a valid endophenotype. Further investigation of both the neural correlates and the genetic association of cognitive phenotypes is needed to identify the mechanisms by which genetic susceptibility impacts brain function in schizophrenia.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

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Declaration of Interest

Professor Murray has received honoraria for lectures from Lilly, Janssen, BMS, AstraZenenca. Dr Picchioni has received travel awards from Pfizer, Janssen-Cilag, and Eli Lilly.

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