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Neuropsychiatric disturbance is associated with executive dysfunction in HIV-1 infection

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Abstract

Prominent apathy and/or irritability are frequently observed among individuals infected with the human immunodeficiency virus (HIV). Although these symptoms often occur as part of a mood disorder, compelling evidence suggests that they may occur independently of depression in neurologic disease/disorder. The current study examined the prevalence of both apathy and irritability among a sample of HIV-infected individuals and explored the degree to which these neuropsychiatric (NP) phenomena were associated with performance on neurocognitive measures thought to be sensitive to the potential CNS effects of HIV-1. Clinician-administered rating scales assessing apathy and irritability were administered to 65 HIV-seropositive (HIV+) and 21 HIV-seronegative (HIV−) participants who also completed a dual-task reaction time paradigm and the Stroop task. NP disturbance was significantly more prevalent among HIV+ participants compared with HIV− controls and was associated with specific neurocognitive deficits suggestive of executive dysfunction. Relative to both HIV− controls and to neuropsychiatrically intact HIV+ participants, those HIV+ individuals with evidence of prominent apathy and/or irritability showed deficits in dual-task, but not single-task, performance and on the interference condition of the Stroop. Unexpectedly, NP disturbance did not show a robust relationship with HIV disease stage. These results suggest that the presence of prominent apathy and/or irritability among HIV+ individuals may signify greater HIV-associated CNS involvement. In HIV/AIDS, the disruption of frontal–subcortical circuits may be a common mechanism causing both executive dysfunction and NP disturbance. (*JINS*, 2000, *6*, 336–347.)

Keywords: HIV/AIDS, Apathy, Irritability, Neurocognitive, Executive, Dual-task, Stroop

INTRODUCTION

Neuropsychiatric (NP) symptomatology such as apathy and irritability are common sequelae of neurologic disease/disorder and are often among the most salient behavioral manifestations of central nervous system (CNS) involvement. Apathy and irritability are especially common following insult or injury to either prefrontal or subcortical structures (Cummings, 1993; Duffy & Kant, 1997; Marin, 1991). For example, one or both are often observed following such diverse conditions as frontotemporal degeneration, anterior communicating artery aneurysm, prefrontal or basal ganglia infarct, closed head injury, multiple sclerosis, Huntington's disease, Parkinson's disease, Wilson's disease, and Alzheimer's disease (Absher & Cummings, 1995; Al-Adawi et al., 1998; Dening & Berrios, 1989; Edwards-Lee et al., 1997; Harris et al., 1994; Iverson & McCracken, 1997; Kant et al., 1995; Marin, 1997; Morriss et al., 1992; Pflanz et al., 1991; Starkstein et al., 1993). In many of these conditions, the mechanism for producing apathy and/or irritability is thought to be disruption of frontal–subcortical circuits.

The human immunodeficiency virus (HIV) is known to show an affinity for subcortical structures and deep white matter tracks (Aylward et al., 1993; Dal Pan et al., 1992; Navia et al., 1986) and to result in neuronal loss in frontal regions as well (Ketzler et al., 1990). Additionally, dopaminergic downregulation may contribute to the development of apathy and irritability (Cummings, 1993; Marin, 1991; Starkstein et al., 1992) and studies have implicated dopaminergic irregularities among a subset of HIV-infected individuals (Berger et al., 1994; Levin et al., 1991). This might explain why NP symptoms–signs such as apathy and irritability are often a prominent part of HIV-infected individuals' clinical presentation (Back et al., 1998; Stern, 1994).

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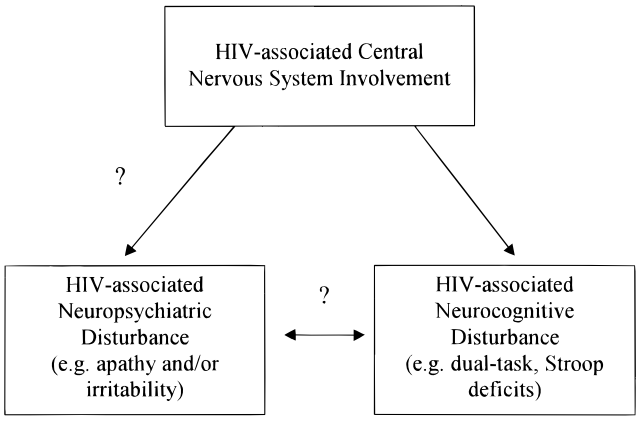
To date, however, there has been little research examining the prevalence and clinical correlates of apathy and irritability in HIV infection. One reason for this lack of empirical scrutiny may be that apathy and irritability often occur as part of much more thoroughly studied psychiatric syndromes such as depression, and are thus not independently assessed and examined. So, while depression has received considerable attention in the HIV literature, the same cannot be said for either apathy or irritability. Although apathy and irritability may indeed be symptoms of a depressive syndrome, research suggests that both apathy and irritability *can* and do occur independent of depression in a wide variety of neurologic disorders (Harris et al., 1994; Levy et al., 1998; Marin et al., 1994; Pflanz et al., 1991; Starkstein et al., 1992), including HIV (Castellon et al., 1998; Morriss et al., 1992; Silva et al., 1994).

Apathy and irritability may be better indicators of HIV-associated NP disturbance than depression. There are multiple etiologies of depression in HIV–AIDS including increased exposure to social, medical, and financial stressors, bereavement, and confrontation of mortality issues. In other words, when depression is evident in HIV-infected individuals it is often *not* a direct consequence of the CNS effects of the disease (e.g., Organic Mood Disorder) and therefore not a good marker of HIV-associated CNS disturbance. Perhaps this is why the majority of studies exploring its association with neurocognitive performance in HIV infection have failed to find any relationship (Bix et al., 1995; Bornstein et al., 1993; Goggin et al., 1997; Grant et al., 1993; Harker et al., 1995; Hinkin et al., 1992; Mapou et al., 1993).

To the extent that apathy and irritability *are* reflective of CNS involvement in HIV–AIDS, they should be associated with other indicators of CNS compromise. One potentially useful marker of HIV-associated CNS compromise is the presence of neurocognitive deficits, in particular those deficits associated with frontal–subcortical pathology. Dual-task performance is thought to be mediated by prefrontal structures (Baddeley et al., 1997). Using a dual-task paradigm (in which an individual performs two tasks independently and then concurrently), Baddeley and colleagues found that patients with documented frontal lobe pathology had dual but not single-task performance decrements. Similar results have been found among patients with Parkinson's disease (Dalrymple-Alford et al., 1994; Malapani et al., 1994), which, similar to HIV, is primarily subcortical in nature and involves dopaminergic dysfunction. Another task thought to index the integrity of prefrontal systems is the Stroop task, which requires the ability to rapidly inhibit a prepotent response (e.g., word-reading) in favor of a less habitual one (e.g., color-naming). This task has been shown to discriminate individuals with documented frontal lobe pathology from matched controls (Vendrell et al., 1995), and neuroimaging studies of healthy individuals have implicated prefrontal regions in the mediation of Stroop performance (Bench et al., 1993; Pardo et al., 1990).

A commonality between both the dual-task and Stroop paradigms is that each contains component tasks that vary in the extent to which they engage controlled, rather than automatic, attentional processing. Briefly, automatic processing occurs through rapid activation of a learned sequence of elements initiated by appropriate inputs and proceeds without conscious control; it does not stress the capacity limitations of the system. Controlled processing on the other hand occurs via temporary activation of a sequence of elements under the control of the participant, is effortful, and demanding of attentional capacity (see Schneider & Schiffrin, 1977, for in-depth discussion of controlled *vs.* automatic processing). These attentional processing modes may depend on relatively independent neuroanatomical and neurochemical mechanisms, with the activation and deployment of controlled processing especially mediated by prefrontal structures (Cohen et al., 1982; Posner & Petersen, 1990; Weingartner et al., 1984). Our group (Hinkin et al., 1999) as well as Eileen Martin and colleagues (Martin et al., 1992) have shown that a subset of HIV-infected individuals, including some who are medically asymptomatic, show deficits on the portions of the Stroop task most demanding of controlled processing (i.e., interference condition). In contrast, HIV-infected participants do not differ from uninfected controls on the less demanding components of the Stroop task (i.e., color-naming and word-reading).

Figure 1 illustrates our main objectives in the current study. We sought to explore whether the CNS effects of HIV disease might lead to *both* cognitive and psychiatric sequelae that potentially share similar mechanisms (e.g. frontal–subcortical and/or dopaminergic dysfunction) and would therefore be expected to be related. In an earlier study (which included 49 of the HIV+ participants whose data is reported in the current study) our group showed that apathy, but not depression, was associated with working memory



? = main objectives of current study:

1. Are apathy and irritability more common among HIV-infected individuals?

2. Are apathy and irritability associated with HIV-associated neurocognitive deficits?

Fig. 1. Conceptual model of the relationship between apathy and irritability and neurocognitive performance in HIV-1 infection.

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compromise (Castellon et al., 1998). We suggested that disruption of frontal–subcortical circuits might potentially explain this association. The current study seeks to extend these previous findings by exploring participants' performance on two other neurocognitive tasks thought to be sensitive to frontal–subcortical integrity by basis of their demands for controlled attentional processing. Additionally, the current study sought to examine irritability as a potentially meaningful neuropsychiatric symptom that has previously not been studied in HIV but is commonly seen in other diseases–disorders causing frontal–subcortical disruption. To address these objectives, we used measures of apathy and irritability that are easily and briefly administered that attempt to capture the cognitive, behavioral, and emotional components of these two, often subtle, neuropsychiatric symptoms. Our definition of *apathy* is based on that provided by Marin (1991) and refers to diminished motivation that leads to a reduction in goal-related thoughts, actions, and emotional responses. *Irritability* refers to the constellation of symptoms related to being easily annoyed or provoked to feelings of anger and its expression. The neurocognitive tasks in the current study vary in the extent to which they engage controlled attentional processing. The dual-task reaction time (RT) paradigm used in the current study provides sensitive measures of performance under single and dual-task conditions on simple and choice RT tasks and allows for the direct comparison of single with dual-task performance. Dual-task performance is thought to be more demanding of controlled attentional processing and therefore more dependent upon prefrontal systems than is single-task performance (Baddeley et al., 1997). We also used the Stroop task, a task with an interference condition that requires the rapid inhibition of word-reading in favor of naming the incongruous color in which the word is printed. The interference condition of the Stroop task is thought to engage controlled attentional processing (Cohen et al., 1990; Martin et al., 1992).

Specifically, we hypothesized the following: (1) neuropsychiatric (NP) disturbance, in the current study defined as prominent apathy and/or irritability, will be relatively common among HIV-1 infected individuals; (2) NP disturbance will be associated with compromised performance on tasks thought to be subserved by prefrontal cortex and associated subcortical structures, specifically dual-task performance and the interference condition of the Stroop task; and (3) NP disturbance will be more common among HIV+ individuals with more advanced disease (i.e., medically symptomatic and/or AIDS).

METHODS

Research Participants

Demographic data for the 86 participants in the current study are shown in Table 1. Sixty-five HIV+ and 21 HIV-seronegative (HIV−) participants, all with ELISA-verified serostatus and Western Blot confirmation, were enrolled in the current study. HIV+ participants were assigned to one of two disease stage groups based upon medical symptomatology and CD4 cell counts obtained within 3 months (typically less than 1 month) of study participation: *Asymptomatic* (ASP; $N = 28$) participants were those in CDC 1993 (Centers for Disease Control, 1993) Group A while *Symptomatic* (SSP; $N = 37$) individuals were those in Groups B and C. Two of the ASP participants met CDC 1993 criteria for AIDS based upon CD4 cell counts less than 200/mm^3. Of the SSP participants, the majority (81%) met CDC surveillance criteria for AIDS. Approximately 71% (46) of the HIV-infected participants were taking antiretroviral medications at the time of testing and approximately 35% (23)

Table 1. Demographic data describing participant groups

Variable	HIV− ($N = 21$)	ASP ($N = 28$)	SSP ($N = 37$)	p
Age (years)	38.1 (10.1)	38.4 (7.8)	40.1 (8.2)	.65
Education (years)	15.1 (2.3)	14.7 (2.1)	14.5 (2.1)	.56
Estimated premorbid IQ (NAART)	112.5 (10.1)	112.0 (9.4)	108.5 (9.5)	.22
BDI	9.8 (6.7)	13.8 (10.4)	16.4 (9.9)	.01*
Ethnicity (percent)				.22
African American	43	61	43	
White	48	32	43	
Latino	9	4	11	
Other	–	4	3	
Sex (percent)				.45
Male	81	93	89	
Female	19	7	11	

Note. Standard deviations appear in parentheses. HIV− = HIV-seronegative controls. ASP = HIV+ and medically asymptomatic. SSP = HIV+ and medically symptomatic. NAART = North American Adult Reading Test (Blair & Spreen, 1989). BDI = Beck Depression Inventory.
*For group comparisons, either one-way ANOVA or chi-square was used. All comparisons failed to reach significance except for BDI where $F(2,83) = 5.3$, $p < .05$; HIV− < ASP = SSP.

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had an anti-HIV medication regimen that included a protease inhibitor. Any potential participant was excluded if they had an actual or suspected history of neurologic disease, head injury with subsequent loss of consciousness greater than 10 min, seizure disorder, current substance use disorder, or history of psychotic-spectrum disorder. Anyone with history of HIV-associated CNS opportunistic infection (e.g., CNS lymphoma, PML, cryptococcal meningitis) was excluded. All HIV+ participants were recruited from an infectious disease clinic at a university-affiliated medical center and from a community agency specializing in serving HIV-infected individuals. HIV− controls were recruited from flyers and referrals from both of these agencies and from newspaper advertisements.

The majority of participants in the current study were self-identified gay or bisexual men (52% of controls and 61% of HIV+ group). Male–male sexual contact was the most common suspected mode of infection with HIV although 19 of the 65 HIV+ participants denied this risk factor and/or suspected some other mode of infection (e.g., heterosexual sexual contact; injection drug use). In the current sample 48% of all participants were African American, 41% White, and approximately 8% Hispanic. The mean age of participants in the current study was 39.1 years (range = 20–63) and only 8 of the 86 participants did not have at least a high school education (M = 14.7 years, range = 8–22). Overall, the estimated premorbid verbal IQ of the sample was in the high average range (M = 110.7, range = 91–129). HIV+ participants did not differ from seronegative controls on either current (p = .36) or past alcohol use (p = .72) or current drug use (p = .54) but did show greater history of past drug use (p = .03). This difference reflected greater past use of marijuana among HIV+ patients. Although no participant met DSM–IV criteria for a current substance use disorder, 2 control participants and seven HIV+ individuals admitted to at least weekly marijuana use. As can be seen in Table 1, HIV+ participants were equivalent to HIV− controls on all demographic variables with the exception of Beck Depression Inventory scores, on which both of the seropositive groups scored significantly higher than controls but did not differ from one another. Finally, it should be noted that data from many of the individuals in the current study were reported in an earlier paper by our laboratory comparing performance on the paper–pencil version of the Stroop to that seen on a computerized reaction time version of the task (Hinkin et al., 1999). However, the focus of the previous paper was on HIV serostatus group differences and there was no exploration of the association of neuropsychiatric symptoms with the Stroop performance.

Measures

For the computerized information processing measures (dual-task paradigm) stimuli were presented using an IBM compatible computer with a video graphics array color monitor.

1. *Dual-task choice with auditory probe reaction time paradigm*: *Single-task simple RT*: This task required participants to respond with a button press (using the index finger of their dominant hand) to a 1000-Hz tone. Stimulus onset was always preceded by a visual cue with interstimulus interval between cue offset and stimulus onset quasirandomly varied at either 250, 500, 1000, or 2000 ms. Eight practice trials were administered to ensure that participants understood the task followed by two experimental blocks of 60 trials.

2. *Single-task choice RT*: Participants were required to rapidly determine whether two sequentially presented polygons were identical or not. Exactly 1000 ms following a visual warning cue, a complex geometric design (nine-sided polygon) subtending 11° vertically and 10° horizontally was presented to the center of the monitor for a duration of 1000 ms. A second polygon, either identical to or slightly different from the first, was then presented 1000 ms after offset of the first design. Participants then had to vocally respond "same" or "different" into a microphone with the response detected by voice-activated relay and computer-recorded to the nearest millisecond. Following eight practice trials, two blocks of 30 trials were administered.

3. *Dual-task visual choice with auditory probe RT*: In the dual-task condition participants simultaneously engaged in both the simple and choice RT tasks just described above. The same 1000-Hz tone is randomly presented during the visual choice task and the participant must respond as quickly as possible to the tone with a button push while also completing the same visual discrimination task described above. This dual-task RT paradigm is a modification of a task originally described by Posner and Boies (1971) and refined by Nestor et al. (1991). The dependent variables are median RTs on each task (simple or choice) in each condition (dual-task or single-task). For choice RT trials, only those trials on which the visual discrimination was correct were used in calculating median RTs. RTs shorter than 125 ms (anticipatory responses) and longer than 2000 ms (nonresponses) were excluded from analyses.

4. *Stroop task*: The 100-item, paper-and-pencil version of the Stroop task was administered. This version of the Stroop task measured the time required for participants to complete three blocks of 100 items. The first condition, *color-naming*, required rapid naming of 100 swatches of red, blue, or green ink. *Word-reading* required the rapid reading of color words (red, blue, green) printed in black ink. In the *interference* condition participants had to rapidly name the discordant color of ink in which color words were printed (e.g., for the word "blue" printed in red ink the correct response is "red"). The paper and pencil version of the Stroop was always administered after the dual-task paradigm.

5. *Neuropsychiatric measures*: The apathy and irritability measures used in the current study are adaptations of subscales from the Neuropsychiatric Inventory (NPI;

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Cummings et al., 1994), a brief, validated, clinician-administered interview for assessing psychiatric symptoms (e.g., agitation, apathy, anxiety, delusions, irritability, etc.) among patients with neurologic disease. The NPI is typically administered to the caregivers of individuals with neurologic disease to assess the duration and intensity of associated psychiatric symptoms. Although the NPI has not been used with HIV-infected individuals, it was chosen because it contains both an apathy and an irritability subscale that are easily and briefly administered in interview format (with minor changes in the wording of items to allow for direct, rather than caregiver, assessment of participants). The apathy subscale contains seven yes–no questions sampling the domain of apathy (e.g., "Do you feel like you are less spontaneous or less active than usual?" "Are you less interested in the activities and plans of other people?" "Are you less likely to initiate a conversation with somebody?") and is consistent with the definition of apathy as a reduction in goal-related thoughts, actions, and emotional responses in which amotivation is the dominant feature of the clinical presentation (Marin, 1991, 1997). Participants are asked to rate the presence of these symptoms/signs over the 4 weeks preceding the interview. The irritability scale contains six yes–no questions pertaining to increased irritability–hostility (e.g., "Are you more argumentative and difficult to get along with?" "Do you find yourself having sudden flashes of anger?" "Are you more impatient, having trouble coping with delays?") and is consistent with the definition of irritability as a constellation of symptoms (behavioral, cognitive, and emotional) related to being easily annoyed or provoked to anger. Again, these symptoms–signs were rated for the 4 weeks preceding the interview. A participant's apathy and irritability score was equal to the total number of positively endorsed items; therefore, apathy scores could range from zero to 7 and irritability scores from zero to 6.

In order to determine the relationship of the aforementioned neuropsychiatric constructs to depression, the Beck Depression Inventory (BDI; Beck et al., 1961), a 21-item self-report measure of depressive symptomatology was also administered to all participants. The BDI contains questions pertaining to the presence and intensity of various cognitive, affective, and somatic symptoms and signs of depression over the prior 2-week period. Scores on each item can range from zero (*symptom absent*) to 3 (*presence of symptom is pronounced*), yielding a potential range of scores from zero to 63. As noted above, our group (Castellon et al., 1998), as well as others (e.g., Marin et al., 1993; Starkstein et al., 1992) have shown that depression is correlated with, but ultimately discriminable from, apathy.

Procedure

After providing written informed consent, participants were administered a detailed demographics questionnaire, a substance use questionnaire, the apathy and irritability subscales from the Neuropsychiatric Inventory (Cummings et al., 1994), and the mood, psychotic-spectrum, and substance use disorders modules from the Structured Clinical Interview for DSM–IV (First et al., 1995). All diagnostic interviewing (i.e., SCID, apathy, and irritability scales) was conducted by the same interviewer (S.A.C.) who was blind to participant's cognitive performance at the time of interview. Following completion of all interviews and questionnaires, participants were administered a neurocognitive battery that included the reaction time and Stroop measures described above. All neurocognitive testing was conducted by research assistants thoroughly trained in the administration of these tasks under the supervision of a board-certified neuropsychologist (CHH). Upon completing the study, all participants were paid $25.00 for their participation.

Data Analyses

The Statistical Package for Social Sciences, Version 8.0 (1997) was used for all analyses. To assess the significance of any differences in continuously distributed variables among groups, analysis of variance (ANOVA) and *post-hoc* Tukey's *t* test were applied. To determine the correlation between continuously distributed variables Pearson's *r* was calculated. For any correlation using a nonnormally distributed variable Spearman's *r* was used. The normality of all neurocognitive data was assessed by visual examination of histograms with normal distribution overlays. Following Tabachnick and Fiddell (1995), any out-of-range RT values (i.e., greater than 3 standard deviations from control group mean) were Windsorized (i.e., set to the next highest in-range value); this technique was necessary on only three occasions.

RESULTS

Exploration of the internal validity of the NPI apathy and irritability subscales in the current sample revealed high internal consistency for both scales (Cronbach's $\alpha = .88$ and .73 for apathy and irritability scales, respectively). Although tests of test–retest reliability were not specifically planned (one rater conducted all 86 neuropsychiatric interviews), 3 participants were administered both the apathy and irritability scales on the same day by two different examiners with high interrater correlations observed for both scales (apathy $r = .97$; irritability $r = .96$).

Apathy, Irritability and HIV Serostatus

Among HIV+ participants apathy and irritability scores were significantly correlated ($r = .5$, $p < .01$) while this pattern was not observed among control participants ($r = -.02$, $p = .94$). Also, both apathy and irritability were significantly correlated with self-reported depression among HIV+ patients (apathy and BDI: $r = .52$, $p < .01$; irritability and BDI: $r = .32$, $p = .02$). Figure 2 shows the distribution of apathy and irritability scores as a function of HIV serostatus. Promi-

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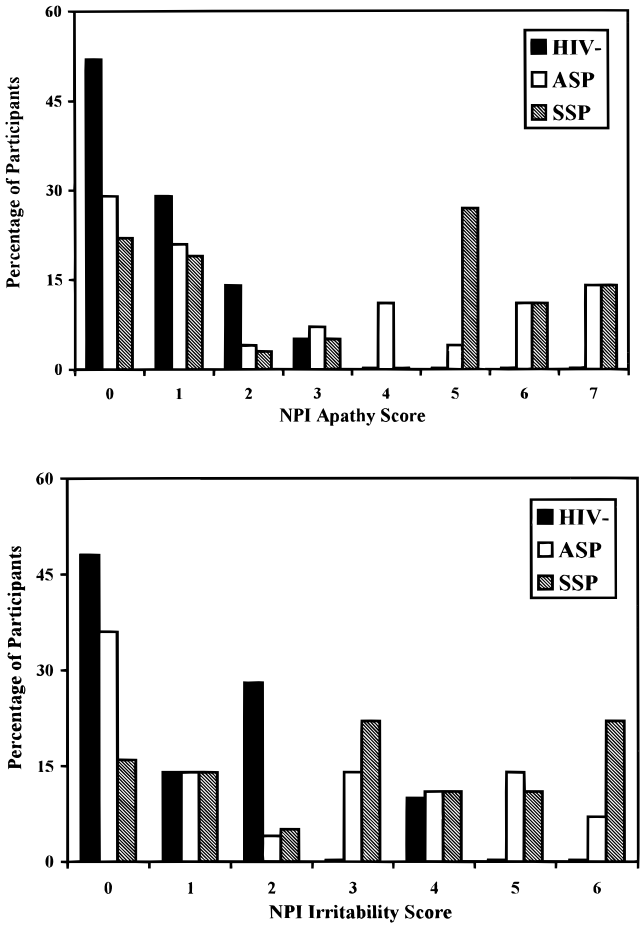

Fig. 2. Distributions of apathy and irritability as a function of HIV serostatus.

nent apathy was virtually absent among seronegative controls with no HIV− participant scoring greater than 4. Among HIV+ participants there was a bimodal distribution of apathy scores with all but 9 of the 65 HIV+ participants scoring either 1 or less, or 5 or more. ANOVA with *post-hoc* Tukey tests showed that both the SSP and the ASP participants obtained higher apathy scores than did controls [$F(2,83) = 8.6$, $p < .01$], but did not differ from each other ($p = .57$). Irritability was also less common among HIV− controls than among HIV+ participants [$F(2,83) = 7.3$, $p < .01$], and, again, the ASP and SSP participants did not differ from one another ($p = .14$). Unlike apathy scores, irritability scores were not bimodally distributed among HIV+ participants; nearly one third of all participants scored in the middle range (2, 3, or 4) of the scale.

Neuropsychiatric Disturbance Among HIV+ Participants

HIV+ participants were dichotomized into groups of neuropsychiatrically disturbed (NP+) and neuropsychiatrically normal (NP−) as follows: any participant with pronounced apathy (apathy scale score of 5 or more) and/or pronounced irritability (irritability scale score of 4 or more) was considered to be NP+, while any participant with low levels of *both* apathy (1 or less) and irritability (1 or less) was considered to be NP−. Thirty-seven of the 65 HIV+ participants (57%) were classified as NP+ while 21 (32%) were NP−. Seven HIV+ participants (11%) were unable to be classified as either NP+ or NP− and were excluded from all subsequent analyses. Of the 37 NP+ participants, 16 (43%) were both apathetic and irritable, while 13 (35%) were apathetic but not irritable and 8 (22%) were irritable but not apathetic. Table 2 shows demographic and disease progression variables among NP+ and NP− participants. These groups did not differ from each other in terms of age ($p = .56$), education ($p = .35$), estimated premorbid Verbal IQ ($p = .52$), or current alcohol ($p = .71$) and drug ($p = .20$) use. NP+ participants did endorse more depressive symptomatology than NP− individuals ($t = 4.51$, $df = 56$, $p < .01$). In terms of disease progression variables, relative to ASP participants there was a trend towards a higher percentage of SSP patients being NP+ ($\chi^2 = 2.5$, $df = 56$, $p > .10$). Contrary to expectations, NP+ participants did not have lower CD4 counts than did NP− participants ($p > .65$) and were not any more likely to be on anti-retroviral medications than were NP− participants ($p > .40$).

Neuropsychiatric Disturbance and Neurocognitive Performance

Because of the significant zero-order correlation between apathy and BDI score ($r = .52$, $p < .01$ among HIV+ group) and irritability and BDI score ($r = .32$, $p < .05$) and because neuropsychiatric groups (NP+, NP−, HIV−) differed significantly on this variable, BDI score was included as a covariate in all analyses comparing neurocognitive performance between neuropsychiatric groups. However, it should be noted that BDI total score was not consistently

Table 2. Demographic and disease progression variables among HIV+ participants with (NP+) and without (NP−) evidence of neuropsychiatric disturbance

Variable	NP− ($N = 21$)		NP+ ($N = 37$)		p
Age (years)	40.1	(7.6)	38.8	(8.3)	.56
Education (years)	14.8	(2.4)	14.5	(1.8)	.35
NAART (premorbid IQ)	111.1	(10.4)	109.4	(9.7)	.52
BDI	8.2	(7.8)	18.6	(8.6)	.01
CD4 cells/mm^3	276.8	(196.8)	306.9	(307.8)	65
Percent SSP	48		68		.13
Percent on antiviral medications	53		71		.40

Note. Standard deviations appear in parentheses. All comparisons conducted using independent samples *t* tests. NP− = neuropsychiatrically normal. NP+ = neuropsychiatrically disturbed. NAART = North American Adult Reading Test. BDI = Beck Depression Inventory. SSP = symptomatic HIV-seropositive

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related to any aspect of neurocognitive performance examined in the current study; this finding is similar to that of several other studies of depression and neuropsychological performance in HIV (e.g., Bornstein et al., 1993; Grant et al., 1993; Harker et al., 1995; Hinkin et al., 1992).

Dual-task RT

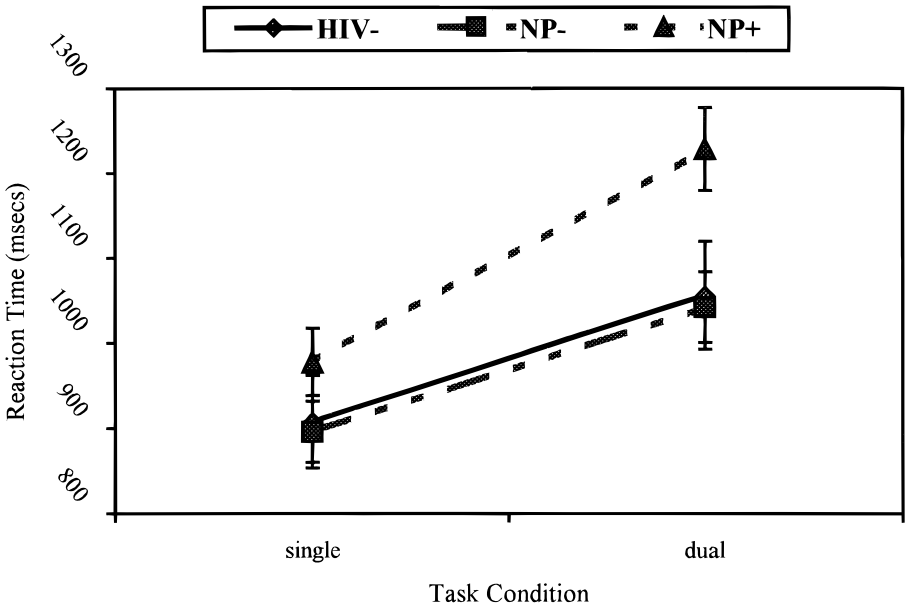
As described above, median reaction times were calculated for each participant's responses to each of four conditions: single-task simple RT, single-task choice RT, dual-task simple RT and dual-task choice RT. These median RTs were analyzed using a $3 \times 2 \times 2$ mixed-model ANOVA with group (HIV-, NP-, NP+) as the between-subjects factor and task condition (single *vs.* dual) and RT type (simple *vs.* choice) as within-subjects factors. This analysis revealed significant main effects for group [$F(2,72) = 6.5$, $p = .003$] for task condition [$F(1,72) = 185.2$, $p < .001$], and for RT type [$F(1,72) = 1241.2$, $p < .001$] and a significant Group $\times$ Task Condition interaction [$F(2,72) = 6.9$, $p = .002$]. Neither the Group $\times$ RT Type ($p = .52$) or the three-way interaction ($p = .30$) was significant. Figure 3 depicts these results.

Analysis of simple main effects showed that NP+ participants were significantly slower than HIV− controls ($p = .008$) and NP− participants ($p = .002$) while NP− and control participants did not differ from each other ($p = .84$). As expected, RTs were significantly longer in the dual-task rather than single task condition and for choice rather than simple stimuli. Follow-up analyses exploring the interaction between Group $\times$ Task Condition (i.e., single *vs.* dual) revealed that NP+ participants produced significantly longer RTs than both NP− and control participants under dual-task conditions [$F(2,74) = 10.4$, $p < .001$], but not under single-task conditions ($p = .10$). Because there was a trend towards the NP+ group being slower on single-task RT, we created a difference score using the following formula: Difference RT = (Dual-task simple RT + dual-task choice RT) − (single-task simple RT + single-task choice RT). Univariate ANOVA on this difference RT showed that the groups did indeed differ [$F(2,73) = 7.7$, $p = .001$], with Tukey *post-hoc* comparisons showing that both HIV− controls ($p = .003$) and NP− participants ($p = .01$) had significantly smaller difference scores than did NP+ participants. NP− and control participants did not differ from each other ($p = .81$). Smaller difference scores reflect less decrement under dual-task conditions relative to single-task performance and suggest a differential decrement in dual-task processing speed among NP+, but not NP−, participants relative to seronegative controls.

Error rates on both single and dual-task choice RT performance did not differ between the three groups (single-task CRT, $p = .26$; dual-task CRT, $p = .39$) suggesting that although the NP+ participants were slower they were no less accurate. Also, there was no suggestion of speed *versus* accuracy trade-off across either single or dual-task conditions.

Stroop task

Task completion time for the paper-and-pencil Stroop was recorded by the examiner to the nearest second and number



Note. No group differences on single-task condition. On dual-task performance, reaction times of NP+ > NP- = HIV-.

Fig. 3. Performance on dual-task RT paradigm by HIV−, neuropsychiatrically normal (NP−) and neuropsychiatrically disturbed (NP+) groups.

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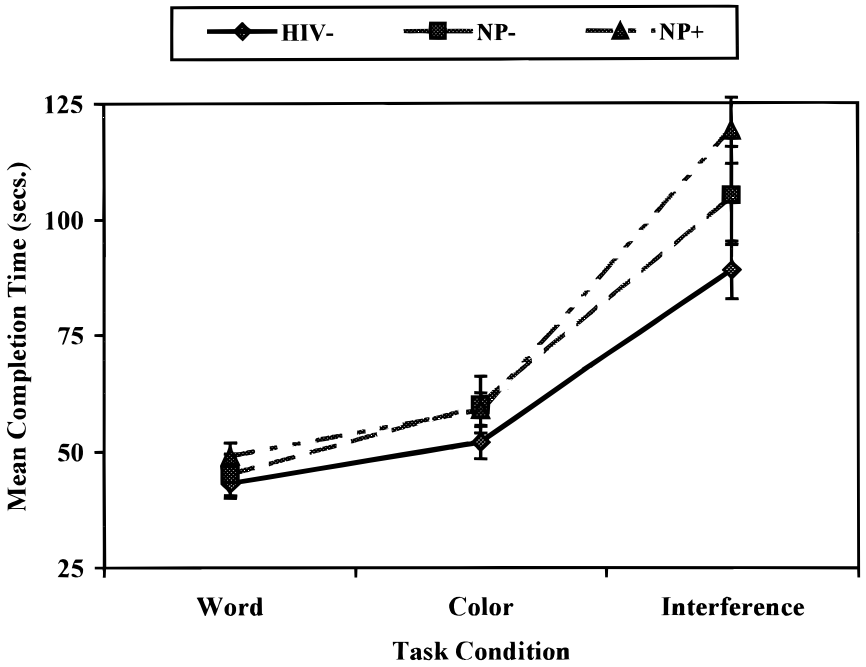
of errors for each condition were noted. Completion time results were analyzed using 3 × 3 mixed-model ANOVA with group (HIV−, NP−, NP+) as the between-subjects factor and condition (word reading, color naming, interference) as the within-subjects factor. As depicted in Figure 4, this ANOVA revealed significant main effects for group [$F(2,75) = 5.8$, $p < .01$] and condition [$F(2,150) = 305.9$, $p < .001$], and a significant Group × Condition interaction [$F(4,150) = 5.6$, $p < .01$]. As expected, analyses exploring these significant effects showed that completion times were longest for the interference condition and shortest for the word-reading condition. Color naming completion times were significantly longer than word-reading times ($p < .01$) but significantly shorter than interference condition completion times ($p < .001$). Collapsed across Stroop condition, NP+ participants were significantly slower than the HIV− controls ($p < .01$) but did not differ from NP− participants ($p = .22$). NP− participants showed a trend towards slower completion times than HIV− controls ($p = .06$). As shown in Figure 4, the significant Group × Condition interaction observed resulted from NP+ participants performing significantly slower than HIV− controls in the interference condition ($p < .01$) but not in either the word-reading or color-naming conditions. NP− participants did not differ from either seronegative controls or from NP+ participants in any task condition (all ps $> .25$).

As noted in an earlier paper (Hinkin et al., 1999), as well as by other investigators (Becker et al., 1997; Martin et al., 1992), when comparing HIV+ individuals to seronegative controls, it is important to consider whether differences in processing speed might mediate group differences in higher-order cognitive processes (e.g., executive functions). To account for the potential effects of HIV-associated psychomotor slowing in explaining differences in the interference condition we examined Stroop word-reading facilitation and color-naming interference effects. Word-reading facilitation effect was calculated by subtracting each participant's word reading time from their color naming completion time; color-naming interference was calculated by subtracting color naming completion time from interference condition completion time. Word-reading facilitation and color-naming interference effects were then analyzed separately using a one-way ANOVA with neuropsychiatric group (HIV−, NP−, and NP+) as the grouping factor. As depicted in Figure 5, there was no significant group difference in word-reading advantage but there were significant color-naming interference differences [$F(2,77) = 6.96$, $p < .01$]. *Post-hoc* Tukey tests showed that NP+ participants suffered greater interference than HIV− controls ($p < .01$) and also showed a trend towards greater interference than NP− participants ($p = .07$). There was no color-naming interference difference between NP− participants and HIV− controls ($p = .45$)

Finally, errors were analyzed using a 3 × 3 mixed-model ANOVA with group (HIV−, NP−, and NP+) as the between-subjects variable and task condition (word reading, color naming, and interference) as the within-subjects variable. Across groups, mean error rate was higher in the



Note. No group differences on color-naming or word-reading conditions. On interference condition, completion times of NP+ > HIV- but did not differ from NP-. NP- participants did not differ from HIV-.

Fig. 4. Mean completion times for the three conditions of the Stroop task.

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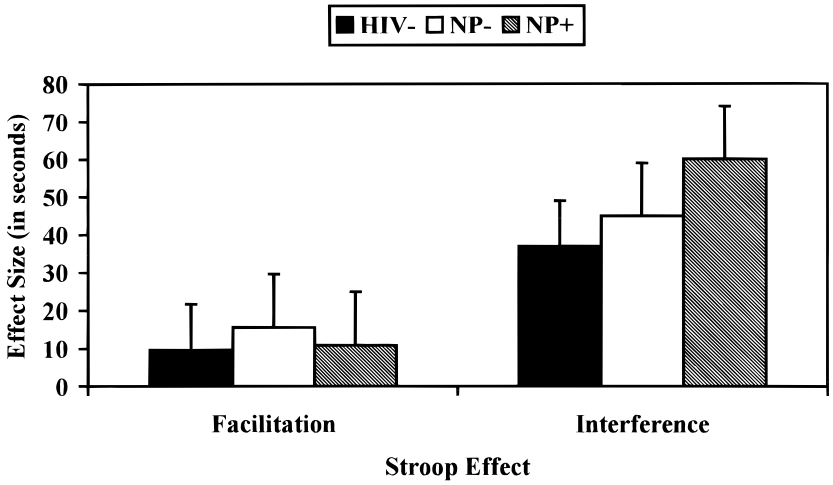

Fig. 5. Stroop word-reading facilitation and color-naming interference scores as a function of neuropsychiatric group status.

interference condition than in either the word reading or color naming conditions (error rates = 3.0%, 0.5%, and 0.6%, respectively). The three groups did not differ in number of errors made ($p = .85$) and there was no significant interaction between Stroop Condition × Group ($p = .91$).

DISCUSSION

Given the wealth of studies that have examined the neurocognitive performance of HIV-1 seropositive individuals, it is somewhat surprising that there has been relatively little study of neuropsychiatric disturbance such as apathy and irritability in HIV-1 infection. Both cognitive and psychiatric changes may accompany brain insult/injury making *both* classes of symptoms potentially useful markers of HIV-associated CNS involvement. Results of the current study suggest that apathy and irritability may be relatively common neuropsychiatric consequences of HIV-associated CNS disturbance. Nearly 65% of the current sample of HIV-infected participants showed either prominent apathy, irritability, or both while demographically matched HIV− controls showed dramatically lower rates of prominent apathy (0%) and irritability (10%). In the current study, depression, while more prevalent among HIV-infected participants, was not uncommon among seronegative controls, suggesting that apathy and irritability are more specific markers of HIV-associated CNS involvement. As we have noted elsewhere, depression in HIV disease may be a response to living with medical, social, and occupational stressors, part of a bereavement reaction, or physical illness misdiagnosed as depression due to the somatic disturbance involved (Castellon et al., 1998). We are not suggesting that depression *cannot* occur as a consequence of HIV-associated CNS involvement, but rather that its etiology is more heterogeneous than that of prominent apathy or irritability.

Interestingly, 16 of the 65 HIV+ participants (25%) were both apathetic and irritable. While apathy and irritability may seem to be relatively orthogonal symptom domains, in other neurologic diseases and disorders these symptoms often coexist (Baddeley et al., 1997; Levy et al., 1998). When there is involvement of frontal–subcortical circuits and structures, especially if the site of pathology is subcortical, these symptoms may arise together. Aspects of both the orbitofrontal syndrome, characterized by increased agitation and irritability, and the medial cingulate syndrome characterized by prominent apathy and affective blunting may arise together when subcortical–thalamic involvement disrupts both circuits (Cummings, 1993).

Contrary to expectations, neuropsychiatric disturbance was not limited to more advanced disease stage (as reflected in medical symptom status) nor was it significantly associated with CD4 cell count. While a greater proportion of NP+ participants were medically symptomatic, there were 12 NP+ participants who were not. However, of the 12 NP+ participants who were ASP, all but 3 showed CD4 cell counts below 400, suggesting that neuropsychiatric disturbance is unlikely in the absence of advanced disease and/or immunosuppression. We did not have access to viral load information in the current study but are planning to explore the relationship between plasma and CSF viral burden and the presence of apathy and irritability. In the current study, the presence of NP disturbance was more robustly associated with neurocognitive performance than were either CD4 cell count or medical symptom status. As such, measures such as CD4 count and medical symptom status may be less sensitive markers of CNS involvement than measures of neurocognitive and neuropsychiatric disturbance.

Perhaps the most compelling argument that neuropsychiatric disturbance is a marker of HIV-associated CNS involvement was its association with *specific* neurocognitive deficits among HIV+ participants. Pronounced apathy and/or irritability were associated with poor performance on those components of the neurocognitive tasks thought to be dependent on effortful, controlled, attentional process-

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ing (e.g., dual-task RT, Stroop interference). In contrast, on those components of the neurocognitive tasks that were less demanding of effortful processing (e.g., single-task simple and choice RT, Stroop word-reading or color-naming), NP+ participants performed similarly to both NP− participants and seronegative controls.

The types of deficits seen among NP+ individuals are suggestive of executive dysfunction. Both the decreased ability to rapidly coordinate and execute the simultaneous performance of two tasks and the ability to rapidly inhibit a prepotent response in favor of a less habitual one are perhaps indicative of frontal–subcortical dysfunction. Brown and Mardsen (1991) found that patients with Parkinson's disease, which is known to disrupt nigrostriatal structures, had deficits relative to age-matched controls on dual-task performance. Activation studies with normal controls have shown that the type of effortful, controlled attentional processing demanded by the neurocognitive tasks in the current study increases blood flow in prefrontal cortex as well as striatum (Corbetta et al., 1991; Pardo et al., 1991). There is compelling evidence suggesting that performance of the Stroop interference condition is mediated by prefrontal structures with deficits in inhibition of the word reading response suggestive of compromised executive function (Bench et al., 1993; Vendrell et al., 1995). Indeed, the pattern of deficits observed among NP+ participants in the current study suggests a dysexecutive syndrome in HIV-1 characterized by deficits on effortful, controlled attentional tasks accompanied by prominent apathy and/or irritability. This is similar to recent findings by Baddeley et al. (1997) who found patients with frontal lobe pathology *who also* evidenced behavioral disturbance (apathy and/or disinhibition) showed executive dysfunction on a dual-task experiment relative to patients with equivalent frontal pathology without such behavioral disturbance.

Limitations of the current study must be noted. Because of the relatively small number of participants in the current study, one should exercise caution in generalizing these findings to the entire population of HIV-infected patients. Nonetheless, the effect sizes observed in the current study suggest a fairly robust relationship between apathy, irritability and executive dysfunction. We made a concerted effort to include a diverse group of HIV-infected participants and matched the control participants accordingly, but we lacked adequate sample size to perform separate analyses on subgroups of infected participants of theoretical interest (e.g., women *vs.* men; injection drug users *vs.* nonusers; heterosexual *vs.* homosexual). Another potential limitation of the current study is that we administered the apathy and irritability interviews only to the study participants themselves and did not obtain ratings from other informants. While other informants play a crucial role in providing information in more cognitively and psychiatrically debilitating diseases such as Alzheimer's, we feel that they are less crucial in the assessment of relatively cognitively intact HIV+ patients (no participants noted the use of, or need for, caregivers, and few, if any, of the participants in the current study would be classified as demented). Although unlikely, it is nonetheless possible that some participants may not have been able to accurately perceive and report on their levels of apathy and irritability. As many of the questions of interest pertain to internal–subjective constructs (e.g., motivation, initiative, frustration), it is not clear how accurate most third-party informants (e.g., romantic partners, roommates, family members etc.) would be with this information.

These limitations noted, this study suggests that neuropsychiatric disturbance is both prevalent and meaningful in HIV infection. The types of behavioral disturbance seen among the NP+ individuals (i.e., apathy, irritability, and neurocognitive deficits) in the current study are likely to negatively impact social, occupational, and instrumental functioning. Accordingly, assessment of these neuropsychiatric symptoms, in addition to cognitive functioning, appears to be an important facet of a thorough neuropsychological evaluation of the HIV-infected patient.

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