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 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.

Declaration of interest  This study was financed by the Medical Research Council, which supports S.M.L. and R.C.


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, 2001a); 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...
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 (2001a) 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...
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, 2001a), 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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**Table 3** Differences (mean (s.d.)) between first and second neuropsychological assessments in the ‘perfects’ and the newly developed schizophrenia group

<table>
<thead>
<tr>
<th></th>
<th>‘Perfects’ (n=22)</th>
<th>New schizophrenia (n=8)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Assessment 1</td>
<td>Assessment 2</td>
<td></td>
</tr>
<tr>
<td>RBMT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Standardised score1</td>
<td>22.5 (21–24)</td>
<td>22.0 (20–24)</td>
<td></td>
</tr>
<tr>
<td>Story (immediate recall)</td>
<td>10.4 (2.9)</td>
<td>9.2 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Story (delayed recall)</td>
<td>8.7 (3.1)</td>
<td>8.2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>RAVLT delayed recall</td>
<td>10.7 (2.9)</td>
<td>10.3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Stroop trial 3-I</td>
<td>12.4 (5.7)</td>
<td>11.3 (4.5)</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td>21 (18.5–22.8)</td>
<td>20 (18.5–22.8)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th></th>
<th>‘Perfects’ (n=22)</th>
<th>New schizophrenia (n=8)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>(mean, s.d.) mm³</td>
<td>(mean, s.d.) mm³</td>
<td></td>
</tr>
<tr>
<td>Amygdala–hippocampus left</td>
<td>–164.8 (458.9)</td>
<td>–164.5 (590.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Amygdala–hippocampus right</td>
<td>152.1 (514.2)</td>
<td>10.5 (515.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Temporal lobe left</td>
<td>–1089.9 (3826.8)</td>
<td>–1854.0 (3708.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>Temporal lobe right</td>
<td>–139.2 (3579.2)</td>
<td>–2245.2 (3234.5)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

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

**ACKNOWLEDGEMENTS**

This study was supported and conducted under the auspices of the ethics committees relevant to the districts in which the subjects lived. We are most grateful to Suheib Abukmeil, Majella Byrne, Bobby Clafferty, Elizabeth Grant, Anne Hodges and Jane Morris who recruited the subjects and conducted some of the assessments, and to Norma Brealey who carefully prepared the manuscript. We greatly appreciate the helpfulness of the subjects and their extended families, general practitioners and psychiatrists throughout Scotland.

**REFERENCES**


Cosway, R., Byrne, M., Clafferty, R., et al. (2000) Neuropsychological change in young people at high risk for schizophrenia: Results from the first two neuropsychological assessments of the Edinburgh High Risk Study. Psychological Medicine, 30, 1111–1121.


**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.
- The number of subjects with two assessments before illness supervenes is small.

**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.

**REFERENCES**


Cosway, R., Byrne, M., Clafferty, R., et al. (2000) Neuropsychological change in young people at high risk for schizophrenia: Results from the first two neuropsychological assessments of the Edinburgh High Risk Study. Psychological Medicine, 30, 1111–1121.


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