Neurocognitive Complaints in HIV-Infection and Their Relationship to Depressive Symptoms and Neuropsychological Functioning*

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ABSTRACT

We examined the degree to which depressive symptoms, clinical staging of HIV disease, and neuropsychological (NP) functioning were related to neurocognitive complaints in HIV-infection. One hundred adults with HIV-infection (12 asymptomatic, 41 mildly symptomatic, and 47 with AIDS) were administered NP tests of attention and working memory, language, psychomotor speed, verbal memory, and conceptual problem-solving, the Beck Depression Inventory, and the Patient’s Assessment of Own Functioning Inventory (Chelune, Heaton & Lehman, 1986), a subjective neurocognitive complaint questionnaire where patients rated their problems with memory, language and communication, sensory-motor skills, and higher-level cognitive and intellectual functions. Neurocognitive complaints (regardless of specific type) were correlated significantly with depressive symptoms and with NP measures of attention and working memory, psychomotor skills, and learning efficiency. However, multiple regression analyses revealed that depressive symptoms accounted for the majority of variance explained in neurocognitive complaints with psychomotor efficiency generally predicting the remaining variance. Neurocognitive complaints did not differ according to HIV clinical staging.

The risk for neurocognitive impairment due to primary HIV-infection (i.e., the effect of HIV-1 infection on the central nervous system that is not due to infections, tumors, cerebrovascular complications, or metabolic disorders) increases with each successive stage of HIV disease (Center for Disease Control, 1993 revised classification system for HIV infection [CDC93]; Heaton et al., 1995). Recent reviews of the literature suggest that 35% of asymptomatic (CDC93-A), 44% of mildly symptomatic (CDC93-B), and 55% of patients with acquired immunodeficiency syndrome (AIDS; CDC93-C) exhibit neuropsychological impairments, particularly in the areas of attention, speed of information processing, learning efficiency, and psychomotor skills (Heaton et al., 1995; White, Heaton, & Monsch, 1995), and the presence of these impairments is associated with higher rates of unemployment and decreased work efficiency in those still working (Albert et al., 1995; Heaton et al., 1996; Heaton et al., 1994), problems with medication adherence (Albert et al., 1998), decreased quality of life (Kaplan et al., 1995), and increased risk for mortality (Ellis et al., 1997; Marder, Albert, McDermott & the DANA Consortium, 1998; Mayeux et al., 1993; Sacktor et al., 1996).

Neuropsychological testing is well established as the most reliable and valid method for

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detecting HIV-related cerebral impairments (Butters et al., 1990; Grant & Martin, 1994; Heaton et al., 1995; Heaton et al., 1996; Miller, Satz, & Visscher, 1991; Miller et al., 1990; White et al., 1995), especially in the initial stages of HIV-infection when the impairments tend to be mild and ‘spotty’ (Butters et al., 1990; Heaton et al., 1996; White et al., 1995). Up to 52% of persons with HIV-infection report neurocognitive complaints, particularly problems with memory or concentration (Mehta et al., 1996; Wilkins et al., 1991), but the nature, clinical significance, and predictive value of these neurocognitive complaints is poorly understood.

Due to declining health care resources, neuropsychological services, despite their significant clinical benefit in HIV management, are not often available in the clinic or hospital. Because of this, clinical decisions regarding the presence and severity of HIV-related brain impairments, and the timing of when to initiate pharmacologic treatments with brain penetrating antiretroviral or neuroprotective agents, are often based solely on patients’ self-reported neurocognitive complaints. However, the reliance on patients’ neurocognitive complaints as reliable and valid indicators of brain functioning has not consistently been supported by empirical studies. For example, studies by van Gorp and colleagues (Hinkin et al., 1996; Moore et al., 1997; van Gorp et al., 1991) and Wilkins (Wilkins et al., 1991) indicated that neurocognitive complaints were not related to neuropsychological functioning but rather to level of depressive or psychiatric symptoms, whereas several other groups of investigators have found significant associations between neurocognitive complaints and neuropsychological test performance (Beason-Hazen, Nasrallah, & Bornstein, 1994; Mapou et al., 1993; Poutiainen & Elovaara, 1996; Stern et al., 1991). In two of these latter studies, neurocognitive complaints (regardless of the specific type of complaint) were related to performance on measures of attention, psychomotor processing speed, and memory, but also to depressive symptoms (Beason-Hazen et al., 1994; Mapou et al., 1993). These findings led Mapou and colleagues (1994) to suggest that the relationship between neurocognitive complaints and neuropsychological test performance is likely independent from the relationship between neurocognitive complaints and mood.

The present study was designed to further clarify the nature and clinical significance of neurocognitive complaints in HIV-infection. Our main objectives were to determine which specific neuropsychological abilities were associated with neurocognitive complaints, and to quantify the independent contributions of both neuropsychological test performance and depressive symptoms to neurocognitive complaints. We administered the Patient’s Assessment of Own Functioning Inventory (Chelune, Heaton, & Lehman, 1986), a subjective neurocognitive complaint questionnaire, to 100 HIV-infected individuals with varying levels of systemic disease, and examined the degree to which subjective neurocognitive complaints related to neuropsychological functioning and depressive symptomatology. We predicted that neurocognitive complaints would: (1) increase with depressive symptoms but also with HIV disease progression (i.e., from CDC93-A to CDC93-C stages); (2) correlate with neuropsychological measures that reflect complex psychomotor speed, attention, and working memory; and (3) independently reflect both neuropsychological impairments and mood disturbance, although mood symptoms were expected to explain most of the variance in neurocognitive complaints.

METHOD

Participants
One hundred HIV-infected adults (96 males, 4 females; 95% Caucasian) with no history of neurological disease (e.g., seizure disorder), significant developmental problems (e.g., diagnosis of learning disability), CNS opportunistic infection, head trauma with loss of consciousness exceeding 30 min, or substance abuse or dependence in the past 2 months, participated in this study. Of the 100 participants, 12 were asymptomatic (CDC93 A1 and A2), 41 were mildly symptomatic (CDC93 B1 and B2), and 47 had AIDS-defining illnesses or CD4 Lymphocyte counts less than 200 (CDC93 A3 \[n = 3\], B3 \[n = 14\] and C1-C3 \[n = 30\]) (Center for Disease Control, 1992). Eighty-six percent of
the sample was on combination antiretroviral treatment.

Seventy-four percent of our sample was referred for neuropsychological examination (n = 74), of which 15 participants were referrals from general medical or infectious disease clinics, and the remaining 59 participants were referrals from psychiatric clinics. The two most common reasons for referral were to determine the nature and clinical significance of a patient’s subjective cognitive complaints, and/or to provide a baseline of the patient’s neuropsychological status. The remaining 26 participants (i.e., 26% of sample) were recruited for this research study through local AIDS Service Organizations, postings in clinics, newspaper advertisements, and by word of mouth. Participants from the three recruitment sources were not different in age [F(2,97) = 0.07, p = .93], education [F(2,97) = 1.23, p = .30], CD4 Lymphocyte count [F(2,96) = 0.07, p = .93] or CDC93 stage of HIV-infection [Chi-Square = 2.37 (df = 4), p = .67].

The mean age and education of the sample was 40.9 (SD = 8.9) and 14.7 (SD = 2.6) years, respectively. Mean ANART was 118.4 (SD = 6.6). The sample had mean WAIS-R Information and Picture Completion demographically-corrected T scores (Heaton, 1992) of 49.2 (SD = 8.5) and 49.6 (SD = 8.6), respectively. The mean level of depressive symptoms for the sample was 16.8 (SD = 10.4) on the Beck Depression Inventory (Beck, & Steer, 1992; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

Participants in each of the three CDC93 clinical stages of HIV-1 disease were similar in age [F(2,97) = 1.16, p = .32], education [F(2,97) = 1.20, p = .31], ANART [F(2,94) = 1.24, p = .29], WAIS-R Information T Score [F(2,91) = 0.58, p = .56], WAIS-R Picture Completion T Score [F(2,93) = 2.19, p = .12], depressive symptoms [F(2,96) = 0.31, p = .73], and in the level of their subjective neurocognitive complaints [F(2,97) = 0.60, p = .55] on the Patient’s Assessment of Own Functioning Inventory (Chelune et al., 1986). CD4 Lymphocyte counts, as expected, were significantly different across the three CDC93 categories [F(2,96) = 32.77, p < .0001]. See Table 1 below for demographics, symptoms and CD4 Lymphocyte counts across the three CDC93 groups.

Table 1. Demographic Data (N = 100).

<table>
<thead>
<tr>
<th></th>
<th>CDC-A (n = 12)</th>
<th>CDC-B (n = 41)</th>
<th>CDC-C (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.3 (9.2)</td>
<td>42.4 (8.6)</td>
<td>39.5 (9.0)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.3 (2.5)</td>
<td>14.4 (2.7)</td>
<td>15.1 (2.5)</td>
</tr>
<tr>
<td>ANART (estimated VIQ)</td>
<td>115.6 (7.5)</td>
<td>118.3 (6.1)</td>
<td>119.1 (6.7)</td>
</tr>
<tr>
<td>WAIS-R Informationa</td>
<td>47.7 (9.5)</td>
<td>50.3 (8.8)</td>
<td>48.6 (8.1)</td>
</tr>
<tr>
<td>WAIS-R Picture Completiona</td>
<td>46.3 (7.8)</td>
<td>51.5 (6.9)</td>
<td>48.6 (9.9)</td>
</tr>
<tr>
<td>Beck Depression Total</td>
<td>18.2 (9.9)</td>
<td>15.9 (10.1)</td>
<td>17.2 (11.0)</td>
</tr>
<tr>
<td>Total Neurocognitive Complaintsb</td>
<td>50.7 (23.6)</td>
<td>55.8 (28.5)</td>
<td>49.0 (31.3)</td>
</tr>
<tr>
<td>Recent CD4 Lymphocyteb</td>
<td>524.9 (181.2)</td>
<td>381.8 (135.6)</td>
<td>186.1 (150.5)</td>
</tr>
</tbody>
</table>

*a Demographically-corrected T score (Heaton et al., 1992).

*b Patient’s Assessment of Own Functioning Inventory (Chelune et al., 1986).

*p < .05 (all groups significantly different from each other).

Measures

The neuropsychological test battery was selected according to guidelines that emanated from the National Institute of Mental Health Workshop on Neuropsychological Assessment Approaches of AIDS-related Cognitive Changes (Butters et al., 1990). The tests were as follows: (1) ANART (Spreen & Strauss, 1991); (2) WAIS-R Digit Span and Digit Symbol (Wechsler, 1981); (3) Trail Making Test: Parts A and B (Reitan & Wolfson, 1993); (4) Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and verbal fluency (Spreen & Strauss, 1991); (5) Finger Tapping and Grooved Pegboard (Heaton, Grant, & Matthews, 1991; Reitan & Wolfson, 1993) (6) California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987); (7) Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993); and (8) Beck Depression Inventory (Beck & Steer, 1993).

To assess subjective neurocognitive complaints, we administered the Patient’s Assessment of Own Functioning (PAOF) Inventory (Chelune et al.,
1986). The PAOF is a self-report instrument that was “designed to elicit patients’ self-perceptions regarding the adequacy of their functioning in various everyday tasks and activities” (Chelune et al., 1986, p. 96). The first 33 items of this questionnaire cover aspects of memory (10 items), language and communication (9 items), sensory-perceptual and motor skills (5 items), and higher-level cognitive and intellectual functions (primarily executive-type skills; 9 items). Participants were instructed to rate how often they experienced a particular kind of difficulty on a 6-point scale (0 = almost never; 1 = very infrequently; 2 = once in a while; 3 = fairly often; 4 = very often; and 5 = almost always). The PAOF is reproduced, with permission, in the appendix.

Procedure

Recruitment and testing of participants for this study was approved by our hospital Research Ethics Board. Questionnaires and neuropsychological tests were administered in two sessions (1.5-2.0 hr each) that were separated by a 30-45 min break. In over 90% of cases, testing was completed on the same day; for the remaining cases, the elapsed time between test sessions was generally within 1-7 days.

For the purposes of our PAOF analyses, we summed individual ratings in each of the four major areas (i.e., memory, language, sensory-perceptual skills, and higher-level cognitive and intellectual functions) and divided that number by the number of items in each major area to reflect a mean rating for each complaint area. We also calculated a ‘total’ PAOF score (sum of 33 items) and divided this number by 33 to reflect a mean level of total subjective neurocognitive complaints.

We used standard clinical cut-offs (Beck & Steer, 1993) to define severity of depressive symptoms on the Beck Depression Inventory (BDI) total score: ‘minimal’ (BDI < 10), ‘mild’ (BDI = 10-16), ‘moderate’ (BDI = 17-29), and ‘severe’ (BDI = 30+). In order to ensure that the somatic or vegetative items that are included in the Beck Depression Inventory were not confounding our findings (i.e., by causing elevations on the total BDI score because of the effects of HIV-infection and not depression), we re-ran our analyses using a modified BDI score which included only the sum of the first 13 cognitive and affective items: subjects with modified BDI scores of 10 or less were classified as ‘not depressed’ and those with scores greater than 10 were suggestive of ‘moderate’ depression (Beck & Steer, 1993). For the purposes of certain analyses, we grouped those participants who were asymptomatic (CDC93-A) or mildly symptomatic (CDC93-B) together (n = 53) and compared them to the 47 participants with AIDS (CDC93-C: A3, B3, and C1-C3).

All data analyses were carried out with SPSS for the Power Macintosh (version 6.1.1). Statistical significance was defined as p < .05 for all analyses.

RESULTS

Impact of Depressive Symptoms and CDC93 HIV Staging on Neurocognitive Complaints

To address our first prediction that neurocognitive complaints would increase with depressive symptoms but also with HIV disease progression, we carried out a 4 × 2 ANOVA with four levels of depressive symptoms (‘minimal’, ‘mild’, ‘moderate’, and ‘severe’) and two categories of HIV disease (asymptomatic/mildly symptomatic and AIDS). Our first prediction was only partially supported. Total mean level of subjective neurocognitive complaints on the Patient’s Assessment of Own Functioning Inventory were affected by depressive symptoms on the Beck Depression Inventory [F(3,91) = 26.56, p < .001], but not by CDC93 clinical staging of HIV-1 disease [F(1,91) = 0.98, p = .32], and there was no significant interaction between depressive symptoms and CDC93 staging [F(3,91) = 0.43, p = .73]. This pattern of results (significant main effect for ‘depression’ and nonsignificant results for CDC93 staging and BDI × CDC93 interaction) was the same across the four neurocognitive complaint areas (memory, language, sensory-motor, and higher-level cognitive and intellectual functions) regardless of whether we used a total or modified Beck Depression Inventory score. See Figure 1 for mean level of subjective neurocognitive complaints according to severity of HIV disease (CDC93) and Figure 2 for mean level of neurocognitive complaints according to ‘depression’ severity using the total Beck Depression Inventory score.

In order to ensure that the somatic or vegetative items that are included in the Beck Depression Inventory were not confounding our ANOVA results (i.e., symptoms which may cause elevations on the total BDI score because of the
effects of HIV-infection and not depression), we re-ran our ANOVAs using a modified BDI score which included only the sum of the first 13 cognitive and affective items. In these posthoc analyses, subjects with modified BDI scores of 10 or less were classified as ‘not depressed’ and those with scores greater than 10 were classified into the ‘moderate’ depression group (Beck and Steer, 1993). The results from the 2 × 2 ANOVAs were exactly the same (i.e., main effect for depression but nonsignificant effects for CDC93 staging or for the interaction between depression and CDC93).

**Neuropsychological Correlates of Neurocognitive Complaints**

In our next set of analyses, we examined the associations between subjective neurocognitive complaints (total and four complaint areas), depressive symptoms, and selected measures of neuropsychological functioning (i.e., attention and working memory [Digit Span forward and backward scores]), language (Boston Naming and verbal fluency), psychomotor speed (Digit Symbol and Trail Making Test, Parts A and B), verbal learning and memory (California Verbal Learning Test), conceptual skills and problem-solving ability (Wisconsin Card Sorting Test) and simple motor skills (Finger Tapping and Grooved Pegboard).
The results, as shown in Table 2, indicate that there are strong relationships between subjective neurocognitive complaints and depressive symptoms (most correlations were generally in the +0.50 to +0.60 range), and less strong, but statistically significant, associations between subjective neurocognitive complaints and measures of attention and working memory (Digit Span forward and backwards), simple and complex psychomotor speed (Digit Symbol, Trail Making Test, Parts A and B, and Grooved Pegboard), and verbal learning (Trial 1 correct from List A and total List A words over Trials 1-5). These latter associations did not appear to be specific to the type of neurocognitive complaint (i.e., aspects of attention and working memory, psychomotor speed, and verbal recall correlated similarly with all four types of neurocognitive complaints). There were generally no significant relationships between subjective neurocognitive complaints and language skills (confrontational naming or verbal fluency), simple motor speed (Finger Tapping), or with executive skills involving conceptual processing and problem-solving (i.e., those executive-type skills that are captured by the Wisconsin Card Sorting Test). See Table 2 for Pearson product-moment correlation coefficients.
Table 2. Subjective Neurocognitive Complaints (PAOF) and Their Associations with Depressive Symptoms (BDI) and Neuropsychological Test Performance.

<table>
<thead>
<tr>
<th>Depressive Symptoms/Neuropsychological Abilities&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total</th>
<th>Memory</th>
<th>Language</th>
<th>Sensory-Motor</th>
<th>Higher-Level Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI total&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.67*</td>
<td>+0.57*</td>
<td>+0.63*</td>
<td>+0.48*</td>
<td>+0.66*</td>
</tr>
<tr>
<td>BDI (modified: items 1-13)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.59*</td>
<td>+0.50*</td>
<td>+0.57*</td>
<td>+0.41*</td>
<td>+0.61*</td>
</tr>
<tr>
<td>Attention / Psychomotor Speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R Digit Span: Forward</td>
<td>-0.21*</td>
<td>-0.16</td>
<td>-0.27*</td>
<td>-0.06</td>
<td>-0.22*</td>
</tr>
<tr>
<td>WAIS-R Digit Span: Backward</td>
<td>-0.25*</td>
<td>-0.17*</td>
<td>-0.31*</td>
<td>-0.20*</td>
<td>-0.23*</td>
</tr>
<tr>
<td>WAIS-R Digit Symbol&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.40*</td>
<td>-0.36*</td>
<td>-0.38*</td>
<td>-0.36*</td>
<td>-0.36*</td>
</tr>
<tr>
<td>Trail Making Test: Part A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.28*</td>
<td>+0.29*</td>
<td>+0.25*</td>
<td>+0.16</td>
<td>+0.26*</td>
</tr>
<tr>
<td>Trail Making Test: Part B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>+0.30*</td>
<td>+0.25*</td>
<td>+0.29*</td>
<td>+0.20*</td>
<td>+0.31*</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>-0.03</td>
<td>-0.03</td>
<td>-0.06</td>
<td>+0.09</td>
<td>-0.06</td>
</tr>
<tr>
<td>Phonemic fluency (FAS)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-0.08</td>
<td>-0.07</td>
<td>-0.11</td>
<td>-0.03</td>
<td>-0.06</td>
</tr>
<tr>
<td>Category fluency</td>
<td>-0.16</td>
<td>-0.09</td>
<td>-0.16</td>
<td>-0.17*</td>
<td>-0.19*</td>
</tr>
<tr>
<td>Verbal Memory (CVLT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total # words: Trials 1-5</td>
<td>-0.19*</td>
<td>-0.18*</td>
<td>-0.16</td>
<td>-0.12</td>
<td>-0.20*</td>
</tr>
<tr>
<td>Trial 1 correct</td>
<td>-0.26*</td>
<td>-0.24*</td>
<td>-0.22*</td>
<td>-0.21*</td>
<td>-0.24*</td>
</tr>
<tr>
<td>Trial 5 correct</td>
<td>-0.16</td>
<td>-0.16</td>
<td>-0.12</td>
<td>-0.09</td>
<td>-0.17*</td>
</tr>
<tr>
<td>Long-delay free recall</td>
<td>-0.12</td>
<td>-0.08</td>
<td>-0.12</td>
<td>-0.09</td>
<td>-0.15</td>
</tr>
<tr>
<td>Discriminability</td>
<td>-0.13</td>
<td>-0.11</td>
<td>-0.14</td>
<td>-0.08</td>
<td>-0.13</td>
</tr>
<tr>
<td>Executive Skills (WCST)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of categories&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+0.04</td>
<td>+0.09</td>
<td>-0.04</td>
<td>-0.01</td>
<td>+0.06</td>
</tr>
<tr>
<td>Total number of errors&lt;sup&gt;d&lt;/sup&gt;</td>
<td>+0.02</td>
<td>-0.02</td>
<td>+0.07</td>
<td>+0.05</td>
<td>+0.01</td>
</tr>
<tr>
<td>Simple Motor Skills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger tapping: DH&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-0.20</td>
<td>-0.14</td>
<td>-0.18</td>
<td>-0.14</td>
<td>-0.23*</td>
</tr>
<tr>
<td>Finger tapping: NDH&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-0.20</td>
<td>-0.17</td>
<td>-0.16</td>
<td>-0.12</td>
<td>-0.24*</td>
</tr>
<tr>
<td>Grooved pegboard: DH</td>
<td>+0.33*</td>
<td>+0.30*</td>
<td>+0.22*</td>
<td>+0.22*</td>
<td>+0.38*</td>
</tr>
<tr>
<td>Grooved pegboard: NH&lt;sup&gt;g&lt;/sup&gt;</td>
<td>+0.30*</td>
<td>+0.28*</td>
<td>+0.21*</td>
<td>+0.17*</td>
<td>+0.33*</td>
</tr>
</tbody>
</table>

Note. * p < .05 (1-tailed); BDI = Beck Depression Inventory; CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test; DH = dominant hand; NH = non-dominant hand.

<sup>a</sup> Raw scores.
<sup>b</sup> n = 99.
<sup>c</sup> n = 98.
<sup>d</sup> n = 93.
<sup>e</sup> n = 69.
Predicting Neurocognitive Complaints: Contribution of Neuropsychological Abilities and Depressive Symptoms

In our final set of analyses, we used Stepwise Linear Regression to examine if neuropsychological performance would account for a significant amount of variance in subjective neurocognitive complaints, once depressive symptomatology had been taken into consideration. For these analyses, we selected one measure from each neuropsychological ability that had the highest statistically significant correlation across each neurocognitive complaint domain. We selected WAIS-R Digit Span backwards to reflect attention and working memory, WAIS-R Digit Symbol to reflect psychomotor speed, Grooved Pegboard (dominant hand) as a measure of fine-motor dexterity, and Trial 1 correct from the California Verbal Learning Test to reflect verbal learning. We did not include measures of language (verbal fluency or confrontation naming) or conceptual skills and problem-solving (i.e., measures from the Wisconsin Card Sorting test) because these abilities did not correlate significantly with neurocognitive complaints. We regressed subjective neurocognitive complaints (PAOF total and four complaint areas) on the Beck Depression Inventory total score and the four neuropsychological abilities (attention and working memory, psychomotor speed, fine-motor dexterity, and verbal learning).

Total neurocognitive complaints on the PAOF were significantly predicted by a combination of depressive symptoms \( (R^2 = 0.439) \) and complex psychomotor speed \( (R^2 \text{ change} = 0.085, \ p < .001) \), with depressive symptoms accounting for 84% of the total explained variance \( [F(2,94) = 51.74, \ p < .0001] \). This pattern was similar across the four complaint areas (i.e., memory, language and communication, sensory-motor, and higher-level cognitive and intellectual functions), with depressive symptoms accounting for the majority of variance explained in neurocognitive complaints (i.e., from 75 to 88% of the total explained variance in the different complaint areas). Complex psychomotor speed was a unique and significant predictor of total complaints and in all four neurocognitive complaint areas, but it accounted for a much smaller amount of variance (i.e., from 12 to 25% of the explained variance). Working memory was also a significant predictor but only with respect to language and communication complaints (i.e., it predicted 7% of the variance). Results were similar regardless of whether total or modified BDI scores were used. See Table 3 for regression results.

DISCUSSION

Our study design and methodology allowed us to determine and quantify the unique contribution of depressive symptoms and neuropsychological functioning to subjective neurocognitive complaints in HIV-infection. Our results indicated that depressive symptoms, as reflected by the Beck Depression Inventory, correlate highly with reporting of subjective neurocognitive complaints of problems with memory, language and communication, sensory-motor skills, and higher-level cognitive and intellectual functions. In our regression analyses, depressive symptoms accounted for the majority of variance explained in neurocognitive complaints (i.e., from 75% in sensory-motor complaints to 88% of the total explained variance in higher-level cognitive and intellectual functioning complaints). These findings add to the growing literature in HIV-infection that, as depressive symptoms increase, so does the reporting of neurocognitive complaints. We are the first group, however, to quantify the degree to which depressive symptoms contribute to neurocognitive complaints.

In our exploration of the relationship between neurocognitive complaints and neuropsychological test performance, we have replicated the findings of Beason-Hazen et al. (1994) and Mapou et al. (1993) in a broader spectrum of patients with HIV-infection (i.e., by including patients with asymptomatic or mildly symptomatic illness and those with AIDS-defining illnesses and/or with severe immunosuppression). Specifically, our analyses indicated that neuropsychological measures which reflect attention and working memory, psychomotor efficiency, and recall of verbal information correlated sig-
Table 3. Predictors of Subjective Neurocognitive Complaints on PAOF: Stepwise Linear Regression Results.

<table>
<thead>
<tr>
<th>Depressive Symptoms/Neuropsychological Abilitiesb</th>
<th>Amount of Variance Explaineda</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient’s Assessment of Own Functioning Inventory (PAOF)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>BDI total score</td>
<td>43.9 (34.5)c</td>
</tr>
<tr>
<td>WAIS-R Digit Span: backwards</td>
<td>ns</td>
</tr>
<tr>
<td>WAIS-R Digit Symbol</td>
<td>8.5 (12.9)</td>
</tr>
<tr>
<td>CVLT trial 1 # correct</td>
<td>ns</td>
</tr>
<tr>
<td>Grooved Pegboard: DH</td>
<td>ns</td>
</tr>
<tr>
<td>Total Explained Variance:</td>
<td>52.4 (47.4)</td>
</tr>
</tbody>
</table>

Note. CVLT = California Verbal Learning Test; DH = dominant hand.

a Numbers listed \( p < .05 \).
b raw scores.
c Numbers in parentheses represent regression results using modified BDI score (sum of items 1-13).
significantly with both total neurocognitive complaints as well as with specific complaint areas (e.g., memory, language, etc.). We extended the research in this area by conducting multiple regression analyses to determine which neuropsychological abilities would be the most important predictors of neurocognitive complaints. Psychomotor efficiency, as reflected by performance on WAIS-R Digit Symbol, was the most important neuropsychological predictor of total neurocognitive complaints but also consistently predicted across the four complaint areas of the PAOF. It is important to stress, however, that although psychomotor efficiency was a significant predictor, it only accounted for 12 to 25% of the total amount of explained variance in neurocognitive complaints; as such, further research will need to be carried out to determine whether this finding has any clinical utility.

Nevertheless, our current results support the initial findings by Mapou and colleagues (1993) that subjective neurocognitive complaints can reflect mood disturbance, neuropsychological impairments, or both. In this way, the conclusions of previous studies that subjective neurocognitive complaints were either related to neuropsychological test performance or to mood were, in fact, both correct.

Because there is no systematic relationship between depressive symptomatology and neuropsychological impairment in HIV-infection (Bornstein et al., 1993; Grant et al., 1993; Hinkin et al., 1992; Mapou et al., 1993; Moore et al., 1997; van Gorp et al., 1991), inferring that a patient’s report of increased neurocognitive problems is a reflection of neurological disease can be problematic when depression is also present. However, our current results suggest that despite the confounding effects of depressive symptoms, increased complaints of difficulty with memory, language and communication, sensory-motor skills, and higher-level and intellectual functions may also reflect neuropsychological impairments in psychomotor efficiency.

Our current findings highlight that in persons with HIV-infection who present to the clinic with elevations in subjective neurocognitive complaints, it is important to assess for mood disturbance or elevations in depressive symptoms, and to have patients receive neuropsychological testing (specifically testing abilities of attention and working memory, and psychomotor speed). Furthermore, neuropsychological testing will likely have the most impact on differential diagnosis and treatment decisions in the asymptomatic or mildly symptomatic phases (i.e., CDC93 stages A and B) of the disease, when the presence of neuropsychological impairments tend to be the most ‘spotty’ and difficult to quantify clinically (Grant et al., 1987; Heaton et al., 1995; Miller et al., 1991; Miller et al., 1990; White et al., 1995).

We did not find an increase of subjective neurocognitive complaints in our study with advancing HIV disease, as others have shown (Mehta et al., 1996; Poutiainen & Elovaara, 1996). Mehta and colleagues (1996) reported that 22% of HIV-infected asymptomatics (CDC93-A) endorsed having neurocognitive symptoms, as compared to 48% in the CDC93-B stage and 52% in the CDC93-C stage. Our failure to find a difference may have been due to our CDC93 grouping (we collapsed CDC93-A with CDC93-B and compared them to patients with AIDS and those with CD4 Lymphocyte counts < 200). However, this seems unlikely given the similarity in the mean level of complaints across the three CDC93 groups (see Table 1). One possibility that might explain the difference in the level of neurocognitive complaint reporting in the Mehta et al. (1996) study, may be the difference in the level of affective symptoms endorsed across CDC93 stages. Because affective symptoms were elevated only in the CDC93-B and CDC93-C groups, and not in the CDC93-A group, the increased reporting of neurocognitive complaints in the two symptomatic groups may have been due to elevations in depressive symptomatology. As such, failure to assess, or control for, the level of affective or depressive symptomatology may lead to poor correspondence between subjective neurocognitive complaints and objective neuropsychological test performance and also to inaccurate estimates of subjective neurocognitive complaints in HIV-infection.

Although our results clarify the relationship between mood symptoms, neuropsychological
test performance, and subjective neurocognitive complaints in HIV-infection, it is important to stress that we can only generalize our findings to Caucasian samples of well-educated, gay men who are medically stable and are free from other neurological confounds (e.g., significant head trauma, epilepsy, CNS opportunistic infections) and who are not actively using significant amounts of alcohol or illicit drugs. Further studies will be needed to examine how our findings may generalize to other groups with HIV-infection (e.g., women, other ethnic groups), those with different risk factors for HIV-infection (e.g., HIV-infection acquired through blood products or IV drug use), and to those with concurrent neuromedical and drug comorbidities (e.g., history of traumatic head injury and current substance use).

Finally, in terms of future directions, we believe that it will be important to carry out follow-up studies to examine the reliability and predictive value of neurocognitive complaints in HIV-infection. In addition, if elevations in neurocognitive complaints reflect mood disturbance to a large degree, prospective studies will be helpful to determine the degree to which subjective neurocognitive complaints may change with the implementation of efficacious treatment(s) for depression.

REFERENCES


APPENDIX*

Patient’s Assessment of Own Functioning Inventory

Instructions: Please answer each of the following questions by placing a check next to the response which most accurately describes the way you have been recently.

**MEMORY**

1. How often do you forget something that has been *told* to you within the *last day or two*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

2. How often do you forget *events* which have occurred in the *last day or two*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

3. How often do you forget *people* whom you met in the *last day or two*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

4. How often do you forget *things* that you knew a *year or more ago*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

5. How often do you forget *people* whom you knew or met *a year or more ago*?

   ( ) almost always
   ( ) very often
   ( ) fairly often

6. How often do you lose track of time, or do things either earlier or later than they are usually done or are supposed to be done?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

7. How often do you fail to finish something you start because you forgot that you were doing it? (Include such things as forgetting to put out cigarettes, turn off stove, etc.)

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

8. How often do you fail to complete a task that you start because you have forgotten how to do one or more aspects of it?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

9. How often do you lose things or have trouble remembering where they are?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

10. How often do you forget things that you are supposed to do or have agreed to do (such as putting gas in the car, paying bills, taking care of errands, etc.)?

    ( ) almost always
    ( ) very often
    ( ) fairly often
    ( ) once in a while
    ( ) very infrequently
    ( ) almost never
11. How often do you have difficulties understanding what is said to you?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

12. How often do you have difficulties recognizing or identifying printed words?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

13. How often do you have difficulty understanding reading material which at one time you could have understood?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

14. Is it easier to have people show you things than it is to have them tell you about things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

15. When you speak, are your words indistinct or improperly pronounced?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

Note: If this happens, how often do people have difficulty understanding what words you are trying to say?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
16. How often do you have difficulty thinking of the names of things?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

17. How often do you have difficulty thinking of the words (other than names) for what you want to say?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

18. When you write things, how often do you have difficulty forming the letters correctly?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

19. Do you have more difficulty spelling, or make more errors in spelling, than you used to?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

**MOTOR / SENSORY-PERCEPTUAL**

20. How often do you have difficulty performing tasks with your right hand (including such things as writing, dressing, carrying, lifting, sports, cooking, etc.)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never
21. How often do you have difficulty performing tasks with your left hand?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

22. How often do you have difficulty feeling things with your right hand?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

23. How often do you have difficulty feeling things with your left hand?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

24. Lately, do you have more difficulty than you used to in seeing all of what you are looking at, or all of what is in front of you (in other words, are some areas of your vision less clear or less distinct than others)?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

   Note: If you are having this kind of trouble with your vision, is it more difficult to see things located to your right or your left?
   ( ) to the left
   ( ) to the right
   ( ) cannot tell whether one side is worse than the other

**HIGHER LEVEL COGNITIVE AND INTELLECTUAL FUNCTIONS**

25. How often do your thoughts seem confused or illogical?
   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never
26. How often do you become distracted from what you are doing or saying by insignificant things which at one time you would have been able to ignore?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

27. How often do you become confused about (or make a mistake about) where you are?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

28. How often do you have difficulty finding your way about?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

29. Do you have more difficulty now than you used to in calculating or working with numbers (including managing finances, paying bills, etc.)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never

30. Do you have more difficulty now than you used to in planning or organizing activities (i.e., deciding what to do and how it should be done)?

( ) almost always
( ) very often
( ) fairly often
( ) once in a while
( ) very infrequently
( ) almost never
31. Do you have more difficulty now than you used to in solving *problems* that come up around the house, at your job, etc.? (In other words, when something new has to be accomplished, or some new difficulty comes up, do you have more trouble figuring out what should be done and how to do it)?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

32. Do you have more difficulty now than you used to in following *directions to get somewhere*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never

33. Do you have more difficulty now than you used to in following instructions concerning *how to do things*?

   ( ) almost always
   ( ) very often
   ( ) fairly often
   ( ) once in a while
   ( ) very infrequently
   ( ) almost never