Original Article

Five-year follow-up of cognitive impairment in older adults with bipolar disorder

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Objectives: To date, cognitive impairment has been thought to be an integral part of bipolar disorder. In clinical staging models, cognitive impairment is one of the hallmarks to define the clinical stage and it plays an important role in identifying the risk factors for progression to later stages of the illness. It is important to examine neurocognitive performance over longer periods to test the hypothesis of neuroprogression of bipolar disorder.

Methods: A comprehensive neuropsychological test battery was applied at baseline and five years later to 56 euthymic older outpatients with bipolar disorder (mean age = 68.35 years, range: 60–90 years) and to a demographically matched sample of 44 healthy subjects. A group-by-time repeated measures multivariate analysis of variance was performed to measure changes over time for the two groups. The impact of baseline illness characteristics on the intra-individual change in neurocognitive performance within the bipolar disorder group was studied by using logistic regression analysis.

Results: At baseline and at follow-up, patients with bipolar disorder performed worse on all neurocognitive measures compared to the matched healthy subjects. However, there was no significant group-by-time interaction between the patients with bipolar disorder and the comparison group.

Conclusions: Although older patients with bipolar disorder had worse cognitive function than healthy subjects, they did not have greater cognitive decline over a five-year period. The change in acquired cognitive impairment of patients with bipolar disorder might parallel the cognitive development as seen in normal aging.

Bipolar disorder is a psychiatric illness characterized by periods of elevated mood and of depression. It is a chronic illness that is associated with functional impairment, including impairment of cognitive functioning. A large number of cross-sectional studies have revealed cognitive impairment in patients with bipolar disorder of any age, even in the euthymic state (1–3). Although some studies suggest that there is a progressive increase in cognitive impairment in older patients with bipolar disorder, even exposing them to an increased risk of dementia (4), the debate continues as to whether the illness is related to (progressive) neurodegeneration (5). New models are emerging to understand the long-term development of severe mental illnesses such as bipolar disorder (6). In these clinical staging models, earlier and milder symptoms are distinguished from later, more impairing factors. Later stages of the illness might mimic accelerated aging – that is, oxidative damage to cells due to chronic stress associated with mood disorders. The process of a lifetime accumulation of toxic processes and cerebrovascular brain changes may lead to more cognitive impairment later in life (7). It is...
imported to identify the risk factors that underlie these changes, as an implicit aim of staging is to prevent progression to advanced stages of the illness. On the one hand, this knowledge can enable personalized interventions for individual patients in clinical psychiatry, and on the other hand it can shed light on specific neurophysiological pathways involved in the progression of the bipolar disorder. Cognition can thus be seen both as an indicator of their functional impairment and as a profiler of psychopathological progression of the disease.

Recent longitudinal studies in older patients with bipolar disorder, including one from our group, have not found a faster cognitive decline when compared to matched, healthy subjects, despite cognitive impairment at baseline (8, 9). However, in these studies, a two-year interval was used, which may be too short to detect declines in cognitive functioning. Although it is anticipated that persons with bipolar disorder would exhibit more cognitive deficits than a healthy comparison group, and that they would exhibit a faster decline at follow-up, it is not clear from the existing literature what the outcomes might be. There is some evidence that individuals with bipolar disorder develop dementia at a higher rate than expected compared to healthy subjects (10), while other studies suggest that lithium treatment could reduce the risk of Alzheimer’s disease in patients with bipolar disorder (11). The association between risk factors such as course of the illness and cognitive deterioration is not clear (12).

The main object of the present study was to examine the course of cognitive functioning during a five-year period in a sample of older patients with bipolar disorder meeting strict criteria for euthymia as compared to a healthy cohort. We controlled for residual affective symptoms at both time points because even small degrees of residual manic or depressive symptoms may have a negative impact on cognition. Mortality, dropout, and cognitive status were compared with outcomes for healthy comparison subjects. In addition, we studied whether clinical characteristics predicted the course of cognitive function.

**Methods**

**Subjects**

As previously described, patients (>60 years) with bipolar I and bipolar II disorder, who were currently euthymic, were recruited from outpatient clinics in four regions in the Netherlands (13). With help from the Dutch bipolar patient association (VMDB, Association for Manic Depressives and their Relatives), additional patients were recruited. Extensive care was taken to exclude patients with current mood symptoms, which could influence cognition. Eligible subjects were reported by their psychiatrist to have been euthymic for at least three weeks. Excluded were patients with a primary diagnosis of alcohol dependence or substance abuse and those with dementia. The control group consisted of persons who had no current or lifetime history of psychiatric or addiction disorders or recent memory complaints. They were recruited from community centers for older people and through advertisements in local newspapers. In Figure 1, a flow diagram shows inclusion and attrition in the study. The study was approved by the institutional review board, and written informed consent was obtained from all subjects.

The original sample consisted of 119 patients with bipolar disorder and 78 healthy controls. At follow-up after five years, all subjects were invited to participate in reassessment of their neuropsychological functioning. Patients with current mood symptoms that could influence their cognitive functioning were excluded. From the original sample, 56 patients (47%) and 44 healthy persons (56%) participated in the follow-up assessment. The main reasons for loss to follow-up were: refusal (25 patients and six controls), death (seven patients and four controls), not euthymic (13 patients and three controls), not able because of physical illness (eight patients and five controls), and could not be reached (ten patients and 16 controls). Compared to persons who were lost to follow-up, the longitudinal sample (completers) did not differ with respect to age or gender. However, subjects from the longitudinal sample had a significantly higher premorbid intelligence quotient (IQ) than subjects who were lost to follow-up (p < 0.05). In addition, the completers performed significantly better at baseline on the learning condition of the 10-word Test and Occupation Naming Test compared to subjects who were lost to follow-up (both p < 0.05).

**Clinical measures**

At baseline (T1), the clinical diagnosis of bipolar disorder was obtained using the Structured Clinical Interview for DSM-IV (SCID) (14). Illness characteristics such as age at onset and medication were derived from patient interviews and hospital medical records. Premorbid intelligence was estimated using the Dutch Reading Test for Adults (NLV) and the Dutch version of the New Adult Reading Test (15). At baseline (T1) and at the five-year follow-up (T2), current depressive symptoms were assessed using the Centre for Epidemiologic
Studies Depression Scale (CES-D) (16), and current mania symptoms using the Young Mania Rating Scale (YMRS) (17). The Mini Mental State Examination (MMSE) (18) was used to provide an overall assessment of cognitive functioning. For the present study, a cerebrovascular risk score [range: 0–2; 0 = no cerebrovascular diseases (CDs), 1 = 1 CD, and 2 = more than one CD] was determined by asking respondents whether they currently or had ever had any of the following chronic diseases or disease events: disease of the circulatory system (myocardial infarction, angina pectoris, heart failure, cardiac arrhythmia), hypertension, a history of ischemic attack or stroke, or diabetes. Answers were coded as either yes or no for each of these diseases.

Neuropsychological test battery

at T1 and T2, all subjects completed a comprehensive battery of neuropsychological tests, grouped into four cognitive domains:

(i) **Attention**: Digit Span subtest of the Wechsler Adult Intelligence Scale (19), Trail Making Test–Part A (20), and The Amsterdam Short-Term Memory Test (ASTM) (21);

(ii) **Learning and memory**: The 10-Word Test, a modified version of the Auditory Verbal Learning Test (22);

(iii) **Executive functioning**: Trail Making Test–Part B (17), modified version of the Stroop Color Word Test (23), and Mazes (1–4) subtest of the Wechsler Intelligence Scale for Children (24); and

(iv) **Verbal fluency**: Control Oral Word Association Test (COWAT) (25) and Animal and Occupation Naming subtest of the Groningen Intelligence Test (26).

Statistical analyses

We compared patients with bipolar disorder and comparison subjects on each of the demographic and clinical variables, using t-tests for continuous measures and chi-square tests for categorical ones at baseline and follow-up. Distributions of the continuous measures were examined prior to analyses. Differences between mood symptoms (CES-D and YMRS) and MMSE scores of patients with bipolar disorder and comparison subjects at baseline and follow-up were compared using multivariate analyses of variance.

Composite scores for each neurocognitive domain were calculated by converting the subject’s raw scores to standardized z-scores. These were then summed in each domain to provide a single score. A higher score indicated better neurocognitive performance.

Repeated measures analyses of covariance (mancova) were employed to analyze the longitudinal changes on neuropsychological testing of the two groups. Analyses were adjusted for age, premorbid intelligence, and manic symptoms. Effects of group, time, and group-by-time interactions were examined. A significant group-by-time interaction would indicate that the change in cognitive functions over time differed between the groups. Effect sizes were calculated by means of eta-squared (with $\eta < 0.15$ indicating small to medium effects and $\eta > 0.14$ indicating large effects) (27).
In order to examine inter-individual differences in patients with bipolar disorder with respect to cognitive decline over a five-year period, we dichotomized the difference scores from the domain scores in 0 = highest two tertiles representing no cognitive decline and 1 = lowest tertile representing relevant cognitive decline. The categorization into tertiles was chosen to distinguish persons with relevant cognitive decline from those with no or minor decline, given the sample size. To test whether demographic and illness characteristics were associated with cognitive decline, we firstly carried out a univariate logistic regression analysis. We then performed multivariate logistic regression analyses on the variables that influence cognitive changes, adjusted for age and premorbid intelligence.

Two-tailed tests were used for all analyses and statistical significance was defined as \( p < 0.05 \). Statistics were processed using spss version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

Demographic and baseline clinical and neuropsychological comparisons

The baseline characteristics of the 56 participants with bipolar disorder and 44 control subjects are displayed in Table 1. There were no significant differences in premorbid IQ, education, or vascular risk factors. Subjects with bipolar disorder were significantly younger than controls and included more males (\( \chi^2 = 7.61, \ p < 0.01 \)). Lithium (71% of the patients), valproic acid, and carbamazepine were the typical medications for remitted patients in the present study. Among the 56 patients, only three subjects (5%) did not use any medication.

The scores on the YMRS and CES-D were below the cut-off at each time point, confirming a euthymic state both in patients with bipolar disorder and healthy controls. However, the bipolar disorder group had significantly higher YMRS scores than the comparison group on both measurements. The bipolar disorder group did not differ from the comparison group on CES-D scores, either at baseline or after five years, but both the patient group and the comparison group had higher CES-D scores after five years (\( F = 21.81, \ p < 0.01 \)).

Table 2 shows the mean [standard deviation (SD)] of the raw neurocognitive scores at baseline and after five years. As in our earlier study with the original, larger sample (13), the subset of patients with bipolar disorder in the present study did less well on all cognitive tests when compared to the healthy subjects (all tests \( p < 0.05 \)) at baseline and after five years.

### Rate of cognitive decline in cognitive domains

Table 2 shows the mean (SD) of the z-scores on the different cognitive domains at baseline and at

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**Table 1. Sociodemographic and clinical characteristics in patients with bipolar disorder and healthy comparison subjects**

<table>
<thead>
<tr>
<th></th>
<th>Bipolar disorder (n = 56)</th>
<th>Healthy subjects (n = 44)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>62.16 (7.0)</td>
<td>70.16 (7.6)</td>
<td>1.36</td>
<td>0.24</td>
</tr>
<tr>
<td>Premorbid IQ, mean (SD)</td>
<td>111.21 (11.4)</td>
<td>114.3 (8.7)</td>
<td>1.48</td>
<td>0.11</td>
</tr>
<tr>
<td>Education, years, mean (SD)</td>
<td>5.18 (1.5)</td>
<td>5.32 (1.3)</td>
<td>0.48</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender, male, n (%)a</td>
<td>28 (50)</td>
<td>11 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors, mean (SD)</td>
<td>0.41 (0.6)</td>
<td>0.50 (0.7)</td>
<td>0.66</td>
<td>0.11</td>
</tr>
<tr>
<td>Hospital admissions, mean (SD)</td>
<td>3.84 (3.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive episodes, mean (SD)</td>
<td>4.25 (3.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manic episodes, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotic episode, n (%)</td>
<td>37 (66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months euthymic, mean (SD)</td>
<td>55.63 (63.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness duration, mean (SD)</td>
<td>31.31 (12.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset, years, mean (SD)</td>
<td>38.52 (14.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first psychiatric treatment, years, mean (SD)</td>
<td>43.25 (15.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking lithium, n (%)</td>
<td>40 (71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score, mean (SD)</td>
<td>28.75 (1.2)</td>
<td>27.80 (2.6)</td>
<td>0.92</td>
<td>0.34</td>
</tr>
<tr>
<td>YMRS scores, mean (SD)</td>
<td>0.96 (1.7)</td>
<td>1.18 (2.2)</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>CES-D score, mean (SD)</td>
<td>10.00 (7.1)</td>
<td>15.1 (4.9)</td>
<td>14.79</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

CES-D = Centre for Epidemiologic Studies Depression Scale; IQ = intelligence quotient; MMSE = Mini Mental State Examination; SD = standard deviation; YMRS = Young Mania Rating Scale.

\(^{a}\chi^2 = 7.61, p < 0.01.\)

\(^{b}F\) repeated-measures multivariate analyses of variance of the main effects of groups (tests of between-subject effects).
The five-year follow-up. In order to compare changes over time for each cognitive domain, a group-by-time repeated-measures mancova was performed, controlling for the covariates (premorbid IQ and age). The results show the main effects of groups for all cognitive domains (attention, memory, executive function, and language function) but no significant interactions with time were found. This suggests that the rate of decline over the five-year follow-up was the same for patients with bipolar disorder and the mentally healthy comparison group.

Predicting cognitive decline

To test whether demographic and illness characteristics were associated with cognitive decline within the group of patients with bipolar disorder, univariate logistic regression analysis was performed. This showed that the severity of manic symptoms at baseline predicted a decline in the domain of memory [odds ratio (OR) = 0.73, 95% confidence interval (CI): 0.52–0.98], and the number of hospitalizations predicted a decline in language function (OR = 0.85, 95% CI: 0.73–0.97). Multivariate logistic regression analysis controlling for age and premorbid intelligence showed that more manic symptoms were significantly associated with a greater decline in memory (OR = 0.72, 95% CI: 0.53–0.99). The association between number of hospitalizations and language function was no longer significant.

Discussion

Older adults with bipolar disorder exhibit worse cognitive functioning compared to healthy older subjects but no greater cognitive decline at a five-year follow-up. None of the demographic or illness characteristics were associated with cognitive decline in the domains of attention, and executive and language function. Only subclinical manic symptoms at baseline predicted a decline in memory. This is in agreement with earlier suggestions (28) that the recurrence of mania may have a long-term neuropsychological impact.

Our findings are in line with those of Depp et al. (29), Santos et al. (12), and our previous follow-up study over a two-year period (8), despite the differences in study design. Depp et al. did not establish the euthymic state of patients, which may have influenced the results, and the patients studied by Santos et al. were much younger – the mean age was 44.7 years.
The patients with bipolar disorder studied by Dhingra and Rabins (10) and Gildengers et al. (30) exhibited significant cognitive decline in contrast to our results. In the former study, no control group was included, so it is difficult to detect the effect of other variables such as aging. In the relatively small group studied by Gildengers et al., almost one-third of patients had a history of alcohol use disorder, which may have influenced the results negatively. Furthermore, these authors did not control for the effect of mood symptoms, to check whether a change in cognitive impairment corresponded to changes in mood symptoms. It seems likely that the group studied by Gildengers et al. had a greater impairment and was more prone to deterioration.

It has been suggested that lithium may have neuroprotective abilities and may reduce the risk of developing dementia (11), and that longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder (31). In the present study, more than two-thirds of the patient group used lithium, while in the study by Gildengers et al. (31) only one-third of the patients used lithium. This could mean that in the present study the use of lithium may have compensated for cognitive decline, although the very large number of patients in our study using lithium led to a restricted range of scores and thus made it difficult to detect an effect of lithium on cognition. The finding that patients with bipolar disorder do not have a faster rate of cognitive decline may have been due to the shorter interval between baseline and follow-up than in the study of Dhingra and Rabins (10). A more appropriate follow-up interval for detecting cognitive changes might be between seven years (as used by Dhingra and Rabins) and ten years.

Although our naturalistic study had several strong points, such as the inclusion of a relatively large group of patients, using a comprehensive battery of neuropsychological tests, and including a careful selection of patients who were in a euthymic state at both time points, it also had some limitations. As a result of the nature of the study design, and due to old age, not all subjects completed the follow-up. Ten patients were excluded from the follow-up because they were not euthymic. There was no association between age of onset and decline in cognitive function for the group-as-a-whole. However, we observed that all of the five patients who had a more rapid cognitive decline or converted to a dementia (MMSE <25) had a late onset. These persons may have been the most severely ill, and may have had greater cognitive decline. Finally, although efforts were made to recruit a representative bipolar disorder sample, this was not a catchment area study, so our euthymic outpatients and comparison subjects comprised a convenience sample. They may have belonged to a better outcome subgroup (survivors), in which case the results would only have applied to the subset of patients with bipolar disorder.

Conclusions
In spite of the limitations cited above, cognitive impairment is part of bipolar disorder in older people, and seems to be fairly consistent over time for at least a subgroup of patients. We speculate that patients with bipolar disorder may have reached their clinical stage in adulthood and do not decline in later life faster than healthy older subjects, or progress to more advanced clinical stages of bipolar disorder because of aging. The acquired cognitive impairment of patients with bipolar disorder might parallel the cognitive development seen in normal aging once patients reach 60–65 years of age. Prospective studies, following heterogeneous bipolar disorder samples, collecting a detailed description of past and current drug treatment and clinical features, are awaited. An important issue to be solved is whether cognitive impairment in bipolar disorder might be associated with relapse and poor clinical outcome. An important implication of the present study is that mood stabilizing seems important for preventing a decline in cognitive functioning as even subclinical symptoms may be associated with cognitive decline. Furthermore, late-life bipolar disorder patients may provide a perfect sample for studying clinical staging and profiling as these patients may have reached a stable clinical stage.

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Disclosures
The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript.

References
31. Gildengers AG, Butters MA, Aizenstein HJ et al. Longer lithium exposure is associated with better white matter integrity in older adults with bipolar disorder. Bipolar Disord 2015; 17: 248–256.