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Relationship between psychiatric status and frontal–subcortical systems in HIV-infected individuals

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Abstract

Human immunodeficiency virus (HIV)-infected adults frequently evidence both neurocognitive and psychiatric dysfunction. It was hypothesized that apathy and irritability, but not anxiety and depression, are related to HIV effects on frontal–subcortical systems. This hypothesis was evaluated by determining the degree to which these psychiatric features are associated with neurocognitive functioning that is dependent upon frontal–subcortical circuitry and, therefore, thought to be sensitive to the central nervous system effects of HIV. Rating scales assessing irritability, apathy, depression, and anxiety and a dual-task paradigm were administered to 189 HIV-seropositive (HIV+) and 53 HIV-seronegative participants. Deficits in dual-task performance and greater anxiety, depression, apathy, and irritability were observed in HIV+ participants. Simultaneous multivariate regression and communality analyses revealed that only apathy and irritability were associated with dual-task performance in HIV+ participants. Thus, these findings suggest that apathy and irritability, but not depression and anxiety, are likely associated with the effects of HIV on frontal–subcortical circuitry.

Keywords

Human immunodeficiency virus; Apathy; Irritability; Depression; Anxiety; Cognition

INTRODUCTION

Insults to the central nervous system (CNS) can generate psychiatric symptomatology such as depression, anxiety, irritability, and apathy. The extent to which these psychiatric features are direct results of alterations of the CNS, or secondary sequelae to medical, social, and occupational stressors remains unclear. Apathy and irritability, in particular, can be observed following lesioning of the frontal lobe(s) and/or frontal–subcortical circuits (Cummings, 1993) and have been observed in several neurological conditions known to preferentially affect frontal–subcortical systems, including Parkinson's disease, Alzheimer's disease (AD), basal ganglia infarct, and Huntington's disease (Absher & Cummings, 1995; Cummings et al., 1994).

Human immunodeficiency virus (HIV) is not only lymphotropic but also neurotropic and consequently directly affects the CNS. Unfortunately, the CNS remains relatively unprotected in the highly active antiretroviral therapy (HAART) era given the limited ability of most medication regimens to cross the blood–brain barrier. Although the specific mechanisms and

effects of HIV infiltration of the CNS continue to be elucidated, it has become increasingly clear that a primary target is the frontal–subcortical circuitry.

Many individuals infected with HIV report experiencing either prominent apathy, irritability, or both, and disruptions in frontal–subcortical systems may underlie the presence of these psychiatric features (Castellon et al., 2000). Castellon et al. (1998) found prominent symptoms of apathy to be associated with working memory deficits in HIV-positive individuals and, in a second study, found that prominent irritability and apathy were highly related to poorer performance on those neuropsychological tasks most dependent upon executive functioning (Castellon et al., 2000). In contrast, Rabkin et al. (2000) found that apathy was not related to performances across several neuropsychological domains, including frontal systems, in HIV-seropositive (HIV+) individuals. The authors concluded that the absence of a significant relationship between cognition and apathy indicated that apathy may not represent a direct CNS affect of HIV infection, and they called for a reconsideration of the relationship between apathy and cognitive impairment in HIV infection. In subsequent studies published by Paul and colleagues, higher levels of apathy correlated with poor frontal systems functioning such as cognitive flexibility (Paul et al., 2005a) and were strongly associated with nucleus accumbens volume measurements (Paul et al., 2005b).

Prominent depressive and anxiety symptoms are also commonly observed in HIV+ individuals (Chandra et al., 2005). Several studies demonstrated a lack of relationship between depression and neuropsychological decrements in HIV-infected individuals (Castellon et al., 1998; Grant et al., 1993; Hinkin et al., 1992; Rabkin et al., 2000). Similarly, studies suggest that anxiety is not related to poor neuropsychological performances (Mapou et al., 1993; Perdices et al., 1992), but has been found to be associated with psychological and psychosocial symptoms (Perdices et al., 1992). Taken together, these findings suggest that anxiety and depression represent secondary effects of HIV infection.

Putative primary (i.e., apathy and irritability) and secondary (i.e., anxiety and depression) psychiatric features have yet to be directly compared or quantified in the degree to which they relate to frontal–subcortical neurocognitive deficits in HIV infection. The current study addressed these issues by testing the hypothesis that the psychiatric symptoms of apathy and irritability, but not anxiety and depression, are related to dual-task paradigm performance (a proxy for frontal–subcortical systems dysfunction) in HIV-infected individuals.

METHODS

Participants

A total of 53 HIV-seronegative (HIV–) and 189 HIV+ participants were enrolled in the present study. Demographic data are shown in Table 1. All HIV+ participants were taking antiretroviral medications at the time of testing. Potential participants were excluded if they had an actual or suspected history of neurologic disease, head injury with subsequent loss of consciousness greater than 10 minutes, seizure disorder, learning disorder, or history of psychotic-spectrum disorder. HIV+ subjects with a history of HIV-associated CNS opportunistic infection (e.g., CNS lymphoma, progressive multifocal leukoencephalopathy, cryptococcal meningitis) were excluded. Subjects who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for current drug or alcohol abuse/dependence were excluded. Individuals with a history of drug or alcohol abuse/dependence were excluded if they were not in remission for the past year. HIV+ subjects were recruited from infectious disease clinics at the UCLA Medical Center and West Los Angeles VA Medical Center and from community agencies specializing in serving individuals infected with HIV. HIV– subjects were recruited from flyers and referrals from the above-mentioned recruitment sources.

Psychiatric Measures

Depression was measured by the Beck Depression Inventory, Second Edition (BDI-2; Beck et al., 1996), and anxiety was measured by the Beck Anxiety Inventory (BAI; Beck et al., 1988). Irritability and apathy were measured by adaptations of the apathy and irritability subscales of the Neuropsychiatric Inventory (NPI), developed by Cummings and colleagues (1994) and modified for use with HIV-infected subjects (Castellon et al., 1998, 2000).

Cognitive Measure

As dual-task paradigms have been shown to be sensitive to frontal–subcortical deficits following HIV infection (Castellon et al., 2000; Hinkin et al., 2000) and lesions to the frontal lobe (Baddeley et al., 1997), the Baddeley dual-task paradigm (Baddeley et al., 1997) was used. A memory span baseline was first determined by the maximal span at which the participant could successfully repeat a specific number span in three consecutive trials. The digit span single-task condition consisted of the participant being presented with lists of digits at their own span continuously for a period of 60 s. A visual tracking and cancellation task was used for the other single-task condition. Participants were required to cross out an indicated target letter or symbol located in an array of letter and symbols, each in a 1-square-cm box. The dual-task condition consisted of participants performing the digit span and tracking tasks simultaneously for 60 s. The number of lists given in 60 s varied across individuals, as it was dependent on the participant's baseline span. Dual-task performance was, therefore, measured by the percentage of complete digit span sequences correctly recalled.

Experimental Procedures

After providing written informed consent, participants were administered a battery of neuropsychological tests, which included the Baddeley dual-task paradigm. Participants then completed the BAI, BDI-2, and the apathy and irritability scales of the NPI. Participants received US\$80.00 for participating in the study. This study was approved by the institutional review boards of both UCLA and West LA VA Medical Center.

Statistical Procedures

Analysis of covariance (ANCOVA) was performed to determine whether psychiatric symptomatology (i.e., depression, anxiety, apathy, and irritability) and dual-task performance varied depending on HIV serostatus. The covariates were age, sex, ethnicity, and years of education. Multivariate regression analyses were then conducted with the HIV+ group to evaluate the extent to which the increased incidence of psychiatric features is related to variance in dual-task performance. Total scores for depression, anxiety, apathy, and irritability measures were standardized using *t* scores derived from the mean and standard deviation of the HIV+ group. In accordance with the *a priori* hypothesis, apathy and irritability were then combined into a single variable by averaging the *t* scores for these two variables for each subject. The depression and anxiety variables were likewise combined into a single variable. A simultaneous regression analysis was performed with the apathy/irritability variable, anxiety/depression variable, and the demographic variables of age, sex, ethnicity, and education to examine the relationship of these predictors to performance on the dual-task. In addition, a communality analysis was performed to determine the predictive variance in the dual-task performance that was *unique* to, and *shared* among, the apathy/irritability, anxiety/depression, and demographic variables (Pedhazur, 1982).

RESULTS

Psychiatric Features and HIV Serostatus

Analysis of covariance was performed with HIV serostatus as the independent variable, psychiatric symptoms (i.e., depression, anxiety, irritability, or apathy) as the dependent variables, and age, sex, ethnicity, and years of education as covariates to determine whether group differences existed in each of the psychiatric measures (Table 1). Results of the ANCOVAs indicated significantly greater levels of irritability [$F(1,236) = 11.1, p < .01$, Cohen's $d = .5$], apathy [$F(1,236) = 16.2, p < .01$, Cohen's $d = .6$], depression [$F(1,236) = 13.9, p < .01$, Cohen's $d = .5$], and anxiety [$F(1,236) = 21.1, p < .01$, Cohen's $d = .6$] in the HIV+ group as compared with the HIV− group.

Dual-Task Performance and HIV Serostatus

Analysis of covariance was performed with HIV serostatus as the independent variable, percent correct digit span sequences during the dual-task as the dependent variable, and age, sex, ethnicity, and years of education as covariates to determine whether dual-task performance differences were present between HIV+ and HIV− groups (Table 1). HIV+ subjects performed significantly worse on the dual-task paradigm than HIV− subjects [$F(1,236) = 4.6, p = .03$, Cohen's $d = .4$].

Relationship Between Psychiatric Features and Dual-Task Performance in HIV+ Individuals

The following analyses evaluated the hypothesis that the psychiatric symptoms of apathy and irritability, but not anxiety and depression, are associated with HIV disease-related processes that affect frontal–subcortical systems. A simultaneous regression analysis was performed with the apathy/irritability variable, anxiety/depression variable, and the demographic variables of age, sex, ethnicity, and education to examine the contribution of these predictors to performance on dual-task performance (Table 2). Results indicated that the apathy/irritability variable was the only predictor that accounted for a significant amount of variance in dual-task performance ($p < .05$). The possibility for multicollinearity was explored given that each of the psychiatric variables significantly correlated with each other (Pearson's correlation, $r > .35$ and $p < .01$ for each comparison). Testing for multicollinearity, as suggested by Belsey and colleagues (1980), generated condition indices that were less than 6 and were, therefore, within an acceptable range.

A communality analysis was performed in latent space to determine the predictive variance in dual-task performance that was *unique* to, and *shared* among, the psychiatric features and primary demographic variables (Pedhazur, 1982). The anxiety/depression and apathy/irritability variables were entered as individual predictive blocks. The third predictive block included the demographic variables of age, sex, ethnicity, and years of education. Estimates of the unique and shared variance components were obtained by allowing the combinations of the anxiety/depression, apathy/irritability, and block of demographic variables to predict dual-task performance, while maintaining the predictive paths between the apathy/irritability, anxiety/depression, and demographic variables blocks (Table 3). The apathy/irritability variable was able to uniquely explain 3.4% of the variance in dual-task performance, while the anxiety/depression variable uniquely explained 0.9% of the variance. The demographic variables uniquely accounted for 2.6% of the variance. The three predictor blocks shared 0.6% of the variance in dual-task performance.

DISCUSSION

Individuals infected with HIV had elevated levels of anxiety, depression, apathy, and irritability and experienced decrements in dual-task performance. The effect size for the presence of the

psychiatric symptomatology was consistently in the moderate range, and the effect size for dual-task decrements was more subtle, although significant. Apathy and irritability, but not depression and anxiety, were associated with declines in dual-task performance and, thus, may be associated with the frontal–subcortical systems dysregulation observed in HIV.

Although the dual-task paradigm has been consistently found to be sensitive to frontal–subcortical systems, it was the only probe of frontal–subcortical systems used in the current study. However, these findings are consistent with other studies that used frontal–subcortical systems-dependent tests investigating cognitive flexibility, Stroop interference, working memory, and a different form of dual-task performance, each finding a similar relationship between performance on these tasks and the presence of apathy and/or irritability symptomatology (Castellon et al., 1998, 2000; Paul et al., 2005a). The current study furthered this work by providing a direct comparison of apathy and irritability with anxiety and depression and by quantifying the extent to which apathy and irritability share predictive variance with dual-task performance. Depression and anxiety uniquely accounted for 0.9% of variance in dual-task performance, while apathy and irritability uniquely accounted for 3.4% variance (which was more than the combined demographic variables of age, sex, ethnicity, and years of education).

Given the nominal relationship of depression and anxiety with dual-task performance, it is unlikely that these psychiatric features are associated with frontal–subcortical dysfunction in HIV-infected individuals. It is possible that depression and anxiety symptomatology may relate to other neural systems affected by HIV that were not measured in the current study, although other work evaluating primary neuropsychological domains have thus far not found that to be the case (Castellon et al., 1998; Grant et al., 1993; Hinkin et al., 1992; Mapou et al., 1993; Perdices et al., 1992; Rabkin et al., 2000). Alternatively, these psychiatric features may be more related to psychological and psychosocial factors (Perdices et al., 1992).

Potential limitations of this study include the cross-sectional design. It cannot be ruled out that some of the psychiatric symptoms and/or frontal–subcortical system dysregulation could have predated HIV infection as these symptoms could lead to an increased risk of contracting HIV. Also, while it is possible that poor performance on neuropsychological testing could have unduly influenced the self-report psychiatric measures that followed, it is not anticipated that adverse reaction to neuropsychological performance would differentially influence apathy and irritability versus anxiety and depression. Another potential limitation is that the psychiatric symptoms predicted to be associated with frontal–subcortical systems were measured with same instrument (i.e., NPI) and that the psychiatric symptoms predicted to not be associated with frontal–subcortical systems were also measured with the same instrument (i.e., Beck), which could introduce measurement error into the tested hypothesis.

The coexistence of the psychiatric symptoms of apathy and irritability is not a symptomatology profile unique to HIV infection, as it has been observed in other patient populations in which frontal and/or subcortical systems are disrupted (i.e., AD, Huntington's disease, and Parkinson's disease). For instance, the psychiatric symptoms of apathy and irritability in AD are thought to be generated by frontal lobe dysfunction (Cummings, 1997), and decrements in dual-task performance are also present (Della Sala et al., 1995). Even though AD pathology is primarily cortical while HIV is more subcortical, the symptomatology overlap between AD and HIV infection lends further support to frontal systems involvement in prominent apathy and irritability in HIV-infected individuals. Along these lines, it is of interest that cholinomimetic therapy in AD patients has been found to ameliorate symptoms of apathy and irritability (Cummings, 1997) as this treatment might prove efficacious for treatment of these psychiatric symptoms in HIV-infected individuals.

The introduction of HAART has substantially improved the survival of individuals infected with HIV and reduced the severity of both cognitive and psychiatric symptoms experienced. However, individuals continue to experience significant CNS disturbances. Recent evidence provided by Thompson et al. (2005) demonstrated the impressive extent to which HIV exerts deleterious effects on the CNS, even during successful HAART treatment. The authors reported several brain regions to be reduced as much as 15% in volume. Findings from the current study and others (Castellon et al., 1998, 2000; Paul et al., 2005a, 2005b) converge on not only neuropsychological functioning as a representative biomarker of HIV effects on the CNS, but also the possibility of using psychiatric features such as apathy and irritability. These neuropsychological and psychiatric biomarkers will be necessary gauges for the success of experimental neuroprotective therapies (e.g., memantine, *N*-methyl-D-aspartate receptor antagonists, and CPI-1189) for individuals infected with HIV.

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Table 1

Demographic, psychiatric, and neuropsychological data describing participant groups with standard error of the mean in parentheses

Variable	HIV–	HIV+	<i>p</i> value
Age (years)	45.5 (1.2)	44.2 (.6)	.36
Education (years)	14.2 (.3)	13.1 (.2)	<.01
Ethnicity (percent)			<.01
African American	47	69	
White	42	17	
Latino	8	9	
Other	4	4	
Sex (percent)			<.01
Male	53	77	
Female	47	23	
MSM (percent of men)	20	64	
Neuropsychiatric measures			
Depression (BDI-II)	9.0 (1.5)	14.4 (.8)	<.01
Anxiety (BAI)	5.7 (1.3)	11.5 (.7)	<.01
Irritability (NPI)	.9 (.3)	1.9 (.1)	<.01
Apathy (NPI)	1.3 (.3)	2.6 (.2)	<.01
Dual-task performance (percent digit span correct)	67 (4)	56 (2)	.03

Note. For age and education group comparisons, a one-way analysis of variance was performed. For ethnicity and sex group comparisons, a Pearson χ^2 was performed. For psychiatric status and dual-task performance, a one-way analysis of covariance was performed with age, ethnicity, sex, and years of education as covariates. HIV– = HIV-seronegative controls. HIV+ = HIV-seropositive participants; MSM = men who have sex with other men; BDI-II = Beck Depression Inventory, Second Edition; BAI = Beck Anxiety Inventory; NPI = Neuropsychiatric Inventory (Cummings et al., 1994) with adaptation for irritability and apathy measures found in Castellon et al. (2000).

Table 2

Summary of the simultaneous multivariate regression analysis for variables predicting performance on the dual-task paradigm in HIV-seropositive participants ($N=189$)

Variable	<i>B</i>	<i>SE B</i>	β
Age (years)	.006	.003	.128
Sex	−.037	.056	−.048
Ethnicity	−.028	.022	−.093
Education	.004	.010	.028
Depression/anxiety	−.003	.005	−.077
Apathy/irritability	.010	.004	.274*

Note. $R^2 = .075$ ($p < .05$). HIV = human immunodeficiency virus.

The asterisk denotes a significance of $p < .05$.

Table 3

Unique and shared variance estimates for anxiety/depression, irritability/apathy, and demographic variables in predicting dual-task performance in HIV-seropositive and HIV-seronegative participants

Component	Variance explained (%)	
	HIV+	HIV–
Demographic variables	2.9	11.3
Anxiety/depression	1.2	.2
Apathy/irritability	3.7	.2
Unique demographic variables	2.6	11.6
Unique anxiety/depression	.9	.5
Unique apathy/irritability	3.4	.5
Shared among anxiety/depression, apathy/irritability, and demographic variables	.6	–.6

Note. HIV– participants are included only for comparative purposes. The relationship between dual-task performance and psychiatric symptomatology (i.e., depression/anxiety or apathy/irritability) was not significant in the HIV– group. Demographic variables were entered as a single block and include age, sex, ethnicity, and years of education. HIV = human immunodeficiency virus; HIV– = HIV-seronegative controls. HIV+ = HIV-seropositive participants.