Cognitive performance in presumed obligate carriers for psychosis

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Summary We report cognitive performance of a group of individuals who are likely to have transmitted liability to psychosis to their offspring. Out of 230 relatives of patients with psychosis, 27 met our criteria for a presumed obligate carrier, that is a non-psychotic individual who had a parent or a sibling as well as an offspring with psychosis. The presumed obligate carriers showed impairments in verbal memory and in visuospatial manipulations, suggesting that these individuals transmit vulnerability for psychosis to their offspring in terms of a disability to recall verbal information and an impaired capacity to perceive spatial relations.

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Deficits in cognition may represent a genetic vulnerability for schizophrenia because cognitive deficits, particularly in verbal learning and memory, are found in both individuals with schizophrenia and their healthy relatives (Byrne *et al*, 2003; Toulopoulou *et al*, 2003*a*,*b*). A similar pattern has emerged in bipolar disorder, with both patients and their healthy relatives showing decreased performance in certain aspects of cognition (Keri *et al*, 2001). The distinction of psychosis into schizophrenia and bipolar disorder has been increasingly questioned, with recent evidence suggesting that the two disorders share some common characteristics in terms of cognition and genetic liability (Murray *et al*, 2004). We explore further the idea that specific cognitive dysfunction may be a marker of genetic susceptibility to psychosis by assessing a very selected group of relatives derived from a large sample of pedigrees containing multiple cases of psychosis. The relatives had passed the normal age threshold for developing psychosis (mean age=57.2 years, s.d.=6.5) and, although healthy themselves, the structure of their pedigrees suggests that they are likely carriers of susceptibility genes for psychosis.

METHOD

Participants and procedures

Our sample comprised a subgroup of first-degree relatives (n=27) of individuals with schizophrenia or bipolar I disorder with psychotic features. The subgroup had been identified as being more likely to have transmitted the liability to schizophrenia and/or bipolar disorder (obligate carriers for psychosis) because, although healthy themselves, they have a parent or sibling, as well as an offspring, with schizophrenia or bipolar I disorder. The sample constitutes a sub-population of a larger cohort of relatives of individuals with schizophrenia, bipolar disorder and controls from the Maudsley Family Study of Psychosis (Toulopoulou *et al*, 2003*a*,*b*, 2005; McDonald *et al*, 2004). The 27 presumed obligate carriers were from a total of 230 non-psychotic relatives who were neurocognitively assessed, and derived from 27 separate families. Eleven of these non-psychotic relatives were from families with documented multiple cases of schizophrenia, six from families with documented multiple cases of bipolar disorder (with at least one member with bipolar I disorder with psychotic features), and ten from families with documented cases of both bipolar I disorder with psychotic features and schizophrenia. After complete description of the study to the participants, written informed consent was obtained. The study was approved by the South London and Maudsley NHS Trust/Institute of Psychiatry Ethical Committee (Research). A control group comprised 32 individuals with no family history of schizophrenia or bipolar disorder, matched for age, gender, education and handedness.

Structured diagnostic interviews were administered to all participants using the Schedule for Affective Disorders and Schizophrenia–Lifetime version (Spitzer *et al*, 1978). Information regarding the timing and nature of any psychopathology was collected to enable DSM–IV diagnoses to be made (American Psychiatric Association, 1994). Eight of the presumed obligate carriers had fulfilled criteria for a DSM–IV Axis I disorder at some point in their lives, five for a major depressive disorder, two for panic disorder and one for anxiety disorder; one also fulfilled criteria for schizotypal personality disorder. Three of the controls had also fulfilled criteria for a major depressive disorder at some point in their lives. All participants were recovered and were not in treatment at the time of assessment.

The neuropsychological tests assessed:

(a) IQ, as measured by a five sub-test short form (vocabulary, similarities, comprehension, block design, object assembly) of the Wechsler Adult Intelligence Scale–Revised (WAIS–R); Wechsler, 1981; and

(b) verbal and visual memory and learning, as measured by (i) immediate recall, (ii) 30-min delayed recall and (iii) saving scores of two stories and designs – two procedures taken from the Wechsler Memory Scale (WMS; Wechsler & Stone, 1945).

The savings score was calculated using the following formula: saving score=(delayed recall/immediate recall)×100.

Data analyses

All data were analysed with independent-samples two-tailed t-tests except for handedness and gender where Pearson's χ^2 tests were used. Analyses were performed primarily to compare the presumed obligate carriers with the controls. We also re-ran all the analyses after excluding all those with a history of psychiatric disorder. We report findings without correcting for multiple testing as we consider Bonferroni corrections too conservative since many of the tests are correlated and not independent. Furthermore, although the presumed obligate sample is abstracted from a very large population of relatives, the numbers are sufficiently low to warrant initially less-stringent criteria.

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RESULTS

The groups were matched and therefore compatible in terms of age ($t=-0.66$, d.f.=58, $P=0.51$), gender ($\chi^2=0.06$, d.f.=1, $P=0.81$), education ($t=-0.88$, d.f.=57, $P=0.38$) and handedness ($\chi^2=2.5$, d.f.=1, $P=0.12$). We found no differences between the presumed obligate carriers for psychosis and the controls in estimated IQ and visual memory (Table 1). However, the presumed obligate carriers scored lower than the controls on object assembly, a task that assesses perception of visual relationships, and on the delayed recall of verbal memory. A trend was also found for immediate recall of verbal memory to be poorer in obligate carriers. This became significant after excluding all those with a history of psychiatric disorder ($t=2.86$, d.f.=42, $P=0.007$). The differences in delayed recall of verbal memory remained significant even after excluding all those with a history of psychiatric disorder ($t=2.5$, d.f.=41, $P=0.02$), but the significant difference in the object assembly disappeared after excluding those with a history of psychiatric disorder ($t=1.8$, d.f.=44, $P=0.08$).

Table 1 Current general intellectual and verbal and visual memory function (means (s.d.)) for presumed obligate carriers and normal controls

	Presumed obligate carriers ($n=27$)	Controls ($n=32$)
WAIS–R IQ	106.3 (14.2)	109.6 (11.5
Verbal sub-tests		
Vocabulary	10.9 (2.6)	11.2 (2.5)
Similarities	9.5 (2.5)	10.1 (1.7)
Comprehension	10.8 (3.1)	11.2 (2.7
Performance sub-tests		
Block design	9.6 (2.9)	10.09 (2.08)
Object assembly	7.3 (2.4)*	8.8 (2.7)
Verbal memory		
Immediate recall[1]	9.96 (3.9)†	11.6 (3.3)
Delayed recall[2]	7.3 (3.5)‡	9.2 (3.6)
Saving scores[2]	72.9 (20.10)	77.8 (15.8)
Visual memory		
Immediate recall[1]	8.2 (3.9)	8.7 (3.2)
Delayed recall[1]	6.3 (2.9)	6.5 (3.3)
Saving scores[1]	82.6 (22.5)	77.2 (29.9)

WAIS–R, Wechsler Adult Intelligence Scale–Revised.
1. Data on one presumed obligate carrier and one control are missing; therefore analyses are based on 26 presumed obligate carriers and 31 controls.
2. Analyses are based on 26 presumed obligate carriers and 30 controls.
*$P=0.03$, †$P=0.08$, ‡$P=0.05$ *v.* controls.

DISCUSSION

The presumed obligate carriers for psychosis represent a group who, although not suffering from psychosis themselves, are likely to have transmitted to their offspring a liability to psychosis. This group had a similar IQ and educational attainment to controls, with both groups falling within the average range of ability. However, they performed worse on object assembly, a test that evaluates visual–motor speed and visuospatial manipulation. Furthermore, the presumed obligate carriers showed decreased performance in delayed recall of the logical memory sub-test, a test that assesses long-term verbal memory. These findings remained statistically significant when we excluded those with any Axis I disorder; moreover, when we excluded those with an Axis I disorder differences between the immediate recall of the logical memory sub-test also became statistically significant. Consistent with some studies of those with bipolar disorder and their relatives (Quraishi & Frangou, 2002) and of the relatives of those with schizophrenia (Laurent *et al*, 2000), visual memory was not impaired among our presumed obligate carrier subjects, suggesting that this does not reflect genetic liability to psychosis.

To conclude, our data suggest that presumed obligate carriers for psychosis transmit liability to their offspring in the form of impairments in verbal memory and ability to perceive spatial relationships. These impairments cannot be explained by an overall decreased level of general intellectual ability or by deprivations related to education.

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