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Human Action Switching in HIV

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Human Action Switching in HIV

by

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Each person whose signature appears below certifies that this thesis in his/her opinion is adequate, in scope and quality, as a thesis for the degree Doctor of Philosophy.

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ABBREVIATIONS

PASAT	Paced Auditory Serial Addition Test
Stroop CW	Stroop Color-Word Test interference trial
TMT-B	Trail Making Test part B
LNS	Letter-Number Sequencing Test
WCST	Wisconsin Card Sorting Test Perseverative errors
HIV	The Human Immunodeficiency Virus
CNS	Center Nervous System
HAD	HIV-associated dementia
HAART	Highly active antiretroviral therapy

ABSTRACT OF THE THESIS

Human Action Switching in HIV

by

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We evaluated switching in human action/verb fluency to examine how it associates with other measures of executive functioning and with difficulties in the performance of IADLs in a HIV+ sample. Our sample was comprised of 29 HIV+ participants. All the participants completed measures of phonetic fluency (FAS) and semantic fluency [Animals, Human Actions (HA)] in addition to the Paced Auditory Serial Addition Test (PASAT), Stroop Color-Word Test (Stroop), Trail-making Test Part B (TMT B), Letter-Number Sequencing (LNS), Wisconsin Card Sorting Test, and the Boston Naming Task (BNT). The first regression model with phonetic and semantic switching produced $R^2 = .260$, $b = 5.957$, 95% CI [1.889, 10.025], $p < .01$. The second model with phonetic, semantic, and human action switching produced $R^2 = .263$, $F(2, 26) = 4.568$, $p > .05$. FAS switching had a significant positive regression weight indicating that greater FAS switching is associated with performance on executive functioning tasks in the first regression model. Verbal fluency switching did not significantly predict difficulties in the performance of instrumental activities of daily living, each model accounted for 2.5% and 11% of the variance, respectively. Verbal fluency switching, specifically phonetic switching demonstrated merit in assessing executive ability. Verbal fluency switching was not indicated in the prediction of difficulties in the performance of

IADL's. Human action switching was not a significant predictor of executive ability or IADL performance above and beyond the other forms of switching.

CHAPTER ONE

INTRODUCTION

Human Immunodeficiency Virus Infection

The Human Immunodeficiency Virus (HIV) is a lentivirus that invades the central nervous system (CNS) early in the disease process and leads to marked neuronal and white matter pathology (Cummings & Mega, 2003). HIV infects, destroys, and depletes CD4 T cells; the virus directly kills T cells, which results in immunosuppression (Rosenberg and Fauci, 1991). There are three categories of CD4 T cell counts that correspond to a diagnosis of HIV. Category 1 is a count that is greater than or equal to 500 cells/mL, Category 2 is a count that is 200-499 cells/uL, and Category 3 is a count that is less than 200 cells/uL (CDC, 1993). The Center for Disease Control (CDC) views T cell counts below 200 as acquired immunodeficiency syndrome (AIDS) defining.

When HIV infiltrates the CNS, continued replication occurs within the macrophages (Gendelman, Lipton, Tardieu, Bukrinsky, & Nottet, 1994). The presence of HIV in the brain appears to result in disturbances in memory, attention, executive function (planning, evaluating, problem solving), and perceptual skills (Grant, 2008). Neurodegeneration is present in cortical (hippocampus) and subcortical (basal ganglia/putamen) regions (Nath, et al., 2000; Moore, et al., 2006). Millikin, Trepanier, & Rourke (2004) showed evidence of progressive frontal-striatal dysfunction. Finally, Gonzalez-Scarano and Martin-Garcia (2005) suggest that HIV infection- associated neuropathologies are most apparent in the basal ganglia, frontal neocortex, hippocampus, and white matter. Diffuse white matter abnormalities are commonly detected in HIV (Filippi, Ulug, Ryan, Ferrando, & van Gorp, 2001; Harrison et al., 1998).

Of the various neuropathologies witnessed in HIV, frontal-striatal injuries have received the most research interest. Deficits in frontal-striatal functioning appear to result in neuropsychological deficits in information processing, psychomotor abilities, executive difficulties, and deficient encoding and retrieval of episodic memories (Reger, Welsh, Razani, Martin, & Boone, 2002). Furthermore, decrements in daily living skills may also be tied to frontal-striatal injury in HIV (Heaton et al., 2004). In the current proposal, HIV-related executive deficits, namely difficulties with verbal fluency, will be discussed with regard to HIV-related neuropathology and instrumental activities of daily living.

CHAPTER TWO

VERBAL FLUENCY

Phonemic/Semantic Verbal Fluency

Measures of verbal fluency are commonly utilized in clinical and experimental settings (Troyer, Moscovitch, &Winocur, 1997). These tasks require a participant to rapidly generate as many words as possible within 60 seconds given certain rules. Verbal fluency trials are commonly focused on either the generation of words that begin with a given letter (phonemic fluency) or words that belong to a certain category (semantic fluency). Additionally, the general rules require that participants not use proper nouns or the same word with a different ending.

Measures of verbal fluency are widely evaluated in different populations. Phonemic and semantic fluency are often examined separately. A meta-analytic review by Henry and Crawford (2004) was conducted to examine the sensitivity of verbal fluency to the presence of focal lesions. Phonemic and semantic verbal fluency were separately examined in 31 published studies. The examination showed that for phonemic fluency, the largest deficits were demonstrated in the participants with unilateral left frontal damage and left hemispheric damage in general. The authors interpreted this as providing strong evidence that phonemic fluency is more sensitive to frontal than non-frontal and left as opposed to right cortical lesions as deficits on this task are more apparent in participants with frontal and left cortical lesions. Semantic fluency showed unilateral left and left damage in general, however temporal injury patients were significantly more impaired on semantic fluency than on phonemic fluency. These

results suggest phonemic verbal fluency to be associated with frontal systems and semantic fluency to be associated with the medial temporal lobes.

A study by Tucha et al. (2005) examined phonemic and semantic verbal fluency in adults with ADHD and healthy controls. Participants with ADHD show impairments of attention, working memory, impulsivity, shifting, and divergent thinking (Corbett & Stanczak, 1999), deficits that are thought to be executive in nature. In fact, a study by Almeida et al., 2010 of MRI data showed regions in the right superior frontal gyrus where cortical thickness was reduced in children, adolescents, and adults with ADHD in contrast to their respective healthy controls. Additionally, adults with childhood ADHD and persisting behavioral symptoms show similar patterns of fronto-striatal and parietal dysfunction to those observed in childhood ADHD during tasks of inhibitory control (Cubillo, Halari, Ecker, Giampietro, Taylor, and Rubia, 2009). Results showed that participants with ADHD produced significantly fewer words than healthy controls. Participants with ADHD show executive deficits as indicated by the generation of fewer words and deficits in switching and clustering on verbal fluency.

A study by Backman, Robins-Wahlin, Lundin, Ginovart, & Farde (1997) of verbal fluency in Huntington's disease revealed that dopaminergic markers as well as brain volume were related to performance. Also, they found that thalamic volume contributed significantly to performance. Positron emission tomography (PET) and magnetic resonance imaging (MRI) data were used as predictors of performance in tasks assessing executive function as well as other cognitive domains. Dopaminergic markers and brain volume were gathered before performance of the tasks. Reduced dopamine receptors and striatal volume (caudate and putamen) resulted in poorer performance on

verbal fluency as compared to controls. These findings suggested that verbal fluency may be mediated by subcortical structures.

Stuss et al. (1998) compared phonemic and semantic fluency performance in participants with focal brain lesions and in healthy controls. When lesion sites were classified as right frontal, left frontal, or non-frontal results indicated that damage to left frontal or left non-frontal areas affected phonemic and semantic fluency. Additionally, patients with right frontal damage were mildly impaired in phonemic fluency and more impaired in semantic fluency. When specific lesion sites were examined in the frontal lobes, damage to the right dorsolateral cortical or striatal areas, the right posterior region, or the medial inferior frontal lobe of either hemisphere did not result in significantly diminished performance in phonemic fluency as compared to the control group. This finding is of particular importance in that HIV/AIDS is associated with frontal-striatal injury and has in previous research been seen as a factor attributing to poor phonemic fluency, yet in this study participants with frontal and striatal lesions did not show significant phonemic fluency impairment as compared to controls.

With regard to temporal lobe contributions to verbal fluency, the left temporal lobe (Cappa, et al., 2005; Piatt, Fields, Paolo, & Troster, 1999; Davis, et al., 2010) and left temporo-parietal networks (Woods, Carey, Troster, Grant, & the HNRC group, 2005) have been implicated. Some specific evidence for the involvement of the temporal lobe is supported by a case study by Damasio and Tranel (1993). They demonstrated deficient phonemic verbal fluency in two patients with mesial temporal lobe damage. Warburton et. al (2005) used positron emission tomography (PET) activation studies to examine regional cerebral blood flow (rCBF) during verbal fluency and demonstrated that it is

mediated by the left inferolateral temporal lobe and the posterior part of the inferior parietal lobe. Still, HIV infection is found to be associated with frontal lobe functioning (Chang et al., 1999) and has been associated with frontal-striatal dysfunction (Millikin, Trepanier, & Rourke, 2004). The studies that follow will illustrate the deficits in verbal fluency the participant's with HIV infection display and how they relate to frontal-striatal functioning.

HIV and Verbal Fluency

Verbal fluency is widely studied in HIV-infection, as those with HIV infection tend to show greater impairments as compared to controls in verbal fluency. Woods, Carey, Troster, Grant, & the HNRC Group (2005) in a meta analysis reported that 26% of HIV studies demonstrated phonemic fluency deficits and 13% showed semantic fluency deficits. Verbal fluency appears to be mediated by executive abilities and verbal abilities (Troyer, 1997) such as switching and clustering. Switching is the ability to shift efficiently to a new subcategory, which involves cognitive flexibility in shifting from one subcategory to another (Troyer et al., 1997). Clustering is defined as the production of words within semantic or phonemic subcategories. It involves phonemic analysis on phonemic fluency, semantic categorization on semantic fluency, and appears to be associated with temporal lobe functioning (Troyer et al., 1997, 1998). With this regard, participants with HIV infection have executive deficits (Reger et al., 2002), tend to generate fewer words than healthy controls (Iudicello et al., 2007), and switch less during verbal fluency (Iudicello et al., 2007). However, they generate comparable clusters on phonemic verbal fluency as compared to healthy controls, suggesting intact linguistic abilities. Switching is correlated with standard clinical measures of executive function

(Iudicello, et al., 2008).

A study by White et al. (1997) examined episodic and semantic memory of participants with HIV-associated dementia (HAD), HIV-infected participants without dementia, and HIV-negative controls. The purpose of this investigation was to provide a detailed analysis of the memory deficits associated with HAD, and to determine if the same types of deficits are consistent with a subcortical dementing process. HAD performances on cognitive tasks were compared to non-demented HIV infected and HIV negative participants. It was hypothesized that participants with HAD would exhibit deficits resembling participants with subcortical dementias. All groups were administered phonemic fluency (F, A, and S) and semantic fluency (animals, fruits, and vegetables) as well as other cognitive tests. Results indicated that the HAD group showed deficits in episodic memory, with relatively intact semantic memory. No significant differences were found between the three groups for the semantic fluency test. However, on phonemic fluency, the HAD group scored significantly lower than the HIV-positive participants without dementia and the HIV-negative controls. Overall, the authors indicated that the results suggest a retrieval deficit in HAD and that this pattern is consistent with the presence of a subcortical dementing process. However, of particular importance to the current proposal but not highlighted by the authors, the non-demented HIV infected and HIV negative groups performed similarly on phonemic fluency (M= 49.3 SD= 14.6; M=50.3 SD= 7.2) respectively.

A meta-analytic review of HIV verbal fluency literature conducted by Iudicello et al., (2007) evaluated the assumption that given the prefrontostriatal neuropathogenesis of HIV, it leads to greater impairment on phonemic versus semantic fluency. Hypotheses

were formed based upon previous studies that showed that while semantic fluency is impaired in conditions with apparent temporolimbic neuropathology (e.g., focal temporal lesions; Henry & Crawford, 2004), both phonemic and semantic fluency are impaired with frontal systems damage (e.g., focal frontal lesions; Henry & Crawford, 2004); this would ultimately refute the long held idea that verbal fluency deficits in HIV infection are related to prefrontostriatal pathology. In this meta-analytic review it was hypothesized that HIV infection is associated with differentially greater deficits in phonemic versus semantic fluency or HIV infection is associated with comparable impairment in phonemic and semantic fluency. Additionally it was hypothesized that HIV is associated with greater semantic fluency deficits and that disease progression would be associated with more severe verbal fluency deficits. Thirty-seven studies were included in the meta-analysis. Across all studies, the mean effect size of semantic fluency was significantly larger than was observed for phonemic fluency, $p < .01$. However, when a more stringent analysis of only the studies that included both tests, there was no significant discrepancy between phonemic and semantic fluency effect sizes, $p = .58$. Overall, the authors suggested that HIV infection-associated impairments in phonemic and semantic fluency appear to be of similar magnitude, suggesting that mild word generation deficits are evident in HIV infection regardless of the particular lexical or semantic cue used to guide word search and retrieval. Being that phonemic and semantic fluency were of the same magnitude in this evaluation, the long held idea that verbal fluency deficits in HIV infection are related to frontal-striatal pathology, was not refuted.

A study by Millikin, Trepanier, & Rourke (2004) was conducted to examine the relationship between HIV infection illness severity, depressive symptoms, highly active

antiretroviral therapies (HAART) medication status, and verbal fluency (FAS and animals; clustering and switching with the Troyer et al., 1997 method) in a sample of adults with HIV infection and AIDS. The study evaluated the following hypotheses: Rates of impaired verbal fluency performance (particularly switching) would be higher in the subgroup with more severe illness (AIDS); Individuals with an AIDS diagnosis and elevated depressive symptoms would show poorer switching performance; clustering performance would not be affected by illness severity or depressive symptoms; and adults with AIDS who were receiving HAART at the time of testing would demonstrate better switching performance as compared to participants with AIDS who were not receiving HAART treatment. All participants were administered the phonemic and semantic verbal fluency tasks and the Beck Depression Inventory (BDI). Results showed that the presence of an AIDS diagnosis was associated with higher incidence of impaired performance on FAS total words produced and FAS switching. FAS clustering rates of impairment did not differ significantly as a function of HIV illness severity. Results also showed that rates of impairment did not differ between the AIDS and the non-AIDS groups on any of the animal fluency variables. Overall, advanced HIV infection was associated with a greater incidence of impairment in phonemic fluency performance relative to normative data. Participants with AIDS performed significantly worse on FAS switching and tended to score lower on animal switching as compared to participants who did not have AIDS. The authors concluded that to the extent that switching is a marker of frontal-striatal dysfunction, these results provide further indication of progressive frontal-striatal dysfunction with greater severity of HIV infection.

Throughout the aforementioned studies and other research, the verbal fluency

task is described as a task that measures executive abilities. The measurement of executive abilities should implicate involvement of the frontal systems, however, verbal fluency in most studies has been shown to be mediated by the temporal lobe (left temporal lobe, left temporo-parietal lobe, anterior and posterior temporal regions). While temporal lobe function is involved in some aspects of verbal fluency, frontal and frontal-striatal involvement appear to be associated with switching during verbal fluency performances. HIV infection is associated with frontal-striatal pathology. Thus, methods of analyzing executive functioning in HIV infection should involve tasks that are sensitive to frontal-striatal pathology. More recently, human action fluency, another form of verbal fluency, has begun to gain significant research interest in HIV/AIDS.

Human Action (Verb) Fluency

Human action fluency is a newly developed verbal fluency task that requires the examinee to rapidly generate as many verbs (i.e., "things that people do") as possible within 60 seconds (Woods, Carey, Troster, Grant, & HNRC, 2005). While performing this task, participants are also asked to generate only single verbs and to avoid repeating earlier generated verbs with a different ending (e.g., eat, eating, and eaten). Verb responses that humans cannot plausibly perform (e.g., photosynthesize) and questionable noun-verb homonyms (e.g., bear) are further questioned and coded as intrusions if indicated. Human action fluency is measured by calculating the number of correct verbs generated minus intrusions (interruptions) and perseverations (repeats). Human action fluency has shown associations with other executive measures and frontal-striatal injury.

A study by Piatt, Fields, Paolo, & Troster (1999) was conducted to evaluate the construct validity of human action fluency as an executive function measure in a group of

healthy elderly control subjects. Participants were all administered the human action/verb fluency task, Trail Making Test part B (TMT B), the Boston Naming Test (BNT), and the Wisconsin Card Sorting Test (WCST). Results showed moderate associations between human action fluency, Trails B, and the WCST's perseverative responses, perseverative errors, correct responses and categories. An association with the BNT was not found, possibly suggesting that there is less of a relationship between language and human action fluency. Overall, these findings may suggest that human action fluency is a good tool for measuring executive functioning.

Davis et al., (2010) hypothesized that patients with subcortical dementia, normal pressure hydrocephalus (NPH) and behavioral variant fronto-temporal dementia (bv-FTD) or progressive non-fluent aphasia (PNFA) would have more difficulty on human action fluency versus phonemic fluency. Furthermore, they suggested that patients with Alzheimer's Dementia (AD), who have temporo-parietal cortical dysfunction, should have more difficulty on phonemic versus human action fluency. All participants were administered animal fluency, human action fluency, phonemic fluency (F, A, and S), and the Mini Mental Status Examination (MMSE) according to standard directions. Results showed that participants with NPH and bv-FTD/PNFA had significantly higher MMSE scores (NPH and bv-FTD/PNFA; $F(2, 199) = 40.8$, $p < .0001$) and animal fluency than AD patients. However, NPH and bv-FTD/PNFA human action fluency tended to be lower than in AD. The NPH, bv-FTD/PNFA patients showed significantly lower human action than animal fluency. These results suggest that human action naming relies more on frontal-subcortical circuits while phonemic fluency relies more on the temporo-

parietal cortex. Therefore, human action/verb fluency may be more sensitive than phonemic fluency at identifying frontal-subcortical dysfunction.

A study by Perani et al., (1999) suggests that the left frontal lobe is necessary for the processing of verbs. This was demonstrated through the use of PET. 14 right-handed healthy male volunteers participated in this study. They were presented with four categories of words: concrete verbs (to cut, to comb), abstract verbs related to psychological states (to think, to hope, to believe), concrete nouns (manipulable tools: comb, hammer, screwdriver), and abstract nouns (future, justice). Additionally, they were shown pseudo words. The words were presented for 1200 ms with a 300 ms inter-stimulus interval. Participants were told to read the word silently and when a pseudo word appeared on the screen, respond by pressing a button on the response box with their right hand. Left dorsolateral frontal cortex, superior parietal, anterior temporal, middle temporal, and the occipital area were metabolically active to tasks involving the processing of verbs.

Piatt, Fields, Paolo, Koller, & Troester (1999) compared phonemic fluency, semantic, and human action fluency in groups of patients with Parkinson's disease (PD) with dementia, PD without dementia, and an elderly control group. Previous research has demonstrated that phonemic and semantic verbal fluency are differentially sensitive to the effects of cortical and subcortical dementias, however, the authors wanted to see what affect human action fluency would produce. Results showed that human action fluency discriminated demented Parkinson's disease (PD) patients from non-demented PD patients and healthy control subjects. Phonemic and semantic verbal fluency were unable

to discriminate amongst the three groups. The authors suggest that human action fluency is sensitive to the fronto-striatal pathophysiology associated with PD dementia.

Human action/verb fluency may be mediated by frontal systems so it appears to better assess executive dysfunction related to frontal-striatal pathology. Thus, human action fluency may be more sensitive to HIV infection -associated neuropsychological impairment. Indeed research has shown that human action fluency is poor in HIV-infected persons. It is possible that HIV infection- associated deficits on human action fluency may reflect inefficiencies engaging motor representations during action retrieval in this population due to motor impairment (Woods et al., 2006).

Human Action Fluency and HIV

A study by Woods, Carey, Troster, Grant, and the HNRC group (2005) examined human action (verb) and semantic (noun) fluency in participants with HIV infection as compared to healthy controls. They hypothesized that persons with HIV infection would generate significantly fewer actions (verbs), but not animals (nouns) relative to healthy comparison subjects and that human action fluency would accurately discriminate between HIV infected persons with and without global HIV infection-associated neuropsychological impairment. Results showed that the HIV infected group produced significantly fewer human action words as compared to controls. Furthermore, as suspected, they did not generate fewer nouns as compared to controls. There was no difference in human action fluency performance found between HIV infected participants with and without AIDS, but a follow-up analysis indicated that HIV infected persons with deficits in human action fluency were more likely to have AIDS. These conclusions are in line with previous results considering the frontal-striatal

neuropathophysiology associated with HIV infection, and that noun fluency appears to be related to temporal functioning. Overall, this study demonstrates that participants infected with HIV experience difficulty rapidly generating verbs, but not nouns from semantic memory, further showing that verb fluency is more sensitive to HIV infection deficits than other types of verbal fluency.

Woods et al., (2006) sought to evaluate the human action fluency task as a predictor of Instrumental Activities of Daily Living (IADLs) among participants with HIV infection. Individuals were deemed IADL dependent if their self-reported current level of functioning was endorsed as lower than their highest level of functioning in at least two of the following categories: 1) housekeeping; 2) finances; 3) groceries; 4) cooking; 5) transportation; 6) telephone use; 7) home repairs; 8) shopping; 9) laundry; 10) medication management (Woods et al., 2006). Human action, phonemic (FAS), and semantic (animal) fluency were compared between HIV infected participants with self-reported IADL dependence and HIV infected participants without self-reported IADL dependence. The IADL dependent group performed below the IADL independent sample on action ($p = .002$) and phonemic fluency ($p = .04$); however, the groups did not differ on animal fluency ($p > .10$). Furthermore, human action fluency was more sensitive than phonemic fluency in classifying IADL dependent participants, with 76% accuracy (84% specificity). Results also indicated that participants with impaired human action fluency had a fivefold risk of IADL dependence as compared to those who performed within normal limits. Overall, these findings suggest that human action fluency is effective in identifying HIV infection- associated neurocognitive disorders.

Despite human action fluency's ability to discriminate between groups with frontal deficits, its association with executive measures, and its sensitivity to frontal-striatal pathophysiology, switching abilities as they pertain to this form of verbal fluency have not yet been examined.

Assessing the Executive Aspects of Verbal Fluency

Traditional methods of scoring and analyzing verbal fluency involve adding up the number of words produced. This type of analysis may not fully represent a participant's performance (Troester et al., 1998; Troyer, Moscovitch, & Winocur, 1997). This score provides little information about the cognitive processes underlying fluency performance in a given population. Additional information is needed to examine the behavioral components that determine fluency performance (Troyer, 2000). The best performance on these verbal fluency tasks involve utilizing efficient strategies. These strategies involve the generation of words within phonemic and semantic subcategories (clustering) and then switching to new subcategories when a subcategory is exhausted (Troyer, 2000).

Troyer, Winocur, and Moscovitch (1997) developed a scoring method for analyzing switching and clustering abilities. Clustering is defined as the production of words within semantic or phonemic subcategories; and switching is the ability to shift to a new subcategory. Clustering involves phonemic analysis on phonemic fluency and semantic categorization on semantic fluency. Switching involves cognitive flexibility in shifting from one subcategory to another (Troyer, et al., 1997). Analysis of clustering and switching on the verbal fluency task has proven effective in providing information that the number of words produced simply cannot. For example, as mentioned earlier it

has been shown that switching is closely related to frontal lobe functioning, while clustering seems to be associated with temporal lobe functioning (Troyer et al., 1997, 1998). This is further demonstrated through the executive deficits seen in persons with ADHD and how they produce significantly fewer switching responses on verbal fluency tasks and tend to generate smaller clusters as compared to controls. Additionally, decreased switching is seen in patients with disorders that cause frontal dysfunction, such as Parkinson's disease (Troster et al., 1998). The Troyer et al., 1997 scoring method has proven useful in evaluating phonemic and semantic fluency, however this method has not been applied in the evaluation of human action fluency.

CHAPTER THREE

MATERIALS AND METHODS

Sample and participant selection

The current study was part of a larger project examining the interaction between advancing age and HIV-infection on cognitive and functional outcome. UCLA and VA Institutional Review Board (IRB) approval was obtained prior to implementing the study procedures. Written informed consent was obtained from all participants in the study. Participants were included in the study if they were 18 years of age or older, HIV positive (status confirmed based upon serologic testing for HIV antibody [screening ELISA, confirmed by Western blot if positive]), willing and able to comply with study procedures, willing and able to provide written informed consent, and demonstrated at least a 6th grade English reading level. Participants were excluded if they met DSM-IV-TR diagnostic criteria for drug or alcohol abuse or dependence within the past year, presented with a current psychiatric disorder with psychotic features, history of neurologic disorder, and/or history of HIV-associated CNS opportunistic infection (e.g. toxoplasmosis) or neoplasm. Additionally, for the current study participants were included if they completed multiple verbal fluency trials, including phonemic fluency (FAS) and semantic fluency [animals, human actions (HA)]. Participants in the current study were comprised of 29 HIV infected participants (see Table 1 for additional detail).

Table 1

Sample Characteristics

Demographics (N=29)	*M (SD)*
Age (yrs)	48.93 (10.278)
Education	13.59 (2.062)
% Male	69
% Ethnicity	
Caucasian	34.5
Hispanic/Latino	20.7
African American	41.4
Asian/Pacific Islander	3.4
Recent CD4	435.89 (240.391)
Nadir CD4	144.63 (170.991)
% Current AIDS	14.3
% Past AIDS	70.4

Note. Participants ranged in age from 23-63 years of age. Recent CD4= most recent CD4 count reported by participants; Nadir CD4= the lowest ever CD4 count reported by participants; % Current AIDS= current AIDS diagnosis based on CDC criteria; % Past AIDS= past AIDS diagnosis based on CDC criteria.

Assessments and Measures

Verbal Fluency

Participants completed multiple verbal fluency trials, including phonemic fluency (FAS) and semantic fluency [animals, human actions (HA)]. Participants were also administered the first two trials of the Paced Auditory Serial Addition Task (PASAT), Stroop Color Word Test (Stroop CW), Trails B (TMT B), Letter-Number Sequencing (LNS), and the Wisconsin Card Sorting Task-64 (WCST-64) to assess executive ability independent of verbal fluency. Additionally, all of the participants were administered the

Boston Naming Test (BNT) to assess language ability. These measures were administered and scored per standard instructions.

For phonemic verbal fluency, participants were given these instructions: I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say "B", you might give me "bad, battle, bed…" I do not want you to use words that are proper names, such as "Boston, Bob, or Buick." Also, do not use the same word again with a different ending, such as "box", "boxer", and "boxing". Any questions? Begin when I say the letter. The first letter is F. Ready, go. [Repeat for letter A and S].

For semantic verbal fluency (animals), participants were given these instructions: Tell me the names of as many animals as you can. Name them as quickly as possible.

Instructions for human action fluency were as follows:

> I'd like you to tell me as many different things as you can think of that people do. I do not want you to use the same word with different endings, like eat, eating, and eaten. Also, just give me single words such as eat, rather than a sentence or phrase. Can you give me an example of something that people do?" If the response was unacceptable, participants were asked to provide another example of an action word (any verb response is acceptable). If the response was acceptable, the examiner stated: "That's the idea. Now you have one minute to tell me as many different things as you can think of that people do" (Piatt, Fields, Paolo, &Troster, 1999).

Paced Auditory Serial Addition Task (PASAT)

The Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) is a serial addition task used to assess working memory, divided attention, and information processing speed. There are several forms of the test (computer based, audio tape, short form, long form, children and adult forms). In the current study we utilized the first two trials from the audio taped version. The internal reliability for the adult form is very

high. The Cronbach's alpha is r= .90 (Crawford et al., 1998). Mc Caffrey et al. (1995) found the test re-test reliability for (7-10 days) was excellent at an r= >.90. In terms of validity, the PASAT short and long forms are highly correlated in healthy individuals (r= .86 for the PASAT 50 and r= .95 for the PASAT-100) and in HIV patients (Diehr et al., 2003).

Stroop Color Word Test (Stroop CW)

The Stroop color Word Test (Stroop CW) (Golden, 1978; Golden & Freshwater, 2002) is part of the Stroop test, which is a measure of cognitive control. This test assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favor of a less familiar one. There are several versions of the test. A version developed by Golden (1978), a version developed by Trenerry et al., (1989), or the Victoria version. The test-retest reliability reported by Golden (1975) was .89 (Word), .84 (Color), and .73 (Color-Word) for a group administered test. For an individually administered test, reliabilities were .86 (Word), .82 (Color), and .73 (Color-Word). Franzen et al. (1987) gave the Golden Version to 62 healthy individuals on two occasions, spaced one or two weeks apart. The coefficients were .83 for Word, .74 for Color, and .67 for Color-Word. In terms of validity, correlations among test trials for the Golden version are moderate to high (Chafetz & Matthew, 2004). The diagnostic validity of the Golden version of the Stroop has been examined. A study by Cicerone and Azulay (2002) screened for symptom exaggeration in a group of patients with post concussion syndrome (PCS) and matched controls. Results showed high specificity (96.6 Color, 93.3 Color-Word). Suggesting high utility of ruling in PCS.

Trail Making Test Part B (TMT B)

The Trail Making Test (Reitan and Wolfson, 1985) is a measure of attention, speed, and mental flexibility. Test re-test reliability in young adults retested after an interval of three weeks on the TMT B was .75 (Bornstein et al., 1987). Dikmen et al. (1999) examined 384 normal or neurologically stable adults (age 15-83 years). They were retested 11 months after the initial test session and high reliability was discovered for Part B (.89). Levine et al. (2004) reported moderate reliability in a well-educated mostly Caucasian sample of male subjects (.70 part A & B). Test re-test reliabilities for older adults after a one-year time period were low for part A (.53 to .64) and moderate for part B (.67 to .72) (Mitrushina and Satz, 1991; Snow et al., 1988). Interrater reliability for the TMT has been reported as .94 for part A and .90 for part B (Fals-Stewart, 1991). The validity of the TMT shows that Parts A and B correlate moderately well with each other (r= .31 to .60) suggesting that they measure similar although somewhat different functions (Heilbronner et al., 1991; Pineda and Merchan, 2003; Royan et al., 2004). Royan et al. (2004) reported that the TMT-B correlated moderately well with scores on other measures of speeded processing (i.e., Symbol Digit Modality Test and a variant of the PASAT).

Letter-Number Sequencing (LNS)

The Letter Number-Sequencing Task is a subtest of the WAIS-III (The Psychological Corporation, 1997). The WAIS-III measures general intellectual functioning in older adolescents and adults. The internal consistency for the Letter Number Sequencing subtest is high, at .80-.89. The test re-test reliability is adequate, falling between .70 and .79 (Psychological Corporation, 1997). The validity of the

WAIS-III as a whole is good. There is a substantial correlation between the WAIS-III and its predecessor, the WAIS-R (WAIS-III/WMS-III Technical Manual, 1997).

The Wisconsin Card Sorting Task (WCST-64)

The WCST assesses the ability to form abstract concepts, to shift and maintain set, and to utilize feedback (Berg, 1948; Grant & Berg, 1948). In our study we used the abbreviated form of the WCST, the WCST-64 (Axelrod, Woodard, et al., 1992; Kongs et al., 2000). The long form of the WCST has excellent interrater reliability, specifically, inter-scorer and intra-scorer reliability (interclass correlations above .83; Axelrod, Goldman, et al., 1992; Greve, 1993). The WCST-64 measures correlate highly (r values above .7) to corresponding scores on the long form (Axelrod, 2002; Donders & Wideboer; Merrick et al., 2003; Sherer et al., 2003; Smith-Seemiller et al., 2001; Vayalakkara et al., 2000). In terms of validity, in the acute recovery period following TBI (median time postinjury of 34 days) both the standard and short form are equally sensitive (or insensitive) to severity of injury defined as length of coma (Merrick et al., 2003).

Boston Naming Test (BNT)

The Boston Naming Test (Kaplan, et al., 1978) assesses visual naming ability using black and white drawings of common objects. The internal consistency for the 60-item test has been reported between .78 and .96 (Graves et al., 2004, Fastenau et al., 1998; Franzen et al., 1995; Saxton et al., 2000; Tombaugh & Hubley, 1997; Storms et al., 2004; Williams, et al., 1989). In terms of validity, the BNT correlates highly (r=.76 to

.86) with the Visual Naming Test of Multilingual Aphasia Examination (Axelrod et al., 1994; Schefft et al., 2003).

Scoring

The T-scores for the PASAT, Stroop Color-Word, TMT B, LNS, and WCST-64 were averaged in order to provide an executive domain score. Table 2 contains the minimum and maximum scores and means and standard deviations of the individual scores and the executive domain score.

Table 2

Executive Function Means and Standard Deviations

	N	Minimum	Maximum	Mean	Std. Deviation
PASAT	29	20	62	42.14	10.69
Stroop CW	29	22	60	43.83	9.17
TMT B	29	27	76	45.03	10.61
LNS	29	30	73	46.90	9.79
WCST-64	29	34	59	45.76	6.69
Domain Score	29	132.20	245.60	187.05	29.76

Note. PASAT= Paced Auditory Serial Addition Test; Stroop CW= Stroop Color-Word Test interference trial; TMT B= Trail Making Test part B; LNS= Letter-Number Sequencing; WCST= Wisconsin Card Sorting Test perseverative errors; Domain Score= Executive function composite score. Means and standard deviations of executive tasks based on T-scores.

We employed the clustering and switching methods from Troyer et al., (1997) for phonemic and semantic fluency. Since human action clustering and switching had not

been examined previously, we adapted the Troyer et al. scoring procedure to verb fluency and included the following action categories: 1) Sport and Exercise; 2) Work/School Related; 3) Basic ADLs; 4) Instrumental ADLs; 5) Basic/Homeostatic; 6) Games, Play, and Leisure; 7) Verbal Communication; 8) Affective and Non-verbal Communication; and 9) Drug Related. These categories were derived by consensus based on review of typical responses from a subsample of the participants utilized in this study. Table 3 contains the minimum and maximum verbal fluency and switching scores for the phonemic, semantic, and human action fluency trials.

Table 3

Verbal Fluency Means and Standard Deviations

	N	Minimum	Maximum	Mean	Std. Deviation
FAS switching	29	1	15	5.2759	3.24
Animals	29	2	7	4.14	1.38
Human Action	29	0	6	3.10	1.47

Note. FAS= Total phonemic switches; Animals= Total semantic switches; Human Action= Total human action switches.

Instrumental Activities of Daily Living (IADLs)

Instrumental activities of daily living (IADLs) were assessed by a modified version of the Lawton and Brody (1969) ADL scale, which consists of numerous instrumental daily tasks (e.g., managing finances, grocery shopping, housekeeping, medication adherence, and employment). Participants were asked to rate their current

and best previous levels of functioning. The ratings ranged from 0 to 8 with higher scores indicating greater disability. Total current and best IADL scores were calculated as the sum of individual IADLs. Declines in functioning/IADL composite score was calculated as the total current IADL functioning minus the total best IADL functioning. Table 4 contains the means and standard deviations of the IADL current, best, and composite scores.

Table 4

Means and Standard Deviations of Now, Best & Composite IADL Score

	N	*Minimum*	*Maximum*	*Mean*	*Std. Deviation*
IADL Now	29	0	11	4.72	2.95
IADL Best	29	0	12	2.69	3.50
IADL Composite	29	-6	11	2.03	3.57

Note. Mean and standard deviations of current IADL, best IADL performance, and IADL composite. IADL composite score was calculated as the current IADL functioning minus best IADL functioning.

Hypotheses

Our objective was to evaluate switching methods in human action/verb fluency to examine how it associates with other measures of executive functioning in a HIV infected sample. We utilized the Troyer (1997) clustering and switching methods to accomplish this. The Troyer method provides an improved measure of functioning in comparison to the traditional method of calculating the number of words produced. The evaluation of the human action/verb fluency task with the Troyer (1997) method is novel and adds to the body of research. Additionally, this project included the evaluation of switching in

human action/verb fluency to predict difficulties in the performance of instrumental activities of daily living (IADL) in participants with HIV infection. Previously, Woods et al. (2006) established that individuals with impaired human action fluency had a high risk of concurrent IADL dependence as compared to those who performed within normal limits. These objectives were evaluated through the examination of the following hypotheses:

1. Human action switching, as opposed to phonemic switching and semantic switching, will better predict executive functioning.
2. Human action switching, as opposed to phonemic switching and semantic switching, will better predict difficulties in the performance of instrumental activities of daily living.

Analyses

Pearson's Correlations

Pearson's correlations were calculated to determine the convergent and discriminant validity amongst the executive measures and to determine the convergent and discriminant validity amongst the executive measures and the executive domain score.

Hierarchical Linear Regression Analysis

Hierarchical linear regression was used to evaluate the hypothesis that human action switching, as opposed to phonemic switching and semantic switching, would better predict executive function. This analysis was used to determine if the addition of human action switching would improve prediction of executive function beyond that

afforded by phonemic switching and semantic switching. Phonemic and semantic switching was entered into the first model and human action switching into the second model. The dependent variable was an executive domain score, which was created based upon the average of the T-scores of executive performance.

We also employed hierarchical linear regression to determine if human action switching would be a more robust predictor of difficulties in the performance of instrumental activities of daily living as opposed to phonemic switching and semantic switching. This analysis was used to determine if the addition of human action switching would improve prediction of difficulties in the performance of instrumental activities of daily living beyond that afforded by phonemic and semantic switching. Phonemic and semantic switching was entered into the first model and human action switching into the second model. The dependent variable was an IADL composite score created from the subtraction of the total IADL best score from the total IADL current score. Analyses were performed using SPSS PASWS Statistics 18.0.

Power Analysis

A post hoc power analysis was conducted using the software package, G*Power (Faul and Erdfelder 1992). Our sample size of 29 was utilized for the statistical power analysis with a 3-predictor variable equation as a baseline. The alpha level employed was $p < .05$. The post hoc analysis revealed statistical power for this study as .08 for detecting a small effect and .34 for a medium effect. The power for detecting a large effect was .69. Thus, there was adequate power to detect a large effect but less than adequate power to detect a small effect.

CHAPTER FOUR

RESULTS

Pearson's correlations were calculated to determine the convergent and discriminant validity of the executive performance measures and to determine the convergent and discriminant validity amongst the executive measures and the executive domain score. Given the number of correlations, we utilized a more stringent alpha level of .01. As can be seen in Table 5, TMT B was significantly associated with the PASAT, LNS, and the executive function domain composite score (p<.01). The PASAT was significantly associated with LNS and the executive function domain composite score (p< .01). The executive function domain composite score was significantly associated with Stroop CW and LNS (p< .01).

Table 5

Summary of Correlational Analyses

Executive Measures	TMT-B	PASAT	Stroop CW	LNS	WCST	Domain Score
TMT-B	_					
PASAT	.526*	_				
Stroop CW	.126	.302	_			
LNS	.505*	.501*	.313	_		
WCST	.144	.178	.192	-.203	_	
Domain Score	.757*	.812*	.573*	.776*	.152	_

Note. PASAT= Paced Auditory Serial Addition Test; Stroop CW= Stroop Color-Word Test interference trial; TMT B= Trail Making Test part B; LNS= Letter-Number Sequencing; WCST= Wisconsin Card Sorting Test perseverative errors. Correlational analyses between executive measures and executive domain score. Executive domain score is an average of the T-scores of the executive tasks.
*p< 0.01

Hierarchical regression was utilized to address the hypothesis that human action switching as opposed to phonemic switching and semantic switching would better predict the executive function composite score. As can be seen in Table 6, model 1 was significant $p < .05$ but model 2 was not $p > .05$. Results revealed that the optimal linear combination of phonemic and semantic total switching in model 1 accounted for 26% of the variance in executive function ($R^2 = .260$). On average for every one-point increase in phonemic switching, executive function performance increased by 5.957 points ($b = 5.957$, 95% CI [1.889, 10.025], $p < .01$). This model was driven by phonemic switching; neither human action nor semantic switching were significant predictors of the executive composite score.

Table 6

Hierarchical Regression Predicting Executive Function

	b	β	t	Sig.	95% CI (b)	ΔR^2
Step 1						.260*
(Constant)	187.426		11.789	.000	[154.745, 220.106]	
Phonemic Switching	5.957	.648	3.010	.006	[1.889, .10.025]	
Semantic Switching	-7.687	-.357	-1.657	.110	[-17.224, 1.851]	
Step 2						.003
(Constant)	185.052		10.270	.000	[147.940, 222.164]	
Phonemic Switching	5.686	.619	2.574	.016	[1.137, 10.235]	
Semantic Switching	-7.661	-.356	-1.622	.117	[-17.391, 2.068]	
Human Action Switching	1.192	.059	.300	.767	[-7.002, 9.387]	

Note. Hierarchical regression with human action switching, phonemic switching, and semantic switching, predicting executive function domain score. $p < .05$

Hierarchical regression was also utilized to address the hypothesis that human action switching as opposed to phonemic switching and semantic switching would better predict difficulties in the performance of instrumental activities of daily living. As can be seen in Table 7 neither model was significant ($p > .05$) and there were no significant individual predictors ($p > .05$).

Table 7

Hierarchical Regression Predicting Instrumental Activities of Daily Living

	b	β	t	Sig.	95% CI (b)	ΔR^2
Step 1						.001
(Constant)	1.798		.811	.424	[-2.757, 6.354]	
Phonemic Switching	-.019	-.017	-.069	.945	[-.586, .548]	
Semantic Switching	.081	.032	.126	.901	[-1.248, 1.411]	
Step 2						.012
(Constant)	1.204		.481	.634	[-3.948, 6.357]	
Phonemic Switching	-.087	-.079	-.284	.779	[-.719, .545]	
Semantic Switching	.088	.034	.134	.895	[-1.263, 1.439]	
Human Action Switching	.298	.123	.540	.594	[-.839, 1.436]	

Note. Hierarchical regression with human action switching, phonemic switching, and semantic switching predicting instrumental activities of daily living overall score. Overall score calculated by subtracting IADLs at best from current IADLs.
*$p < .05$

CHAPTER FIVE

DISCUSSION

Our intention was to evaluate switching methods in human action/verb fluency to examine how it associates with other measures of executive functioning and difficulties in the performance of instrumental activities of daily living in a HIV infected sample. We hypothesized that human action switching as opposed to phonemic switching and semantic switching would better predict executive function. The results of this investigation did not fit with our hypothesis. Phonemic switching significantly predicted the executive ability composite score, accounting for approximately 26% of the variance. Human action switching did not add meaningfully to the prediction of executive ability above and beyond phonemic switching, as it (and semantic switching) was not found to be a significant predictor. It is possible that our study lacked the power to detect a significant result as we had a 34% chance of detecting a medium effect and an 8% chance of detecting a small effect.

Additionally, this phonemic driven result is indicative of greater phonemic switching being associated with performance on executive functioning tasks. However, this result is in line with previous work indicating that switching ability is correlated with standard clinical measures of executive function (Iudicello et al., 2008). Although human action switching may be mediated by frontal systems and appear to better assess executive dysfunction related to frontal-striatal pathology, it is a form of switching just as phonemic and semantic switching. Each category of switching may be measuring a similar construct, in fact, human action fluency could be considered to be a more difficult form of semantic fluency, as it requires the generation of words in a very specific

category. Given this consideration, it is not surprising that human action switching did not predict an omnibus executive score above and beyond phonemic and semantic switching. In fact, in this sample, phonemic and human action switching are significantly correlated (See Table 8).

Table 8

Verbal Fluency Correlational Analyses

	FAS	Animals	Human Action
FAS	-		
Animals	.622*	-	
Human Action	.488*	.291	-

Note. FAS= Total phonemic switches; Animals= Total semantic switches; Human Action= Total human action switches
*p< .01

Previous studies have indicated that switching is closely related to frontal lobe functioning (Troyer et al., 1997, 1998) and executive measures are mediated by frontal systems. HIV infection- associated deficits in human action fluency may reflect inefficiencies engaging motor representations during action retrieval in this population due to motor impairment (Woods et al., 2006). With regard to this, participants with HIV infection generate fewer words than healthy controls on verbal fluency tasks (Iudicello et al., 2007). In previous research the generation of fewer words may have contributed to human action switching's inability to demonstrate merit in prediction. In theory this

should have been the case for our sample as well, but it was not. It is likely that the lack of sufficient power led to this.

We also hypothesized that human action switching would better predict difficulties in the performance of instrumental activities of daily living than phonemic and semantic switching. However, we did not find support for this hypothesis.

We speculated that this result is related to the use of highly active antiretroviral therapy (HAART) medication in this population. Since the introduction of HAART, in 1996 there has been improved virological, immunological, and clinical outcomes, including reduced mortality rates, in individuals infected with HIV (Ory & Mack, 1998). Prior to this medication, patients with HIV-associated dementia (HAD) typically experienced a rapid deterioration over a few months, with a mean survival of three to six months (Portegies et al., 1993).

The most prominent feature of HAD is severe cognitive impairment resulting in significant dysfunction in daily activities (Navia, Jordan, & Price, 1986). In 2004, Hinkin et al. demonstrated that neurocognitive impairment resulted in a greater risk of poor adherence and poor adherers performed significantly worse on neuropsychological testing, particularly on measures of executive function and psychomotor speed. It was suggested that a bi-directional relationship exists, with cognitive impairment adversely affecting patients' ability to adhere to their medication regimen, which in turn results in further disease progression and a worsening of cognitive function. Given that the participants in this study were being treated with HAART and showed fairly intact executive ability, and demonstrated little IADL decline, it follows that a strong relationship between switching and IADLs was not detectable in our sample.

Future Directions

Human action switching was not predictive of executive function and performance of IADL's above and beyond phonemic and semantic switching. Verbal switching abilities (phonemic and semantic) have been assessed by modified scoring procedures on standard verbal fluency trials (Troyer et al., 1997) and by forced switching manipulations (Delis, Kaplan, & Kramer, 2001), where participants are asked to alternate between producing words from two categories or that start with two different letters. The application of Troyer's method to human action fluency is novel. Future directions should involve modifications to the consensus driven human action fluency categories, which may make indices of human action fluency switching more sensitive to executive ability and IADL decline.

Future research should account for the number of words produced. A study by Troyer et al. (1997) suggested that clustering and switching were highly correlated with the number of words generated on semantic fluency. Furthermore, they suggested that switching was highly correlated to the words generated on phonemic fluency in comparison to clustering. In this regard, participants with HIV infection have executive deficits (Reger et al., 2002), tend to generate fewer words than healthy controls (Iudicello et al., 2007), and switch less during verbal fluency (Iudicello et al., 2007). Creating an equation to account for fewer words produced may do well to improve human action switching prediction.

Future evaluations should also examine the utility of human action switching in predicting HIV- associated neurocognitive disorders and HIV-related declines as assessed by other measures of instrumental activities of daily living. Previous research has examined deficits in human action fluency in predicting HIV-associated declines,

however, human action switching has not been examined in the same way. An exploration of human action switching's ability to predict HIV-associated neurocognitive declines will provide a better avenue for how best to improve upon indices of human action fluency switching. Additionally, in terms of IADL difficulties, we speculate that specific activities related to executive function may be affected by HIV-associated neurocognitive deficits. Thus, an analysis of specific IADL's such as medication, work, and finances with human action switching should be conducted in the future.

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