Distinguishing characteristics of subjects with good and poor early outcome in the Edinburgh High-Risk Study*

EVE C. JOHNSTONE, RICHARD COSWAY and STEPHEN M. LAWRIE

Background 'High-risk' studies of schizophrenia have the potential to clarify the pathogenesis of schizophrenia. Here, results of extreme outcome groups in the Edinburgh High-Risk Study are presented.

Aims To compare groups of good and poor outcome from the Edinburgh High-Risk Study and clarify the nature of the change from the state of vulnerability to that of developing psychosis.

Method The recruitment procedure is described. Good and poor outcome are defined. These groups are compared in terms of genetic liability and of baseline and change in neuropsychology and neuroanatomy.

Results Demographic characteristics and genetic liability do not differ between the groups. The good outcome group perform better at baseline in some neuropsychological tests, but there is little neuroanatomical difference. The poor outcome group show consistently impaired memory function and a tendency to reduction in temporal lobe size.

Conclusions In genetically predisposed subjects, the change from vulnerability to developing psychosis may be marked by a reduced size and impaired function of the temporal lobe.

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The biological basis of schizophrenia is poorly understood although genetic factors are known to be important. Individuals who develop schizophrenia may have abnormalities of language (Jones *et al*, 1994), behaviour (Done *et al*, 1994) and motor development (Walker *et al*, 1994) in childhood, but whether these features represent a vulnerability to schizophrenia or are precursors of the disorder is unclear. 'High-risk' studies of individuals at enhanced risk of developing schizophrenia could potentially clarify this but have mainly concerned individuals identified in infancy as the children of mothers with schizophrenia and thus extend for decades (Asarnow, 1988; Cornblatt & Obuchowski, 1997). The Edinburgh High-Risk Study (Byrne *et al*, 1999; Hodges *et al*, 1999; Lawrie *et al*, 1999, 2001*a*,*b*; Cosway *et al*, 2000; Johnstone *et al*, 2000; Miller *et al*, 2001, 2002) differs from others as the subjects have been recruited as young adults who will pass through the period of maximum risk of developing schizophrenia during the planned 10 years of the study. The investigation concerns young people aged between 16 and 25 years at ascertainment (when they were considered well) who have at least two close blood relatives with schizophrenia. A total of 229 such young people were identified and 162 of them have so far provided data. They were compared with 34 age- and gender-matched well young people, with no family history from the same communities (Hodges *et al* 1999; Johnstone *et al*, 2000), and 36 age-matched subjects with first episodes of schizophrenia. The numbers in the control and first-episode groups were chosen to reflect the number of high-risk subjects eventually predicted to develop schizophrenia (approximately 30 individuals). The study has now been in progress for more than 6 years and some results have been presented (Byrne *et al*, 1999; Lawrie *et al*, 1999, 2001*a*,*b*; Miller *et al*, 2001, 2002). This report compares those individuals from within the high-risk sample who so far have achieved the best and the worst outcomes.

METHOD

Case ascertainment

The methods of the study have been described in detail in earlier papers. Essentially, subjects were assessed, at ascertainment and every 18 months until they develop schizophrenia or reach the age of 30 years, in terms of the following variables: (a) psychopathology as determined by the Present State Examination (PSE; Wing *et al*, 1974); (b) structural magnetic resonance imaging (MRI) (Lawrie *et al*, 1999, 2001*a*); and (c) an extensive programme of neuropsychological tests (Byrne *et al*, 1999). In addition, assessments of social function, personality and behaviour and life events were made (Hodges *et al*, 1999; Miller *et al*, 2001, 2002).

Definition of outcome categories

As previously described (Johnstone *et al*, 2000), to simplify consideration of the psychopathology as determined by PSE, a simplified classification was drawn up on the basis of the PSE profiles whereby a score of 4=Catego S+ together with a clinical diagnosis of schizophrenia; 3=fully rated psychotic symptom(s) 55–92 and/or fully rated behavioural item(s) 128, 129, 135, 136, 137; 2=3, but features partially rated or features 49–54 partially or fully rated and/or 108, 109, 118, 125, 126 fully and 133 partially or fully rated; 1=none of the above, but any other items fully rated; 0=none of the above. For the purposes of this study, those with the best outcome were those who have never achieved any fully rated score on any psychopathological item at PSE on any occasion of assessment (i.e. they always scored 0 on the study score), and who, in addition, had a record of sustained employment (or successful study towards employment) at a level higher or at least as high in terms of the Registrar General's ratings (Her Majesty's Stationery Office, 1991) of social class as their parents. Furthermore, at interview they were noted to have no abnormalities of social presentation and gave an account of unimpaired social performance. Within the context of the high-risk study, these individuals are referred to as the 'perfects'. Those with the worst outcomes have developed schizophrenia, i.e., they achieved a

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score of 4 on the study score at the last time of assessment and in addition all fulfilled the diagnostic criteria for schizophrenia according to ICD–10 (World Health Organization, 1993).

Comparisons

The 'perfects' and the individuals with newly developed schizophrenia were compared in terms of basic demographics, degree of genetic liability, baseline neuropsychology and neuroanatomy, and in those where there were at least two assessments before development of illness, change in neuropsychology and change in neuroanatomy. It will be appreciated that whereas most of the 'perfects' provided at least two assessments the numbers of individuals with newly developed schizophrenia were reduced by the fact that some of them became unwell before the second assessment could be carried out.

RESULTS

There are 24 'perfects', i.e. 13 males and 11 females of mean age 21.2 years at ascertainment (range 16–24). Thirteen high-risk subjects have developed schizophrenia (8 males and 5 females) who at ascertainment were of mean age 20.3 years (range 16–23). This difference in age is not significant.

Genetic liability

Genetic liability was assessed categorically in terms of the numbers of relatives of first and second degree known to be affected but this does not, of course, take account of the entire numbers of relatives that the subjects had, and a continuous measure of genetic liability was devised by Professor Pak Sham at the Institute of Psychiatry. It has been described by Lawrie *et al* (2001*a*) and takes account of the total number of relatives ill and well of each subject and their degree of relationship to the high-risk individual. On this scale, a higher score indicates a greater degree of genetic liability. The mean score of the 'perfects' was 0.25 (range −0.02 to +0.70) and that of those with new schizophrenia 0.16 (−0.01 to +0.40) but this difference is not significant. In the 'perfects', 18 had a genetic liability from the maternal side and 6 from the paternal. As far as those with new schizophrenia are concerned, six are known to have maternal genetic liability and five paternal. In the remaining two cases, it is possible that the inheritance is from both sides, but we do not have complete data on both maternal and paternal branches of these families.

Baseline measures

An extensive programme of neuropsychological tests was carried out at baseline on all entrants to the study and these are compared between the 'perfects' and those with new schizophrenia. Many of these tests showed no differences between these two groups (Table 1). Differences that were present were always in the direction that those who were destined to develop schizophrenia performed less well (Table 1). Baseline scans were available on 23 of the perfects and 10 of those destined to develop schizophrenia. Reasons for non-availability include pregnancy as well as reluctance to be scanned. The results are shown in Table 2. The significant difference in whole brain relates to the fact

Table 1 Comparison of baseline neuropsychological test results between the 'perfects' and the newly developed schizophrenia group

	'Perfects', mean (s.d.)	New schizophrenia, mean (s.d.)	*P*
NART IQ	98.8 (9.6)	97.6 (11.1)	NS
WAIS–R	103.1 (14.1)	94.9 (9.8)	0.1
Absolute difference PIQ–VIQ	12.2 (7.6)	18.1 (6.3)	0.03
Arithmetic	10.5 (2.5)	8.5 (2.2)	0.03
Object assembly	10.3 (2.4)	8.5 (2.7)	0.06
Verbal fluency FAS	39.8 (14.2)	40.8 (14.1)	NS
Verbal fluency animal	16.6 (5.7)	16.1 (4.4)	NS
Stroop			
Trial 3	23.1 (6.2)	23.2 (5.7)	NS
Trial 3-1	12.8 (5.8)	13.8 (5.3)	NS
Trial 3-2	10.3 (5.6)	10.8 (4.4)	NS
[2]Hayling time for A	18.4 (1.7)	21.9 (1.9)	NS
Type A errors	0 (0–6)[1]	3 (3–10)[1]	NS
Type B errors	2 (0–14)[1]	3 (0–9)[1]	NS
Total errors	2 (1–14)[1]	5 (2–12)[1]	NS
RBMT standardised	22 (21–24)[1]	20 (19–22)[1]	0.02
RBMT story	10.2 (2.9)	7.6 (4.1)	0.04
RAVLT total recall	52.2 (10.3)	45.1 (8.6)	0.06
RAVLT delayed recall	10.7 (2.9)	8.6 (2.8)	0.06
SCOLP spot the word	47 (4.3)	42.5 (4.7)	0.01
Token test	163 (162–163)[1]	162 (160–163)[1]	0.04

NART, National Adult Reading Test; RBMT, Rivermead Behavioural Memory Test; RAVLT, Rey Auditory Verbal Learning Test; WAIS–R, Wechsler Adult Intelligence Scale–Revised; PIQ, Performance IQ; VIQ, Verbal IQ; SCOLP, Speed and Capacity of Language Processing.
1. Median (interquartile range).
2. Analysis was conducted on the natural logarithm of response times for section A of the Hayling. Geometric means are presented here with 95% CI for the mean calculated on the log scale and converted back to the original.

Table 2 Whole-brain volumes (cm^3) and regional proportions (%), at baseline on the 'perfects' and the newly developed schizophrenia group

	'Perfects' (12 males, 11 females) mean (s.d.)	New schizophrenia (7 males, 3 females) mean (s.d.)	*P*
Whole brain	1336.5 (120.4)	1432.4 (93.7)	0.033
Amygdala–hippocampus left	0.34 (0.039)	0.34 (0.042)	0.83
Amygdala–hippocampus right	0.36 (0.048)	0.36 (0.038)	0.75
Thalamic nucleus left	0.46 (0.043)	0.44 (0.054)	($P < 0.05$ in females)
Thalamic nucleus right	0.46 (0.047)	0.43 (0.049)	($P < 0.05$ in females)
Third ventricle	0.033 (0.018)	0.030 (0.025)	0.75

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Table 3 Differences (mean (s.d.)) between first and second neuropsychological assessments in the 'perfects' and the newly developed schizophrenia group

	'Perfects' (n=22)		New schizophrenia (n=8)		P
	Assessment 1	Assessment 2	Assessment 1	Assessment 2	
RBMT					
Standardised score[1]	22.5 (21–24)	22 (20–24)	21 (18.5–22.8)	20 (18.5–22.8)	0.02
Story (immediate recall)	10.4 (2.9)	9.2 (3.8)	7.9 (4.4)	6.5 (2.5)	0.04
Story (delayed recall)	8.7 (3.1)	8.2 (3.4)	6.7 (3.1)	6.1 (2.6)	0.04
RAVLT delayed recall	10.7 (2.9)	10.3 (2.9)	9 (2.7)	7.5 (2.6)	0.04
Stroop trial 3-1	12.4 (5.7)	11.3 (4.5)	15.3 (5)	11.1 (2.9)	0.04

RBMT, Rivermead Behavioural Memory Test; RAVLT, Rey Auditory Verbal Learning Test.
1. Median (interquartile range).

Table 4 Differences between first and second scans in the 'perfects' and the newly developed schizophrenia group in terms of volume changes in left and right amygdala–hippocampus and temporal lobes

	'Perfects' (n=22) (mean, s.d.) mm^3	New schizophrenia (n=8) (mean, s.d.) mm^3	P
Amygdala–hippocampus left	−164.8 (458.9)	−164.5 (590.2)	0.99
Amygdala–hippocampus right	152.1 (514.2)	10.5 (515.8)	0.51
Temporal lobe left	−1089.9 (3826.8)	−1854.0 (3708.9)	0.63
Temporal lobe right	−139.2 (3579.2)	−2245.2 (3234.5)	0.16

Mean and s.d. are calculated as scan 2 − scan 1 (i.e. negative value indicates volume reduction).

that there are more males in the newly developed schizophrenia group and where correction is made for gender and height, this difference disappears.

Differences between first and second assessments

We then examined the relationship between the first and second neuropsychological assessment and compared this between the 'perfects' and those of the newly developed schizophrenia group on whom we had two assessments (eight cases). The significant findings are shown in Table 3. There is consistently poorer performance in memory tests in those who will develop schizophrenia and an improvement in function in the Stroop tests in those patients but not in the 'perfects'. All other tests were non-significant. Similarly, we compared the difference between the first and second scan in the 'perfects' and those with newly developed schizophrenia for whom two scans were available before they became ill. Most comparisons showed no tendency to significance. In particular, the amygdala–hippocampus, which has shown clear-cut findings such that this is smallest in the control schizophrenia group, next in the generality of the high-risk cases and largest in the normal controls (Lawrie *et al*, 1999, 2001*a*), showed no tendency to a difference between the 'perfects' and those with new schizophrenia. By contrast, there was an apparent difference in the change in temporal lobe size between scans 1 and 2 (see Table 4). This does not achieve significance because of the small numbers and high variance but is of interest.

DISCUSSION

This paper presents preliminary findings concerning a comparison between two extreme subgroups of a much larger study. The conclusions that can be drawn are, therefore, tentative. None the less, it is clear that in terms of baseline demographic characteristics the two groups are similar and there is no evidence of greater genetic liability in those who will develop schizophrenia. There are neuropsychological differences at baseline between the two groups, such that the good outcome group perform better in terms of memory and some, but not all, measures of IQ. This is redolent of our previous study of treatment-responsive and treatment-resistant schizophrenia (Lawrie *et al*, 1995). Frontal (Hayling test) and cingulate (Stroop test) tasks did not significantly differ between the two groups. The relatively low National Adult Reading Test (NART; Nelson, 1982) scores are likely to be because of the subjects' youth. At baseline there were essentially no neuroanatomical differences between the two groups and this contrasts with the baseline differences we have established between the high-risk subjects and both normal and schizophrenia controls (Lawrie *et al*, 1999). This may well be because of the small size of the groups in the current comparison, in that numbers larger than this are generally required to demonstrate differences between patients with schizophrenia and normal controls (Lawrie & Abukmeil, 1998). Where we have had the opportunity to assess the subjects twice before illness develops in comparison to the 'perfects', those who will develop schizophrenia show consistently poor memory function (Table 3). They also show a significant improvement in performance on the Stroop test, but this is not easy to interpret as it results from an initially non-significantly poorer performance.

The interest of the impaired memory function that we see before the manifestation of psychosis in those destined to develop schizophrenia is enhanced by the tendency of these subjects to show a reduction in temporal lobe size over the same period because, of course, memory function is most localisable to the temporal lobe. This finding reflects our earlier result (Cosway *et al*, 2000) of a pre-psychotic decline in memory. We have already shown that the neuropsychological impairments in subjects at enhanced risk of schizophrenia are widespread and affect many more individuals than are likely to develop the

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condition (Byrne *et al*, 1999). We suggest that the findings may indicate that the feature that marks the change from vulnerability to developing psychosis is a reduction in size and impairment of function of the temporal lobe. Cognitive change seems to be a precursor and not a consequence of psychosis in people who have schizophrenia.

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CLINICAL IMPLICATIONS

- Among genetically predisposed subjects, those who will go on to develop schizophrenia do not have greater genetic liability than those who will remain well.
- Some individuals with high genetic liability to schizophrenia are asymptomatic, with high levels of occupational and social function.
- Memory function may distinguish between those genetically predisposed individuals who will go on to develop schizophrenia and those who will not.

LIMITATIONS

- This is an interim analysis of selected subgroups and thus much information from the sample as a whole is not included.
- The membership of the groups is not yet fixed – more subjects will develop schizophrenia and some of the 'perfects' may deteriorate.
- The number of subjects with two assessments before illness supervenes is small.

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EVE C. JOHNSTONE, FRCPsych, RICHARD COSWAY, BSc, STEPHEN M. LAWRIE, MRCPsych, University Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh, UK

Correspondence: Eve Johnstone, University Department of Psychiatry, Kennedy Tower, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, UK

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