Cognitive Impairment in Early and Late Bipolar Disorder

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Background: *Late onset disorders are often associated with cerebral disfunctioning and cognitive impairment in elderly patients. It is unknown whether the age of onset affects cognition in patients with bipolar disorder. The authors compare cognition and clinical characteristics of early- and late-onset bipolar patients in a stable and euthymic condition.* **Method:** *One hundred and nineteen older patients (age >60) with an early- (<40 years) or late-onset bipolar disorder and a group of 78 comparison subjects were extensively tested for cognitive functioning.* **Results:** *Bipolar subjects scored lower on most cognitive measures. The late-onset patients were more impaired in psychomotor performance and mental flexibility than the early-onset patients. These differences could not be explained by differences in exposure to cerebrovascular risk factors.* **Conclusions:** *Older patients with bipolar disorder have substantial cognitive impairments. Late onset bipolar disorder is associated with more severe cognitive impairment than early-onset bipolar disorder. For clinical practice, it is important to develop treatment strategies which take this into account.*
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Key Words: Bipolar disorder, aged, cognition

There is a growing body of evidence that aged patients with bipolar disorder have impaired cognitive functions across a range of cognitive domains.[1] These cognitive impairments have important clinical implications, such as more functional disability and difficulties in adherence to medical regimes for older patients compared with younger and middle aged patients.[2] As a result, older bipolar patients may require different health services. Although cognitive impairment may be a trait vulnerability factor for bipolar disorder, regardless of age, two other important factors may also have a negative impact on cognition in elderly patients. First, even small degrees of residual manic or depressive symptomatology can partially account for the cognitive impairment observed in bipolar patients, and most studies are confounded by the failure to control for residual affective symptoms.[3,4] Second, elderly pa-

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tients with a bipolar disorder form a heterogeneous group, including early-onset patients who developed their illness during early adulthood and late-onset patients who experienced their first mood episode at an older age.[5] Late onset disorders are often associated with vascular and neurodegenerative changes,[6] which may also lead to cognitive deficits.[7] In such cases, bipolar patients do not develop cognitive deficits in the course or as a consequence of their disorder, but these deficits develop as a consequence of vascular and neurodegenerative changes.

We sought to clarify this issue by examining neuropsychological functioning in a group of elderly patients with bipolar disorder who were euthymic at the time of testing, and comparing them with a group of "normal" elderly people. Our aim was to investigate the associations between cognition and clinical characteristics in a group of early- and late-onset bipolar patients. We hypothesized that late-onset bipolar patients would show more cognitive decline than early-onset bipolar patients, and that these differences would be greater than the differences between the early-onset group and the comparison group.

METHODS

Sample

We included older patients (>60 years) with Bipolar-I and Bipolar-II disorder who were currently euthymic. Because most of the bipolar patients were living in the community, we focused on outpatients who we recruited from outpatient clinics in four regions of the Netherlands. With the help of the Dutch Bipolar Patient Association, we also recruited extra patients. Eligible subjects were reported to be euthymic for at least 3 weeks by their psychiatrist, and none of the patients who were included had received electroconvulsive therapy (ECT) in the previous year. Great care was taken to exclude patients with current mood symptoms, which could influence cognition. We also excluded patients with a primary diagnosis of alcohol dependence or substance abuse and patients with a clinical diagnosis of dementia. The comparison group was recruited from community centers for elderly people and advertisements in local newspapers. This group consisted of 78 persons, who had no current or lifetime history of psychiatric or addiction disorders or recent memory complaints. Written informed consent was obtained from all participants.

With respect to age of onset, we defined late onset as a first affective episode in patients over 40 years of age, as this was the median age of the first mood episode for the total sample in this study.

In the literature, there is a lack of clear consensus concerning the age limits used to differentiate "early" onset from "late onset."[8] In samples of patients with different ages, the median age at onset has generally been used as the criterion. Furthermore, there are two potential ages of onset: the age of the first affective episode and the age of the first manic episode, but only a few studies have used the first manic episode as the criterion.

Measurements

Bipolar disorder was clinically diagnosed with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.[9] Current symptoms of depression were assessed according to the Centre for Epidemiologic Studies Depression Scale,[10] and current mania symptoms according to the Young Mania Rating Scale.[11] Illness characteristics, such as age of onset and medication, were derived from patient interviews and hospital medical records. If the patient had received previous psychiatric treatment, the psychiatric records were examined. For the present study, a cerebrovascular risk score (range = 0–2; 0 = zero risk factors, 1 = one risk factor and 2 = more than one risk factor) was determined as follows: respondents were asked whether they currently or previously had any of the following chronic diseases or disease events: circulatory system diseases (myocardial infarction, angina pectoris, heart failure, cardiac arrhythmia), hypertension, history of ischemic attack or stroke, diabetes. The answers were coded either as "yes" or "no" for each of these diseases. Premorbid intelligence was estimated with the Dutch Reading Test for Adults, which is the Dutch version of the New Adult Reading Test.[12] The Mini Mental State Examination[13] was used to obtain a global assessment of cognitive functioning.

All participants also completed a comprehensive battery of neuropsychological tests covering the following four cognitive domains:

a. Psychomotor Performance and Mental Effort: The Trailmaking Test Part A[14] and the Amsterdam Short-Term Memory Test.[15]
b. Attention and Executive Functioning: The Digit Span subtest of the Wechsler Adult Intelligence Scale-III,[16] the Modified version of the Stroop Color Word Test,[17] the Trailmaking Test Part B,[14] the Control Oral Word Association Test,[18] the Animal and Occupation Naming subtest of the Groningen Intelligence Test,[19] the Mazes (1–4) subtest of the Wechsler Intelligence Scale for Children,[20] and the Rule Shift Cards subtest of the Behavorial Assessment of the Dysexecutive Syndrome.[21]
c. Learning and Memory: The 10 Words Test, which is a modified version of the Auditory Verbal Learning Test.[22]
d. Visuo Constructional Ability: The figure-copying subtest of the Amsterdam Dementia Screening Test (ADS6),[23] and Clock drawing.[24]

Statistical Analyses

Differences between groups were analyzed with analysis of variance, with age, gender, education, and cerebrovascular risk factors as covariates. Two-tailed comparisons were used, and to decrease the risk of Type I error, all results at level $p \leq 0.01$ were considered to be significant. Effect sizes were calculated by means of η^2.[25] Differences for variables containing a skewed distribution were tested by means of a nonparametric test (Kruskal-Wallis test). The data (raw test scores) were analyzed using the Statistical Package of the Social Sciences version 14.0.

RESULTS

Demographic and Clinical Features

The demographic and clinical characteristics and the contrast between the early- and late-onset bipolar groups and the comparison group are presented in Table 1. The patients with early- and late-onset bipolar disorder did not differ on any of the demographic variables studied, except for age: patients with an earlier onset were significantly younger than patients with a late onset and subjects in the comparison group.

The mean age of onset for the early-onset group was 27.6 years, whereas their first treatment started at the mean age of 31.1. The mean age of onset for the late-onset group was 53.7 years, and their first treatment started at the mean age of 55.5 years. The early-onset group was significantly more likely to have a family history of psychiatric illness (77% versus 52%; $X = 9.33$, $p < 0.01$). The patients with early- and late-onset bipolar disorder did not differ with regard to diagnostic subtypes or number of previous episodes and were equally likely to have been admitted for treatment or to have experienced a mood episode with psychotic features. There was no significant difference in the Mini Mental State Examination scores. With regard to residual depressive symptoms, there were no differences between patients in the two bipolar groups, and no differences between the bipolar groups and the comparison groups. With regard to residual manic symptoms, the bipolar patient had significantly higher scores than the comparison group, but there were no differences between the early- and late-onset bipolar groups. According to the inclusion criteria (euthymic state), there were very few mood symptoms among the bipolar patients. The patients in both groups and the comparison group had a similar burden of medical illness, as was reflected in the index of cerebrovascular risk factors. As would be expected, patients with earlier onset bipolar disorder had been taking lithium significantly longer than patients with late-onset bipolar disorder. The early-onset group was significantly more likely to have been treated with ECT in the past (15% versus 3%, $X = 205.9$, $p < 0.01$).

Cognitive Features

Descriptive data and statistical comparisons for all cognitive measures are summarized in Table 2. Both the early- and the late-onset bipolar groups differed from the comparison group with regard to the learning, retention and recognition condition of the Auditory Verbal Learning Test, the Amsterdam Short Term Memory Test, Part A and B of the Trailmaking

TABLE 1. Demographic and Clinical Characteristics

	Comparison Group (N = 78)	Early Onset (N = 59)	Late Onset (N = 60)	Between Group Contrast
Age, years (SD)[a]	71.86 (8.0)	68.41 (6.2)	72.32 (7.5)	EO<CG, LO
Men, n (%)[a]	22 (28)	28 (47)	29 (48)	CG<EO, LO
Education[b]	5.29 (1.2)	5.19 (1.5)	4.87 (1.5)	
Estimated premorbid IQ (SD)	111.63 (9.1)	109.90 (13.9)	105.40 (14.4)	
Marital status, n (%)				
Married/living with someone	34 (43)	24 (40)	22 (37)	
Divorced/separated	13 (17)	13 (22)	16 (27)	
Widowed	20 (25)	9 (15)	15 (25)	
Single	12 (15)	11 (18)	7 (12)	
Living arrangements on admission, n (%)				
Home without supervision	78 (100)	51 (86)	46 (77)	
Home with supervision	0	6 (10)	11 (18)	
Intermediate care facility	0	2 (4)	2 (4)	
Age at onset, years (SD)[a]		27.61 (6.9)	53.78 (9.4)	EO<LO
Fist treatment, years (SD)[a]		31.14 (9.6)	55.50 (10.9)	EO<LO
DSM diagnosis, n (%)				
Bipolar I last episode depressive		25 (42)	24 (40)	
Bipolar I last episode manic		9 (15)	19 (32)	
Bipolar I last episode NS		4 (7)	3 (5)	
Bipolar II		7 (12)	12 (20)	
Rapid cycling		4 (7)	2 (3)	
With psychotic features, n (%)		44 (74)	35 (58)	
Family history psychiatric illness, n (%)[a]		41 (77)	25 (52)	EO>LO
Number of admissions, n (SD)		3.97 (4.2)	2.58 (3.8)	
Number of depressive episodes (SD)		5.52 (7.6)	3.15 (3.0)	
Number of manic episodes		7.35 (14.6)	3.89 (3.4)	
Duration euthymic state, months (SD)		48.39 (71.6)	55.50 (66.4)	
MMSE, total score (SD)	27.87 (5.9)	28.27 (1.5)	27.45 (4.2)	
CES-D, total score (SD)	8.33 (5.5)	10.68 (6.6)	8.85 (7.8)	
YMRS, total score (SD)[a]	0.6 (0.43)	1.32 (1.6)	0.87 (1.6)	CG<EO, LO
Index of cerebrovascular risk factors, n (%)				
Zero risk factors	47 (60)	33 (56)	29 (48)	
One risk factors	24 (31)	22 (37)	20 (33)	
>Two risk factors	7 (9)	4 (7)	11 (18)	
Medications, n (%)				
None		3 (5)	4 (7)	
On lithium, n (%)		40 (68)	39 (65)	
On other mood stabilizer, n (%)		16 (27)	20 (32)	
On other psychopharmaca, n (%)		28 (47)	29 (48)	
ECT in medical history, n (%)[a]		9 (15)	2 (3)	EO>LO

Notes: CES-D: Center for Epidemiologic Studies Depression Scale; MMSE: Mini-Mental State Examination; SCID: Structured Clinical Interview for DSM-IV; YMRS: Young Mania Rating Scale; EO: early onset; LO: late onset; CG: comparison group.

[a]ANOVA for age $df = 2$, $F = 297.04$, $p = 0.01$; for YMRS $F = 27.99$, $df = 2$, $p < 0.01$; for age of onset $F = 297.36$, $df = 1$, $p < 0.01$; for first treatment $F = 166.22$, $df = 1$, $p < 0.01$. Pearson χ^2 for ECT $\chi^2 = 205.97$, $df = 6$, $p < 0.01$; for family history psychiatric illness $\chi^2 = 9.32$, $df = 2$, $p < 0.01$; for gender $\chi^2 = 7.61$, $df = 2$, $p = 0.02$.

[b]Educational level was assessed by a Dutch scoring system consisting of a 7-point scale, ranging from unfinished primary education (Level 1) to university education (Level 7).

Test, the Mazes, the Rule Shift Cards of the Behavorial Assessment of the Dysexecutive Syndrome, the Animal and Occupation naming, the letter fluency of the Controlled Word Association Task, and the Stroop Color Word Task. The effect sizes of the cognitive measures indicate large effects ($\eta^2 > 0.14$) except for mental effort, which indicate a medium effect ($\eta^2 < 0.15$). The late-onset bipolar patients had significantly lower scores than the early-onset bipolar patients for Part A of the Trail-making Test, the Occupation naming and the Rule Shift Cards. The effect sizes of the cognitive measures indicate small to medium effects ($\eta^2 < 0.15$). There were substantial covariate effects for age

TABLE 2. Neuropsychological Performance in Patients With Early- and Late-Onset Bipolar Disorder and Comparison Group: Mean (SD) and Mixed Group Analysis of Variance of Neuropsychological Functioning

Measure	Comparison Group (N = 78)	Early Onset (N = 59)	Late Onset (N = 60)	Patients Versus Comparison Group			Early Versus Late			Between Group Contrast
				F	p	η	*F*	p	η	
Psychomotor performance										
Trailmaking Test Part A, seconds	46.97 (19.6)	63.03 (34.3)	89.78 (68.3)	13.55	<0.01	0.30	7.2	0.01	0.06	CG>EO>LO
Mental effort										
ASTM 1 t/m 10	29.00 (1.0)	28.03 (1.6)	26.77 (5.6)	4.41	<0.01	0.12	2.79	0.09	0.02	CG>EO, LO
Attention and executive function										
Digits forward	5.73 (0.9)	5.32 (0.9)	5.08 (0.9)	7.74	<0.01	0.19	1.74	0.19	0.01	CG>EO, LO
Digits backward	4.71 (1.1)	3.93 (0.9)	3.88 (1.0)	11.27	<0.01	0.26	0.07	0.79	<0.01	CG>EO, LO
Trailmaking Test Part B, seconds	109.68 (58.7)	175.41 (118.6)	218.10 (129.4)	14.87	<0.01	0.32	3.54	0.06	<0.01	CG>EO, LO
Stroop Color Word test,[a] seconds	45.31 (12.8)	61.51 (29.4)	71.40 (33.5)	13.21	<0.01	0.29	2.91	0.09	0.02	CG>EO, LO
D-A-T	35.75 (10.7)	25.66 (11.0)	21.93 (11.5)	23.06	<0.01	0.42	3.22	0.07	0.02	CG>EO, LO
Animal naming	23.23 (6.0)	18.76 (5.1)	17.83 (5.6)	15.14	<0.01	0.34	0.87	0.35	<0.01	CG>EO, LO
Occupation naming	17.41 (4.9)	15.39 (5.4)	12.35 (4.8)	11.43	<0.01	0.26	10.32	<0.00	0.08	CG>EO>LO
Mazes, seconds	121.41 (95.32)	156.64 (108.8)	211.38 (140.4)	14.26	<0.01	0.31	5.63	0.02	0.05	CG>EO>LO
Rule Shift Cards BADS	1.06 (1.6)	1.53 (2.2)	2.70 (2.8)	9.37	<0.01	0.22	6.42	0.01	0.05	CG>EO>LO
Declarative memory										
10 Words Test										
Learning (Trials 1–5)	37.35 (5.7)	30.23 (6.5)	27.73 (7.3)	25.91	<0.01	0.45	3.84	0.05	0.03	CG>EO, LO
Retention	6.74 (1.9)	4.58 (1.9)	4.45 (2.3)	16.99	<0.01	0.34	0.47	0.75	<0.01	CG>EO, LO
Recognition[b]	19.26 (0.9)	18.61 (1.3)	18.00 (2.6)							CG>EO, LO
Visuoconstruction										
Copying ADS6[b]	12.37 (1.6)	12.27 (1.9)	12.33 (0.8)							
Clock drawing[b]	1.41 (0.8)	1.42 (0.8)	1.67 (1.1)							

Notes: ASTM: Amsterdam Short-Term Memory Test; BADS: Behavorial Assessment of the Dysexecutive Syndrome; ADS6: Amsterdam Dementia Screening test; EO: Early onset; LO: Late onset; CG: comparison group.

[a]This is a short form consisting of reading the first 4 lines.

[b]Kruskal-Wallis test patients versus comparison group: for 10 Words Test recognition errors, $\chi^2 = 34.14$, p <0.01; for Figure-copying, $\chi^2 = 14.79$, p = 0.13; for Clock drawing, $\chi^2 = 7.76$ p = 0.65; Mann-Whitney U test early versus late: for 10 Word Test recognition errors, $Z = 0.87$, p = 0.38; for Figure copying, $Z = -1.08$, p = 0.28; for Clock drawing, $Z = -1.17$, p = 0.24.

and education, but virtually none for cardiovascular risk factors.

DISCUSSION

To our knowledge, this is the first study with a large study population of patients with bipolar disorder, both early- and late onset, in which cognitive functioning is studied and compared with a group of normal elderly people. We hypothesized that late-onset bipolar patients would demonstrate more cognitive decline than early-onset bipolar patients, and that these differences would be greater than the differences between the early-onset group and the comparison group. Late onset bipolar patients were, indeed, more impaired with regard to psychomotor performance, word fluency, and mental flexibility than early-onset bipolar patients, but these impairments were not attributable to age, education, or cerebrovascular risk factors. The results suggest that differences between early- and late-onset bipolar patients do exist, but they are not as great as is often suggested. In terms of cognitive sequelae, the distinction between early- and late-onset bipolar disorder does not seem to indicate two different types of disorder. However, these data also show that the cognitive functioning of older bipolar patients is substantially compromised in areas that are important, both for daily functioning and for compliance with treatment.

We found that early-onset bipolar patients are more likely to have a family history of psychiatric

illness and have more often been treated with ECT. Despite these differences in clinical characteristics, our early- and late-onset bipolar patients did not differ with regard to diagnostic subtypes, number of previous episodes or admissions, the presence of psychotic features or pharmacological treatment and both groups had the same burden of cerebrovascular risk factors. Our findings are in line with those of Wylie et al.,[26] who found a higher rate of family history of psychiatric illness in the early-onset group, but they are in contrast with the consistently higher rate of neurological illness in late-onset mania and bipolar disorder that Depp and Jeste[5] found in their review. Neurological illness has been defined differently in the various studies, e.g., "organic brain syndrome" and "cerebrovascular risk/burden." In our study, cerebrovascular risk was not measured physically but asked about in a standardized questionnaire for the participants. Patients with dementia were excluded from the study. In conclusion, we did not find a higher exposure to cerebrovascular risk factors in the late-onset group. Therefore, the differences between the early- and late-onset groups could not be explained by underlying cerebrovascular risk, as defined in our study.

Both bipolar groups demonstrated substantial neuropsychological impairments, when compared with the comparison group. The late-onset bipolar patients were more impaired than the early-onset bipolar patients in the performance of tests that suggest involvement of fronto-subcortical parts of the brain (speed and mental flexibility). This provides indirect evidence that late-onset bipolar patients may have greater frontostriatal dysfunction than early-onset patients, which could be due to a different neuropathology. From another viewpoint, early-onset patients more often have a family history of psychiatric illness, so early onset may have genetic causes and late-onset may be etiologically different.[27] A recent study[28] showed that a decrease in right caudate volume is found in older bipolar patients, compared with normal subjects, but this was not associated with the age of onset. This study did not control for the presence of cardiovascular diseases. De Assis et al.[29] found frontal deep white matter hyperintensities on magnetic resonance imaging in older persons with bipolar disorder. Higher right frontal signal hyperintensities were associated with the onset of mania at a later age. It is difficult to compare these results with the results of our study, because their study population consisted of hospitalized patients whose cognitive status and medical comorbidities were not assessed.

Factors that may limit the generalizability of our study include the distribution of demographic variables. The patients with an earlier onset were significantly younger than the patients with a late onset and the comparison group, but when age was statistically controlled for in our study, all the cognitive differences between the early- and the late-onset group remained. A second limitation is the difficulty of ascertaining the exact age at onset and comparing our findings with those of studies with different criteria for age of onset. Most of the recent studies have used the age at which the first mood episode that met full diagnostic criteria was reported, and this also applies to our study. Whatever the method chosen, recall bias may influence the results. If more cognitively disabled patients were less likely to remember earlier illness episodes (which seems plausible), this would bias the results in the direction of more cognitive decline in the late-onset bipolar patients. However, we found only relatively small differences between the early- and late-onset bipolar groups, so these differences may in reality be even smaller. A third issue is the influence of residual symptoms. Both of the bipolar groups had few but significantly more residual manic symptoms than the comparison group. However, the level of residual manic symptoms in the bipolar groups was low, and there were no differences between the early- and the late-onset groups. Moreover, residual depressive symptoms are known to have more impact on cognitive performance than residual manic symptoms,[30] and in the present study, no differences were found with regard to residual depressive symptoms. Therefore, it is unlikely that residual symptoms have had any significant influence on the results. Another limitation of the study is that the effect of medication on test performance may have biased the interpretation of the results on neuropsychological tests. On the one hand, several studies found no definite associations between the use of lithium and neuropsychological test performance.[31–33] On the other hand, Pachet and Wisniewski[34,35] found that lithium was associated with poorer performance on tests of memory and motor speed. As most of the patients were not receiving monotherapy other psychopharmaca

could also have had potential cognitive side effects, although the use of benzodiazepines, which are known to cause cognitive side effects, was virtually absent. The present findings may also have some limitations with regard to the selection procedure. However, only a very small number of eligible persons were unwilling to participate, so we do not expect any important effect of selection bias. Furthermore, we had no information about the age of onset among patients who were demented, but given the small number of these patients we do not expect any major differences.

Major clinical implications from the present study are that older patients may need different treatment strategies than younger patients, because compliance with treatment could be compromised by substantial cognitive deficits. Furthermore, more information for bipolar patients, and specific psychoeducational rehabilitation programs may be necessary, because cognitive deficits could have severe impact on their psychosocial functioning and performance.[30,36] Longitudinal studies are needed to determine whether cognitive impairment is progressive and to study the factors that determine the rate of cognitive decline among older patients.

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