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Cognitive Mechanisms of Switching in HIV-Associated Category Fluency Deficits

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Abstract

HIV infection is associated with deficits in category fluency, but the underlying cognitive mechanisms of such impairments have not been determined. Considering the preferential disruption of the structure and function of frontostriatal circuits in HIV disease, the present study evaluated the hypothesis that HIV-associated category fluency deficits are driven by impaired switching. Study participants were 96 HIV-infected individuals and 43 demographically comparable healthy comparison volunteers who were administered a standard measure of animal fluency and an alternating category fluency task (i.e., fruits and furniture) in a randomized order. Consistent with prior research on letter fluency, HIV infection was associated with greater impairments in switching, but not semantic clustering within the animal fluency task. Moreover, a significant interaction was observed whereby the HIV-associated deficits in switching were exacerbated by the explicit demands of the alternating fluency task. Across both fluency tasks, switching demonstrated generally small correlations with standard clinical measures of executive functions, working memory and semantic memory. Collectively, these findings suggest that HIV-associated category fluency deficits are driven by switching impairments and related cognitive abilities (e.g., mental flexibility), perhaps reflecting underlying neuropathology within prefrontostriatal networks.

Keywords

Human immunodeficiency virus; verbal fluency; nouns; cognitive processes; neuropsychological assessment

Verbal fluency is impaired in approximately 40% of individuals infected with human immunodeficiency virus (HIV; e.g., Rippeth et al., 2004). The pattern of HIV-associated verbal fluency impairment is characterized by generally comparable mild to moderate deficits in letter and category fluency (Iudicello et al., 2007). As HIV infection is primarily associated with neurophysiological, structural, and functional abnormalities in the fronto-striato-thalamo-cortical loops (González-Scarano & Martín-García, 2005), it is not surprising that this pattern of verbal fluency deficits is consistent with recent meta-analyses of populations with compromised frontal systems (e.g., Henry & Crawford, 2004). Although verbal fluency deficits are fairly mild in the early stages of HIV, they generally increase in magnitude as the disease advances, typically reaching their greatest severity in persons diagnosed with AIDS (Iudicello et al., 2007) or HIV-associated dementia (White et al., 1997). Of clinical importance, HIV-associated verbal fluency deficits are also independently predictive of dependence in instrumental activities of daily living (IADLs; Heaton et al., 2004; Woods et al., 2006).

Considering the prevalence and clinical relevance of HIV-associated verbal fluency deficits, it is important to understand the cognitive architecture such impairments. Several conceptual models have been developed to delineate the cognitive processes involved in optimal fluency performance, which requires rapid, effortful self-initiated search and retrieval from lexico-semantic memory stores to generate words beginning with a specific letter or belonging to a particular semantic category (e.g., animals). Thus, verbal fluency relies on frontal systems and executive processes (e.g., rule-guided search and retrieval strategies), as well as medial temporal lobe networks and the semantic memory stores (Moscovitch, 1994). One conceptual framework that has garnered much attention is Troyer's model of clustering and switching (Troyer, Moscovitch, & Winocur, 1997). In brief, clustering refers to the generation of words within specific lexico-semantic subcategories and is viewed as an automatic retrieval process associated with the integrity of semantic memory and the medial temporal lobes (e.g., Tröster et al., 1998). Switching describes the ability to disengage from one lexico-semantic cluster in order to search for, engage, and retrieve words from another relevant cluster (Troyer et al., 1997). Switching is a more controlled executive ability, which requires processing speed, cognitive flexibility, and rule-guided, self-initiated processes commonly associated with frontal systems (e.g., Eslinger & Grattan, 1993; Ho et al., 2002).

Consistent with the largely frontostriatal neuropathology of HIV infection, two prior studies suggest that HIV-associated verbal fluency deficits are primarily driven by impaired switching. Millikin and colleagues (2004) found that individuals with AIDS diagnoses were impaired in switching, but not clustering on both letter and category fluency as compared to asymptomatic HIV-infected participants. Similarly, Woods et al. (2004) demonstrated that individuals with HIV-associated dementia switched significantly less during letter fluency than demographically similar non-demented HIV-infected individuals and seronegative adults, but generated comparable lexico-semantic cluster sizes. Findings from these studies are interpreted to suggest that HIV-associated fluency impairments reflect inefficient lexico-semantic search strategies, rather than difficulties disengaging from a subcategory, or in accessing and retrieving information from semantic memory. However, three important issues regarding the nature and mechanisms of category switching in HIV remain unanswered.

First, no studies have examined whether HIV is associated with greater switching (versus clustering) impairments in category fluency in comparison to healthy, seronegative individuals.

This is important because category fluency, even more so than letter fluency, depends on both clustering and switching abilities (Troyer et al., 1997), which are dissociable on the basis of the contributions of temporal and frontal systems, respectively. For example, individuals with frontal systems damage (e.g., frontal lobe lesions) demonstrate impaired category switching, but generally intact semantic clustering (Troyer, Moscovitch, Winocur, Alexander & Stuss, 1998a), whereas individuals with temporal systems pathologies (e.g., Alzheimer's disease), evidence impairment in semantic clustering (and switching, although to a lesser extent) on category fluency (Troyer, Moscovitch, Winocur, Leach & Freedman, 1998b). Therefore a profile of impaired category switching, but normal clustering may be a marker of frontal systems pathology, whereas category clustering impairment preferentially reflects the integrity of the medial temporal lobes. Considering the known effects of HIV on frontal systems, it is hypothesized that individuals with HIV infection will demonstrate poorer category switching, but intact clustering in comparison to demographically comparable seronegative participants.

A second important, but previously unexplored issue is whether HIV-associated category fluency switching deficits are exacerbated when the switching demands are explicit, rather than implicit. In contrast to implicit switching measures derived from standard fluency protocols (e.g., Troyer et al., 1997), alternating fluency paradigms (e.g., Delis, Kaplan, & Kramer, 2001) explicitly require an individual to generate words by switching between two categories (e.g., fruits and furniture). In this way, alternating fluency arguably places greater demands on cognitive flexibility (i.e., set switching) and working memory, which are functions closely linked with the prefrontostriatal circuits (e.g., Eslinger & Grattan, 1993). As such, alternating fluency measures may be more sensitive to frontal systems pathologies (e.g., HIV infection) than typical verbal fluency paradigms (e.g., Zec et al., 1999) or implicit switching (e.g., Troyer, 2000). Thus, it is hypothesized that HIV infection will be associated with disproportionate switching deficits in alternating category fluency versus a standard category fluency task.

Finally, no prior studies have examined the cognitive mechanisms underlying HIV-associated category fluency switching deficits. As noted above, category fluency places demands on both executive and semantic processes, which raises questions regarding the cognitive force(s) that may be driving the switching impairment in HIV. The present study evaluates this issue by examining the correlations between standard and alternating category fluency switching measures and standard clinical tests of executive functions, working memory, processing speed and semantic memory.

Method

Participants

A total of 43 healthy, HIV seronegative adults and 96 volunteers with HIV infection as indicated by enzyme linked immunosorbent assays and a Western Blot confirmatory test participated in this study. Participants were excluded if they had prior histories of severe psychiatric (e.g., psychosis) or neurological conditions (e.g., seizure disorders, closed head injuries). In addition, individuals who met *Diagnostic and Statistical Manual of Mental Disorders* (American Psychological Association, 1994) criteria for substance dependence within six months of evaluation or who tested positive for illicit drugs (except marijuana) on a urine toxicology screen conducted on the day of testing were excluded.

The demographic, psychiatric, and HIV disease characteristics of the participants are presented in Table 1. The study groups demonstrated comparable demographic characteristics, with the exception of a significantly greater proportion of women in the seronegative sample ($\chi^2(1,141) = 13.36, p < 0.001$), which also had a lower prevalence of lifetime substance dependence ($p < 0.01$) and Major Depressive Disorder (MDD; $p < 0.05$) diagnoses. Groups were comparable

for premorbid verbal intelligence, which was derived from the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001).

Materials and Procedure

After providing informed written consent, each participant was administered a standard category verbal fluency test (Category Fluency; Benton, Hamsher & Sivan, 1983) and the Alternating Category Switching subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001) in a randomized order. The Category Fluency task required individuals to generate as many animals as possible within 60 seconds and was scored for clustering and switching according to the criteria established by Troyer et al. (Troyer, 2000; Troyer et al., 1997). In short, clustering was indexed by the mean cluster size, or the average number of successive words generated belonging to the same semantic subcategory (e.g., cat and dog). The Category Fluency switching score was determined by the total number of times an individual was able to disengage from one semantic cluster and switch to another. Raw scores for total correct responses and total number of switches were converted to population-based z-scores for standardization and comparison purposes.

The Alternating Category Switching task required individuals to alternatively generate as many words as possible from two different semantic categories (i.e., fruits and furniture) in 60 seconds (e.g., apple-couch, orange-bed). Specific guidelines based on the D-KEFS verbal fluency scoring procedures were used for scoring. Performance was indexed by total correct responses (i.e., sum of total correct responses from both target categories), total errors (e.g., set-loss errors, repetition errors), and total number of accurate switches (i.e., sum of correct across-category switches). Raw scores for total correct responses and number of accurate switches were also converted to population-based z-scores for the analyses. Set-loss errors were defined as words that either do not belong to either semantic category, grammatical variants of given words, or responses that are ordinate or superordinate to either semantic category. Repetition errors were coded for any response that was repeated.

The neuropsychological test battery consisted of a number of tasks selected *a priori* as indicators of cognitive abilities required for fluency performance, including: 1) the Trail Making Test (TMT B minus A; Reitan & Wolfson, 1985); 2) the Tower of London – Drexel Version (ToL total moves; Culbertson & Zilmer, 2001); 3) the Self-Ordered Pointing Task (SOPT total errors; Petrides, & Milner, 1982); 4) the Digits Backward subtest of the Wechsler Adult Intelligence Scale (3rd ed; WAIS-III; Psychological Corporation, 1997); 5) the Famous Faces subtest of the Kaufman Adolescent and Adult Intelligence Test (KAIT; Kaufman & Kaufman, 1993); and 6) the Boston Naming Test (BNT; Goodglass, Kaplan, & Barresi, 2001).

Data Analyses

Given the sample size ($N=139$), this study was adequately powered (>0.80) to detect medium to large effect sizes using a critical alpha at 0.05. The data were screened for significant outliers (i.e., data points > 3.5 SDs from the overall group mean) and were evaluated for normality (i.e., Shapiro-Wilk W test, $p<.05$). Although a few variables (e.g., errors) were non-normally distributed, the results did not differ when nonparametric statistics were used; as such, we adopted a parametric approach throughout the study. First, a repeated measures analysis of variance (ANOVA) was conducted to examine the effects of HIV status on the total word output for the two fluency paradigms, with HIV-status as the between-subjects factor and fluency scores (i.e., z-scores for total correct words for Category Fluency and Alternating Category Switching) as the within-subjects factor. Follow-up independent- and paired-samples *t* tests were conducted in order to further examine between- and within-group differences, respectively. Next, a repeated measures ANOVA was used to determine the effects of HIV

serostatus on the switching components on the two fluency measures, with HIV status as the between-subjects factor and switching verbal fluency component (i.e., *z*-scores for total switches for Category Fluency and Alternating Category Switching) as the within-subjects factor. As above, follow-up analyses were conducted on any significant omnibus effects using independent samples *t* tests. Cohen's *d* and partial eta-squared statistics were used to generate effect sizes for group comparisons. Correlational analyses were conducted within the HIV seropositive sample using Pearson product moment correlation coefficients.

Results

Table 2 presents the means, standard deviations, effect sizes, and 95% confidence intervals for the verbal fluency measures. The first analysis examining the relationship between HIV serostatus and total words generated on the two fluency measures revealed a significant between-subjects effect of HIV-status ($p < .0001$, $\eta^2 = .102$), with a strong trend towards a significant group by fluency interaction ($p = .052$, $\eta^2 = .027$). No significant within-subjects effects were found for fluency task ($p > .10$). Follow-up analyses indicated that HIV-infected individuals generated significantly fewer words on both the Category Fluency ($p = .047$) and the Alternating Category Switching ($p = .001$) tasks than their seronegative counterparts.

Upon examination of the switching components of each fluency paradigm, analyses revealed a significant between-subjects effect of HIV serostatus ($p < .0001$, $\eta^2 = .132$) and a significant interaction between HIV and fluency task ($p = .028$, $\eta^2 = .035$). There was no within-subjects effect for fluency paradigm ($p > .10$). As displayed in Figure 1, follow-up analyses revealed that while HIV-infected individuals tended to switch less than their seronegative counterparts on the Category Fluency paradigm ($p < .10$), they switched significantly less during the Alternating Category Switching task ($p < .001$). There were no differences between groups in mean cluster size for the Category Fluency test or in errors on either fluency measure ($ps > .10$).

Within the HIV sample, there were no significant differences in performance on the variables of interest of each fluency measure (i.e., the total word output or switching) between individuals with and without lifetime histories of MDD or lifetime history of substance dependence (all $ps > .10$). In addition, overall fluency and switching performance was not associated with sex in either sample ($p > .10$). Furthermore, performance on both fluency paradigms with regard to total word output and switching abilities was not associated with use of cART, Centers for Disease Control and Prevention (CDC) stage, AIDS status, plasma HIV RNA, current or nadir CD4 count, or duration of infection ($ps > .10$).

As shown in Table 3 the Category Fluency switching variable demonstrated generally small associations with measures of working memory (i.e., Digits Backward), executive functions (i.e., TMT B-A), and semantic memory (i.e., BNT) in the HIV sample. Similarly, the Alternating Category Fluency switching trial was significantly but weakly correlated with Digits Backward and the BNT ($ps < .05$).

Discussion

The present study extends prior research by clarifying the cognitive mechanisms of HIV-associated category fluency deficits. First, we found that HIV-infection was associated with poorer category fluency performance relative to seronegative volunteers ($d = -0.37$), which is generally consistent with prior reports of small, but significant category fluency deficits in HIV infection (Iudicello et al., 2007). Closer examination of the component processes of this HIV-associated category fluency deficit, which have not been previously explored in comparison to healthy adults, revealed that that HIV infection was associated with a mild impairment in

switching (at a trend level), but not clustering. In other words, the HIV sample experienced mild difficulties in the process of disengaging from one semantic cluster, then searching for, engaging, and retrieving words from another category, but no apparent degradation of the semantic memory stores themselves. Although this trend-level effect did not reach the level of statistical significance, it is worthwhile to note its magnitude ($d=-0.33$) relative to clustering ($d=0.00$), which is consistent with the pattern observed on letter fluency in HIV-associated dementia (Woods et al., 2004), as well as with published data showing that HIV is associated with deficits in set-shifting (e.g., Marsh & McCall, 1994) and cognitive flexibility (Basso & Bornstein, 2003).

Expanding beyond implicit (i.e., embedded) verbal fluency switching measures, we also examined whether HIV-associated category fluency deficits are exacerbated when switching demands are more explicit by using an alternating fluency paradigm. Indeed, results showed that HIV infected individuals made significantly fewer switches on the Alternating Category Switching paradigm than their seronegative counterparts, to an even greater extent than was observed on the implicit switching measure derived from the standard Category Fluency task. These data suggest a differential deficit with regards to explicit switching in HIV infection and are consistent with prior studies showing disproportionate impairment in alternating word fluency in populations with frontal systems involvement (e.g., Baldo et al., 2001; Zec et al., 1999). To the extent that switching abilities are a marker of frontal systems functioning (e.g., Kramer et al., 2007), these results provide support for the role of HIV-associated frontal systems damage in the observed impairment in alternating category fluency. Furthermore, given the relative immune health of our HIV sample, these findings also suggest that alternating fluency paradigms may be a more useful marker of the mild neuropsychological deficits characteristic of less severe HIV disease than standard category fluency measures.

Regarding possible cognitive mechanisms, both category fluency switching paradigms demonstrated small correlations with well-validated tests of working memory and executive functions. These findings are consistent with prior research in Huntington's disease, which shows that higher category fluency switching scores are associated with better performance on standard clinical measures of executive functions and working memory (e.g., Trail Making Test; Ho et al., 2002). In addition, both switching indices correlated significantly with a measure of confrontational naming (e.g., BNT), suggesting that the integrity of the semantic memory stores may also play a role in HIV-associated category fluency deficits. Together, these data indicate that both automatic (i.e., semantic memory) and controlled (i.e., executive functions and working memory) cognitive processes (Craik, 1986) are important contributors to the category fluency deficits observed in HIV. In addition to the small effect sizes, a notable limitation of these correlational analyses is that the neuropsychological battery did not include any established tests of cognitive flexibility (e.g., Stroop Color-Word Test and Wisconsin Card Sorting Test) other than TMT B-A.

Neither fluency switching measure was associated with traditional markers of HIV disease severity or treatment characteristics. For example, in contrast to the findings of Millikin et al. (2004), we did not observe any association between category switching and CDC stage (including AIDS status). Unlike Millikin et al., however, our study was not specifically designed to examine AIDS-related hypotheses; in fact, our AIDS and non-AIDS groups were not matched on important demographic (e.g., age) and disease characteristics (e.g., duration of infection) that may have influenced our negative findings. Moreover, our AIDS cohort ($n = 54$) had significantly less severe immune compromise, with a mean CD4 lymphocyte count of 418 ($SD = 259$) as compared to 276 ($SD = 248$) in the Millikin et al. study. One might therefore surmise that the detrimental AIDS effect on fluency switching may not be present in the setting of immune reconstitution. This finding also represents the difficulties inherent in associating traditional markers of HIV disease severity with central nervous system

complications in the era of cART (e.g., Reger et al., 2005) and underscores the importance of including more sensitive biomarkers (e.g., markers of macrophage activation, neuronal injury, and astrocytosis) in future studies (see Letendre & Ellis, 2006). Regardless, the relative immune health of the current sample, along with its demographic composition (i.e., predominantly Caucasian men), represents a limitation to the generalizability of our findings.

Finally, the potential clinical implications of these findings are worth considering. Prior research demonstrates that HIV-associated impairments in abilities related to frontostriatal damage (e.g., switching) increase the risk of dependence in instrumental activities of daily living (IADLs), including medication management and vocational skills (e.g., Heaton et al., 2004). Clarifying the association between category switching deficits and the prevalence and incidence of IADL dependence will therefore be an important area for future research. For example, it remains to be seen whether alternating fluency paradigms provide incremental ecological validity as compared to traditional fluency tests in classifying IADL dependence in HIV-infected persons (e.g., Woods et al., 2006). Improving the sensitivity of neuropsychological assessments to HIV-associated neurocognitive disorders in this way might enhance the effectiveness of screening measures, potentially resulting in earlier central nervous system focused treatment and more targeted compensatory strategies designed to improve overall quality of life for individuals living with HIV.

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Figure 1. Line graph displaying the interaction between HIV serostatus and verbal fluency switching paradigms

Table 1
Demographic, Psychiatric, and HIV Disease Characteristics of the Study Samples

Variable	HIV+ (<i>n</i> = 96)	HIV- (<i>n</i> = 43)	<i>p</i>
Demographic Characteristics			
Age (years)	44.8 (8.3)	43.3 (12.2)	0.476
Education (years)	14.1 (2.4)	14.8 (2.7)	0.120
Estimated verbal IQ ^a	106.0 (12.5)	106.2 (10.5)	0.919
Sex (% men)	86.5%	58.1%	0.0003
Ethnicity (% Caucasian)	60.4%	55.8%	0.611
Handedness (% right)	90.6%	90.7%	0.989
Psychiatric Characteristics			
Lifetime substance dependence (%)	57.3%	32.6%	0.007
Major depressive disorder (%)	49.5%	28.6%	0.021
Generalized anxiety disorder (%)	6.3%	4.8%	1.000
HIV disease characteristics			
Estimated duration of infection (years)	12.7 (6.9)		
Proportion with AIDS (%) ^b	56%		
HIV RNA plasma viral load (log ₁₀ c/ml) ^c	1.7 (1.7, 2.4)		
Current CD4 count (cells/μL) ^c	542.5 (328, 812)		
Nadir CD4 count (cells/μL) ^c	172 (41, 346)		

Note. For demographic characteristics, means are shown, with standard deviations in parenthesis.

^a Verbal IQ (*M* = 100; *SD* = 15) was derived from the Wechsler Test of Adult Reading (WTAR).

^b AIDS diagnosis defined by Center for Disease Control 1993 Classification System (Centers for Disease Control and Prevention, 1992).

^c Median (interquartile range)

Table 2
Descriptive Verbal Fluency Data for the HIV+ and HIV- Samples

Variable	HIV+ (<i>n</i> = 96)	HIV- (<i>n</i> = 43)	<i>p</i>	Cohen's <i>d</i>
Animals ^a				
Total correct (raw)	20.5 (5.0)	22.3 (4.5)	0.041	-0.37 (-0.73, -0.01)
Total errors	0.5 (0.7)	0.5 (0.7)	0.742	0.00 (-0.36, 0.36)
Total switches (raw)	9.2 (3.0)	10.2 (3.1)	0.090	-0.33 (-0.69, 0.03)
Average cluster size	1.2 (0.7)	1.2 (0.5)	0.580	0.00 (-0.36, 0.36)
Fruits and Furniture ^b				
Total correct (raw)	14.2 (2.5)	16.5 (3.3)	0.0001	-0.83 (-1.20, -0.45)
Total errors	1.0 (1.4)	1.1 (1.8)	0.592	-0.06 (-0.42, 0.29)
Accurate switches	13.0 (2.6)	15.4 (3.3)	<0.0001	-0.84 (-1.22, -0.47)

^aCategory Fluency Task

^bAlternating Category Switching subtest of the Delis-Kaplan Executive Function System (D-KEFS).

Table 3
Correlational analyses between cognitive domains and total word output and switching component of verbal fluency measures in the HIV sample (N = 96)

Neuropsychological Test	Animal Switching	Fruits-Furniture Switching
SOPT	-0.17	-0.13
WAIS-III Digits Backward	0.22 *	0.24 *
TMT B-A	-0.23 *	-0.19
ToL-DX	-0.12	-0.03
KAIT Famous Faces	0.13	0.17
Boston Naming Test	0.25 *	0.24 *

Note. N = 96. SOPT = Self-ordered pointing test; WAIS-III = Wechsler Adult Intelligence Test (3rd ed.); TMT = Trail Making Test; ToL-DX = Tower of London – Drexel version; KAIT = Kaufman Adolescent and Adult Intelligence Test.

*
 $p < .05$.