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The Relationship of Bipolar Disorder Lifetime Duration and Vascular Burden to Cognition in Older Adults

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Abstract

Objective—We describe the cognitive function of older adults presenting with Bipolar Disorder (BD) and mania. We examine whether longer lifetime duration of BD is associated with greater cognitive dysfunction. We also examine whether there are negative, synergistic effects between lifetime duration of BD and vascular disease burden on cognition.

Methods—87 non-demented individuals with BD I ages 60 years and older, experiencing manic, hypomanic, or mixed episodes, were assessed with the Dementia Rating Scale (DRS) and the Framingham Stroke Risk Profile (FSRP) as a measure of vascular disease burden.

Results—Subjects had a mean (SD) age of 68.7 (7.1) years and 13.6 (3.1) years of education; 50.6% (n=44) were females; 89.7% (n=78) white and 10.3% (n=9) black. They presented with overall and domain-specific cognitive impairment: in memory, visuospatial ability, and executive function, compared to age-adjusted norms. Lifetime duration of BD was not related to DRS total score, any other subscale scores, or vascular disease burden. FSRP scores were related to the DRS memory subscale scores, but not total scores or any other domain scores. A negative interactive effect between lifetime duration of BD and FSRP was only observed with the DRS construction subscale.

Conclusions—In this study, lifetime duration of BD had no significant relationship with overall cognitive function in older non-demented adults. Greater vascular disease burden was associated with worse memory function. There was no synergistic relationship between lifetime duration of BD and vascular disease burden on overall cognition function. Addressing vascular disease, especially early on in the course of BD, may mitigate cognitive impairment in older age.

Keywords

Bipolar Disorder; Cognition; Aged

Introduction

Bipolar disorder (BD) affects up to 5% of the general population and is the sixth leading cause of disability in developed countries (1,2). Cognitive impairment exists across BD mood states (3-6) and is related to the significant disability associated with BD (7-9).

Although cognitive deficits are a core feature of BD across the lifespan (10,11), the etiology of these deficits is not clear (12). Additionally, there may be a pattern of cognitive impairment that changes over time, with executive dysfunction and verbal memory deficits more prominent earlier in the disorder and information processing speed deficits becoming more prominent as patients age (13-15).

Some cognitive changes may be related to BD-specific factors. In particular, a number of published reports have shown a strong association between verbal memory deficits and *longer duration of illness* in mixed aged adults with BD (16). Hypothetically, the neurotoxic effect of hypercortisolemia, due to hyper-responsiveness of the hypothalamic-pituitary-adrenal axis observed in BD, may damage neural tissue highly saturated in glucocorticoid receptors, such as the amygdala, hippocampus, and anterior cingulate cortex (17,18).

Other cognitive changes may be related to factors not entirely specific to BD. Patients with BD suffer from high rates of cardiovascular disease, diabetes mellitus, and stroke, possibly due to shared or overlapping pathophysiology (19,20). These factors in isolation may worsen cognitive function. However, structural changes in the central nervous system (CNS) related to BD (21-24) may make the CNS especially vulnerable to these toxic, metabolic, and iatrogenic insults as patients age, leading to greater than expected cognitive dysfunction (based on these factors alone). Hence, there are likely multiple (intercorrelated) mechanisms involved in the development of cognitive dysfunction in BD that can be grossly organized into a) BD specific factors (intrinsic biological mechanisms), b) BD co-morbidity factors (e.g., vascular disease, diabetes mellitus, substance use, medication side-effect), c) “Aging” (age-related brain changes, dementia pathology, diseases not directly related to BD), as well as d) Protective factors (see Figure 1). Multiple mechanisms perhaps accelerate cognitive decline seen in “normal” aging (25).

In older adults with BD, there is considerable heterogeneity of cognitive performance, history of illness course, medical comorbidity, and substance use (26). Using this heterogeneity in examining cognitive function in older adults with BD may help identify whether illness course, medical comorbidity, or a combination of factors over time may have impact on cognition. Performing a long-term (20+ year) study starting in middle-aged adults to prospectively examine the relative contributions of BD, medical and psychiatric comorbidity, and aging, would be ideal, but challenging to complete. Identifying the factors related to “successful aging” in BD may be helpful in developing strategies to preserve cognitive function in younger and middle-aged adults with BD.

Following our prior reports (4-6), we analyzed the relationship among cognition, lifetime duration of BD, and vascular disease burden in a group of older subjects who presented with mania requiring treatment. Our aims were: 1) to describe the cognitive function in older adults with BD who are manic; 2) to examine potential relationships with BD specific and comorbidity factors, such as lifetime duration of BD or age at onset and vascular disease burden; 3) to examine how clinical factors – including lifetime history of psychosis or substance dependence, exposure to lithium or divalproex - are associated with cognitive function. Based on the existing literature cited above, our main hypotheses were: H1a) higher levels of vascular disease burden and longer duration of BD would be separately associated with worse general cognitive function; H1b) higher levels of vascular disease burden would be associated with executive dysfunction. Our exploratory hypotheses were: H2a) longer lifetime duration of BD would be associated with greater vascular disease burden; H2b) longer lifetime duration of BD and greater vascular disease burden would be synergistically (negatively) associated with worse cognitive function.

METHODS

Subjects

The NIMH-funded, multi-site study, Acute Pharmacotherapy of Late-Life Mania is a randomized controlled trial of mood stabilizer treatment in elders with BD (27). Participating sites included Cornell (coordinating center), Baylor College of Medicine, Case-Western Reserve, Duke, University of Pennsylvania, and Western Psychiatric Institute and Clinic-University of Pittsburgh. Inclusion criteria were: age 60 years and older, BD I Manic, Mixed, or Hypomanic Episode (DSM-IV TR; SCID-I/P) (28), Young Mania Rating Scale (YMRS) (29) score greater than or equal to 18. Exclusion criteria were: rapid cycling, chronic psychotic conditions (schizophrenia, schizoaffective disorder, delusional disorder), contraindication or intolerance to lithium or divalproex, active substance dependence, mood disorder due to a general medical condition, dementia, inability to communicate in English, uncorrected clinically significant sensory impairment, recent history of cardiovascular, peripheral vascular events, or stroke, and high risk of suicide in an ambulatory patient. Cognitive test scores (e.g., Mini-Mental State Exam) were not used as exclusion criteria because mania may have impaired performance on these tests (8). The exclusion due to recent history of cardiovascular, peripheral vascular events, or stroke was dictated by the primary aims of the study to compare lithium versus divalproex for acute late-life mania. The rationale for this exclusion included the need to exclude mania due to general medical condition, safety concerns of using lithium or divalproex in medically unstable patients, and concerns about using risperidone, used as an adjunct or augmentation, in subjects with risk for stroke. Depending on the severity of the event, "recent" was interpreted as within 3-12 months of starting the study.

Eight hundred and ninety-six patients were screened across the six sites. Written informed consent was obtained for 151 potentially-eligible subjects. Of the subjects screened, 39 (4.3%) were excluded for pre-existing dementia and 7 (0.7%) for active substance dependence. One-hundred-thirty eight started baseline; 38 exited the study and were not randomized (not eligible: 27; withdrew consent: 8; other: 3). Of the 100 subjects randomized, 87 completed the Dementia Rating Scale (DRS) (30), which constitute the study group (see baseline characteristics in Table 1).

Procedures

During baseline evaluation, all subjects received a comprehensive evaluation including a psychiatric (SCID, YMRS, and GRID Hamilton Rating Scale for Depression-24 item [HAM-D-24]) (31) and general medical assessment (history & physical, laboratory testing, EKG), assessment of prior lifetime medication exposure (modified Antidepressant Treatment History Form) (32), and cognitive evaluation. Lifetime duration of BD was determined by subtracting age of first diagnosable mood episode from the current age. Information on lifetime psychotropic use was limited to exposure (yes/no). Information on dose or duration of medication use was not obtained. Trained research staff performed all assessments. The coordinating center monitored the reliability of the research staff and reviewed the integrity of all data acquired. The University of Pennsylvania site (Brain Behavior Laboratory), under the direction of Paul Moberg, Ph.D., monitored the administration of the cognitive tests at all sites.

Cognitive measures

Cognition was assessed using the Dementia Rating Scale (DRS) (30). This instrument has demonstrated sensitivity and specificity in elderly individuals, including those with mood disorders (33). It assesses cognitive function in several domains, including attention, executive function (Initiation/Perseveration), visuospatial ability (Construction), abstraction

(Conceptualization), and memory. DRS total and subscale scores were transformed and adjusted for age using published norms, where 10 is the mean score for the age group with a SD of 3 (34). Adjustment for age enabled investigation of the impact of the BD specific and comorbidity factors that might accelerate cognitive decline beyond the effects of “normal” aging.

Measures of vascular disease burden

Information gathered during the general medical evaluation was incorporated into the Framingham Stroke Risk Profile (FSRP) (35), as a measure of vascular disease burden that has been used in numerous studies (36-38). Risk factors include current age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, prior cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy by electrocardiogram. Using the algorithm employed by Wolf and colleagues (1991), ten year stroke probabilities were calculated and used as an indicator of vascular disease burden.

Statistical Methods

Descriptive statistics were obtained on the 87 subjects. Comparisons of relationships between demographic and clinical variables were performed using Pearson product-moment correlations. Using General Linear Modeling (GLM), we conducted multivariate analyses to assess the relationships among the baseline variables and to determine correlates of cognitive function.

RESULTS

Aim 1: Cognitive function of older adults with BD who are manic

Subjects' baseline characteristics are presented in Table 1. Our subjects were evenly split along gender. Raw and age-adjusted DRS total and subscale scores are presented in Table 2. As a group, subjects performed at the mean or lower on the DRS and each of its subscales; 39% of subjects scored one standard deviation or more below the age-adjusted mean of the DRS total. In relation to the norms, Attention domain showed the best performance, Memory and Construction domains were worst, and Initiation/Perseveration and Conceptualization domains were intermediate. When considering the percentage of subjects scoring one or more standard deviations below the age adjusted means: Conceptualization (31%) and Memory (31%) domains had the highest percentage of subjects, while Initiation/Perseveration (20%) and Construction (17%) were intermediate, and Attention had the lowest (13%). Higher YMRS (and not HRSD) scores were significantly related to lower DRS total scores (estimate=-0.12, standard error=0.05, $t=-2.16$, $p=0.03$).

Aim 2: Association among cognitive performance, lifetime duration of BD, and vascular disease burden

Table 2 presents the results of the GLM using age-normalized DRS total and subscale scores as the dependent variables and lifetime duration of BD and vascular disease burden (FSRP) as the independent variables.

H1a—Adjusting for mood status (YMRS score) and education, neither lifetime duration of BD nor vascular disease burden (separately) were strongly related to overall cognitive function as measured with the DRS total.

H1b—Higher vascular disease burden was not associated with greater executive dysfunction in our sample.

H2a—Lifetime duration of BD was not related to vascular disease burden. However, later age of first manic episode was related to higher vascular disease burden ($r=0.24$, $p=0.03$, $n=81$). Further, later age of first manic episode was related to worse DRS memory subscale scores (estimate $=-0.06$, standard error $=0.02$, $t=-2.81$, $p=0.006$), although not to DRS total scores or any other of the subscales.

H2b—A negative synergistic effect between BD lifetime duration and FSRP was only observed in the DRS construction subscale (see Table 2). While greater vascular disease burden was related to lower DRS memory subscale scores, and there was a trend of longer lifetime duration of BD related to lower DRS memory subscale scores, there was no interactive effect between lifetime duration of BD and greater vascular disease burden on memory.

Aim 3: Association between cognitive performance and clinical variables of interest

Subjects with a lifetime history of psychosis ($n=28$) had significantly lower age-adjusted DRS total scores than those without one ($n=59$) (6.1 [3.6] versus 8.9 [3.2]; $t=3.05$, $df=47.9$, $p=0.0012$). The age-adjusted total DRS scores did not differ between those with ($n=18$) and without ($n=69$) a lifetime history substance dependence (7.7 [3.1] versus 8.1 [3.7]; $t=0.44$, $df=30.5$, $p=0.66$). Fifteen of the 18 subjects with lifetime history substance dependence had alcohol dependence. The age-adjusted total DRS scores did not differ either between those with ($n=55$) and without ($n=32$) a history of exposure to lithium or divalproex (8.1 [3.8] versus 7.8 [3.2]; $t=-0.48$, $df=85$, $p=0.64$).

DISCUSSION

In 87 older non-demented adults with BD who presented for treatment of mania, overall cognitive performance was lower than expected based on age-adjusted norms. The cognitive domains most *severely* affected were memory and visuospatial ability, while the domains most *frequently* affected were memory and abstraction. Congruent with previous reports, individuals with psychotic symptoms had significantly worse cognitive performance than those without psychosis. However, contrary to previous reports, the cognitive performance of subjects with or without a history of substance use (largely alcohol use disorder) did not differ significantly. We found that later age of first manic episode and greater vascular disease burden were related to lower memory performance. To our knowledge, our report is based on the largest sample of elderly adults experiencing mania.

In accord with certain published reports, later age of first manic episode was related to vascular disease burden in this sample (26,39). Later age of first manic onset was also related to lower memory performance. Worsening cerebrovascular disease may reasonably be related to both later age of first manic episode and memory impairment. Our findings, in context of the current literature, suggest that through different pathophysiological mechanisms greater lifetime BD severity (*BD Specific Factors*; see Figure 1), via hypercortisolemia, and later age of onset, via vascular disease (*BD Co-Morbidity Factors*; see Figure 1), may impair memory. There is arguably a BD “vascular subtype,” similar to the vascular unipolar depression hypothesis of Alexopoulos (40), where vascular brain changes are related to mania and cognitive decrements in late-life (41,42).

Based on reports in middle-aged adults (8,16), we expected, but did not find a relationship between vascular disease burden and executive dysfunction in the DRS Initiation/Perseveration subscale. Further, we did not observe a synergistic relationship between lifetime duration of BD and vascular disease burden. BD lifetime duration in itself does not appear to render individuals with BD at greater risk for overall cognitive impairment due to vascular disease burden. Lifetime duration of BD may not capture the critical illness features

over the lifespan that affect cognition, such as frequency, duration, and intensity of mood episodes. In older adults, lifetime duration may be a more limited proxy for BD severity than in middle age.

Certain limitations need to be considered in interpreting our findings. First, the DRS does not provide the highly-detailed assessment of performance across cognitive domains that would be available through more comprehensive neuropsychological assessment: it does not provide a measure of information processing speed and it is not especially sensitive for examining executive dysfunction (43). Second, while only 4.3% of screened subjects were excluded due to cognitive impairment, the generalizability of our findings to older adults with BD outside of an RCT is presumably limited by the selection criteria necessary for the study (see Methods). Hence, our findings may under-represent cognitive dysfunction in older adults with BD because the sample may have been skewed towards healthier older adults who could tolerate lithium or divalproex. Third, serum anticholinergic activity, which can negatively impact cognitive performance, was not measured (44,45). Last, although the positive associations found in the subscale scores are biologically plausible, the possibility that multiple exploratory hypotheses testing led to type I error needs to be considered.

In addition to the relatively large sample, the strengths of our report include a well-characterized group of patients with BD I, all over the age of 60 years, who underwent a careful psychiatric and general medical assessment. A notable difficulty in conducting research in older adults with BD, who are not acutely ill, is making certain that the study group consists entirely of subjects with BD. Focusing on elders who are acutely manic identifies a group of patients that all have BD and mitigates this concern about diagnostic heterogeneity. Further, while cognitive dysfunctions are present in all BD mood states, they may be particularly evident in individuals who are manic (5).

Our report shows that older adults experiencing mania exhibit a pattern of executive and memory dysfunction similar to what is found in younger adults with mania. Noting the above limitations, we find that longer lifetime duration of BD is not related to greater overall cognitive impairment in non-demented elders with BD. This may be a reassuring message for individuals with BD, who are struggling with a lifelong relapsing and remitting illness. We did not observe an interactive effect of lifetime duration of BD with vascular disease burden. While we could not detect an impact of prior lithium or divalproex exposure on cognitive function, our study did not examine duration or intensity of treatment with either agent.

Our findings preliminarily argue for the necessity of individuals with BD to take care of their general medical problems and in particular, risk factors for vascular disease. Patients with BD and their health care providers generally view their psychiatric care as the most important aspect of medical care (46,47). This view has led to a relative under-recognition and inattention to many of the physical diseases these patients experience. Appropriately addressing medical problems related to vascular disease, such as hypertension, diabetes mellitus, and hypercholesterolemia, may protect against some elements of cognitive dysfunction observed in older adults with BD. Future studies will need to carefully examine the relationships among severity of illness (numbers, durations, and intensities of mood episodes), treatment exposure, medical comorbidity, and cognitive dysfunction to develop interventions intended to prevent, halt, or reverse cognitive dysfunction in patients with BD.

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Figure 1.

Overall model of factors affecting cognitive function in BD. Multiple mechanisms are likely involved in the development of cognitive dysfunction in BD, including A) BD-Specific Factors, B) BD Co-Morbidity Factors, C) Aging, and D) Protective Factors. Mechanisms are likely intercorrelated. *All potential interactions are not depicted.*

Table 1

Demographic and clinical characteristics of elders with BD I (n=87)

Age (years)	68.7 (7.1; 60-84)
Female (n, %)	44 (50.6)
Race (n, %)	
White	78 (89.7)
Black	9 (10.3)
Ethnicity: Latino (n, %)	9 (10.3)
Education (years)	13.6 (3.2; 5-25)
YMRS	26.0 (6.6; 18-47)
HRSD-24	11.8 (8.8; 0-39)
CIRS-G Cumulative Score	8.3 (3.5; 2-19)
CIRS-G Number of Systems	5.0 (2.1; 1-10)
CIRS-G Cardiovascular items (Total items #1 + #2)	1.4 (1.3; 0-5)
Age at Onset of First Manic Episode	44.0 (20.8; 9-82)
Age at Onset Illness	35.3 (18.5; 9-81)
Inpatient, n (%)	Inpatient: 42 (48.3)
Lifetime Drug Exposure: n (%)	
Both Divalproex and Lithium	23 (26.4)
Divalproex	19 (21.8)
Lithium	13 (14.9)
Neither	32 (36.8)

HRSD-24: Hamilton Rating Scale for Depression-24 item; YMRS: Young Mania Rating Scale; CIRS-G: Cumulative Illness Rating Scale-Geriatric

* Mean (SD, range) unless otherwise specified

Table 2

Dementia Rating Scale (DRS) Scores in elderly patients with mania, raw and adjusted for age and education, with relationship to BD lifetime duration and vascular disease burden (FSRP)

n=87	Raw Score	Age-Adjusted Score	Subjects scoring 1 SD or more below age-adjusted mean (n, %)	BD Lifetime Duration	FSRP	BD Lifetime Duration x FSRP
	Mean (SD) [min, max]			Estimate (standard error), t value, p > t		
DRS Total	130.4 (10.9) [85, 144]	8.0 (3.5) [2, 15]	34 (39%)	-0.01 (0.02) t=-0.37 p=0.71	-0.09 (0.06) t=-1.53 p=0.12	0.002 (0.001) t=1.46 p=0.14
Attention	34.7 (2.4) [22, 37]	9.9 (2.7) [2, 14]	11 (13%)	0.005 (0.02) t=0.24 p=0.81	-0.08 (0.05) t=-1.62 p=0.10	0.001 (0.001) t=1.09 p=0.27
Initiation/Perseveration	33.7 (4.3) [19, 37]	8.5 (2.9) [2, 12]	17 (20%)	0.004 (0.02) t=0.17 p=0.86	-0.07 (0.05) t=-1.31 p=0.19	0.002 (0.001) t=1.61 p=0.11
Construction	5.3 (1.1) [1, 6]	8.3 (2.4) [2, 10]	15 (17%)	-0.002 (0.02) t=-0.11 p=0.91	-0.09 (0.04) t=-1.93 p=0.057	0.002 (0.001) t=2.31 p=0.02
Conceptualization	34.7 (3.6) [24, 39]	8.8 (2.6) [2, 14]	27 (31%)	0.02 (0.02) t=1.18 p=0.24	-0.02 (0.04) t=-0.50 p=0.61	0.0007 (0.001) t=0.70 p=0.48
Memory	21.8 (3.3) [10, 25]	8.3 (3.4) [2, 13]	27 (31%)	-0.05 (0.02) t=-1.90 p=0.06	-0.12 (0.06) t=-2.09 p=0.049	0.002 (0.001) t=1.49 p=0.14

BD: Bipolar Disorder; FSRP: Framingham Stroke Risk Profile; DRS: Dementia Rating Scale; "Estimate" refers to the parameter contribution to the slope in the GLM; for example, as BD Lifetime Duration increase the slope of DRS memory decreases by -0.07 units.

* In the general ("normal") population, age-adjusted DRS total and subscale scores have a mean of 10 and a standard deviation of 3.

Table 3

GERI-BD Study Group:	
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