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Executive Dysfunction in Elderly Bipolar Manic Patients

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Abstract

Objective: This study used neuropsychological measures of executive skills to examine the functioning of frontostriatal networks in elderly bipolar patients.

Design: The authors hypothesized that elders with bipolar mania would exhibit poor executive functions relative to both elderly comparison subjects and depressed patients.

Setting: The study was conducted in the geriatric psychiatry services of a university hospital.

Participants: Nondemented elders: 14 with bipolar disorder I, manic (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), 14 with unipolar major depression (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), and 14 nonpsychiatric comparison (NC) subjects.

Measurements: Executive functions were assessed with the initiation/perseveration subscale of the Dementia Rating Scale and the manual Go/No-Go tasks from the extended initiation/perseveration scale.

Results: Manic elders demonstrated poor performance on tasks of initiation/perseveration and response inhibition, and performed significantly worse than both depressed patients and NC subjects. In this sample, there was no evidence for a relationship between severity of manic symptoms and executive performance.

Conclusion: These findings extend the observation that elderly bipolar manic patients have deficits in executive functioning compared with NC samples and provide evidence that the executive deficits demonstrated by bipolar manic elders can be more severe than those in unipolar depressed elders. As executive functions require frontostriatal integrity, these observations support investigation of specific frontostriatal network abnormalities in late-life bipolar disorder.

Keywords

Bipolar; depression; geriatric; aging; cognition; executive functions

Aged patients with manic states and bipolar disorders account for 5% to 19% of psychiatric hospitalizations among elders.¹ Although these patients pose a public health challenge, little is known about the pathophysiology of bipolar illness in late life

The presence of cognitive dysfunction in bipolar elders may provide a window into impairment of particular cerebral networks in these patients. Cognitive impairments occur in bipolar patients across the age spectrum, but they may be more severe in older patients.^{2,3} The cognitive deficits of geriatric bipolar patients include executive dysfunction, slowed processing speed, and memory deficits.⁴⁻⁶ In studying mild to moderately ill community-dwelling bipolar patients using a comprehensive neuropsychological battery, Depp et al.⁷ observed that middle-aged and older bipolar patients have cognitive deficits that are broader than those of young bipolar patients and resemble those in schizophrenia. Furthermore, cognitive deficits seem to persist in recovered⁸ and euthymic states.^{4,5}

Performance on executive tasks can be used as an indirect measure of the functional integrity of frontostriatal networks. Studies of executive functions have helped to elucidate the neurobiological substrate of late-life unipolar depression (UPD). The executive dysfunction that is present in a considerable proportion of aged individuals with major depression⁹⁻¹² seems to be a relatively stable clinical trait that is exacerbated during depressed states, predicts poor treatment response,¹³⁻¹⁸ and is associated with magnetic resonance imaging indices of structural white matter integrity.¹⁹ Cognitive probes of specific network functions can be used to identify and assess biological and behavioral syndromes related to the onset, progression, and treatment responsiveness of major mental disorders, including bipolar disorder.

The primary objective of this study was to examine aspects of frontostriatal network functioning in elderly bipolar manic (BPM) patients, UPD patients, and nonpsychiatric comparison (NC) subjects. We chose to compare performance of aged BPM patients with UPD patients because of early evidence that both groups often manifest executive dysfunction and structural abnormalities in frontostriatal systems.^{19,20} Furthermore, based on the presence of greater executive deficit in young and middle aged bipolar patients relative to depressed patients²¹ and the presence of more extensive subcortical silent cerebral infarcts in older manic patients relative to unipolar depressed,²⁰ we hypothesized that BPM elders also would exhibit poorer performance on executive tasks than would elders with UPD.

We focus on executive skills that we and others have found to be both impaired in late-life depression and related to treatment response, and amenable to administration at bedside. We therefore selected two tasks of executive function, the Initiation/ Perseveration (I/P) domain of the Mattis Dementia Rating Scale (DRS)²² and the manual Go/No-Go tasks from the Extended I/P scale.²³

METHOD

All patients were recruited from the geriatric psychiatry services of a university hospital. Inclusion criteria for all participants were age ≥ 59 years and provision of written informed consent. Inclusion criteria specific to patients were a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of bipolar disorder I, manic (BPM), or UPD.²⁴ Elderly NC subjects were community dwelling individuals recruited through local newspapers. These individuals did not have a history of psychiatric illness or neurological

disease and were in stable physical health. The exclusion criteria for all subjects were 1) active substance abuse; 2) diagnosis of dementia (determined by treating psychiatrist and based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria including history of cognitive decline preceding current manic episode); 3) acute or unstable medical condition; 4) sensory impairment that would interfere with completion of study; 5) lack of fluency in English. UPD and NC subjects were selected so that they were similar in age to the BPM patients. Eight of the bipolar patients and 10 of the comparison subjects were included in the sample reported by Young et al.⁶ All procedures were approved by the local institutional review board. Written informed consent was obtained after the study had been fully explained to each of the subjects.

Executive functions were assessed with the I/P domain of the Mattis DRS,²² and manual Go/No-Go tasks from the Extended I/P scale.²³ The I/P domain of the DRS tests: 1) verbal initiation/perseveration, e.g., “over 1 minute name all the things that you can buy in a supermarket”; 2) alternating movements; and 3) graphomotor design, e.g., reproduce XOXO. The maximum score on the DRS I/P domain is 37. To evaluate cognitive and motor response inhibition, we administered three tasks from the Extended I/P scale,²³ which were derived from Luria’s manual sequencing tasks.²⁵ These tasks consisted of manual opposite responding and Go/No-Go trials: task 1) “If I knock once, you knock twice; if I knock twice, you knock once; if I knock three times, you do nothing.”; task 2) “If I say ‘day,’ point to the floor, If I say ‘night,’ point to the window”; and task 3) “If I say ‘green,’ squeeze my fingers, if I say red, do nothing.” A trained research assistant administered the tasks. Fourteen trials of each of the three tasks were administered. Patients received one point for each correct response; possible scores range from 0 (no correct responses) to 42 (perfect performance).

Manic symptoms were assessed in the BPM patients with the Young Mania Rating Scale (YMRS).²⁶ In both patient groups, depression symptoms were assessed with the 24-item Hamilton Depression Rating Scale (HDRS).²⁷ The manic and depressive symptoms were assessed within 24 hours of the assessment of cognition.

Data Analysis

Group comparisons of demographic variables were conducted using univariate analysis of variance. The relationships of measures of executive dysfunction (I/P and Go/No-Go) to diagnostic group were assessed with univariate analysis of covariance (ANCOVA), with diagnostic group as a between subjects independent variable. In these models, age and years of education were used as covariates because they may influence performance on tasks of executive function. Within group Spearman’s correlations were performed to evaluate the relationship of symptom ratings to performance on executive measures. Two-tailed significance levels are reported. Data analysis was performed with SPSS 14.0 (SPSS, Inc.).

RESULTS

The sample consisted of 14 BPM patients, 14 UPD patients, and 14 NC subjects. The ages of the BPM patients (mean: 69.7 years, SD: 8.7, range: 60–89), UPD patients (mean: 70.5 years, SD: 7.4 years, range: 61–85), and NC subjects (mean: 71.1 year, SD: 7.3, range: 63–85) did not differ ($F[2,39] = 0.13$, $p = 0.88$). The BPM patients and the NC subjects had the

same sex distributions (43% female), whereas the UPD sample was composed of a higher percentage of females (57% female). Years of education ranged from 10 to 22 and did not differ between groups ($F = [239] 0.29, p = 0.75$) (BPM mean: 14.7, SD: 3.9; UPD mean: 14.9, SD: 3.5; NC mean: 15.6, SD: 3.1). The average YMRS score in the BPM patients was 30.1 (SD: 9.1) and the average HDRS rating in the UPD patients was 25.9 (SD: 5.2). Twelve of the BPM patients were inpatients whereas two of the UPD patients were inpatients at the time of the study. The groups did not differ in the frequency of history of diabetes ($X^2 [2, N = 42] 1.82, p = 0.42$) or hypertension ($X^2 [2, N = 42] 0.58, p = 0.75$), but more bipolar patients were current or past cigarette smokers than either UPD patients or NC participants ($X^2 [2, N = 42] 19.66, p < 0.001$).

ANCOVA indicated that the three groups differed in their performance on the DRS I/P ($F[237] = 8.76, p = 0.001$) (Fig. 1). Post hoc comparison using Least Square Difference indicated that BPM patients performed significantly worse than both elderly NC subjects ($t[27] = 4.76, p < 0.001$; Cohen's $d = 1.59$, 95% CI = 0.75–2.45) and depressed patients ($t[27] = 2.10, p < 0.05$; Cohen's $d = 0.79$, 95% CI 0.02–1.56). UPD patients also performed significantly worse than NC subjects ($t[27] 2.133, p < 0.05$; Cohen's $d = 0.81$, 95% CI = 0.04–1.58).

ANCOVA also indicated that diagnostic group had a significant influence on performance on the Go/No-Go items of the Extended I/P ($F[237] = 5.41, p < 0.01$) (Fig. 2). Post hoc analysis of Go/No-Go performance using Least Square Difference revealed that BPM patients performed significantly worse than both NC subjects ($t[27] = 2.92, p < 0.01$; Cohen's $d = 1.11$, 95% CI 0.31–1.91) and UPD patients ($t[27] = 2.78, p < 0.01$; Cohen's $d = 1.04$, 95% CI = 0.26–1.84). However, UPD patients and NC subjects did not differ in their performance ($t[27] = 0.18, p = 0.86$; Cohen's $d = 0.07$, 95% CI = –0.67 to 1.84).

Of note, the BPM patients exhibited greater variability in performance on both the I/P (Levene's test of equality of variance, $F = 12.01, p < 0.01$) and the Go/No-Go test (Levene's test of equality of variance, $F = 6.82, p < 0.01$) than both UPD patients and NC subjects. In the BPM patients, YMRS score was not significantly correlated with scores on DRS I/P ($r = 0.11, df = 12, p = 0.71$) or the Go/No-Go ($r = 0.21, df = 12, p = 0.4$). HDRS scores were not significantly associated with either DRS I/P ($r = -0.19, df = 12, P = 0.50$) or Go/No-Go ($r = 0.02, df = 12, p = 0.95$) performance in the BPM patients. Furthermore, HDRS scores were not significantly correlated with either DRS I/P ($r = -0.34, df = 12, p = 0.23$) or Go/No-Go ($r = -0.34, df = 12, p = 0.23$) in the UPD patients.

DISCUSSION

The main finding of this study is that BPM elders demonstrated poor performance on tasks of initiation/perseveration and response inhibition, performing significantly worse than both elderly UPD patients and elderly NC subjects. This is the first study, to our knowledge, to compare executive functions in elderly BPM patients, UPD elders, and NC subjects. In addition to confirming the observation that elderly BPM patients have deficits in executive functioning compared with NC subjects, these findings provide preliminary evidence that the executive deficits demonstrated by BPM patients can be more severe than those present

in late-life unipolar depression. These data complement findings that elderly bipolar depressed patients exhibit greater deficits in global cognitive functioning and explicit memory than aged unipolar depressed patients.²

Neuroimaging studies suggest that the DRS I/P and the Go/No-Go items of the Extended I/P probe functions that require integrity of frontostriatal circuitry. That is, performance of semantic verbal fluency tasks results in increased activity in the left inferior frontal cortex, often with additional regions of activation that include the dorsal anterior cingulate and neostriatum^{28,29} while learning new motor sequences results in activation of the dorsolateral prefrontal cortex, the dorsal anterior cingulate cortex, and the neostriatum.^{30,31} Furthermore, response inhibition in Go/No-Go paradigms results in activation of dorsal anterior cingulate, dorsolateral and ventrolateral prefrontal cortices, and inferior parietal regions.^{32,33} Thus, this study provides indirect evidence that elderly BPM patients may have greater frontostriatal dysfunction than elderly UPD individuals. Notably, the BPM patients exhibited significantly greater variability in their performance on the executive measures than both the UPD patients and the NC subjects, with 50% of the BPM patients performing similar to the NC subjects. Future studies should examine how neuroimaging indices of frontostriatal networks relate to individual differences in executive performance in elderly bipolar patients.

The presence of executive dysfunction in older BPM patients is consistent with preliminary magnetic resonance imaging findings of frontostriatal network abnormalities. Beyer et al.³⁴ observed that caudate volume is decreased in older bipolar patients compared with comparison subjects. Two reports have found greater frontal deep white matter hyperintensities in bipolar elders relative to elderly comparison subjects.^{35,36} Fujikawa et al.²⁰ reported that relative to older unipolar depressed patients, older manic patients had greater subcortical silent cerebral infarcts. Furthermore, a preliminary diffusion tensor imaging study of mixed age bipolar patients found evidence of microstructural disorganization of white matter tracts involving orbitofrontal cortex.³⁷ Convergent neuroimaging methodologies have linked executive dysfunction to frontostriatal network abnormalities in late-life UPD.^{19,31,38} However, to our knowledge, links between neuroimaging evidence of frontostriatal network abnormalities and executive dysfunction have not yet been examined in geriatric bipolar patients.

The study was conducted while all patients were acutely symptomatic. Thus, we cannot speak directly to the stability and/or persistence of executive deficits in bipolar elders. However, other lines of evidence suggest that executive dysfunction may be a relatively stable trait in bipolar elders that is exacerbated in manic states. First, consistent with other reports (e.g.,^{6,7}), we did not detect a significant relationship between manic symptom severity and executive dysfunction. Second, in a study of 18 euthymic bipolar elders, Gildengers et al.⁵ reported that 56% of the patients exhibited impairment on the I/P scale of the DRS. Third, studies of executive functions in young- and middle-aged bipolar patients suggest that executive deficits are present during euthymia and depression, but are most evident during manic states.³⁹

The findings of this study should be viewed in the context of other methodological limitations. These include, first, the small number of subjects, which increases the likelihood

of Type II errors. Second, we did not control for the potential influence of psychotropic medications that the patients were taking at the time of the assessment. Third, the study was not designed to assess any relationship between duration of illness or number of episodes and executive performance in the patient groups. Fourth, while the neuropsychological tests of executive functions we employed can contribute valuable information about general executive deficits in elderly patient and nonpatient groups, these tests assess complex cognitive functions that are not ideal for studies of specific neural networks. Simpler cognitive tests may facilitate the study of specific cerebral network abnormalities in elder BP patients. Finally, the limited neuropsychological assessment used does not permit us to speak to other executive functions or other cognitive domains.

In conclusion, this study extends observations that elderly BPM patients have executive dysfunction, and it provides preliminary evidence that these executive deficits can be more severe than that in aged individuals with UPD. The heuristic value of this finding is that it supports empirical investigation of the role of frontostriatal networks in the pathophysiology of geriatric bipolar disorder, using cognitive neuroscience tasks that are designed to evaluate specific aspects of frontostriatal system function. In addition, morphometry and diffusion tensor studies can be used to identify specific regional and microstructural white matter abnormalities in frontostriatal networks that may underlie executive dysfunction in elderly bipolar patients. Of clinical significance is the link between poor executive skills and the presence of disability in late-life mood disorders (e.g., ^{4,40}). Functional disabilities may serve as stressors that contribute to ongoing vulnerability to manic or depressive symptom chronicity, relapse or recurrence; clinicians therefore need to take measures to help patients compensate for functional deficits conferred by poor executive skills.

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FIGURE 1.
Performance on the Initiation/Perseveration subscale of the Mattis Dementia Rating Scale

FIGURE 2.
Performance on the Go/No-Go items of the Extended Initiation/Perseveration Scale