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Neuropsychological performance of HIV-1 infected men with major depression

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Abstract

This study sought to determine if human immunodeficiency virus–type 1 (HIV-1) infected depressed men were more likely to be neuropsychologically impaired than their nondepressed counterparts. Subjects were 47 HIV-1 infected men who met DSM–III–R criteria for current major depressive disorder (MDD) and 47 HIV-1 infected nondepressed male controls (*M* age = 34.2 years) equated on HIV-1 disease severity, demographics, and drug use. The psychiatric interview included the Structured Clinical Inventory for the DSM–III–R, and Hamilton Rating Scale for Depression. The neuropsychological battery included tests covering 8 functional domains based on an expanded Halstead-Reitan Battery. The medical assessment included a history and physical examination, immunologic staging, and evaluation of prescription and recreational drug use. Prevalence of global neuropsychological impairment in the two groups (depressed *vs*. control) did not differ [53% *vs*. 38% respectively; $\chi^2(1, N = 94) = 2.11$, $p > .05$]. While syndromically depressed patients performed less well than nondepressed individuals on memory tests [delayed retention portions of the Story Memory Test: $F(1,91) = 5.34$, $p < .05$; and Figure Memory Test: $F(1,90) = 4.16$, $p < .05$], the majority of depressed participants (64%) did not have clinically impaired memory. No relationship between neuropsychological impairment and severity of depression was observed. The results suggest that, while HIV-1 infected men with major depression may perform more poorly than nondepressed men on some aspects of memory tasks, they are not more likely to evidence clinically significant neurocognitive impairment. (*JINS*, 1997, *3*, 457–463.)

Keywords: HIV-1, Major depression, Neuropsychological impairment, Cognitive functioning

INTRODUCTION

While the risk of a major depressive episode for human immunodeficiency virus–type 1 (HIV-1) infected individuals is not as great as was once thought (Perry & Tross, 1984), many such persons (4–10%) are likely to develop a major depression at some point in their disease process (Atkinson et al., 1988; Perry, 1990; Williams et al., 1991; Rosenberger, 1993; Perkins, 1994). Likewise, there is growing evidence of mild neuropsychological impairments in a minority (possibly up to 1/3) of medically asymptomatic HIV-1 infected men (Heaton et al., 1995). Although both major depression (Cassens et al., 1990) and HIV-1 infection (Grant & Heaton, 1990) have been associated with cognitive disturbance (e.g., slowed thinking and decreased concentration, memory, and ability to make decisions), the combined effect of these diagnoses on cognition is unclear.

Men with both HIV-1 infection and major depression may be more frequently, more severely, or qualitatively differently impaired cognitively than individuals with either disorder alone. Further, the source of the cognitive disturbance may be difficult to determine. The distinction is clinically relevant because cognitive disturbances associated with major depression alone may subside when the depression remits, whereas disturbance caused by brain damage from HIV-1 would be expected to remain and possibly worsen.

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Treatments in these two conditions would differ, and may interact. Thus, clarification of the causes and course of cognitive disturbances in HIV-1 infected depressed men could improve both understanding and treatment.

Of the 13 studies of HIV-1 infected patients known to us, 7 were unable to identify any significant association between depression and neuropsychological status (Atkinson et al., 1988; Poutiainen et al., 1988; Fitzgibbon et al., 1989; Kovner et al., 1989; McArthur et al., 1989; Temoshok et al., 1989; Grant et al., 1993). Four studies supported an increased risk of cognitive impairment in depressed patients. Specifically, HIV-1 infected individuals who reported more depressive symptoms demonstrated poorer scores on tests of verbal memory and perceptual–motor speed: [Rey Auditory Verbal Learning and Grooved Pegboard Test (Hinkin et al., 1992), increased simple reaction time (Martin et al., 1992), and decreased sequencing efficiency (Bornstein et al., 1993)] and a worse global rating of neuropsychological functioning (Stern et al., 1991). Two studies found that HIV-1 infected persons who reported more depressive symptoms were also more likely to report higher levels of cognitive impairment, but did not show increased cognitive impairment on objective testing (Kocsis et al., 1989; Mapou et al., 1993). It is also noteworthy that even when researchers have found positive associations between cognitive deficits and depression, they have questioned the clinical significance of their findings. In addition, at least one positive finding (Martin et al., 1992) has been reversed after further investigation revealed that the depressive symptoms used to separate patients into groups more likely reflected CNS effects of HIV-1 rather than symptoms of depression (Law et al., 1993).

While the existing evidence supports the view that major depression does not increase rates of neuropsychological impairment in HIV-1 illness, definitive conclusions cannot be drawn, due to the methodological limitations in the available studies (e.g., small sample size, inadequate exclusion criteria, lack of control groups, small or idiosyncratic neuropsychological batteries, and reliance on self-report measures of depression). Perhaps mild neurocognitive impairments, significant enough to interfere with an individual's daily living, might have been sufficiently subtle and varied (across functional domains) to be overlooked by the simple comparison of group means. Small and inconsistent findings may also be due to the use of brief neuropsychological screening batteries and self-report measures of depressive symptoms rather than clinical diagnosis of a syndromic depression. To date, no studies have utilized an extensive neuropsychological battery to assess functioning in a large number of HIV-1 infected individuals diagnosed with major depressive disorder and well matched controls.

The objectives of this study were to (1) identify and describe neuropsychological correlates of major depression, established by structured diagnostic interviews, in HIV-1 infected individuals; and (2) clarify the relationship between severity of depressive symptoms and neuropsychological impairment.

METHODS

Research Participants

Potential participants were HIV-1 infected men who participated, from 1990 to 1993, in a larger longitudinal study at the San Diego HIV Neurobehavioral Research Center (HNRC) designed to examine the etiology, pathogenesis, natural history, and features of neurobehavioral disorders associated with HIV-1 infection. Those HIV-1 infected men who met DSM–III–R criteria for current major depression comprised the study group ($N = 47$). Carefully matched HIV-1 infected men who were not experiencing a current episode of major depression comprised the control group ($N = 47$). The primary focus of this study was to explore the impact of current (as opposed to past) major depression on neuropsychological functioning. Therefore, individuals with a lifetime history of major depression were included in both the currently depressed ($N = 44$, 94%) and control groups ($N = 12$, 25%). The groups were equated for age, education, race, disease severity (CD4 cell count and CDC classification), current medical symptoms, referral source (U.S. Navy or San Diego civilian community), current alcohol/drug use, and use of antiretroviral and antidepressant medications.[1]

The source of participants and inclusion–exclusion criteria for the parent HNRC study were reported previously (Heaton et al., 1995). In brief, participants had to be HIV-1 infected men between the ages of 18 and 60 years, who completed medical and neuropsychological assessment within 21 days of psychiatric evaluation. Potential participants were excluded if they had a history of non-HIV-related neurological disorder or medical disorder that affected nervous system function (e.g., diabetes, seizure disorder, head trauma with more than 30-min loss of consciousness or other complications), or met clinical criteria for dementia (American Psychiatric Association, 1987). Also excluded were people with histories of learning disability or psychotic disorder, current substance dependence, lifetime intravenous drug use more than 10 times, or insufficient facility with the English language (persons whose first language was not English).

Measures

Biomedical measures of health status

HIV-1 serologic status of all subjects was established by repeated positive enzyme-linked immunoassay (ELISA) with Western Blot confirmation. Staging of HIV-1 disease utilized strata of CD4 lymphocyte counts and clinical history according to the 1993 Revised Classification System following a physical exam, medical interview, and lympho-

[1]The majority of depressed participants were not taking antidepressant medication when the baseline assessments were made because they either had refused medication or had agreed to participate in a randomized clinical trial of an antidepressant that required discontinuation of current medications for 3 weeks before study medications were administered.

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cyte subset phenotype (CD4 and CD8) enumeration in blood (CDC, 1992). Current medical symptoms were assessed via a clinician rated instrument that assessed the frequency and intensity of fever, fatigue, diarrhea, anorexia, and sensory symptoms. Clinically severe symptoms are defined as fever greater than 102° F, fatigue reported as sufficient to interfere with daily living tasks, diarrhea more often that 5 times per day, severe anorexia with minimal food intake, or sensory symptoms severe enough to interfere with daily functioning.

Psychiatric assessments

The psychiatric assessment consisted of the Structured Clinical Interview for DSM–III–R (SCID; Spitzer et al., 1987) and the Hamilton Rating Scale for Depression 24-item scale (HRSD; Hamilton, 1960). The SCID was administered by a team of five trained interviewers (four psychiatric fellows, one clinical social worker) who met every 6 months to establish interrater reliability. Ninety percent agreement on the presence of major Axis I diagnoses was achieved. Similarly interviewers (four psychiatric fellows, one clinical social worker, and two clinical psychologists in training) were trained in the standardized administration of the HRSD, and interrater reliability was reestablished every 6 months. Utilizing an intraclass correlation (Whitehurst, 1984), interrater reliability for the seven HRSD interviewers utilized in the present study was established at .90. The 24-item total score of the HRSD was used in all of the analyses.

Neuropsychological assessment

All neuropsychological assessments were conducted by trained technicians according to the standard instructions contained in the various test manuals. The extensive test battery took about 8 hr to administer to most participants, and was given over at least a 2-day period. Multiple test sessions and rest breaks within sessions were arranged to accommodate the needs of the participants, with the goal being to minimize stress and frustration, in an attempt to obtain the best possible performance from the participant. The comprehensive test battery consisted of the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), as well as an expanded Halstead-Reitan Battery that includes all core Halstead-Reitan tests and the Digit Vigilance Test, the Story Memory Test, the Figure Memory Test, the Boston Naming Test, the Thurstone Word Fluency Test, the Complex Ideational Material subtest of the Boston Diagnostic Aphasia Exam, the Grooved Pegboard Test, the Paced Auditory Serial Addition Test (PASAT), and the oral letter and category fluency test from the Multilingual Aphasia Examination. Summary scores were calculated as described by Heaton et al. (1994). Briefly, the 52 test variables were grouped into eight ability areas according to the skills purportedly tapped (consistent with the clinical literature and factor analytic studies). The eight domains were (1) verbal, (2) psychomotor, (3) attention/speed of information processing, (4) learning and incidental memory, (5) abstraction/flexibility of thinking, (6) memory (retention), (7) sensory, and (8) motor (Heaton et al., 1995).

For all but three test measures (PASAT, letter fluency, and category fluency), raw scores were converted to age-, education-, and sex-corrected T scores based on results of large samples of control subjects collected in previous normative studies (Heaton et al., 1991; Heaton, 1992). Demographically corrected T scores for the remaining three tests were obtained based on data from HIV-1-uninfected men assessed by the HNRC.

Clinical ratings as described by Heaton et al. (1994) were used to classify participants' performance in the eight major ability areas. Briefly, a clinician, who was blind to the diagnosis of depression, was given demographic information, the participant's raw test scores and T scores, and his actual performance on the Aphasia Screening Exam. The clinician then rated each area using a scale from 1 (*above average functioning*) to 9 (*severe impairment*). Based on the eight major ability area ratings, the clinician used the same 9-point scale to produce a measure of overall functioning called the *global neuropsychological rating*. As detailed by Heaton et al. (1994), in order to receive a rating in the impaired range (scores of 5–9), a participant must have received ratings of 5 or above (at least mild impairment) on at least two of the eight major ability areas. For some analyses where the focus was on differential rates of clinically significant impairment, these ratings were used to classify subjects as impaired or unimpaired.

Statistical Analyses

The detection of mild and inconsistent deficits expected in HIV-1 infected depressed individuals has proven to be a difficult task. While no standard approach has been adopted, comparisons of group means can be quite insensitive to these types of deficits (Heaton et al., 1995). In the present study, the evaluation of neuropsychological performance was approached in several ways to ensure the best chance of detecting these deficits, if they exist.

First, a Pearson chi-square test of association was used to determine if the depressed participants were more likely to be globally neuropsychologically impaired than matched controls. Next, a one-way between-subjects multivariate analysis of variance (MANOVA) with the eight major ability area clinical ratings as the dependent variables and group (depressed and control) as the independent variable was utilized to determine if the groups' performance differed in any of the eight major ability areas. For this analysis the total *N* of 94 cases was reduced to 92 with the deletion of one case from each group due to missing data. Square root transformations were utilized for the psychomotor, memory, and verbal dependent variables, and a log transformation was used for the sensory dependent variable to better approximate a normal distribution. *Post hoc* univariate ANOVAs followed to determine in exactly which ability areas the groups' performance differed. In addition, the *clinical* significance of any ability area performance difference was evaluated

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by comparing rates of impairment (i.e., impaired *vs*. unimpaired). Significant differences between the groups were further examined by analyzing the tests that comprise the domain. Lastly, Spearman and Pearson correlations were used to explore the relationship between neuropsychological impairment and severity of depression. Bonferroni corrections to maintain family-wise α at .05 were used for all of the *post hoc* and correlation analyses.

RESULTS

The groups had similar demographic characteristics and CD4 cell counts. As expected, their mean HRSD scores were divergent (see Table 1). Equal numbers of participants from the depressed and control groups were classified in the three CDC 1993 Revised Classification Stages. Seventeen participants from each group were classified as Stage A, 21 participants from each group were classified as Stage B, and 9 participants from each group were classified as Stage C. With the exception of fatigue, the groups reported similar levels of current medical symptoms [i.e., fever: $F(1,90) = .06$, $p = .81$; diarrhea: $F(1,90) = .01$, $p = .91$; anorexia: $F(1,90) = .28$, $p = .60$; and sensory symptoms: $F(1,90) = .64$, $p = .43$]. Consistent with the moderate levels of fatigue commonly associated with depressive episodes, the HIV-1 infected depressed men reported more fatigue than controls [$F(1,90) = 6.61$, $p = .01$] . The depressed and control groups had similar rates of use of antiretroviral medications [64% *vs*. 57% respectively; $\chi^2(1, N = 94) = .14$, $p = .71$], and antidepressants [4% on fluoxetine *vs*. 0% respectively; $\chi^2(1, N = 94) = .04$, $p > .10$].

Data regarding alcohol and drug use were collected via a self-report instrument that measured use of five major classes of drugs [alcohol, cocaine, sedatives/hypnotics, marijuana, and stimulants] in the past 2 weeks, 1 year, and 11 years. There were no significant differences between the groups. However, there were 7 participants (2 depressed and 5 controls) who reported more than minimal use of sedatives and marijuana in the previous 2 weeks. The neuropsychological performance of each of these individuals was evaluated and found to be comparable to the performance of other individuals in their respective groups.

Evaluation of Global Neuropsychological Impairment

Our initial analysis evaluated the likelihood that HIV-1 infected depressed individuals were more globally neuropsychologically impaired than their matched HIV-1 infected nondepressed controls, as defined by a rating of 5 or above on at least two of the eight major ability area ratings. Because the focus was on differential rates of clinically significant impairment, the global ratings were used to dichotomize participants into two groups (*impaired* and *unimpaired*). The prevalence of global impairment was greater in those with depression (53%) than controls (38%), but the difference was not statistically significant [$\chi^2(1, N = 94) = 2.11$, $p = .15$].

Evaluation of the Eight Major Ability Areas

Next we determined if HIV-1 infected depressed men performed more poorly in any of the eight major ability areas relative to the matched controls. A one-way between-subjects multivariate analysis of variance (MANOVA) yielded a significant interaction of Group (depressed *vs*. control) × Dependent Variables [the eight major ability area clinical ratings; $F(7,90) = 2.87$, $p = .01$]. *Post hoc* univariate ANOVAs (utilizing Bonferroni corrections to maintain family-wise α at .05, lowering the critical p value to .006), revealed that the depressed participants performed *more poorly* on the ability areas of memory [$F(1,90) = 13.47$, $p < .001$], attention [$F(1,90) = 6.86$, $p < .005$], and learning [$F(1,92) = 6.66$, $p = .006$]. However, the depressed group tended to have poorer performance than controls on all of the major ability area clinical ratings (see Figure 1).

Table 1. Demographic variables

	Group		
Variable	Depressed ($N = 47$)	Controls ($N = 47$)	Test Statistic
Age, years (*M, SD*)	34.3 (6.8)	34.1 (6.0)	$F = .02$, ns
Education, years (*M, SD*)	13.7 (2.4)	13.7 (1.5)	$F = .02$, ns
Race	41 White	41 White	
	4 Black	4 Black	$\chi^2 = .00$, ns
	2 Latino	2 Latino	
Civilian *versus* Navy	29 Civil	29 Civil	
	19 Navy	19 Navy	$\chi^2 = .00$, ns
Abs CD4 (*M, SD*)	324 (259)	355 (289)	$F = .30$, ns
HRSD (*M, SD*)	23.6 (8.5)	5.9 (5.5)	$F = 12.39$*

Note. Civil = civilian; Navy = Navy personnel; Abs CD4 = absolute CD4 T-lymphocyte count, HRSD = mean 24-item Hamilton Rating Scale for Depression total score.
*$p = .000$.

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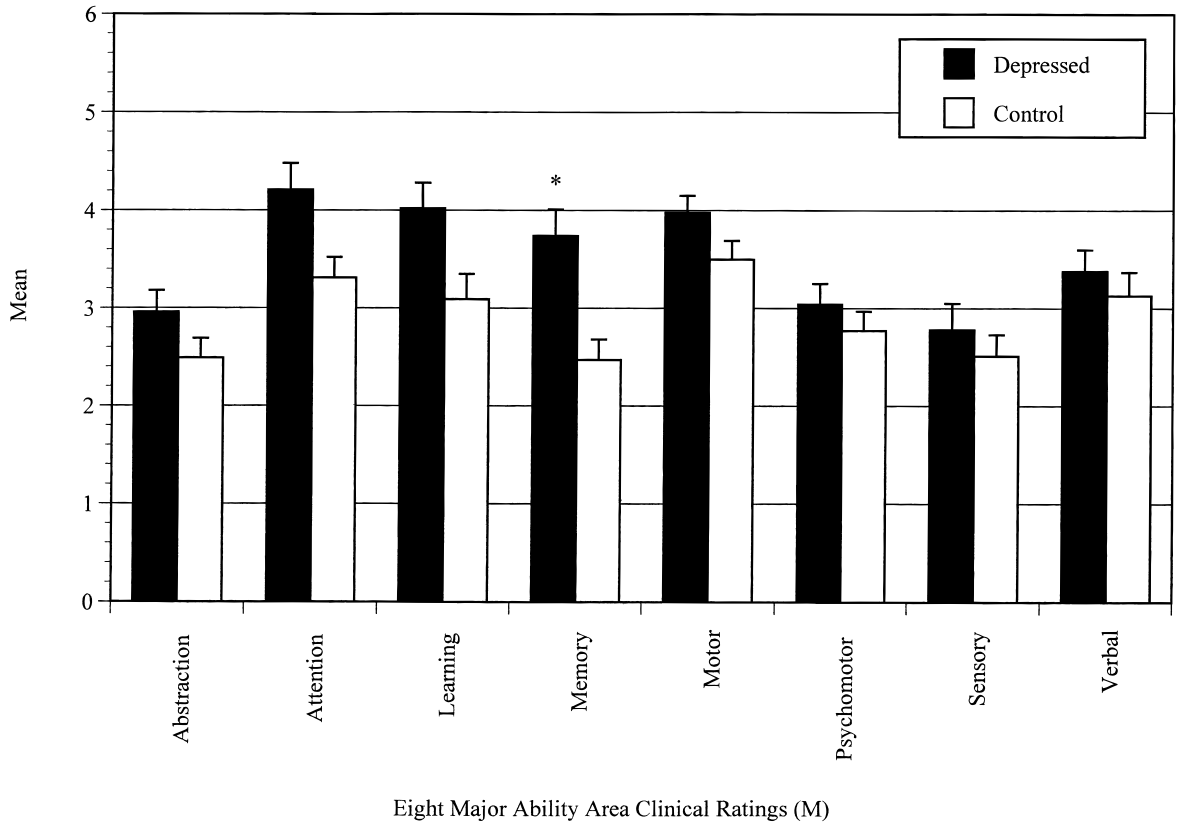

Fig. 1. Mean and standard error of the mean of the eight major ability area clinical ratings. *$p \leq .006$.

In order to evaluate the clinical significance of these performance differences on memory, attention, and learning, we compared the rates of impairment (i.e., impaired *vs.* unimpaired) in each of the eight major ability areas. A Bonferroni correction to maintain family-wise α at .05 was used, lowering the critical p value to .006. There were no significant differences between the groups; only a trend toward significance for the area of memory [36% *vs.* 13%; $\chi^2(1, N = 94) = 6.97$, $p = .008$].

Memory was further examined by analyzing separately the two tests that comprise this domain (i.e., Story Memory Test–Memory and Figure Memory Test–Memory). Two independent one-way ANOVAs were performed on the T scores of these two tests. As before, a Bonferroni correction was made to maintain family-wise $\alpha = .05$, and each ANOVA was evaluated at $\alpha = .025$. Both tests were significant. The depressed participants performed significantly more poorly on the retention portion of the Story Memory Test–Memory [$F(1,91) = 5.34$, $p < .01$], with a mean T score of 42.07 ($SD = 14.25$), as compared to the control group's mean of 48.32 ($SD = 11.68$). Depressed participants also performed significantly more poorly on the retention portion of the Figure Memory Test–Memory [$F(1,90) = 4.16$, $p < .02$], with mean T scores for depressed and controls of 49.63 ($SD = 8.68$), and 52.78 ($SD = 5.89$), respectively.

A similar approach was used to examine the individual tests that comprise the major ability areas of attention and learning; none reached significance.

Evaluation of the Relationship Between Severity of Depression and Neuropsychological Functioning

Spearman correlations were calculated to explore the relationship between the severity of depression and neuropsychological impairment. The baseline Hamilton Rating Scale for Depression total scores (HRSD) of all the depressed participants were correlated with the Global Neuropsychological Rating, and all of the significant major ability area clinical ratings (i.e., memory, learning, and attention). Pearson correlations were used to explore the relationship between severity of depressive symptoms and T scores on the memory portions of the Story Memory and Figure Memory Test. None of the analyses yielded significant results, with Spearman and Pearson correlations ranging from .00 to .11.

DISCUSSION

We evaluated whether HIV-1 infected men with major depression were more likely to be neuropsychologically impaired than nondepressed seropositive controls. While our finding of similar rates of global impairment is consistent with other studies, a global impairment rate of 53% is noticeably higher than those in other reports (26%: Bornstein et al., 1992; 22%: McArthur et al., 1989). Our use of a more comprehensive neuropsychological battery or more liberal criteria for impairment than those in most other studies may

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account for the difference. Nevertheless, the diagnostic standards used here have been found to provide good accuracy in discriminating between individuals with and without various neurologic disorders, with excellent balance between false positive and false negative errors (Heaton et al., 1981, 1991).

Two analytic approaches (comparisons of group means and impairment rates) were used to determine if HIV-1 infected individuals with major depression demonstrated poorer performance relative to controls in any of the eight major ability areas. Depressed participants in this sample exhibited a consistent pattern of poorer performance in all eight of the major ability areas. Statistically significant differences in group means were observed in the areas of memory (retention), attention, and learning. However, the means of both groups were well within the normal range of functioning, and therefore the observed poorer performance of the depressed participants appears to have limited clinical relevance.

This conclusion was supported by analysis of rates of clinically significant impairment. After adjustments for multiple comparisons, no significant differences emerged in any of the eight major ability areas, but a statistical trend was noted towards more impairment for depressed participants in the area of memory. This trend for defective retention, as opposed to learning efficiency, differs from other studies that have assessed memory performance in HIV-1 infected individuals with major depression (Kovner et al., 1989; Grant et al., 1993). While it is possible that our comprehensive study identified a true difference in retention, it seems unlikely that all of the other studies that adequately assessed memory (Atkinson et al., 1988; Poutiainen et al., 1988; Kovner et al. 1989; McArthur et al., 1989; Stern et al., 1991; Hinkin et al., 1992; Martin et al., 1992; Bornstein et al., 1993; Grant et al., 1993; Mapou et al., 1993) failed to observe this difference.

On the other hand, despite the comprehensiveness of our test battery, we failed to compare cued recall and recognition assessment formats that would have differentiated problems in retrieval *versus* storage of memories. A subcortical hypothesis of depression (Massman et al., 1992) predicts deficits in encoding and/or retrieval, but not storage (abnormal forgetting). Future studies in this population should assess the specific mechanism of memory failures.

Consistent with several other studies (Atkinson et al., 1988; Poutiainen et al., 1988; Kocsis et al., 1989; Kovner et al., 1989; McArthur et al., 1989; Grant et al., 1993; Mapou et al., 1993) we found no relationship between the severity of depressive symptoms and neuropsychological impairment. The absence of such a relationship between severity of depression and memory scores and clinically impaired memory in most depressed HIV-1 infected participants further suggests that the poorer performance of our depressed participants on memory measures should be interpreted with caution.

Several studies have found that depressed individuals who see themselves as highly depressed are also more likely to report cognitive difficulties (e.g., Kocsis et al., 1989; Perkins, 1994). However, these depressed individuals are not more likely to evidence impairments on neuropsychological batteries. Future studies that incorporate self-report measures of cognitive functioning along with thorough assessments of psychiatric, neuropsychological, and medical variables would be helpful in determining whether HIV-1 infected individuals with major depression are more likely to evidence neuropsychological deficits, or simply to overreport. While the cross-sectional design of this study prevented us from being able to address the primary *versus* secondary nature of depression, we believe that future research should utilize longitudinal designs to improve our understanding of this important area.

While this study revealed that HIV-1 infected depressed patients demonstrate somewhat poorer memory performance (delayed retention), depression appears to play a minimal role in explaining neuropsychological impairment in HIV-1 infected individuals.

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