SEMANTIC MEMORY IN HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS: AN EVALUATION OF THE 'CORTICAL' VERSUS 'SUBCORTICAL' HYPOTHESIS

A Thesis

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree of

Master of Arts

By

Savanna Tierney

August, 2017

SEMANTIC MEMORY IN HAND: AN EVALUATION OF THE 'CORTICAL' HYPOTHESIS

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ABSTRACT

While HIV- associated neurocognitive disorders (HAND) have historically been characterized as a subcortical process, there is some evidence to suggest that the cortical regions that support semantic memory may also be affected. The current study examined the effects of HAND on semantic memory. Participants were (N = 459) separated into three groups based on neurocognitive status defined by the Frascati criteria: HIV+ individuals with HAND (n = 85), HIV+ individuals without HAND (n= 191), and HIV negative individuals (n=183). All participants completed the Boston Naming Test (BNT) and the Famous Faces subtest of the Kauffman Adolescent and Adult Intelligence Test (KAIT). Analyses of errors committed on the BNT were conducted to further characterize the nature of semantic memory differences across groups. Linear regressions revealed a significant adverse effect of HAND on total scores on the BNT and the KAIT (all *p*s < .01). Analyses of BNT errors showed that individuals with HAND committed increased rates of semantically-related errors as compared to the other two groups (all *p*s < .05). However, there were no group differences in rates of visually based errors, more commonly observed in subcortical diseases (all *p*s > .10). Findings regarding the cognitive correlates of semantic memory show that executive (r_s = -.24, p = .02), speed of processing (r_s = -.31, p = .004), and learning (at trend level) domains were shown to be associated with BNT performance, while only the learning domain (r_s = -.28, p = .01) was significantly related to KAIT scores within the HAND+ group. Results suggest that HAND may impose adverse effects on individuals' object naming and identification abilities and suggest that there are mild semantic deficits in HAND that parallel traditional cortical diseases such as Alzheimer's Disease.

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HIV-associated neurocognitive disorders: Prevalence and Impact

Recent studies estimate that nearly 37 million people worldwide and 1.2 million individuals in the United States (U.S.) are infected with HIV, with about 50,000 new cases occurring each year (CDC, 2015). Although the efficacy and availability of combination Antiretroviral Therapy (cART) has transformed HIV into a chronic yet manageable disease, individuals living with HIV are at increased risk of developing a number of complications including HIV-associated neurocognitive disorders (HAND). Prevalent in as many as 50% of infected adults (Heaton et al., 2010), HAND involves deficits across a wide array of ability areas. Generally, HAND is marked by mild-to-moderate deficits in domains of executive functions (e.g., cognitive flexibility, novel problem solving, and inhibition), episodic learning and memory, attention/working memory, and psychomotor speed and coordination (Heaton et al., 2010). In contrast, cognitive abilities such as basic visuoperception, receptive language, and constructional praxis, as well as the brain regions (i.e., posterior neocortex) that facilitate these functions, tend to be relatively spared in HIV-infected individuals (Heaton et al., 1995). As such, the neuropsychological performance in HAND is consistent with its effects on the fronto-striatal-thalamo-cortical circuits, bearing similarities to disorders such as Parkinson's disease and Huntington's disease which have known subcortical abnormalities (e.g., Tröster & Woods, 2010).

Subcortical and Cortical Neurocognitive Performance Differences

The neurocognitive deficits associated with subcortical dysfunction may be differentiated from those stemming from cortical aberrations by examining the nature and pattern of memory performance, including both episodic (i.e., memory of autobiographical events, and associated contextual information) and semantic (i.e., knowledge of objects, facts, and concepts) memory functions. In general, the episodic memory deficits associated

with frontal-striatal-thalamo- cortical circuit dysfunction reflect executive dyscontrol of encoding and retrieval within episodic memory (e.g., Delis et al., 1995), whereas deficits due to medial-temporal-lobe dysfunction are primarily due a disruption more fundamental to encoding and retention of new information (e.g., Chan et al., 1993). As applied to HIV disease, the pattern of episodic memory deficits is most consistent with dysfunction in the frontostriatal loops. At the group level, HIV-associated episodic memory deficits tend to reflect a mixed encoding and retrieval profile (Woods et al., 2006). This means that persons with HIV demonstrate relatively intact retention of information over time, and while they have difficulties on tests of free recall, HIV-infected individuals tend to accurately identify previously presented information on tests of recognition, whereby the demands of retrieval are reduced. Further supporting the frontostriatal neuropathogenesis of HIV-associated episodic memory deficits, the observed impairments in free recall of verbal material are marked by diminished use of strategic organizational strategies, such as semantic clustering and switching (e.g., Iudicello, Woods, Deutsch, Grant & The HNRP, 2012; Peavy et al. 1994), which may increase in magnitude with the severity of HAND (Gongvatana et al., 2007).

In contrast, degradation of semantic memory is a well-established feature of typical “cortical” dementias (Bayles & Tomoeda, 1983) and is thus not widely considered a feature of HAND. A seminal and widely cited study by White et al. (1997) found that semantic memory was relatively spared in HIV-associated dementia (HAD) participants, as demonstrated by normal performance on the Boston Naming Test (BNT; Kaplan, E., Goodglass, H., & Weintraub, S, 1983). Indeed, the vast majority of research in HIV disease has shown a relative sparing of semantic memory. For example, in a sample of older adults, Scott et al. (2011) observed null effects of HIV on several well-validated measures of semantic memory, including the BNT (Kaplan, E., Goodglass, H., & Weintraub, S, 1983), the the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test

(KAIT; Kaufman & Kaufman, 1993), and the California Verbal Learning Test, 2nd edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). Iudicello, Woods, Deutsch, Grant, and the HIV Neurobehavioral Research Program (HNRP, 2012) Group reported that HIV infection and aging confer adverse additive effects on semantic fluency (i.e., switching), however, this impact is primarily due to disruption of the executive components of semantic memory rather than a degradation of semantic memory stores (i.e., cluster size). Moreover, in a study of remote memory ability in individuals with HAD, probable Alzheimer's disease (AD), and HD, Sadek et al. (2004) reported that HAD was associated with mild deficits in memory for famous faces and public events over time; however, in both the HD and HAD groups there was no evidence for the temporal gradient that was observed in persons with AD. Thus, consistent with the above-described profile of HIV-associated episodic memory deficits, the pattern of impairments observed in semantic memory is hypothesized to stem from deficient retrieval from semantic memory stores secondary to frontostriatal circuit neurotoxicity characteristic of subcortical disorders.

The 'Subcortical vs. Cortical Hypothesis'

Nevertheless, some researchers have recently posited that the expression of HAND in older HIV-infected adults may be qualitatively different from the typically displayed ''subcortical'' cognitive profile observed in younger and middle-aged adults living with HIV (Brew, 2004; Brew, Crowe, Landay, Cysique, & Guillemin, 2009; Valcour & Paul, 2006). This recent controversy suggests a subtle shift toward neocortical (e.g., temporal and parietal lobe) neuropathology as the underlying mechanism of deficits in HIV-associated cognitive impairment in the cART era (e.g., Kieburtz et al, 1996). Older adults with HIV are more likely to experience HIV-associated central nervous system (CNS) complications, including increased neuropathological burden (e.g., beta-amyloid deposition; Green et al., 2005), smaller frontal grey matter volumes (e.g., Jernigan et al., 2005), and spectroscopic evidence of neural injury in the frontal white matter and basal ganglia (e.g., Ernst & Chang,

2004). Together, these complex risk factors in addition to the neuropathological changes in mediotemporal structures associated with aging (Esiri, Biddolph, & Morris, 1998; Gelman & Schuenke, 2004), may impart an increased likelihood that older adults with HAND may be susceptible to cortical dysfunction and more likely to exhibit deficits typically associated with temporal (e.g., rapid forgetting, dysnomia) and parietal lobe functioning (Brew, 2004). Evidence for the shifted "cortical" hypothesis arises from studies showing HIV-associated deficits on tests of spatial cognitive (e.g., visuoperceptual) abilities, which are thought to be particularly reliant on the posterior parietal lobe (e.g., mental rotation; Olesen, Schendan, Amick, & Chronin-Golumb, 2007; Sharma, Amick, Shendan & Chronin-Golomb, 2003), and on tests of verbal and visual episodic memory (Sacktor et al., 2007). Based on this emergent theme of findings, some authors have argued that rather than the classic "subcortical" pattern (e.g., executive dysfunction, bradyphrenia) that has historically been observed in younger and middle-aged HIV-infected adults (e.g., Kieburtz et al., 1996; Ragin et al., 2005), the profile of neurocognitive impairment in older HIV-infected adults may now be more consistent with that seen in "cortical" dementias characterized by rapid forgetting, visuoperceptual deficits, and a degradation of semantic memory.

Limitations of Previous Research

Only three studies thus far have directly evaluated the cortical hypothesis in HAND using rigorous neuropsychological methods. Upon closer examination of a null difference in semantic switching between older HIV-infected adults and older HIV-seronegative adults, Iudicello et al., (2012) found that older HIV-infected participants with HAND demonstrated significantly worse switching relative to both unimpaired older HIV-positive participants and older HIV-seronegative individuals. In addition, the aforementioned study conducted by Scott et al., (2011), argued against the cortical hypothesis, finding that older HIV-infected adults did not demonstrate significant impairment on tasks of semantic memory. A more recent study by Ciccarelli et al., (2016) also failed to support the cortical hypothesis,

reporting null effects of an age by HIV interaction on a measure of verbal list learning. It is worth noting, however, that in addition to the study's small sample sizes (Iudicello et al., 2012; Scott et al., 2011), neither Scott et al., (2011) nor Ciccarelli et al., (2016) specifically examined the effects of HAND. Further, no error analyses were conducted examining the nature of semantic memory task scores, all of which may have increased the risk of type II error. Thus the likelihood of detecting an effect in these studies was reduced and it is possible that the effect of HAND on semantic knowledge may be better observed through use of amore evaluative methodological approach.

It is also important to consider the extent to which evaluative methods such as error analysis are able to characterize semantic processing deficits. Hodges, Salmon, & Butters (1991) explain that the use of broad, largely undefined, categories of error types such as 'language related, no response or perceptual' (Martin & Fedio, 1983), or 'semantically related, semantically unrelated, or near synonyms' (Bowles et al., 1987) fail to distinguish between errors that are visually, semantic-category, or ambiguously based. This is an important distinction, as many of the items within certain categories (e.g., fruit, animals) are very visually similar. Additionally, Hodges, Salmon, and Butters (1991) mention that, "the a priori assumption that all errors sharing category membership are semantically based is clearly a source of considerable potential bias." Applying a more comprehensive error coding system, based on the framework of Kohn and Goodglass (1985), Hodges et al., (1991) were able to further characterize the observed impaired semantic memory performance in HD, a prototypical subcortical disease, as being primarily due to perceptual deficits. Of note, a recent a study by Labuschagne and colleagues (2016) also suggested that impairment in HD may involve regions outside of fronto-striatal areas and provided evidence linking visuospatial deficits in early HD to posterior cortical dysfunction. Indeed, it may be the case that in evaluating the qualitative nature of errors committed in HIV

infection, evidence of the underlying mechanisms contributing to differences in semantic memory may emerge.

Present Study Aims and Hypotheses

With the above "subcortical" versus "cortical" controversy in mind, the proposed study has three primary objectives. First, the current study aims to explore the cortical hypothesis controversy by examining the semantic memory profiles in HIV positive individuals with and without HAND, and HIV negative individuals by utilizing the framework of Boston Naming Test error analysis described in Hodges, Salmon and Butters (1991), in combination with two other semantic tasks: the Pyramids and Palm Trees Test and the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test. Second, to investigate the interactive effects of aging and HAND on semantic memory performance and lastly, to investigate possible HIV disease and cognitive correlates of observed semantic memory deficits in HAND. Viewed through the lens of the cortical hypothesis, we would expect participants to demonstrate a general stepwise decline in performance on semantic memory measures (i.e., NC > HIV > HAND) reflecting a progressive impairment of executive dysfunction and degradation of semantic processes. Alternatively, the traditional perspective of frontostriatal dysfunction would predict more specific declines indicative of subcortical pathology. Specifically seropositive HIV individuals and participants with HAND may demonstrate increased visual based errors compared to controls on the BNT (as seen in HD; Hodges), while there may be no significant differences between groups on the PPT and KAIT. In considering these competing hypotheses, the current study aims to elucidate the neuropsychological profile of semantic memory in HIV.

METHOD

Participants

Study participants included 459 adults, aged 18 to 75 years, recruited from the University of California San Diego HIV Neurobehavioral Research Program. Participants

were excluded if they received an estimated verbal IQ score < 70 on the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001), reported histories of neuromedical (e.g., seizure disorder, stroke, at least moderate traumatic brain injury), current substance use disorder, or severe psychiatric (e.g., psychosis) disorders that might affect cognition. Participant demographic and disease characteristics are displayed in Table 1.

The human research ethics office of the University of California San Diego and the University of Houston approved this study. All participants provided written, informed consent.

Hand Diagnosis

HIV-infected individuals were classified as having HAND if they met recent Frascati research (see Antinori et al., 2007) criteria for one of three conditions: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated Dementia (HAD). Within the 279 HIV-infected individuals, 82 were classified as having HAND (i.e., 29% of the HIV-infected cohort; HAND+ group), and 198 were not cognitively impaired (i.e., HAND- group) as defined by criteria described in Antinori et al., (2007).

Measures of Semantic Memory

Boston Naming Test (BNT). All participants completed the BNT (Goodglass & Kaplan, 1983), a 60-item, widely used neuropsychological assessment of semantic knowledge. The test includes 60 black-and-white drawings of objects and animals graded in difficulty ordered from easiest to most difficult. The images were presented in order and participants were instructed to respond with the name for the object represented in the image. For each image, participants were allowed 20 seconds to provide a response, unless the participant indicates that they did not know the word before 20 seconds has elapsed. Points were awarded based on whether or not the response is correct, and error

scores were designed to characterize incorrect responses. The test was administered according to the following standard protocol: if a subject was unable to name an object, a predetermined stimulus or semantic cue (‘an ocean animal’ for octopus; ‘used for air travel for helicopter, etc.) was given, and if the subject was still unable to name then item, a phonemic cue consisting of the initial sound of the target word, was provided. All responses were graded on a 0 or 1 scale to reflect an incorrect or correct answer respectively. Two scores were obtained: the total number of items named spontaneously and the total number of items named after stimulus cueing. As previous studies have suggested the limited utility of the standard error evaluation on the BNT, errors were evaluated following criteria adopted by Hodges, Salmon, and Butters, 1991. Although all errors produced by the subjects are recorded, only the first response to the target (i.e., before stimulus or phonemic cueing) was classified, and in the case of multiple errors, only the first error was used. The categories used in the error analysis are described below.

Error Classifications

1. *Nonresponse:* includes 'don't know' and nonresponse.
2. *Visual error:* responses visually similar to the target *and* from a different semantic category ('spear', 'snake', 'fountain pen' for asparagus; 'tie' for stethoscope; 'head of hair' for octopus). Also included were whole-part responses where subjects named either a part of the target item ('blocks' for pyramids) or something incidentally present in the picture ('door' for knocker; 'boy' for stilts).
3. *Ambiguous visual/semantic category errors:* responses from the same semantic category as the target *and* visually similar such that the error could be either perceptually or semantically based ('hippopotamus' for rhinoceros; 'otter' for beaver; 'stork' for pelican; 'dice' for dominoes; 'headphones' for stethoscope; 'mountain' for volcano; 'peanut' for acorn).
4. *Semantic: within-category errors:* responses from the same semantic category as the

target but clearly *not* visually similar ('atlas' for globe; 'lettuce' for asparagus; 'violin' for accordion; 'thermometer' for protractor; 'easel' for palette).

5. *Semantic: superordinate errors:* responses denoting the general class or category to which objects belong ('vegetable' for asparagus; 'animal' for rhinoceros; 'musical instrument' for accordion).

6. *Semantic: associative errors:* responses showing an obvious semantic association with the target item including statements of action or function ('painting' or 'artist' for easel; 'blow' or 'music' for harmonica), physical attributes ('ice' for igloo; 'green' for asparagus), contextual associates ('ocean' for octopus; 'desert' for camel; 'Egypt' for pyramid; 'doctor' for stethoscope), and specific subordinate or proper noun examples of the target ('Vesuvius' for volcano).

7. *Semantic: circumlocutory errors:* multiword responses showing accurate identification of the target by physical attribute, function or action ('doctors use them for listening to your heart' for stethoscope; 'African animal with a horn' for rhinoceros; 'used at school for drawing circles' for compass; 'Eskimo's snow house' for igloo).

If the distinction between error types 6 and 7 was unclear, we applied the following criterion: does the response describe a specific item? If it did, the error was categorized as a circumlocutory response. Also included in this category were acceptable slang terms, synonyms and creative neologisms ('squeezebox' for accordion; 'dromedary' for camel; 'toadstool' for mushroom; 'autostairway' for escalator).

8. *Phonemic errors:* mispronunciations or distortions of the target name sharing at least one syllable ('iglow' for igloo; 'propraetor' for protractor).

9. *Perseverations:* reutterances of a response (correct or incorrect), which had previously been used to name 1 of the previous 5 pictures.

10. *Unrelated errors:* in which no clear connection between the target and response could be deduced ('a mess' or 'one of those things' for snail).

The classification of error responses was performed independently by 2 lab members (S.M.T., V.K.). Kappa analyses were conducted to assess inter-reliability of error classifications. Agreement between these 2 coders for 10% of the sample of 450 independently scored items was >85%. Discrepancies were discussed and agreement reached regarding the appropriate classification of errors.

Kaufman Adolescent and Adult Intelligence Test- Famous Faces Test (KAIT). Of the total sample (N= 460), 448 individuals completed the KAIT Famous-Faces Test (Kaufman & Kaufman, 1993). During this measure, participants were shown pictures of famous persons and provided with a verbal cue regarding their identities. Examinees are instructed to then identify the face or faces. For example, the participant may be shown an image of Abraham Lincoln and asked to "name this president of the United States." The subtest measures general factual knowledge and has been carefully constructed to minimize cultural and socioeconomic bias. All items were scored as correct (1) or incorrect (0).

Pyramids and Palm Trees Test (PPT). This test was given at a secondary study visit that not all participants were required to complete. As a result, a total of 117 participants completed the PPT (Howard & Patterson, 1992), a task that assesses the ability to access detailed semantic representations from pictures and is one of the only tests of semantic knowledge that utilizes nonverbal responses. The test involves black-and-white, line-drawn representations of 52 concrete, familiar items. Three images are presented for each item in which two pictures are shown below a target image. Participants were asked to point to indicate which of the bottom two pictures best matches the target image. For example, an image of a palm tree and a pine tree may be positioned below a picture of a pyramid- in this case the correct choice would be to point at the palm tree as it is most semantically related to the image of the pyramid. Scores range from 0-52, with 1 point given for each correct response.

Data Analytic Strategy

A series of linear regression analyses evaluating HIV and HAND status (i.e., HAND+, HAND-, & HIV-) as significant predictors of semantic memory performance were conducted across the three measures of interest (i.e, BNT, KAIT, & PPT). To address the second aim of the study, separate analyses of interaction will be conducted to examine if the relationship of age and serostatus differentially affects semantic memory. Variables were included as covariates in the models investigating BNT and KAIT scores if they were significantly associated with semantic memory outcomes and differed between groups at a critical alpha level of 0.10. It should be noted that variables to be included as covariates in analyses of the subset of individuals who completed the PPT (n=117) were assessed separately, as only a subset of participants had data on this task. The critical alpha level for hypothesis testing will be set at 0.05 for all analyses. Measures were taken to protect against committing type 1 errors (e.g., conservative p-values across analyses).

The G*Power statistical package (Buchner, Faul, & Erdfelder, 1997; Erdfelder, Faul, & Buchner, 1996) was used to calculate the statistical power of each analysis. Specifically, F-test post hoc calculations were generated considering sample size, associated degrees of freedom, and a critical alpha level of .05 to determine power to detect an omnibus 3-group difference. Results indicate that the current study will have adequate power (>.8) to detect medium effect sizes at an alpha level of .05. Separate power analyses were generated for analyses of the PPT, as the subset of individuals who completed this task was significantly smaller than the total sample size. Results indicate that the current study will have adequate power (>.8) to detect large effect sizes at an alpha level of .05.

RESULTS

Basic group demographic and clinical characteristics are displayed in Table 1. Normally distributed variables were evaluated using Analyses of Variance (ANOVA) and all variables that were non-normally distributed as indicated by a Shapiro-Wilk tests of

normality using an alpha level of .05 were analyzed used Wilcoxon Rank Sum tests. Post hoc analyses were conducted using Tukey's Honest Significant Differences tests or Steel-Dwass tests for parametric and nonparametric distributions respectively.

All variables listed in Table 1 were examined as possible covariates for each of the linear regressions on the semantic memory outcome variables. Years of education, sex, WTAR estimated verbal IQ, POMS scores, rates of lifetime diagnosis of MDD and GAD differed significantly between the HAND status groups (i.e., HAND+ ,HAND-, & HIV-; all *p*s < .05). However, only education, lifetime MDD, and sex were also significantly related to the semantic memory outcome variables (all *p*s < .05). Thus, only these three variables were included in the regressions as covariates for analyses of the BNT and KAIT. As described above (see Data Analysis) the subsample of participants who completed the PPT were evaluated separately.

Primary Regression Analyses

BNT. Results indicated that the overall regression model was significant across total score performance on the BNT (Adj R^2 = 0.20, p < .0001). Significant contributors to this model included education, lifetime MDD and HAND status (all *p*s < .05). Individuals in the HAND- (β =4.84, p = .0008) and HIV- groups (β = 3.38, p < .0001) earned significantly higher scores (i.e. better performance) compared to HAND+ participants (see Figure 1). Overall models examining the ten BNT error types showed significant group differences across ambiguous (Adj R^2 = 0.08, p < .0001), semantic superordinate (Adj R^2 = 0.05, p < .0001), semantic associative (Adj R^2 = 0.06, p < .0001), and semantic within category (Adj R^2 = 0.05, p < .0001) errors. HAND- participants and HIV- individuals committed significantly less ambiguous errors, semantic superordinate, and semantic associative based errors compared to participants with HAND (all *p*s < .05; Cohen's *d* [.304-.462]). Results also show that the HAND+ group made significantly more semantic within category errors compared to HIV positive individuals without HAND (β =-2.15, p = .03). There were

no significant differences in the above errors committed between the HIV- and the HAND- groups (all *p*s > .10). Results of error analyses are shown in Figure 2.

Changes in performance following semantic and phonemic cueing for the 4 above specified error types on the BNT were examined. Results of chi-square analyses showed no significant group differences in cue success (i.e., individual provided a correct response after cue) or cue failures (i.e., individual provided incorrect response after cue) across the 4 errors after either a semantic or phonemic prompt (all *p*s > .10). Wilcoxon Rank Sum tests showed no differences in improvement rate (i.e., % improvement) across groups on the 4 considered errors after being provided a semantic cue (all *p*s >.10). Results of separate Wilcoxon Ranked Sum tests evaluating change in performance following a phonemic cue revealed a significant difference in improvement between groups after phonemic prompting of ambiguous errors ($p = 0.035$), such that HIV- participants demonstrated a 69% improvement in scores after receiving a phonemic cue compared to a 52% improvement in scores of participants with HAND (p = .028, Cohen's $d = 0.423$). There were no significant differences in score improvement between HAND+ and HAND- groups, or the HAND- and HIV- groups (see Figure 3).

KAIT. The overall regression model was significant across total score performance on the KAIT Famous Faces subtest (Adj $R^2 = 0.20$, $p < .0001$). Significant contributors to this model included sex, lifetime diagnosis of MDD, education and HAND status (all *p*s < .05). The HAND- (β = 3.15, $p = .002$) and HIV- participants (β = 2.93, $p = .004$) earned significantly higher scores (i.e. better performance) compared to those earned by the HAND+ group (see Figure 1).

PPT. All variables listed in Table 1 were examined as possible covariates. No significant differences across demographic information between the HAND status groups were found (all ps > .10). As such, no variables were included as covariates in the following analyses. Results of a Wilcoxon-Rank Sum test showed no significant between-group

differences in performances on the PPT (X^2 [2, N=117] = 2.18, p = .34; Cohen's d [.441-.529]).

Interaction Effects

HAND-Age Interaction. Analyses investigating the interaction of HAND status and age (i.e., older [≥ 50] vs. younger [<50] groups) were conducted to address the study's second primary aim. Across the semantic memory measures, results show no significant effect of interaction of HAND status and Age (dichotomous) on semantic memory performance (all p's > .10).

Correlates of Semantic Memory Performance

Spearman's p correlation analyses were performed to examine cognitive and disease correlates of the semantic memory performance within the HAND+ group (n = 85). Results show that executive (r_s = -.24, p = .02) and speed of processing (r_s = -.31, p = .004) domains were significantly related to BNT total scores, while the learning domain was associated with BNT performance at trend level (r_s = -.20, p = .066; all other ps > .10; r_s [.03-.17]). The learning domain (r_s = -.28, p = .01) was the only cognitive domain significantly associated with KAIT scores (all other ps > .09 r_s [.02-.18]). In regards to disease characteristics, EDI was the only disease variable significantly associated with BNT (r_s = .32, p = .003) and KAIT (r_s = .23, p = .04) scores, with longer EDIs related to better scores. It should be noted, however, that follow-up analyses suggest that EDIs relationship to BNT and KAIT scores was an artifact of age and no other variable was significantly related to the BNT and KAIT semantic tasks (all ps > .10).

DISCUSSION

While HIV has historically been viewed as a subcortical disease, a recent controversy suggests a subtle shift toward neocortical (e.g., temporal and parietal lobe) neuropathology as a contributing mechanism of deficits in HIV-associated cognitive impairment. To date, neuropsychological support for this so-called 'cortical hypothesis' has

been limited. In fact, studies investigating HIV (not considering HAND) have often failed to observe any significant deficits in traditionally cortical constructs such as semantic memory (e.g., Goodglass and Kaplan, 1983; Scott et al., 2011; Sadek et al., 2004). Results of the current study, however, provide the first neuropsychological evidence of cortical dysfunction in HIV+ persons with HAND, specifically moderate deficits in semantic memory. Individuals with HAND performed worse than HIV positive participants without HAND as well as their HIV negative counterparts on both the BNT and the KAIT famous faces measures. Findings were accompanied by medium effect sizes and were independent of demographic and other clinical factors (e.g., sex, education, and diagnosis of major depression).

Analysis of the specific errors committed on the BNT provides some insights into the types of semantic difficulties exhibited in HAND. Kohn and Goodglass (1985) proposed that specific naming errors on the BNT occur as a result of interruptions during specific stages of the naming process (e.g., Gainotti et al., 1981; Kohn and Goodglass, 1985; Riddoch et al., 1988). The first stage of the naming process, considered to be perceptual, involves the analysis of the structural features of the target picture or object. In this study, results of error analyses did not show an increase of visually based errors within the HAND group, which suggests normal function at the perceptual analysis stage. Following the perceptual stage, a semantic phase occurs in which the visual perception of the item is matched with broad superordinate category knowledge (e.g., vegetable, animal, furniture) before more specified subordinate and identifying semantic information is accessed. Superordinate naming errors suggest that only broad category membership knowledge is accessed indicating a defect at the semantic phase. Similarly, semantic-associative errors suggest that while an individual is able to access some appropriate semantic category knowledge, it is not sufficient to generate a correct descriptive response or a category exemplar of the target item. Next the target word that corresponds to the identified semantic concept is retrieved in the lexical stage. At this stage, errors such as semantic within-category responses result from a defect

at a late stage of the semantic process and circumlocutory responses occur which indicate that appropriate activation of the semantic knowledge network has occurred but that the correct target word cannot be accessed (i.e., defect at lexical level). Lastly, errors during the phonemic or word production stage imply impaired articulatory processing of phonological information. Interestingly, participants with HAND demonstrate high rates of semantically related errors as compared to the other two groups. The heightened occurrence of semantic superordinate and semantic associative errors specifically (shown to occur rarely in subcortical disorders such as HD; Hodges et al., 1991) suggest a defect in the semantic phase of the naming process. These findings indicate neurocognitive dysfunction in HAND similar to that observed among cortical diseases such as AD that are marked by disruption of semantic knowledge including object naming and identification abilities.

Follow-up analyses to determine the benefit of semantic and phonemic cueing showed that semantic prompts were largely ineffective at reducing BNT errors in the HAND group. It is possible that semantic prompts may not offer any additional benefit within this group due to the errors committed by individuals with HAND being largely semantic in nature. For example, if a participant was shown an image of asparagus and they answered with “lettuce”- a semantic within category error response, an examiner providing the semantic cue stating “it is a vegetable” would not provide any additional information for a participant to advance the naming process past the semantic or lexical stage. In contrast, the presentation of the phonemic prompt provided participants with information that allowed them to give a correct response to the target item when they had not previously. Ambiguously based errors were the only type of the four evaluated errors to be differentially reduced by the presentation of the phonemic cue resulting in a greater benefit among HIV- participants compared to the HAND group. One possible explanation for this pattern of findings is that presentation of the phonemic cue may have provided enough information for

HIV negative participants to move to the next stage of the naming model, but the same information was not sufficient to overcome the disruption to the semantic process observed in the HAND group. Future studies may evaluate this hypothesis by investigating the benefits of prompts designed specifically to reduce errors at various points of the naming process.

Interpreting the findings regarding cognitive correlates of semantic memory performance in the context of the cortical and subcortical hypotheses is complicated. Results show that executive functioning, speed of processing, and learning (at trend level) domains were associated with BNT performance, and the learning domain was significantly related to KAIT scores within the HAND+ group. The significant relationship between the executive domain and semantic memory performance converges with previous studies suggesting executive dyscontrol as a principal contributor to semantic difficulties among HIV+ and other individuals with various frontal systems neuropathologies consistent with subcortical pathology (e.g., frontal lobe lesions, Baldo et al., 2002; Huntington's disease, Massman, Delis, Butters, Levin, & Salmon, 1990). The relationship of the learning domain with KAIT performance, however, is consistent with prior research that suggests HIV-associated learning deficits related to medial temporal dysfunction (e.g., Maki et al., 2009), which is often observed among cortical disorders. Still, the significant association between processing speed and the BNT furthers the complexity of interpretation; while this relationship may simply be a function of the timed nature of the task (participants are given a 20-second period to respond), speed of processing as a domain has been linked to both executive functioning and semantic abilities (e.g., McDowd et al., 2011), and thus its relationship to either subcortical or cortical processes in the current study is not clearly dissociable. These findings suggest influence of various cognitive functions and regions alike, and indeed, previous studies have demonstrated that the process of object naming is multifactorial (e.g., Rogers, Ivanoiu, Patterson, and Hodges, 2006). In fact, Chenery,

Murdoch, and Ingram (1996) report that while attention deficits account for a large part of the naming difficulty in early AD, poor object naming performance later in the progression of the disease is more likely due to comprised semantic structures and stores. Similarly, as the neuropsychological profile of HAND both between and within individuals (e.g., Butters et al., 1990) may vary, deficits may reflect diverse domains at early or later stages of progression or among levels of disease severity.

Evidence in support the cortical hypothesis draws heavily from research of aging adults and it is posited that older HIV-infected individuals may be more vulnerable to cortical dysfunction and thus more likely to show deficits associated with temporal and parietal functioning, such as rapid forgetting and semantic ability (Brew, 2004). However, the results of the current study did not show evidence that HAND imparts different effects on semantic memory in older HIV+ adults compared to their younger counterparts. Although this finding may seem to provide evidence against the cortical hypothesis as one may hypothesize that older adults with HAND would demonstrate greater impairment on semantic tasks given the heightened vulnerability described above, these results make sense when we consider that semantic memory is typically unaffected by the aging process (e.g., Nyberg, Backman, Erngrund, Olofsson, and Nilsson, 1996; Tulving, 1995). In fact, it has been suggested that semantic memory improves across midlife (e.g., Nilsson et al., 1997). Of similar note, results of disease correlate analyses found that the significant positive relationship of EDI to performance on the KAIT and BNT was an artifact of age. Together, findings suggest an adverse impact on semantic performance specific to HAND that is not mediated by age.

The sample in this study consisted largely of white men with an average of at least a high school education. Thus, this sample may represent a limitation to the generalizability of these findings as the HIV epidemic increasingly affects women and minorities (CDC, 2015). Another possible limitation in the current study was the sample size of the subset of

individuals who completed the PPT. Results revealed a null effect of HAND on PPT performance. However, this null result may simply be attributed to the sample being underpowered to detect such effects. In support of this explanation effect sizes of the HAND group were comparable in size and direction on the PPT (Cohen's *d* HIV-, HAND- (.441, .529) to those in analyses of the BNT (.402, .601) and the KAIT (.358, .413). Further, post-hoc analyses show that performance on the PPT is significantly related to performance on both the BNT (r_s = .40, p < .0001) and the KAIT (r_s = .33, p = .0003). Thus, the failure to detect an effect of HAND on semantic memory performance by way of the PPT in the current study may likely be the result of type two error. An alternate explanation for this finding may be that the task of matching one image with another that is related may provide enough contextual information, similar to cueing, to facilitate the naming process in the HAND group. It may be the case that the nature of the PPT task is less cognitively taxing than the free recall modality of the BNT making it more difficult to observe an effect of HAND. However, considering results of semantic cueing on the BNT suggest minimal benefit to the naming process, this alternate hypothesis is less likely.

To the author's knowledge, this is the first study to characterize semantic memory deficits in HAND. Results reveal qualitative differences in the nature of semantic memory impairment among HIV positive individuals with and without HAND, seemingly not influenced by age or separate disease factors. Further, findings provide the first evidence of support for the cortical hypothesis in HAND. However, as these results are observational and inferential in nature, they do not allow for the determination of the precise nature of semantic deficits in HAND. Future studies may therefore examine the relationship of qualitative aspects of semantic memory performance and imaging data and/or postmortem neuropathology in HAND. Additionally, as previous studies have suggested some semantic tasks are generally unimpaired in persons with subsyndromic HIV infection (e.g., Damos, John, Parker, & Levine, 1997), future studies may wish to investigate differences in

semantic memory performance as a multifactorial process across severity of HIV-associated impairment (e.g., ANI, MND, and HAD). Moreover, investigations examining the sensitivity of other neuropsychological measures to HAND are needed to assess the extent of cortical dysfunction in HIV disease. While future studies are needed to replicate and expand these findings, results of the current study provide support to the growing body of evidence suggesting the possibility of a shift towards more cortical pathology during the advanced stages of HIV and warrant further investigation of the cognitive mechanisms underlying HIV-associated impairment.

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Table 1. *Participant demographic and disease characteristics*

	Total Sample (N = 459)	HIV+ w/HAND (n = 85)	HIV+ w/o HAND (n = 193)	HIV- Controls (n = 181)	*p*	Group differences
Age (years)	43.5 (12.7)	44.2 (12.2)	44.7 (10.8)	41.9 (14.5)	-	-
Education (years)	13.7 (2.6)	13.1 (2.6)	13.6 (2.6)	14.2 (2.5)	.005	H+ < HIV-
Ethnicity						
African-American	23.3%	28.2%	20.2%	24.3%	-	-
Asian	2.2%	0	3.1%	2.2%	-	-
Hispanic	16.1%	15.3%	16.1%	16.6%	-	-
White	57.5%	55.3%	60.1%	56%	-	-
Gender (men)	78.0%	82.4%	89%	64.1%	< .0001	H+, H->HIV-
Estimated verbal IQ (WTAR)	102.8 (11.5)	98 (12.2)	104.3 (11.2)	103.5 (10.8)	< .0001	H-, HIV- >H+
POMS total (of 200)	54.7 (36.1)	72.4 (42.4)	57.6 (36.2)	43.1 (28)	< .0001	H+>H->HIV-
Major depression	48.8%	65.9%	54.4%	34.8%	< .0001	H+, H->HIV-
Generalized anxiety	10%	11.8%	15%	3.9%	< .001	H+, H->HIV-
Substance dependence	49%	57.6%	52.9%	40.9%	.01	H+, H->HIV-
Hepatitis C Virus	15%	21.69%	17.46%	9.5%	.02	H+, H->HIV-
Estimated duration of Infection (months)	-	148.8 (96.7)	150.8 (101.1)	-	-	-
AIDS (n= 278)	54.7%	52.9%	55.4%	-	-	-
CD4 count (cells/L)	724.3 (349.0)	580.8 (307.3)	569.4 (263.7)	-	-	-
Nadir CD4 (cells/L)	461.2 (424.2)	234.6 (204.2)	217.1 (173.9)	-	-	-
cART status	51.2%	80%	86%	-	-	-
Plasma RNA detectable	15.5%	27.2%	25.3%	-	-	-
Among subjects on cART	-	12.3%	15.2%	-	-	-

Note: WTAR = Wechsler test of adult reading; POMS = Profile of mood states; AIDS = Acquired immune deficiency syndrome; CD4 = Cluster of differentiation 4; cART = combination antiretroviral therapy.

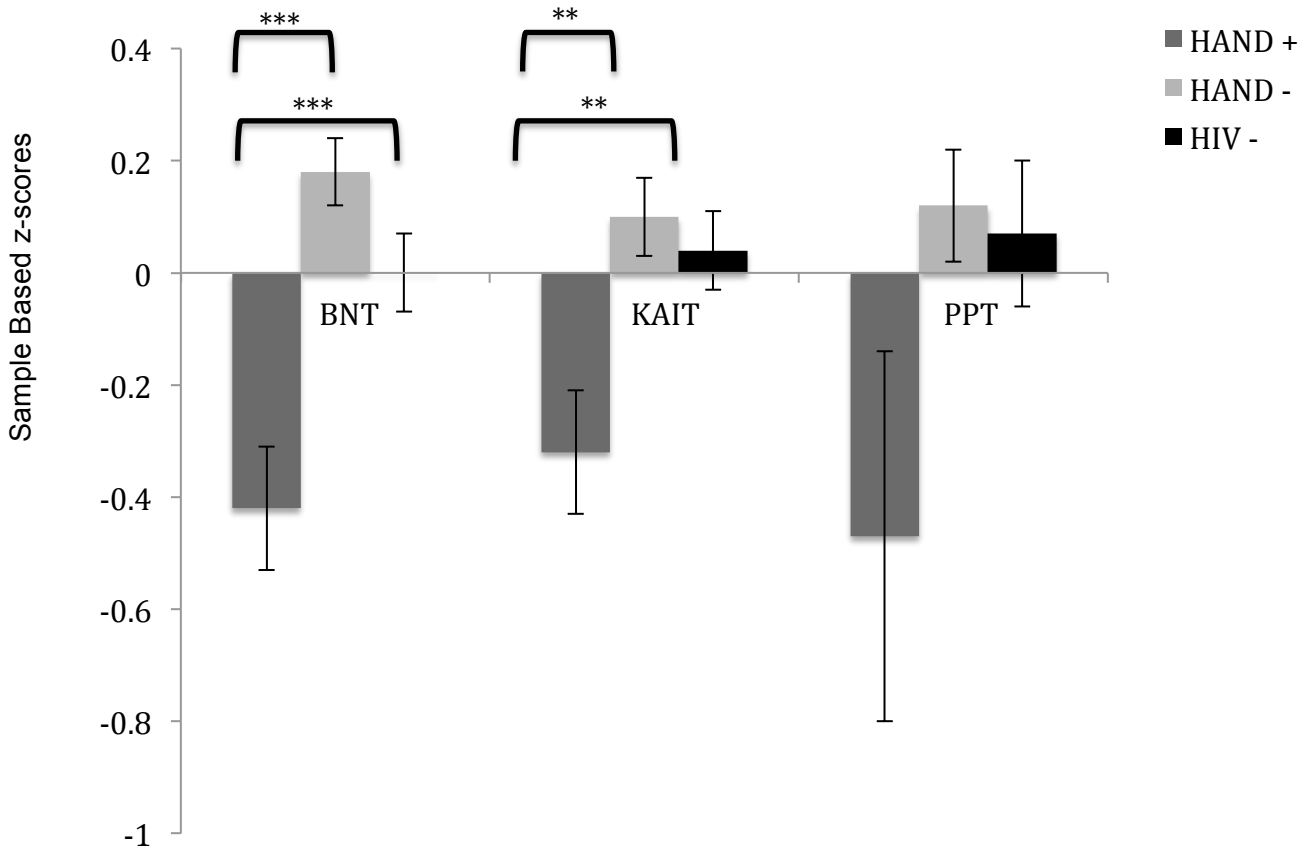

Figure 1. Sample based z-score comparison of performance across HAND status groups on the Boston Naming Test (BNT), the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test (KAIT), and the Pyramids and Palm Trees Test (PPT).
*** $p < .001$
** $p < .01$

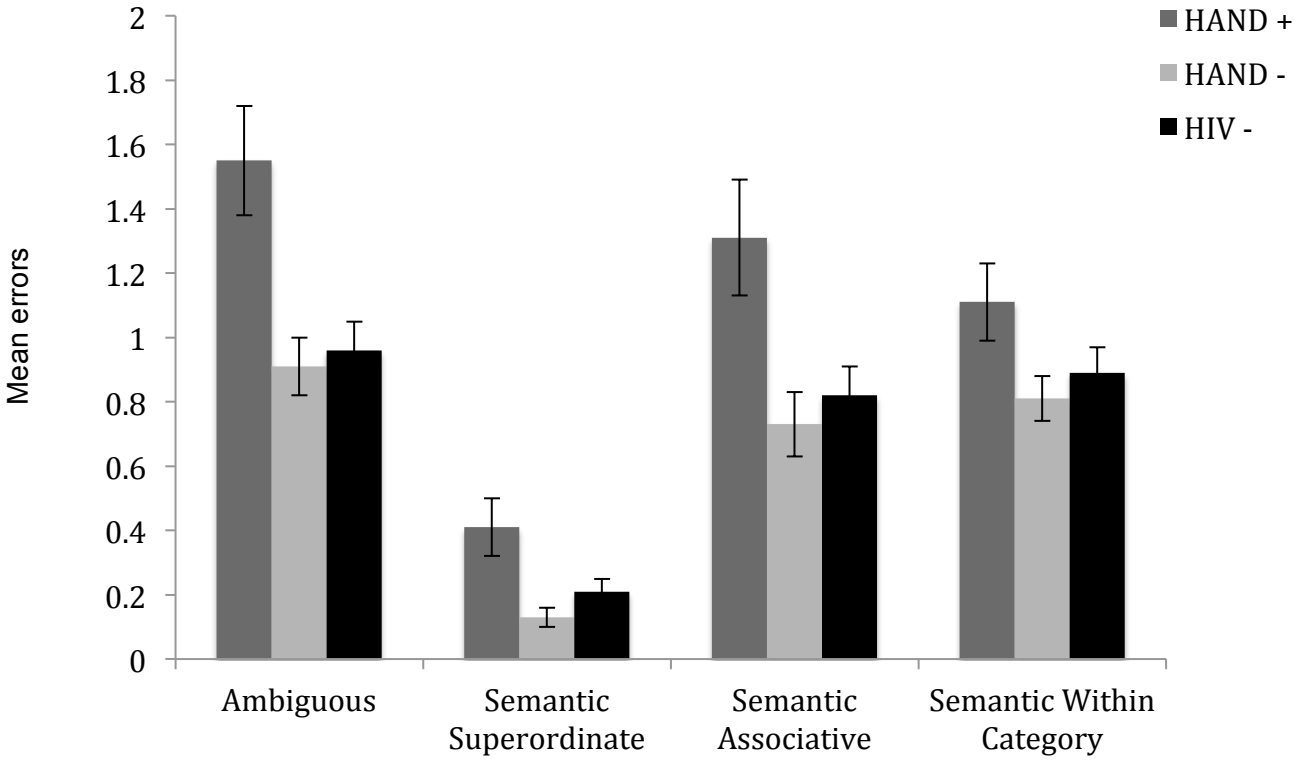

Figure 2. Comparison of mean number of selected BNT errors committed across HAND status groups.
** $p < .01$

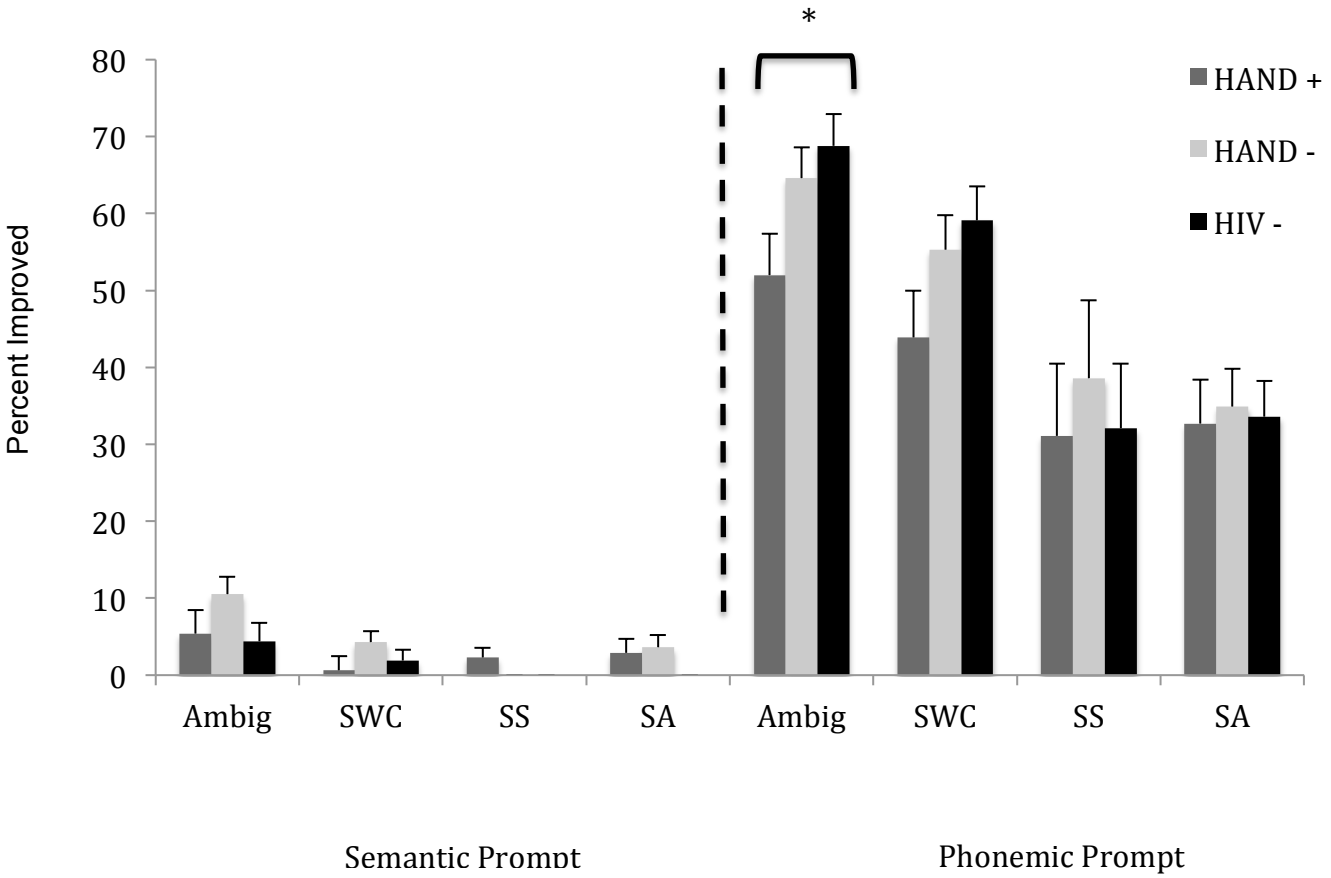

Figure 3. Percent improvement of selected BNT errors following semantic and phonemic prompts across HAND status groups.
* $p < .05$