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Effect of alcohol and illicit substance use on verbal memory among individuals with bipolar disorder

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Abstract

Background—Cognitive impairment is a well-established feature of bipolar disorder (BD). Comorbid BD and substance use leads to poor psychosocial and clinical outcomes. However, knowledge on the neurocognitive functioning of individuals with dual diagnosis is limited. The aim of this study is to assess the cognitive performance of subjects with BD, BD with comorbid alcohol use disorder (AUD), and BD with comorbid illicit substance use disorders (SUD) as compared to healthy individuals.

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Conflict of interest

Drs Cardoso, Bauer, Suchting, Jansen, Zunta-Soares, Quevedo, Glahn have no conflicts of interest with respect to this paper.

Contribution

GZS and JCS designed the study, wrote the protocol and collected the data. RS, TC, IB, KJ undertook the statistical analysis, and TC and IB wrote the first draft of the manuscript. DG and JQ provided statistical consulting and helped finalize the manuscript. All authors contributed to and have approved the final manuscript.

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Methods—We included 270 inpatients and outpatients with BD and 211 healthy controls. The diagnostic of BD and substance use disorder was assessed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I. Demographic and clinical information were also collected. The cognitive assessment included the Wechsler Test of Adult Reading (WTAR), and a revised version of the California Verbal Learning Test (CVLT) as part of the South Texas Assessment of Neurocognition (STAN).

Results—The STAN was administered to 134 BD patients (100 female, M±SD: 37.37±12.74 years), 72 BD patients with AUD (40 female, M±SD: 38.42±11.82), 64 BD patients with SUD (39 female, M±SD: 34.50±10.57), and 211 healthy controls with no lifetime history of mental illness and substance use (127 female, M±SD: 34.80±12.57 years). In terms of clinical characteristics, BD+SUD showed a marginally earlier onset of illness compared to BD. Compared to HC, BD performed poorly in the immediate recall and short-delay free tests of the CVLT, while BD patients with AUD and SUD showed significant memory deficits in both the immediate recall and recognition components of the CVLT. There were no differences in memory performance between BD and BD with either AUD or SUD.

Conclusions—A history of substance use disorders is associated with an earlier onset of BD. BD has marked effects on processes underlying the encoding of new information, while comorbid substance use in BD impairs more specifically the recognition of previously presented information. Future longitudinal studies should evaluate the effects of AUD and SUD on illness progression and therapeutic outcomes.

Keywords

cognitive; bipolar disorder; substance use; verbal memory; South Texas Assessment of Neurocognition (STAN)

1. Introduction

Bipolar disorder (BD) has the highest rate of substance abuse among mood disorders (Asaad et al., 2014; Merikangas et al., 2007). Approximately 40% of patients with BD-I have a lifetime comorbidity with alcohol (AUD) and illicit substance use disorder (SUD), and the prevalence of this comorbidity is around 20% in patients with BD-II (Cerullo & Strakowski, 2007). Dual diagnosis is associated with reduced brain function, poor psychosocial health, and is a predictor of poor clinical outcome (Nery et al., 2013; Tolliver & Hartwell, 2012). This may be particularly costly for BD patients given the pre-existing cognitive deficits that persist across the acute and euthymic phases (Eric, Halari, Cheng, Leung, & Young, 2013). Despite the negative implications of a dual diagnosis, research on the effects of comorbid substance use disorder on the cognitive functioning of BD patients is surprisingly limited.

BD and substance use disorders share common cognitive deficits (Balanzá-Martínez, Crespo-Facorro, González-Pinto, & Vieta, 2015; Gould, 2010; Salloum & Thase, 2000). BD patients typically perform poorly on tests of visuomotor processing speed, verbal memory, sustained attention and executive functioning (Martínez-Arán et al., 2014; Lucy J. Robinson et al., 2006). Impairments of smaller effect size in visual memory, working memory, and sustained attention have also been reported (Albus et al., 1996; Bora, Yucel, & Pantelis,

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2009; Goldberg et al., 1993; Martínez-Arán et al., 2004; Quraishi & Frangou, 2002). In particular, deficits in verbal memory have been found to persist across mood phases, which may indicate that these deficits are traits markers of BD (Gualtieri & Johnson, 2006). Along with neurocognitive impairment, BD has been associated with abnormalities in a range of brain regions (Cao, Bauer, et al., 2016; Javadapour et al., 2010; Radaelli et al., 2015) including the hippocampus, a core region for declarative memory (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000).

Similar cognitive complaints have been observed in BD patients with comorbid substance use disorders. A systematic review including eight studies comparing neurocognitive functioning in BD with and without current or past AUD showed that BD with AUD display deficits in verbal memory and executive functions when compared to BD patients without AUD (Balanzá-Martínez et al., 2015). A history of substance use disorder has also been associated with reduced inhibition, poor visual memory and conceptual reasoning/set-shifting compared to patients with BD without past history of substance use (Houston et al., 2014; Marshall et al., 2012; Sanchez-Moreno et al., 2009; van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998). Findings are however still controversial as at an appropriately powered study including BD patients with past and current lifetime use disorders found no link between cognitive impairment, more specifically in the memory domain, and AUD in BD patients (Van Der Werf-Eldering, Burger, Holthausen, Aleman, & Nolen, 2010).

A methodological limitation of current cognitive studies in BD and substance use disorders is related to the heterogeneity of instruments used to assess cognitive functions found to be impaired in BD, such as verbal and working memory, psychomotor speed, executive function, and attention (Bora et al., 2009; Yatham et al., 2009). Further, given that disorders such as BD and alcohol and drug use have been associated with memory deficits, a thorough assessment of multiple memory components such as encoding, recall, and retrieval may be required to better identify group differences. For this reason, in this study we used a revised version of the California Verbal Learning Test (CVLT) – a standardized test widely used in neuropsychological and research settings that measures verbal learning and declarative memory via a trial list-learning paradigm (Donders, 2008). This version of the CVLT is part of the South Texas Assessment of Neurocognition (STAN) - a validated computerized cognitive battery (Glahn et al., 2007). Notably, the STAN version of the CVLT has been used in clinical and genetic studies in individuals with BD and psychosis (Chaves et al., 2011; Cherkil et al., 2012; Glahn, Almasy, et al., 2007; Glahn, Bearden, et al., 2007). It has not, however, been used in populations with dual diagnosis. Previous studies also differ in terms of exclusion criteria (e.g. concomitant use of alcohol and other illicit drugs, current versus past history of substance use disorder), quantification of alcohol and drug intake (e.g. urine vs self-report), mood phase of BD, and health status (e.g. in some studies cardiovascular disease was not an exclusion criteria).

The biological mechanisms underlying cognitive deficits in BD have previously been associated with mechanisms of “neuroprogression” such as inflammatory processes including oxidative stress and increased stress vulnerability. These factors have been hypothesized to lead to a decline in mental health, reduced cognition, brain atrophy (Bauer, Pascoe, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014; Berk et al., 2010; F. Kapczinski

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et al., 2009; Flavio Kapczinski et al., 2008) and poor psychosocial functioning (Pettorruso et al., 2014; Post & Kalivas, 2013; L. J. Robinson & Ferrier, 2006). Given the small number of longitudinal studies in this field the trajectory of cognitive functioning during the course of the BD is, however, still unclear (Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015). Similarly, substance use disorders have been linked to brain abnormalities and cognitive impairment. Potential biological mechanisms underlying these changes are the neurotoxic effects of alcohol and other substances on the brain (Gupta & Warner, 2008; Momenan et al., 2012; Rocchetti et al., 2013). Although abstinence leads to an overall improvement in clinical outcome and cognitive abilities, it is unknown whether other brain functions return to baseline functioning (Medina, Shear, Schafer, Armstrong, & Dyer, 2004). It becomes apparent that research in dual diagnosis is still in its infancy. Additional research is, therefore, needed to distinguish more “permanent” cognitive sequelae associated with BD from potentially more “temporary” cognitive deficits resulting from substance use.

Considering the cognitive profile of patients with BD and those with substance use disorders it could be postulated that the interaction between BD and substance use leads to an even more compromised cognitive functioning in BD patients (Post & Kalivas, 2013). In the current study we test this hypothesis by comparing the memory performance of BD patients with and without AUD or SUD to a group of healthy controls (HC). Given the dearth of findings related to specific cognitive sequelae associated with alcohol and illicit drug use in BD we adopted an exploratory approach when comparing BD with AUD to BD with SUD.

2. Methods

Our study sample included 134 BD patients with no AUD/SUD comorbidities (100 females, M±SD: 37.37±12.74 years), 72 BD patients with AUD (40 females, M±SD: 38.42±11.82 years), 64 BD patients with SUD (39 females, M±SD: 34.50±10.57 years), and 211 healthy controls (127 females, M±SD: 34.80±12.57 years). 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). HC were recruited via oral presentations and flyers. BD subjects with either AUD or SUD were defined as having had a lifetime history of SUD/AUD or meeting criteria for alcohol or illicit substance abuse or dependence within the past 6 months. The SUD group included cocaine (12), stimulants (2), cannabis (20), other substances, e.g. opiates (8), and polysubstance users (22). Participants were excluded if they had any current serious medical problems including cardiovascular and neurological disorders. Specific inclusion criteria for HC were: no current or lifetime axis I psychiatric diagnosis, no lifetime history of AUD/SUD, 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.

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 and substance use disorders (First, Spitzer, Gibbon, & Williams, 2012). The SCID was administered to all participants by an independent psychiatrist or trained research

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assistant. Clinical characteristics such as current use of psychiatric medication, current mood state, and age of illness onset were assessed on the clinical interview. In HC euthymia was confirmed based on the SCID-I. For BD the interview also included the 17-items Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978). The study protocol was approved by the Institutional Review Board at UTHSCSA and UNC, and informed consent was obtained from all the participants.

2.1 Cognitive performance

All participants were administered the Wechsler Test of Adult Reading (WTAR), which is a measure of premorbid intellectual quotient (IQ) (Wechsler, 2001). The South Texas Assessment of Neurocognition (STAN) neuropsychological battery (D. C. Glahn et al., 2010) is a 90-minute computerized battery of standard and experimental neuropsychological tests. It has previously been used in BD (Cherkil et al., 2012; David C Glahn et al., 2010). For the aim of this study, we administered the STAN version of the CVLT (Delis, Kramer, Kaplan, & Ober, 2000). In the current CVLT task participants are presented orally with 16 words for 5 times (List A) and asked to recall as many words as possible in any order (immediate recall). Participants are then 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). Unlike the original version of the CVLT the STAN-CVLT does not include the interference List B. 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. Following this, participants were presented with a yes/no recognition task, in which they had to respond yes or no as to whether a word had been presented on List A (Recognition).

2.2 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 with AUD (BD+AUD) and BD with SUD (BD+SUD) and healthy controls were compared using χ^2, ANOVA, Mann-Whitney U test, and Kruskal-Wallis test. SAS PROC MEANS and PROC FREQ were used to screen the data. Tests of normality, linearity, multicollinearity and homogeneity of covariance assumptions were performed. Our analyses used the following CVLT measures: immediate recall, short delay-free recall, short delay-cued recall, long delay-free recall, long delay-free cued recall, and recognition. We examined group differences via profile analyses (Tabachnick & Fidell, 2001) with sex and education as covariates. To avoid underpowered data analyses YMRS, HRSD and medication load as covariates only if there were significant differences between the BD groups. Post-hoc tests examined differences in performance across the four participant group (HC, BD, BD+AUD, BD+SUD). Multiple comparisons were adjusted for using Bonferroni and Tukey's methods. The statistical threshold for these analyses was set at $p \leq 0.05$.

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3. Results

3.1 Demographics and clinical description

Demographics and clinical features for BD, BD+AUD, BD+SUD, and HC are reported in Table 1. Age differences between groups approached significance (p=.061). There were significant differences in gender, years of education, ethnicity, and current employment between the four groups. 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. In terms of clinical characteristics there was a significant difference in the age of onset of BD (p=.043) with BD +SUD showing a marginally earlier onset of illness compared to BD (p=.053). There were no differences in the current use of psychiatric medication (p=.937), current mood episode (p=.201), severity of depressive symptoms (p=.123), and severity of manic symptoms (p=. 439) across BD groups.

3.2 Cognitive assessment

WTAR scores did not differ across groups (p=.265) (Table 1). The profile analysis of the CVLT measures adjusted for sex and education showed that there were significant differences across groups [F(3,268) = 3.50, p =0.016]. Tukey-corrected post-hoc tests found that HC had a higher immediate recall score than BD (p=.009), BD with AUD (p=.005) and BD with SUD (p=.046). HC performed better than BD on the short delay free recall component of the CVLT task (p=.039), and had a higher recognition score compared to BD with AUD (p=.012) and BD with SUD (p=.028) (Figure 1). There were no other differences in CVLT scores between BD, BD+AUD and BD+SUD. Table 2 provides a summary of the post hoc results of the CVLT profile analysis.

4. Discussion

The current study examined the memory functioning of patients with and without AUD or SUD using the STAN version of the CVLT task. The most compelling finding of this study is that BD patients with comorbid AUD or SUD displayed pronounced deficits in tests of immediate recall and recognition. By comparison, individuals with BD without substance use disorders demonstrated impaired verbal memory abilities in immediate and short-delay free recall, but preserved delayed recall and recognition abilities. These findings suggest that, while BD has marked effects on the encoding of new information, comorbid substance use including alcohol and illicit drugs in BD impairs more specifically the recognition of words previously presented (Banich, 2004).

The memory profile of our BD patients with no substance use comorbidities is similar to that reported in previous studies. Indeed, verbal memory deficits of large effect size have been consistently reported in BD (Bora, Yücel, Pantelis, & Berk, 2011), in particular with regard to immediate and delayed recall (Bora et al., 2009; Martínez-Arán et al., 2004; Van Der Werf-Eldering et al., 2010; van Gorp et al., 1998). Another study showed that immediate recall was significantly impaired in BD patients with more than 3 manic episodes when compared to HC (Cao, Passos, et al., 2016). Notably, although belonging to the same age

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group, illness duration was considerably greater (ranging from 18.81 to 22.47 years) than that reported by our participants (approximately 9 years). Further, findings from another study showed that individuals with BD-I display a poorer memory profile compared to BD-II (Bourne et al., 2015). These findings suggest that deficits in immediate recall may be more strongly related with the (re-)occurrence of manic episodes than the early or late onset of the disease.

As expected, BD patients with AUD/SUD displayed greater memory deficits than HC. However, there were no memory differences between individuals with BD and BD patients with comorbid substance use disorders. Previous literature showed that when comparing BD with and without dual diagnosis, BD with a lifetime history of substance use disorders (including both alcohol and illicit drugs) exhibit significantly worse performance in visual memory and conceptual reasoning/set-shifting than BD without such history (Marshall et al., 2012). Another study detected no memory differences between BD patients with remitted dependence (defined by abstinence in the previous 12 months) and HC (Levy, Monzani, Stephansky, & Weiss, 2008). Notably, BD patients with remitted dependence performed worse on measures of executive functioning than HC, and scored lower than BD patients diagnosed with substance dependence in the past 6 months on measures of fluid intelligence. Thus, it could be concluded that abstinence does not reverse all aspects of damage resulting from substance dependence. Further, substance dependence may accelerate the age-related decline in fluid intelligence (Manard, Carabin, Jaspar, & Collette, 2014). The lack of memory differences in immediate and free recall between BD patients and BD patients with comorbidities may also be due to the fact that, unlike Marshall et al.'s study, our BD +SUD/AUD sample comprised of individuals that were either fully remitted or diagnosed with dependence in the last 6 months. It is noteworthy mentioning that our study included patients in different mood phases (the majority of the participants were depressed). Previous meta-analyses and empirical studies found that, relative to euthymic BD patients, depressed and manic patients present with deficits in immediate and delayed verbal, and visual memory (as measured by the CVLT and the logical memory and visual reproduction subtests of the Wechsler Memory Scale) (Bora et al., 2011; Sweeney, Kmiec, & Kupfer, 2000). Thus, variations in memory performance across mood phase may be a major confounder in this study. Of relevance is, however, the poor recognition performance observed in BD+AUD and BD+SUD when compared to HC. Given that previous studies primarily report deficits in encoding and recall in BD (Bora et al., 2011), the current finding indicates that the presence of SUD and AUD comorbidities compromises the consolidation and/or storage of new memories.

Of relevance is the poor recognition performance observed in BD+AUD and BD+SUD when compared to HC. In contrast to previous findings in the field that primarily reported deficits in encoding and recall in BD (Bora et al., 2011), our results indicate that the presence of SUD and AUD comorbidities compromise the consolidation and/or storage of new memories. It is important to highlight the consequences of having recognition deficits on daily functioning. The yes/no recognition task is the least demanding component of the CVLT: it involves the presentation of previously learned words and new words, and requests the patient to respond either “yes” or “no” based on whether the word was on the immediate learning list A. The poor recognition scores observed in BD with SUD or AUD suggest that

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the patients did not benefit from cues, possibly because they did not memorize the contextual details needed to accurately encode new pieces of information (Strauss, Sherman, & Spreen, 2006). Recognition deficits are likely to interfere with all aspects of daily functioning (Riddle & Glisky, 2007) as they are associated with reduced ability to discriminate between relevant and irrelevant information. Research on the link between neuropsychological deficits and psychosocial functioning in BD is still a poorly investigated area. Based on the current findings additional work is therefore warranted on the relationship between recognition abilities and functional outcomes in dual diagnosis, as this may prove to be a large contributor to disability.

Given the dearth of findings in the field of cognition and dual diagnosis, we had no specific hypothesis concerning potential differences in memory performance between BD patients with AUD and those with SUD. The lack of significant differences between these two groups may be related to the number of confounding factors in the literature of substance use disorders. To start with, there is a large degree of overlap in terms of cognitive impairment observed across licit and illicit substance use disorders. Indeed, cannabis, methamphetamine ecstasy, opioids and alcohol use are associated with deficits in episodic memory of medium to large effect size (Fernández-Serrano, Pérez-García, & Verdejo-García, 2011). Given that polysubstance use is common and that individuals' drugs of choice, their amount and frequency of use may change over time, identifying the cognitive sequelae specific to a certain drug may be challenging. Further, even during long-term abstinence, individuals with a history of cocaine and alcohol use may display deficits in episodic memory of small effect size (Bartzokis et al., 2002; Fein, Torres, Price, & Di Sclafani, 2006; Jovanovski, Erb, & Zakzanis, 2005). It is also important to mention that while deficits in episodic memory are present across substance use disorders, executive functions are compromised specifically in alcohol and ecstasy users, while poor planning abilities are more characteristic of cannabis and ecstasy users (Cadet & Bisagno, 2015). This data suggests that the use of executive measures may help distinguish BD patients from BD patients with AUD/SUD comorbidities. In sum, future large-scale, longitudinal studies should consider comparing the cognitive effects of multiple classes of drugs. Important factors such as the amount of substance used or the duration of use on cognition and mood should also be taken into account.

It is noteworthy mentioning that, in our study, subjects with BD and SUD comorbidities showed a marginally earlier onset of BD as compared to subjects with BD without SUD comorbidity. There is evidence that patients with BD and AUD display an earlier onset of illness compared to patients with BD without lifetime history of substance use (Levy, Manove et al. 2012). An early onset BD is typically associated with increased rates of suicide attempts, rapid cycling, alcohol and drugs misuse, high prevalence of psychotic symptoms, and comorbid anxiety disorders (Krishnan 2005, Geoffroy, Etain et al. 2013). Further, an early onset BD is characterized by poorer cognitive and clinical status compared to late onset BD (Perlis, Miyahara et al. 2004). Our finding may therefore indicate that individuals with early onset BD are more likely to use illicit substance and display cognitive impairment than those with late onset BD.

We acknowledge that our study has a number of methodological limitations. Our groups were not matched by variables such as gender, education and employment. These variables

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are typically associated with a more several clinical status and/or increased risk of substance use. However, when we co-varied our results with these variables their impact on the CVLT was found to be not significant. Furthermore the majority of our BD sample was medicated. Given that there were no differences in medication load across BD groups the memory deficits observed in BD with and without AUD/SUD are unlikely to be attributed to medication side-effects. The cross-sectional nature of our study did not allow us to evaluate potential changes in participants' cognitive performance over time. Further, given the small sample size we probably did not have the statistical power to detect the full extent of the memory differences associated with AUD and SUD. Along the same line, we did not covary our analyses for mood symptoms (YMRS, HRSD) and medication load to avoid underpowered data analyses. Since we did not observe any group difference on either mood scale, it is unlikely that subsyndromal symptoms affected memory performance in these individuals. At an instrument level it could be argued that the STAN-CVLT task (D. C. Glahn et al., 2010) may have not been sensitive enough to detect minor differences in memory performance between BD and BD with comorbid AUD/SUD. However, the CVLT has been found to be sensitive to verbal memory deficits in individuals with substance use disorders (Medina, Shear, & Schafer, 2006). Further, a study using the STAN-CVLT found differences in verbal memory between BD and HC (Chaves, Lombardo et al. 2011)(Glahn, Almasy et al. 2010). Therefore, the use of the CVLT does not appear to be a confounder in this study.

Overall, our findings show that a history of substance use comorbid to BD compromise memory function. Our results have important clinical implications as they highlight the importance of screening and monitoring substance use in individuals with BD in the early stages of the disorder to prevent and reduce future cognitive sequelae. Additional studies are needed to assess the long-term effects of substance use on cognitive performance and their impact on global functioning and remission rates.

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Abbreviations

IMMREC	immediate recall
SDFR	short delay-free recall
SDCR	short delay-cued recall
LDFR	long delay-free recall
LDFCR	long delay-free cued
BD	bipolar disorder

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HC healthy controls

AUD alcohol use disorder

SUD substance use disorder;

*p<.05;

**p<.01

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Highlights

- We used the STAN - a standardized cognitive battery
- We investigated the role of comorbid alcohol or illicit substance use in BD
- A history of use disorders is associated with an earlier onset of BD.
- BD has marked effects on the encoding of new information
- Comorbid substance use in BD impairs recognition

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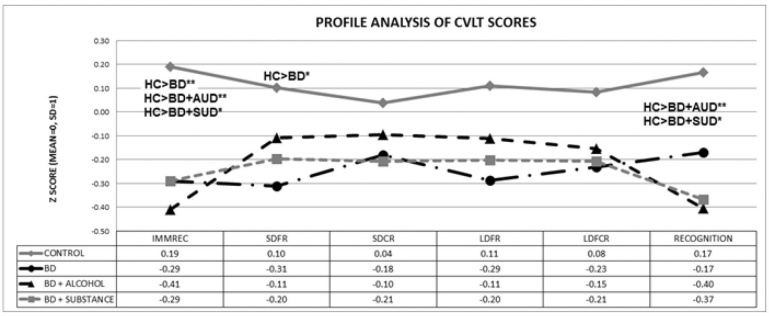

	IMMREC	SDFR	SDCR	LDFR	LDFCR	RECOGNITION
CONTROL	0.19	0.10	0.04	0.11	0.08	0.17
BD	-0.29	-0.31	-0.18	-0.29	-0.23	-0.17
BD + ALCOHOL	-0.41	-0.11	-0.10	-0.11	-0.15	-0.40
BD + SUBSTANCE	-0.29	-0.20	-0.21	-0.20	-0.21	-0.37

Figure 1.

Composite z-scores of the CVLT scores.

Abbreviations: IMMREC=immediate recall; SDFR=short delay-free recall; SDCR=short delay-cued recall; LDFR=long delay-free recall; LDFCR=long delay-free cued; BD=bipolar disorder; HC=healthy controls; AUD=alcohol use disorder; SUD=substance use disorder; *p≤.05; **p≤.01

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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)	.017
Age **	34.80 ±12.57	37.37 ±12.74	38.42 ±11.82	34.50 ±10.57	.061
Years of education **	16.08 ±3.03	14.08 ±2.90	14.30 ±3.52	13.95 ±2.56	<.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)	.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)	.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)	<.001
Current mood state Euthymic	211 (100)	46 (35.9) 60	15 (21.4) 38	19 (29.7) 33	<.001
Depressive episode	---	(46.9) 14	(54.3) 6 (8.6)	(51.6) 7 (10.9)	
Manic/hypomanic episode Mixed episode		(10.9) 8 (6.3)	11 (15.7)	5 (7.8)	
Age of onset BD ##, **	-	32.99 ±12.57	29.15 ±12.27	26.91 ±10.76	.043
HDRS score ***	-	13.00 (5.00–19.00)	15.00 (9.00–20.00)	12.00 (6.00–18.50)	.123
YMRS score ***	-	4.00 (1.00–8.00)	5.00 (2.00–10.00)	4.00 (1.00–10.25)	.439
WTAR **	39.53 ±8.34	37.22 ±8.95	39.18 ±8.30	38.40 ±8.01	.265

Abbreviations: 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).

* Relative and absolute frequencies, 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.

BD > BD+SUD (p=.053).

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Table 2

Profile analyses on CVLT measures - statistical significance of post hoc tests (Tukey adjusted p-values). Statistical threshold of significance was p<.05.

TUKEY-ADJUSTED P-VALUES				
IMMEDIATE RECALL				
	HC	BD	BD+AUD	BD+SUD
BD	.009	-	.9312	-
BD+AUD	.005	.931		.948
BD+SUD	.046	1	.948	-
SHORT-DELAY – FREE RECALL				
	HC	BD	BD+AUD	BD+SUD
BD	.039	-	.931	-
BD+AUD	.640	.739	-	.948
BD+SUD	.373	.945	.979	-
SHORT-DELAY – CUED RECALL				
	HC	BD	BD+AUD	BD+SUD
BD	.507	-	.975	.999
BD+AUD	.885	.975	-	.962
BD+SUD	.568	.999	.962	-
LONG DELAY – FREE RECALL				
	HC	BD	BD+AUD	BD+SUD
BD	.054	-	.812	.975
BD+AUD	.615	.812	-	.978
BD+SUD	.346	.975	.978	-
LONG DELAY – FREE DELAYED CUED RECALL				
	HC	BD	BD+AUD	BD+SUD
BD	.186	-	.980	.999
BD+AUD	.564	.980	-	.995
BD+SUD	.415	.999	.995	-
RECOGNITION				
	HC	BD	BD+AUD	BD+SUD
BD	.150	-	.658	.782
BD+AUD	.012	.658	-	.999
BD+SUD	.028	.782	.999	-