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Selective neurocognitive deficits and poor life functioning are associated with significant depressive symptoms in alcoholism–HIV infection comorbidity

Stephanie A. Sassoon [a], Margaret J. Rosenbloom [a,b], Rosemary Fama [a,b], Edith V. Sullivan [b], Adolf Pfefferbaum [a,b,*]

[a] Neuroscience Program, SRI International, 333 Ravenswood Ave, Menlo Park, CA 94025, USA
[b] Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

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ABSTRACT

Alcoholism, HIV, and depressive symptoms frequently co-occur and are associated with impairment in cognition and life function. We administered the Beck Depression Inventory-II (BDI-II), measures of life function, and neurocognitive tests to 67 alcoholics, 56 HIV+ patients, 63 HIV+ alcoholics, and 64 controls to examine whether current depressive symptom level (significant, BDI-II $\geq$ 14 vs. minimal, BDI-II $<$ 14) was associated with poorer cognitive or psychosocial function in alcoholism–HIV comorbidity. Participants with significant depressive symptoms demonstrated slower manual motor speed and poorer visuospatial memory than those with minimal depressive symptoms. HIV patients with depressive symptoms showed impaired manual motor speed. Alcoholics with depressive symptoms showed impaired visuospatial memory. HIV+ alcoholics with depressive symptoms reported the poorest quality of life; alcoholics with depressive symptoms, irrespective of HIV status, had poorest life functioning. Thus, significant depressive symptoms were associated with poorer selective cognitive and life functioning in alcoholism and in HIV infection, even though depressive symptoms had neither synergistic nor additive effects on cognition in alcoholism–HIV comorbidity. The results suggest the relevance of assessing and treating current depressive symptoms to reduce cognitive compromise and functional disability in HIV infection, alcoholism, and their comorbidity.

1. Introduction

One of the greatest challenges in developing effective treatment for individuals with HIV infection is distinguishing the effects of the disease from the effects of common comorbidities such as alcoholism and depression (Bing et al., 2001; Havlik et al., 2011). Individuals with any one of these conditions (HIV infection, alcoholism, or depression) carry a liability for cognitive impairments, and observed cognitive deficit patterns likely reflect neural pathways affected in each condition. Whether the trimorbidity of HIV infection, alcoholism and depressive symptoms leads to synergistic deficits in any particular cognitive domain remains largely unexplored.

Alcoholism is highly prevalent in the HIV-infected community (Conigliaro et al., 2006; Galvan et al., 2002; Petry, 1999). Not only is excessive alcohol use a significant factor in the acquisition of HIV infection through its role in facilitating risky behaviors (Fritz et al., 2010; Kalichman et al., 2007), but heavy alcohol use can exacerbate susceptibility to HIV infection, induce change in mood (Kelley and Dantzer, 2011), and may impair adherence to antiretroviral medication (Hendershot et al., 2009). Cognitive processes found to be disproportionately affected with chronic, heavy alcoholism and HIV infection include motor and visuomotor speed and coordination (Fama et al., 2007; Rothlind et al., 2005), sustained attention and associative learning (Sassoon et al., 2007), remote semantic memory (Fama et al., 2011), and immediate episodic memory for verbal and visual material (Fama et al., 2009).

Affective disorders, particularly depression, are highly prevalent in individuals with either HIV infection or alcoholism alone (Sullivan et al., 2008, 2011). Depression spectrum disorders are the most common psychiatric comorbidity in HIV infection (Dube et al., 2005), with upwards of one-third of HIV-infected individuals having co-occuring mood disorders or significant depressive symptoms (Bing et al., 2001; Morrison et al., 2002). Over the course of their illness, individuals with an alcohol use disorder (AUD) are almost twice as likely as those without an AUD to experience depression (Fergusson et al., 2009).

While cognitive impairment is widely documented in advanced HIV infection, it is increasingly recognized that asymptomatic HIV-positive individuals may also show mild cognitive impairment

* Corresponding author. Tel.: +1 650 859 2927; fax: +1 650 859 2743.
E-mail address: dolf@synapse.sri.com (A. Pfefferbaum).

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(Heaton et al., 2011; Maki and Martin-Thormeyer, 2009). Disruption of frontostriatal circuits and other networks depending on these circuits have been implicated in HIV (Heaton et al., 1995; Woods et al., 2009). Some studies suggest that executive and motor skills and information processing speed show the greatest decline from early to later disease stages (Reger et al., 2002) with psychomotor slowing a significant predictor of progression to AIDS, dementia, and death (Sacktor et al., 1996). Impairment in episodic memory for verbal and visual material is also highly prevalent in HIV and also increases with disease progression (Heaton et al., 1995; Martin et al., 2007; Woods et al., 2009).

Long-term, heavy alcohol consumption has deleterious effects on frontal–parietal cortical systems and frontocerebellar circuits, with deficits consistently observed in visuospatial construction, memory, executive functions, and motor abilities including gait and balance (Oscar-Berman and Marinkovic, 2007; Parsons and Nixon, 1998, Smith and Fein, 2011; Sullivan et al., 2000, 2002). Some deficits, particularly in visuospatial functioning, mental flexibility, abstract reasoning, short-term memory, and balance may persist even after significant abstinence (for a review, see Fein et al., 1990; Sullivan et al., 2010).

Depressive symptoms have been associated with verbal and visual memory impairments (Austin et al., 2001), executive deficits (e.g., set shifting and verbal fluency), and motor slowing (Beats et al., 1996; Channon and Green, 1999; Purcell et al., 1997). While some studies of asymptomatic HIV positive individuals failed to find a significant effect of depression on neurocognitive function, e.g., (Bornstein et al., 1993), others found that depressive symptoms were related to poorer performance on measures of attention and executive skills and slower information processing (Baldewicz et al., 2004). Furthermore, depressive symptoms and impairment in executive functioning, learning, attention, working memory, and verbal abilities in persons with HIV predicted failures in everyday functioning (Heaton et al., 2004).

In the social functioning arena, alcoholism and depressive symptoms are associated with greater suicidality (Conner et al., 2007) and greater social and occupational functional impairment (Cornelius et al., 1995). Furthermore, depressive symptoms and poor neurocognitive functioning are predictors of relapse in alcoholics (Parsons, 1998). Likewise, HIV-infected individuals with significant depressive symptoms have poorer adherence to medication (Gonzalez et al., 2011), poorer life functioning (Rabkin, 2008), increased progression to AIDS (Bouhnik et al., 2005), and increased HIV-related mortality (Cook et al., 2004). Patients with alcohol and HIV comorbidity have poorer health-related quality of life than those with either disease alone, with depression symptomatology being the strongest predictor of quality of life (Rosenbloom et al., 2007).

To date, few studies have explicitly addressed the increasingly common disease "trimorbidity" of HIV infection, alcoholism, and depressive symptoms even though HIV-infected patients with this combined disease burden who received no treatment for psychiatric symptoms or substance problems carry the highest risk of mortality (DeLorenze et al., 2010).

The current study used the Beck Depression Inventory-II (BDI-II), a comprehensive questionnaire commonly used in clinical and research settings, to categorize patients as having significant or absent/minimal depressive symptoms (Beck et al., 1996; Coleman et al., 2012; Dutton et al., 2004). We explicitly focused on current depressive symptomatology but also documented whether patients met lifetime DSM-IV criteria for a unipolar mood disorder. We examined whether a significant level of current depressive symptoms, regardless of prior diagnosis of mood disorder, place a greater burden on cognition, life functioning in those with both HIV and alcoholism than in those with either disease alone. We also examined whether a significant level of depressive symptoms affects HIV disease severity as measured by CD4 counts and viral load in HIV positive patients and lifetime alcohol use and length of sobriety in patients with alcohol dependence. Specifically, we tested the hypotheses that, irrespective of DSM-IV diagnosis of past history of a unipolar mood disorder, (1) participants with either HIV infection and current significant depressive symptoms, or alcoholism and current significant depressive symptoms, would show poorer cognitive function and life function, and greater disease severity than their counterparts with minimal depressive symptoms; (2) participants with HIV–alcoholism comorbidity and current significant depressive symptoms (trimorbid patients) would show poorer cognitive function and life function, and greater disease severity than either single disease group with depressive symptoms or than the HIV–alcoholism comorbid participants with absent/minimal depressive symptoms.

2. Methods

2.1. Participants

Data reported here were from initial visits of participants in a longitudinal study investigating CNS sequelae of alcoholism and HIV comorbidity and also from participants in a cross-sectional neuroimaging study examining the effects of alcoholism and aging on brain structure and function. Participants were recruited from the greater San Francisco Bay area between the years 2002–2010 through referrals from community treatment centers, clinics, hospitals, flyers, or through word of mouth. Participants ($n=186$) were grouped in a 2 depressive symptom level (BDI-II score ≥ 14 or <14) $\times 3$ disease status (HIV infection, alcoholism, alcoholism–HIV comorbidity) factorial design: 24 alcohol-dependent HIV-positive participants with significant depressive symptoms (SDS+ALC+HIV), 39ALC+HIV with minimal depressive symptoms (MDS+ALC+HIV), 19 ALC with significant depressive symptoms (SDS+ALC), 48 ALC with minimal depressive symptoms (MDS+ALC), 22 HIV with significant depressive symptoms (SDS+HIV), and 34 HIV with minimal depressive symptoms (MDS+HIV). In addition to the patient groups, a healthy "normal" comparison (NC) group of 64 individuals with neither HIV, significant depressive symptoms, nor heavy drinking in their lifetime participated in this study.

2.2. Procedure

Studies were reviewed and approved by the institutional review boards at SRI International, Stanford University, and Santa Clara Valley Medical Center. All participants provided written informed consent after receiving a detailed explanation of the study procedures and received a modest stipend for study participation.

Participants were screened to exclude anyone with a history of bipolar disorder or schizophrenia, a medical illness or trauma potentially affecting the central nervous system, loss of consciousness greater than 30 min, neurological disease not related to HIV infection or alcohol use, or factors precluding MR scanning. Those who met initial criteria were invited to our laboratory for a more detailed medical and psychiatric assessment. All participants provided a blood sample to confirm HIV and Hepatitis C status. CD4 T-lymphocyte count and plasma viral load were obtained for HIV-positive participants. Blood draws for laboratory tests typically occurred within a month of neuropsychological testing.

To assess psychiatric history and to characterize lifetime alcohol use, experienced clinicians administered the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1998) and a lifetime alcohol use interview (Pfefferbaum et al., 1992, Skinner, 1982; Skinner and Sheu, 1982) to all participants. Participants included in the high-alcohol-consuming groups met DSM-IV criteria for an alcohol use disorder (AUD): either alcohol dependence ($n=121$) or abuse ($n=9$) within the past 3 years, did not have any drug abuse/dependence more recently than alcohol dependence, and did not have drug abuse/dependence within the prior three months. In this sample, median for reported sobriety from drugs was >70 weeks for all groups. Healthy comparison participants had no history of any Axis I disorder.

Current depression symptomatology was assessed using the Beck Depression Inventory, Second Edition (BDI-II) (Beck et al., 1996). This 21-item self-report instrument measures the severity of depressive symptoms. Each item is rated on a scale of 0–3. Scores of 0–13 are considered indicative of no to minimal depressive symptoms, 14–19 mild, 20–28 moderate, and 29–63 severe depressive symptoms. A cutoff score of 14 or greater is often used to indicate clinically significant depressive symptoms (Beck et al., 1996; Coleman et al., 2012; Dutton et al., 2004), and this cut-off score was used here to differentiate those with and without significant depressive symptoms. The diagnostic interview established that 25% of HIV, 36% of ALC, and 48% of ALC+HIV met formal criteria for a history of lifetime DSM-IV unipolar mood disorder, of whom $<12\%$ in each group met criteria for a current episode.

Overall level of functioning in the past month was rated by clinicians using the Global Assessment of Functioning scale (Endicott et al., 1976). Scores range from 1–10 (reflecting "persistent danger of hurting self or others" or "gravely disabled")