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NEUROCOGNITIVE CORRELATES OF ALEXITHYMIA IN ASYMPTOMATIC INDIVIDUALS WITH HIV

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Abstract

Alexithymia, an impairment of affective and cognitive emotional processing, is often associated with human immunodeficiency virus (HIV) and may reflect effects of the virus on brain areas that are also important for multiple cognitive functions, such as the prefrontal and anterior cingulate cortices. We hypothesized that there would be a correlation between extent of alexithymia and cognitive performance associated with these brain areas, including attention, executive function, and visuospatial processing. Thirty-four asymptomatic HIV+ participants and 34 matched healthy HIV− volunteers were administered the Toronto Alexithymia Scale, a series of neuropsychological tests, and measures of apathy, depression, and quality of life (QoL). The HIV+ participants had significantly higher levels of alexithymia, depression and apathy than the HIV− group. The extent of alexithymia and two of its processing components (Difficulty Describing Feelings [DDF] and Externally Oriented Thinking), but not depression, correlated with performance on measures of executive and visuospatial abilities, consistent with dysfunction of the frontostriatal circuits and their cortical projections. Apathy was related to alexithymia and two processing components (Difficulty Identifying Feelings and DDF) but to only one cognitive measure. The higher rate of alexithymia, as well as cognitive dysfunction, in HIV may be a consequence of the infection on the frontostriatal system and its cortical connections. Our findings also demonstrated a dissociation of apathy and alexithymia in HIV, pointing to overlapping but distinct neural substrates within frontostriatal circuits. Alexithymia correlated strongly with QoL ratings, underscoring the importance of assessment and treatment of HIV-associated emotional and cognitive processing deficits.

Keywords

emotion; cognition; frontostriatal; anterior cingulate; apathy; nadir CD4 cell count

1. INTRODUCTION

Infection with human immunodeficiency virus (HIV) is associated with deficits in cognition and emotion, but the relation between them is not understood. This study explores the association between alexithymia and cognition in individuals with HIV in its early asymptomatic stage.

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HIV affects frontostriatal thalamo-cortical circuits (Everall et al., 1999) early in the course of the disease (Avison et al., 2004; Berger & Nath, 1997; Chang et al., 2004; Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Gray, 1996). Structural magnetic resonance imaging (MRI) has shown that HIV infection is associated with reduced volumes of frontal cortex, thalamus, hippocampus, and caudate (Jernigan et al., 1993), as well as with tissue loss in frontal and parietal areas (Thompson et al., 2005). Neuroimaging studies of asymptomatic HIV+ patients have documented reduced brain volume (Aylward et al., 1993), cerebral metabolic asymmetry (left or right) in prefrontal and specifically orbitofrontal areas (Pascal et al., 1991), and differences in signal changes in lateral frontal and posterior parietal areas (Castelo, Sherman, Courtney, Melrose, & Stern, 2006).

Neuropsychological studies of cognition in HIV have shown that asymptomatic HIV+ individuals exhibit cognitive deficits consistent with dysfunction of frontostriatal circuits (Bogdanova, Neargarder, & Cronin-Golomb, 2008; Castelo, Courtney, Melrose, & Stern, 2007; Heaton et al., 1995) and parietal cortical areas (Bogdanova & Cronin-Golomb, 2005; Bogdanova et al., 2008; Olesen, Schendan, Amick, & Cronin-Golomb, 2007). Disruption of frontostriatal circuits affects neuropsychological performance in HIV, specifically on tests of frontal-lobe functioning, such as processing speed, working memory, and executive function (Heaton et al., 1995; Paul, Cohen, & Stern, 2003; Reger, Welsh, Razani, Martin, & Boone, 2002). It has been proposed that HIV-associated cognitive deficits are caused by neuropathological changes produced by the HIV infection in the basal ganglia and associated pathways (Grant & Martin, 1994), including the prefrontal cortex and parietal lobes (Ernst, Chang, & Arnold, 2003; Woods, Moore, Weber, & Grant, 2009).

Alexithymia and HIV

HIV produces changes in emotion regulation and emotional cognition. In particular, patients experience alexithymia, an impairment of affective and cognitive emotional processing (Fukunishi, Hirabayashi, Matsumoto, Yamanaka, & Fukutake, 1999; Lumley, Neely, & Burger, 2007; Temoshok et al., 2008; Thome, 1990). Alexithymia is a multifaceted construct characterized by: a) difficulty identifying and distinguishing between feelings and bodily sensations of emotional arousal, b) difficulty describing feelings, c) reduced imaginal processes as evidenced by a paucity of fantasies, and d) a stimulus bound, externally oriented cognitive style (Bagby & Taylor, 1997). These characteristics reflect deficits in the cognitive processing and regulation of emotions, which may contribute to the development and course of several medical and psychiatric disorders. The inability to apply adaptive processes for affect regulation, such as modulating arousal, expressing or suppressing emotions, using social support, tolerating painful emotions, and cognitive assimilation, is thought to be a core factor contributing to conditions such as depression, anxiety, compulsive and addictive behavior, heightened physiological arousal, and physical symptoms (Lumley et al., 2007; Lumley, Stettner, & Wehmer, 1996; Taylor, Bagby, & Parker, 1997).

The construct of alexithymia remains a subject of ongoing scientific debate, which has produced a large body of empirical literature that has introduced several measures. The 20-item Toronto Alexithymia Scale (TAS-20) (Taylor et al., 1997) is the most widely used brief self-report measure of alexithymia that has good validity and reliability (Bagby, Taylor, Quilty, & Parker, 2007; Taylor et al., 1997). Three TAS-20 factors reflect affective and cognitive dimensions of alexithymia and assess its distinct components: Factor 1 - difficulty identifying feelings and distinguishing them from bodily sensations of emotion (DIF); Factor 2 - difficulty describing feelings (DDF); and Factor 3 - externally oriented thinking (EOT), which refers to a pragmatic thinking style without affective involvement. The TAS–20 correlated three-factor model was reported to be acceptably well fitting (Bagby et al., 2007; Taylor et al., 1997). Multiple studies have used the three-factor structure to examine

affective and cognitive aspects of alexithymia in clinical and non-clinical populations (Bagby et al., 2007; Bankier, Aigner, & Bach, 2001). The TAS-20 three factors (DIF, DDF, and EOT) are associated with neuroticism, introversion, and low openness, respectively (Lumley et al., 2007). Because these three personality constructs are theoretically independent, the authors argued, the three alexithymia factors will have differential validity. High scores on DIF may be associated with complaints of somatic symptoms, DDF with difficulty connecting with others, and EOT with decreased bodily awareness, which in turn may result in decreased health care use.

Two studies have indicated that the TAS-20 factors may be associated with distinct brain regions. In particular, EOT is thought to depend on different brain structures than do DIF and DDF. One study found that DIF and DDF, but not EOT, were related to right-hemisphere lesions (Spalletta et al., 2001), and a second study reported that EOT, but not DIF and DDF, was associated with the size of the anterior cingulate cortex (ACC) (Paradiso, Vaidya, McCormick, Jones, & Robinson, 2008). These findings may explain why scores on DIF and DDF are reported to have stronger correlations with each other than with EOT scores.

While the exact neural mechanisms of alexithymia remain a subject of ongoing investigation, a current model attributes alexithymia to dysfunctional mechanisms in the frontal cortex (Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Gainotti, 1989), specifically, in the ACC and prefrontal cortex (Lane, Ahern, Schwartz, & Kaszniak, 1997). The implication of the ACC and prefrontal cortex in alexithymia has been supported by neuroimaging studies (Borsci et al., 2009; Gundel, Lopez-Sala, Ceballos-Baumann, Deus, Cardoner, & Marte, 2004; Huber et al., 2002; Kano, Fukudo, Gyoba et al., 2003; Karlsson, Naatanen, & Stenman, 2008).

ACC and emotional cognition

The ACC's role in emotional cognition has been studied extensively in recent years. Since Papez postulated that the ACC is involved in emotion regulation (Papez, 1937), several investigations using cytoarchitectonic, lesion and neuroimaging data have identified two ACC subdivisions: an *affective* (rostral) and a *cognitive* (dorsal) division (Bermond, Vorst, & Moormann, 2006; Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995; Paus, 2001; Vogt, Finch, & Olson, 1992). The rostral subdivision has reciprocal connections with the amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex (Carmichael & Price, 1996;Van Hoesen & Solodkin, 1993). It has been implicated in a variety emotional processing tasks (Bishop, Duncan, Brett, & Lawrence, 2004; Bush et al., 2000; Vuilleumier, Armony, Driver, & Dolan, 2001), but also in cognitive processing, such as conflict monitoring (Milham & Banich, 2005), resolving conflicts between stimulus–response associations when performing two tasks simultaneously (Dreher & Grafman, 2003), and monitoring errors (Kiehl, Liddle, & Hopfinger, 2000; Van Veen & Carter, 2002).

The dorsal subdivision is connected to lateral prefrontal cortex, parietal cortex, and premotor and supplementary motor areas (Van Hoesen & Solodkin, 1993) and plays an important role in attention and executive function, as it is involved in response selection, working memory, motor imagery and selection, detection of mismatch, and establishing changes in processing for new programs (Bush et al., 2000; Paus, 2001). It is also involved in emotional processing, such as attention-demanding tasks involving emotional content (Davis et al., 2005; Phan, Wager, Taylor, & Liberzon, 2002). The two ACC subdivisions are interconnected (Bush et al., 2000; Musil & Olson, 1988a, 1988b; Van Hoesen & Solodkin, 1993). Some authors view dissociation between cognitive and emotional processing as a reflection of a cross-modal interaction of the two separable reciprocal systems (Drevets &

Raichle, 1998). Another view postulates that the two subdivisions of the ACC support a continuum of processing that blends cognitive and emotional components (Mohanty et al., 2007). Using neuroimaging and behavioral techniques, Mohanty and colleagues provided direct evidence for the differential engagement of both ACC subdivisions in cognitive and emotional function.

With regard to alexithymia, Lane (2000) discussed the possibility of both ACC subdivisions participating in different aspects of emotional processing, with dorsal ACC reflecting direct experience of emotion, and rostral ACC (with its connections to medial prefrontal cortex) participating in cognitive operations based on direct experience of emotion (knowing how one is feeling). The structural connectivity between the rostral and dorsal ACC forms the basis for interaction between direct experience of emotion and the formation of mental representations of that emotional experience. Their reciprocal connections with amygdala (involved in implicit emotional cognition) and prefrontal cortex (involved in explicit emotional cognition) provide additional evidence that both ACC subdivisions have a role in emotionalizing and emotional cognition (Bermond et al., 2006).

A recent neuroimaging study examined the association between alexithymia and gray matter volumes of ACC subregions as a function of age (Paradiso et al., 2008). They reported a significant correlation between right rostral ACC volume and alexithymia ratings on TAS-20, for both total score and Factor 3 (EOT). Older age was correlated with higher alexithymia and with smaller overall right ACC total gray matter volume in rostral and dorsal subregions, and in the left rostral subregion. These findings suggest that deterioration in the rostral subregion of ACC may contribute to greater alexithymia in older age and more specifically to EOT. In this study, alexithymia was significantly associated with cognitive performance, specifically executive functioning (verbal fluency). Other studies of verbal fluency have found ACC activation as well as activation of several prefrontal regions (Audenaert et al., 2000; Cardebat et al., 1996). HIV-associated fluency deficits are thought to reflect executive dyscontrol of rule-guided search and retrieval processes secondary to dysregulation of frontostriatal systems (Woods et al., 2009). Specifically, verbal fluency deficits are associated with neurodegeneration of frontostriatal systems, such as basal ganglia atrophy; the ACC was not examined (Hestad et al., 1993).

Taken together, current HIV and alexithymia/emotional cognition research has suggested the possibility of an overlap in brain areas, specifically ACC and prefrontal areas. The strong connections of the ACC to prefrontal and parietal cortices (Posner & DiGirolamo, 1998), dysfunction in each of which has been also implicated in HIV, provide additional support to the idea that alexithymia may be secondary to (or concurrent with) HIV–associated frontostriatal pathology. The presence of alexithymia in HIV-infected individuals may reflect direct and /or secondary effects of the virus on the brain, especially on the ACC and prefrontal areas that are important for multiple cognitive functions. There are no reports in the literature about the interaction of cognitive functioning and alexithymia in asymptomatic HIV individuals.

Alexithymia, Depression and Apathy in HIV

Alexithymia is often associated with depression (Honkalampi, Hintikka, Saarinen, Lehtonen, & Viinamaki, 2000; Müller, Bühner, & Ellgring, 2003; Saarijärvi, Salminen, & Toikka, 2001), with some investigators suggesting that these should be considered distinct though partially overlapping constructs (Parker, Bagby, & Taylor, 1991; Wise, Jani, Kass, & al., 1988; Wise, Mann, & Hill, 1990; Wood & Williams, 2007). Depression in HIV has been documented by multiple studies. A recent prospective study of depression in HIV-infected men found that *symptomatic* HIV disease, but not HIV infection itself, increases the risk of depression in this population, as asymptomatic patients were not depressed (Atkinson et al.,

2008). Many studies have used the Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 1996) to assess the existence and severity of symptoms of depression, though it is acknowledged that positively endorsed somatic items on BDI may be related to physical difficulties in a medically ill population and therefore could be diagnostically ambiguous (Schulberg, McClelland, & Burns, 1987). In regard to HIV, there are reports of the possibility of inflating depression scores due to endorsement of somatic symptoms (Kalichman, Rompa, & Cage, 2000). To address this issue, several HIV studies used cognitive-affective and somatic sub-scores (Castellon, Hinkin, Wood, & Yarema, 1998; Harker, Satz, & Jones, 1995; Law, Martin, & Salazar, 1993). Castellon et al. (1998) found that in HIV+ individuals, the cognitive/affective but not somatic BDI component was strongly associated with reaction time (slowing) and with apathy ratings. Their findings also showed a differential relation of depression and apathy to neurocognitive performance in HIV. Apathy, but not depression, was related to working memory impairment, whereas depression, but not apathy, was related to slower reaction time.

Several previous HIV studies have documented associations between the presence of apathy and poor performance on measures of executive function, suggesting that apathy and HIV-related cognitive dysfunction may share common neurophysiological substrates (Cole et al., 2007; Paul, Flanigan et al., 2005). Apathy is associated with damage to the frontal lobes and disruption of the frontal-subcortical anterior cingulate circuits (Cummings, 1993; Paul, Cohen, Navia, & Tashima, 2002; Tekin & Cummings, 2002). Neuroimaging has indicated that the severity of apathy is associated with the volume of the nucleus accumbens, one of the central structures in the anterior cingulate frontal-subcortical circuit (Paul, Brickman et al., 2005). There was also the suggestion of a relation between ratings of apathy and the volume of the caudate nucleus, though the investigators noted that the correlation was not statistically significant due to the small sample size. The anatomical overlap in neural networks involved in apathy and alexithymia, together with the aforementioned neuropsychological findings, raises the question of the potential overlap of apathy symptoms with the expressions of alexithymia in asymptomatic HIV+ individuals.

Alexithymia and quality of life in HIV

Impairments in mood and cognition can interfere with everyday functioning in HIV-affected individuals, leading to problems in vocational functioning, increased unemployment, and decreased ability to effectively manage medications (Albert et al., 1995; Benedict, Mezhir, Walsh, & Hewitt, 2000; Heaton et al., 1996; Marcotte et al., 1999; Stern et al., 1991). Changes in emotional cognition likewise may seriously compromise daily function, particularly the individual's ability to cope with the physical and emotional consequences of HIV-related illness. Recent studies have documented the impact of alexithymia on the immune system, such as diminished immune-mediated cellular response in alexithymics with oversecretion of glucocorticoids, suggesting that alexithymic individuals may suffer undiagnosed chronic stress with physiological, endocrine and immune consequences (Guilbaud, Corcos, Hjalmarsson, Loas, & Jeammet, 2003). Another study reported that alexithymia is associated with decreased production of anti-HIV β-chemokine-MIP1α(Temoshok et al., 2008). Identifying and treating alexithymia is important as it may help to predict the course and outcome of treatment (Parker, Keefer, Taylor, & Bagby, 2008). The degree of alexithymia as measured by TAS-20 has been shown to predict the outcome of psychotherapy in patients with complicated grief (McCallum, Piper, Ogrodniczuk, & Joyce, 2003) and predicted outcome with regard to persistent symptoms and medical treatment in patients with gastrointestinal disorders (Porcelli, Bagby, & Taylor, 2003; Porcelli, Lorusso, Taylor, & Bagby, 2007). The assessment of alexithymia in medical and mental health settings is recommended (Lumley et al., 2007), as knowing a patient's

level of alexithymia can inform the understanding of the patient's health status, clinical presentation, behavior, and response to treatment.

Aims

Though there is a significant literature on cognition, mood, and emotional processing in HIV, how these disease effects are related has not to date been investigated. The relation between emotional and cognitive function is important to explore from both clinical and theoretical perspectives as it may provide insights into the interaction of emotional and cognitive systems. The present study had three main aims. The first was to explore the association between alexithymia and cognition in individuals with HIV in its early asymptomatic stage and to consider the mechanisms underlying an association. The ACC connections with the prefrontal and parietal cortex make it important for both cognitive (executive in particular) and emotional function (Bush et al., 2000; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001; Posner & DiGirolamo, 1998). Accordingly, we hypothesized that there should be an association between the extent of alexithymia and cognitive dysfunction associated with these brain areas, including attention, executive function, and visuospatial processing. Because neuroimaging studies have suggested differential involvement of distinct aspects of alexithymia, separating rostral and dorsal subdivisions of ACC, we explored the association between three different aspects of alexithymia and cognitive performance in HIV.

The second aim was to examine the potential overlap between alexithymia and apathy in HIV. Based on the results of imaging and behavioral studies as noted above, we predicted that apathy and alexithymia share common neurophysiological substrates within frontostriatal circuits. We examined the extent of alexithymia and apathy overlap and their differential relation to cognition.

The third aim was to investigate the relation between alexithymia and quality of life in HIV. Alexithymia-related deficits in the cognitive processing and regulation of emotions have been shown to contribute to the development, progression and outcome of the disease in other medical and psychiatric disorders, as described above, with these contributions arising from the inability to use adaptive processes for affect regulation (e.g., modulating arousal, using social support, tolerating painful emotions). Converging evidence suggests that the relation between alexithymia and health status in HIV may be bidirectional, where the progression of HIV infection can cause alexithymia, and alexithymia in turn can lead to chronic stress with physiological, endocrine and immune consequences, possibly causing additional immune compromise. Based on previous findings, we hypothesized that alexithymia may affect physical, emotional, and social aspects of life of the HIV+ individuals, and accordingly we expected to find an association between alexithymia and quality of life ratings.

2. METHODS

2.1. PARTICIPANTS

Thirty-four asymptomatic HIV+ individuals were recruited from Boston area clinics (Table 1). Thirty-four healthy control adults (HIV−) matched on socio-demographic variables were recruited from the local community as well as from the same referral sources as the HIV+ group. All participants were native speakers of English and received financial compensation. Exclusionary criteria for all participants included co-existing serious chronic medical illness (including psychiatric or neurological), use of psychoactive medications, score above 30 on the Beck Depression Inventory II, history of intracranial surgery, traumatic brain injury (loss of consciousness), alcoholism or other substance abuse in the past 12 months, and eye

disease or abnormalities. The HIV+ and HIV− groups were matched for verbal IQ as indexed by the American modification of the National Adult Reading Test (ANART) (Nelson, 1982), implying similar overall premorbid cognitive ability. Handedness was assessed with the Edinburgh Inventory (Oldfield, 1971).

Additional exclusionary criteria for HIV+ participants included complications of HIV infection that may have affected neurological systems (e.g., opportunistic infections such as toxoplasmosis or cryptococcal meningitis). HIV+ participants were screened to rule out associated dementia through use of the HIV Dementia Scale (Power, Selnes, Grim, & McArthur, 1995), with a score of 10 or below resulting in exclusion. The group mean was 14.1 (± 1.8). Those participants with a remote substance abuse history were asked to report duration, frequency, and means of administration. Data were collected with regard to each participant's complete medication regimen, including anti-retroviral therapies, and detailed immunological information, including current and historically lowest CD4 count, number of times CD4 count fell below 200, plasma viral load, and history of opportunistic infections. We used this information to determine clinical staging, as recommended by the Centers for Disease Control and Prevention (CDC, 1992). CDC classifies patients into three groups based on their stage of illness. Individuals are categorized as (A) asymptomatic HIV (T-cell counts at or above 200 and not demonstrating any significant clinical symptoms of the illness); (B) symptomatic HIV (T-cell counts at or above 200 and manifesting less severe clinical symptoms e.g., thrush, cervical dysplasia, herpes zoster, peripheral neuropathy); or (C) having AIDS (acquired immunodeficiency syndrome: T-cell counts below 200/mm^3 or a history of at least one serious opportunistic infection presumed to be associated with HIV disease, e.g., pneumocystis carinii pneumonia, Kaposi's sarcoma, HIV-associated wasting syndrome). The participants in our study were all in Stage A.

2.2 PROCEDURES

Each participant provided informed consent in accordance with regulations of the Boston University Institutional Review Board prior to their inclusion in the study, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants completed demographic and health questionnaires, as well as standardized self-report measures of alexithymia and depression, and a series of standard neuropsychological tests.

2.2.1 COGNITIVE FUNCTIONING ASSESSMENT—The neuropsychological series included a number of tests that we expected to be sensitive to fronto-striatal and parietal dysfunction (attention, executive function, visuospatial ability) as well as tests that we expected would elicit unimpaired performance in the asymptomatic HIV+ group (naming abilities, story memory). The focus of interest was the former group, cognitive abilities that would be most relevant to the association between emotional processing and cognitive functioning in asymptomatic persons with HIV.

2.2.1.1 Attention and Executive Function: The Trail Making Test (Armitage, 1946) is a standardized test of psychomotor speed and executive functioning that consists of two subtests: Trails A and Trails B. Trails A is a test of simple attention and psychomotor speed, in which participants connect numbered circles in ascending order (1-2-3, etc). Trails B is a measure of combined visual search, psychomotor speed, and cognitive flexibility, assessing the ability to shift and maintain the response set, in which participants sequentially alternate between alpha-numeric sequences (1-A-2-B, etc). Time to completion was used for the group comparisons.

Digit Span and Spatial Span, Wechsler Memory Scale III (Wechsler, 1997) are standardized measures of efficiency of attention (Forward Span) and working memory (Backward Span)

in verbal and nonverbal domains (Lezak, Howieson, & Loring, 2004). The standard total score was used for the group comparisons of Digit Span and Spatial Span. Additionally, Backward Span scores were used as a measure of working memory.

Subtracting from 100 by 7's (Luria, 1962) is a task of sequential arithmetic operation. There is neuroimaging evidence for bilateral prefrontal and posterior parietal cortex activation during silent subtraction by sevens in healthy adults (Rueckert et al., 1996). The task was presented verbally and required a spoken verbal answer. Time to completion and number of errors was used for the group comparisons.

Controlled Oral Word Association Test (Benton & Hamsher, 1989). This is a standardized test of verbal fluency: (1) phonemic fluency, in which participants were required to generate words beginning with a particular letter (F, A, S), and (2) category fluency, in which participants generate words that belong to a particular category (Animals). Total number correct within a 60-s time period for each condition was recorded.

2.2.1.2 Verbal Functioning: Similarities, Wechsler Adult Intelligence Scale III (Wechsler, 1997). This is a standardized measure of abstract verbal reasoning, in which participants are required to identify categorical similarities between verbally presented pairs of objects or concepts. Total number of points was recorded.

The Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983) is a test of confrontation naming, in which the participant names 60 black and white line drawings of objects presented one at a time. The total number correct was recorded.

2.2.1.3 Visuospatial Functioning: Raven's Coloured Progressive Matrices (Raven, 1965). This standardized measure requires the performance of visual closure and spatial analogies, thereby assessing visuospatial skills and spatial reasoning ability. The task is to choose one of six possible completions of an incomplete pattern matrix. Total score (the number correct out of 36 items) was recorded.

Visual Symbol Search Test (Mesulam, 1985) provides a measure of visual scanning abilities and sustained attention. Participants search and cancel the target symbol in the non-verbal array. Time to completion was used for the group comparison.

Right-Left Orientation Subtest, Boston Visuospatial Quantitative Battery (BVSQB; Goodglass & Kaplan, 1983). This test assesses right-left orientation with reference to the body parts, and requires the identification of right and left on 20 different body parts drawn in various positions. The number of errors was recorded. Right-left discrimination may be disrupted by left posterior lesions (Lezak et al., 2004).

Drawing and Copy Subtests, BVSQB (Goodglass & Kaplan, 1983). On the Drawing to Command subtest, participants are required to draw six objects. On the Copy condition, models for copying are provided one at a time. Total number of points was recorded. Visuo-constructional abilities are vulnerable to injuries of both frontal and parietal lobes.

2.2.1.4 Memory: Rey-Osterrieth Complex Figure Drawing Test (ROCF) (Osterrieth, 1944). In an assessment of visuospatial memory, participants were asked to recall the abstract figure image by re-drawing it immediately after copying (incidental) and again after 25 minutes (delayed recall). We employed the 36-point scoring system evaluating the presence and accuracy of the 18 elements of the ROCF (Taylor, Bagby, & Parker, 1991), and a total score was recorded.

Logical Memory subtests, Wechsler Memory Scale III (Wechsler, 1997). This test assesses the ability to learn and spontaneously recall details of narrative material presented orally in paragraphs immediately after presentation (Logical Memory 1 [LM1]) and after a 25 minute delay (Logical Memory 2 [LM2]).

2.2.1.5 Psychomotor functioning: Purdue Pegboard Test (Tiffin, 1968) is a measure of psychomotor speed, wherein participants fit small pegs into holes on a board, using the preferred, non-preferred, and finally both hands together to fill two rows (top to bottom) within 30 seconds (described in Spreen & Strauss, 1998). Total number of pegs inserted was recorded for each condition. Patients with Parkinson's disease, another fronto-striatal disorder, demonstrate impairment of bimanual movements on this test (Brown, Jahanshahi, & Marsden, 1993). We report bimanual scores.

2.2.2 ALEXITHYMIA, APATHY AND DEPRESSION ASSESSMENT—We assessed alexithymia and depression using standardized self-report measures. The 20-item Toronto Alexithymia Scale (TAS-20) was administered to evaluate alexithymia (Bagby, Parker, & Taylor, 1994). Item responses were rated on a 5-point Likert scale ranging from 1 (complete disagreement) to 5 (complete agreement). Higher scores reflect greater alexithymia. Based on the total score, individuals can be categorized as non-alexithymic (scores ranging from 20 to 51), borderline alexithymic (scores ranging from 52 to 60), or alexithymic (scores ≥ 61). Items for Factor 1 (difficulty identifying feelings and distinguishing them from bodily sensations of emotion, DIF) were #1, 3, 6, 7, 9, 13, and 14; for Factor 2 (difficulty describing feelings, DDF), #2, 4, 11, 12, and 17; and for Factor 3 (externally oriented thinking, EOT), #5, 8, 10, 15, 16, 18, 19, and 20 (Bagby et al., 1994).

Apathy was assessed using the modified 14-item Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991; Starkstein et al., 1992). Items are rated on a 0-to-3 Likert scale. Sample items include, "Are you interested in learning new things?" and "Are you indifferent to things?" AES and its modified version were reported to have excellent psychometric properties and have been used in studies of HIV (Paul, Brickman et al., 2005; Paul, Flanigan et al., 2005) and Parkinson's disease (Starkstein et al., 1992).

The Beck Depression Inventory, Second Edition (BDI-II) (Beck et al., 1996) is a 21-item self-report instrument that assesses the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 1994). There is a four-point scale for each item ranging from 0 to 3. Total score in the range of 0–13 is considered indicative of minimal depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe. BDI cognitive-affective and BDI somatic sub-scores were calculated, following a standard procedure outlined in the BDI manual.

2.2.3 QUALITY OF LIFE ASSESSMENT—We administered a self-report questionnaire that focused on several aspects of quality of life. The Medical Outcomes Study HIV Health Survey (MOS-HIV) examines health-related quality of life and functional issues in HIV with 35 questions (Wu et al., 1991). It is a brief, comprehensive measure that is used extensively in HIV/AIDS. Ten dimensions assessed include health perceptions, pain, physical, role, social and cognitive functioning, mental health, energy, health distress, and quality of life (QoL). Subscales are scored on a 0–100 scale (a higher score indicates better health). The MOS-HIV has been used in numerous studies and has been shown to be internally consistent, correlate with concurrent measures of health, discriminate between distinct groups, predict future outcomes and be responsive to changes over time (Wu, Revicki, Jacobson, & Malitz, 1997).

The study used a within-subject design, with each participant receiving all assessments.

3. RESULTS

Analyses of performance of men and women in both the HIV+ and HIV− groups revealed no significant differences in neuropsychological profile or mood ratings, and data were accordingly collapsed across gender.

The results are divided into four sections: (1) effects of HIV on cognitive function; (2) relation between alexithymia and cognitive functioning; (3) relation between apathy, depression, and alexithymia; (4) association of alexithymia with quality of life.

3.1 COGNITIVE FUNCTION

In order to examine whether the HIV+ group exhibited cognitive deficits compared to the HIV− group, independent groups *t*-tests were conducted (Table 2). Alpha was adjusted to 0.002 (0.05/22) to account for multiple comparisons. The HIV+ group performed significantly more poorly than the HIV− group on measures of attention, executive function, and visuospatial functioning abilities, the domains subserved by frontostriatal and parietal circuitry. There were no significant differences observed for tests of verbal functioning, memory, or psychomotor speed.

For the HIV+ group, there were no significant correlations between performance on any of the neuropsychological measures and current CD4 cell count, disease duration, or viral load (all p's > 0.05). There was a significant correlation between past immune status (nadir CD4 cell count since HIV diagnosis) and a measure of psychomotor function (Pegboard) [$r(34) = 0.56$, $p < 0.003$].

3.2 ALEXITHYMIA AND COGNITION

Independent groups *t*-tests revealed that the HIV+ participants were significantly more alexithymic than the HIV− group (Table 2). TAS-20 mean total score was 45.6 (SD: 14.5; range: 24–74). Using the categorical approach of TAS-20 guidelines, 65% ($n = 22$) of HIV+ sample were within the non-alexithymic range, 15% ($n = 5$) were borderline, and 20% ($n = 7$) were alexithymic. In the HIV− group, 97% of participants were non-alexithymic, 3% borderline alexithymic, and none were alexithymic. The HIV+ participants showed significantly higher scores than the HIV− group on the three TAS-20 factors: DIF [$F(1,67) = 13.03$, $p < 0.001$], DDF [$F(1,67) = 4.47$, $p < 0.02$], and EOT [$F(1,67) = 6.68$, $p < 0.01$]. We also conducted comparisons that revealed no differences between men and women in the total score or three factors of the TAS-20 (all p's > 0.08). Alexithymia ratings did not correlate with current or past immune status (current CD4 and nadir CD4 cell count) or disease duration, but did correlate with quality of life ratings (section 3.4).

To explore the nature of the relation between alexithymia and cognitive functions, in particular the contribution of the frontostriatal systems affected by HIV to emotional cognition, we performed Pearson correlations between alexithymia ratings and neuropsychological performance. Because we expected alexithymia scores to positively correlate with executive function and visuospatial abilities, one-tailed tests were used. To achieve a reasonable balance between Type I and Type II errors and to allow the examination of potential relations among variables, we divided alpha by two, thereby adopting a more conservative significance level of 0.025. There were significant correlations between severity of alexithymia and poorer performance on several measures of cognitive functioning in the asymptomatic HIV+ individuals. TAS-20 total score significantly correlated with HIV+ performance on measures of attention and working memory (verbal and spatial spans), category fluency (animals), spatial reasoning (RCPM), and visuospatial

organization (BVSQB Drawing and Copy). These findings are summarized in Table 3. For the HIV− group, there were no correlations between alexithymia ratings and any of the neuropsychological measures (all p's > 0.09).

Further analyses revealed associations between the processing components of alexithymia (Factors 2 [DDF] and 3 [EOT]) and cognitive performance in HIV (Table 3). The HIV+ group showed no association between Factor 1 (DIF) and cognitive performance. DDF significantly correlated with measures of category fluency, spatial attention and working memory, spatial reasoning and visuospatial organization and construction. EOT showed significant association with the majority of measures of attention and executive functioning and visuospatial organization and construction measures. There were no significant correlations between alexithymia ratings and measures of verbal reasoning, naming, and psychomotor functioning (all r's < 0.15, p's > 0.26).

3.3 APATHY, DEPRESSION, AND ALEXITHYMIA

The HIV+ participants showed greater apathy (Alexithymia Evaluation Scale, [AES] total) than the HIV− group [$F(1,67) = 5.78$, $p < 0.02$]. There was a significant association between apathy (AES total) and alexithymia ratings in the asymptomatic HIV+ sample: TAS-20 total score [$r(34) = 0.56$, $p < 0.005$], DIF [$r(34) = 0.61$, $p < 0.002$], and DDF [$r(34) = 0.55$, $p < 0.005$], but not EOT [$r(34) = 0.32$, $p = 0.126$]. Apathy correlated significantly with only one cognitive measure (spatial working memory, backward span) [$r(34) = -0.43$, $p < 0.025$]. For the HIV− group, there were no correlations between apathy and alexithymia ratings or any of the neuropsychological measures (all p's > 0.1).

The HIV+ group reported significantly more depressive symptoms than the HIV− group (Table 2). For this group, the correlation between the alexithymia score and rating of mood disturbance on the BDI-II was significant [$r(34) = 0.53$, $p < 0.001$]. Severity of depression (BDI-II total score) or BDI-II cognitive-affective and somatic factors did not correlate significantly with any of the cognitive measures (all r's < 0.24, p's > 0.22). There were no significant correlations between severity of depression and current or past immune status (current and nadir CD4 cell count) or disease duration (all r's < 0.19, p's > 0.31).

3.4. ALEXITHYMIA AND QUALITY OF LIFE

Higher alexithymia scores were reported among HIV+ individuals with lower ratings of quality of life. Alexithymia ratings (TAS-20 total) correlated strongly with several subscales on the HIV MOS self-report measure: General Health [$r(34) = -0.46$, $p < 0.009$], Cognitive Function [$r(34) = -0.62$, $p < 0.0001$], and Health Distress [$r(34) = -0.57$, $p < 0.001$]. While there were no significant correlations between QoL ratings and current immune status (current CD4 cell count) or disease duration (all r's < 0.33, p's > 0.11), nadir CD4 cell count since diagnosis was significantly associated with scores on the HIV MOS Pain subscale [$r(34) = -0.46$, $p < 0.017$].

4. DISCUSSION

We examined alexithymia in asymptomatic individuals with HIV and its relation to cognition, mood, and quality of life. First, we found HIV-related changes in multiple cognitive domains in the early, asymptomatic stage of the disease. The affected domains included attention, executive function and visuospatial function, which is reflective of frontostriatal and parietal dysfunction associated with HIV. Second, HIV+ participants were significantly more alexithymic than the HIV− group, implicating disruption of specific fronto-striatal neural pathways. The extent of alexithymia and two of its processing components (Factor 2, DDF, and Factor 3, EOT), but not depression, significantly correlated

with performance on neuropsychological measures of attention, executive and visuospatial function, which are the cognitive domains associated with fronto-striatal pathology. Third, the HIV+ group showed higher apathy ratings than HIV− participants. While there was a significant association between apathy and alexithymia ratings, apathy level correlated with only a single aspect of cognition (spatial working memory). Further analyses revealed correlations between two alexithymia factors (DIF and DDF) and apathy. Finally, we found that alexithymia ratings in HIV were associated with multiple aspects of quality of life, particularly for the categories of cognitive functioning, general health, and health distress.

Recent HIV and alexithymia research has implicated common affected brain areas, such as prefrontal cortex and ACC. We hypothesized that alexithymia may be secondary to (or concurrent with) HIV because of the disruption of frontostriatal circuitry in HIV. The prediction was that there should be a correlation between extent of alexithymia and cognitive dysfunction associated with these brain areas, including attention, executive function, and visuospatial processing. Our results supported this hypothesis by demonstrating a significant association between severity of alexithymia (TAS-20) and performance on the predicted subset of neuropsychological measures. To our knowledge, this is the first study that has related alexithymia to cognitive performance in HIV.

Our finding of executive dysfunction in HIV is in accord with the “frontal” alexithymia model that postulates that alexithymia is the result of dysfunctional mechanisms in the frontal cortex (Davidson et al., 1990; Gainotti, 1989; Lane et al., 1997). A second cognitive domain affected is visuospatial, reflecting parietal dysfunction. The ACC, which has been implicated in alexithymia, has multiple connections with the prefrontal and parietal cortices, which may explain the significant relation between visuospatial dysfunction and the extent of alexithymia in the HIV+ group. These findings support the idea that HIV-related cognitive deficits and alexithymia may involve overlapping neural systems that include ACC and prefrontal cortex. Our findings accord with neuroimaging research (Gundel, Lopez-Sala, Ceballos-Baumann, Deus, Cardoner, Marten-Mittag et al., 2004; Huber et al., 2002; Kano, Fukudo, Hongo, Itoh, & Yanai, 2003) demonstrating the roles of the prefrontal cortex and ACC in executive and regulatory aspects of emotional processing and self-awareness in alexithymia.

In the healthy HIV− control group, there were no correlations between alexithymia ratings and any neuropsychological measures. It appears that the interaction between the processing components of alexithymia and cognitive dysfunction occurs only in the presence of cognitive deficits, or our measures of alexithymia are sensitive to this interaction only in such afflicted individuals.

Dissociations between affective and cognitive aspects of alexithymia reflected by individual alexithymia factors have been reported in several clinical and non-clinical populations (Larsen, Brand, Bermond, & Hijman, 2003). Our results revealed dissociations between the three TAS-20 factors and cognitive performance in asymptomatic HIV+ individuals, reflecting the underlying dimensions of alexithymia affected in this population. There were specific associations between the two processing components of alexithymia (Factors 2 [DDF] and 3 [EOT]) and cognitive performance in HIV, whereas there was no association between Factor 1 (DIF) and cognitive performance. DIF reflects the affective dimension of alexithymia, and was found to be strongly associated with depression ratings in a clinically depressed group (Bankier et al., 2001). Our results are consistent with this finding, as neither depression ratings nor DIF correlated with cognitive performance in either group. By contrast, the other two factors, DDF and EOT (a cognitive style that is concrete and reality based) significantly correlated with the cognitive performance of the HIV+ group. Notably, EOT showed significant association with most of the executive and visuospatial cognitive

tests, suggesting the possibility of overlap in neural systems subserving these cognitive functions and the processing component of alexithymia measured by EOT. As noted earlier, EOT was found to be significantly associated with smaller rostral ACC volume in healthy adults (Paradiso et al., 2008). Similarly, Bankier and colleagues (2001) reported a significant association of EOT with diagnosis of obsessive-compulsive disorder, a fronto-striato-thalamocortical disorder associated with dysfunction of the orbitofrontal cortex, ACC, thalamus and caudate nucleus (Adler et al., 2000; Kwon, Jang, Choi, & Kang, 2009; Saxena, Brody, Schwartz, & Baxter, 1998).

Taken together, these findings by other investigators provide indirect evidence for the possibility of anatomically and functionally distinct neural substrates for the processing components of alexithymia. Our findings provide additional support for this idea. Specifically, EOT was related to cognitive performance on verbally and non-verbally mediated tasks of executive and visuospatial function, while DDF was associated only with a specific (non-verbally mediated) subset of executive and visuospatial measures. Another notable dissociation between the two factors was on the fluency tasks: DDF was only associated with category fluency, while EOT was associated only with verbal (letter) fluency. As noted earlier, another study related EOT to smaller rostral ACC, and associated alexithymia with performance on verbal fluency (Paradiso et al., 2008). It is possible that EOT is more dependent on the neural areas serving verbally mediated executive functioning tasks (including rostral ACC), while DDF is more dependent on the areas involved in non-verbally mediated executive tasks. This idea is consistent with earlier reports of DDF but not EOT being related to right-hemisphere lesions (Spalletta et al., 2001).

In our study, DIF was not associated with any of the cognitive measures, suggesting potentially distinct neural regions associated with this factor, which appears to be affected differently from the other factors by HIV-related neural injury. There are at least three potential reasons: (1) DIF is not associated with executive or visuospatial function; (2) the underlying neural substrate for this factor is not affected by HIV neurodegenerative processes, or (3) it was too early in the course of the disease to detect the change in our sample. Future studies are needed to better determine the relation between DIF and cognition in HIV.

The evidence from our results and others' studies of emotional cognition, alexithymia and HIV points to the specific areas of potential overlap of neural substrates of the cognitive processing component (EOT) and HIV-associated cognitive deficits: ACC (rostral subdivision) and its projections. There is converging evidence that while rostral and dorsal ACC subdivisions are differentially involved in emotional and cognitive processing, they are anatomically and functionally connected as part of the overlapping networks subserving complex emotional and cognitive functions/ processes (Lane, 2000; Mohanty et al., 2007). Both ACC subdivisions may support cognitive processing component of alexithymia, and this topic warrants further research.

In our study, the severity of depression co-varied with alexithymia ratings but did not correlate with performance on any of the cognitive tests. To evaluate whether positively endorsed somatic items on the BDI–II might have influenced the outcome of the analyses in our study, we calculated cognitive-affective and somatic sub-scores. Neither was associated with cognitive performance in our asymptomatic HIV+ sample. These findings are consistent with those of a previous study (Bornstein et al., 1993) that showed that neuropsychological abnormalities observed in asymptomatic HIV+ participants cannot be attributed to depression.

Previous studies have related apathy and alexithymia to cognitive dysfunction in HIV, specifically to poor performance on measures of executive and visuospatial function (in alexithymia), suggesting that apathy, alexithymia and HIV-related cognitive dysfunction may share common neurophysiological substrates within the fronto-striatal circuits and their cortical projections. To further examine this potential overlap, we investigated the relation of apathy to cognition and to alexithymia in asymptomatic HIV+ individuals. HIV+ participants showed greater apathy than the HIV− group. There was a significant association between apathy and alexithymia ratings in the asymptomatic HIV+ sample, in particular between apathy and DIF and DDF, but not EOT, suggesting distinct neural substrates for the individual processing components of emotional cognition. When we examined the interaction between apathy, alexithymia and cognition, the following pattern emerged: whereas apathy correlated significantly with only one cognitive measure (spatial working memory), alexithymia correlated with multiple measures of attention and working memory, category fluency, spatial reasoning, and visuospatial organization, indicating differential contributions of apathy and alexithymia to cognition in HIV. These findings suggest that while apathy and alexithymia may share common neurophysiological susbtrates, they can be dissociated in this population, implying partially overlapping but distinct neural substrates within frontostriatal circuits.

We found strong correlations between alexithymia ratings and several items on the QoL self-report measure (HIV MOS). Greater alexithymia was reported among HIV+ individuals with lower ratings of quality of life. Affected aspects of daily life included cognitive functioning, general health, and health distress. By contrast, there were no significant correlations between QoL ratings and current immune status (current CD4 cell count, which may fluctuate in the course of the disease), or disease duration. Past immune status (nadir CD4 cell count since diagnosis) was associated with the Pain subscale of the HIV MOS. Living with pain significantly affects QoL. Alexithymic patients, who have difficulty using adaptive processes to regulate affect, such as tolerating painful emotions and using social support, can be in double jeopardy dealing with the effects of HIV disease. Alexithymia may contribute to the exacerbation and course of disease by causing heightened physiological arousal and physical symptoms, and by affecting already compromised immune function of HIV+ individuals. Our findings emphasize the importance of assessment and treatment of the emotional processing deficits associated with HIV infection, given that the extent of alexithymia substantially correlated with both cognitive functioning and quality of life in our asymptomatic sample. The assessment of alexithymia in HIV should be recommended in medical and mental health settings to understand the clinical presentation, inform the treatment, and predict response to treatment.

5. Conclusions

This study examined the association between alexithymia and cognitive function in asymptomatic HIV. Our findings indicated that the higher rate of alexithymia among HIV+ individuals than in the general population may be a direct consequence of the infection on the frontostriatal system and its cortical connections, resulting in both cognitive deficits and alexithymia. Examination of the individual processing components of alexithymia suggested anatomically and functionally distinct neural substrates. Our findings also demonstrated a dissociation of apathy and alexithymia in this population, pointing to overlapping but distinct neural substrates within frontostriatal circuits. Finally, we found that alexithymia was related to lower perceived quality of life in asymptomatic individuals living with HIV.

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Table 1

Participant demographic and immunological characteristics, group means (SD)

	HIV−	HIV+	*p*
DEMOGRAPHIC DATA			
N	34	34	
Age (years)	45.8 (6.1)	47.5 (6.0)	0.23
Years of education	15.4 (1.7)	14.8 (1.8)	0.14
Men:Women	22:12	25:9	
ANART	122.8 (7.4)	121.1 (7.5)	0.38
IMMUNOLOGICAL DATA			
Years since diagnosis		12.2 (6.3)	
CD4 count (copies/mL)			
Group average		543.3 (254.7)	
# of times below 200		0.8 (1.9)	
Viral load			
Undetectable (<75 copies/mL)		*N* = 26	
Low (<400 copies/mL)		*N* = 1	
High (>400 copies/mL)		*N* = 7	

Demographic data are presented for all participants, and immunological data are presented for HIV+ participants. *p*-values reflect results of independent-samples t-tests.

All HIV+ participants were Stage A as determined by the CDC (1993) guidelines.

ANART: American modification of the National Adult Reading Test

Table 2

Neuropsychological performance; raw score mean values (SD)

Measure	HIV−	HIV+	*p*
Attention & executive function			
Trails A (time in s)	28.4 (9.3)	40.8 (16.2)	**0.0001**
Trails B (time in s)	55.4 (16.2)	89.9 (46.9)	**0.0001**
WMS-III Digit Span (total)	13.0 (3.5)	10.4 (3.0)	**0.001**
WMS-III Spatial Span (total)	11.5 (2.3)	8.7 (2.7)	**0.0001**
Subtracting by 7's (time in sec)	46.5 (22.2)	85.3 (60.8)	**0.001**
Subtracting by 7's (errors)	0.5 (0.9)	2.6 (2.9)	**0.0001**
COWAT Animals (total)	22.2 (4.4)	17.1 (5.4)	**0.0001**
COWAT FAS (total)	51.9 (15.0)	41.6 (13.0)	0.009
Verbal function			
WAIS-III Similarities (total)	28.1 (3.4)	26.4 (3.5)	0.066
BNT (total)	56.1 (3.2)	54.0 (4.3)	0.157
Visuospatial function			
RCPM (total)	34.7 (1.6)	31.1 (4.5)	**0.0001**
Visual Symbol Search time (time in s)	71.2 (20.1)	95.3 (29.6)	**0.0001**
BVSQB R-L Orientation (errors)	1.6 (1.7)	4.3 (3.6)	**0.0001**
BVSQB Drawing (total)	11.0 (1.9)	8.1 (3.1)	**0.0001**
BVSQB Copy (total)	11.9 (1.3)	9.4 (2.3)	**0.0001**
Memory			
Visuospatial Memory			
ROCF Immediate recall (total)	20.1 (7.0)	15.0 (7.1)	0.005
ROCF Delayed recall (total)	20.0 (5.9)	15.5 (7.4)	0.009
Verbal Memory			
WMS LM 1 Immediate recall (total)	47.9 (5.8)	42.8 (9.3)	0.085
WMS LM 2 Delayed recall (total)	30.0 (7.5)	24.9 (7.2)	0.103
Psychomotor function			
Purdue Pegboard (total)	13.5 (2.2)	11.6 (2.0)	0.014
Emotion & Mood			
Toronto Alexithymia Scale-20 (total)	36.1 (8.5)	45.6 (14.5)	**0.002**
Beck Depression Inventory-II (total)	5.0 (4.0)	12.7 (8.3)	**0.0001**

p-values reflect results of independent-samples *t*-tests; *alpha* was adjusted using Bonferroni orrection to 0.002. Significant *p*-values are in bold.

Table 3

Correlations between alexithymia factors (TAS-20) and neuropsychological performance in HIV+ individuals; Pearson product-moment coefficients

	TAS-20 Total	TAS-20 Total	TAS-20 Factor 2	TAS-20 Factor 3
Attention & executive function				
Trails A (time)	0.09	−0.21	0.11	**0.41** *
Trails B (time)	0.32	−0.01	0.33	**0.46** **
Digit Span (total)	**− 0.36** *	−0.26	− 0.25	**− 0.37** *
Spatial Span (total)	**− 0.44** *	−0.23	**− 0.48** *	**− 0.47** **
Subtracting by 7s (errors)	0.30	−0.03	0.28	**0.45** **
Animals (total)	**− 0.43** *	−0.28	**− 0.57** **	− 0.34
FAS (total)	− 0.22	−0.06	− 0.18	**− 0.42** *
Visuospatial functions				
RCPM (total)	**− 0.45** *	− 0.12	**− 0.46** **	**− 0.51** **
BVSQB Draw (total)	**− 0.39** *	− 0.03	**− 0.45** *	**− 0.53** **
BVSQB Copy (total)	**− 0.42** *	− 0.09	**− 0.49** **	**− 0.51** **
Visual Symbol Search (time)	0.25	0.17	0.25	0.17
BVSQB R-L Orientation (errors)	0.23	0.09	0.08	− 0.02

Significant *p*-values are in bold.

* $p < 0.025$;

** $p < 0.005$