Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives

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Background Neuropsychological abnormalities in schizophrenia are well replicated and are present in unaffected relatives. Cognitive findings in bipolar disorder are less clearly established.

Aims To examine the possibility that these abnormalities may provide a means by which the disorders might be separated and to clarify the associations of phenotypic expression and genetic liability.

Method A neuropsychological test battery was administered to 50 control participants, 74 patients and 76 unaffected relatives recruited for the study. Patients included those with schizophrenia from families affected by schizophrenia alone, those with bipolar disorder from families affected by bipolar disorder alone and those with bipolar disorder from families affected by both disorders. Unaffected relatives were also recruited.

Results Current, verbal and premorbid IQ were impaired in people with schizophrenia and in their close relatives. Memory was impaired in all patient and relative groups. Psychomotor performance and performance IQ were impaired in patients, regardless of diagnosis.

Conclusions This study finds evidence that intellectual abnormalities are related to a genetic liability to schizophrenia. Abnormalities of memory appear to be related to an increased liability to psychosis in general. No impairment was specific to bipolar disorder.

Declaration of interest None.

Impairments in neuropsychological function have been demonstrated in people with schizophrenia at first presentation and in their unaffected relatives (Cannon *et al*, 1994; David *et al*, 1997; Heinrichs & Zakzanis, 1998; Johnson-Selfridge & Zalewski, 2001). Some impairments are also found in people with bipolar disorder (Quraishi & Frangou, 2002), although deficits in general intellectual function are not generally shown (Robertson & Taylor, 1985). We sought to clarify these issues by examining neuropsychological functioning in families affected by schizophrenia, bipolar disorder or both. Relatives were compared with controls to examine abnormalities contingent upon genetic liability, whereas phenotypic abnormalities were inferred from patient–relative differences. Specifically, we predicted that intellectual and executive abnormalities would be related to a genetic liability to schizophrenia, whereas memory impairments would be found in all people affected by functional psychotic illness, regardless of diagnosis.

METHOD

Sample

Patients diagnosed with schizophrenia or bipolar disorder were identified at the Royal Edinburgh Hospital and associated hospitals and their informed consent was sought. Those with a family history of one or both disorders were selected, and DSM–IV operational criteria (American Psychiatric Association, 1994) were applied to the patients and to their affected relatives wherever possible using the Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuffin *et al*, 1991). Healthy relatives from the families were also invited to participate. The intention was to recruit 24 people in each of the following groups.

(a) Patients with schizophrenia from 'schizophrenia' families: this group consisted of people with DSM–IV schizophrenia with at least one first- or second-degree relative with schizophrenia.

(b) Unaffected participants from 'schizophrenia' families: this group consisted of healthy people with at least two first- or second-degree relatives with schizophrenia.

(c) Patients with bipolar disorder from 'bipolar' families: this group consisted of people with DSM–IV bipolar I disorder with at least one first- or second-degree relative with bipolar disorder.

(d) Unaffected participants from 'bipolar' families: this group consisted of unaffected people with at least two first- or second-degree relatives with bipolar disorder.

(e) Patients with bipolar disorder from 'mixed' families: this group consisted of people with DSM–IV bipolar I disorder with at least one first- or second-degree relative with schizophrenia.

(f) Unaffected participants from 'mixed' families: this group consisted of unaffected people with at least one first- or second-degree relative with schizophrenia and one with bipolar disorder.

All people fulfilling study inclusion criteria were interviewed using version 9 of the Present State Examination (PSE; Wing *et al*, 1974). The PSE was used to supplement the information obtained from case notes, confirm the diagnosis of affected participants and confirm that apparently healthy people were indeed unaffected.

A control group consisting of 50 people with no personal or family history of schizophrenia or affective disorder was also recruited from the social network of the participants. Control status was confirmed using the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS–L; Endicott & Spitzer, 1978) and using data about previous medical treatment obtained at interview. Unaffected relatives were similarly interviewed to confirm the lifetime absence of major depressive disorder, bipolar disorder or schizophrenia.

Additional demographic and historical information was collected at interview on all participants using a semi-structured questionnaire. All eligible subsample members and controls were interviewed using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987), the Hamilton Rating Scale for Depression (HRSD;

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Hamilton, 1960) and the Young Mania Rating Scale (YMRS; Young *et al*, 1978).

All relatives and controls gave informed consent to their participation. The study protocol and consent procedures were approved by the relevant ethics committees. Sample sizes were chosen on the basis of a power calculation for two independent groups at a significance level of 0.05.

Neuropsychological assessments

All neuropsychological assessments were administered by two investigators (L.H. and K.F.), masked to diagnosis. The test battery chosen included tests that had previously been shown to distinguish individuals with schizophrenia or bipolar disorder from controls and was organised according to domain of neuropsychological function (see Appendix). Genetic liability to psychosis was estimated using a continuous measure described elsewhere (Lawrie *et al*, 2001), developed originally by Professor Sham of the Institute of Psychiatry, which assumes a liability threshold model (Pearson & Lee, 1901) of genetic disease. Using the estimated prevalence of the disorder and published heritability estimates, the average genetic liability of someone selected at random from a population can be calculated. Using this information on average genetic liabilities combined with family history data, a revised liability estimate for individuals is given.

Statistical analysis

The distribution of each neuropsychological variable was examined for normality using a normal probability plot for each group. Where data were not normally distributed a ladder of transformations was applied, and that resulting in the greatest approximation to normal distribution was chosen. The assumption of multivariate normality was checked further using a Mahalanobis plot. Standardised residuals from the mixed-effects analyses of variance (ANOVAs) conducted were also examined for normality.

Domains of neuropsychological function (IQ, executive function and psychomotor performance) were compared between groups using a multivariate analysis of covariance (MANCOVA). All tests conducted included psychiatric symptoms and, where appropriate, age as covariates. Tests of executive function and psychomotor performance were conducted, adjusting additionally for Wechsler Abbreviated Scale of Intelligence (WASI) Full-Scale IQ (Wechsler, 1999). All multivariate analyses were conducted using the PROC GLM procedure within the statistical package SAS, version 8.2 (SAS Institute, Cary, North Carolina, USA). Memory, having only one measure, the Extended Rivermead Behavioural Memory Test (E–RBMT; de Wall *et al*, 1994), was compared between groups using mixed-effects ANOVA.

Where the MANOVA showed an overall difference within a domain of neuropsychological function, further tests were conducted to examine first, which specific neuropsychological variable means differed between the groups, and second, specific pairwise effect sizes. Both analyses were conducted using a mixed-model ANOVA, with 'family' modelled as a random factor to take account of the correlation within pedigrees. Where differences were found in the overall ANOVA, controlling for WASI Full-Scale IQ (for memory and executive function) and psychiatric symptoms (HRSD, PANSS positive sub-scale and YMRS scores), the pairwise between-group contrasts were estimated, controlling for the comparison-wise error rate. Age was also included as a potential confound where this was not adjusted for in the calculation of individual test scores. All analyses were conducted using the PROC MIXED procedure within SAS.

The influence of medication and alcohol consumption were checked by plotting the unstandardised residuals (unexplained variation) from each analysis against current conventional antipsychotic dosage (in chlorpromazine equivalents), lithium dosage and estimated weekly alcohol consumption.

RESULTS

The flow of participants through the study is shown in Fig. 1. Over 300 patients with a diagnosis of either schizophrenia or bipolar disorder were identified. Of the 110 patients with a family history of either schizophrenia or affective disorder who were invited to participate, 102 gave their consent. On the basis of combined information from the PSE and case notes, 80 patients met study inclusion criteria and 74 provided complete clinical data and near-complete neuropsychological data. From the families of eligible patients meeting study inclusion criteria, a further 160 apparently unaffected close family members were identified; 85 of them then underwent a semi-structured interview about previous psychiatric problems using the PSE. On the basis of this information 80 persons met study inclusion criteria, of whom 76 provided complete clinical data and near-complete neuropsychological data. Fifty-four potential control participants were identified. All completed a semi-structured interview using the SADS–L. Three were excluded because of a history of previous psychiatric disorder (one with anorexia nervosa and two with a major depressive episode). Fifty individuals provided near-complete neuropsychological data. Demographic information about the participants is given in Table 1.

The patient groups were closely balanced in terms of duration of illness (estimated from current age minus age at first presentation), but differed in terms of psychiatric symptom measurements and prescribed medication (Table 2). Patients with schizophrenia were prescribed more

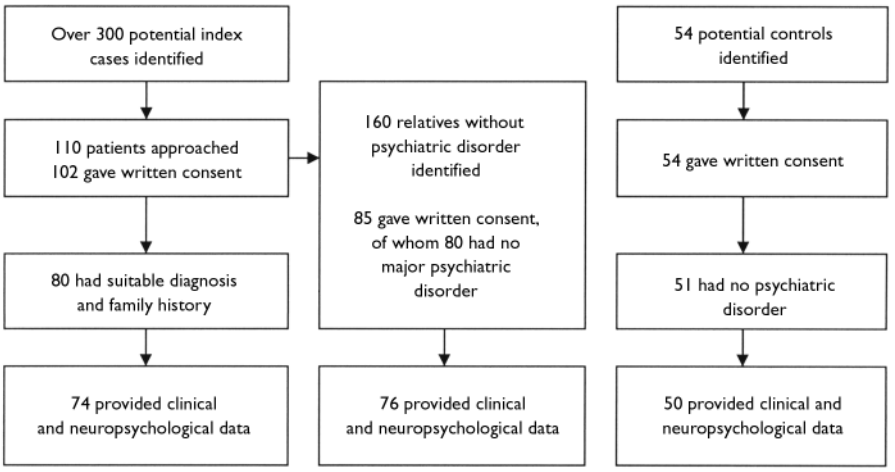

Fig. 1 Flow of participants through the study.

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Table 1 Demographic details of participants

Group	Number of participants/families *n*/*n*	Age; years Mean (s.d.)	Male *n* (%)	Education[1] *n* (%)	Parental SES[2] *n* (%)	Married[3] *n* (%)
Control	50/50	35.5 (11.2)	23 (46)	39 (78)	32 (64)	22 (44)
SCZ from SCZ family	27/24	37.6 (14.0)	13 (48)	10 (37)	16 (59)	3 (11)
UA from SCZ family	25/18	38.8 (12.6)	11 (44)	11 (44)	13 (52)	13 (52)
BPD from BPD family	27/21	40.3 (11.9)	14 (52)	20 (74)	15 (56)	11 (41)
UA from BPD family	24/10	33.5 (12.8)	9 (38)	17 (71)	13 (54)	10 (42)
BPD from 'mixed' family	20/18	40.5 (9.6)	7 (35)	12 (60)	10 (50)	5 (25)
UA from 'mixed' family	27/14	34.4 (12.8)	14 (52)	13 (48)	9 (33)	14 (52)

BPD, bipolar disorder; SCZ, schizophrenia; SES, socio-economic status; UA, unaffected.
1. Number having education past compulsory school-leaving age.
2. Parental socio-economic status: number whose father's occupation was non-manual.
3. Number married.

Table 2 Illness duration, prescribed medication and current symptoms

Group	*n*	Illness duration, years Mean (s.d.)	Antipsychotic dosage[1] Median (IQR)	Lithium dosage[2] Median (IQR)	PANSS[3] Median (IQR)	HRSD Median (IQR)	YMRS Median (IQR)
Control	50				7 (0)	0 (0)	0 (0)
SCZ from SCZ family	27	15.8 (11.4)	171.5 (200)	0 (0)	12 (7)	10 (12)	3 (8)
UA from SCZ family	25				7 (0)	1 (2.50)	0 (0)
BPD from BPD family	27	16.2 (9.2)	37.0 (0)	433.3 (800)	8 (5)	5 (9)	2 (8)
UA from BPD family	24				7 (1)	1.5 (3.50)	0 (1)
BPD from 'mixed' family	20	15.7 (10.5)	21.9 (0)	173.7 (100)	8 (5.75)	7 (14.25)	4.5 (6.5)
UA from 'mixed' family	27				7 (0)	1 (3)	0 (0)

BPD, bipolar disorder; HRSD, Hamilton Rating Scale for Depression; IQR, interquartile range; PANSS, Positive and Negative Syndrome Scale; SCZ, schizophrenia; UA, unaffected; YMRS, Young Mania Rating Scale.
1. Chlorpromazine equivalents.
2. Lithium carbonate equivalents.
3. Positive sub-scale (items 1–7).

antipsychotic medication and had higher levels of (positive) psychotic and depressive symptoms than patients with bipolar disorder from either 'bipolar' or 'mixed' families. In contrast, patients with bipolar disorder from 'bipolar' families had the highest doses of lithium prescribed and patients with bipolar disorder from 'mixed' families had the highest numbers of manic symptoms compared with the other groups.

Neuropsychology

The vectors of intellectual function ($F_{(20,203)}$=2.02, $P<0.01$) and psychomotor function ($F_{(15,166)}$=2.0, P=0.02) differed significantly between the groups using MANCOVA. Executive function showed no evidence of variation between the groups overall ($F_{(20,196.6)}$=1.29, P=0.19). Since the numbers in each group were not sufficiently large to allow the conclusion that the groups were equal in terms of executive function, further mixed-effects ANOVAs were conducted to explore whether any single measure of executive function differed between the groups, despite the absence of a statistically significant difference overall. The means and standard deviations of test performance scores are shown in Table 3; these are raw scores unadjusted for confounders and for the effects of intrafamilial clustering.

General intellectual function

Premorbid intellectual function, measured using the National Adult Reading Test (NART; Nelson, 1982), and current intellectual function measured by WASI Full-Scale IQ, Performance IQ and Verbal IQ scores (Wechsler, 1999) all differed significantly between the groups. Patients with schizophrenia and unaffected participants from families with schizophrenia had significantly lower NART IQ scores than the control group, and patients with schizophrenia also had significantly lower scores on this measure compared with people with bipolar disorder from either group. Patients with bipolar disorder from families with bipolar disorder had significantly higher NART scores than their unaffected relatives (Table 4).

Patients with schizophrenia, patients with bipolar disorder from 'mixed' families and unaffected relatives from 'schizophrenia' families had significantly lower WASI Full-Scale IQ scores than the control group. Although unaffected relatives from 'mixed' families did not differ significantly from controls in terms of WASI Full-Scale IQ, the difference was similar to that found between unaffected relatives from 'schizophrenia' families and controls (7 IQ points *v.* 10). Patients with schizophrenia also had significantly lower WASI Full-Scale IQ scores than patients with bipolar disorder from either group and indeed than their own healthy relatives.

In terms of Verbal IQ, patients with schizophrenia and their healthy relatives

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Table 3 Neuropsychological measures analysed by group membership

Test	Neuropsychological test score: mean (s.d.)						
	Control	SCZ from SCZ family	UA from SCZ family	BPD from BPD family	UA from BPD family	BPD from 'mixed' family	UA from 'mixed' family
Intellectual function							
NART FSIQ	110.8 (8.5)	101.3 (12.6)	101.2 (9.6)	111.5 (10.9)	104.4 (11.1)	105.9 (10.8)	104.7 (10.0)
WASI FSIQ	114.0 (13.3)	90 (14.2)	99 (12.1)	106.7 (13.3)	105.3 (12.1)	101.6 (16.2)	104.6 (14.4)
WASI VIQ	111.2 (12.9)	94.0 (14.9)	99.7 (11.7)	109.9 (13.1)	105.4 (12.2)	103.4 (15.4)	105.7 (14.4)
WASI PIQ	113.5 (13.1)	87.9 (16.2)	98.7 (15.0)	102.0 (13.6)	104.1 (14.2)	99.0 (14.9)	102.8 (14.9)
Memory							
E-RBMT	34.6 (4.4)	26.4 (5.3)	29.0 (6.3)	27.2 (6.8)	32.5 (4.9)	28.1 (6.2)	33.0 (4.6)
Executive function							
FAS total	44.5 (10.4)	31.9 (11.6)	42.0 (10.4)	37.0 (10.7)	38.8 (8.5)	34.8 (11.5)	41.6 (14.0)
SOC total	9.2 (2.3)	6.8 (2.2)	7.6 (2.3)	7.6 (2.3)	8.1 (1.9)	6.8 (1.9)	7.5 (2.7)
HSCT total[1]	325.6 (86.4)	241.4 (96.5)	273.5 (98.6)	266.4 (95.4)	320.4 (95.1)	262.2 (104.9)	315.6 (73.3)
Psychomotor performance							
DSST	63.8 (11.7)	40.1 (16.4)	53.8 (13.3)	47.2 (13.5)	58.3 (9.4)	46.6 (11.1)	58.7 (13.1)
SRT (ms)	313.8 (40.3)	395.7 (102.5)	332.4 (57.3)	379.5 (110.8)	332.3 (50.9)	406.1 (88.3)	338.2 (56.3)
CRT (ms)	323.6 (35.8)	411.5 (91.5)	330.1 (60.5)	418.4 (271.2)	309.0 (42.5)	400.4 (87.9)	341.3 (77.6)

BPD, bipolar disorder; CRT, Choice Reaction Time; DSST, Digit–Symbol Substitution Test; E–RBMT, Extended Rivermead Behavioural Memory Test; FSIQ, Full-Scale IQ; HSCT, Hayling Sentence Completion Test; NART, National Adult Reading Test; PIQ, Performance IQ; SCZ, schizophrenia; SOC, Stockings of Cambridge test; SRT, Simple Reaction Time; UA, unaffected; VIQ, Verbal IQ; WASI, Wechsler Abbreviated Scale of Intelligence.
1. Total scaled scores were transformed by squaring the raw values.

had significantly lower WASI scores than controls, but both bipolar disorder groups and their unaffected relatives did not differ significantly from controls. A greater difference was observed between unaffected relatives from 'mixed' families and controls than between unaffected relatives from 'bipolar' families and controls. Patients with schizophrenia also had significantly lower WASI Verbal IQ scores than either their own relatives (difference −9.8, 95% CI −17.45 to 1.83) or either group of patients with bipolar disorder. The latter two groups did not differ significantly from their unaffected relatives on this measure.

The pattern of impairment in terms of WASI Performance IQ differed from that of other intellectual measures. Patients with schizophrenia or bipolar disorder (whether from 'bipolar' or 'mixed' families) had significantly lower Performance IQ scores than controls. The effect size was greatest in those with schizophrenia (difference 25.3, 95% CI 16.68 to 33.92), intermediate in patients with bipolar disorder from 'mixed' families (difference 14.50, 95% CI 5.79 to 23.20) and least in patients with bipolar disorder from 'bipolar' families (difference 10.43, 95% CI 2.50 to 18.37). Unaffected relatives from 'schizophrenia' or 'mixed' families were also significantly more impaired in terms of Performance IQ than controls. No trend to significance was found for the unaffected relatives from 'bipolar' families. Patients with schizophrenia were also significantly more impaired than their own relatives. Although no significant differences between the unaffected relative groups were found, impairments were greatest in the unaffected relatives from 'schizophrenia' families, intermediate in the unaffected relatives from 'mixed' families and least in the unaffected relatives from 'bipolar' families.

Memory

Scores on the E–RBMT were lower in all patient and relative groups compared with controls. There was no evidence of disease specificity among affected individuals although unaffected relatives from 'schizophrenia' families were more impaired than unaffected relatives from either 'bipolar' families (difference −3.96, 95% CI −7.25 to −0.67) or 'mixed' families (difference −4.11, 95% CI −7.25 to −0.97). Once WASI IQ was taken into account, the nature of the results changed little. Controls performed better than all other groups and, among affected participants, there was little evidence of disease specificity. However, patients with bipolar disorder from 'mixed' families performed worse than their unaffected relatives (difference 3.8, 95% CI 0.5 to 7.1).

Executive function

No difference was found between the groups in terms of performance on the Hayling Sentence Completion Test (HSCT; Burgess & Shallice, 1996), whether controlled for current IQ or not. Total verbal fluency and performance on the Stockings of Cambridge test (Sahakian & Owen, 1992) differed among the groups in the non-IQ-controlled analysis. Patients from all groups performed worse in terms of verbal fluency and the Stockings of Cambridge test than controls. Unaffected relatives from either 'schizophrenia' or 'mixed' families also performed significantly worse than controls on the Stockings of Cambridge test. Once these analyses were adjusted for current intellectual function, no significant difference remained.

Psychomotor performance

The number of correct substitutions on the Digit–Symbol Substitution Test (DSST; Erber, 1976) differed significantly between

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Table 4 Mixed-effects analysis of variance by domain of neuropsychological function

Function	*F* ratio for group	*P*	Between-group contrasts[1]
General intellectual function			
NART	$F_{6,65}$=3.12	0.01	CTR, BPD, MIX > SCZ
			uBPD > BPD and CTR > uSCZ, uMIX
WASI FSIQ	$F_{6,64}$=6.42	<0.0001	CTR, BPD, MIX, uSCZ > SCZ
			CTR > uSCZ
WASI PIQ	$F_{6,64}$=5.93	<0.0001	CTR > MIX, BPD > SCZ
			CTR > uMIX, uSCZ and uSCZ > SCZ
WASI VIQ	$F_{6,64}$=4.04	0.002	CTR > uSCZ > SCZ
			BPD, MIX > SCZ
Memory			
E–RBMT	$F_{6,64}$=8.8	<0.0001	CTR > BPD, MIX > SCZ
			CTR > uBPD, uMIX > uSCZ
E–RBMT (IQ corrected)	$F_{6,64}$=5.9	<0.0001	CTR > SCZ, MIX, BPD
			CTR > uSCZ, uBPD, uMIX and uMIX > MIX
Executive function			
FAS total	$F_{6,64}$=2.98	0.013	CTR > SCZ, MIX, BPD
FAS total (IQ corrected)	$F_{6,62}$=2.00	0.08	
SOC total	$F_{6,62}$=3.53	0.005	SCZ, MIX, BPD, uSCZ, uMIX > CTR
SOC total (IQ corrected)	$F_{6,60}$=1.41	0.23	
HSCT TSS	$F_{6,64}$=1.25	0.29	
HSCT TSS (IQ corrected)	$F_{6,62}$=0.55	0.77	
Psychomotor performance			
DSST	$F_{6,64}$=4.81	0.0004	CTR > SCZ, MIX, BPD
			CTR > uSCZ and uSCZ > SCZ
SRT[2]	$F_{6,62}$=3.54	0.005	CTR < SCZ, MIX, BPD
			BPD < MIX and uMIX < MIX
CRT[2]	$F_{6,62}$=2.91	0.015	CTR < SCZ, BPD
			SCZ < uSCZ and uBPD < BPD

CRT, Choice Reaction Time; DSST, Digit–Symbol Substitution Test; E–RBMT, Extended Rivermead Behavioural Memory Test; FSIQ, Full-Scale IQ; HSCT, Hayling Sentence Completion Test; NART, National Adult Reading Test; PIQ, Performance IQ; SOC, Stockings of Cambridge test; SRT, Simple Reaction Time; TSS, total scaled score; VIQ, Verbal IQ; WASI, Wechsler Abbreviated Scale of Intelligence.
1. Key to groups: BPD, patients with bipolar disorder; CTR, controls; MIX, patients with bipolar disorder from 'mixed' families; SCZ, patients with schizophrenia; UBPD, unaffected relatives from 'bipolar' families; uMIX, unaffected relatives from 'mixed' families; uSCZ, unaffected relatives from 'schizophrenia' families.
2. Checked using Satterthwaite approximation, making adjustment of inhomogeneity of variance.

groups ($F_{(6,64)}$=4.81, P=0.0004). All patient groups were impaired relative to controls. Similarly, unaffected relatives from all families made fewer correct substitutions than controls, although only unaffected relatives from 'schizophrenia' families performed significantly worse than controls (difference 6.91, 95% CI 0.94 to 12.87). Patients with schizophrenia did significantly worse than their unaffected relatives (difference 10.6, 95% CI 3.7 to 17.5) and showed a tendency to do worse than the other patient groups. There was no evidence of a difference between patients from 'mixed' or 'bipolar' families.

Simple reaction time differed significantly between groups. All patient groups were significantly impaired compared with controls, although no difference was found between controls and any unaffected relative group. Patients with bipolar disorder from 'mixed' families did significantly worse than those from 'bipolar' families (difference −56.41, 95% CI −104.94 to −7.89). Patients with schizophrenia and patients with bipolar disorder from 'mixed' families did significantly worse than their unaffected relatives.

Choice reaction time also differed between groups. All patient groups were significantly impaired compared with controls, although no difference was found between the control group and any unaffected relative group. Patients with schizophrenia performed less well than their unaffected relatives (difference 77.93, 95% CI 30.11 to 125.76) and patients with bipolar disorder also did less well than their unaffected relatives (difference −104.70, 95% CI −178.79 to −30.61). However, no significant difference was found between patients with bipolar disorder from 'mixed' families and their unaffected relatives. Differences between affected or unaffected groups showed no diagnostic or familial specificity.

Effects of medication and weekly alcohol consumption

There was no statistically significant association between weekly alcohol consumption, prescribed daily lithium or conventional antipsychotic dosages and any measure of psychomotor performance.

Relationship of neuropsychology to genetic liability

The relationship of measures of intellectual and mnemonic function (NART IQ and WASI Full-Scale, Verbal and Performance IQ scores) to genetic liability was computed for all six groups where there was a family history of psychiatric disorder. Within the group of patients with schizophrenia, genetic liability to schizophrenia was inversely related to NART IQ (r=−0.49, P=0.01), WASI Full-Scale IQ (r=−0.33, P=0.1) and WASI Verbal IQ (r=−0.55, P=0.004) (Fig. 2) but not WASI Performance IQ (r=−0.01, P=0.94). However, within the unaffected relatives from 'schizophrenia' families, genetic liability to schizophrenia was positively related to Performance IQ (r=0.45, P=0.03) (Fig. 3) and Full-Scale IQ (r=0.36, P=0.08, trend only). No relationship was found between NART IQ (r=0.31, P=0.13) or WASI Verbal IQ and genetic liability (r=0.06, P=0.78).

Within the group of patients with bipolar disorder from 'mixed' families there was no significant relationship between genetic liability to schizophrenia and measures of IQ, and no suggestion of any trend. Within unaffected relatives from 'mixed' families, genetic liability was not related to NART IQ or WASI Full-Scale or Performance IQ; however, WASI Verbal IQ showed a trend to a negative association with genetic liability to schizophrenia (r=−0.39, P=0.05). There was no evidence of a relationship between genetic liability to schizophrenia and scores on the E–RBMT within any group. There

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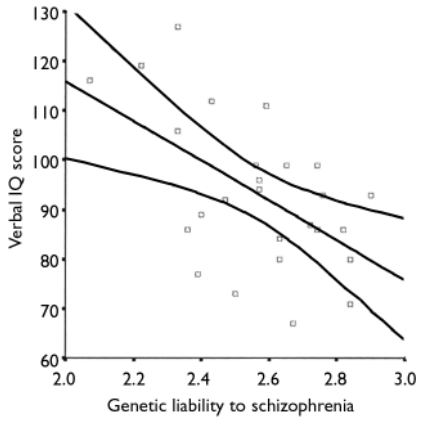

Fig. 2 Relationship between genetic liability to schizophrenia and Verbal IQ in patients with schizophrenia (r^2=0.3).

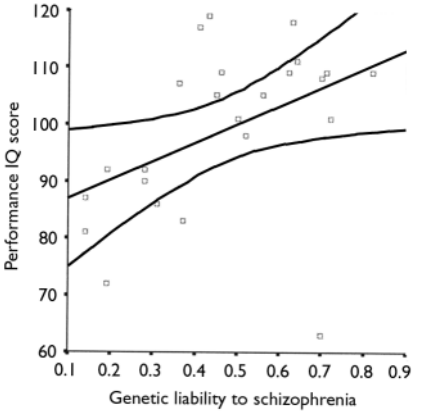

Fig. 3 Relationship between genetic liability to schizophrenia and Performance IQ in the relatives of patients with schizophrenia (r^2=0.2).

was no evidence of a relationship between genetic liability to bipolar disorder and any measure of IQ within the groups of patients with bipolar disorder from 'bipolar' families, their unaffected relatives or patients with bipolar disorder from 'mixed' families. However, unaffected relatives from 'mixed' families showed negative associations between genetic liability to bipolar disorder and WASI Full-Scale (r=−0.50, P=0.009), Verbal IQ (r=−0.47, P=0.01) and Performance IQ (r=−0.40, P=0.04), but not NART IQ. There was no evidence of a relationship between genetic liability to bipolar disorder and scores on the E–RBMT within any group.

DISCUSSION

In a study of 200 people – patients with functional psychosis, their healthy relatives and controls – several measures of neuropsychological function were estimated with correction for current psychiatric symptoms, the non-independence of observations within families and, where appropriate, age and current IQ. Current, verbal and premorbid IQ were impaired in people with schizophrenia and in their relatives. People with bipolar disorder and their relatives were not impaired on these measures, unless at least one other family member had schizophrenia. Performance IQ, in contrast, was impaired in all the patient groups, but not in unaffected individuals who had two or more relatives with bipolar disorder only. Memory was impaired across all patient and relative groups compared with controls, although patients with schizophrenia were affected more severely than those with bipolar disorder. This difference was not accounted for by differences in IQ. Psychomotor performance was impaired in patients compared with controls, regardless of diagnosis and regardless of whether the test involved a strong motor (reaction time) or cognitive (DSST) component. However, unaffected individuals with two or more relatives with schizophrenia showed impairments on the DSST test that were not present in the other unaffected relative groups.

This study did not find an overall difference in executive function across the groups. *Post hoc* testing revealed possible impairments in verbal fluency within all patient groups and reductions in planning ability (Stockings of Cambridge test) in all patients and in unaffected individuals with at least one relative with schizophrenia. However, neither of these findings survived correction for current intellectual function.

These findings suggest that intellectual function, planning ability and psychomotor tests with a high cognitive component are preferentially impaired in the relatives of people with schizophrenia. The fact that, among relatives of people with schizophrenia, Verbal IQ is positively related to a genetic liability to schizophrenia is somewhat counterintuitive. However, it finds precedent in an earlier study showing that 'obligate carriers' (unaffected people who appear to transmit a parental diagnosis of schizophrenia to their offspring) of schizophrenia had a higher IQ than controls (Steel *et al*, 2002). Since our sample included people who will develop schizophrenia or other psychiatric illnesses in later years, it is possible that their inclusion explains the reduced mean IQ in this group overall. Furthermore, the positive association between IQ and genetic liability provides some evidence that genes for schizophrenia may convey an advantage in unaffected individuals.

Strengths and weaknesses of the study

All groups were well balanced in terms of age, gender, paternal social class and weekly alcohol consumption. A history of compulsory education only or less was more common both in patients with schizophrenia and in their unaffected relatives than in the other five groups. Although all groups had relatively low scores on the HRSD, YMRS and PANSS, none of the groups was symptom-free and most patients were taking medication. However, allowance for current symptoms was made at the analysis stage and none of the remaining variation in test scores could be accounted for by medication.

Relationship to other research

This study confirms others that suggest that intellectual deficits are related to a genetic liability to schizophrenia, but is one of the few to study contemporaneously patients with schizophrenia and bipolar disorder. The positive association between genetic liability to schizophrenia and IQ in unaffected relatives is novel, as far as we know.

Studies of patients with schizophrenia (Aleman *et al*, 1999) and bipolar disorder (Quraishi & Frangou, 2002) have shown reductions in memory compared with controls which are also evident in direct comparisons (Seidman *et al*, 2002; McClellan *et al*, 2004) and are of similar magnitude regardless of diagnosis. However, the propensity of psychotropic medication and symptoms to confound these results has rarely been investigated.

For the HSCT, no difference was observed between any groups and controls for overall scaled score or error score. This finding is in contrast to several others, including one from the Edinburgh High-Risk Study (Byrne *et al*, 2003). However, patients in our study were on average 10–20 years older than those in the Edinburgh study. The unaffected sample therefore includes fewer people likely to develop psychosis in future.

Deficits in cognitive tasks with a high attentional component have previously been found in the relatives of patients with

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schizophrenia (Pogue-Geile *et al*, 1991; Franke *et al*, 1993). This has suggested to some that attentional deficits may be a mechanism by which schizophrenia might develop. The finding of attentional deficits in unaffected individuals with relatives with schizophrenia supports this view. However, their presence in people with bipolar disorder suggests that once the disease is apparent, attentional deficits show no diagnostic specificity and may possibly act to maintain psychiatric symptoms regardless of the factors leading to their development.

Future work

Although our study examined groups of people with 'functional psychosis', it is unclear whether the differences observed relate only to diagnosis or whether they relate to psychotic symptoms. Most people included in this study had such symptoms, although the numbers involved do not allow enough statistical power to perform sensitivity analyses. It has also been suggested that dimensions of psychotic symptoms found in affected individuals represent the extremes of a range of variation within the population as a whole. Brain anatomy and physiology may be more closely related to these dimensions than to diagnosis. A future study could usefully re-examine symptom dimensions in a range of people with psychotic illness and relate these findings to neuropsychological test performance, brain structure and perhaps function.

CLINICAL IMPLICATIONS

- Intellectual impairments are related to increased genetic liability to schizophrenia.
- Within relatives of people with schizophrenia, genetic liability is positively associated with performance IQ.
- No single neuropsychological measure was related specifically to the expression of or liability to bipolar disorder.

LIMITATIONS

- The measure of genetic liability used may be confounded by differences in memory and IQ between groups.
- Unaffected relative groups might have included people who would develop schizophrenia or other disorders in later years.
- The small number in each group might have led to false negative results.

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APPENDIX

Neuropsychological test battery

Current intellectual function

Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

Premorbid intellectual function

National Adult Reading Test (Nelson, 1982).

Memory

Extended Rivermead Behavioural Memory Test, version A (de Wall *et al*, 1994).

Executive function

(a) Response inhibition: Hayling Sentence Completion Test.

(b) Spontaneous production: verbal fluency and semantic category ('FAS' test) (Spreen & Strauss, 1991).

(c) Planning: CANTAB Stockings of Cambridge Test (Sahakian & Owen, 1992).

Psychomotor performance

(a) Digit–Symbol Substitution Test (Erber, 1976).

(b) CANTAB Simple and Choice Reaction Times (Sahakian & Owen, 1992).

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