Neuropsychological examination of elements of attention in HIV infection in HIV+ adults and HIV- controls and their relationship to demographic, virologic, cognitive, and drug variables

Tsamis, VJ [1] and Latimer, WW [1]
Johns Hopkins Bloomberg School of Public Health

Abstract
We assessed the applicability of Mirsky and colleagues (1991; 2001) five-factor attention model in a sample of 147 HIV-infected adults with a history of drug use as compared to a sample of 258 HIV- adult controls who also reported drug use in the past. Our analysis of the HIV+ sample revealed a five-factor model which explained 65.48% of the variance. A five-factor model was also derived from the HIV- sample which explained 62.96% of the variance. We suggest the construct of attention includes the element of disinhibition, and propose that additional neural substrates are involved. Further analysis revealed that global neurocognitive functioning (GNF) was significantly related with the sustain, shift, focus/execute, and encode elements of attention in our HIV+ sample. In addition, GNF was significantly associated to viral load while CD4 levels were associated with some of the attention elements. Further examination revealed a significant positive association between the disinhibition element of attention and education level in our HIV+ sample. In turn, we also found a robust significant association between the encode element of attention and heroin use in our HIV+ sample. Possible explanations for these associations are posited and suggestions for further research in this critical area are discussed.

Keywords: attention, HIV, encoding, drug use, neurocognition, attention substrates, viral load, CD4 levels

Introduction

Attentional deficits are well recognized as a symptom in a number of medical conditions including HIV infection (Hardy and Hinkin, 2000; Heaton, Grant, Butters, White, Kirson, Atkinson et al., 1995; Levine, Hardy, Barclay, Reinhard, Cole, and Hinkin, 2008). Within a broad context, attention refers to the mental operation that cognitively processes information and the ability to attend to one's environment (Mirsky, Anthony, Duncan, Ahearn, and Kellam, 1991). A view of attention has emerged that attention is not just a single entity, but a set of brain processes that interacts with other brain processes in the performance of cognitive, perceptual, and motor skills (Mirsky et al., 1991; Parasuraman, Greenwood, and Alexander, 2000). Despite the research efforts devoted to identifying the multifaceted nature of attention, there is consensus that the construct remains poorly defined while little is known regarding the attention processes of HIV-infected individuals.

The following is a brief literature review of how we arrived at the point that we now recognize attention as a multi-element process. Posner (1982) suggests that attention theory emerged in three successive steps, with each step contributing to (1) the cumulative development of methods used to measure attention, (2) the practical application of these methods, and (3) theories regarding the nature of the systems underlying attention. Early on, researchers investigated an individual's level of performance in regards to the ability to attend to more than one task at a time. Attention experiments focused on the ability to perform simultaneous tasks in an effort to gather information regarding the nature of the structures underlying attention processing. Results suggested that an individual's ability to process information on dual tasks was limited, and that each task interfered with the other. These findings prompted the notion that attention was a single-channel process and provided little insight into general attention mechanisms. Eventually, researchers focused on the individual's level of subjective experience which involved a separation of conscious and unconscious events. This approach may be described within the context of Pavlov's work on two internal patterns of behavior – facilitation and inhibition- and suggested that attention may be inhibited by higher levels of the nervous system exercising control over lower levels. As a result, attention research then focused on the connection between aspects involved in conscious attention and the putative neural systems that may underlie the attention process. During this period, research suggested the presence of an orienting reflex in attention. This reflex acted on outward signs and internal signals to shift attention to a new stimulus. The re-alignment required for the detection of a new stimulus led to speculation that multiple neural mechanisms controlled a complex cognitive task (Posner, 1982).

An early model by Pribram and McGuiness model (1975) suggested that attention control encompassed the processes of *arousal, activation*, and *effort*. This model was derived from animal data research and posited that "arousal is more or less defined by the orienting response to sensory input…and…concluded that this may be the core that mediates the action of an effective external stimulus" (Pribram and McGuiness, 1975, p. 123). This model portrayed attention as a threefold process*: orienting, detecting stimuli*, and *maintaining vigilance*. The three processes were purported to be supported by the prefrontal cortex, the parietal cortex, and selected brain stem structures (Pribram and McGuiness, 1975). In other models that followed, Heilman, Watson, Valenstein, and Damasio (1983) and Mesulam (1987), guided by the symptom of neglect, suggested that attention was dependent upon a system called the "cortico-limbic-reticular circuit." The symptom of neglect which they defined as a "reported lack of awareness of visual, auditory, or somatosensory stimuli from one half of space" (Mirsky, 1996, p. 80) led to their development of a neural attention system. Given the reliance on a single symptom, the Heilman and Mesulam models were perceived as a narrow view of what constitutes attention (Heilman, 1979; Heilman et al., 1983; Mesulam, 1987). Yet another attention model proposed by Sohlberg and Mateer (1989) was based on data gathered in the assessment and rehabilitation of persons with brain injuries. Specifically, this model was derived from empirical and theoretical analysis of tests employed in cognitive therapy and was presented within the context of a treatment model (Sohlberg and Mateer, 1989). Sohlberg and Mateer proposed that attention is a multidimensional cognitive capacity comprised of five levels: (1) the ability to focus attention; (2) the capacity to sustain attention; (3) adequately detecting stimuli; (4) the competence to alternate attention between stimuli; and (5) being able to divide attention between tasks. Posner and Peterson (1990) introduced an attention model that was comprised of three major functions supported by two major loci in the human brain. These researchers suggested that the function of orienting to sensory events is supported by a posterior attention system that is located in the dorsal visual pathway and continues to the parietal lobe. The function of detecting signals for focal or conscious processing appeared to be supported by an anterior attention system whose structures are located in the frontal lobe of the brain. However, the function of maintaining vigilance or alertness was not clearly anatomically defined, but posited to be structurally supported by the norepinephrine innervation system, extending from the brainstem to the right hemisphere of the brain (Posner and Peterson, 1990). Mirsky et al. (1991) suggested that attention is the result of the common action of four elements linked into a system. Mirsky et al. (1991) introduced a heuristic neural model of attention based on data derived from of a battery of neuropsychological tests administered to children and adults. This model builds on the work of Zubin (1975) who attempted to explain attention deficits in schizophrenia. The notion that attention abilities are functions of a major and distinct cerebral system reflects a recent development in attention research. Research suggested that each element of attention may be anatomically linked to putative cerebral structures. This characteristic made this model unique and represents an emerging theory for studying attention (Mirsky et al., 1991).

Mirsky's neural model of attention proposed four elements of attention: *focus/execute, shift, sustain,* and *encode* (mnemonic). The *focus/execute* element is the ability to examine materials quickly and thoroughly for a preset target and the ability to make a response. The inferior parietal, superior temporal, and striatal region of the brain are important to the focus/execute element of attention. The *shift* element involves the ability to make a transition of focus in a flexible manner from one stimulus to another. This element of attention appears to be supported by the prefrontal cortex. The *sustain* element encompasses the ability to maintain focus and the capability to be vigilant over time. The rostral midbrain structures, which include the mesopontine reticular formation and midline and reticular thalamic nuclei, are strategic to the *sustain* element of attention. The norepinephrine innervation system appears to also play a role in this element of attention. The *encode* element refers to mentally manipulating and recalling information stored in memory. Limbic structures, including the hippocampus (Blakemore, Iversen, and Zangwill, 1972), and amygdala appear to be involved in the encode element of attention. Overall, claims Mirsky "it would be premature to attempt to achieve a complete synthesis of the neuropsychological and cognitive approaches to attention…the complexities of some models proposed are beyond our current knowledge of the correspondence between structure and function in the brain" (Mirsky et al., 1991, p. 136). Mirsky and Duncan (2000) proposed a fifth factor to their attention model termed 'stabilize' based on variables from the Continuous Performance Test (CPT; Visual CPT variability of reaction time and Auditory CPT variability of reaction time; Rosvold, Mirsky, Sarason, Bransome, and Beck, 1956) that represents response consistency over time (Mirsky and Duncan, 2001). Levine et al. (2008) factor structure somewhat similar to the Mirsky and Duncan (2001) attention model in a sample which included HIV infected participants in that they also extracted five factors, however, Levine and colleagues found some measures did not have factor loadings similar to those described by Mirsky and Duncan (2001). Our goal for this study was four-fold: (1) to examine whether similar attention factors as those reported by Mirsky and colleagues (1991; 2001) and Levine et al. (2008) could be extracted in our HIV-infected sample; (2) to investigate whether similar elements of attention could be extracted in a sample of HIV- controls; (3) to determine any correlations between attention elements and demographic characteristics of our sample, as well as virologic variables and cognitive measures in our HIV+ sample; and (4) whether any relationship exists between the elements of attention reported by Mirsky and drug use. To our knowledge, this is the first time elements of attention has been derived using mostly HIV+ participants as 63.5% of Levine and colleagues' (2008) sample met the diagnostic criteria for AIDS set by the Centers for Disease Control (CDC; 1994) as compared to 19.1% in our sample while concurrently examining elements of attention in an HIV- control sample from the same culture.

METHOD

Participants

This study was NIDA-funded and fully approved by the Johns Hopkins University Bloomberg School of Public Health and the South Africa Medical Association Institutional Review Boards with both review boards having Federal Wide Assurance and both conducting annual study reviews. The sample consisted of 147 HIV-infected adults aged 18 to 38 recruited in South Africa from local clinics, treatment centers, and other community locales using various community recruitment methods. Trained assessors were available that were familiar and spoke the various dialects associated with the ethnicity of the participants. The average age in years of the sample was 25.3 (SD=4.3). A total of 44 (29.9%) participants were male and 103 (70.1%) were female. The sample was predominantly black with 140 (94.6%) participants describing themselves as falling into this category. Average last grade completed by the sample was 9.5 (SD=2.2). Viral load was established via blood draws. In addition, CD4 was obtained. There was a history of drug use by participants in our sample - 88 (59.5%) reported heroin use, 3 (2.0%) reported cocaine use, 23 (20.1%) reported crack use, 136 (91.9%) reported marijuana use, 3 (2.0%) reported mandrax use, and 1 (.7%) reported methcathinone use. Data from participants was collected regarding whether they had previously been diagnosed with any psychological illnesses, attention problems, any head injury, and head injury followed by unconsciousness. Forty-five (30.4%) participants reported having been seen by a doctor or at a hospital for head injury and one participant reported head injury followed by unconsciousness for longer than one hour. Three (2.0%) of the participants reported having been told previously that they had Attention Deficit/Hyperactivity Disorder (AD/HD), one (.7%) participant reported a diagnosis of depression, six (4.1%) participants reported having seen a psychiatrist for an emotional and/or behavioral problem, and one (.7%) participant reported having a learning disability, learning disorder, or dyslexia. The demographic, cognitive, and virologic characteristics of the sample are presented in Table 1.

Our control sample consisted of 258 HIV- adults aged 18 to 40 recruited in South Africa. The average age in years of the sample was 24.22 (SD=5.25). A total of 155 (59.6%) participants were male and 103 (39.6%) were female. The sample was predominantly black with 244 (93.8%) participants describing themselves as falling into this category. Average last grade completed by the sample was 9.4 (SD=2.1). There was also a history of drug use by participants in this sample - 144 (55.6%) reported heroin use, 4 (1.5%) reported cocaine use, 65 (25.5%) reported crack use, 249 (96.1%) reported marijuana use, 1 (.4%) reported mandrax use, and 1 (.4%) reported methcathinone use. Data from the HIV- participants was also collected regarding whether they had previously been diagnosed with any psychological illnesses, attention problems, any head injury, and head injury followed by unconsciousness. Fifty-one (19.6%) participants reported having been seen by a doctor or at a hospital for head injury and three (1.2%) participants reported head injury followed by unconsciousness for longer than one hour. Seven (2.7%) of the participants reported having been told previously that they had Attention Deficit/Hyperactivity Disorder (AD/HD), two (.8%) participants reported a diagnosis of depression, fourteen (5.4.%) participants reported having seen a psychiatrist for an emotional and/or behavioral problem, and six (2.3%) participants reported having a learning disability, learning disorder, or dyslexia. The demographic and cognitive characteristics of the control sample are also presented in Table 1.

Measures

As part of the study protocol, the global neurocognitive functioning of participants was assessed using the Shipley Institute for Living Scale (SILS; Shipley, 1940). The SILS is a self-administered test that consists of two subtests: (1) the Vocabulary subtest which is a 10-minute test consisting of 40 multiple choice questions during which participants are asked to select which one of four words closest represents the meaning of a target word. The Vocabulary subtest tests verbal skills which includes acquired knowledge, verbal comprehension, reading ability, concept formation, as well as long-term memory; and (2) the Abstraction subtest which is 10-minute test consisting of 20 questions in which sequences of words, letters, and numbers appear with the final element in each sequence omitted. Participants are asked to complete each of the sequences. The Abstraction subtest is reliant upon word, letters, and numbers abilities, as well as on the ability of letter, word, and number concept formation, attention ability, abstract thinking, cognitive flexibility, analysis and synthesis, processing speed, long-term memory, and specific vocabulary and arithmetic skills. Scores are converted to a T-score (mean=50, SD=10) using normative tables that adjusted for the respondent's age (Shipley, 1940). The Verbal t-score was used as a measure of verbal intelligence quotient (VIQ) while the overall score was used as a measure of global neurocognitive functioning (GNF) status.

As previously reported by Mirsky et al. (1991), the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) Digit Span subtest, and specifically the Digit Span Backwards and the Digit Span Forward were used to assess the *encode* element of attention. Based on functional neuroimaging that indicates that the Digits Backwards and Digits Forward do have distinct neurophysiological components (Gerton, Brown, Meyer-Lindenberg, Kohn, Holt, Olsen, and Berman, 2004), we chose not to use their aggregate score, e.g. Digit Span scaled score. During the Digit Span subtest, both Digits Forward and Digits Backward, the examiner recites group of numbers and asks the participants to recall the numbers. In Digits Forward, a participant recites the numbers in the same order as given, while the Digits Backward administration requires the participant to recite the numbers backwards. The number of sequences of randomized digits correctly recalled is recorded.

Further departing from the Mirksy et al. (1991) who used measures of the CPT (Rosvold et al., 1956) to assess the *sustain* element of attention, we used the Test of Variables of Attention (TOVA; Greenberg and Waldman, 1993) which uses geometric stimuli in an effort to minimize the effects of cultural differences. The TOVA is a 21.6 minute long computer test and requires study participants to click a switch when the target figure appears and not clicking when a non-target figure appears on the computer screen. Omission errors (misses), commission errors, and reaction time were used as measures of the sustain element of attention, while the TOVA variability of reaction time was included as a measure of the *stabilize* element of attention. The *shift* element of attention was measured using the Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948) which measures concept formation and the ability to shift from one stimulus concept to another. Participants are given a set of cards and must place each card under a four-choice display which differs by color, form, and number. No further instruction is provided to the participant, but feedback is provided after each card placement. The number of categories achieved, the number of correct responses, and the number of failures to maintain set were used to assess the shift element of attention. Finally, the *focus/execute* element of attention was assessed using the raw scores of the Trail Making Test A and B which is part of the Halstead-Reitan (Reitan and Davidson, 1974) and requires participants to visually scan for ordered stimuli. The test required participants to draw lines connecting numbers (Part A) and numbers alternating with letters (Part B). The Stroop Color-Word Interference Test (Stroop, 1935) was also used to assess the *focus/execute* element of attention. This test assesses the ability to read words more quickly and automatically than naming colors. The Stroop word t-score, the color t-score and the word-color t-scores were used to assess the *focus/execute* of attention. We point out that "specific measures of attention are often derived from the [researchers'] preconception of the tests that best assess attention…and…may be used to provide indices of attention" (Mirsky, Fantie, and Tatman, 1995, p. 136) as our rationalization for not including the exact neuropsychological attention battery administered by Mirsky et al. (1991) and Mirsky and Duncan (2001).

Statistical Analysis

The mean and standard deviation for the attention measures for both samples were computed which, in turn, were submitted to further analysis to determine any significant mean differences. Analysis was also conducted to determine if our samples met the homogeneity of variance assumption. A principal component analysis (PCA) with promax rotation was then employed to explore the factor structure of our attention measures in both samples. These measures are listed in Table 2. We found some overlap with elements of attention with those reported by Mirsky and Duncan (1991; 2001). An eigenvalue cutoff of 1 was the criterion for inclusion in a factor in the final model. The factors were then saved as variables so that we may conduct additional analysis. Pearson bivariate correlation analysis were computed between the factors and a number of the demographic, cognitive, virologic, and drug use variables in order to determine any contribution of the obtained elements of attention. We also investigated for any gender differences in the elements of attention between the HIV+ sample and the HIV- controls.

Results

Initial analysis of the means and standard deviations of the attention measures revealed that both samples performed similarly on most of the neuropsychological tests, however, significant differences on TOVA reaction time (t=-2.23, p=.02) and TOVA reaction time variability (t=-2.01, p=.04) were found. A Levene's Test for Equality of Variances for the HIV+ sample and HIV- controls revealed no significant differences. Five factors with eigenvalues greater than 1 were then found to explain a cumulative total of 65.82% of the variance in the HIV+ sample and five factors with eigenvalues greater than 1 were found to explain a cumulative total of 62.96% of the variance in the HIV controls. The factor structure in both models is somewhat similar to that of Mirsky et al. (1991; 2001), that is, some similar measures loaded on similar factors when compared to their model. Factor 1, interpreted by Mirsky and colleagues as the *encode* element of attention, had high loadings on the WAIS-III Digit Backwards (.805) and Digits Forward (.697), and explained 22.83% of the variance. Factor 2, interpreted by Mirsky as the sustain element of attention, had loadings on the TOVA omission errors (.728), reaction time (.818), and variability of reaction time (.915) and explained 14.61% of the variance. This deviates from Mirsky and colleagues model' in that in our analysis variability of reaction time that Mirsky proposes as a measure of the *stabilize* element of attention loaded on Factor 2 (*sustain*). Factor 3 had high loadings from the Wisconsin Card Sorting Test number of correct responses (.964), number of categories completed (.746), and failures to maintain set (.718), is similar to Mirsky's *shift* element of attention, and explained 11.45% of the variance. Factor 4 had high loadings on the Stroop Color-Word Interference Test word t-score (.655), color t-score (.474), and color-word t-score (.767), is similar to Mirsky's *focus/execute* element of attention, and explained 8.97% of the variance. The TOVA commission errors had high loadings on Factor 5 (.910) and explained 7.61% of the variance (we will term this element *disinhibition*). The Trails A and B had high negative loadings on Factor 1 (*encode*; -.578 and -.547 respectively). This is a departure from Mirsky's model as these measures had previously loaded on the *focus/execute element* of attention.

In our HIV controls, the elements of attention loaded in a dissimilar order as follows: *shift, encode, focus/execute, sustain, and disinhibition*. Factor 1 (shift) had high loadings on the WCST number correct (.967), WCST categories completed (.768), and WCST failures to maintain set (.648) and explained a cumulative total of 22.03% of the variance. Factor 2 (encode) had high loadings on the Digits Forward (.714) and Digits Backwards (.767) as well as negative loadings from the Trails A (-.651) and Trails B (-.546) and explained a cumulative total of 12.92% of the variance. Factor 3 (focus/execute) had high loadings on the Stroop Interference measures, and specifically, the Stroop word t-score (.818), the Stroop color t-score (.726), and the Stroop color word t-score (.737) and explained a cumulative total of 11.85% of the variance. Factor 4 (sustain) had loadings on the TOVA omission errors (.902), TOVA response time (.292), and the TOVA reaction time variability (.853). As in our HIV+ sample, the TOVA commission errors (.789) loaded on Factor 5 (disinhibition). The correlations between the individual attention measures and the PCA factors we extracted in the HIV+ sample are presented in Table 3.

Pearson's bivariate correlations revealed a number of significant correlations in our HIV+ sample. We found a significant positive association between Factor 5 (*disinhibition*) and last grade in school (r=.17, p=.03). We also found a robust association between Factor 1 (*encode*) and heroin use (r= .34, p=.000). In addition, we found correlations between participants' Global Neurocognitive Functioning and the *encode* element of attention (r=.54, p=.000), the *sustain* element of attention (r=.34, p=.000), the *shift* element of attention (r=.19, p=.02), and the *focus/execute* element of attention (r=.28, p=.001). We created a CD4 level variable based on the CDC CD4 classification system (CD4 Level 1 <200 cells/□L, CD4 Level 2 = 200 – 499 cells/□L, and CD4 Level 3 ≥500 cells/□L) so that we may examine for any relationship between CD4 levels and the attention elements. We did not find a relationship between any of the elements of attention and CD4 Level 1, however, we did find a modest significant inverse association between CD4 Level 2 and the *shift* element of attention (r=-.25, p=.04), as well as a modest positive significant association between CD4 Level 2 and the *focus/execute* element of attention (r=.28, p=.04). In addition, we found a robust significant inverse relationship between CD4 Level 3 and the *encode* element of attention (r=-.33, p=.01). We also found a modest positive significant association between viral load and GNF (r=.20, p=.02). Lastly, we found gender differences in the *disinhibition* element of attention in the HIV+ sample (t=2.27, p=.007). We also found gender differences in the *focus/execute* (t=-2.34, p=.02) and the *disinhibition* (t=2.39, p=.01) elements of attention in our HIV- controls.

Discussion

The current study examined the factor structure of a neuropsychological battery of tests that have been commonly conceptualized as assessing attention. Our goals were to (1) assess the applicability of Mirsky's multiple element model of attention in a sample of HIV-infected adults, many of whom had reported drug use; (2) compare elements of attention in the HIV+ sample to HIV- controls; (3) determine whether any of the individual derived factors were associated with a variety of demographic, virologic, and cognitive variables; and (4) determine any contribution of the obtained elements of attention to drug use. To our knowledge, this is the first that attention has been evaluated in an HIV+ sample and compared to a sample of HIV- controls. We used the Mirsky et al. (1991; 2001) attention model as the benchmark with which to evaluate attention in both samples.

While Levine et al. (2008) reported a factor structure similar to Mirsky and colleagues in an HIV+ sample that included HIV-infected participants in that there were some similar loadings of the neuropsychological measures across five factors including the CPT commission errors that had a negative loading on the *sustain* factor, five factors resulted from our PCA with some dissimilar loadings of the measures in both samples.

In our HIV+ sample, Factor 1 is consistent with Mirsky's encode element of attention. Our study is further distinctive in that we recognize that while there are shared neurophysiological mechanisms, there are also distinct neuropsysiological components between the Digits Backwards and Digit Forward based on recent functional neuroimaging evidence (Gerton et al., 2004) and therefore we chose to include these measures individually rather than collectively as an aggregate score. Data from experiments conducted by Gerton and colleagues suggest that the Digit Backwards and Digits Forwards rely upon an overlapping functional neural system, specifically the right dorsolateral prefrontal cortex as well as the bilateral inferior parietal lobule, and the anterior cingulate. In addition, the medial occipital cortex which includes higher and lower visual processing areas were robustly activated both in the Digits Backwards and Digits Forward. However, the Digits Backwards additionally recruits the bilateral dorsolateal prefrontal cortex, the left inferior parietal lobule, as well as Broca's area (Gerton et al., 2004). These findings suggest additional underlying neural substrates are involved in the attention process.

Factor 2 is consistent with Mirsky' model in that three of the four TOVA measures (omission errors, reaction time, variability of reaction time) did load on the *sustain* element of attention. The loading of the TOVA commission errors on Factor 5 which we have termed *disinhibition* may reflect a temporary loss of vigilance in the attention process that may be caused by another stimulus, a possible distraction by involuntary or emotional stimuli, or alternately, through influence of the sample's HIV status, other external stimuli such as drug use, or may perhaps be a result of brain damage in our sample.

Factor 3 is consistent with Mirsky's model which is conceptualized as the *shift* element of attention, however, we conceptualized the WCST failures to maintain set as a measure of this attention element. Shifting is the ability to switch attention in a flexible manner from one stimulus to another, an ability which is arguably necessary for successful performance in maintaining a set. We point out that Levine et al. (2008) suggest that "it will be necessary to include additional, yet more simple, measures of set shifting in future analysis" (Levine et al., 2008, p. 59).

Factor 4 is consistent with Mirsky's model of attention relative to the *focus/execute* element of attention in that measures of the Stroop Color-Word Interference Test had high loadings on this factor. We consider an open debate as to whether the *focus/execute* element of attention should include descriptors of some measures included by Mirsky in his model such as the Symbol Search (form discrimination) and Digit Symbol (visual-motor integration). We partly addressed this debate in that we used the Stroop Color-Word Interference Test which had high factor loadings on the *focus/execute* element of attention while Trails Making Part A and B had negative loadings on another factor conceptualized as the *encode* element of attention.

Our findings of the Trails A and B negative loadings on Factor 1 may heuristically suggest an inverse relationship between the encode process during which individuals recall/reorder information stored in memory process in the midst of other cognitive demands as it relates to visual-motor coordination and visual-spatial ability adequate enough is required in the attention process. The Digit Span Forward and the Digit Span Backward tasks of the Wechsler Adult Intelligence Scale - III (WAIS – III; Wechsler, 1997) used to assess encoding ability in this study are often conceptualized within a tripartite model involving working memory (Baddeley, 1992). This model consists of a central component that is executive in nature. The system not only appears to manipulate information stored in memory, but purportedly controls two subordinate systems. One is a phonological loop that is dedicated to short term storage and the rehearsal of acoustic information while the second is a visuospatial sketchpad that serves a similar function for visual and spatial information (Gerton et al., 2004). Along this realm, it may be posited that the intact encoding ability may require less pursuit of spatial organization and visual pursuit while the ability to processes distinctions between numbers and letters, be able to integrate numbers and letters, and the ability to apply organization principles systematically is more easily recalled in those whose encoding ability is undamaged.

We did find a modest association between the encode element and last grade in school as did Levine et al. (2008). These finding may suggest that as *encode* ability improves so does education level. A possible explanation may be that those with difficulties with this element of attention may not have attended school. That is, it is plausible that participants with a history of encoding problems had successfully managed their disability while those persons who had not successfully adapted were less likely to attend school. If this is true, then, a selection bias may have been introduced in this study. The hypothesized effect would, therefore, more likely occur among persons who experienced attention difficulties, but did not attend or continue on in school. For the first time to our knowledge, we also found significant robust relationship between drug use, and specifically, heroin use, and the *encode* elements of attention. This finding may reflect a person's reduced or increased tendency to engage in drug use. Alternately, drug use may exert influence upon this attention element.

Our findings regarding a significant positive association between participants' Global Neurocognitive Functioning (GNF) with all but one (disinhibition) of the elements of attention may suggest an association between GNF performance and intact attention performance in our HIV+ sample. This notion is supported by our finding that GNF is significantly related to viral load and supports previous findings by

Ferrando, van Gorp, McElhiney, Goggin, Sewell, and Rabkin (1998) who reported that HIV+ individuals with decreased viral load levels or undetectable viral loads may have a neuropsychological function benefit, and, in turn, may assist in explaining differences in cumulative variance in the HIV+ sample as compared to the HIV controls. In addition, the correlations found between CD4 levels and some of the attention elements may further aid in explaining the nature of the cumulative variance in our HIV+ sample. Alternately, the GNF score represents the aggregate t-score of the Shipley Vocabulary and Abstraction subtests. We did not find a significant difference in the Vocabulary t-score between the two samples, but we found significant difference in the Abstraction t-score between the HIV+ sample and the HIV- controls resulting in a significant difference in the overall t-score which may further assist in explaining the nature of the differences in the factors' cumulative variance. We also found gender effects in the *disinhibition* element of attention in the HIV+ sample, as well as gender differences in the *focus/execute* and *disinhition* elements of attention in the HIV- controls that may further assist in elucidating the nature of the cumulative variances of the two samples. Along this realm, it should be noted that the cumulative variance of factors by Levine and colleagues' factors differed as compared to both ours and Mirsky and colleagues' model. It should be noted that Mirsky and colleagues' factors 1 and 2 (shift and encode) loaded in the same order in our HIV controls.

It has been said that intelligence is a part of and not separate from the process of attention (Personal communication with George W. Rebok, 1996). Tsamis (1996) found that intelligence accounted for a significant portion of the variance when previously examining the Mirsky et al. (1991) elements of attention in second grade as predictors of aggressive behavior in sixth grade. Collectively, these findings suggest (1) the need to determine whether our model and newly proposed element of attention can be replicated; and (2) the need to further investigate the *focus/execute, shift, encode,* and *disinhibition* elements of attention to determine what short-term and long-term problematic difficulties may be associated with these elements of attention. For example, for the first time, Tsamis (1996) reported that impaired encoding ability in second grade predicted aggressive behavior in sixth grade in both genders, while Tsamis, Rebok, and Montague (2009) found that encoding ability was related with aggressive behavior in young adulthood. In addition, investigations grounded in the newer field of neuropsychoimmunology may provide additional information relative to how HIV infection may act upon the condition of attention elements.

There are several limitations to our study. It may be argued because we attempted to assess the validity of Mirsky's model of attention, a confirmatory analysis may have been preferable, however, we were constrained by the sample size. Alternately, structural equation modeling may be worthy of consideration, however, Strauss, Thompson, Adams, Redline, and Burant (2000) using such an approach failed to validate Mirsky's model.

Different classes of drugs have different neurocognitive morbidities. Some like opiates have little long term consequences. Others like cocaine, can have significant deficits. This is a considerable confound, but there is no data to address this confound and to account for this potential difference. Additionally, it is likely that the participants abused more than one drug, and we cannot account for this or recency of use. Consequences of some drugs of abuse are mitigated by time. Likewise, recency of head injury is not addressed other than the data we have presented. This is a meaningful confound. Furthermore, we have no data on how many of our participants are taking anti-retrovirals. This is a confound. Finally, it is curious that so few patients have depression. Rates of depression are generally higher in people with HIV. This raises questions about the sample. The patient and control groups have different rates of sexes which is also a potential confound.

Lastly, there is no functional neuroimaging data available for Mirsky's model to guide its expansion which may be due to the psychometric nature of the multifaceted battery of attention tests. We recommend that additional research to empirically verify the elements of attention found in our study as well as in previous attention models that are solely derived from widely used neuropsychological tests. While it may be difficult to achieve, functional neuroimaging may identify specific underlying neural substrates involved in each element of attention in this study and Mirsky's model and whether a specific network may be identified that links attention elements.

Conclusion

This study using a theoretical view of attention proposed by Mirsky and colleagues (1991; 2000) examined for the first time to our knowledge an HIV-infected sample as compared to HIV- controls. We used some different tests and some additional measures to conceptualize the attention processes. We proposed that the attention involves five elements. It is also suggested that further research be undertaken using functional neuroimaging to identify the neuroanatomical underpinnings of our elements and Mirsky's model, as well as further expand upon the associations between the elements of attention in our study, and cognitive and behavioral outcomes.

Table 1

Characteristics of the study samples

	HIV+ (n=147)			*HIV- (n=258)*		
Variable	*Mean*	*SD*	*% of n*	*Mean*	*SD*	*% of n*
Age [a]	25.4	4.3		24.22	5.25	
Education [b]	9.5	2.2		9.4	2.1	
Viral Load	23,933	41,601				
CD4	454.2	252.8				
1)<200 cells/□L			13.2			
2) 200-499 cells/□L			50.7			
3) ≥500 cells/□L			36.1			
GNF[c]	26.0	5.2		27.27	6.49	
Verbal IQ	22.9	7.9		31.57	5.86	
Gender						
Male			29.9			59.6
Female			70.1			40.4
Ethnicity						
Caucasian			1.4			3.1
Black			94.6			93.8
Mixed			3.4			3.1
South African			.7			

[a] In years [b] Last grade completed [c] Global Neurocognitve Functioning Status

Table 2
Comparison of factor results to Mirsky et al. (1991; 2000)

Proposed factor	*Mirsky et al. measure*	*Tsamis et al.measure*
Sustain	Visual CPT (Accuracy, RT)	TOVA (omission errors, RT, variability of RT)
Shift	WCST (# categories, number correct, errors)	WCST (# categories, number correct, failures to maintain set)
Focus/Execute	Digit Symbol Stroop (all trials) Trail Making Test A, B Letter Cancellation	Stroop (all trials)
Encode	Digit Span scaled score	Digit Span DF and DB
Disinhibition	not applicable	TOVA (commission errors)
Stabilize	Visual CPT (Variability of RT) Auditory CPT (Variability of RT)	not applicable

CPT=Continuous Performance Test (Rosvold et al., 1956), WCST=Wisconsin Card Sorting Test (Grant and Berg, 1948), RT=Reaction Time.

Table 3
Correlations of individual measures with PCA factors in HIV+ sample

	Factor				
	1	2	3	4	5
Measure	Encode	Sustain	Shift	Focus	Disinhibition
TOVA Omissions	.062	**.667**	-.006	.143	.394
TOVA Commissions	.040	.057	-.021	.053	**.878**
TOVA Hit RT	.290	**.791**	.161	.176	.380
TOVA Variability	.247	**.871**	.120	.137	.059
WCST FMS	-.078	-.140	**.718**	-.184	.033
WCST Categories	.383	.375	**.724**	.072	-.196
WCST Correct	.222	.172	**.958**	-.039	-.088
Stroop word	.329	.351	-.029	**.825**	.277
Stroop color	.610	.413	-.124	**.782**	.041
Stroop color-word	-.048	-.096	-.098	**.636**	-.094
Trails Making A	-.671	-.150	-.274	-.398	.345
Trails Making B	-.717	-.458	-.349	-.342	.165
Digit Span DB	**.667**	.055	-.027	.185	.037
Digit Span DF	**.774**	.222	.187	.075	.077

TOVA=Test of Variables of Attention, WCST=Wisconsin Card Sorting Test, FMS=WCST failures to maintain set, DB=Digit Span Digits Backward, DF=Digit Span Digits Forward. Large factor loadings are in bold typeface.

References

American Psychological Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders – IV*. Washington, DC: American Psychological Association.

Baddeley, A. 1992. Working memory. *Science*, 255: 556-559.

Blakemore, C., Iversen, S., & Zangwill, O. 1972. Brain functions. *Annual Review of Psychology*, 23: 413-456.

Centers for Disease Control and Prevention. 1994. *HIV counseling, trends, testing and referral: Standards and Guidelines.* Atlanta, GA: Centers for Disease Control and Prevention.

Ferrando, S., van Gorp, W., McElhiney, M., Goggin, K., Sewell, M., and Rabkin, J.
1998. Highly active antiretroviral treatment in HIV infection: Benefits for neuropsychlogical function. *Aids*, 12: 65-70.

Gerton, K., Brown, T., Meyer-Lindenberg, A., Kohn, P., Holt, J., Olsen, R. & Berman, K. 2004. Shared and distinct neurophysiological components of the digits forward and backward tasks as revealed by functional neuroimaging. *Neuropsychologia*, 42: 1781-1787.

Grant, D. and Berg, E. 1948. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem. *Journal of Experimental Psychology*, 38: 404-411.

Greenberg, L. M., & Waldman, I. D. (1993). Developmental normative data on the test of variables of attention (T.O.V.A.). *Journal of Child Psychology and Psychiatry*, 34: 1019-1030.

Hardy, D. and Hinkin, C. 2002. Reaction time performance in adults with HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology*, 24: 912-929.

Heaton, R., Grant, I., Butters, N., White, D., Kirson, D., Atkinson, J. et al. 1995. The HNRC 500: Neuropsychology of HIV infection at different disease stages. *Journal of International Neuropsychological Society*, 1: 231-251.

Heilman, R. 1979. Neglect and related disorders. In: K. Heilman and E. Valenstein (Eds.), *Clinical Neuropsychology*, pp. 268-307. New York: Oxford University Press.

Heilman, R., Watson, R., Valenstein, E. & Damasio, A. 1983. Localization of lesions in neglect. In: A. Kertesz (Ed.), *Localization in Neuropsychology*, pp. 319-331. New York: Academic Press.

Levine, A., Hardy, D., Barclay, T., Reinhard, M., Cole, M., and Hinkin, C. 2008. Elements of attention in HIV-infected adults: Evaluation of an existing model. *Journal of Clinical and Experimental Neuropsychology*, 30: 53-62.

Mesulam, M. 1987. Attention, confusional states, and neglect. In: M. Mesulam (Ed.), *Principles of Behavioral Neurology*, pp. 125-168. Philadelphia: F. A. Davis.

Mirsky, A. 1996. Disorders of attention: A neuropsychological review. In: G. Lyon & N. Krasnegor (Eds.), *Attention, Memory, and Executive Function*, pp. 71-95. Baltimore: Paul H. Brooks.

Mirsky, A., Anthony, B., Duncan, D., Ahearn, M. and Kellam, S. 1991. Analysis of the elements of attention: A neuropsychological approach. *Neuropsychology Review, 2*, 109-148.

Mirsky, A., Fantie, B., & Tatman, J. 1995. Assessment of attention across the lifespan. In: R. Mapoo & J. Spector (Eds.), *Clinical neuropsychological assessment: A cognitive approach*. New York: Plenum Press.

Parasuraman, R., Greenwood, P., & Alexander, G. 2000. Alzheimers disease reduces the dynamic range of spatial attention in visual search. *Neuropsychologia*, 38: 1126-1135.

Posner, M. 1982. Cumulative development of attention theory. *American Psychologist*, 37: 168-179.

Posner, M. & Petersen, 1990. The attention system of the human brain. *Annual Review of Neuroscience*, 13: 25-42.

Pribram, K. & McGuiness, D. 1975. Arousal, activation, and effort in the control of attention. *Psychological Review*, 2: 116-149.

Reitan, R. and Davidson, L. (eds.) 1974. *Clinical Neuropsychology: Status and Applications*. Winston & Sons: Washington, DC.

Rosvold, H., Mirsky, A., Sarson, I., Bransome, E. and Beck, E. 1956. A continuous performance test of brain damage. *Journal of Consulting Psychology*, 20: 343-350.

Shipley, W. 1940. The Shipley Institute of Living Scale (SILS).

Sohlberg, M. and Mateer, C. 1989. *Introduction to Cognitive Rehabilitation: Theory and Practice.* New York: Guilford.

Strauss, M., Thompson, P., Adams, N., Redline, S. and Burant, C. 2000. Evaluation of a model of attention with confirmatory factor analysis. *Neuropsychology*, 14: 201-208.

Stroop, J. 1935. Studies of interference in serial verbal reaction. *Journal of Experimental Psychology*, 8: 643-662.

Tsamis, V. 1996. A developmental epidemiological investigation of the relationship between impaired attention and aggressive behavior. OCLC's Experimental Thesis Catalog (United States). Paper presented at the annual meeting of the American Society of Criminology, Chicago, Illinois, November 1996.

Tsamis, V., Rebok, G., and Montague, D. 2009. The relationship between encoding ability and aggressive behavior. Applied Psychology in Criminal Justice, 5(1): 57-72.

Weschler, D. (1997). *Wechsler Adult Intelligence Scale–III*. New York: Psychological Corporation.
Zubin, J. 1975. Problem of attention in schizophrenia. In: M. Kietzman, S. Sutton, & J. Zubin (Eds.), *Experimental Approaches to Psychopathology*. New York: Academic Press.

Correspondence should be addressed to Vasiliki J. Tsamis, Ph.D., Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, 624 North Broadway, Room 895, Baltimore, Maryland 21205 USA, Telephone: +1 443.869.2663 or email at vtsamis@jhsph.edu or vkavouras52@gmail.com

The study was conducted with support from Supplement to NIDA Study DA014498 and the NIDA Drug Dependence Epidemiology Training Program T-32 DA007292. The authors acknowledge Dr. Nicholas Ialongo who read multiple versions of this manuscript and the trainees of the Drug Dependence Epidemiology Training Program, Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health directed by Dr. William Latimer .