Brief Report

Memory functioning in familial bipolar I disorder patients and their relatives


Objective: The aim of this study was to compare the memory function of patients with familial bipolar I disorder (BD I) who had shown psychotic features, their non-psychotic, non-bipolar first-degree relatives, and normal controls.

Method: We assessed 38 patients with a lifetime diagnosis of BD I who had experienced psychotic symptoms, 49 of their non-psychotic, non-bipolar first-degree relatives, and 44 controls. Patients and relatives were from families multiply affected with functional psychotic illness. A five-subtest short form of the Wechsler Adult Intelligence Scale–Revised and three Wechsler Memory Scale subtests were administered to all participants.

Results: BD I patients showed deficits in verbal memory and verbal learning but not in visual memory. Compared to controls, relatives showed worse verbal learning at a statistically significant or suggestive level and performed significantly worse in both immediate and delayed verbal memory. Similar to patients, there were no differences between the relatives and control group for visual memory.

Conclusion: Impaired verbal memory and learning were found in patients and their relatives. These deficits may represent candidate endophenotypic markers for bipolar disorder.

Deficits in memory, particularly verbal memory, have been reported in bipolar disorder (BD) patients (1) and their well relatives (2), but there have been some contradictions among the findings (3, 4). Such inconsistencies between studies may be accounted for by methodological variation (such as differences in sample sizes or test instruments) and also heterogeneity among patient groups, i.e., combining patient groups with bipolar I disorder (BD I), bipolar II disorder (BD II), and those with psychotic symptoms.

It has been suggested that clinical variability in BD may reflect underlying heterogeneity at the biological and genetic levels (5). If this is true, the use of heterogeneous patient groups may contribute to the difficulties in determining the contribution of genetic risk for BD to impairments in memory function. To test whether memory impairments are a familial risk marker, and therefore a promising endophenotype for BD I, we compared measures of memory function among BD I patients, their non-psychotic, non-bipolar relatives from families multiply affected with functional psychotic illness, and a group of controls with no family history of BD or other psychotic disorders.
Methods

Subjects

The recruitment and assessments of the sample are described elsewhere (6–8). Briefly, 38 patients with a lifetime diagnosis of BD I who had experienced psychotic symptoms during episodes of illness exacerbation were assessed. All were outpatients at the time of assessment. A total of 49 non-bipolar, non-psychotic first-degree relatives of the BD I patients were also assessed. Patients and their relatives were recruited from 30 multiply affected families. In each family, the index patient had at least one first- or second-degree relative affected with BD with psychotic symptoms (n = 19 families, BD only among relatives; n = 2 families, BD and schizophrenia) or with another functional psychotic disorder (n = 5 families, schizophrenia; n = 2 families, major depressive illness with psychosis; n = 1 family, major depressive illness with psychosis and schizoaffective disorder; n = 1 family, psychotic disorder not otherwise specified).

A total of 44 controls recruited from the local community were chosen to reflect the characteristics of the total group of patients and relatives in terms of age, gender, and parental social class. Ten relatives and 16 controls from the current study had been previously included in another neuropsychological study from our research group (9).

All participants were Caucasian, between the ages of 17 and 69 years, and English was their first language. Participants were excluded if they suffered from any organic brain disease, met criteria for substance or alcohol dependency in the previous 12 months, or had a history of head injury resulting in a loss of consciousness for over five minutes. Local ethics committees approved the study.

Clinical assessments

Structured diagnostic interviews using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS-L) (10) were performed on all study participants and additional clinical information was collected on the nature and duration of symptoms to enable DSM-IV diagnoses to be made. DSM-IV Axis I diagnoses other than bipolar or psychotic disorders were not exclusion criteria for the first-degree relatives. Subscales on the Positive and Negative Syndrome Scale (PANSS) were used to evaluate depression and mania in the bipolar patients. An excitement scale, which combines four items from the PANSS—uncooperativeness, poor impulse control, excitement, and hostility—was used to measure manic symptoms (11). A depression scale, constructed from four individual items from the PANSS—somatic concern, anxiety, guilt, and depression—was used to examine depressive symptoms (12). Individual items on the depression and excitement scales are rated from 1–7, with 1 indicating no impairment and 7 indicating extreme impairment. Information regarding history of psychiatric illness was obtained from the most reliable informants available using the Family Interview for Genetic Studies (13) and from medical notes where available.

Neuropsychological assessment

General intellectual function. General intellectual functioning was assessed using a five-subtest short form (Vocabulary, Comprehension, Similarities, Block Design, Object Assembly) of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (14).

Memory and learning. Verbal memory and learning were assessed using three Wechsler Memory Scale (15) subtests: Logical Memory (both immediate and delayed recall conditions); Visual Reproduction (both immediate and delayed recall conditions); and Paired Associative Learning (immediate recall condition). The Paired Associative Learning test comprises six easy (e.g., rose–flower) and four hard (e.g., crush–dark) word associations. Three learning trials are administered and scores obtained for both the easy and hard components of the scale.

Data analysis

Multivariate analysis was carried out (STATA version 9.0; Stata Corp., College Station, TX, USA) with clustered robust standard errors to account for the non-independence of individuals within families and for possible violations of normality and equal variance assumptions. Multiple linear regression was used to compare verbal memory, visual memory, and verbal learning scores (dependent variables) of each of the patient and relative groups (independent variables) with the control group, controlling for age, gender, and IQ. Partial correlation coefficients controlling for age and gender were used to assess the relationship between depression or mania and memory function in the patient group. All tests were two-tailed using a 0.05 level of significance.
Results

Demographic, IQ, and clinical characteristics

The demographic characteristics of the bipolar patients, their relatives, and control subjects are shown in Table 1. The groups did not differ in age and gender distribution, years of education, or parental social class. Patients had a lower WAIS-R IQ than controls [estimated mean difference (EMD) −11.34 points, 95% confidence interval (CI): −17.65 to −5.02, p < 0.001] and their relatives (EMD = −6.39 points, 95% CI: −12.49 to −0.30, p = 0.04). For the WAIS-R subtests, BD I patients have significantly lower scores than controls for Similarities (EMD −1.41 points, 95% CI: −2.55 to −0.27, p = 0.01), Comprehension (EMD −2.58 points, 95% CI: −3.89 to −1.28, p < 0.001), Object Assembly (EMD −2.16 points, 95% CI: −3.67 to −0.64, p = 0.002), and the Vocabulary subtest (EMD −1.27 points, 95% CI: −2.55 to 0.02, p = 0.05). Relatives differed from controls for Comprehension (EMD = −2.11 points, 95% CI: −3.33 to −0.88, p < 0.001) and showed a trend toward poorer scores on the Similarities subtest (EMD −0.97 points, 95% CI: −2.04 to 0.10, p = 0.09), but not for IQ or other subtest scores (all p > 0.1).

A total of 23 patients were taking lithium (16 in combination with other mood stabilisers, antipsychotics, and/or antidepressants), 9 were taking other mood stabilisers (7 in combination with other antipsychotics and/or antidepressants), 2 were taking antipsychotic medication (one in combination with an antidepressant), and 4 patients were on no medication at the time of the assessment. Ten relatives had a history of a non-psychotic, non-bipolar DSM-IV Axis I disorder [major depressive disorder (n = 8); panic disorder with agoraphobia (n = 1); panic disorder without agoraphobia (n = 1)]. Seven of the control subjects had a lifetime diagnosis of major depressive disorder but were euthymic and not taking psychotropic medication at the time of study participation.

Table 1. Demographic, IQ, and clinical characteristics of the sample

<table>
<thead>
<tr>
<th>Demographic measures</th>
<th>Bipolar patients n = 38</th>
<th>Relatives n = 49</th>
<th>Controls n = 44</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female)</td>
<td>n = 24, 63</td>
<td>n = 24, 49</td>
<td>n = 23, 52</td>
<td>χ² = 2.7, p = 0.26</td>
</tr>
<tr>
<td>Current social class (I &amp; II)²</td>
<td>n = 16, 42</td>
<td>n = 30, 61</td>
<td>n = 18, 41</td>
<td>F = 4.6, p = 0.10</td>
</tr>
<tr>
<td>Age, years</td>
<td>Mean 41, SD 11.5</td>
<td>Mean 45, SD 15.3</td>
<td>Mean 43, SD 13.6</td>
<td>F = 0.78, p = 0.46</td>
</tr>
<tr>
<td>Education, years</td>
<td>Mean 14, SD 3.2</td>
<td>Mean 14, SD 3.7</td>
<td>Mean 13, SD 3.0</td>
<td>F = 0.90, p = 0.41</td>
</tr>
<tr>
<td><strong>WAIS-R</strong></td>
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<td></td>
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<tr>
<td>IQ²</td>
<td>n = 96, 13.8</td>
<td>n = 102, 9.1</td>
<td>n = 107, 12.4</td>
<td>χ² = 9.5, p &lt; 0.001</td>
</tr>
<tr>
<td>Object assembly⁵</td>
<td>7, 3.2</td>
<td>9, 2.6</td>
<td>10, 2.6</td>
<td>F = 5.98, p = 0.003</td>
</tr>
<tr>
<td>Block design⁵</td>
<td>10, 2.6</td>
<td>11, 2.9</td>
<td>11, 2.3</td>
<td>F = 2.46, p = 0.09</td>
</tr>
<tr>
<td>Vocabulary⁵</td>
<td>10, 2.3</td>
<td>10, 2.1</td>
<td>11, 2.7</td>
<td>F = 3.33, p = 0.04</td>
</tr>
<tr>
<td>Comprehension⁵</td>
<td>8, 2.3</td>
<td>8, 2.1</td>
<td>10, 2.8</td>
<td>F = 13.52, p &lt; 0.001</td>
</tr>
<tr>
<td>Similarities⁵</td>
<td>9, 2.4</td>
<td>9, 1.9</td>
<td>10, 2.0</td>
<td>F = 4.82, p = 0.01</td>
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<tr>
<td><strong>Clinical measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at onset, years</td>
<td>22, 5.6</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>No. of hospitalisations³</td>
<td>5.3, 5.6</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>PANSS depression subscale</td>
<td>6.3, 2.7</td>
<td>–</td>
<td>–</td>
<td></td>
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<tr>
<td>PANSS excitement subscale</td>
<td>4.6, 1.1</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

aSocial class I and II refer to professional/managerial and technical occupations, respectively.

bWAIS-R IQ data missing for two control subjects.

cData missing for one subject.

WAIS-R = Wechsler Adult Intelligence Scale–Revised; PANSS = Positive and Negative Syndrome Scale.

Memory functioning in bipolar I disorder

As shown in Table 2, the bipolar patients performed significantly worse than controls on the memory measures, which comprised verbal memory (immediate and delayed recall) and verbal learning (easy and hard pairs). They did not differ from controls for visual memory (immediate and delayed recall). In a post-hoc analysis, we assessed whether current mood states—depression or mania—were associated with memory function. Partial correlational analyses, covarying for age and gender, did not reveal a statistically significant
relationship between the depression scale or the mania scale and any of the measures of memory function ($r = -0.03$ to 0.11, $p \geq 0.53$).

Memory performance of relatives

Verbal memory (immediate and delayed recall) and the hard component of the verbal learning task were all significantly lower in relatives compared to controls (Table 2). There was a strong trend for relatives to have worse scores than controls for the easy verbal learning condition (Table 2). No differences were found between relatives and controls for the immediate and delayed recall components of the visual memory task (Table 2).

The analyses were repeated excluding the 10 relatives and seven controls with an Axis I diagnosis. Their exclusion made no difference to the overall results of the study and the differences between the effect sizes for all six memory variables before and after the exclusion of Axis I relatives and controls were small, ranging from –0.3 to 0.1.

Family history comparisons

We compared the cognitive functioning of BD patients with a family history of BD ($n = 27$) to BD patients with a family history of other psychotic disorders ($n = 11$) and repeated these analyses in the relative groups [relatives with a family history of BD ($n = 34$), relatives with a family history of another psychotic disorder ($n = 15$)]. No differences were found between the two patient groups and two relative groups for any of the memory variables used in this study (all data analyses available on request).

Discussion

A pattern of cognitive impairment in relatives of psychotic bipolar patients, similar to that found in individuals who develop bipolar disorder, suggests that such deficits may be related to genetic risk for the disorder. In the current study, an overlap of impairment between patients and relatives was found for verbal memory and verbal learning but not for visual memory. Impairments in verbal memory in patients and relatives were complemented by the deficits found for these two groups in verbal subtests of the WAIS-R. Our findings are consistent with those of Gourovitch et al. (16) and Keri et al. (17), who have demonstrated deficits in verbal memory in patients with bipolar disorder and their unaffected relatives compared to controls. There are also similarities with the study of Toulopoulou et al. (9), where verbal memory and verbal learning but not visual memory deficits were found in the unaffected relatives of bipolar patients (although there is some overlap with the current study: see Methods section for details). There is inconsistent reporting in the literature for visual memory deficit in BD I patients. For example, Coffman et al. (18) and Albus et al. (19) found differences, but Jones et al. (20) and Verdoux and Liruad (21) did not. With relatively few studies of visual memory in bipolar patients and their relatives, further investigations are likely to be required to establish whether this domain of neuropsychological functioning is associated with genetic risk for bipolar disorder. Our findings contrast with the current study.
those of Antila et al. (4), Clark et al. (3), and Ferrier et al. (22), who did not find verbal memory deficits in bipolar relatives.

As mentioned in the introduction, inconsistent results across studies may be related to methodological differences across studies. Genetic studies have in recent years favoured a distinction within the bipolar construct on the basis of psychotic symptoms, i.e., bipolar disorder with and without psychotic features, as there are suggestions that bipolar disorder with psychotic features may share more susceptibility genes with schizophrenia (23). Neurobiological abnormalities (24) and neuropsychological functioning have also been found to overlap. Tabares-Seisdedos et al. (25) reported that patients with schizophrenia and patients with bipolar disorder with a positive family history of psychotic illness performed significantly worse on tests of visual-motor processing and attention than patients without such a history. Glahn et al. (26) reported that spatial working memory performance distinguishes non-psychotic bipolar disorder patients from patients with functional psychosis. Deficits in cognitive functioning have also been reported in the first-degree relatives of patients with psychosis. In addition to cognitive deficits, our research group has shown that relatives of patients with bipolar disorder and schizophrenia have white matter structural deviations (27); we also demonstrated electrophysiological abnormalities in an overlapping sample of non-psychotic, non-bipolar relatives compared to healthy comparison subjects (7, 24).

The correlational analysis in the BD I patient sample suggests that the memory deficits observed are independent of clinical variables (i.e., mood states—depression and mania), and therefore are not artefacts of symptomatology. In addition, findings in relatives cannot be readily attributed to medication, subclinical or residual symptomatology, severity of illness, or other variables that usually confound neurocognitive functioning in patient populations. However, about 20% of the relatives in the present study had a lifetime diagnosis of a non-psychotic, non-bipolar Axis I diagnosis; thus, in theory, any residual symptomatology might have contributed to deficits in memory functioning. Nevertheless, when these relatives were excluded from the analysis, the results remained unchanged.

Limitations of the study

Our assessment of current affective symptomatology (depression and mania) was carried out using two subscales extracted from the PANSS. Both these subscales have been validated and correlate highly with the Hamilton Rating Scale for Depression (12) and the Young Mania Rating Scale (11), respectively. Although all BD I patients were clinically stable, they were not euthymic at the time of testing. According to the PANSS depression scale, BD I patients were experiencing some minor depressive symptoms. This corresponds with the study of Judd et al. (28), who report that in long-term follow-up of BD I patients such symptoms are common. However, in our post-hoc analysis, current affective symptomatology did not account for the memory deficits found in patients.

Another factor known to influence neurocognitive performance is psychotropic medication. Thirty-four of the 38 patients in the study were medicated and in some cases treated with more than one class of drugs. A recent study by Donaldson et al. (29) examined the contribution to and likely predictors (including medication) of intellectual functioning and memory in a treatment sample of BD I patients. They found that current antipsychotic use was the only medication-related variable that had a significant effect and was associated with lower current general IQ scores and lower general and working memory index scores. This significant result persisted after adjustment for family history of affective disorder, duration of illness, and a history of psychosis. Unfortunately, our study cannot specifically address the effect of medication on cognitive performance, as only 10% of patients were medication free at the time of assessment. However, an advantage of this study was the inclusion of non-medicated relatives. This allowed for comparisons between relatives and controls that were not confounded by the effects of psychotropic medication.

In conclusion, this study assessed a homogeneous sample of BD I patients with a history of psychotic symptoms and their non-bipolar, non-psychotic first-degree relatives from multiply affected families. Both patients and their relatives showed significant memory deficits when compared to controls. These findings indicate that components of memory processing are promising candidate endophenotypes for psychotic BD I.

Acknowledgement

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References


