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HIV-infected persons with bipolar disorder are less aware of memory deficits as compared to HIV-infected persons without bipolar disorder

Kaitlin Blackstone¹, Alexis Tobin², Carolina Posada¹, Ben Gouaux², Igor Grant², David J. Moore², and HIV Neurobehavioral Research Program (HNRP)

¹San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology; San Diego, California, USA

²University of California, San Diego, Department of Psychiatry; San Diego California, USA

Abstract

Episodic memory deficits are common in HIV infection and bipolar disorder, but patient insight into such deficits remains unclear. Thirty-four HIV-infected individuals without bipolar disorder (HIV+/BD−) and 47 HIV+ individuals with comorbid bipolar disorder (HIV+/BD+) were administered the Hopkins Verbal Learning Test-Revised and the Brief Visuospatial Memory Test-Revised to examine objective learning/memory functioning. Subjective memory complaints were assessed via the memory subscale of the Patient's Assessment of Own Functioning Inventory. HIV+/BD+ individuals performed poorer on tests of visual learning and visual/verbal recall compared to HIV+/BD− participants ($p < 0.05$). Memory complaints only predicted verbal learning (at a trend level, $p = 0.10$) and recall ($p = 0.03$) among the HIV+/BD− individuals. Memory complaints were not associated with memory performance within the HIV+/BD+ group ($p > 0.10$). Memory complaints were associated with affective symptoms in both groups. These complaints were also predictive of immunosuppression, higher unemployment, and greater dependence on Activities of Daily Living among the HIV+/BD+ individuals ($p < 0.05$). Awareness of memory abilities was particularly poor among HIV+/BD+ individuals (i.e., objective learning/memory did not correspond to reported complaints), which has important implications for the capacity of these individuals to engage in error-monitoring and compensatory strategies in daily life. Memory complaints are associated with depressed mood regardless of group membership. Among HIV+/BD+ individuals, these complaints may also signify worse HIV disease status and problems with everyday functioning. Clinicians and researchers should be cognizant of what these complaints indicate in order to lead treatment most effectively; use of objective neurocognitive assessments may still be warranted when working with these populations.

Keywords

Self report; Infectious Diseases; Affective Disorders; Episodic Memory; Cognition

Introduction

Both HIV infection and bipolar disorder (BD) are independent risk factors for neurocognitive impairment. Specifically, up to 50% of individuals with HIV evidence at least mild neuropsychological deficits particularly in attention, executive functions,

information processing, verbal fluency, learning and delayed recall (Heaton et al., 2010). Additionally, BD, which appears to be particularly elevated among persons with HIV-infection (Beyer et al., 2005; Cournos et al., 1997; Evans et al., 2003; Walkup et al., 1999), is also associated with impaired cognitive functioning in the domains of executive functioning, learning, and memory (Bearden et al., 2001; Kurtz & Gerraty, 2009; Robinson et al., 2006). Taken together, the above research plus a preliminary report from our group (Moore et al., 2008), suggests that HIV+ individuals with comorbid BD (HIV+/BD+) may evidence greater neurocognitive deficits particularly in the areas of learning and memory than HIV+ persons without BD (HIV+/BD-; Moore et al., 2008). Importantly, neuropsychological deficits in learning and memory are strongly associated with poorer everyday functioning (e.g., Woods et al., 2008; Heaton et al., 1994; Andrade et al., 2005; van Gorp et al., 2007; Benedict, Mezhr, Walsh, & Hewitt, 2000), therefore suggesting that these individuals may be particularly susceptible to subsequent daily functioning declines.

Complaints of cognitive functioning are also commonly reported in both individuals with HIV infection and BD; however, the extent to which these complaints reflect actual functioning is not clear. For example, up to 52% of HIV individuals endorse neurocognitive complaints in everyday functioning including problems with multitasking, organizing day-to-day activities, processing complex information and perhaps most frequently, complaints in episodic memory (Maj et al., 1994; Stern et al., 1991; Mehta et al., 1996; Wilkins et al., 1991). Although several studies have reported a modest association between objective neuropsychological performance and self-reported cognitive complaints in HIV (Beason-Hazen, Nasrallah, & Bornstein, 1994; Mapou et al., 1993; Poutianinen & Elovaara, 1996; Stern et al., 1991), a large proportion have found no consistent relationship (Hinkin et al., 1996; Moore et al., 1997; van Gorp et al., 1991; Thames et al., 2010; Rourke et al., 1999a; Woods et al., 2007). Similarly, BD patients' self-reports of cognitive impairment fail to reliably predict objective neuropsychological functioning (Burdick et al., 2005). For example, in a study of euthymic BD patients, Martinez-Aran et al. (2004) found that a subset of the participants reported cognitive complaints that were associated with neuropsychological impairments, however, those BD patients without complaints also performed poorer than controls.

In particular, mood has been implicated as a potential moderator in the relationship between cognitive complaints and objective cognitive performance. Higher levels of depression in HIV are associated with over-reporting problems in everyday functioning including medication management, driving, prospective memory and cognition, whereas genuine cognitive impairment may be most associated with underestimation of functional abilities (Thames et al., 2010; Cysique et al., 2007; Rourke et al., 1999b; Woods et al., 2007). In fact, depression has been shown to be dissociable to neuropsychological performance in HIV (Cysique et al., 2007; Grant et al., 1993; Mapou et al., 1993), suggesting that mood may be most indicative of complaints but not objective neurocognitive abilities. Additionally, Rourke et al. (1999a) found that depressive symptoms were significantly associated with metamemory inaccuracies in HIV-infection. Few studies have examined predictors of subjective cognitive complaints in bipolar disorder. Of the two we found, Martinez et al. (2005) reported that subclinical mood symptomatology was one of the best predictors of cognitive complaints in patients with BD; additionally, Burdick et al. (2005) reported that more severe ratings of depression and less severe ratings of manic symptoms tended to be associated with more cognitive complaints, though these findings were not significant. We are not aware of any studies that have examined the relationship between subjective learning and memory complaints and actual learning and memory performance among HIV+ individuals with co-occurring BD.

Given the prevalence of neuropsychological impairment independently reported in HIV infection and BD as well as the unreliable nature of self-reported cognitive complaints in these populations, HIV+/BD+ may represent a unique group of individuals who may be particularly susceptible to a dissociation between actual versus reported abilities. Determining the validity of patient cognitive complaints in HIV+/BD+ individuals has important implications for diagnostic determination and treatment planning as memory deficits are strongly linked to everyday functioning outcomes. Therefore, our study aimed to examine the relationship between reported memory complaints and objective multimodal (i.e., verbal and visual) learning/memory performances in HIV+/BD+ individuals compared to HIV+/BD− individuals as well as examine potential predictors of memory complaints among both groups.

Methods

Participants

Forty-seven HIV+/BD+ and 34 HIV+/BD− participants were recruited from the HIV Neurobehavioral Research Center (HNRC) as part of a larger cross-sectional study aimed at examining the role of cognitive impairment on medication adherence among these groups. All participants had a current prescription for antiretroviral medications, and the HIV+/BD+ participants were additionally required to have a current prescription for psychotropic medication aimed at treating BD. Participants were excluded from the study if they had histories of neurological conditions (e.g., stroke, traumatic brain injury with loss of consciousness greater than 30 minutes) known to adversely impact cognitive functions.

Procedure

Psychiatric and Substance Use Assessment—The DSM-IV Structured Clinical Interview for Diagnosis (SCID; First, 1995) was used to determine mood disorder diagnoses (lifetime diagnosis of Bipolar Disorder I or II, or Major Depressive Disorder and current mood episode). The Young Mania Rating Scale (YMRS; Young, 1978) was used to determine the severity of current mania symptoms, while current depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II; Beck, 1996). Diagnosis of alcohol and/or substance abuse or dependence was obtained using the Composite International Diagnostic Interview (CIDI; Wittchen et al., 1991). The CIDI assessed for both current and lifetime alcohol, cannabis, cocaine, methamphetamine, and opioid abuse or dependence.

Neuropsychological Assessments—As part of a larger test battery, verbal learning and memory were assessed via the Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt, 1991). The HVLT-R consists of three groups of four (non-consecutive) semantically related words and three consecutive learning trials, a 20- to 25-minute delayed free recall trial, and a recognition trial. The Brief Visuospatial Memory Test-Revised (BVM-T-R; Benedict et al., 1997) assessed visuospatial learning and memory. The BVM-T-R consists of three consecutive learning trials involving presentation of a display comprising six geometric designs, a 25-30-min delayed free recall trial, and a recognition trial. Outcome variables for both tests were learning (the number of correctly recalled words/figures on trials 1 to 3), and delayed recall (the total correctly recalled words/figures on delayed free recall). Raw scores for each test variable were converted into demographically corrected *T*-scores using comprehensive normative standards which corrected for age, education, sex, and ethnicity, as appropriate (Heaton, Taylor, Manly & Tulsky, 2003; Heaton et al., 2004; Normal et al., 2011). *T*-scores were then converted to deficit scores to determine the prevalence of memory impairment in the study samples (*T*-score 40=0, 39-35=1, 34-30=2, 29-25=3, 24-19=4, 19=5 (0 = *normal*, 5 = *severe impairment*); Heaton et al., 2004), with a

deficit score greater than 0.5 on the HVLT-R or BVMT-R indicating impairment (Carey et al., 2004).

Self-Reported Memory Functioning—The Patient's Assessment of Own Functioning Inventory (PAOFI; Chelune, 1986) was administered to determine perceived cognitive complaints in everyday functioning. The PAOFI is a self-report, 41-item questionnaire in which the participant reports the frequency with which he has difficulties with memory, language and communication, use of hands, sensory-perception, higher-level cognitive and intellectual functions, work, and recreation. Only the memory subscale (i.e., the first 10 items of the questionnaire) was included in analyses in this study as we were specifically interested in the association between memory complaints and objective memory impairment. Specific memory complaints were rated on a 6-point scale from 1 = “*almost always*” to 6 = “*almost never*,” therefore lower scores on the PAOFI indicate higher complaint severity. Total memory complaints ranging from 10 (endorsed “*almost always*” on all memory items) to 60 (endorsed “*almost never*” on all memory items) were utilized in all analyses. Additional between group analyses examined the number of “significant” memory complaints by summing the number of items on which an individual endorsed a 1 (“*almost always*”), 2 (“*very often*”), or 3 (“*fairly often*”); this method of determining significant complaints is further outlined in a previous study that utilized the PAOFI to determine daily functioning abilities in individuals with HIV (i.e., Woods et al., 2004).

Instrumental Activities of Daily Living—To assess dependence in performing instrumental activities of daily living (IADLs), a modified version of the Lawton and Brody scale was used (Heaton et al., 2004). Eleven items were included from this scale detailing the degree to which individuals independently function in the areas of Financial Management, Home Repair, Medication Management, Laundry, Transportation, Grocery Shopping, Shopping, Housekeeping (Cleaning), Cooking, Work, and Telephone Use. For each activity, the participant separately rates his/her current level of independence and highest previous level of independence. The total score is the total number of activities for which there is currently a need for increased assistance (ranging from minimal to complete assistance), with a range of zero (no change) to 11 (increased dependence in all activities).

Statistical analyses

Demographic and clinical differences between the HIV+/BD+ and HIV+/BD− individuals were examined using a series of one-way analysis of variance (ANOVAs). The groups were comparable across all demographic and clinical variables. Participants were also comparable across all recent and lifetime substance abuse/dependence diagnoses (i.e., alcohol, marijuana, cocaine, and opioid) except methamphetamine abuse/dependence diagnoses (see Table 1); therefore lifetime methamphetamine abuse/dependence diagnoses were included as a covariate in all analyses examining group differences. HIV+/BD− versus HIV+/BD+ group performances on the HVLT-R and BVMT-R (i.e., impaired vs. not impaired) were compared via chi-square analyses. The total PAOFI memory subscale score (range 10-60) as well as the number of memory complaints (i.e., number of items qualifying as a “significant” complaint; range 0-10) were examined between groups. Lower scores reflect more severe complaints on the PAOFI. Memory complaint predictors were assessed in both groups including actual learning and memory impairment (i.e., HVLT-R and BVMT-R), mood (i.e., BDI-II and YMRS), HIV disease variables (i.e., current CD4 count, log₁₀ plasma HIV RNA viral load, and AIDS status), current and lifetime substance abuse/dependence diagnoses, employment status, and IADL dependence utilizing nonparametric correlations (i.e., Spearman's rho) and univariate logistic regressions analyses, where appropriate.

Results

A significantly higher proportion of individuals in the HIV+/BD+ group were impaired on visuospatial learning (42% vs. 7%; $\chi^2 = 10.2$, $p < 0.001$) and recall compared to the HIV+/BD- group (45% vs. 9%; $\chi^2 = 12.6$, $p < 0.001$; see Figure 1). HIV+/BD+ individuals were also more impaired on verbal recall at 45% compared to 21% of the HIV+/BD- ($\chi^2 = 7.6$, $p = 0.006$); however, there were no group differences on verbal learning ($\chi^2 = 2.7$, $p = 0.10$). Verbal and visual learning and recall were not associated with HIV disease characteristics ($ps > 0.05$; i.e., worse HIV disease was not associated with worse learning/recall performance).

No significant differences were found between groups on the total memory complaints or on any individual memory complaint (i.e., memory subscale items; $ps > 0.05$). Additionally, number of “significant” memory complaints (i.e., number of items endorsed as 1, 2, or 3) did not differ between groups ($F(1,79) = 2.6$, $p = 0.11$). Most participants (74/81; 90%) did not report “significant” memory complaints on the PAOFI, while the remaining individuals ($n = 8$) reported 1 “significant” complaints (one HIV+/BD- individual reported 1 “significant” complaint while seven HIV+/BD+ individuals reported 1 “significant” complaints). Within the HIV+/BD- group, total memory complaints significantly predicted verbal recall ($\chi^2 = 4.61$, $p = 0.03$; see Table 2) and also tended to predict verbal learning ($\chi^2 = 2.67$, $p = 0.10$), though this finding did not reach significance; there was no association between memory complaints and visual memory abilities among the HIV+/BD- individuals ($ps > 0.05$). Memory complaints also were not associated to any objective memory performance among the HIV+/BD+ individuals ($ps > 0.05$).

Greater depressive symptoms were associated with more severe total memory complaints within both the HIV+/BD+ ($\rho = -0.63$, $p < 0.001$) and the HIV+/BD- ($\rho = -0.55$, $p = 0.004$) groups. Manic symptom severity within the HIV+/BD+ group was not associated with complaints ($p > 0.05$). Higher current CD4 counts were associated with fewer total memory complaints within the HIV+/BD+ group ($\rho = 0.40$, $p = 0.02$); however, no other HIV disease marker was associated with memory complaints in either group ($ps > 0.05$). Importantly, in the HIV+/BD+ group, greater total memory complaints predicted unemployment ($\chi^2 = 4.34$, $p = 0.037$) and dependence on IADLs ($\chi^2 = 4.38$, $p = 0.036$). No current or lifetime substance abuse/dependence diagnoses were associated with complaints in either group (i.e., alcohol, marijuana, cocaine, methamphetamine, hallucinogen, opioids, sedative; $ps > 0.05$).

Discussion

Overall, HIV+/BD+ persons have significant learning and memory difficulties compared to HIV+/BD- individuals. These results support the notion that both HIV infection and BD confer adverse additive effects on cognitive functioning, which is consistent with research demonstrating an increased neuropathological burden of HIV and BD on frontal and temporal systems (Aylward et al., 1993; Cherner et al., 2002; Moore et al., 2006; Bearden et al., 2001; Mahon et al., 2010; Phillips et al., 2008; Strakowski et al., 2005). Despite these neurocognitive differences, HIV+/BD+ participants did not report more memory complaints than the HIV+/BD- participants. However, memory complaints did predict impairment in verbal learning (at a trend level) and recall within the HIV+/BD- individuals whereas no associations between memory complaints and performance were found among the HIV+/BD+ individuals. This finding suggests that while neither group was able to provide a fully accurate assessment of their objective learning/memory performance, individuals with HIV+/BD- showed better memory awareness than HIV+/BD+ individuals.

Importantly, while the HIV+/BD- participants showed poor awareness of visual memory abilities, they performed within the normal range on both the HVLT-R and the BVMT-R whereas participants with HIV+/BD+ showed difficulties on awareness of both visual and verbal memory abilities and performed below average as a group. Therefore, the more severe learning/memory difficulties with comparable perceived memory abilities (i.e., memory complaints) among the HIV+/BD+ individuals suggests a potentially more severe lack of awareness of memory abilities and thus lack of understanding of one's memory limitations, which may have significant clinical implications. For example, these individuals may be more likely to engage in everyday tasks, which are beyond their memory capabilities to complete; in particular, they may be less able to identify when a problem does arise during a task and therefore less likely to employ compensatory strategies during such tasks. Previous studies have also indicated that difficulties in impairment awareness is associated with decreased motivation for rehabilitation (Toglia & Kirk, 2000), which may suggest that HIV+/BD+ individuals represent an important group of individuals with a unique set of needs for intervention, including awareness training. Additionally, although the HIV+/BD- individuals showed better awareness of verbal memory abilities, this is likely not due to the psychometric properties of the PAOFI as there are queries of both visual (e.g., "How often do you forget people whom you met in the last day or two?") and spatial (e.g., "How often do you lose things or have trouble remembering where they are?") memory abilities on this measure. Instead, this differential insight into memory abilities may simply reflect a specific weakness among HIV+/BD- individuals for understanding one's visual memory abilities.

Importantly, our findings also suggest that self-reported memory complaints are unlikely to indicate the considerable learning and memory impairments observed in the HIV+/BD+ group, as well as potentially in the HIV+/BD- group. Consistent with prior reports, memory complaints were most strongly related to depressive symptoms and not objective performance regardless of group membership (Heaton et al., 2004; Rourke et al., 1999b; Hinkin et al., 1996). Nevertheless, we found that the severity of memory complaint was associated with greater immunosuppression (i.e., current CD4 count), unemployment status, and dependence on IADLs within the HIV+/BD+ group. Therefore, although cognitive complaints are not associated with actual neurocognitive functioning among individuals with HIV+/BD+, complaints in this group may in fact be an indicator of overall affective, physical, and everyday functioning distress. This suggests that although memory complaints are indicative of affective state in both groups, they also may be uniquely predictive of objective distress among HIV+/BD+ individuals. Clinicians and researchers should be aware of the differential importance of such complaints depending on the clinical population at hand in order to lead treatment most effectively.

There are several limitations to the current study including a small sample size in both groups and the absence of a BD-only (i.e., HIV seronegative) comparison group. Additionally, as only 10% of participants reported "significant" memory complaints, there was a small range when examining the "significant" complaints in our sample limiting the statistical power of our analyses. Lastly, future studies could benefit by including a collateral report of memory impairments from an independent informant (e.g., significant other, family member, physician), which may be a more accurate indicator of "real life" memory performance than self-report; in this manner, the extent to which perceived memory complaints and performance on objective learning/memory measures related to a potentially more ecologically valid report of "real life" memory functioning could be examined.

Findings from this study suggest that although awareness of memory abilities may not be optimal in both HIV+/BD- and HIV+/BD+ individuals, the severity of these difficulties may be most apparent and clinically relevant to the HIV+/BD+ group. Notably, depressed mood is a more important predictor of memory complaints than actual memory

performance; and HIV disease severity and functional distress predict memory complaints only among HIV+/BD+ individuals. In sum, it is important for practitioners and researchers to be aware of the limitations of self-reported cognitive complaints and cognizant of when objective neuropsychological assessment may be most appropriate in order to capture objective cognitive difficulties. However, use of self-report measures may still be useful particularly in capturing the relative difficulties a patient may feel s/he is experiencing in his/her daily life (versus on a standardized neuropsychological test) as well as use as a potential *indicator* of disease severity, everyday functioning, and, particularly, affective state (rather than a result of such variables), particularly among HIV+/BD+ individuals. Future research is needed to develop cognitive interventions for these populations, particularly targeting awareness training (e.g., self-monitoring, self-evaluation) in order to increase the likelihood for such individuals to appropriately employ compensatory strategies to improve the observed memory difficulties.

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*p < 0.05

Figure 1.

HIV+/BD+ individuals exhibit worse multimodal memory performance than HIV+/BD- individuals.

Table 1

Participant demographic and clinical characteristics.

	HIV+/BD- (n = 34)	HIV+/BD+ (n = 47)	p-value
Demographics			
Age, mean years (SD)	46.4 (9.2)	44.3 (7.5)	0.260
Education, mean years (SD)	13.1 (2.1)	13.4 (2.3)	0.598
% Male	76%	85%	0.330
% Caucasian	65%	70%	0.380
% Employed	42%	52%	0.392
% IADL dependent	21%	21%	0.982
Substance Abuse/Dependence diagnosis			
Alcohol (lifetime)	44%	58%	0.229
Alcohol (past month)	0%	0%	----
Marijuana (lifetime)	15%	31%	0.091
Marijuana (past month)	3%	2%	0.840
Methamphetamine (lifetime)	21%	49%	0.010
Methamphetamine (past month)	0%	7%	0.125
Cocaine (lifetime)	21%	38%	0.100
Cocaine (past month)	0%	0%	----
Opioid (lifetime)	6%	13%	0.277
Opioid (past month)	0%	2%	0.382
Psychiatric			
# psychiatric meds, mean (SD)	1.7 (1.8)	2.9 (1.8)	0.005
YMRS , mean (SD)	3.2 (3.3)	7.7 (6.7)	0.002
BDI-II, mean (SD)	9.5 (7.3)	15.4 (11.3)	0.023
% current MDE	6%	16%	0.180
% lifetime MDE	59%	71%	0.254
HIV disease characteristics			
Current CD4 count, median (IQR)	423.5 (205.3-858.5)	605.0 (363.5-872.0)	0.224
Plasma HIV RNA viral load (log ₁₀), Median (IQR)	1.69 (1.69-1.69)	1.69 (1.69-1.90)	0.514
% AIDS	73%	68%	0.666

Note: IADL = Instrumental Activities of Daily Living; YMRS = Young Mania Rating Scale; BDI-II = Beck Depression Inventory-II; MDE = Major Depressive Episode

Table 2

Univariate logistic regressions showing memory complaints predict impaired verbal memory functioning among HIV+/BD− individuals, but not in HIV+/BD+ individuals.

	Total Memory Complaints (R ²)	p-values
HIV+/BD−		
Verbal Learning [§]	0.07	0.10
Verbal Recall [*]	0.18	0.03
Visual Learning	0.002	0.84
Visual Recall	0.06	0.28
HIV+/BD+		
Verbal Learning	0.02	0.28
Verbal Recall	0.02	0.29
Visual Learning	<0.001	0.90
Visual Recall	0.001	0.79

Note: Verbal = HVLT-R (impaired vs. unimpaired); Visual = BVMT-R (impaired vs. unimpaired)

[§] p<0.10

^{*} p<0.05