Rapid Assessment of Neurocognitive Deficits in Bipolar Disorder

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Abstract

The purpose of this study is to illustrate the clinical usefulness of a computerized neuropsychological battery for identifying neurocognitive deficits in adults with bipolar disorder. Participants were 47 outpatients with bipolar disorder who were individually matched on age, education, sex, and ethnicity to 47 control subjects from the CNS Vital Signs normative database. CNS Vital Signs is comprised of seven common neuropsychological measures, and it generates 15 primary scores that are used to calculate five domain scores (Memory, Psychomotor Speed, Reaction Time, Cognitive Flexibility, and Complex Attention. There was a significant multivariate effect and statistically significantly worse scores for those in the bipolar group on all five domain scores (medium to large effect sizes). When using two or more scores below the 5th percentile as a cutoff for neurocognitive impairment, 42.6% of the bipolar sample and 6.4% of the control sample scored in this range [$\chi^2(1)=16.6$, p=<.001; Odds Ratio=10.9, 95% CI=3.1–37.3; Sensitivity=.43, Specificity=.94, Positive Predictive Value=.87, 95% CI=.70–.95, Negative Predictive Value=.62, 95% CI=.56–.65]. A subset of high functioning patients with bipolar disorder have frank neurocognitive impairments identifiable with this 30-40 minute computerized assessment battery.

Key Words: Bipolar disorder, Neurocognition, Computerized testing, impairment

Introduction

Clinicians and researchers are interested in neurocognitive deficits associated with bipolar disorder (Bearden, Hoffman, & Cannon, 2001; Osuji & Cullum, 2005; Savitz, Solms, & Ramesar, 2005). Researchers have reported that some children and adolescents (Doyle et al., 2005; Pavuluri et al., 2006), adults (Altshuler et al., 2004; Bearden et al., 2001; Seidman et al., 2002; Smith, Muir, & Blackwood, 2006), and older adults (Burt, Prudic, Peyser, Clark, & Sackeim, 2000; Depp et al., 2007) with bipolar disorder have neurocognitive deficits. The cognitive deficits appear to persist into remission, and have been reported in several studies of patients who are euthymic (Cavanagh, Van Beck, Muir, & Blackwood, 2002; El-Badri, Ashton, Moore, Marsh, & Ferrier, 2001; Goswami et al., 2006; Thompson et al., 2005). Moreover, there is some evidence to suggest that euthymic patients with bipolar II disorder perform better on some neuropsychological tests than euthymic patients with bipolar I disorder (Torrent et al., 2006).

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In a meta-analysis, Robinson and colleagues reported that euthymic patients with bipolar disorder perform poorly on numerous neuropsychological tests. Those tests with the largest effect sizes (all with d > .70) were category verbal fluency (d = 1.1), digit span backwards (d = .98), verbal learning (d = .90), Trail Making Test Part B (d = .78), and perseverative responses from the Wisconsin Card Sorting Test (d = .76) (Robinson et al., 2006). In general, when considering all patients with bipolar disorder, greater neurocognitive impairment is associated with worse illness course, such as number of manic episodes, hospitalizations, and length of illness (Robinson & Ferrier, 2006).

There is considerable interest, in diverse areas of research relating to bipolar disorder, to include neurocognitive testing as an outcome measure. It is advantageous to have computerized neurocognitive assessment batteries for use in clinical research and clinical practice in psychiatric settings. Researchers have used computerized testing with adolescents (Dickstein et al., 2004; Gualtieri & Johnson, 2006a; Pavuluri et al., 2006) and adults with bipolar disorder (Sweeney, Kmiec, & Kupfer, 2000; Tam & Liu, 2004). Computer-based testing offers important benefits over conventional testing, including greater reliability due to the decreased variability and errors in test presentation, and more precise response recording (Tien et al., 1996). Computerized testing also allows for more control over test stimuli, including intensity, frequency, and location. It is also capable of presenting the stimuli at a controlled fixed rate, or randomizing the stimuli order. This is beneficial for populations in which follow-up testing at short intervals is important (Kane & Kay, 1997). Computerized testing does not require highly skilled psychometrists, making it more practical and affordable for many studies. In addition, brief computerized testing can be easily repeated at a later date to track neurocognition over time, particularly in conjunction with treatment.

A new co-normed computerized neurocognitive assessment battery, called the Central Nervous System (CNS) Vital Signs (Gualtieri & Johnson, 2006c), appears to be appropriate for use with patients with bipolar disorder (Gualtieri & Johnson, 2006a). The CNS Vital Signs battery is normed across the lifespan for children, adolescents, and adults. It is presented at a grade four reading level. CNS Vital Signs is administered on a personal computer, uses the keyboard for participant responses, and it takes approximately 30-40 minutes to complete all measures. The results are summarized on a printout with raw scores, normative scores, percentiles, classifications, and test descriptions. The purpose of this study is to compare the computerized neurocognitive test performance of a sample of outpatient adults with bipolar disorder to healthy adults, and to illustrate a clinical methodology for identifying frank neurocognitive deficits in adults with bipolar disorder.

Method

Subjects & Procedures

The clinical participants for this study were 47 adults who were diagnosed with Bipolar Disorder by clinicians at the North Carolina Neuropsychiatry Clinics according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition criteria (American Psychiatric Association, 1994). All patients completed brief computerized neurocognitive testing using the CNS Vital Signs battery during an intake evaluation or a routine office visit. This is a sample of convenience; no formal diagnostic interviewing or symptom rating scales were collected.

The patients with bipolar disorder were carefully and precisely matched on age, education, sex, and ethnicity to 47 control subjects from the CNS Vital Signs normative database. Their demographic characteristics are presented in Table 1. The sample was relatively young, well educated, and predominately Caucasian. Their average self-reported years of education was 15.2 (SD = 2.3 years). Our experience is that some patients "over-estimate" their years of education, when relying on self report. Thus, their level of education might be a slight over-estimate. It is likely, however, that the average education of this sample is clearly greater than high school, with most of the sample (87.3%) having some form of technical, college, or university education. Regarding occupational status in the bipolar patients,

40.4% were professional/technical, 8.5% were students, 6.3% were in a labor position (evenly split between unskilled, semi-skilled, and skilled), 4.3% were in managerial/office positions, 4.3% were clerical/sales, and 4.3% were retired/not working. In this sample, 23.4% were identified as disabled. The occupational status was not known for 8.5% of the bipolar patients. In the control sample, 42.5% were listed as professional/technical, 12.8% were students, 2.1% were in skilled labor, 8.5% were in managerial/office positions, 2.1% were clerical/sales, and 6.4% were retired/not working. None of the control sample was identified as disabled. The occupational status was missing for 25.5% of the control participants.

Measures

CNS Vital Signs is comprised of seven common neuropsychological measures, including verbal and visual memory, finger tapping, symbol digit coding, the Stroop test, a shifting attention test, and a continuous performance test. The battery generates 15 primary scores, which are used to calculate 5 domain scores (Memory, Psychomotor Speed, Reaction Time, Cognitive Flexibility, and Complex Attention) and a summary score (Neurocognition Index). The measures have good test-retest reliability (mean interval of 62 days, range = 1 to 282 days), adequate concurrent validity with traditional paper and pencil measures and other computerized tests, and the index scores have been shown to discriminate between various clinical groups (Gualtieri & Johnson, 2005, 2006b; Gualtieri, Johnson, & Benedict, 2006).

The five CNS-VS domain scores, initially established through a factor analysis of the raw data (Gualtieri & Johnson, 2006c), are derived by summing multiple primary raw scores. Domain scores are presented as index scores, with a mean of 100 and standard deviation of 15. Correct responses from the verbal and visual memory tests are summed to generate a composite *Memory Domain* score. The total of right and left taps from the Finger Tapping Test and the total correct responses on the Symbol-Digit Coding Test generate a composite score for *Psychomotor Speed*. Averaging the two complex reaction time scores from the Stroop Test generates a domain score for *Reaction Time*. However, it would be more precise to refer to this domain score as "information processing speed in a test of executive function." The number of correct responses on the Shifting Attention Test, minus the number of errors on the Shifting Attention Test and the Stroop Test, is used to create a domain score for *Cognitive Flexibility*. A domain score for *Complex Attention* is generated by adding the number of errors committed in the Continuous Performance Test, the Shifting Attention Test, and the Stroop Test. The overall summary score, called the *Neurocognition Index*, is derived from the average of the five domain scores.

Analyses

Analysis of the CNS Vital Signs test results involved (1) comparing the mean domain score performances across the groups using multivariate and univariate analyses of variance (MANOVA and ANOVA, respectively), and (2) examining the base rates of low domain scores across the three groups (i.e., neuropsychological profile analysis), followed by chi-square analyses.

Calculations for the base rates of low scores involve simultaneously examining the five domain scores, rather than performance on each domain in isolation. The base rates of low domain scores were calculated by using four cutoff scores that might be routinely used in clinical practice, including: (a) more than 1 standard deviation (SD) below the mean (i.e., < 85), (b) below the 10^{th} percentile (i.e., < 81), (c) at or below the 5^{th} percentile (i.e., ≤ 76), and (d) more than 2 SDs below the mean (i.e., < 70).

Results

The two groups were compared on the five index scores using multivariate analysis of variance (MANOVA) followed by univariate ANOVAs. Box's M test was significant, indicating that the covariance matrices differed ($p < .001$). Moreover, Levene's test was significant for four of the five index

scores, indicating heterogeneity of variance between groups. MANOVA and ANOVA tend to be quite robust to violations of underlying general linear model assumptions; thus, the results will be reported. There was a significant multivariate effect [Wilks' Lambda = .785; F (5, 88) = 4.82, p < .001, partial eta squared = .215]. The univariate ANOVA results revealed significantly worse neuropsychological test scores for those in the Bipolar group on the Memory Index (Cohen's d = .53), Processing Speed Index (d = .73), Reaction Time Index (d = .71), Cognitive Flexibility Index (d = .84), and Complex Attention Index (d = .95). Nonparametric analyses also were conducted because of the violations of the underlying GLM assumptions. Mann Whitney U tests also revealed significant differences between groups on all five of the index scores.

Table 1. Demographic characteristics and test performance in bipolar and matched control samples.

		Bipolar Disorder	Matched Controls	F statistic (p value)	Cohen's Effect Sizes (d)
Sample Sizes (n)		47	47		
Gender	Male (%)	34.0	34.0		
	Female (%)	66.0	66.0		
Ethnic Background	Caucasian (%)	93.6	93.6		
	African American (%)	4.3	4.3		
	Asian (%)	2.1	2.1		
Age (SD)		38.2 (11.0)	38.5 (10.7)	0.11 (.92)	0.02
Education (SD)		15.2 (2.3)	15.2 (2.3)	0.00 (1.0)	0.00
Memory Index (SD)		90.2 (20.1)	99.2 (14.0)	6.40 (.013)	0.53
Processing Speed Index (SD)		89.0 (22.9)	103.6 (17.1)	12.19 (.001)	0.73
Reaction Time Index (SD)		85.2 (26.8)	101.1 (18.2)	11.33 (.001)	0.71
Cognitive Flexibility Index (SD)		84.5 (30.8)	103.5 (14.6)	14.63 (<.001)	0.84
Complex Attention Index (SD)		80.7 (32.6)	103.5 (15.5)	18.68 (<.001)	0.95
Base Rates of Low Scores*		C %	C %		
1 or More Indexes < 1 SD		68.1	40.4		
2 or More Indexes < 1 SD		55.3	14.9		
3 or More Indexes < 1 SD		34.0	4.3		
1 or More Indexes < 10^{th} Percentile		61.7	31.9		
2 or More Indexes < 10^{th} Percentile		46.8	10.6		
3 or More Indexes < 10^{th} Percentile		34.0	0.0		
1 or More Indexes ≤ 5^{th} Percentile		57.4	23.4		
2 or More Indexes ≤ 5^{th} Percentile		42.5	6.4		
3 or More Indexes ≤ 5^{th} Percentile		29.7	0.0		
1 or More Indexes < 2 SDs		46.9	14.9		
2 or More Indexes < 2 SDs		34.1	2.1		
3 or More Indexes < 2 SDs		19.2	0.0		

*The cumulative percentage of each sample with a score at or below the cutoff is presented. Note: There are slight variations due to rounding.

Of the patients with bipolar disorder, 55.3% obtained two or more index scores below 1 SD, compared to 14.9% of the control group [$\chi^2(1) = 16.9$, p = <.001; Odds Ratio = 7.1, 95% CI = 2.7 – 18.6]. When using two or more scores below the 5^{th} percentile as the cutoff, 42.6% of the bipolar sample and 6.4% of the control sample scored in this range [$\chi^2(1) = 16.6$, p = <.001; Odds Ratio = 10.9, 95% CI = 3.1 – 37.3; Sensitivity = .43, Specificity = .94, Positive Predictive Value = .87, 95% CI = .70 – .95, Negative Predictive Value = .62, 95% CI = .56 – .65]. When using two or more scores below 2 SDs as the cutoff, 34.0% of the bipolar sample and 2.1% of the control sample scored in this range [$\chi^2(1) = 16.2$, p = <.001;

Odds Ratio = 23.7, 95% CI = 3.8 – 145.8; Sensitivity = .34, Specificity = .98, Positive Predictive Value = .94, 95% CI = .75 – .99, Negative Predictive Value = .60, 95% CI = .56 – .61].

Discussion

The results of this study are largely consistent with the neuropsychological theories and empirical studies on the neurocognitive effects of bipolar disorder. Patients with bipolar disorders performed more poorly on computerized tests of memory, processing speed, reaction time, cognitive flexibility, and complex attention. The effect sizes in this study were similar to the effect sizes in euthymic patients reported by Robinson and colleagues on traditional neuropsychological tests measuring similar abilities (Robinson et al., 2006). Therefore, this computerized neurocognitive battery appears to be sensitive to cognitive impairment associated with bipolar disorder.

This study has significant methodological limitations that reduce its generalizability. This was a clinical sample of convenience, derived from an archival database. Information regarding duration of illness, number of hospitalizations, severity of illness, and medication status was not available. These variables are related to neurocognitive functioning (Robinson & Ferrier, 2006). The major strength of this study was the precise matching on relevant demographic variables. Because we had access to a large normative data set, we were able to precisely match each patient, in a case-control fashion, on age, education, sex, and ethnicity. These demographic variables are important to consider in neurocognition research because small differences in demographic variables can mimic or obscure group differences.

This study has practical clinical implications. The patients in this study obtained significantly more low domain scores across the entire battery compared to healthy adults. As seen in clinical practice, a subset of patients with bipolar disorder have frank cognitive impairment. In this study, patients with bipolar disorder were 24 times more likely to have two or more index scores that were below two SDs (95% CI = 3.8 – 145.8). Using the criteria of two index scores below two SDs as a marker for neurocognitive impairment, the battery had low sensitivity (.34) but very high positive predictive power (PPP = .94, 95% CI = .75 – .99). This is not surprising, because only a subset of high functioning patients with bipolar disorder likely have frank impairments. Based on the results of this preliminary study, the clinician could be 94% confident that having two unusually low index scores reflects neurocognitive impairment and not broadly normal cognitive functioning. This information might be helpful for better understanding the nature of some patients' illness, for making recommendations regarding coping with and compensating for their cognitive difficulties, and for encouraging them to adhere to treatment.

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