Psychiatry Research 200 (2012) 252–257

Contents lists available at SciVerse ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder

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ARTICLE INFO

Article history:
Received 9 April 2012
Received in revised form
31 May 2012
Accepted 11 June 2012

Keywords:
Mood disorders
Alcohol
Dual diagnosis
Cognition
Neuropsychology

ABSTRACT

Measures of cognitive dysfunction in Bipolar Disorder (BD) have identified state and trait dependent metrics. An influence of substance abuse (SUD) on BD has been suggested. This study investigates potential differential, additive, or interactive cognitive dysfunction in bipolar patients with or without a history of SUD. Two hundred fifty-six individuals with BD, 98 without SUD and 158 with SUD, and 97 Healthy Controls (HC) completed diagnostic interviews, neuropsychological testing, and symptom severity scales. The BD groups exhibited poorer performance than the HC group on most cognitive factors. The BD with SUD exhibited significantly poorer performance than BD without SUD in visual memory and conceptual reasoning/set-shifting. In addition, a significant interaction effect between substance use and depressive symptoms was found for auditory memory and emotion processing. BD patients with a history of SUD demonstrated worse visual memory and conceptual reasoning skills above and beyond the dysfunction observed in these domains among individuals with BD without SUD, suggesting greater impact on integrative, gestalt-driven processing domains. Future research might address longitudinal outcome as a function of BD, SUD, and combined BD/SUD to evaluate neural systems involved in risk for, and effects of, these illnesses.

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1. Introduction

Bipolar Disorder (BD) is a severe psychiatric disorder characterized by recurrent episodes of mania and/or hypomania, as well as depressive episodes. Lifetime prevalence estimates of BD range from 1% when including only BD I to approximately 3.9% of the population in the United States when BD II and BD NOS are included (Kessler et al., 2005; Merikangas et al., 2007). Bipolar disorders are chronic and associated with increased morbidity and mortality (Angst et al., 2002), including significant cognitive difficulties with associated impact upon everyday functioning. Specifically, difficulties in processing speed, attention, executive functioning, memory, and fine motor skills have been well-documented (van Gorp et al., 1998; Robinson et al., 2006), even among individuals in the euthymic state (Zubieta et al., 2001; Thompson et al., 2005). Our group's previous work demonstrated that individuals in the euthymic state of BD had significantly poorer performance compared to healthy individuals in processing speed with interference resolution, visual memory, and fine motor dexterity (Langenecker et al., 2010); comorbidities with other diagnoses, such as history of SUD, were not considered in that investigation.

There is an increased prevalence of substance use disorders (SUD) among individuals with bipolar illness (Kessler et al., 1994; Regier et al., 1990), with a reported lifetime occurrence as high as 60% (Cassidy et al., 2001). Specifically, patients with BD and excessive substance use have poorer educational attainments, reduced occupational standing, lower Global Assessment of Functioning-scores and degraded medication compliance, in addition to more suicide attempts compared to those with BD without SUD (Lagerberg et al., 2010). Additionally, impulsivity has been shown to be a prominent feature of both BD and SUD and those with BD who are more impulsive may be more susceptible to SUD (Martin et al., 1994). Likewise, those with comorbid BD and SUD tend to show greater risk-taking behaviors compared to those with BD without SUD, a potential interpretation of which is that individuals with BD and SUD may have an inaccurate perception of risk (Holmes et al., 2009).

While cognitive functioning has been extensively studied in BD and SUD, most studies have been underpowered to detect differences and results have been inconsistent. Specifically, BD patients with and without alcohol dependence have been shown to demonstrate impairment in verbal memory compared to healthy controls, but only those with BD and alcohol dependence show significantly

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0165-1781/$ - see front matter Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.psychres.2012.06.013

worse executive functioning compared to controls (van Gorp et al., 1998); however, the BD groups were too small ($n=12$ and 13) to detect significant differences between them. Another comparison of BD groups with and without co-occurring alcohol dependence has shown that individuals with alcohol dependence exhibit worse performance on tasks of executive functioning, verbal and visual memory, and fluid intelligence (Levy et al., 2008), suggesting that co-occurring alcohol dependence adds a degree of severity to a pattern of cognitive impairment already found in BD. In contrast, other studies found that BD patients have poorer performance in verbal memory and executive functioning regardless of being euthymic and independent of alcohol history (Sanchez-Moreno et al., 2009) and that lifetime alcohol use disorder added no further explanation to performance on tests of other cognitive domains (van der Werf Eldering et al., 2010). While these reported findings provide inconsistent results, interpretations are limited by small sample sizes, effects of residual mood symptoms, and medication effects, all of which are factors specifically addressed in the current study.

The present study aimed to investigate the cognitive performance of BD (i.e., Bipolar I, II, and NOS) patients with or without a lifetime history of SUD, in addition to a healthy control group for comparison, while addressing previous limitations such as small sample size, phase of illness, and medication effects. While cognitive impairment has been extensively documented in BD and SUD, few studies have examined potential differential, additive, or interactive cognitive dysfunction in these often comorbid conditions. We hypothesized that individuals with BD with a lifetime history of SUD would perform more poorly on cognitive tasks compared to those BD without a lifetime history of SUD and healthy controls.

2. Method

2.1. Participants

Study participants were recruited for the Prechter Bipolar Repository between October 2005 and December 2011 at the University of Michigan for a study of phenotypic and biological outcomes of bipolar disorder (for description, see Langenecker et al., 2010). Of the 586 participants recruited for the longitudinal cohort, 256 individuals with confirmed Bipolar Disorder (201 Bipolar I Disorder, 36 Bipolar II Disorder, 19 Bipolar Disorder NOS) and 97 healthy controls were included in the present study. We chose to group all three BD diagnoses together in order to increase sample size; the results remained unchanged after running the same analyses with only the BD I group. The BD and HC samples were matched on age and verbal intelligence using the Wechsler Vocabulary score (Wechsler, 1997). Of those with confirmed BD, 158 had a lifetime history of SUD, while 98 did not. Furthermore, of those individuals meeting DMS-IV diagnostic criteria for SUD, there were 130 with Alcohol, 84 with Cannabis, 32 with Cocaine, 20 with Stimulant, 16 with Sedative, and 21 with Opiate Abuse and/or Dependence. Overall, 52.5% ($n=83$) of those in the SUD group met diagnostic criteria for only one substance, while 47.5% ($n=75$) met for multiple substances.

Recruitment of psychiatric participants occurred through an outpatient specialty psychiatry clinic, an inpatient psychiatric unit, and advertisements on the web and in the newspaper. Individuals were initially screened via telephone and those who qualified were offered an in-person baseline evaluation. All participants gave informed consent prior to participation. Participants were evaluated with Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994), neuropsychological testing, life event and symptom questionnaires, Hamilton Depression Rating Scale (HDRS), and Young Mania Rating Scale (YMRS). Final diagnoses were determined through a best estimate process and confirmed by at least three of the authors. Participants with BD were excluded from the study if they had a history of schizophrenia or schizoaffective disorder depressive type, active or current substance dependence (within six months of baseline evaluation), or a medical illness specifically associated with depressive symptoms (including but not limited to: terminal cancers, Cushing's disease, or stroke). Those with active manic symptoms were also excluded by using a YMRS cut-off of 7 or less for inclusion ($n=8$ (without SUD) and $n=21$ (with SUD)); there were too few of these individuals to do meaningful comparisons. HC participants were recruited from on-line and print advertisements. HC participants were not eligible to participate if they had a history of any DSM-IV axis I disorder, active and current substance use disorder diagnosis, any medical illness specifically associated with depressive symptoms, or any first-degree family member who had been diagnosed or hospitalized for mental illness. This study was approved by the University of Michigan Institution Review Board (IRBMED: HUM00000606).

Table 1 contains demographic characteristics of the HC and BD (with and without SUD) groups. There were no significant differences between BD and HC groups for age, $F(2)=0.76$, $p=0.47$. There was also no significant difference for Wechsler Vocabulary, $F(2)=1.7$, $p=0.18$, a traditionally defined "hold" test that would not be expected to change based upon scar or burden effects of illness (Torres et al., 2007). This task was conceptualized as an index of the examinee's general mental ability as word knowledge is shown to be correlated with learning, stable over time, and relatively resistant to psychological disturbance and to neurological deficit (Sattler, 2001). Education attainment was likely to be adversely affected by illness course, as typical onset of BD and SUD occurs during completion of high school and college. As such, there was a significant effect for education, $F(2)=7.48$, $p=0.001$; individuals with BD with SUD had fewer years of education relative to BD without SUD and HC. There was also a significant effect for gender, $\chi^2(2, N=353)=11.85$, $p=0.003$, with both BD groups having more females than males relative to the HC group. This was addressed specifically in each subsequent analysis in order to eliminate these potential confounds. Note that results are similar when groups are matched on these demographics, and results are therefore reported for the entire sample.

2.2. Assessments and measures

Clinical variables were collected during the baseline DIGS interview. Clinical variables of interest include years of illness, medication loading (Hassel et al.,

Table 1
Clinical and demographic characteristics in bipolar patients with and without a history of substance use disorder and in healthy controls.

Variable	BD With SUD ($n=158$) M(S.D.)	BD Without SUD ($n=98$) M(S.D.)	Controls ($n=97$) M(S.D.)	p
Age	*38.47 (12.02)*	39.92 (11.92)	37.74 (14.23)	0.47
Education	14.97 (2.18)	15.90 (1.97)	15.79 (2.17)	0.001 BD, HC > BD+
WASI vocabulary	12.29 (2.25)	12.78 (1.98)	12.30 (2.45)	0.18
Gender[a]				
% females	60.1	73.5	49.5	0.003
HDRS-17	9.04 (6.16)	7.91 (5.86)	1.52 (0.15)	< 0.001 BD+ > BD
YMRS	3.54 (4.35)	2.50 (3.04)	0.59 (0.06)	< 0.001 BD+ > BD
Years ill	20.98 (12.45)	19.89 (12.45)	–	0.50
First age at onset	*17.37 (6.79)*	20.22 (8.69)	–	0.004
Depression age at onset	*16.97 (7.85)*	20.52 (10.21)	–	0.002
Depression episodes	*26.61 (52.38)*	17.91 (38.63)	–	0.16
Mania age at onset	*18.83 (11.57)*	20.89 (14.00)	–	0.21
Mania episodes	*9.40 (18.25)*	5.34 (11.87)	–	0.05
Number of hospitalizations	3.25 (3.74)	2.69 (4.38)	–	0.39
Medication load	2.68 (2.02)	3.15 (2.22)	–	0.08
Total episodes	65.91 (111.85)	50.56 (89.04)	–	0.25
SUD age at onset	19.97 (5.16)			
Length of SUD (years)	9.58 (8.22)			

[a] Chi-Square. WASI=Weschler Adult Scale of Intelligence; HDRS-17=Hamilton Depression Rating Scale 17-item; YMRS=Young Mania Rating Scale; BD=Bipolar Disorder without Substance Use Disorder; BD+=Bipolar Disorder with Substance Use Disorder; HC=Healthy Control