Genetic overlap between schizophrenia and selective components of executive function

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Abstract

Impairments in selective components of executive function are seen in unaffected family members of patients with schizophrenia and may represent the biological expression of increased genetic risk. However no study has quantified the extent to which liability to schizophrenia overlaps genetically with that of executive dysfunction. We studied a total of 418 monozygotic and dizygotic twins, including pairs concordant and discordant for schizophrenia. Participants completed the trail making test part A and verbal fluency tasks to assess initiation, TMT part B to test mental flexibility, and the WAIS-III to assess general intellectual function. Bivariate genetic modeling was used to investigate whether selective measures of executive processing are genetically linked to schizophrenia and to quantify the genetic (i.e. heritability) and environmental contributions to their variability. Genetic influences contributed substantially to test variance for initiation and mental flexibility. Genetic factors were the main source of the phenotypic correlations between schizophrenia and these processes. Verbal fluency tasks shared a large genetic correlation with IQ whilst TMT scales did not, suggesting that they measure discreet processes, and therefore indexing discreet endophenotypes. Both verbal fluency and mental flexibility meet some of the criteria for endophenotypes, but our data suggest that mental flexibility is a purer cognitive process sharing very little common variance with general intellectual functioning. The inclusion of this mental flexibility phenotype in linkage or association analysis should improve the power to detect susceptibility genes for schizophrenia.

Keywords:
Twin
Schizophrenia
Genetic
Endophenotype
Neurocognition
Verbal fluency
Trail making test
Executive function

1. Introduction

Twin studies have reliably established the genetic contribution to schizophrenia, estimating its heritability to be in the region of 80–85% (Cardno and Gottesman, 2000). Gene searches have been impeded by the disorder’s polygenic inheritance, reduced penetrance, heterogeneity and the illness’ non-specific clinical presentation. Endophenotypes, discrete genetically determined disease related phenotypes that gauge genetic predisposition (Gottesman and Gould, 2003), represent a possible solution to this problem in schizophrenia (Tan et al., 2008). Executive functioning deficits are among the most promising endophenotypes (Sitskoorn et al., 2004).

Executive control failure is thought to be a core feature of schizophrenia resulting in avolition, perseveration and incoherent behavior. Tests of verbal fluency and the (TMT) part A...
We have previously applied this method to intellectual functioning—using monozygotic (MZ) and dizygotic (DZ) twin pairs, can isolate genetic and shared environmental factors, confounded in other family designs. Twin studies of the WCST (Campana et al., 1996; Kremen et al., 2007; Nicole and Del Miglio, 1997; Taylor, 2007) have found that it is not heritable suggesting that it does not represent a useful endophenotype. Heritability estimates from multiplex families range from small to moderate for the TMT (Glahn et al., 2007; Husted et al., 2009; Quiñones et al., 2009), and moderate to high for verbal fluency (Chen et al., 2009; Glahn et al., 2007; Husted et al., 2009). Along with the problem of confounding in family studies of heritability, an additional issue has been raised in the literature (Friedman et al., 2009; Quinn et al., 2009), namely, the role that general intelligence, itself a highly heritable trait (Toulopoulou et al., 2007), plays on heritability estimates for other cognitive tests. Twin studies are needed to further investigate this issue.

In addition to the heritability of executive function, it remains to be established whether the covariance of executive impairment with schizophrenia is due to an overlap in genes responsible for both the illness and the neurocognitive impairment, or alternatively whether the covariance is due to common environmental effects (e.g. birth complications). This question can be addressed only using structural equation modeling, or genetic modeling, in a classic twin design. A formal genetic model-fitting approach can discriminate the genetic and environmental contributions to schizophrenia and its endophenotypes and examine the extent of their genetic overlap (Rijndijk and Sham, 2002). We have previously applied this method to intellectual functioning and its four indices (Toulopoulou et al., 2007) and episodic memory (Owens et al., 2011; Toulopoulou et al., 2010). We found a strong genetic overlap between schizophrenia and IQ, working memory and episodic memory. In the current study we extended the sample used in the previous work by approximately 120 twins, and investigated whether executive functioning components are valid endophenotypes.

1.1. The current study

Firstly we hypothesized that patients would be more impaired than healthy controls, whilst their non-psychotic co-twins would be intermediate, with MZ co-twins more impaired than DZ co-twins reflecting their hypothetically greater genetic loading for psychosis. Secondly we used bivariate genetic modeling to investigate the genetic (i.e. heritable) and environmental sources of variation for selective aspects of executive functioning. Thirdly to test our central hypothesis, we estimated the genetic and environmental overlap between executive test and the liability for schizophrenia. Finally, we estimated the proportion of the covariance between selected components of executive function and general intelligence that is due to the same genetic and/or environmental factors.

2. Materials and methods

2.1. Participants

The participants contributed to the Maudsley Twin Study of Schizophrenia. This sample has been described in detail previously (Ettinger et al., in press; Picchioni et al., in press; Toulopoulou et al., 2007).

2.2. Clinical assessments

DSM-IV diagnoses were made using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (Spitzer and Endicott, 1978), or by using the Structured Clinical Interview for DSM-IV (First et al., 1997) supplemented by information from medical notes. Zygosity was determined by assessment of 12 highly polymorphic microsatellite markers and a standardized twin likeness questionnaire (Cohen et al., 1975).

In concordant pairs, both members fulfilled the criteria for DSM-IV schizophrenia or schizoaffective disorder. In discordant pairs, 1 member was diagnosed with DSM-IV schizophrenia or schizoaffective disorder, whereas the co-twin was free of any psychotic illness. In control pairs, both members were free of personal and family history of psychosis or schizophrenia spectrum disorder. The probability that any of the discordant pairs would become concordant for schizophrenia in the future was low given that a mean (SD) time of 10.88 (8.70) years had elapsed since the onset of illness in the affected members of the MZ discordant patients and 17.71 (13.19) years in the affected members of the DZ patients.

2.3. Neuropsychology assessments

Semantic fluency was assessed by asking participants to name “four legged animals” for 1 min. Phonological fluency was assessed by participants to generate words beginning with the letter “S” for 1 min without using proper names or word variations.

The trail making test (Reitan, 1992) consists of two parts (A and B) which must be completed as quickly and accurately as possible. The difference between part A and B was also calculated, to remove the motor speed component of the task (Lezak et al., 2004).

2.4. Statistical analyses

In some cases the second member of a twin pair whilst completing the clinical assessment to confirm zygosity and
illness status, did not complete the neuropsychology assessment due to attrition. Data from one twin can still be used in regression analyses and in estimating variances in structural equation modeling. Therefore to optimise the data set we included the first twin in our subsequent analyses.

2.4.1. Mean comparisons between patients, healthy co-twins and controls

We investigated the hypothesis that patients and healthy co-twins would perform significantly worse than controls on executive measures and whether co-twins perform intermediate between patients and controls, using a regression analysis in STATA version 10 software (Stata Corp, College Station, Texas). 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. Finally DZ equivalents for non-psychotic MZ co-twins were compared. Age, sex and years of education were included as covariates.

Generalized estimating equations (GEE) were used to account for the lack of independence, and specifically an exchangeable correlation structure was assumed to account for the within-family correlation. 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 and p-values (Williams, 2000). Scores from the TMT are positively skewed and were therefore log transformed to achieve normality.

2.4.2. Genetic model fitting

Using the programme Mx (Neale, 1999) we applied liability threshold models which assume that the risk is distributed normally and that the disorder occurs only when a certain threshold is exceeded. Maximum-likelihood genetic model fitting was used to directly estimate the model parameters (additive genetic effects, A; environmental effects that are shared between twins, C; and unique influences that twins do not share, E) from the observed raw MZ and DZ twin data. 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, respectively.

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 actually explain a very small portion of the observed covariation between these 2 traits. Therefore the model also combines the information from the r_g, r_c, and r_e with the heritabilities h^2, c^2 and e^2 of each trait to calculate the part of the phenotypic correlation (r_p), due to genetic effects (r_p-h), by \( \sqrt{h_g^2 \cdot r_g + h_c^2 \cdot r_c} \), the part due to common environment (r_p-c) by \( \sqrt{c_g^2 \cdot r_g + c_c^2 \cdot r_c} \) and the part due to unique environment (r_p-e) by \( \sqrt{c_e^2 \cdot r_g + c_c^2 \cdot r_c} \).

Because data were from twin pairs selected for schizophrenia rather than from a random sample, the model parameters for schizophrenia were fixed to the point estimates derived by meta-analysis (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%. Prior to model fitting the effects of age, sex and education on the neuropsychology variables were regressed out and ordinalized into 5 equal classes to facilitate raw ordinal data analysis in Mx. More information on this model can be found in the articles by Owens et al. (2011), Toulopoulou et al. (2007), and Rijssijk et al. (2005).

The genetic overlap between intelligence and executive measures was also estimated using the above model; however the model parameters (h^2, c^2, and e^2) did not need to be fixed as was the case for schizophrenia. This model was used to

### Table 1

Demographics and summary statistics of means and standard deviations on neuropsychology variables for patients, unaffected co-twins and controls.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>MZ CC twins with schizophrenia</th>
<th>MZ DC twins with schizophrenia</th>
<th>DZ DC twins with schizophrenia</th>
<th>MZ DC non-psychotic twins</th>
<th>DZ DC non-psychotic twins</th>
<th>MZ control twins</th>
<th>DZ control twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>37.22 (9.71)</td>
<td>34.45 (11.12)</td>
<td>38.60 (11.52)</td>
<td>34.66 (11.38)</td>
<td>38.45 (11.79)</td>
<td>43.11 (12.59)</td>
<td>42.72 (12.74)</td>
</tr>
<tr>
<td>Sex, female, N (%)</td>
<td>16 (26.2)</td>
<td>7 (35.00)</td>
<td>6 (30.00)</td>
<td>7 (36.80)</td>
<td>9 (45.00)</td>
<td>92 (63.89)</td>
<td>90 (76.27)</td>
</tr>
<tr>
<td>Education, mean (SD)</td>
<td>12.76 (2.46)</td>
<td>12.15 (2.28)</td>
<td>14.25 (2.89)</td>
<td>12.44 (2.46)</td>
<td>14.63 (2.94)</td>
<td>13.90 (2.79)</td>
<td>14.65 (2.79)</td>
</tr>
</tbody>
</table>

**Executive functions**

<table>
<thead>
<tr>
<th>TMT A</th>
<th>48.63 (19.56)</th>
<th>40.87 (16.55)</th>
<th>43.28 (19.40)</th>
<th>37.07 (16.29)</th>
<th>33.09 (18.91)</th>
<th>29.63 (11.65)</th>
<th>28.25 (7.76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT B</td>
<td>129.63 (61.78)</td>
<td>112.80 (50.26)</td>
<td>110.95 (93.68)</td>
<td>89.22 (46.96)</td>
<td>64.91 (27.55)</td>
<td>63.35 (21.35)</td>
<td>59.03 (22.67)</td>
</tr>
<tr>
<td>TMT B-A</td>
<td>82.28 (54.73)</td>
<td>71.93 (38.06)</td>
<td>67.67 (78.39)</td>
<td>52.15 (34.20)</td>
<td>31.82 (21.27)</td>
<td>31.70 (17.78)</td>
<td>31.05 (19.57)</td>
</tr>
<tr>
<td>Verbal fluency phonemic</td>
<td>13.04 (5.40)</td>
<td>12.68 (6.27)</td>
<td>14.32 (6.41)</td>
<td>12.82 (4.64)</td>
<td>18.94 (6.45)</td>
<td>19.16 (5.88)</td>
<td>17.83 (5.05)</td>
</tr>
<tr>
<td>Verbal fluency semantic</td>
<td>14.19 (4.49)</td>
<td>12.26 (5.10)</td>
<td>14.63 (4.60)</td>
<td>13.71 (4.43)</td>
<td>19.22 (7.22)</td>
<td>18.59 (5.88)</td>
<td>18.59 (4.71)</td>
</tr>
</tbody>
</table>

**Intelligence**

| WAIS FSIQ | 86.30 (14.66) | 81.45 (19.59) | 100.80 (21.98) | 91.91 (15.43) | 110.73 (14.63) | 111.12 (14.96) | 112.80 (11.85) |

**Abbreviations:** CC, concordant; DC, discordant; MZ, monozygotic; DZ, dizygotic.
investigate the extent to which aspects of executive functioning are genetically correlated with general intelligence.

3. Results

3.1. Demographics and clinical variables

Table 1 summarizes the demographic data. Of 418 participants (124 MZ pairs, two sets of MZ triplets and 82 DZ pairs) 16 did not complete the neuropsychology assessment. When this occurred, their co-twin who did complete the assessment was retained in the analysis, leaving a final sample of 402, 61 MZ twins concordant and 39 discordant for schizophrenia (20 probands and 19 healthy co-twins), 40 DZ discordant twins (20 probands and 20 healthy co-twins), and 144 MZ and 118 DZ non-psychotic control twins. None of the patients was unwell at the time of testing. Unaffected co-twins or healthy control subjects were not under medical supervision, or receiving any psychotropic medication at the time of assessment.

3.2. Results from the GEE analysis

Summary statistics are presented in Table 1. Table 2 presents the results of the GEE analyses. Grouping had a significant effect on all variables. Patients and well co-twins from both concordant and discordant MZ twin pairs performed significantly worse than the control subjects on all sub-tests. DZ patients performed worse than controls on all TMT scales and phonemic fluency, but not phonemic fluency, whilst their co-twins only showed impairment on TMT A. All patient and co-twin groups, except non-psychotic DZ co-twins, performed significantly worse than controls on WAIS intelligence.

3.3. Results from the bivariate twin modeling analyses

3.3.1. Heritabilities for neurocognitive variables

Table 3 shows the genetic ($h^2$), shared environmental ($c^2$), and the unique environmental ($e^2$) effects on variance in the cognitive measures. All TMT scales and phonemic verbal fluency were significantly heritable. The heritability of semantic fluency was 0.25 but did not reach significance. Shared environment effects did not significantly contribute to variances. Individual-specific environmental effects (including measurement error) accounted for the remaining variance.

3.3.2. A, C and E overlap between executive function and schizophrenia

Genetic modeling also tested the central hypothesis that the covariance between schizophrenia and deficits in executive control would be due to their genetic overlap. The significant phenotypic correlations ($r_{ph}$) ranged from $-0.30$ to $0.54$ and confirm that increased liability to schizophrenia was associated with worse performance on all measures, see Table 3.

All tests had significant genetic correlations ($r_g$) with schizophrenia. TMT indices in particular had very high genetic correlations with schizophrenia, ranging from $-0.67$ to 1.00. The shared ($r_c$) and unique ($r_e$) environment correlations were non-significant for all tests.

The model also combines the information from the $r_g$, $r_c$, and $r_e$, with the heritabilities of each trait to calculate that part of the phenotypic correlation ($r_{ph}$) due to genetic ($r_{ph,a}$), common environmental ($r_{ph,e}$), and to unique environmental effects ($r_{ph,c}$). However, the opposite sign contributions of A to the phenotypic overlap, make it impossible to express the A, C and E contributions to the phenotypic correlations in terms of proportions. Nevertheless, the phenotypic correlations between schizophrenia and the executive measures were almost entirely due to shared genetic influences. For example the majority of the phenotypic correlation between TMT A and schizophrenia ($r_{ph} = 0.48$) was due to shared genetic influences ($r_{ph,a} = 0.49$).

3.3.3. A, C and E overlap between executive function and IQ

Table 4 shows the genetic modeling analysis between intelligence and executive measures. The sources of the moderate phenotypic correlations were largely due to shared intelligence and executive measures. All TMT tests have been log transformed. Statistical significance of $p < 0.05$ is given in bold.
Table 3

The full ACE genetic model \(^*\), with the phenotypic correlations between schizophrenia and neuropsychology variables \((r_{ph})\), and the decomposed sources of the correlations \((r_{ph-a}, r_{ph-c}, r_{ph-e})\), and A, C and E correlation estimates, all with S.C.F. Chi b.

<table>
<thead>
<tr>
<th>Covariance components</th>
<th>h(^2)</th>
<th>c(^2)</th>
<th>e(^2)</th>
<th>TMT A</th>
<th>TMT B</th>
<th>TMT A-B</th>
<th>Semantic verbal</th>
<th>Phonic verbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>r_{ph}</td>
<td>0.48</td>
<td>0.49</td>
<td>0.49</td>
<td>0.40</td>
<td>0.40</td>
<td>0.42</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>r_{ph-a}</td>
<td>0.42</td>
<td>0.43</td>
<td>0.43</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
</tr>
<tr>
<td>r_{ph-c}</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
</tr>
<tr>
<td>r_{ph-e}</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; TMT, Trail Making Test; AE, additive genetic and environmental effects that are shared between twins; and unique environmental effects that twins do not share; h\(^2\) = 0.81, c\(^2\) = 0.11, e\(^2\) = 0.08.

4. Discussion

4.1. Impairment in co-twins

We investigated whether two popular tests of executive function are valid endophenotypes for schizophrenia. We first investigated whether impairment in verbal fluency and the TMT increases linearly with genetic risk for the disorder. 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 intermediate between their ill co-twins and controls, as they share approximately 50% of their genes with their ill co-twin. DZ non-psychotic co-twins differed from controls only on TMT part A, though a look at their mean scores would suggest that this finding might be related to a power issue. Overall the regression analysis suggested that higher genetic loading for schizophrenia predicts poorer executive performance.

4.2. Heritability

We confirmed our hypothesis that TMT scales \( (h^2 = 0.28-0.43) \) and phonemic fluency \( (h^2 = 0.51) \) are significantly heritable; however semantic fluency was not \( (h^2 = 0.25) \). The remaining variation on these traits was due to individual-specific environmental factors, with common environmental factors not significant. Our findings are similar to estimates from Glahn et al. (2007) multiplex family study (TMT part A = 0.463, part B = 0.414, phonemic VF = 0.378, semantic VF = 0.446), and support a recent sibling study (affected and non-affected sib pairs) which found executive functioning composite score based on 5 tests to have a heritability of 0.40 (Chen et al., 2009). On the other hand they are at odds with a study by Quiñones et al. (2009) also using multiplex families (TMT parts A = 0.015, B = 0.136, B-A = 0.22).

We also estimated the genetic overlap between executive tests and general intelligence. The moderate phenotypic correlations were primarily due to shared genetic influences for verbal fluency, but due to shared environment for TMT scales. These findings suggest that IQ–VF share large genetic overlap, whilst TMT A and B are separate from IQ, suggesting that the genetic effects that influence the former are separable from those that affect the latter. The findings are broadly similar to those reported in the literature. For example, Aukes et al. (2009) found that 76% of phenotypic correlation between VF and IQ was genetic whilst Husted et al. (2009) found the genetic correlation between TMT B and IQ to be even lower \( (r_g = 0.34) \) than our estimate.

A thorough examination of the heritability of executive function has been provided by Friedman et al. (2008) in a large sample of healthy twins. Using three latent executive variables (inhibition, updating, and shifting) they demonstrated that these executive functions have unity and diversity (Miyake et al., 2000) which are genetic in origin. They found the genetic correlation between IQ and the common EF factor to be 0.57. For the latent variables the
Table 4
The phenotypic correlations between intelligence and executive variables (r_{ph}), the decomposed sources of these correlations (r_{ph-a}, r_{ph-c}, and r_{ph-e}) as predicted by the full ACE models and A, C and E correlation estimates (r_g, r_c, and r_e) with 95% CIs.

<table>
<thead>
<tr>
<th></th>
<th>r_{ph-a}</th>
<th>r_{ph-c}</th>
<th>r_{ph-e}</th>
<th>r_{ph}</th>
<th>r_g</th>
<th>r_c</th>
<th>r_e</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT A</td>
<td>-0.06</td>
<td>-0.40</td>
<td>-0.03</td>
<td>-0.48</td>
<td>-0.17</td>
<td>-0.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-0.37, 0.17)</td>
<td>(-0.60, -0.35)</td>
<td>(-0.11, 0.03)</td>
<td>(-0.59, -0.36)</td>
<td>(-0.79, 1.00)</td>
<td>(-1.00, -0.98)</td>
<td>(-0.42, 0.18)</td>
</tr>
<tr>
<td>TMT B</td>
<td>-0.18</td>
<td>-0.35</td>
<td>-0.08</td>
<td>-0.60</td>
<td>-0.57</td>
<td>-0.77</td>
<td>-0.35</td>
</tr>
<tr>
<td></td>
<td>(-0.54, 0.10)</td>
<td>(-0.60, -0.25)</td>
<td>(-0.15, -0.02)</td>
<td>(-1.00, 1.00)</td>
<td>(-1.00, 1.00)</td>
<td>(-0.50, -0.08)</td>
<td></td>
</tr>
<tr>
<td>TMT B-A</td>
<td>-0.31</td>
<td>-0.11</td>
<td>-0.05</td>
<td>-0.46</td>
<td>-0.82</td>
<td>-0.46</td>
<td>-0.16</td>
</tr>
<tr>
<td></td>
<td>(-0.57, 0.02)</td>
<td>(-0.41, 0.15)</td>
<td>(-0.13, 0.03)</td>
<td>(-1.00, 1.01)</td>
<td>(-1.00, 1.00)</td>
<td>(-0.44, 0.12)</td>
<td></td>
</tr>
<tr>
<td>Phonemic verbal fluency</td>
<td>0.38</td>
<td>0.00</td>
<td>0.00</td>
<td>0.38</td>
<td>0.74</td>
<td>0.28</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>(0.10, 0.58)</td>
<td>(-0.21, 0.04)</td>
<td>(0.00, 0.05)</td>
<td>(0.24, 0.44)</td>
<td>(0.24, 1.00)</td>
<td>(0.00, 1.00)</td>
<td>(0.00, 0.21)</td>
</tr>
<tr>
<td>Semantic verbal fluency</td>
<td>0.33</td>
<td>0.15</td>
<td>0.05</td>
<td>0.53</td>
<td>1.00</td>
<td>0.44</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(0.03, 0.43)</td>
<td>(-0.13, 0.33)</td>
<td>(0.03, 0.12)</td>
<td>(0.41, 0.63)</td>
<td>(1.00, 1.00)</td>
<td>(-1.00, 1.00)</td>
<td>(-0.13, 0.45)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence intervals; TMT, trail making test. ACE refers respectively to: additive genetic effects, environmental effects that are shared between twins; and unique influences that twins do not share. r_{ph-a}, r_{ph-c}, and r_{ph-e} indicate the phenotypic correlations due to additive genetic, shared environmental, and specific environmental influence, respectively. r_g indicates the total phenotypic correlation, r_c, r_e indicate the genetic, shared environmental, and specific environmental correlations, respectively. The 95% CIs not including 0 indicate statistical significance, given in bold.

genetic correlation with IQ was only −0.2 for Shifting, whilst Updaging was strongly related to IQ (r_g = 0.56).

4.3. Genetic overlap with schizophrenia

The central hypothesis was supported; there was a highly significant genetic correlation with schizophrenia for the TMT scales (e.g. r_g = 1.0 for TMT B). Verbal fluency (semantic r_g = −0.88; phonemic r_g = −0.67) also had a significant genetic correlation with schizophrenia. The genetic modeling approach also estimates what part of the phenotypic correlation between traits is due to genetic effects, by combining r_g with the heritability of each trait. This revealed that common additive genetic factors were the main source of the phenotypic correlations between schizophrenia and all the executive tests.

This study was novel in the estimation of the genetic covariance between TMT, verbal fluency and liability to schizophrenia. We have previously demonstrated that intelligence; working memory and episodic memory also share genetic variance with schizophrenia (Owens et al., 2011; Toulopoulou et al., 2007). Further research on the genetic associations of these cognitive deficits will shed light on the mechanisms by which genetic susceptibility impacts brain function in schizophrenia.

4.4. Limitations

Firstly the limitations include assumptions of the genetic modeling approach, which we have discussed previously (Owens et al., 2011; Toulopoulou et al., 2007). Secondly whilst the sample was recruited nationally this was not a population based study, which might have biased the results. Nonetheless our results on heritability are compatible with those in healthy populations supporting the findings of this study. Thirdly the study may have been underpowered to estimate shared environmental effects on executive functions and liability to schizophrenia, reflecting the very large sample sizes required in genetic modeling. However there was enough power to detect the significant genetic correlations between the traits.

4.5. Conclusion

In summary, we have found strong evidence for the validation of executive impairment as a cognitive endophenotype, independent of age, sex and educational history. Tests of verbal fluency and the TMT scales share a substantial genetic overlap with liability to the disorder. Verbal fluency and IQ are highly genetically correlated whilst TMT scales are influenced by genetic effects that are unique to them.

Role of funding source

The funders had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Prof Murray designed the study and wrote the Maudsley Twin Study protocol. Dr Nenadic co-ordinates the EUTwinsS network. Dr Piccioni, Dr Toulopoulou and Ms Owens collected the data. Dr Rijjsdijk and Dr Stahl managed the statistical analysis. Ms Owens undertook the statistical analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Prof. Murray received lectures’ honoraria from Astra-Zeneca, Janssen, Lilly, and BMS. Dr. Piccioni has received travel awards from Pfizer, Janssen-Cilag, and Eli Lilly and an educational grant from Janssen-Cilag. Dr. Nenadic has previously received lecture honoraria from Bristol Myers Squibb, but not related to the present work, and therefore has no conflicts of interest to disclose. Ms Owens, Dr. Rijjsdijk, Dr. Toulopoulou, and Dr. Stahl report no conflict of interest.

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