**Evaluation of the effect of alcohol and illicit substance use on verbal memory of subjects with bipolar disorder** *Running title:* Cognition in bipolar disorder and substance use disorder

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**Abstract**

*Background:* Cognitive impairment is a well-established feature of bipolar disorder (BD). Comorbid BD and substance use lead to poor psychosocial and clinical outcomes. However, the knowledge on the neurocognitive functioning of individuals with dual diagnosis is still scarce. Thus, the aim of this study is to assess the cognitive performance of subjects with bipolar disorder, bipolar disorder plus alcohol use disorder, and bipolar disorder plus illicit substance use disorder as compared to healthy controls.

*Methods:* This was a cross-sectional study. Patients were recruited from clinics of the University of Texas Health Science Center at San Antonio (UTHSCSA) and at the University of North Carolina at Chapel Hill (UNC). Healthy participants were recruited via oral presentations and flyers. The diagnostic of Bipolar Disorder and substance use disorder was assessed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I). Demographic and clinical information were also collected. The cognitive assessment included the Wechsler Test of Adult Reading (Wtar), California Verbal Learning Test (CVLT).

*Results:* The sample included 134 BD patients (100 female, M±S.E: 37.37±12.74 years), 72 BD patients with lifetime alcohol use disorder (40 female, M±S.E: 38.42±11.82), 64 BD patients with lifetime illicit substance use disorder (39 female, M±S.E: 34.50±10.57), and 211 healthy controls (127 female, M±S.E: 34.80±12.57 years). Compared to HC, BD patients with and without a lifetime of substance use showed a significant impairment in verbal memory, in addition, specifically on recognition domain of CVLT test, BD+AUD (p=0.0203) and BD+SUD (p= 0.0434) showed higher impairment compared to controls, and no difference were found comparing BD without comorbidity (p=0.2157) and controls.

*Conclusions:* Our results are consistent with previous reports of verbal memory impairment in BD.

*Keywords:* cognitive, bipolar disorder, substance use, verbal memory, STAN

**Introduction**

Based on epidemiological studies the prevalence of bipolar disorder (BD) in the general population ranges from 1.1% to 3.8% ([Kozloff, Cheung et al. 2010](#_ENREF_29), [Hoertel, Le Strat et al. 2013](#_ENREF_24), [Subramaniam, Abdin et al. 2013](#_ENREF_41)). Further, BD appears to be the highest rate of substance abuse among mood disorders. Indeed, at least a 40% of patients with BD-I have a lifetime comorbidity with alcohol and other substance use disorder, and the prevalence of this comorbidity is at least 20% of patients with BD-II ([Cerullo and Strakowski 2007](#_ENREF_12)).

Alongside mood disturbance cognitive deficits are core features of the disorder in both acute and euthymic states ([Eric, Halari et al. 2013](#_ENREF_17)), that are also observed in relatives of BD ([Bora, Yucel et al. 2009](#_ENREF_7)) compared to healthy controls. In particular, BD patients perform poorly on tests of visuomotor processing speed, verbal memory, sustained attention and executive functioning. Impairments of smaller effect size in visual and verbal memory, working memory, and sustained attention have also been reported ([Goldberg, Gold et al. 1993](#_ENREF_23), [Albus, Hubmann et al. 1996](#_ENREF_1), [Quraishi and Frangou 2002](#_ENREF_36), [Martínez-Arán, Vieta et al. 2004](#_ENREF_33), [Bora, Yucel et al. 2009](#_ENREF_8)). Systematic reviews showed that during the acute phase individuals with BD display significant impairment in cognitive flexibility, while remitted BD patients showed deficit in working memory ([Dixon, Kravariti et al. 2004](#_ENREF_16), [Aminoff, Hellvin et al. 2013](#_ENREF_2), [Daglas, Yucel et al. 2015](#_ENREF_15)). Notably in these studies patients had recently experienced their first mania episode and were compared to groups of healthy controls.

The presence of substance use disorders has detrimental effects on both the clinical profile and cognitive functioning of patients with BD ([Salloum and Thase 2000](#_ENREF_39)) but only a small number of studies have focused on the contribution of alcohol and illicit drug use on the neurocognitive profile of BD patients has received limited attention. A recent systematic review including eight studies comparing neurocognitive functioning in BD with and without current or past alcohol use disorder (AUD) showed that BD with AUD displayed more cognitive impairment, specifically in verbal memory and executive functions, than the bipolar disorder patients without AUD ([Balanzá-Martínez, Crespo-Facorro et al. 2015](#_ENREF_4)). A history of SUD has been associated with increased impairment in executive functions and inhibition skills ([van Gorp, Altshuler et al. 1998](#_ENREF_46), [Sanchez-Moreno, Martinez-Aran et al. 2009](#_ENREF_40), [Houston, Derrick et al. 2014](#_ENREF_25)) and poorer visual memory and conceptual reasoning/set-shifting compared to patients with BD without SUD ([Marshall, Walker et al. 2012](#_ENREF_32)). Findings are however still controversial as a study found no association between cognitive functioning in patients with BD and AUD ([Van Der Werf-eldering, Burger et al. 2010](#_ENREF_44)).

Recent studies have associated the decline in neurocognitive functioning typically observed in BD with the concept of “neuroprogression” which refers to processes of increased stress vulnerability and brain atrophy ([Kapczinski, Vieta et al. 2008](#_ENREF_27), [Kapczinski, Dias et al. 2009](#_ENREF_26), [Berk, Conus et al. 2010](#_ENREF_6)). The concept of “staging” has also been applied to the pathophysiology of BD to explain the progressive decline in mental health, cognitive ([Bauer, Pascoe et al. 2014](#_ENREF_5), [Cardoso, Bauer et al. 2015](#_ENREF_11)) and psychosocial functioning over the course of the disease ([Robinson and Ferrier 2006](#_ENREF_37), [Pettorruso, De Risio et al. 2014](#_ENREF_34)). Given the harmful consequences of SUD to brain function and physical health it is possible that individuals with dual diagnosis are at greater risk for developing a more severe illness profile including neuroanatomical abnormalities, cognitive deficits and clinical symptoms.

Post et al. (2013), postulated that the cross-sensitization among stressors, episodes and substance misuse can contribute to illness progression ([Post and Kalivas 2013](#_ENREF_35)). In addition, Rosa et al (2014) showed a worse cognitive performance in subjects with bipolar disorder in late stage of illness as compared to healthy controls, in contrast, subjects with bipolar disorder in early stage of illness have a similar cognitive performance as compared to healthy controls ([Rosa, Magalhaes et al. 2014](#_ENREF_38)). However, the role of substance use disorder comorbidity on cognition of subjects with bipolar disorder has received a limited attention. Thus, the aim of the current study is to assess the cognitive performance of subjects with bipolar disorder, bipolar disorder plus alcohol use disorder, bipolar disorder plus illicit substance use disorder, as compared to healthy controls.

([Yatham, Kennedy et al. 2009](#_ENREF_47))([Glahn, Almasy et al. 2010](#_ENREF_19))([Glahn, Almasy et al. 2010](#_ENREF_18), [Cherkil, Satish et al. 2012](#_ENREF_14))([Glahn, Almasy et al. 2007](#_ENREF_20), [Glahn, Bearden et al. 2007](#_ENREF_21), [Chaves, Lombardo et al. 2011](#_ENREF_13), [Cherkil, Satish et al. 2012](#_ENREF_14))

**Methods**

This is a cross-sectional study. Patients were recruited from inpatient and outpatient clinics of the University of Texas Health Science Center at San Antonio (UTHSCSA) and at the University of North Carolina at Chapel Hill (UNC). Healthy participants were recruited via oral presentations and flyers. Specific inclusion criteria for healthy controls were: no current or lifetime axis I psychiatric diagnose, previous history of neurologic disorders including head injury with loss of consciousness for any period of time, pregnancy, family history of hereditary neurologic disorder, psychiatric disorder in first-degree relatives, use of any prescribed psychiatric medication in their lifetimes. The study protocol was approved by the Institutional Review Board and informed consent was obtained from all the participants.

All participants underwent the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I) to confirm or rule out the diagnosis of BD ([Association 2000](#_ENREF_3)). Clinical characteristics, such as: current use of psychiatric medication, current mood state, age of illness onset, and number of hospitalizations were assessed on the clinical interview. In addition, we use the Hamilton Depression Rating Scale (HDRS) to assess the severity of depressive symptoms and Young Mania Rating Scale (YMRS) to assess the severity of manic symptoms.

*Cognitive performance*

All participants were administered the Wechsler Test of Adult Reading (WTAR), which is a measure of premorbid intellectual quotient (IQ) (66). ([Glahn, Almasy et al. 2010](#_ENREF_19))([Glahn, Almasy et al. 2010](#_ENREF_18), [Cherkil, Satish et al. 2012](#_ENREF_14))([Glahn, Cannon et al. 2000](#_ENREF_22))And the revised version of the *CVLT* – a standardized test measuring verbal learning and declarative memory via a trial list-learning paradigm (67). In the CVLT task participants are presented orally with 16 words for 5 times and asked to recall as many words as possible in any order (immediate recall). After being presented with an intrusion list (List B), participants are asked to recall the words included in the List A one more time via cues (short delay cued recall) and without cues CVLT short-delay (free recall). After a 20-minute delay participants are asked to recall words from List A both with the aid of categorical cues (long delay cued recall) and spontaneously (long delay free recall). Scores of each CVLT variable represented the number of correctly recalled words.

*Statistical analysis*

Statistical analyses were performed using SPSS Statistics (IBM - version 21) and SAS v. 9.3 (SAS Institute Inc., Cary, N.C.). Demographic characteristics and cognitive scores of the STAN of patients with BD, BD+AUD and BD+SUD and healthy controls were compared using *χ2*, ANOVA, Mann-Whitney U test, and Kruskal Wallis test. SAS PROC MEANS and PROC FREQ were used to screen the data.

The present analyses utilized a three-step approach to examine multivariate differences between individuals grouped by one of four bipolar diagnoses (healthy control, bipolar, bipolar with alcohol use disorder, bipolar with substance use disorder) in the South Texas Assessment of Neurocognition (STAN). The first step was to eliminate uninformative variables (i.e., those variables with zero variance) and to reduce the dimensionality of the dataset by creating composites. The second step employed principal components analysis (PCA) to further reduce the dimensionality of the composite variables. The third step was to examine group differences via profile analysis, following guidelines described by Tabachnik and Fidell (2001). This analysis provides two advantages over traditional univariate analyses. The first advantage is that profile analysis statistically accounts for correlations between the dependent measures of interest. The second advantage is that this analysis does not require correction for Type I error in the same manner as separate univariate analyses. A follow-up profile analysis examined group differences in the California Verbal Learning Test (CVLT), which itself is a subcomponent of the STAN, without the use of principal components analysis for data reduction. All analyses were conducted using SAS v. 9.3 (SAS Institute Inc., Cary, N.C.).

Three tests provide the statistical argument in profile analysis: flatness, levels, and parallelism. The flatness test examines differences in instrument components, collapsed across group membership. This effect is typically only relevant with time-series data; that is, statistically reliable differences across components (irrespective of group membership) would not be particularly relevant to the present analyses, and as such this effect can safely be ignored. The levels test examines overall differences in group membership, collapsed across all instrument components. In essence, this is a test of the main effect of bipolar diagnosis group assignment. The parallelism test examines whether groups have different patterns across the instrument components, akin to an interaction between flatness and levels. This test is considered the most important here, as it tests whether the groups have significantly different profiles. Follow-up tests of profile analysis typically include univariate tests of group differences (controlling for Type I error) to further examine any statistically reliable findings for flatness, levels, and/or parallelism ([Tabachnick and Fidell 2001](#_ENREF_43)).

Tests of normality, linearity, multicollinearity and homogeneity of covariance assumptions were performed. The cognitive profile of all groups was compared using a profile analysis – a multivariate alternative to repeated measure ANOVAs - with age, sex and education included as covariates. This type of analysis accounts for correlations between variables (in this case the STAN variables) and is treated as an individual test. Thus, multiple comparison corrections are not needed. *Post-hoc* t-test analyses were performed to compare variables scores between BD, BD+AUD, BD+SUD and HC using an FDR-corrected statistical threshold (*p*=0.0064).

**Results**

*Demographics and clinical description*

Our study sample included 134 BD patients (100 female, M±S.E: 37.37±12.74 years), 72 BD patients with lifetime alcohol use disorder (40 female, M±S.E: 38.42±11.82), 64 BD patients with lifetime illicit substance use disorder (39 female, M±S.E: 34.50±10.57), and 211 healthy controls (127 female, M±S.E.: 34.80±12.57 years). 113 BD patients (56 BD, 31 BD+AUD, 26 BD+SUD) were on psychiatric medication (mood stabilizer, antipsychotics, antidepressants, anticonvulsants, benzodiazepines, and stimulants) at the time of assessment. Demographics and clinical features for BD, BD+AUD, BD+SUD, and HC are reported in Table 1. There was significant difference in gender, years of education, ethnicity, and current employ between the four groups. There was a trend to significant difference between groups regarding age (p=0.061). Regarding the clinical features between BD groups, we found significant difference in number of hospitalization (p=0.029), individuals with BD+SUD have significantly higher number of hospitalization as compared to BD without comorbidity (p=0.032) as well as compared to BD+AUD (p=0.014). We also verified a difference between BD groups regarding the age of onset of BD (p=0.043), BD+SUD showed an early onset of illness compared to BD (trend to significance: p=0.053). There was a trend to significant difference in current mood state between BD groups (p=0.097). There was no difference about the current use of psychiatric medication (p=0.828), severity of depressive symptoms (p=0.123), and severity of manic symptoms (p=0.439) (Table 1).

*Cognitive assessment* Regarding Wechsler Test of Adult Reading test, there was no significant difference between BD groups and healthy controls (p=0.265) (Table 1).

A profile analysis examined group differences across subtests of the California Verbal Learning Test (CVLT). The CVLT is comprised of scores on six indicators: total score composite (# of correct responses across 5 trials), short delay-free recall, short delay-cued recall, long delay-free recall, long delay-free cued recall, and recognition. This profile analysis reduces the complexity of the analyses by eschewing the principal components analysis entirely. After controlling for the effects of sex, age, and education, parallelism for the subtest by bipolar diagnosis group was not statistically reliable: *F*(15,729.19) = 1.37, *p* = 0.1574. The tests of levels (group differences) yielded statistically reliable findings: *F*(3,268) = 2.72, *p* = 0.0447. Post-hoc tests examined the group differences within subtests in univariate fashion; after Tukey correction for Type I error, three of these effects were statistically reliable: in the total score indictor of the CVLT, the control group was reliably different from the bipolar group (*p* = 0.0362) and the bipolar with AUD group (*p* = 0.0151). In the recognition indicator of the CVLT, the control group was reliably different from the bipolar with alcohol use disordergroup (*p* = 0.0203). Table 4 provides a summary of the post hoc testing from the CVLT profile analysis.

**Table 1:** Sociodemographic and clinical characteristics between groups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variables** | **HC**  **n=211** | **BD**  **n=134** | **BD+AUD**  **n=72** | **BD+SUD**  **n=64** | ***p*-value** |
| **Gender#**  Male  Female | 84 (39.8%)  127 (60.2%) | 34 (25.4%)  100 (74.6%) | 32 (44.4%)  40 (55.6%) | 24 (38.1%)  39 (61.9%) | 0.017 |
| **Age+** | 34.80±12.57 | 37.37±12.74 | 38.42±11.82 | 34.50±10.57 | 0.061 |
| **Years of education+** | 16.08±3.03 | 14.08±2.90 | 14.30±3.52 | 13.95±2.56 | <0.001 |
| **Ethnicity#**  Hispanic or latino  Non-Hispanic or latino | 72 (34.8%)  135 (65.2%) | 25 (20.2%)  99 (79.8%) | 17 (23.9%)  54 (76.1%) | 14 (22.6%)  48 (77.4%) | 0.018 |
| **Currently employed#**  No  Yes | 81 (39.1%)  126 (60.9%) | 75 (59.1%)  52 (40.9%) | 36 (53.7%)  31 (46.3%) | 32 (51.6%)  30 (48.4%) | 0.003 |
| **Current medication\*,#**  No  Yes | 211 (100%)  - | 73 (56.6%)  56 (43.4%) | 39 (55.7%)  31 (43.3%) | 37 (58.7%)  26 (41.3%) | <0.001 |
| **Current mood state\*\*,#**  Euthymic  Current mood episode | 211 (100%)  - | 46 (35.7%)  83 (64.3%) | 15 (21.1%)  56 (78.9%) | 19 (29.7%)  45 (70.3%) | <0.001 |
| **Age of onset BD+, ##** | - | 32.99±12.57 | 29.15±12.27 | 26.91±10.76 | 0.043 |
| **Number of hospitalizations++, ###** | - | 0.00 (0.00 - 1.00) | 0.00 (0.00 - 1.00) | 1.00 (0.00 - 2.00) | 0.029 |
| **HDRS score++** | - | 13.00 (5.00 - 19.00) | 15.00 (9.00 - 20.00) | 12.00 (6.00 - 18.50) | 0.123 |
| **YMRS score++** | - | 4.00 (1.00 - 8.00) | 5.00 (2.00 - 10.00) | 4.00 (1.00 - 10.25) | 0.439 |
| **WTAR+** | 39.53±8.34 | 37.22±8.95 | 39.18±8.30 | 38.40±8.01 | 0.265 |

\*No significantly difference between BD groups (p=0.828); \*\*Trend to significantly difference between BD groups (p=0.097).

**#**Differences assessed by chi-square test; **+**Mean and standard deviation, differences assessed by ANOVA test; **++**Median and interquartile range, differences assessed by kruskal wallis test.

##Differences assessed by bonferroni test: BD vs BD+SUD (p=0.053).

###Differences assessed by Mann-Whitney U test: BD vs BD+SUD (p=0.032) and BD+AUD vs BD+SUD (p=0.014).

**Legend:** Healthy Control (HC), Bipolar Disorder (BD), Alcohol Use Disorder (AUD), Illicit Substance Use Disorder (SUD), Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS), Wechsler Test of Adult Reading (WTAR).







*Figure 1 – CVLT Profile Analysis*

*Table 2 – CVLT Profile Analysis - Post Hoc Testing*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Tukey Adjusted P-Values** | | | | |
|
| **Total Score** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.0362 | 0.0151 | 0.1037 |
| Bipolar | 0.0362 |  | 0.9205 | 1 |
| Bipolar w/ Alc | 0.0151 | 0.9205 |  | 0.9546 |
| Bipolar w/ SUD | 0.1037 | 1 | 0.9546 |  |
| **Short Delay - Free Recall** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.0871 | 0.8314 | 0.5406 |
| Bipolar | 0.0871 |  | 0.7095 | 0.9428 |
| Bipolar w/ Alc | 0.8314 | 0.7095 |  | 0.9732 |
| Bipolar w/ SUD | 0.5406 | 0.9428 | 0.9732 |  |
| **Short Delay - Cued Recall** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.5995 | 0.9291 | 0.6348 |
| Bipolar | 0.5995 |  | 0.976 | 0.9989 |
| Bipolar w/ Alc | 0.9291 | 0.976 |  | 0.9592 |
| Bipolar w/ SUD | 0.6348 | 0.9989 | 0.9592 |  |
| **Long Delay - Free Recall** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.2508 | 0.6845 | 0.5149 |
| Bipolar | 0.2508 |  | 0.9726 | 0.999 |
| Bipolar w/ Alc | 0.6845 | 0.9726 |  | 0.9942 |
| Bipolar w/ SUD | 0.5149 | 0.999 | 0.9942 |  |
| **Long Delay - Free Cued Recall** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.2508 | 0.6845 | 0.5149 |
| Bipolar | 0.2508 |  | 0.9726 | 0.999 |
| Bipolar w/ Alc | 0.6845 | 0.9726 |  | 0.9942 |
| Bipolar w/ SUD | 0.5149 | 0.999 | 0.9942 |  |
| **Recognition** | | | | |
|  | Control | Bipolar | Bipolar w/ Alc | Bipolar w/ SUD |
| Control |  | 0.2157 | 0.0203 | 0.0434 |
| Bipolar | 0.2157 |  | 0.6617 | 0.776 |
| Bipolar w/ Alc | 0.0203 | 0.6617 |  | 0.9989 |
| Bipolar w/ SUD | 0.0434 | 0.776 | 0.9989 |  |

**Discussion**

The current study examined the cognitive functioning of patients with and without a history of substance use (alchol / illicit drugs), and HC using CVLT test. Compared to HC our BD patients, regardless of their substance use comorbidities, demonstrated impaired verbal memory abilities. In addition, specifically on recognition domain of CVLT test, subjects with BD plus substance use disorder (alcohol / illicit drugs) demonstrated a higher impairment as compared to healthy controls, and no differences were found for BD without comorbidity compared to controls. These results indicated that substance use disorder comorbidity affect specifically the recognition domain.

Our results are consistent with Bora et al.’s meta-analytical review of 12 cognitive studies that found impairments of large effect size in verbal memory in BD ([Bora, Yücel et al. 2011](#_ENREF_9)), in particular deficits in both immediate and delayed recall ([Martínez-Arán, Vieta et al. 2004](#_ENREF_33), [Bora, Yucel et al. 2009](#_ENREF_8)). In line with these findings a previous study using the STAN battery showed a deficits in recall and recognition that approached significance ([Chaves, Lombardo et al. 2011](#_ENREF_13)). In another paper CVLT performance was impaired in individuals with bipolar disorder ([Glahn, Almasy et al. 2010](#_ENREF_19)). Another study found that relative to hypomanic, depressive and euthymic BD patients, manic patients present with extensive deficits in immediate and delayed verbal and visual memory (measured by the California Verbal Learning Test – CVLT and the logical memory and visual reproduction subtests of the Wechsler Memory Scale) ([Sweeney, Kmiec et al. 2000](#_ENREF_42)). Furthermore, our clinical sample was heterogeneous and included patients with BD Types I, II and NOS.

Studies have investigated the cognitive performance in subjects with bipolar disorder and alcohol use disorder comorbidity. A study verified that subjects with bipolar disorder, independently of comorbidity, have presented a worse performance on verbal memory compared to healthy controls, in addition, subjects with bipolar disorder and history of alcohol dependence had an additional decrements in executive functions compared to healthy controls ([van Gorp, Altshuler et al. 1998](#_ENREF_45)). Another study showed that subjects with bipolar disorder and alcohol dependence comorbidity presented a more severe impairment on tests of executive functioning than subjects with BD without that comorbidity, in addition, the study showed that subjects with BD and alcohol dependence in the past six months, showed a worse performance in verbal and visual memory as compared to subjects with BD without comorbidity ([Levy, Monzani et al. 2008](#_ENREF_31)). In the same way, another study showed a higher impairment in executive functioning and verbal memory in subjects with bipolar disorder and alcohol dependence comorbidity when compared to subjects with BD without substance use disorder comorbidity, in addition, they found that subjects with BD and alcohol dependence comorbidity have an early onset of illness and more hospitalizations than subjects with BD without SUD comorbidity([Levy, Manove et al. 2012](#_ENREF_30)). However, another study showed that both bipolar disorder with alcohol abuse or dependence comorbidity and bipolar disorder without alcohol abuse or dependence comorbidity presented a poor performance in verbal memory and executive function as compared to healthy controls, the authors discussed that probably the cognitive function appears to be more strongly associated with BD than with the history of alcohol abuse or dependence factor ([Sanchez-Moreno, Martinez-Aran et al. 2009](#_ENREF_40)). This finding is similar to ours, because we found impairment on verbal memory associated with BD, independently of alcohol use disorder, except for a recognition domain that is impaired in BD with alcohol use disorder and not in BD without comorbidity, both as compared to controls. Additionally, a recent systematic review including eight studies found that BD patients with current or past history of alcohol use disorder showed a more severe impairment in verbal memory and executive functions than the subjects with BD without comorbidity ([Balanzá-Martínez, Crespo-Facorro et al. 2015](#_ENREF_4)).

Besides the comorbidity between bipolar disorder and alcohol use disorder has been studied and the studies have showed the cognitive impairment associated with this comorbidity, a few studies have assessed the cognitive impairment in bipolar disorder with illicit substance use disorder comorbidity. Marshall et al. (2012), showed that BD with lifetime history of SUD (including alcohol and illicit substances) exhibited significantly worse performance than BD without SUD in visual memory and conceptual reasoning/set-shifting ([Marshall, Walker et al. 2012](#_ENREF_32" \o "Marshall, 2012 #116)). Controversially, another study showed that subjects with bipolar disorder and a history of cannabis use disorder demonstrated significantly better performance on measures of attention, processing speed, and working memory, as compared to patients with BD without history of cannabis use disorder ([Braga, Burdick et al. 2012](#_ENREF_10" \o "Braga, 2012 #74)). Our findings indicated that the history of illicit substance use disorder is associated with impairment in recognition as compared to healthy controls, and no difference was observed for comparison between BD without comorbidity and healthy controls.

Our findigns can be interpretated in the light of neuroprogression, once that substance misuse can contribute to illness progression ([Post and Kalivas 2013](#_ENREF_35" \o "Post, 2013 #9)), and worse cognitive performance is associated with illness progression ([Rosa, Magalhaes et al. 2014](#_ENREF_38" \o "Rosa, 2014 #34)), our results add to existent literature showing that the impairment in verbal memory (specifically on recognition) is worse in subjects with BD and substance use disorder comorbidity compared to controls.

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