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Short-Term Course of Neuropsychological Abilities in Middle-Aged and Older Adults with Bipolar Disorder

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Abstract

Objectives—There are few longitudinal studies of neurocognition in bipolar disorder, and the short-term course of cognitive deficits in later-life bipolar disorder is unknown.

Methods—We administered a battery of neurocognitive tests, repeated one to three years after baseline, to 35 community-dwelling outpatients with bipolar disorder (mean age = 58), and compared their performance on a composite measure of cognitive functioning to that of demographically-matched samples of normal comparison subjects (NCs; n=35) and patients with schizophrenia (n=35). Using regression analyses, we examined group differences in baseline performance, trajectory of change over time, and variability in performance across time. Within the bipolar group, we examined the impact of baseline severity and change in severity of psychiatric symptoms on intra-individual change in neurocognitive performance.

Results—At baseline, the group with bipolar disorder differed in overall neurocognitive functioning from the NCs, but did not differ significantly from the schizophrenia group. The bipolar group did not differ from the NCs or schizophrenia group in the mean trajectory of change between time points, but the bipolar patients showed more intra-individual variability over time than the NCs or schizophrenia group. In the bipolar group, change in neurocognitive function was not related to baseline or change in psychiatric symptom severity.

Conclusions—Middle-aged and older community-dwelling adults with bipolar disorder have greater short-term variability in level of neurocognitive functioning relative to NCs or people with schizophrenia. The developmental course of and risk factors for cognitive deficits in bipolar disorder should be examined in future longitudinal studies.

Keywords

Bipolar disorder; neuropsychology; memory; aging; schizophrenia; depression

There is growing recognition that bipolar disorder involves cognitive deficits which persist between affective episodes and account for a substantial portion of the disability associated

with this illness (1,2). Recent data suggest that as many as 50% of euthymic older adults with bipolar disorder demonstrate clinically significant cognitive impairment relative to their age-matched peers in the general population (3-5). Given the fluctuating course of symptoms that typify this condition, as well as cross-sectional evidence that the cognitive deficits increase with cumulative lifetime affective episodes (6), older patients with bipolar disorder may be prone to fluctuations or long-term decline in their cognitive functioning. Such fluctuations and/or decline would be in marked contrast to schizophrenia. With the exception of a subset of chronically institutionalized/“poor outcome” patients (7,8), the cognitive deficits associated with schizophrenia appear remarkable stable among younger and older patients regardless of acute changes in severity of psychotic symptoms (9-12).

Despite the clinical relevance of the potentially non-stable cognitive functions in bipolar disorder, there are very few longitudinal studies of cognitive deficits in later life. To our knowledge, the only prior published longitudinal study of the course of cognitive ability in older adults with bipolar disorder showed that among cognitively intact older patients hospitalized for mania at baseline, a total of 32% were found to be cognitively impaired at a 5- to 7-year follow-up evaluation (13). However, the preceding study was limited by both a small sample (N=25), lack of comparison groups, and the cognitive measure that was used (cognitive impairment was defined by an Mini-Mental State Examination below 25 of 30 points.)

In the present study, we conducted a preliminary examination of the short-term course of cognitive abilities in 42 community-dwelling middle-aged and older outpatients with bipolar disorder who received two comprehensive neurocognitive assessments, with test-retest intervals ranging from 1 to 3 years. We first examined baseline differences between the bipolar group and demographically-matched samples of normal comparison subjects (NCs; n=35) and outpatients with schizophrenia (n=35) on a comprehensive battery of neurocognitive tests. We then compared the direction of mean level change in neurocognitive performance over the two time points across study groups. We also assessed the degree of variability across time points controlling for baseline performance. We hypothesized that the bipolar group would be intermediate in cognitive functioning between NCs and the schizophrenia group. We also hypothesized that, relative to comparison groups, bipolar patients would demonstrate greater variability in performance over time. Finally, we explored whether baseline and changes in psychiatric symptom severity correlated with change in neurocognitive change in the bipolar group.

METHOD

Participants

The present report is based on analyses of data collected as part of several studies in the NIMH-funded Advanced Center for Interventions and Services Research at the University of California, San Diego (UCSD). NCs were volunteers recruited through local advertisements. Some of the baseline cognitive and symptom severity data from the bipolar and schizophrenia patients and NCs have been included in prior reports (4,14,15), but this is our first attempt to evaluate the longitudinal course of cognitive deficits in bipolar patients. All the participants provided a written informed consent prior to participating in the research. The UCSD Human Research Protections Program (IRB) reviewed and approved the original protocols, as well as our plan for the secondary analyses of these data. For the present study, we included all bipolar participants who received two neurocognitive assessments over a 1- to 3-year interval, out of 88 persons with bipolar disorder in our database and 67 with data available from baseline neurocognitive evaluations(4). One of the co-authors (GNS) then matched the participants from the bipolar group to the larger schizophrenia and NCs samples with repeated neuropsychological test data (N= 116 and 113, respectively) by age, length of test-retest

interval, and education (prioritized in that order). Matching was done on a one-to-one basis, the window for the first two matching variables being ± 6 months, and that for education being ± 12 months. GNS was kept unaware of the participants' neuropsychological scores during the selection matching procedure. The final sample for this analysis included 35 community-dwelling outpatients with bipolar disorder, 35 outpatients with schizophrenia, and 35 NCs between ages 40 and 80 years.

All the participants were screened with a medical history questionnaire and with laboratory and physical examinations to exclude the following: 1) history of major neurological disorders or head trauma, 2) DSM-III-R (16) or DSM-IV (17) diagnosis of dementia, 3) current systemic medical disease requiring inpatient treatment, 4) diagnosis of current substance abuse or dependence. Diagnoses were made with administration of the Structured Clinical Interview for the DSM-III-R (16) and DSM-IV (17) by trained psychology or psychiatry fellows, and confirmed during a subsequent consensus meeting. For the present analyses, we did not exclude bipolar disorder patients with mood episodes at the time of data collection, as in some previous reports (2,3,18), given that one aim of our investigation was to examine short-term course of neuropsychological performance in a representative sample of older bipolar patients.

All bipolar participants were diagnosed with Bipolar I, with one participant diagnosed with Bipolar II. A total of 83% of the participants had been previously psychiatrically hospitalized. All participants were community dwelling at the time of both of the assessments. Among the bipolar participants, current medication data were available on all but 7 of the participants. A total of 50% were taking lithium, 17% were on valproic acid, and 14% were taking either carbamazepine or another anticonvulsant. In addition, 51% were taking an antipsychotic medication (66% on antipsychotics were on a typical antipsychotic and 33% on an atypical agent). In the schizophrenia group, medication data was missing on three patients. A total of 77% were taking antipsychotic medications, with 77% being on typical antipsychotics and 23% on atypical antipsychotics. The low proportion of the bipolar and schizophrenia groups taking atypical antipsychotic medications versus typical agents is because some of the data were collected prior to the widespread use of atypical antipsychotics.

Neuropsychological Measures

All study participants were administered a comprehensive neuropsychological test battery by trained research assistants. The data reported in the present study were collected as part of larger neuropsychological test batteries within the individual studies for which these data were originally collected. For the present report, we used only those test scores which were relatively common among the various original protocols, and for which longitudinal data were available. The specific tests scores used for the present report include the Boston Naming Test (total correct) (19), Block Design and Digit Span subtests from the Wechsler Adult Intelligence Scale-Revised Edition (WAIS-R), Trails A and B (total time), Letter Fluency (FAS, total correct), Story Memory (learning and delayed recall), Figure Memory (learning and memory scores), Grooved Pegboard Test (dominant and nondominant hands, total time), Digit Vigilance (time) (20), California Verbal Learning Test (CVLT, total trials 1 through 5; long delay free recall) (21), and Wisconsin Card Sorting Test (Preservative Errors) (22). In light of the relatively small sample size, our focus for the present report was on overall cognitive functioning, which we evaluated with a Global Composite Neurocognitive Functioning Score. Specifically, the raw score from each test was converted to a T-score scale, with a normative mean of 50 and SD of 10 (coded such that higher scores indicate better performance) using published normative data (23). The Global Composite Neurocognitive Functioning Score was then calculated as mean T-score for each participant. We required that each participant have at least 10 available test scores out of 16 at both baseline evaluation and retest to ensure that all subjects have the majority of test measures in common.

Clinical Evaluation

Participants were administered the Hamilton Depression Rating Scale (HAM-D) (24), and Brief Psychiatric Rating Scale (BPRS) (25). The research assistants who administered and scored these scales were kept unaware of the participant's diagnostic status (to the extent possible) and his or her neuropsychological performance during administration and scoring of the measures.

Statistical Analysis

Analyses were conducted with SPSS 12 software. Distributions for each variable were checked for normality, and transformations were conducted when needed to meet assumptions for parametric analyses. We first conducted a one-way ANOVA to compare the baseline Global Composite Neurocognitive Functioning Score for NCs, bipolar, and schizophrenia groups, and also examined the pairwise differences between groups with Tukey post-hoc tests. We then repeated these analyses controlling for HAM-D and BPRS scores, as well as the previous alcohol use disorder. To examine whether groups differed in trajectory of neurocognitive performance across time, we then calculated differences between baseline and follow-up Global Composite Neurocognitive Functioning Scores, and regressed dummy coded bipolar and schizophrenia grouping variables onto the Composite change score. To address whether groups differed in terms of the degree of variability in Composite Score performance between time points, we regressed centered baseline Composite Scores onto follow-up Composite Scores in the first step and, in the second step, we entered an interaction term that was calculated as dummy coded grouping variables multiplied by centered baseline scores(26). NCs and schizophrenia served as the reference groups in two separate analyses. Finally, within the bipolar group, we explored whether baseline HAM-D and BPRS as well as change in these variables predicted change in the Composite Score, controlling for inter-assessment time interval. We included inter-assessment time interval into all longitudinal models due to the variable time intervals between baseline and follow-up assessments. We elected not to examine predictors of change other than psychiatric symptoms to mitigate the risk of Type 1 errors. All the tests were two-tailed, $p < .05$.

RESULTS

Demographic and Baseline Clinical and Neuropsychological Comparisons

The three groups did not differ significantly in age or ethnicity. Relative to the HC group, the two patient groups both had higher proportions of women. The bipolar group had a higher mean level of education than the schizophrenia group, despite our matching procedure (education was prioritized last in the order of matching variables). Mean duration of illness in both bipolar and schizophrenia groups was approximately 25 years. The bipolar group had more severe depressive symptoms (HAM-D scores) than the schizophrenia group, although both groups had mean scores on the HAM-D and BPRS that represented a mild or minimal level of psychopathology.

At baseline, Global Composite Neurocognitive Functioning Score was significantly different across the three subject groups, with pairwise comparisons indicating the NCs had significantly better performance than the two patient groups. There was no significant pairwise difference between two patient groups. The omnibus comparison by group remained significant after controlling for HAM-D score, BPRS scores, and previous diagnosis of alcohol abuse or dependence ($F(2,85)=12.0$, $p < 0.001$).

Comparison of Longitudinal Change in Neuropsychological Functioning

The mean change in the Global Neurocognitive Functioning Composite Score was approximately one point in the positive direction (on a T-score with a mean of 50 and SD of 10) for each of the groups (NCs mean change = 1.3, SD=2.0, bipolar group mean change = 0.84, SD=4.5; schizophrenia group mean change = 0.33, p=3.9). The regression predicting change in neurocognitive functioning with the NCs as a reference group revealed no main effect for bipolar disorder ($b=-0.10$, S.E. = 0.88, $p=0.554$) or for schizophrenia ($b=-1.14$, S.E.=0.89, $p=0.201$), indicating that the mean level change in the Composite Score in both patient groups was not different from that of the NC group.

Comparison of Longitudinal Variability in Neurocognitive Functioning

The partial correlation (controlling for inter-assessment interval) between baseline and follow-up Composite Scores was $r=0.575$, $p<0.001$ for the bipolar group, compared to $r=0.898$, $p<0.001$ for the NCs group and $r=0.843$, $p<0.001$ for the schizophrenia group. To test whether the degree of variability from baseline to follow-up scores differed between groups, we regressed centered baseline Composite Score onto follow-up Composite Score, controlling for follow-up interval, and, in the second step, the interaction of centered baseline composite scores and the group variables for bipolar disorder and schizophrenia groups (with the NCs as the reference group). The overall F-value was significant ($F(2,103)=50.7$, $p<0.001$). Examination of the coefficients revealed the bipolar group variable was significant ($b=-0.366$, S.E.=0.178, $p=0.043$) but the schizophrenia group variable was not ($b=0.027$, S.E.=0.161, $p=0.867$), indicating that only the bipolar group was more variable than the NCs across time points. We re-ran the analysis with the SC group as the reference group, and the bipolar group was significantly more variable than the SC participants ($b=-0.392$, S.E.=0.151, $p=0.011$), but the NCs were not ($b=-.027$, S.E.=0.161, $p=0.867$).

Relationship of Symptoms to Longitudinal Composite Neurocognitive Functioning in the Bipolar Group

Within the bipolar group, we conducted separate regression analyses examining the relationship of baseline HAM-D and BPRS scores on baseline Composite Score and change in Composite Score. The mean change in HAM-D scores was -1.06 points ($\pm$ standard deviation of 7.62) and the mean change in BPRS scores was -0.97 ($\pm$ standard deviation of 6.65). Neither baseline HAM-D nor BPRS scores predicted baseline neurocognitive functioning ($b=-0.69$, S.E.=0.134, $p=0.613$, $b=-0.01$, S.E.=0.122, $p=0.442$, respectively). In addition, baseline HAM-D ($b=-0.9$, S.E.=0.110, $p=0.431$) and BPRS score ($b=-0.06$, S.E.=0.100, $p=0.553$) did not predict change in Composite Score. Finally, controlling for inter-assessment interval, change in HAM-D ($b=-0.06$, S.E.=0.137, $p=0.680$) and change in BPRS ($b=-0.02$, S.E.=0.112, $p=0.854$) had no significant effect on change in Composite Score.

DISCUSSION

This study is among the first longitudinal studies of neurocognitive functioning in middle-aged and older persons with bipolar disorder, and our results indicate several aspects of the short-term course of cognitive deficits in these patients. As expected, cognitive functioning was impaired in the bipolar group; their performance was closer to that of patients with schizophrenia than to that of a healthy comparison group. Longitudinal neurocognitive performance in each of our study groups was, on average, characterized by a flat trajectory over a 1- to 3-year period, but there was greater variability between time points in the bipolar group as compared to the NCs or the schizophrenia group. Neither baseline severity of nor change in severity of psychiatric symptoms in the bipolar group related to significant change in neuropsychological functioning. Overall, these findings suggest that neurocognitive performance is substantially worse among middle-aged and older persons with bipolar disorder

compared to NCs. Over a short time period, their average performance may not necessarily worsen, but there may be greater variability among bipolar patients in cognitive functioning than among either NCs or people with schizophrenia

There are several limitations of this small study that could provide directions for future studies. First, we measured change in cognitive performance over two time points spaced between one to three years apart, providing a fairly rough indication of short-term course. The ideal longitudinal study would include three or more assessments over a longer time period, which would permit the use of more sophisticated statistical analyses (e.g., hierarchical linear modeling) that could better tease apart the factors that contribute the intra-individual trajectory and variability in these deficits. Furthermore, due to concerns over multiple comparisons and statistical power given our small sample size, we elected not to examine the longitudinal course within specific domains of neurocognitive functioning (e.g., memory, executive function). Future studies of bipolar disorder should examine whether change (or variability) in particular neurocognitive domains over the lifespan is observed in the absence of others. Second, the bipolar and schizophrenia samples were composed of outpatients who were, in general, experiencing a mild level of psychopathologic symptoms at both time-points. Therefore, these findings may not apply to hospitalized or acutely ill persons or those with more substantial fluctuations in symptoms, in that greater severity of symptoms, or fluctuations in such severity, may be linked to greater variability in cognitive functioning. Third, the mean age of the sample was about 60 years, so the degree of change in neurocognition among elderly people (i.e., persons over age 65) as well as among younger persons may be different than that found in our study.

Despite the above the limitations, our findings suggest that older clinically stable/community-dwelling persons with bipolar disorder have an overall level of cognitive functioning that is more commensurate with the cognitive performance observed in middle-aged and older outpatients with schizophrenia than cognitive ability among NCs. Similar to our previous cross-sectional report concerning the frequency of cognitive impairment in later-life bipolar disorder (4), as well as that found in other research centers in later-life bipolar disorder (3,5), we found large significant baseline differences between the NCs and bipolar patients. The magnitude of the difference between bipolar and NC groups was greater than one standard deviation (Cohen's $d = 1.28$). We did not identify a statistically significant difference in our Composite measure between the bipolar group and age-matched patients with schizophrenia (although all were in the direction of worse performance in the schizophrenia group). The mean level performance among patients with bipolar disorder was similar to the comparison groups, which is in contrast to the apparent decline seen over a 5 to 7 year period among elderly patients hospitalized with mania (13). The lack of a general decline identified in our study sample could be because of the short interval (1 to 3 years), the mild severity of symptoms of the majority of the sample, and the age range of 50 to 70 of the majority of our participants. The finding that average cognitive performance remains stable over time parallels what has been found in larger samples of middle-aged and older outpatients with schizophrenia by our research group (12,14).

As hypothesized, neurocognitive performance was considerably less consistent over time in the bipolar group than in either of the comparison groups. If replicated, this relative instability of cognitive functioning has implications for research on neurocognition in bipolar disorder, in that the attenuated reliability of neurocognitive functioning may need to be accounted for in studies cross-sectional studies estimating cognitive functioning in bipolar disorder. Given the fluctuating course of depressive and manic symptoms in bipolar disorder (27) and the evidence for cross-sectional differences between manic, depressive, and euthymic patients (2), we assumed that change in cognitive impairments would correspond to changes in mood symptoms. However, we did not find evidence for a relationship of baseline psychiatric

symptom severity, nor change in severity of symptoms, with change in neurocognitive abilities. The bipolar patients in our study varied by approximately 7 points (one standard deviation) in the direction of improvement or decline on symptom scales, so it is unlikely that the shifts in symptoms reflect full syndromal changes.

As there is a dearth of longitudinal studies of neurocognition in bipolar disorder, it difficult to determine whether the pattern of observed short-term variability is a partial function of the older age of patients in the study. The factors that influence the instability of neurocognitive performance in bipolar disorder, as well as whether or not change in performance tends to become more or less independent from concurrent psychiatric symptoms across the lifespan, should be a subject of future longitudinal study. However, the primary implication of our study is that cognitive deficits are likely a major part of the clinical picture of later-life bipolar disorder, even among outpatients with relatively mild severity of symptoms. Our study suggests that these deficits may be less consistent over time than cognitive abilities found among NCs or patients with schizophrenia, and future research should examine the impact of this instability in cognitive functioning on treatment response and everyday functioning. In the meantime, rehabilitative approaches for later life bipolar disorder should incorporate strategies to compensate for these neurocognitive impairments.

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References

1. Bearden CE, Hoffman KM, Cannon TD. The neuropsychology and neuroanatomy of bipolar affective disorder: a critical review. *Bipolar Disord* Jun;2001 3(3):106–150. [PubMed: 11465675]discussion 151-103
2. Martinez-Aran A, Vieta E, Reinares M, et al. Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *Am J Psychiatry* Feb;2004 161(2):262–270. [PubMed: 14754775]
3. Gildengers AG, Butters MA, Seligman K, et al. Cognitive functioning in late-life bipolar disorder. *Am J Psychiatry* Apr;2004 161(4):736–738. [PubMed: 15056521]
4. Depp C, Moore DJ, Sitzer DI, et al. Neurocognitive impairment among middle-aged and elderly adults with bipolar disorder: Comparison to schizophrenia and normal comparison subjects. *Journal of Affective Disorders*. In Press
5. Young RC, Murphy CF, Heo M, Schulberg HC, Alexopoulos GS. Cognitive impairment in bipolar disorder in old age: literature review and findings in manic patients. *J Affect Disord* May;2006 92(1): 125–131. [PubMed: 16469389]
6. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. *Bipolar Disord* Apr;2006 8(2):103–116. [PubMed: 16542180]
7. Harvey PD, Parrella M, White L, Mohs RC, Davidson M, Davis KL. Convergence of cognitive and adaptive decline in late-life schizophrenia. *Schizophr Res* Jan 4;1999 35(1):77–84. [PubMed: 9988843]
8. Friedman JI, Harvey PD, Coleman T, et al. Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. *Am J Psychiatry* Sep;2001 158(9):1441–1448. [PubMed: 11532729]
9. Palmer BW, Bondi MW, Twamley EW, Thal L, Golshan S, Jeste DV. Are late-onset schizophrenia spectrum disorders neurodegenerative conditions? Annual rates of change on two dementia measures. *J Neuropsychiatry Clin Neurosci* Winter;2003 15(1):45–52. [PubMed: 12556570]
10. Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. The stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry* Jan;2001 58(1):24–32. [PubMed: 11146755]

11. Rund BR. A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophr Bull* 1998;24(3):425–435. [PubMed: 9718634]
12. Nayak Savla G, Moore DJ, Roesch SC, Heaton RK, Jeste DV, Palmer BW. An evaluation of longitudinal neurocognitive performance among middle-aged and older schizophrenia patients: use of mixed-model analyses. *Schizophr Res* Apr;2006 83(23):215–223. [PubMed: 16507344]
13. Dhingra U, Rabins PV. Mania in the elderly: a 5-7 year follow-up. *J Am Geriatr Soc* Jun;1991 39(6): 581–583. [PubMed: 2037748]
14. Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV. Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry* Jan;2001 58(1):24–32. [PubMed: 11146755]
15. Gladsjo JA, McAdams LA, Palmer BW, Moore DJ, Jeste DV, Heaton RK. A six-factor model of cognition in schizophrenia and related psychotic disorders: Relationships with clinical symptoms and functional capacity. *Schizophr Bull* 2004;30(4):739–754. [PubMed: 15957196]
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Third Edition - Revised. American Psychiatric Association; Washington, DC: 1987.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition.. American Psychiatric Association; Washington,DC: 1994.
18. Altshuler LL, Ventura J, van Gorp WG, Green MF, Theberge DC, Mintz J. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. *Biol Psychiatry* Oct 15;2004 56(8):560–569. [PubMed: 15476685]
19. Kaplan, E.; Goodglass, H.; Weintraub, S. The Boston Naming Test. 2nd Edition. Lea & Febiger; Philadelphia: 1983.
20. Lewis, RF.; Rennick, PM. Manual for the Repeatable Cognitive-Perceptual-Motor Battery. Axon Publishing Co; Grosse Point Park, MI: 1979.
21. Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test (CVLT). The Psychological Corporation; San Antonio, TX: 1987.
22. Heaton, R.; Chelunem, G.; Talley, J.; Kay, G.; Curtis, G. Wisconsin Card Sorting Test (WCST) Manual Revised and Expanded. Psychological Assessment Resources; Odessa, Florida: 1993.
23. Heaton, R.; Miller, W.; Taylor, M.; Grant, I. Revised comprehensive norms for an Expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African-American and Caucasian adults (HRB). Psychological Assessment Resources, Inc.; Odessa, Fla.: 2004.
24. Hamilton M. Development of a rating scale for primary depressive illness. *British Journal of Psychiatry* 1967;6:278–296.
25. Overall J, Gorham D. The Brief Psychiatric Rating Scale. *Psychological Reports* 1962;10:799–812.
26. Cohen, J.; Cohen, P.; West, SG.; Aiken, LS. Applied multiple regression/correlation analysis for the behavioral sciences. 6th Edition. Erlbaum; London: 2003.
27. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* Jun;2002 59(6):530–537. [PubMed: 12044195]

Table 1
Demographic, Psychiatric, and Neurocognitive Characteristics of the NC Bipolar, and Schizophrenia Groups

	Normal Comparison Subjects (NCs) N=35 Mean (SD)	Bipolar Disorder Group (BD) N=35 Mean (SD)	Schizophrenia Group (SC) N=35 Mean (SD)	F(df) or χ^2 (df)	p-value	Pair-wise differences ^a
Age (years)	59.9 (11.6)	57.7 (10.0)	59.4 (10.2)	F(2, 1030)=0.38	0.8680	N/A
Education (years)	13.1 (2.3)	14.6 (3.1)	12.8 (2.9)	F(2, 103)=4.19	0.019	SC<BD
Gender (% Female)	58.8%	28.6%	25.7%	χ^2 (2)=9.8	0.0607	BD=SC<NC
Ethnicity (% Caucasian)	81.0%	95.2%	85.7%	χ^2 (2)=4.00	0.135	N/A
Past Alcohol Abuse/Dependence (%)	2.9%	22.9%	7.1%	χ^2 (2)=7.49	0.024	NC<BD
Number of Medical Diagnoses	1.5 (1.4)	2.2 (1.9)	2.2 (1.9)	F(2, 94)=1.6	0.196	N/A
Duration of Illness (years)	N/A	25.6 (14.4)	28.8 (15.9)	F(1, 59)=0.65	0.422	N/A
HAM-D Total Score (Baseline)	2.8 (2.9)	11.3 (6.7)	8.0 (5.2)	F(2, 98)=22.5	<0.001	NC<SC<BD
BPRS Total Score (Baseline)	22.4 (3.6)	30.9 (7.2)	30.6 (6.56)	F(2, 98)=21.8	<0.001	NC<BD=SC
Mean Duration of Follow-Up (months)	17.0 (6.3)	16.1 (6.3)	15.0 (4.3)	F(2, 103)=1.16	0.317	N/A
Global Cognitive Functioning Time 1	49.6 (4.5)	43.2 (4.9)	41.8 (6.7)	F(2, 101)=19.4	<0.001	SC=BD<NC
Global Cognitive Functioning Time 2	50.9 (5.3)	44.0 (4.9)	42.2 (7.1)	F(2, 101)=22.1	<0.001	SC=BD<NC

HAM-D: Hamilton Depression Rating Scale; BPRS: Brief Psychiatric Rating Scale; T-Scores (Mean of 50, SD of 10)

^aTukey post-hoc correction