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Age as a Predictor of Cognitive Decline in Bipolar Disorder

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Abstract

Objective—Cognitive dysfunction is a core feature of Bipolar Disorder (BD) in both adult and geriatric patients. However, little is known about whether cognitive functioning declines at a faster rate in patients with BD and there are conflicting reports regarding the relationship between age and cognitive functioning in this population. This cross-sectional study examined the relationship between age and cognitive functioning in patients with BD.

Methods—Patients with BD I (n=113) and healthy adults (n=64) ages 18–87 completed measures of processing speed, attention, executive functioning, verbal fluency, and clinical symptomatology. Groupwise comparisons were used to examine differences between patients and the comparison group and adult and geriatric BD cohorts. A series of linear regressions was conducted to examine the relationship of age and cognitive functioning, and clinical variables and cognition.

Results—Patients performed significantly worse than the comparison group on all neuropsychological measures. Age was a significant predictor of Trails A scores with older age associated with worse performance.

Conclusions—Older age was associated with poorer performance on Trails A in patients with BD but not healthy adults. These results are suggestive of greater dysfunction in processing speed with older age in patients with BD compared to a healthy comparison group. As cognitive functioning is associated with community outcomes, these findings suggest a need for treatments targeting cognitive symptoms across the lifespan. Future research exploring neurobiological

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evidence for neurodegenerative processes in bipolar disorder will pave the way for potential therapeutic interventions.

Keywords

Bipolar; Cognitive; Aging; Lifespan

OBJECTIVE

Cognitive dysfunction is increasingly recognized as a core feature of bipolar disorder (BD). The severity of neuropsychological deficits in BD may rival those described in schizophrenia and related psychotic disorders (1–3). However, the longitudinal course of these deficits in BD is unclear. Neuropsychological deficits are commonly reported in both adult and geriatric patients with BD (4,5); however, few studies have examined the course of neuropsychological dysfunction in patients with BD across the lifespan.

Adults with BD exhibit a range of cognitive deficits that persist across illness stages and during symptom remission, suggesting that cognitive dysfunction is a trait feature of BD (6–10). Executive functioning and verbal learning and memory are the most consistently reported impaired cognitive domains in adults with BD (6,11). Other studies report significant deficits in working memory, visuospatial learning and memory, verbal fluency, attention, and processing speed compared to healthy adults (2,3,7,10,12), although not all studies report deficits in the same domains or of the same magnitude (13).

Studies of cognition in geriatric BD samples are consistent with cognitive findings in adult BD, with performance deficits of medium to large effect and falling one or more standard deviations below the mean (14,15). Deficits have been demonstrated in executive functioning (16), working memory, verbal memory, attention, construction (17,18), and processing speed (19). Depp et al. found that geriatric BD patients display a diffuse range of deficits and perform similarly to geriatric patients with schizophrenia on at least half of the neuropsychological measures tested (5). Similar to findings in younger adult samples, cognitive deficits in geriatric patients with BD appear to persist during periods of euthymia (19,20,21).

The course of cognitive functioning over the adult lifespan in BD is not well understood. Few studies have examined neuropsychological deficits in BD across the age continuum either longitudinally or cross-sectionally. In some reports aging has been found to correlate with worse performance on neuropsychological measures in BD (14). Older adults with BD and healthy adults both exhibited a decline in neuropsychological functioning over a 3-year follow-up period; however, the rate of decline was more rapid for the older BD patients (20). A recent cohort study reported that the presence of psychotic symptoms in older adults without dementia was associated with poorer cognitive functioning and more rapid cognitive decline over a 6-year follow up (22). Conversely, others have found no decline in cognition over the illness course in BD. In a 6-year follow-up study of euthymic BD, Mora et al. found stable neuropsychological deficits (23), Gildengers et al. found no evidence of accelerated cognitive decline during a 2-year follow-up (24), and Burdick et al. found that patients with BD actually improved on measures of verbal memory and executive functioning – but not

attention – after a 5-year follow-up (25). However, it is possible that cognitive decline occurs gradually and the follow-up periods above were not long enough to detect these trends.

Goals and hypotheses

The present study aimed to clarify the relationship between aging and neuropsychological functioning in a large cross-sectional sample of adults with BD I disorder and an age-comparable comparison group of adults without psychiatric illness across a broad age range (18–87). We hypothesized that both adult and geriatric patients with BD would perform significantly worse on all measures of neuropsychological functioning relative to adult and geriatric healthy adults. Further, we expected greater cognitive dysfunction with older age in BD compared to the comparison group.

METHODS

Participants

Participants were pooled from independent samples of subjects collected from the Schizophrenia and Bipolar Disorder Program and the Geriatric Mood Disorders Research Program at McLean Hospital. All procedures were approved by the McLean IRB. Subjects from the Geriatric Program were drawn from five studies of mood disorders in patients aged 55 to 89 including treatment trials of older adults with bipolar depression, a non-treatment three-year longitudinal study of older adults with psychiatric illness and healthy control subjects from both the treatment and longitudinal studies. Subjects were recruited through McLean Hospital inpatient and outpatient programs, community flyers, media advertising, and referrals from local physicians, psychiatrists, and other clinicians. Diagnosis was confirmed by Structured Clinical Interview for DSM-IV (SCID) conducted by a licensed geriatric psychiatrist. All subjects in the BD group had a diagnosis of BD I disorder; subjects with BD II or BD NOS diagnoses were excluded from the analyses. Subjects were excluded from study participation due to serious or unstable medical conditions, history of substance dependence in the past 12 months, substance abuse in the past month, schizophrenia, schizoaffective disorder or seizure disorder, or acute ECT. Patients with a DSM-IV diagnosis of dementia (assessed by a geriatric psychiatrist) were not eligible to participate, and subjects with Mini Mental Status Exam scores < 24 were excluded from the present analyses.

Adults were recruited through the Schizophrenia and Bipolar Disorder Program as part of a study examining cognition in a cross-diagnostic sample of patients with psychosis; non-psychiatric comparison subjects were recruited from the program or through online advertisements. Participants were between the ages of 18 and 55, had no lifetime history of substance dependence, no substance abuse within the past three months, were not receiving ECT, and had no history of seizure disorder or history of head injury with loss of consciousness. Diagnosis was established using the Structured Clinical Interview for DSM-IV-TR (SCID) administered by trained clinicians to diagnose primary mood and psychotic disorders and comorbid substance use or anxiety disorders. All subjects in the BD group had a diagnosis of BD I. The SCID was never administered by the same study staff conducting

the cognitive assessments. SCID interviewers met routinely for reliability exercises and to discuss difficult cases and arrive at a consensus diagnosis.

Materials

Participants were administered clinical and neuropsychological assessments and a diagnostic interview. The neuropsychological battery included: Trails A and B (Trails; processing speed, executive functioning); Stroop Color and Word Test, Color and Color-Word forms (Stroop; attention, processing speed, executive functioning); and Category Fluency (verbal fluency). Raw scores were converted to standard scores using published normative data (26–28). Standardized scores were converted to z-scores for ease of comparison. Clinical assessment included the Young Mania Rating Scale (YMRS) and the Montgomery-Asberg Depression Rating Scale (MADRS). Information about lifetime history of psychosis was obtained from the SCID interviews. Lifetime history of psychosis was coded based on a response of 3 on any item of the SCID Psychosis Module (Module B), which asks about lifetime history of psychotic experiences.

Information about medications at time of assessment was obtained from the discharge medication list or by patient report. Chlorpromazine (CPZ) equivalents were calculated for all patients with complete medication and dosing information ($n=105$; 4 subjects from the geriatric samples and 4 from the adult sample did not have complete data) based on the recommendation of Baldessarini (29) and following the guidelines set forth by Gardner et al. (30).

Procedures

For the younger adult cohort, clinical and neuropsychological assessments were typically completed during the same visit. In the event that clinical and cognitive data were not collected on the same day, they were assessed within one week of each other. These assessments were conducted as part of a larger, ongoing study on Genotype and Phenotype in psychosis. For the older adult cohorts, assessments of cognition were completed at baseline prior to administration of the adjunctive therapeutic intervention although subjects were allowed to continue concomitant psychotropic medications at the time of the cognitive assessment.

Statistical Approach

Groupwise comparisons of patients and comparison subjects using the pooled samples, and within patient comparisons of geriatric and adult subjects with BD, were performed in order to examine demographic, cognitive and clinical variables by group. A series of linear regressions was conducted examining the effects of age on neuropsychological outcomes after controlling for demographic variables (sex, education, race) and CPZ equivalents. An interaction term (patient status * age) was created to examine differential effects of age on cognition between patients and our comparison group. Lastly, within the BD groups the effects of state mood symptoms, CPZ dose and lifetime history of psychosis on neurocognitive outcomes were examined.

RESULTS

Demographic data comparing patients and healthy comparison subjects and comparing the adult and geriatric patient groups are presented in Table 1. Patients and comparison subjects differed on age, sex, level of educational attainment and employment status, with patients exhibiting slightly younger age, higher percentage of female subjects, lower educational attainment and higher rates of unemployment. Within patients, adult and geriatric groups differed on education, with geriatric subjects having higher educational attainment.

Patients and comparison subjects were compared on neuropsychological functioning. Patients performed significantly worse than the comparison group on all neuropsychological variables (see Figure 1). Adult and geriatric BD samples were compared on neuropsychological and clinical variables. Patient groups differed on YMRS and MADRS scores (Table 2) (YMRS: adult BD >geriatric BD; MADRS: geriatric BD >adult BD). Patients also differed by age cohort on CPZ equivalents, lifetime history of psychosis, and age of onset. Patient groups did not differ on any neuropsychological variable.

A series of linear regressions was conducted examining age as a predictor of cognitive functioning after accounting for the effects of education, sex, race and CPZ equivalents. An interaction term (patient status (patient vs. comparison) * age) was computed and included in the model. The interaction term was associated with Trails A scores ($\beta=.024$, $t(170)=2.01$, $p=.04$). The interaction term was not a significant predictor of any other neuropsychological variable.

Within the patient group YMRS and MADRS, CPZ equivalents and lifetime history of psychosis were examined as predictors of neurocognitive functioning after accounting for demographic variables. MADRS score, lifetime psychosis, and CPZ were not significant predictors of any neurocognitive variable. YMRS was a significant predictor of Trails B ($\beta=-.019$, $t(107)=-2.07$, $p=.04$).

CONCLUSIONS

The present study examined neuropsychological functioning in a cross-sectional sample of patients with bipolar I disorder and non-psychiatric adults across the adult lifespan. The sample ranged in age from 18–87 years, providing an opportunity to study associations between neuropsychological domains from late adolescence/young adulthood through advanced age. As predicted, we found that patients with BD differed significantly from the comparison group on all neuropsychological measures. We also hypothesized an association between older age and poorer cognition in patients but not comparison subjects. We did find that older age was associated with poorer processing speed in patients with BD but not in comparison subjects; however, we did not find evidence of poorer cognitive functioning with increasing age in our other cognitive measures. These findings suggest that patients with BD exhibit poorer cognitive functioning across domains than adults without psychiatric illness and that speed of processing of individuals with BD may show greater dysfunction with older age compared to their healthy peers. As all neuropsychological scores were age-normed, cognitive scores would not be expected to decline with older age in a healthy

population. Thus, decreasing performance with advancing age represents a departure from expected performance in our BD sample. These results should be interpreted with caution until replicated, however, as groups were heterogeneous and findings suggestive of accelerated cognitive decline were limited to one domain.

Bipolar disorder has been associated with various neurobiological factors that may reflect a neurodegenerative process. A number of interacting neurobiological mechanisms, such as glutamatergic excitotoxicity, neuroinflammation, oxidative stress and mitochondrial dysfunction, have been implicated in the pathophysiology of bipolar disorder (31). These neurobiological mechanisms may be associated with increased risk for cognitive impairment in BD and set the stage for progressive cognitive decline with advancing age. There is some evidence to suggest that morphometric and structural changes in the brain are not found in patients with BD who do not have accelerated cognitive decline across the lifespan. For instance, Sarnicola et al. found no decrease in brain volume in patients with BD and no age-related cognitive decline (32). Their sample may have been functioning at a higher level than our sample and others, and neurobiological abnormalities may be more closely associated with cognitive phenotypes than with diagnosis. Further studies of brain structure and neurobiological mechanisms are necessary to elucidate the relationship between accelerated cognitive decline, neurodegeneration, and bipolar disorder. In addition, understanding this pathophysiology may help identify appropriate targets for therapeutic interventions that may slow or prevent cognitive decline in aging individuals with bipolar disorder.

As cognitive functioning predicts community outcomes in patients with BD (33,34), our findings suggestive of accelerated cognitive decline over the adult lifespan in patients with BD indicates that this domain is a key area for evaluation and intervention. Several studies have found that adult patients with BD had significant levels of psychosocial impairment that was associated with cognitive impairment (24, 35). Pratt et al. found similar results in geriatric patients with BD (36). These findings highlight the importance of early cognitive interventions.

There are several limitations to the present study. Most notably, data were collected from two different labs in the context of several separate (but related) studies, and a number of inclusion and exclusion criteria differed by lab group. Within the present sample these differences are reflected in differences in state clinical symptomatology and other clinical variables. CPZ equivalents, lifetime history of psychosis, and depression scores were not associated with any neurocognitive variable; however, mania ratings were associated with Trails B. As the younger adult cohort had significantly higher YMRS scores at testing it is possible that the higher-level symptomatology in the younger cohort actually obscured associations between increasing age and decreasing cognitive scores on this measure. These findings highlight the need for future studies of cognition across a broad age range within the same protocol to ensure homogeneity of the sample. Issues such as survivor bias may also differentially impact our two groups. For example, our geriatric sample may represent patients who are medically or mentally healthier than would be expected. This possibility also suggests that our findings may actually underestimate the relationship of cognitive decline and older age.

Unfortunately, comparable measures of verbal memory were not collected between the adult and geriatric BD cohorts preventing us from examining this important domain of cognitive function. Future studies should examine verbal memory across the adult lifespan in BD, as this domain is among the most commonly reported deficits in patients. Also of note, Stroop Color score is lower than would be expected in the comparison sample. It is also the lowest-scoring measure in the BD sample, suggesting that all of our subjects were performing worse than would be expected based on published norms. We excluded patients with substance use disorders to increase homogeneity and eliminate a potentially serious confounder; however, substance use comorbidities are highly prevalent in BD, limiting the generalizability of these findings. Lastly, this study was cross-sectional limiting the ability to detect cognitive changes over time within subjects. Longitudinal studies of cognition would permit the examination of cognitive course within the same cohort, although admittedly the logistics of such studies may be prohibitive.

The present study presents evidence of greater dysfunction of processing speed with older age in patients with BD compared to an age-comparable sample of healthy adults. Interventions targeting cognitive dysfunction in bipolar disorder are critical as accelerated cognitive decline may put patients with BD at an increasingly elevated risk for poor community outcomes. Further study of the neurobiology of aging in BD may help to identify relevant targets for therapeutic interventions for cognitive symptoms and, ultimately, develop successful prevention strategies.

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Figure 1.

Neurocognitive Functioning by Patient Status. Graph of neurocognitive performance on each measure separately by patients and comparison subjects.

= $p < .01$ *= $p < .001$

Stroop C: $t(171) = -5.12, p < .0001$; Stroop C-W: $t(171) = -5.17, p < .0001$; Fluency: $t(171) = -3.03, p = .003$; Trails A: $t(173) = -3.22, p = .001$; Trails B: $t(170) = -4.82, p < .0001$

Table 1

Demographics by Patient Status or Age Cohort

	BD (n=113)	Control (n=64)	Test statistic
Age	48.7 (17.1)	54.9 (15.0)	$t(176) = -2.39^*$
Education ^a	5.4 (1.4)	6.0 (1.1)	$t(175) = -2.83^{**}$
Sex (% female)	53%	36%	$\text{Chi}2(1, n= 177) = 4.83^*$
Race (% C)	81%	86%	$\text{Chi}2(1, n= 177) = 4.12$
Employment (% unemployed)	39%	8%	$\text{Chi}2(1, n= 171)=32.77^{***}$

	Adult BD (n=64)	Geriatric BD (n=49)	Test statistic^a
Age	36.3 (10.9)	65.0 (7.4)	$t(111) = -15.80^{***}$
Education	5.1 (1.4)	5.7 (1.4)	$t(111) = -2.14^*$
Sex (% female)	61%	43%	$\text{Chi}2(1, n= 113) = 3.64$
Race (% C)	77%	88%	$\text{Chi}2(1, n= 113) = 3.96$
Employment (% unemployed)	43%	35%	$\text{Chi}2(1, n= 112) = 0.45$

^a Education is coded based on the SCID Education and Work History scale: 1=grade 6 or less; 2= grade 7–12 (without graduating); 3= high school grad or equivalent; 4= part college; 5= graduated 2 year college; 6= graduated 4 year college; 7= part graduate/professional school; 8= completed graduate/professional school.

*
 $p < .05$

**
 $p < .01$

 $p < .001$

Table 2

Clinical Variables by Age Cohort (Patients Only)

	Adult BD (n=64)	Geriatric BD (n=49)	Test statistic
Age of Onset	21.4 (7.2)	25.5 (15.0)	$t(107) = -1.92$
Hx Psychosis	81%	73%	$\text{Chi}^2(1, n=97) = 0.72$
YMRS	18.6 (15.4)	4.3 (3.7)	$t(111) = 6.37^{***}$
MADRS	12.8 (9.6)	25.0 (11.3)	$t(111) = -6.18^{***}$
CPZ	238.7 (230.1)	51.8 (100.8)	$t(104) = 5.12^{***}$

*
 $p < .05$ ***
 $p < .001$