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Cognitive and clinical outcomes associated with cannabis use in patients with bipolar I disorder

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Abstract

Studies investigating the impact of cannabis use on bipolar clinical characteristics and neurocognition are limited. The objective of the present study was to compare clinical and neurocognitive measures in individuals with bipolar disorder with a history of cannabis use disorder (CUD) versus those without a history of CUD. We conducted a retrospective analysis of a large cohort (N=200) of bipolar I subjects, either with (CUD+; N=50) or without (CUD−; N=150) a history of CUD. We compared the groups on clinical and demographic variables, as well as on performance on neurocognitive tests. Patient groups did not differ regarding age, age of onset or global assessment of functioning. Compared to the CUD− group, the CUD+ group had a higher proportion of men and a higher proportion of patients with a history of psychosis. CUD+ subjects demonstrated significantly better performance on measures of attention, processing speed, and working memory. The history of CUD is associated with history of psychosis, suggestive of poorer clinical prognosis. Interestingly, bipolar patients with history of CUD had *better* neurocognitive performance as compared to patients with no history of CUD.

Keywords

Bipolar Disorder; Cannabis; Neurocognition; Prognosis

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1. Introduction

Cannabis is the most widely used illicit substance in western countries, with lifetime prevalence of 8-12% in United States (Conway et al., 2006; Stinson et al., 2006). Cannabis use has been associated with a number of clinical and functional impairments, such as impaired educational attainment (Lynskey et al., 2000) and reduced workplace productivity (Lehman et al., 1992). Cannabis has also been associated with cognitive impairments, particularly in heavy users (Pope, Jr. et al., 1996; Schweinsburg et al., 2008).

The impact of cannabis use disorders (CUD) is particularly pertinent among subjects with major psychiatric disorders. Compared to the general population, patients with schizophrenia or bipolar disorder have a 2 to 3 fold increase in CUD rates (Stinson et al., 2006; Koskinen et al., 2010). Moreover, studies have suggested that cannabis increases risk of psychotic presentations (Moore et al., 2007), but the topic is still controversial (Arseneault et al., 2004), and evidence for affective outcomes is even less clear (Strakowski et al., 2007). Among subjects with bipolar disorder, most studies suggest that cannabis use is associated with deleterious effects, such as greater treatment non-compliance and impaired psychosocial functioning (Goldberg et al., 1999; van Rossum et al., 2009). In addition, patients with bipolar disorder who use cannabis are more likely to have psychotic symptoms (van Rossum et al., 2009), make more frequent suicide attempts (Dalton et al., 2003; Weiss et al., 2005), and show a poorer response to lithium (Goldberg et al., 1999), when compared with bipolar patients who do not use cannabis. In contrast, at least one study has reported that cannabis use is associated with a more complete affective symptom remission in bipolar patients (Strakowski et al., 2007).

Several studies of CUD in schizophrenia have reported a somewhat counterintuitive finding with regard to the effects of comorbid CUD on neurocognitive functioning. Specifically, patients with schizophrenia who use cannabis outperform patients with schizophrenia without comorbid CUD on neurocognitive functions, such as tasks of motor speed, attention, memory and verbal fluency (Yucel et al., 2010; DeRosse et al., 2010). However, the direction of this relationship is unclear and causality has not yet been established. There is a paucity of data on the cognitive effects of comorbid CUD in patients with other severe psychiatric illnesses such as bipolar disorder. The only study that evaluated the relationship between cannabis use and cognition in bipolar disorder patients reported superior performance on a single measure of verbal fluency in 133 bipolar patients with a history of cannabis use when compared to patients with no CUD history (Ringen et al., 2010).

Therefore, the goal of the current study was to further explore the relationship between CUD history in bipolar disorder and neurocognitive functioning. In addition, we compared patient groups on several clinical features to determine the effects of CUD on course of illness.

2. Methods

2.1 Sample

The study cohort was recruited from The Zucker Hillside Hospital (ZHH)-North Shore LIJ Health System (NSLIJHS), in Glen Oaks, N.Y. Subjects included in these analyses were

selected from all patients with a diagnosis of bipolar I disorder for whom we had complete or nearly complete data on measures of interest. Data were collected over a 9 year period (2000- 2009) as a part of a larger genetics study including multiple DSM-IV diagnoses. All subjects provided written informed consent to a protocol approved by the Institutional Review Board of the NSLIJHS. Subjects were between the ages of 18 and 65, with no history of neurological disorders, and no major CNS trauma. Subjects had an estimated premorbid IQ (based on the Wide Range Achievement Test-3rd edition (WRAT-3) Reading subtest) of greater than 70.

2.2 Clinical assessment

Each participant completed the Structured Clinical Interview for the DSM-IV (SCID-IV) administered by trained and reliable raters. Information obtained from the SCID was supplemented by a review of medical records and interviews with family informants when possible, and compiled into a narrative case summary. Primary and secondary diagnoses were then determined by a consensus among a minimum of three expert diagnosticians from the ZHH faculty. All subjects included in the current analyses met full DSM-IV criteria for bipolar I disorder; bipolar II patients were excluded. Cannabis use history was also documented by the SCID interview and patients who met criteria for a history of cannabis abuse or dependence were included in the bipolar disorder with a cannabis use disorder (CUD+) and were compared with bipolar disorder patients who had never met criteria for abuse or dependence (CUD−). Subjects were included with current, early partial, and sustained full remission (data below).

An index of the severity of mood symptoms at the time of assessment was derived from SCID data by summing the scores for each symptom item used to determine diagnostic criteria for current episodes of mania and depression. Ratings on each of the items were recorded based on the subject's report during the interview, observation, as well as medical records. Symptoms at the time of assessment were rated on a scale such that 1 = absent, 2 = subthreshold, and 3 = present at threshold level. Summation of each symptom contributing toward the determination of episode severity captured the overall symptom severity of each polarity at the time of SCID interview.

2.3 Neurocognitive assessment

Participants were administered a battery of standardized cognitive measures comprised of the California Verbal Learning Test (CVLT)-Abridged; Controlled Oral Word Association Test (COWAT); Animal Naming; Wechsler Adult Intelligence Test-Revised (WAIS-R)-Digit Span; and Trail Making Parts A and B. Following common practice in the psychiatric literature (Keefe et al., 2005), we estimated premorbid IQ using the Wide Range Achievement Test-Third Edition-Reading (WRAT-3). The WRAT-3 is a test that assesses single word reading skill which, like command of general knowledge and vocabulary, is particularly resistant to the effects of deterioration associated with brain disease and is considered an estimate of premorbid IQ in patient populations. All participants completed cognitive testing in a single session within one week of the SCID interview.

2.4 Statistical analyses

Analyses compared bipolar patients without a history of comorbid CUD (CUD−) to bipolar patients with CUD (CUD+). Initially, groups were compared on demographic variables including sex, race, parental socioeconomic status (PSES) (Hollingshead, 1975) and family history of psychotic illness using Chi square analyses. Group comparisons of current age, age at onset of bipolar disorder, global assessment of functioning (GAF) score, illness duration, premorbid IQ (as measured by WRAT-3), and education level were carried out using independent t-tests. Any demographic variable that was shown to differentiate groups was used as a covariate in the analysis comparing CUD+ and CUD− groups on symptom and neurocognitive measures using multivariate analyses of covariance (MANCOVAs). Neurocognitive data are presented in raw format (mean and standard deviation) as well as in a z-score scale for graphic presentation and easy interpretation. Z-scores were calculated using a demographically-matched healthy control sample (n=245) for illustrative purposes only.

3. Results

A total of 200 bipolar I patients were included in the analyses; 50 of whom met criteria for a past cannabis use disorder, while 150 never met CUD criteria. Of the 50 with CUD history, 9 subjects met criteria for current abuse/dependence; 5 met for early partial remission; 3 met for early full remission; 13 met for sustained full remission; and the remaining 20 subjects met for remote past CUD. *Demographics:* Patient groups did not differ regarding age, racial background, or highest education level achieved (Table 1). Sex distribution differed significantly among groups such that a larger proportion of patients with a history of CUD (CUD+) were male as compared with patients without CUD history (CUD−) (62% vs 43.3%, p=0.02). *Course of illness*: Bipolar patients with CUD had similar age at onset as patients without CUD (Table 1). CUD groups differed significantly with regard to history of psychosis dring mood episodes such that patients with a history of CUD were more likely to have experienced psychosis at some time during their illness course than patients who never met criteria for a CUD (82% vs 67.3%, x^2= 3.91, p=0.048). Current functioning and clinical severity at the time of assessment: Global assessment of functioning (GAF score) was comparable between groups and the proportion of patients meeting SCID criteria for a current affective episode (symptomatic vs non-symptomatic) was similar (Table 1). Controlling for sex and psychosis history, subjects with or without history of CUD had similar scores on measures of current manic (12.1 +/− 6.3 vs 12.7 +/− 6.1, F=1.9; df=196; p=0.17) and current depressive psychopathology (11.8 +/− 5.5 vs 13.0 +/− 6.7, F=0.04; df= 196; p=0.83), as measured by SCID item severity. *Neurocognitive functioning*: All neurocognitive variables were normally distributed and Levene's Test for Equality of Variance revealed no significant group differences – thus raw data were used for subsequent analyses. The neurocognitive analyses indicated a relatively generalized pattern of superior performance in the CUD+ subjects in comparison with the CUD− subjects. After controlling for variables that differed significantly by cannabis group (sex distribution and psychosis history included as fixed factors), MANCOVAs revealed significant group differences for measures of attention (Digits forward; F=4.1; df= 1,103; p=0.04), processing speed/set-shifting (Trails B; F=4.6; df=1,147; p=0.03), and working memory (Digits Backward;

F=4.7; df=1, 103; p=0.03). On all significant measures, CUD+ subjects performed *better* than CUD− subjects. Figure 1 presents these data on a z-score scale with a mean of zero and standard deviation of one. There were no significant main effects of sex or psychosis history and no significant 2-way or 3-way interaction effects for any of the neurocognitive measures.

In secondary analyses, we tested the hypothesis that perhaps a history of alcohol misuse might explain the somewhat counterintuitive results of the cognitive analyses. Specifically, it could be argued that cognitive deficits in the CUD− subjects when compared with the CUD+ subjects could result from alcohol misuse in the CUD− subjects. On testing this, we found the opposite pattern: CUD+ subjects were much more likely to have a history of alcohol misuse (29/50) as compared with CUD− subjects (36/150; Chi-square = 19.76; df=1; p<0.001). Thus, a higher rate of alcohol use in CUD− subjects cannot explain our neurocognitive results.

4. Discussion

Results from our analysis suggest that subjects with bipolar disorder and history of cannabis use disorders demonstrate significantly better neurocognitive performance, particularly on measures of attention, processing speed, and working memory. These findings are consistent with a previous study that demonstrated that bipolar subjects with history of cannabis use had superior verbal fluency performance as compared to bipolar patients without a history of cannabis use (Ringen et al., 2010). Similar results have also been found in schizophrenia in several studies (Rabin et al., 2011). These data could be interpreted to suggest that cannabis use may have a beneficial effect on cognitive functioning in patients with severe psychiatric disorders. However, it is also possible that these findings may be due to the requirement for a certain level of cognitive function and related social skills in the acquisition of illicit drugs. Therefore, more intact patients may be more likely to successfully acquire cannabis and develop substance use disorders than less cognitively intact patients. This would suggest that the group differences on cognitive performance noted in our study may have been present before the onset of either CUD or bipolar disorder. It should be noted, however, that in our sample individuals with or without history of cannabis use did not differ significantly on estimates of premorbid IQ.

We also found that in our sample of patients with bipolar disorder, a history of cannabis use disorder was associated with an increased rate of psychosis during acute episodes. This observation suggests a more severe clinical presentation for subjects with bipolar disorder and comorbid cannabis use versus bipolar patients who do not use cannabis. These data are consistent with a large prospective study which indicated that bipolar cannabis users demonstrated less treatment compliance and more severe overall illness severity, mania, and psychosis symptoms during 1 year of treatment when compared to non-users. Interestingly, in that study social outcomes were only moderately affected by cannabis use, and in fact users engaged in more social activities than non users (van Rossum et al., 2009). The implications of these findings are difficult to determine. Certainly, results that indicate a worsened course of illness, as marked by more psychosis, contradict the findings of superior cognitive performance in CUD+ subjects. Treatment implications might include the

potential development of pharmacologic agents with similar properties as cannabis, without its psychotomimetic effects, to be tested in cognitive enhancement trials in patients with bipolar disorder or schizophrenia.

Some limitations should be noted. The retrospective design of this analysis and the lack of a quantification variable for history of cannabis use prevent the determination of causality underlying the reported associations. Future prospective studies may help to elucidate the nature of these relationships. Symptom severity at the time of assessment was not characterized with commonly used scales (e.g. Hamilton Rating Scale for Depression). However, we were able to classify patients as symptomatic or non-symptomatic based on current levels of symptomatology from the SCID interview. Finally, it is possible that group differences regarding neurocognitive function might be explicable by differences in secondary clinical characteristics of the groups such as frequency of antipsychotic drug use or duration of illness. Nonetheless, the groups were similar in most relevant clinical features and results remained significant after correction for variables with significant between-group differences. Multiple testing is a concern in many studies making group comparisons across multiple cognitive and clinical measures, and this study is no exception. Nonetheless, we felt that the comprehensive analyses outweighed the reduced power due to multiple tests.

Despite potential limitations, these analyses indicate an interesting pattern suggesting superior neurocognitive performance among bipolar patient with comorbid CUD when compared to bipolar patients with history of cannabis use. Moreover, this cognitive advantage is noted in spite of evidence of a more severe clinical course. These results extend previous findings of similar studies reported in patients with schizophrenia and add significantly to the limited literature on cannabis use in bipolar illness. We hope that the results from our study will help guide and encourage future large studies and help further elucidate the multifaceted associations and possible impact of cannabis use in bipolar disorder.

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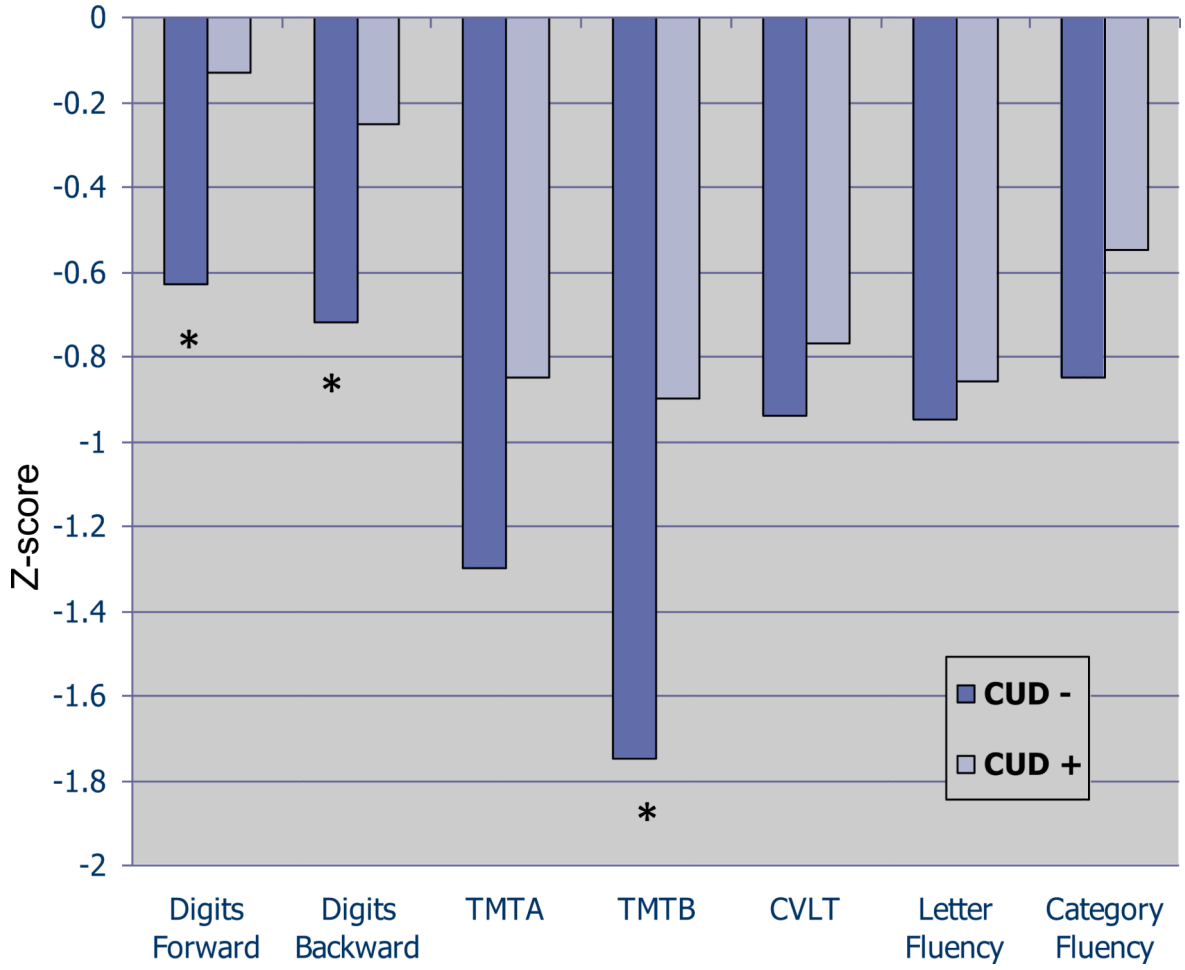

Figure 1. Neurocognitive performance by history of Cannabis Use

Subjects with history of cannabis use demonstrated significantly *better* performance on measures of attention (Digits forward; F=4.1; df= 1,103; p=0.04), processing speed/ setshifting (Trails B; F=4.6; df=1,147; p=0.03), and working memory (Digits Backward; F=4.7; df=1, 103; p=0.03).

Table 1

Clinical and Demographic Characteristics of the Sample

Characteristics	CUD +	CUD –	Statistic, df (p-value)
Age	34.3(12.5)	37.5(12.1)	t= 1.6, 198 (0.11)
Sex-Male (%)	62%	43.3%	Chi^2= 5.24,1 **(0.02)**
Race - White (%)	66%		Chi^2= 0.03, 1 (0.86)
Education (yrs)	13.8 (2%)	14.4 (2.3)	t= 1.34, 151 (0.18)
Parental Socioeconomic status (Hollingshead Index)	2.6 (1.2)	2.6(0.8)	t=0.55, 147 (0.58)
Estimated premorbid IQ	98.02 (9.19)	96.4(11.1)	t= 0.80, 137 (0.42)
GAF score	46.2 (14.7)	44.14 (14.6)	t= 0.6, 94 (0.55)
Duration of illness (yrs)	13.0 (10.8)	15.0 (11.3)	t= 1.11, 198 (0.27)
Age of onset	21.3 (7.2)	22.5 (8.4)	t= 1.02, 198 (0.32)
History of psychosis (%)	82.0%	67.3%	Chi^2= 3.92, 1 **(0.05)**
Family history of Psychosis (%)	22.8%	25.0%	Chi^2= 0.48, 1 (0.49)
Mean number of drugs	3.54 (2.8)	2.89 (2.5)	t= 1.54, 198 (0.13)
Antipsychotic use (%)	93.8%	73.6%	Chi^2 = 2.14,1(0.14)
Anticonvulsants use (%)	58.5%	56.9%	Chi^2= 0.03 (0.86)
Lithium use (%)	36.6%	33.1%	Chi^2= 0.171, 1 (0.68)
Clinically symptomatic at time of assessment (%)	46%	59.9%	Chi^2= 2.92, 1 (0.09)

Table 2

Descriptive Raw Neurocognitive Data by Group

Test	Cannabis History	N	Mean	Std. Deviation
Trails A (Time)	Absent	107	46.22	39.35
	Present	44	36.56	19.66
Trails B (Time)	Absent	104	120.77	71.25
	Present	44	93.32	61.70
Digits Forward	Absent	75	6.25	1.40
	Present	29	7.00	1.28
Digits Backward	Absent	75	4.23	1.24
	Present	29	4.93	1.58
CVLT Learning	Absent	98	41.19	11.51
	Present	42	43.00	12.83
Letter Fluency	Absent	105	32.00	11.78
	Present	44	33.07	12.40
Animal Fluency	Absent	97	17.57	5.71
	Present	43	19.14	6.39