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The Maudsley Family Study: Premorbid and Current General Intellectual Function Levels in Familial Bipolar I Disorder and Schizophrenia

TIMOTHEA TOULOPOULOU, SEEMA QURAISHI, COLM MCDONALD, AND ROBIN M. MURRAY

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The distinction of psychosis into schizophrenia and bipolar disorder has been increasingly challenged with some evidence suggesting that the two conditions may have common etiologic and pathogenic mechanisms. We compared the premorbid and current intellectual function of bipolar patients from multiply affected families, and those of their first-degree relatives, with those of a similar series of schizophrenic subjects, as well as their relatives, and normal controls. Only schizophrenic subjects showed lower premorbid IQ, suggesting that they, but not the bipolar patients or either relative group, had suffered neurodevelopmental impairment. However, both groups of patients had comparably poor current general intellectual levels, implying that some common pathogenic process operates once illness has begun. The two groups of relatives showed distinct differences in intellectual function but we cannot exclude the possibility that these were a function of our sampling methods.

Introduction

Kraepelin’s distinction of psychosis into schizophrenia and bipolar disorder has come under increasing criticism (Crow, 1990; Keri, Kelemen, Benedek, & Janka, 2001; Taylor, 1992; Van Os et al., 1999). Recent evidence suggests that the two disorders share some epidemiological and clinical characteristics, as well, neuropharmacological mechanisms, structural/functional brain abnormalities, and probably predisposing genes (Kremen, Faraone, Seidman, Pepple, & Tsuang, 1998; Seidman et al., 2002; Walker, Curtis, & Murray, 2002).

Nevertheless, there remains dispute over the extent to which the two disorders share cognitive characteristics. Neurocognitive deficit is well documented in patients with schizophrenia and is considered to be a core feature of the illness; indeed, there is growing speculation that genes which modulate cognitive function may contribute to schizophrenia (Egan et al., 2001; Faraone et al., 1999; Hoff & Kremen, 2003; Toulopoulou, Morris, Rabe-Hesketh, & Murray, 2003a; Toulopoulou, Rabe-Hesketh, King, Murray, & Morris, 2003b; Toulopoulou & Takei, 2004). Evidence for cognitive impairment in bipolar disorder, especially in patients who have experienced many illness episodes, has also emerged (Bearden, Hoffman, & Cannon, 2001); verbal memory, sustained attention and executive control of working memory appear the most impaired (Chowdhury, Ferrier, & Thompson, 2003; Quraishi & Frangou, 2002; Seidman et al., 2002). The deficits are present in some
cases even during remission, challenging the long-held views that patients with bipolar disorder always make a full inter-episode recovery (Chowdhury et al., 2003; Ferrier, Stanton, Kelly, & Scott, 1999). This raises the possibility that, as seems to be the case in schizophrenia, cognitive impairment may be a trait marker for bipolar disorder.

Nonetheless, bipolar patients perform better than their schizophrenia counterparts on tasks assessing higher-level cognitive functions (Goldberg, 1999); and even though the differences in the cognitive level between the two patient groups may disappear when they are acutely symptomatic, bipolar patients in remission seem to outperform stable schizophrenic patients (Quraishi & Frangou, 2002). However, we do not know yet whether these differences result from methodological deficiencies in the investigations or whether they reflect genuine variation between the two conditions. To date, few studies have compared the two groups directly; for example some investigations compared affective disorder in general, rather than bipolar disorder in particular, with schizophrenia. Others that specifically compared bipolar disorder with schizophrenia did not differentiate between bipolar I and II, or between patients with and without psychotic features. Moreover, only a small number of investigations have compared the neurocognitive performance of the relatives of patients with bipolar disorder with that of the relatives of patients with schizophrenia.

Contrary to schizophrenia where impairments in general intellectual function have been well established (Aylward, Walker, & Bettes, 1984; Bilder et al., 2000), patients with bipolar disorder do not appear to have a global intellectual impairment (Bearden et al., 2001). Though there are several reports suggesting a lower performance IQ compared to verbal IQ in bipolar disorder, this is often due to patients having above average verbal IQ rather than below normal performance IQ scores (Bearden et al., 2001). Nonetheless, when studies have compared the two patient groups directly, patients with schizophrenia appear to have lower current IQ (Seidman et al., 2002) and premorbid function levels (McClellan, Breiger, McCurry, & Hlastala, 2003).

Evidence for significant deficits on intellectual and behavioral measures preceding the illness in schizophrenia are diverse coming from population-based cohort investigations (David, Malmberg, Brandt, Allebeck, & Lewis, 1997; Davidson et al., 1999; Jones, Rodgers, Murray, & Marmot, 1994; Reichenberg et al., 2002), studies using child and adolescent school exam records (Fuller et al., 2002) and from reports on children at high-risk for schizophrenia (Ott et al., 1998). In contrast, similar evidence concerning bipolar disorder is sparse; though developmental deviations have been reported for depression with an early onset (van Os, Jones, Lewis, Wadsworth, & Murray, 1997), data are less consistent (Gilvarry et al., 2000; McDonough-Ryan et al., 2002; Reichenberg et al., 2002). Again, most studies have reported on the premorbid levels of affective disorder in general rather than specifically on bipolar disorder.

Therefore, we set out to compare the premorbid and current general intellectual function levels of a series of patients with familial bipolar disorder with a similar series of schizophrenic patients and controls. In addition, we assessed the general cognitive level of their respective first-degree relatives and compared these levels with those of a healthy comparison group. We used a homogenous subgroup of patients with bipolar-I disorder with psychotic features from multiply affected families. This design has several advantages: (1) Previous studies observing the cognitive function of patients with bipolar disorder have included patients with various diagnoses (bipolar disorder-I, -II); this makes it hard to delineate which of the specific cognitive deficits are associated with a defined clinical symptomaticatology; (2) we aimed to generate subgroups of greater aetiological homogeneity, among the patient populations, by assessing only bipolar and schizophrenia patients with a family history of psychotic disorder; (3) patients were assessed while in a remitted state to avoid the
effects of symptoms on cognitive function, and hence probing more trait-related neurocognitive impairments; (4) in addition to assessing the patients, we also examined their healthy first-degree relatives as a means of exploring whether intellectual impairment may represent a common or distinct inherited endophenotype for the two conditions.

Methods

Subjects

We assessed thirty-nine bipolar probands (25 females, 14 males) with a lifetime diagnosis of bipolar-I disorder who had experienced psychotic symptoms during episodes of illness exacerbation. All patients were outpatients at the time of assessment and had one or more first or second-degree relatives with bipolar disorder or another psychotic disorder. Fifty of their well first-degree relatives were also assessed, comprising 17 parents, 23 siblings and 10 children. The bipolar families were compared to a similar series of schizophrenia families, drawn from a larger cohort that has been described previously (Toulopoulou et al., 2003a; Toulopoulou et al., 2003b). The subsample of schizophrenia patients and relatives used in this report was carefully chosen to match as closely as possible, in terms of age and sex, the bipolar families. The schizophrenia sample comprised 36 outpatients with schizophrenia from multiply affected families who had at least one first or second-degree relative with schizophrenia or another psychosis. Fifty-five of their well relatives are also included in the present paper, this group consisting of 25 parents, 26 siblings and 4 children. Well relatives were defined as relatives who had never fulfilled criteria for a schizophrenic, bipolar or another psychotic disorder.

Families were ascertained by referrals from psychiatric clinics and voluntary care organizations across the United Kingdom. Recruitment letters for referral of patients with a family history of bipolar disorder or schizophrenia were sent to consultant psychiatrists working in psychiatric hospitals throughout the UK and to major voluntary care organizations and charitable bodies. Recruitment of a family was done in two ways, either by approaching the patients themselves first and then asking permission to contact their healthy relatives, or by approaching patients and their unaffected relatives together at meetings of voluntary support organizations. Nine bipolar relatives had major depressive disorder and one was diagnosed with panic disorder. Of the relatives of patients with schizophrenia, ten were diagnosed with major depression, six of whom had recurrent episodes.

The bipolar and schizophrenia families were compared to 69 normal controls, 40 of whom had been previously assessed as part of the schizophrenia family study mentioned above (Toulopoulou et al., 2003a; Toulopoulou et al., 2003b). A further 29 controls were recruited via newspaper adverts as well as through communication via other volunteers. None of the controls had been diagnosed with a psychotic illness or had a family history of psychotic disorders. However, five controls had depression at some point in their lives.

Inclusion-exclusion Criteria

The inclusion criteria for subjects in the present study were (i) Caucasian and aged 17 and above, (ii) first language was English, (iii) patients had at least one relative who was willing to participate in the study. The exclusion criteria included (i) any neurological disorders, (ii) substance or alcohol dependence in the previous twelve months and (iii) a history of head injury resulting in loss of consciousness for over five minutes. The study was approved by the Ethics (Research) Committee of the South London & Maudsley NHS Trust and informed consent was obtained in writing from all participants.
Psychiatric Assessment

The Schedule for Affective Disorders and Schizophrenia-Lifetime Version (Spitzer, Endicott, & Robins, 1978) was administered to all subjects in the sample (patients, relatives and controls) and combined with additional clinical information on the nature and duration of symptoms to enable DSM-IV diagnoses to be made. Lifetime symptomatology was assessed by the Operational Criteria Checklist for Psychotic Illness (McGuffin, Farmer, & Harvey, 1991). Familiality was established by administering the Family Interview for Genetic Studies (Maxwell, 1992) to the most reliable informants in each family.

Neuropsychological Assessment

Premorbid and current general intellectual functioning were assessed by the National Adult Reading Test – Revised (Nelson, 1982) and by Canavan, Dunn, and Mcmillan’s, (1986) five-subtest short form of the Weschler Adult Intelligence Scale – Revised (Wechsler, 1981), respectively.

Premorbid IQ. The high association of reading ability with general intellectual function and the resistance of reading skill to processes of cognitive deterioration (Nelson & McKenna, 1975) make the National Adult Reading Test (NART) a quick and sensitive measure of estimating premorbid intelligence levels. The NART comprises a list of 50 phonetically irregular words where the application of the common grapheme-phoneme and stress rules would result in incorrect pronunciation. It provides a sensitive measure of previous familiarity with words in that they can be pronounced correctly only if there is prior knowledge of them. WAIS-R IQ can be estimated from the number of NART errors. The correlation between the NART generated IQ score and the WAIS-R IQ is very high (Nelson & Willison, 1991; Crawford et al., 1992).

Current IQ. Canavan et al.’s (1986) short form of the WAIS-R includes three verbal (vocabulary, comprehension, similarities) and two performance subtests (block design, object assembly). Each subtest is designed to assess a different cognitive ability. Vocabulary assesses an individual’s knowledge of word meanings and the skill to provide definitions, while comprehension measures practical reasoning ability and evaluates capacity to exercise social judgment. The third verbal subtest we used, similarities, taps concept formation and reasoning ability and assesses the capacity to formulate thoughts into words. Each item is scored dependent on the degree to which the response contains an abstract and general categorization or a specific and concrete type of reasoning. In terms of the performance subtests, block design assesses the ability to perceive spatial component relationships and evaluates the capacity to assemble, within a time limit, replicas of block constructions made by the examiner or of two-dimensional printed designs. Finally, object assembly measures the capacity to perceive spatial relations and evaluates visual-motor speed and visuospatial manipulation. To compute IQ scores, each subtest’s raw score was converted to scaled score equivalents and the sum of scaled scores was prorated to obtain the estimated, age-graded full-scale IQ in addition to performance and verbal scales.

Data Analysis

A series of analyses were performed to compare the scores between each experimental group (bipolar and schizophrenia patients and their respective relatives) and controls. In
addition, further analyses were done to compare performance between the two patient groups and between their respective relatives. A linear regression model was employed with each dependent variable analyzed co-varying for age, gender, and education. An inherent problem with any family study is that observations of family members cannot be considered as independent since they are more likely to share a similar value of a variable. An analysis without correcting for this effect may artificially inflate group differences. To overcome this problem, a random effect for family was built into the linear regression equation. The significance of individual regression coefficients was tested using z-statistics, that is, the estimated regression coefficient divided by its estimated standard error. Differences in demographic characteristics between groups were further explored using a Wald test ($\chi^2$ – test). Our models are described further in Toulopoulou et al. (2003b) and in Rabe-Hesketh et al. (Rabe-Hesketh, Toulopoulou, & Murray, 2001). Analyses were conducted using the STATA program (Stata Corporation 1984–1997. *Stata Statistical Software: Release 7.0*).

**Results**

**Demographic Characteristics of Bipolar and Schizophrenic Patients, Their Well Relatives, and Normal Control Subjects**

The demographic characteristics of the bipolar and schizophrenic patients, their well relatives, and normal control subjects are shown in Table 1. No significant differences were found in the age ($\chi^2 = 246.4; \text{df} = 220; p = 0.11$); sex ($\chi^2 = 5.33; \text{df} = 4; p = 0.26$); social class ($\chi^2 = 30.5; \text{df} = 24; p = 0.17$) or level of education ($\chi^2 = 87.3; \text{df} = 84; p = 0.38$) between the groups.

**Bipolar Patients Compared to Schizophrenia Patients and Normal Controls**

Table 2 shows the mean scores, standard deviations and the age, sex and years of education adjusted $z$ and p-values in premorbid and current intellectual ability in bipolar patients, patients with schizophrenia, and normal control subjects. The mean scores, standard deviations, and $z$ and p-values for the discrepancy between the verbal and performance IQ, and the mean differences between premorbid and current intellectual function are also given in Table 2.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>The demographic characteristics of bipolar and schizophrenia patients, their well relatives, and normal control subjects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia patients</th>
<th>Bipolar patients</th>
<th>Relatives of schizophrenia patients</th>
<th>Relatives of bipolar patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>36</td>
<td>39</td>
<td>55</td>
<td>50</td>
<td>69</td>
</tr>
<tr>
<td>Age (range)</td>
<td>21–70</td>
<td>22–64</td>
<td>18–72</td>
<td>17–72</td>
<td>18–72</td>
</tr>
<tr>
<td>Age (mean/SD)</td>
<td>37.0 (9.9)</td>
<td>41.3 (11.4)</td>
<td>46.3 (15.2)</td>
<td>45.1 (16.0)</td>
<td>43.6 (5.7)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>61.1</td>
<td>64.1</td>
<td>67.3</td>
<td>50.0</td>
<td>49.3</td>
</tr>
<tr>
<td>Education (mean/SD)</td>
<td>13.90 (2.8)</td>
<td>12.88 (3.6)</td>
<td>13.6 (2.7)</td>
<td>12.5 (3.0)</td>
<td>13.6 (2.5)</td>
</tr>
</tbody>
</table>
Table 2
Premorbid and current general intellectual ability in bipolar patients, schizophrenia patients and normal control subjects

<table>
<thead>
<tr>
<th></th>
<th>BD Patients</th>
<th>Sz Patients</th>
<th>Controls</th>
<th>BD vs Controls</th>
<th>SZ vs Controls</th>
<th>BD vs Sz</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>39</td>
<td>36</td>
<td>65</td>
<td>z = −0.27 p = 0.785</td>
<td>z = −2.69 p = 0.007</td>
<td>z = −2.21 p = 0.03</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>111.30 (11.60)</td>
<td>102.88 (12.44)</td>
<td>111.50 (10.69)</td>
<td>z = −3.55 p &lt; 0.0001</td>
<td>z = −3.69 p &lt; 0.0001</td>
<td>z = −0.55 p = 0.58</td>
</tr>
<tr>
<td>FIQ</td>
<td>95.95 (13.71)</td>
<td>94.30 (14.46)</td>
<td>107.43 (12.29)</td>
<td>z = −1.26 p = 0.21</td>
<td>z = −1.08 p = 0.28</td>
<td>z = −0.02 p = 0.98</td>
</tr>
<tr>
<td>VIQ</td>
<td>94.95 (11.74)</td>
<td>91.40 (13.82)</td>
<td>105.12 (13.19)</td>
<td>z = −2.81 p = 0.005</td>
<td>z = −2.74 p = 0.006</td>
<td>z = −0.22 p = 0.83</td>
</tr>
<tr>
<td>PIQ</td>
<td>99.26 (17.91)</td>
<td>99.70 (16.77)</td>
<td>110.14 (14.48)</td>
<td>z = 0.09 p = 0.93</td>
<td>z = −0.21 p = 0.83</td>
<td>z = 0.18 p = 0.86</td>
</tr>
<tr>
<td>Verbal/Performance IQ discrepancy</td>
<td>−4.92 (14.47)</td>
<td>−8.30 (14.51)</td>
<td>−5.02 (17.11)</td>
<td>z = −2.30 p = 0.02</td>
<td>z = −2.66 p = 0.001</td>
<td>z = −0.61 p = 0.54</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>9.72 (2.28)</td>
<td>8.80 (2.93)</td>
<td>10.91 (2.49)</td>
<td>z = −1.67 p = 0.09</td>
<td>z = −1.14 p = 0.25</td>
<td>z = 0.35 p = 0.72</td>
</tr>
<tr>
<td>Comprehension</td>
<td>7.87 (2.30)</td>
<td>7.83 (2.41)</td>
<td>10.23 (2.57)</td>
<td>z = −2.97 p = 0.003</td>
<td>z = −2.98 p = 0.003</td>
<td>z = −0.31 p = 0.76</td>
</tr>
<tr>
<td>Similarities</td>
<td>8.95 (2.41)</td>
<td>8.67 (2.76)</td>
<td>10.27 (2.32)</td>
<td>z = −1.80 p = 0.07</td>
<td>z = −1.87 p = 0.06</td>
<td>z = −0.26 p = 0.80</td>
</tr>
<tr>
<td>Block Design</td>
<td>10.08 (2.57)</td>
<td>10.17 (3.00)</td>
<td>10.92 (2.58)</td>
<td>z = −3.92 p &lt; 0.0001</td>
<td>z = −2.59 p = 0.009</td>
<td>z = 0.79 p = 0.43</td>
</tr>
<tr>
<td>Object Assembly</td>
<td>7.44 (3.17)</td>
<td>8.37 (2.59)</td>
<td>9.31 (2.65)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Preomribd IQ minus Current IQ</td>
<td>15.36 (8.78)</td>
<td>9.37 (12.14)</td>
<td>4.43 (12.35)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Premorbid IQ. Schizophrenic patients had lower premorbid IQ scores compared to bipolar patients (z = −2.21 p = 0.03) and to controls (z = −2.69, p = 0.007). There were no statistically significant differences in premorbid IQ between bipolar and schizophrenia patients, and controls (controls as baseline = 0). The adjusted mean differences on premorbid IQ for bipolar patients and controls and between schizophrenic patients and controls were −0.61 (95% C.I.: −4.98, 3.76) and −6.50 (95% C.I.: −11.24, −1.76) respectively.

Current Intellectual Function (IQ). The bipolar and schizophrenic groups performed significantly worse than controls but were comparable to one another on estimated full-scale and performance IQ (FIQ: BP vs. controls: z = −3.55 p < 0.0001; SZ vs. controls: z = −3.69 p < 0.0001. PIQ: BP vs. controls: z = −2.81 p = 0.005; SZ vs. controls: z = −2.74 p = 0.006). The age, sex and years of education, adjusted mean differences on overall sum of scaled IQ scores between bipolar patients and controls and between schizophrenic patients and controls were −10.53 (95% C.I.: −16.34, −4.72) and −12.61 (95% C.I.: −19.32, −5.91) respectively. The adjusted mean differences on prorated scaled scores for performance IQ between bipolar patients and controls and between schizophrenic patients and controls were −10.22 (95% C.I.: −17.35, −3.09) and −11.20 (95% C.I.: −19.20, −3.20) respectively. No significant differences emerged between the bipolar and schizophrenic patients and controls, when prorated scaled verbal IQ scores were compared. Similarly, no significant differences were found in the discrepancy between verbal and performance IQ scores between any of the groups compared.

Individual WAIS-R Subtests. Further analysis on the individual WAIS-R subtests that were used to calculate IQ scores, showed that there were no significant differences between the two patient groups. However, both groups achieved significantly lower scores

Figure 1. Age, sex and years of education adjusted premorbid IQ for bipolar and schizophrenia patients in relation to controls (controls = 0).
compared to controls on the vocabulary (BP vs. controls: $z = -2.30 \ p = 0.02$; SZ vs. controls: $z = -2.66 \ p = 0.001$) and similarities tests (BP vs. controls: $z = -2.97 \ p = 0.003$; SZ vs. controls: $z = -2.98 \ p = 0.003$) of the verbal domain and on the object assembly task (BP vs. controls: $z = -3.92 \ p < 0.0001$; SZ vs. controls: $z = -2.59 \ p = 0.009$), a measure of performance intellectual function.

**Premorbid IQ – Current IQ scores.** Figure 2 illustrates the differences in mean IQ points between NART ( premorbid IQ) and WAIS-R (current IQ) scores for each of the two patient groups compared to the difference between the two measures found in controls. As the graph depicts, the greatest decline is evident in the bipolar patient sample, a mean decrease of more than 15 points, the schizophrenic patients showing a decrease of 9 points. The controls showed the least discrepancy (4 points) between the IQ estimations based on NART and WAIS.

**Relatives of Bipolar Patients Compared to Relatives of the Schizophrenia Sample and Controls**

Table 3 shows the mean scores, standard deviations and the adjusted $z$ and $p$-values in NART scores and general intellectual ability for the relatives of bipolar and schizophrenia

![Figure 2](image-url)
<table>
<thead>
<tr>
<th></th>
<th>BD rels</th>
<th>Sz rels</th>
<th>Controls</th>
<th>BD rels vs Controls</th>
<th>SZ rels vs Controls</th>
<th>BD rels vs Sz rels</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>49</td>
<td>52</td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre – IQ</td>
<td>112.24 (13.31)</td>
<td>108.63 (12.70)</td>
<td>111.50 (10.69)</td>
<td>z = -0.64 p = 0.525</td>
<td>z = -1.81 p = 0.07</td>
<td>z = -1.12 p = 0.26</td>
</tr>
<tr>
<td>FIQ</td>
<td>102.65 (10.03)</td>
<td>103.64 (19.29)</td>
<td>107.43 (12.29)</td>
<td>z = -2.00 p = 0.05</td>
<td>z = -1.14 p = 0.25</td>
<td>z = 0.57 p = 0.57</td>
</tr>
<tr>
<td>VIQ</td>
<td>96.24 (16.72)</td>
<td>101.64 (18.60)</td>
<td>105.12 (13.19)</td>
<td>z = -1.31 p = 0.19</td>
<td>z = -0.75 p = 0.45</td>
<td>z = 0.31 p = 0.78</td>
</tr>
<tr>
<td>PIQ</td>
<td>107.96 (20.96)</td>
<td>104.88 (18.57)</td>
<td>110.14 (14.48)</td>
<td>z = -0.85 p = 0.40</td>
<td>z = -1.53 p = 0.13</td>
<td>z = -0.67 p = 0.50</td>
</tr>
<tr>
<td>Verbal/Performance</td>
<td>-11.71 (17.91)</td>
<td>-3.24 (13.00)</td>
<td>-5.01 (17.11)</td>
<td>z = -2.17 p = 0.03</td>
<td>z = -0.79 p = 0.43</td>
<td>z = 2.26 p = 0.02</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>10.04 (2.30)</td>
<td>10.26 (2.97)</td>
<td>10.91 (2.49)</td>
<td>z = -2.29 p = 0.02</td>
<td>z = -0.56 p = 0.57</td>
<td>z = 1.32 p = 0.19</td>
</tr>
<tr>
<td>Comprehension</td>
<td>8.84 (2.17)</td>
<td>9.34 (3.40)</td>
<td>10.23 (2.57)</td>
<td>z = -0.16 p = 0.87</td>
<td>z = -0.67 p = 0.50</td>
<td>z = -0.48 p = 0.63</td>
</tr>
<tr>
<td>Similarities</td>
<td>9.49 (1.95)</td>
<td>9.60 (3.37)</td>
<td>10.27 (2.32)</td>
<td>z = -2.43 p = 0.01</td>
<td>z = -1.18 p = 0.24</td>
<td>z = 1.00 p = 0.32</td>
</tr>
<tr>
<td>Block Design</td>
<td>11.27 (2.89)</td>
<td>9.72 (3.13)</td>
<td>10.92 (2.58)</td>
<td>z = 0.39 p = 0.69</td>
<td>z = -1.72 p = 0.08</td>
<td>z = -1.91 p = 0.06</td>
</tr>
<tr>
<td>Object Assembly</td>
<td>8.31 (2.68)</td>
<td>8.46 (2.88)</td>
<td>9.31 (2.65)</td>
<td>z = -2.01 p = 0.04</td>
<td>z = -1.19 p = 0.23</td>
<td>z = 0.63 p = 0.52</td>
</tr>
<tr>
<td>Premorbid minus</td>
<td>9.59 (13.88)</td>
<td>4.37 (12.01)</td>
<td>4.43 (12.35)</td>
<td>N/A</td>
<td>N/A</td>
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</table>
patients, and normal control subjects. No significant differences emerged between relatives of either patient group and controls in NART scores.

Bipolar relatives had significantly lower estimated full-scale IQ (z = −2.00 p = 0.05) compared to controls, though their IQ score was well within the normal range. There were no significant differences in verbal IQ for bipolar relatives compared to controls. There were no significant differences in any IQ score for the schizophrenia relatives compared to controls. Further analysis for each of the WAIS-R subtests separately revealed that the bipolar relatives group scored below controls on the vocabulary (z = −2.29 p = 0.02), similarities (z = −2.43 p = 0.01) and object assembly (z = −2.01 p = 0.04) tasks.

Verbal – Performance IQ Discrepancy. The analysis of the verbal-performance IQ discrepancy revealed that the relatives of bipolar patients showed significantly greater discrepancy in their verbal and performance scores when compared to the difference found in the control group (z = −2.17 p = 0.03) and to the schizophrenia relatives (z = 2.26 p = 0.02), indicating that relatives of bipolar patients had a much higher performance IQ when compared to their verbal IQ.

Discussion

Premorbid IQ

Overall all groups performed within the normal range, but schizophrenic patients had significantly lower premorbid IQ scores, as estimated by the NART, compared to the patients with bipolar disorder and to the controls. The patients with bipolar illness had similar NART scores to those of the normal comparison subjects. Similarly, there were no differences in the reading scores between the two groups of relatives, or between each of the relative groups and controls.

Consistent with our results, Gilvarry et al. (2000) also found that patients with schizophrenia had a lower premorbid IQ, as measured by the NART, compared to their relatives, affective psychotic patients and normal comparison subjects. In addition, as with the present report, the relatives of schizophrenic patients in the study by Gilvarry did not differ significantly from controls. Our finding of lower premorbid IQ in schizophrenia is also compatible with a study on children at risk for schizophrenia and affective disorder which suggested that IQ at 9.7 years is lower in those children with high risk for schizophrenia compared to those with high risk for affective disorder (Ott et al., 1998). Indeed, impairments have been shown to predate the onset of schizophrenia across a range of developmental domains including motor, speech, social and behavioral (Jones et al., 1994).

In addition, school performance also may be a precursor to the cognitive deficit seen in people experiencing their first episode of schizophrenia. Fuller et al. (2002) found that children who developed schizophrenia as adults were significantly below state norms obtained at grade 11 in reading ability, language, sources of information, and composite scores. However, results acquired at grades 4 and 8 were not significantly below average, suggesting that a decline must have occurred between grades 8 and 11 or, in other words, between the ages of 13 to 16. These findings suggest that, in this case at least, the neurodevelopmental deviance may have been the result of pathological processes occurring during adolescence. Two other population based cohort studies on adolescents also support the notion that individuals who subsequently develop schizophrenia have deficits that exist before the onset of the condition (David et al., 1997; Davidson et al., 1999). In the study by David et al., a linear relationship was found between low IQ and risk for schizophrenia,
while Davidson et al. showed that intellectual social functioning, and organizational skills are strongest predictors for the condition.

Premorbid IQ deficits and developmental anomalies are not exclusive to schizophrenia. For example, intelligence appears to be an independent predictor of lifetime risk of general psychiatric contact, with each standard deviation decrease in IQ resulting in a 12% increase in the risk of contacting psychiatric services (Walker, McConville, Hunter, Deary, & Whalley, 2002). McClellan et al. (2003) found premorbid behavioral problems and academic difficulties in all groups of early onset psychotic disorders including schizophrenia, bipolar disorder and psychosis not otherwise specified. Nonetheless, those suffering from schizophrenia had higher rates of premorbid social withdrawal and global impairment, suggesting that the developmental anomalies are more pronounced in schizophrenia. In the Dunedin birth cohort study, emotional and conduct problems were common in children destined to suffer all adult psychiatric illnesses. However, neurocognitive impairments were specific to pre-schizophreniform children, and these were not found in excess among children destined to develop mania or non-psychotic anxiety or depression (Cannon et al., 2002). Similarly, our results indicate a premorbid IQ deficit in schizophrenia, but not bipolar disorder, arguing against a common underlying developmental process before the onset of the two disorders.

Lower premorbid IQ than expected can indicate early abnormal neural development that could be a consequence of a genetic defect associated with the control of cerebral growth (Jones & Murray, 1991), or a result of antecedent environmental insults. It is thought that early environmental hazards acting in utero and post-natally increase the risk for developing schizophrenia in later life (Cannon, Jones, & Murray, 2002). The mechanism may be by the induction of cerebral pathology and cognitive disadvantage. Thus, individuals who are born very preterm show decrements in brain volumes and large increases in lateral ventricles as adolescents (Nosarti et al., 2002), indicating an association between perinatal problems and brain abnormality; such individuals also show increased risk for learning disabilities (Johnson & Breslau, 2000; Stewart et al., 1999).

There are many reports indicating that patients with schizophrenia are more likely than normal comparison subjects to experience pregnancy and birth complications (Geddes, Verdoux, Takei, Lawrie, & Murray, 1997; Mcneil, 1995) such as prematurity, pre-eclampsia, prolonged labor, asphyxia and fetal distress while there is little such evidence for bipolar disorder (Tsuchiya, Byrne, & Mortensen, 2003). Our results suggest a neurodevelopmental etiology in schizophrenia, but not in bipolar disorder. This is compatible with a hypothesis put forward by Walker and colleagues (Walker et al., 2002) that suggests that what differentiates individuals who develop schizophrenia from those who experience bipolar disorder is that the former but not the latter suffer developmental impairment; this may be related to the effects of the genes involved in early cortical development, and/or to neurodevelopmental insults.

In this study, the relatives of the patients with schizophrenia did not show deviances in reading ability, and therefore there is no evidence for a familial deficit in this sample, at least when using the NART as an estimate of general intellectual function. Thus, we found no evidence that genetic factors determine the premorbid intellectual deficit found in the patients with schizophrenia. Moreover because groups were matched in terms of education, which is highly predictive of the NART scores, variations in this variable cannot explain the result; an impairment, therefore, in cortical development as a consequence of early environmental factors such as obstetric complications, maybe acting on genetically predisposed individuals, cannot be discounted.
Current IQ

All groups scored within the average IQ range based on the WAIS-R intelligence norms; though patients with schizophrenia and bipolar disorder scored at the lower end of the average range in estimated full scale and verbal IQ. Both groups of patients had statistically significant lower estimated adjusted full-scale and performance IQ scores, as measured by a short-form of the WAIS-R, than controls. Both groups of patients scored significantly lower than normal comparison subjects on vocabulary, similarities and object assembly subtests.

That schizophrenic patients have lower IQ than normal control subjects is consistent with numerous other investigations (Aylward et al., 1984). The results also support previous reports suggesting that probands with schizophrenia score lower, even when performing within the normal limits, than would be expected from their genetic and environmental potential (Aylward et al., 1984). Their relatives had similar IQ to that of normal comparison subjects. This is compatible with most studies (Goldberg et al., 1995; Laurent et al., 1999) indicating that relatives of schizophrenic patients have an average intellectual ability with no gross cognitive abnormalities; indeed it raises the possibility that the absence of deficit in the general intellectual function in the relatives of schizophrenic patients may represent a protective factor. The idea that IQ may play a protective role was initially suggested by Offord (Offord, 1974), but it seems that whatever underlies high IQ score measurements (e.g., in terms of neurophysiology, neurochemistry, perhaps more efficient brain wiring etc.) may act favorably for those with a genetic loading for schizophrenia.

Reports on general intellectual function in patients with bipolar disorder are less consistent. Some studies show no differences between patients and controls, others suggest patients have a verbal advantage and yet others show lower performances in bipolar patients compared to controls; these inconsistencies are thought to reflect assessments of heterogeneous populations at different stages of the illness (reviewed by Quraishi (Quraishi & Frangou, 2002)). Our results suggest that patients in remission with Bipolar I disorder with psychotic features show impairments of general intellectual function compared to controls. In addition, we found that the two patient groups have very similar profiles, in terms of both overall general intellectual function, deficits in specific subtests, and in terms of magnitude. As we discussed previously, the two patient groups had different premorbid IQs with the bipolar patients having much higher scores, and therefore showing the biggest drop in IQ points compared to their schizophrenia counterparts. It is possible that some common processes relating specifically to psychosis give rise to this profile.

The performance IQ was significantly different compared to controls for both groups of patients, which is compatible with most studies (Bearden et al., 2001). Nonetheless, we have found no evidence for a large discrepancy between verbal and performance IQ when we directly compared the two. Both groups of patients showed impairment in vocabulary and similarities suggesting deficits in ability to provide definitions, capacity to exercise social judgment and practical reasoning. In addition, patients with bipolar disorder and schizophrenia showed a lower performance in the object assembly subtest indicating impairments with the ability to perceive spatial relations and conduct visuospatial manipulations; it also suggests problems with visuo-motor speed.

The relatives of bipolar patients, although scoring within the average range, had statistically significant lower performances compared to controls on estimated full scale IQ, and on the vocabulary, similarities and object assembly subtests. Thus, the relatives of the bipolar patients also showed impairment in the same subtests as did the patients. This may
indicate a familial, presumed genetic, liability for the functions assessed by these tests. This reinforces the idea that such impairments might represent susceptibility traits for bipolar disorder rather than being epiphenomena or secondary factors, and as such may provide clues to the pathophysiology of the condition. Gourovitch et al. (1999) have also found deficits among the relatives of bipolar patients using a twin design. The impairments we found in the relatives of the bipolar patients did not extend to the relatives of the schizophrenia patients so the two relative groups did not seem to share the same cognitive markers; though we cannot exclude the possibility that this might be the case if we were to examine other domains. Kremen et al., (Kremen, Faraone, Seidman, Pepple, & Tsuang, 1998) also argued against a common underlying process between bipolar and schizophrenia disorders, since only relatives of schizophrenic patients showed impairments in verbal and visual memory and dichotic attention. In contrast, Keri et al., (2001) found healthy bipolar and schizophrenic siblings to share similar latent information processing and cognitive markers; though they also found some impairments that differentiated the two groups of relatives.

Methodological Considerations

Matching for education. In schizophrenia research, the issue of matching patients and normal control subjects on education is an area of ongoing controversy (Goldstein, 1996). On the one hand, association between performance on neuropsychological measures and level of education is almost unquestionable (Heaton & Grant, 1986). On the other hand, educational level is in itself confounded by the emergence of psychiatric disorder. It has been argued that equating schizophrenic patients and control subjects on education (or IQ) may lead to systematic mismatching of theoretically expected ability (i.e., predicted level of ability unencumbered by genetic risk for schizophrenia) (Kremen et al., 1995). Therefore, we cannot exclude the possibility that we have included an overachieving group of patients with schizophrenia and matched it with an underachieving group of controls or of patients with bipolar disorder. Perhaps the latter is more likely as there are some suggestions for example of a familial association between bipolar affective disorder and high achievement (Coryell et al., 1989); in addition there is evidence that patients with bipolar disorder come from higher social classes and complete higher education (Goodwin & Jamison, 1990). Therefore it is possible that our bipolar sample might not be representative of the standard bipolar population.

The present study should be viewed in a context of other methodological limitations. First, the investigation was not epidemiologically based and therefore we cannot be certain about the representativeness of the bipolar and schizophrenia samples and of the relatives who decided to take part in the investigation. Therefore, as with any non-epidemiological study, caution should be exercised in extending these findings to other individuals (e.g., non-familial groups of patients and relatives; groups who did not achieve the same educational level, etc.). Indeed, it is probable that the study included those relatives that were the most motivated, the least socially anxious and suspicious, the most active and probably the most “mentally” strong. Even so, the performances of the relatives with bipolar disorder were marked by subtle attenuations. It might not be unreasonable to expect that those relatives who did not participate have even greater neuropsychological abnormalities. Indeed, Gilvarry et al. (2000), compared those relatives that agreed to participate in an investigation with those that did not in terms of several characteristics including social class and gender, and found that those who did not complete the NART were more likely to come from lower social classes and be male.
Second, we did not directly compare the effect of medication, symptomatology and chronicity between the schizophrenic and bipolar populations, all of which may affect different functions in different ways. However, all patients were remitted at the time of testing. Furthermore the results on the bipolar patient sample were corroborated by the similar performance of their healthy relatives.

Third, as with other family and twin studies, there is a risk of misclassification in that some unaffected relatives may yet develop a psychotic disorder, for example those relatives who have previously experienced episodes of depression could have a manic episode in the future. However this is likely to apply to very few subjects since the relatives groups’ mean age was in the mid-forties and thus most had lived through the highest risk period for the onset of a first manic episode. Some of the control sample had also experienced a major depressive disorder at some point in their lives. Since a previous history of depression was not an exclusion criterion for relatives, we did not exclude controls with such a history, in order that controls would not represent a ‘supernormal’ sample but rather be matched to unaffected relatives for all variables except the one under study, that is, having a relative with a psychotic illness (Kendler, 2003).

Conclusion

Our findings in the schizophrenic sample suggest some deficit in premorbid IQ and a further acquired impairment in current IQ; this points towards neurodevelopmental abnormalities compounded by further impairments related to the illness. Since the bipolar patients did not share the deficit in premorbid IQ, we cannot support the notion that the two disorders have similar premorbid underlying developmental processes. However, the similarities in current general cognitive impairment may reflect a common mechanism related to the onset and subsequent course of psychotic illness. The bipolar relatives appear to transmit deficits in ability to provide definitions, capacity to exercise social judgment or practical reasoning and ability to perceive and manipulate spatial relations; this suggests that specific cognitive deficits may act as a risk factor for bipolar disorder. These deficits were not present in the relatives of the schizophrenic patients.

References


