

Intellectual asymmetry and genetic liability in first-degree relatives of probands with schizophrenia

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Summary Intellectual asymmetry with superiority of verbal skills to spatial skills frequently characterises patients with schizophrenia, but it is unclear whether this pattern also reflects genetic susceptibility to the disorder. We examined the association of a continuous measure of genetic liability to schizophrenia with Verbal–Spatial Contrast IQ (an index of intellectual asymmetry) in 108 first-degree relatives without psychosis of probands with schizophrenia. Higher genetic liability was significantly associated with greater intellectual asymmetry in favour of verbal skills. Intellectual asymmetry with a relative superiority of verbal skills to spatial skills represents a putative endophenotype of schizophrenia.

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A profile consisting of superior verbal IQ to performance IQ, usually regarded as indicative of lateralised brain dysfunction, has frequently been reported in people with schizophrenia (Heinrichs & Zakzanis, 1998; Purcell *et al*, 1998) and has also differentiated between young people with schizophrenia outcomes and those with affective disorder or normal outcomes (Amminger *et al*, 2000). To investigate in more detail whether this profile characterises the schizophrenia diathesis, we examined the association of a continuous measure of genetic liability to schizophrenia with a measure of intellectual asymmetry in first-degree relatives of probands with schizophrenia, drawn from the Maudsley Family Study of Psychosis (McDonald *et al*, 2004).

METHOD

The study sample consisted of 108 first-degree relatives of probands with schizophrenia (39 men and 69 women), drawn from 64 families with one or more affected members. All participants were White, aged 16–69 years (mean=47.8, s.d.=13.9), spoke English as their first language and had no history of organic brain disease, significant head trauma or substance/alcohol dependence. The study was approved by the local ethics committee, and all of the participants provided written informed consent.

Parental socio-economic status at birth was assessed using the Standard Occupational Classification (Office of Population Censuses and Surveys, 1990) and handedness was determined using the Annett Scale (Annett, 1970) right-handed, $n=97$; left-handed, $n=11$. Participants were assessed using the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (Spitzer & Endicott, 1978), supplemented with additional clinical information to enable DSM-IV (American Psychiatric Association, 1994) diagnoses to be made. All of the relatives were well at the time of assessment, but 19 relatives had fulfilled the criteria for major depressive, dysthymic, panic, anxiety or phobic disorder at some time in their life. To reach diagnoses for those individuals who were not directly assessed, a structured family history was taken from the most reliable informants in each family, using the Family History Research Diagnostic Criteria (Endicott *et al*, 1975) or, more recently, the Family Interview for Genetic Studies (Nurnberger *et al*, 1994), supplemented by clinical notes.

Genetic liability to schizophrenia was represented by a continuous quantitative measure which has been described in detail by McDonald *et al* (2004). Briefly, the calculation of this scale is based upon normal distribution theory and assumes a polygenic multifactorial liability threshold

model of schizophrenia. Patients, relatives with schizophrenia-spectrum disorders, and unaffected relatives were initially assigned imputed liabilities within the normal distribution (2.78, 2.08 and -0.08 respectively), based upon the population prevalence of these disorders. For each family, imputed liabilities for all adult members were then adjusted to account for family size, age, affected/unaffected status and genetic relatedness as far as second degree from the index patient. Higher scores on this scale reflect higher presumed genetic liability to schizophrenia.

Verbal–Spatial Contrast IQ

A short form of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981), consisting of vocabulary, comprehension, similarities, block design and object assembly sub-test, was administered to all participants. Employing the formulas provided by Canavan and Beckmann (1993), we estimated scores (with population mean=100, s.d.=15) on two orthogonal factors derived from a principal-component analysis of the WAIS-R, namely General Ability IQ (equivalent to Wechsler's Full-Scale IQ; mean=100.1, s.d.=14.6) and Verbal–Spatial Contrast IQ (mean=95.6; s.d.=13.8). The latter is an index of asymmetry of brain function and can produce markedly different characterisations of ability compared with Verbal IQ (VIQ) and Performance IQ (PIQ) (Canavan *et al*, 1986). Scores below 100 indicate asymmetry in favour of verbal skills, whereas scores above 100 indicate asymmetry in favour of spatial skills (Canavan & Beckmann, 1993).

Data analysis

The data were analysed using Stata version 7.0 for Windows. The association of genetic liability with Verbal–Spatial Contrast IQ was examined using multiple regression analysis, adjusting for characteristics that showed significant associations with Verbal–Spatial Contrast IQ in preliminary simple regression analyses (age, gender, number of years of education and parental socio-economic status, but not handedness), and also adjusting for General Ability IQ (larger differences between verbal and performance skills are more common at the higher IQ levels (Iverson *et al*, 2001), although in our sample General Ability IQ and Verbal–Spatial Contrast IQ were non-significantly, albeit positively correlated ($P>0.1$)). To take into account the lack

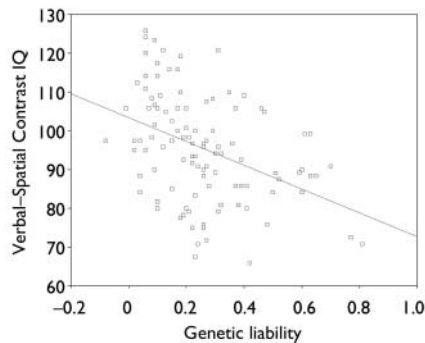


Fig. 1 Scatter plot of genetic liability scores and Verbal-Spatial Contrast IQ (unadjusted values).

of independence of observations among related participants, we used multilevel modelling, incorporating a robust estimator for the variances of the regression coefficient estimates. The analysis was repeated after excluding participants with any lifetime psychiatric diagnosis, and those at the extremes (<20 or >60 , $n=19$) of the age distribution (in whom the interpretation of the component scores requires some caution; Canavan *et al*, 1986). The analysis was also repeated separately for male and female participants (because of the skewed gender distribution).

RESULTS

Verbal-Spatial Contrast IQs were normally distributed (Kolmogorov-Smirnov test of normality statistic=0.05, $P=0.2$). About 65% of the participants had Verbal-Spatial Contrast IQs of <100 (i.e. their verbal skills were superior to their spatial skills), and the negative distance from the population mean reached or exceeded 1 s.d. in 23% of the sample. Genetic liability was significantly negatively associated with Verbal-Spatial Contrast IQ (coefficient= -17.95 , 95% CI -27.84 to -8.06 , $P=0.001$), indicating that increases in genetic liability co-occurred with increases in asymmetry of brain function, with a relative superiority of verbal to spatial skills. This pattern was consistent, and it remained significant or near significant after participants with psychiatric diagnoses or age extremes had been excluded ($P<0.05$), and after performing the analyses separately for female ($P<0.05$) and male ($P=0.06$) participants. A scatter plot of Verbal-Spatial Contrast IQ and genetic liability in the total sample is shown in Fig. 1.

DISCUSSION

To our knowledge, this is the first study to examine the association of a continuous

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measure of presumed genetic liability to schizophrenia with intellectual asymmetry in first-degree relatives of probands with schizophrenia. The study included a large, well-characterised sample, and used a quantitative genetic liability scale, which is likely to reflect more closely than a dichotomous scale (e.g. familial/non-familial schizophrenia) the presumed polygenic nature of schizophrenia. Our analyses controlled for the confounding effects of socio-demographic characteristics, and the proposed association between higher IQ levels and greater differences in verbal and performance skills (Iverson *et al*, 2001) was both non-significant and corrected for. Our results suggest that intellectual asymmetry with a relative superiority of verbal to spatial skills is not only manifested in individuals with schizophrenia and those who go on to develop the disorder (Heinrichs & Zakzanis, 1998; Amminger *et al*, 2000), but also in their non-affected relatives to a degree that is proportional to the individual's genetic susceptibility to schizophrenia. These characteristics have been proposed to form useful criteria for the identification of endophenotypes (Gottesman & Gould, 2003). However, a substantial minority of the participants showed more highly developed spatial than verbal skills. Lower Verbal-Spatial Contrast IQ may therefore reflect the impact of *some* susceptibility genes, and may help to dissect the genetic heterogeneity of schizophrenia, rather than model the totality of genetic risk for the latter.

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