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## BRIEF COMMUNICATIONS

# Verbal fluency in HIV infection: A meta-analytic review

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### Abstract

Given the largely prefrontostriatal neuropathogenesis of HIV-associated neurobehavioral deficits, it is often presumed that HIV infection leads to greater impairment on letter *versus* category fluency. A meta-analysis of the HIV verbal fluency literature was conducted ( $k = 37$ ,  $n = 7110$ ) to assess this hypothesis and revealed generally small effect sizes for both letter and category fluency, which increased in magnitude with advancing HIV disease severity. Across all studies, the mean effect size of category fluency was slightly larger than that of letter fluency. However, the discrepancy between category and letter fluency dissipated in a more conservative analysis of only those studies that included both tests. Thus, HIV-associated impairments in letter and category fluency are of similar magnitude, suggesting that mild word generation deficits are evident in HIV, regardless of whether traditional letter or semantic cues are used to guide the word search and retrieval process (*JINS*, 2007, 13, 183–189.)

**Keywords:** HIV, AIDS dementia complex, Neuropsychology, Neuropsychological tests, Verbal fluency, Cognitive processes

### INTRODUCTION

Although HIV RNA is detectable throughout the brain, HIV-associated neuropathologies are most frequently evident in the basal ganglia, frontal neocortex, hippocampus, and white matter (Gonzalez-Scarano & Martin-Garcia, 2005). Corresponding cognitive deficits are commonly observed in areas of motor control, information processing speed, working memory, executive functions, and episodic memory (Reger et al., 2002). Impairment in verbal fluency is also common in persons infected with HIV (White et al., 1997). Verbal fluency requires rapid, self-initiated search and retrieval from lexico-semantic memory stores to orally generate words beginning with a particular letter or belonging to a specific semantic category (e.g., animals). Although verbal fluency

taxes both frontal and temporal systems (Parks et al., 1988), letter fluency is historically associated with executive functions and frontal systems, whereas category fluency is more closely tied to semantic memory and the medial temporal lobes (Henry & Crawford, 2004a). Whether HIV-associated neuropathology produces a differential impairment in letter and category fluency is not known.

HIV-associated verbal fluency deficits are customarily presumed to be driven by prefrontostriatal neuropathologies (Hestad et al., 1993). Accordingly, it is often asserted that individuals with HIV evidence differential impairment on letter *versus* category fluency. In fact, it was recently reported that 26% of HIV studies demonstrate letter fluency deficits *versus* only 13% for category fluency (Woods et al., 2005). However, this qualitative review did not report inclusion/exclusion criteria, calculate effect sizes, examine disease effects, or consider results from only those studies that included both letter and category fluency tasks. Therefore, this study aimed to systematically review the verbal

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fluency literature in HIV to investigate possible differential impairments in letter and category fluency. Our approach to hypothesis generation was informed by recent meta-analyses showing that, while category fluency is preferentially impaired in conditions with prominent temporolimbic neuropathology (e.g., focal temporal lesions; Henry & Crawford, 2004a), both letter and category fluency are impaired with frontal systems damage (e.g., focal frontal lesions; Henry & Crawford, 2004a), which refutes the aforementioned, long-held convention in neuropsychology.

In accordance with this literature and the preferential neurotoxic effects of HIV on prefrontostriatal circuits, one of two outcomes was anticipated: (1) HIV infection is associated with differentially greater deficits in letter *versus* category fluency; or (2) HIV is associated with comparable impairment in letter and category fluency. A third, arguably less tenable possibility is that HIV is associated with greater category fluency deficits. Indeed, hippocampal pathology predicts HIV-associated cognitive impairment (Moore et al., 2006) and a few HIV studies have shown preferential deficits in category fluency (Levin et al., 1992). Finally, considering prior research suggesting that neuropsychological functions generally worsen with advancing HIV disease (Reger et al., 2002), we hypothesized that disease progression would be associated with more severe verbal fluency deficits.

## METHODS

A preliminary search using key terms such as neuropsychology, cognition, executive, verbal fluency (e.g., letter fluency, semantic fluency, COWAT), HIV, and AIDS was conducted in the *PubMed*, *PsychInfo*, and *ISI Web of Science* databases for dates between January 1985 and August 2005. Manual searches of the reference sections of relevant articles and the tables of contents of several HIV and neuroscience journals (e.g., *AIDS*, *Neuropsychology*, and *Neurology*) were also performed to identify any studies that may have been omitted from the electronic database query.

All articles were manually reviewed to determine whether they met the following inclusion criteria: (1) published in English in peer-reviewed journals; (2) assessed English-speaking adults with a standardized verbal fluency test; (3) included participants with documented HIV infection and without other severe neurologic or psychiatric illness (e.g., psychosis); (4) provided sufficient verbal fluency data from which to derive precise effect sizes; and (5) included a seronegative comparison group without severe neurologic or psychiatric illnesses. All eligible studies published by the same group of authors were carefully reviewed to minimize the inclusion of overlapping data from a single HIV cohort. A total of 37 studies with 7110 participants, including 4090 HIV seropositive and 3020 seronegative participants, were deemed eligible for inclusion. All data included in this manuscript was obtained in compliance with institutional regulations.

The following information was extracted from each study: (1) HIV disease (i.e., seronegative, asymptomatic, symptomatic, and AIDS) and treatment characteristics; (2) demographic variables (e.g., age and education); (3) verbal fluency task; (4) sample size; and (5) summary statistics for the calculation of effect sizes. Participants' demographic, disease, and treatment characteristics are listed in Table 1.

## Data Analysis

An unbiased estimation (Cohen's *d*; Cohen, 1988) was calculated separately for letter and category fluency in each study, in which the effect size was weighted by a sample size based constant (Hedges & Olkin, 1985). Collapsed weighted means and pooled standard deviations based on HIV serostatus were calculated for studies that reported only subgrouped samples (e.g., age-based groups). Effects were pooled and weighted to obtain a mean estimate for calculation of a random effects meta-analytic model (Shadish & Haddock, 1994).

Analysis of continuous outcomes involved comparing standardized differences in means for HIV+ and HIV- groups (Hedges & Olkin, 1985). Standardization allowed the study results to be transformed to a common scale (standard deviation units), which assisted pooling (Hedges & Olkin, 1985). Adjustments were made to correct for upward bias of effect size estimation in small samples. Standardized mean differences were calculated and analyzed for each study. In particular,  $d = (M_h - M_c)/S$ , where  $M_h$  and  $M_c$  were the mean verbal fluency scores for HIV+ and HIV- groups, respectively, and  $S$  was the standard deviation for the pooled sample (Shadish & Haddock, 1994). The variance for each *d* value was then calculated and used to determine a weighting factor for the unbiased effect size.

Effect sizes were disaggregated to define groups sharing a common population effect size. Cochran's Q statistic (Cochran, 1954) was computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in the meta-analysis (Hedges & Olkin, 1985). Subsequently, the Q statistic was compared with a

**Table 1.** Participants' demographic data and HIV disease characteristics

	K	HIV+		HIV-	
		N	Mean (SD)	N	Mean (SD)
Age	35	4009	35.88 (6.92)	2968	36.16 (8.23)
Education	28	3596	14.83 (2.34)	2614	15.72 (2.27)
% Male	36	4078	98.23	3008	96.70
% AIDS	34	4010	9.52		
% ART	13	2392	13.7		
CD4	15	2665	487.50 (256.52)		

Note. K = number of studies; N = number of participants; ART = anti-retroviral therapy; CD4 = CD4 lymphocyte count.

$\chi^2$  distribution with  $k-1$  degrees of freedom (where  $k$  is the number of studies). Given apparent heterogeneity ( $p$ 's  $< .10$ ; Lau et al., 1997), data analysis was performed using a random effects model (Shadish & Haddock, 1994), which assumes a different underlying effect for each study that is considered as an additional source of variation (Fleiss & Gross, 1991). Furthermore, the random effects model offers broader confidence intervals around the point estimate and includes an extra term in the variance (DerSimonian & Laird, 1986). Finally, computation of the significance of the difference between the letter and category fluency effect sizes involved  $Z$  score conversions and an estimate of the standard error of difference between the two effect sizes. Next, the difference between the two  $Z$  scores was divided by the standard error (Snedecor & Cochran, 1989).

## RESULTS

Table 2 displays descriptive statistics for the weighted mean effect sizes. Letter fluency was examined in 91.9% ( $k = 34$ ;  $n = 6597$ ) of the 37 eligible studies, of which 47% used the letters FAS, 6% CFL, and 6% PRW (41% did not specify). Of the 41.2% ( $k = 14$ ;  $n = 2092$ ) that included a measure of category fluency, 43% used only animals, while 43% used both animals and an additional category (e.g., supermarket items), and 7% used food categories (7% did not specify). Both letter and category fluency were examined in 27.0% of the eligible studies ( $k = 10$ ;  $n = 1535$ ).

The mean effect sizes for both letter and category fluency across all studies ( $k = 37$ ) and for those studies that included both tasks ( $k = 10$ ) were small, but statistically significant (see Table 2). These effect sizes indicate an approximate overlap of 80% in the distributions of verbal fluency scores in the HIV+ and HIV- groups (Zakzanis, 2001). The potential dampening effects of unpublished or omitted studies were evaluated using fail-safe  $N$  technique (Rosenthal, 1979). Results showed that 60 letter fluency and 195 category fluency studies equal to the average size of those in our meta-analysis and showing no HIV effect would be required to lower the observed effect sizes below the threshold of statistical significance. Across all studies, the mean effect size of category fluency was significantly

larger than that which was observed for letter fluency,  $p < .01$ . However, when a more rigorous analysis was undertaken of only those studies that included both tests, there was no significant discrepancy between letter and category fluency effect sizes,  $p = .58$ .

Figure 1 displays effect sizes by HIV disease stage for studies that clearly defined their HIV sample as belonging to specific disease stages (e.g., CDC, 1992) and contained either letter ( $k = 24$ ) or category fluency ( $k = 9$ ). These data show that medically asymptomatic subjects demonstrated smaller deficits in both letter ( $d = -.10$ ) and category ( $d = -.24$ ) fluency as compared with those subjects with medically symptomatic disease (letter fluency  $d = -.36$ ; category fluency  $d = -.27$ ) or AIDS (letter fluency  $d = -.44$ ; category fluency  $d = -.34$ ). This analysis was not repeated for those studies that contained both letter and category fluency measures due to the paucity of studies available for inclusion.

Given our sampling error corrections, substantive heterogeneity may exist across studies. However, the observed heterogeneity was not attributable to extreme values alone as only one outlier was identified (i.e., age in HIV+ group). Removal of this outlier did not change the basic pattern of results observed and, therefore, the study was retained in the analysis. Correlations between effect size and possible moderators [i.e., age, education, and antiretroviral therapies (ART)] were not significant (all  $p$ 's  $> .10$ ). Furthermore, semipartial correlations did not reveal any significant associations between effect size and (1) education (controlling for ART and age); (2) age (controlling for education and ART); or (3) ART (controlling for education and age; all  $p$ 's  $> .10$ ).

## DISCUSSION

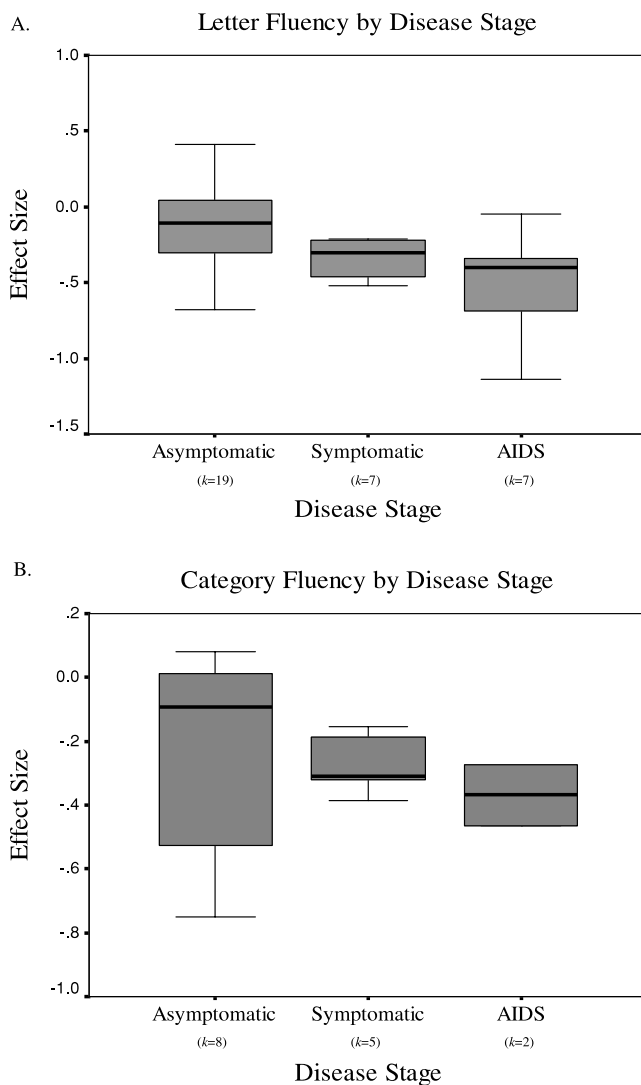
Findings from this meta-analytic review revealed that HIV infection is associated with generally small, but significant deficits in verbal fluency. When all eligible studies were considered, category fluency effects were surprisingly larger than those observed for letter fluency. This finding ran contrary to our primary hypotheses, but was nevertheless commensurate with research indicating that HIV-associated

**Table 2.** Mean effect sizes for letter and category fluency

	<i>K</i>	HIV+		HIV-		<i>M</i>	<i>SE</i>	Var	95% CIs of mean		<i>Q</i>
		<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>				Lower	Upper	
All Studies											
Letter Fluency	34	3749	2848	-.20	.045	.002	-.29	-.11	68.36*		
Category Fluency	14	1330	762	-.36	.077	.006	-.51	-.21	27.55*		
Studies with both fluency tests											
Letter Fluency	10	971	564	-.26	.098	.010	-.45	-.07	22.38*		
Category Fluency	10	971	564	-.31	.066	.004	-.44	-.18	11.12*		

Note. Var = variance; CI = confidence interval.

\* $p < .10$ .



**Fig. 1.** Box and whisker plots showing the effect sizes for letter (A) and category (B) fluency by HIV disease stage.

cognitive deficits are related to hippocampal neuropathology (Moore et al., 2006), which may preferentially disrupt category fluency performance (e.g., Henry & Crawford, 2004a). However, a more rigorous comparison of only those studies in which both verbal fluency tasks were administered was undertaken to ensure that discrepancies in the demographic and clinical characteristics of the variable study samples were not contaminating this unexpected finding. Results of this secondary analysis revealed no statistically significant differences between letter and category fluency. Thus HIV-associated impairments in letter and category fluency appear to be of similar overall magnitude, suggesting that mild word generation deficits are evident in HIV regardless of the particular lexical or semantic cue used to guide word search and retrieval.

Although the precise cognitive and neural substrates of HIV-associated verbal fluency deficits remain to be determined, the results of this meta-analysis raise interesting hypotheses that may guide future research. One possibility

is that both letter and category fluency deficits in HIV disease reflect generalized bradyphrenia driven by diffuse neuropathology. As noted above, HIV-associated neuropathologies are evident throughout brain parenchyma, including cerebral white matter, basal ganglia, and the hippocampus (Gonzalez-Scarano & Martin-Garcia, 2005). In support of this contention, comparable deficits in letter and category fluency were reported in meta-analyses of traumatic brain injury and multiple sclerosis, two conditions associated with diffuse neuropathology at the group level (Henry & Crawford, 2004b; Henry & Beatty, 2006). Another possibility is that HIV-associated verbal fluency deficits reflect executive dyscontrol of search and retrieval from lexico-semantic memory stores, perhaps of a more frontostriatal neuropathogenesis. For example, Hestad et al. (1993) found a negative correlation between verbal fluency and caudate atrophy in HIV-infected individuals. In addition, analyses of the component processes of HIV-associated verbal fluency deficits has revealed impairments in switching (i.e., a marker of executive function entailing the number of times an individual disengages from one lexico-semantic cluster and switches to another), but not clustering (i.e., the average number of consecutively generated words within a lexico-semantic category that demonstrates validity as an indicator of medial temporal lobe integrity; Millikin et al., 2004; Woods et al., 2004). Nevertheless, we cannot rule out a third possibility, which is that HIV-associated letter and category fluency deficits have relatively separable neural mechanisms, despite being of similar severity. For instance, frontostriatal pathology may primarily underlie letter fluency impairment, whereas temporolimbic pathology may play a larger role in the category fluency deficit. Prospective studies that incorporate analyses of component cognitive processes and regional measures of HIV-associated neuropathology are needed to clarify the cognitive and neural mechanisms of verbal fluency deficits in HIV.

Consistent with past research indicating negative effects of HIV disease progression on cognition (e.g., Reger et al., 2002), the magnitude of verbal fluency deficits increased with advancing HIV disease severity. The largest effect sizes were evident in persons with AIDS, suggesting an increased neurotoxic burden associated with immunocompromise (e.g., Stout et al., 1998). Despite prior evidence of the beneficial effects of immune reconstitution and ART on cognition (e.g., Martin et al., 1998), as well as a possible interaction between highly active ART (HAART) and disease status specifically on verbal fluency (Millikin et al., 2004), our moderator analyses revealed no significant effects of HAART. Of note, the studies used in this meta-analysis include data from the current and pre-HAART eras, which may suggest that the overall prevalence and severity of letter and category fluency impairment did not change significantly after the introduction of HAART. In fact, a recent meta-analysis of studies published in the pre-HAART era showed similar language fluency effect sizes in nondemented symptomatic and AIDS groups as were identified in the current investigation (Cysique et al., 2006).

Nevertheless, the external validity of these cross-sectional moderator analyses remains speculative and is hindered by the small number of eligible studies that provided detailed information regarding treatment status. Unfortunately, moderator analyses of several other important HIV disease cofactors (e.g., hepatitis C infection, substance abuse, and affective disorders) and demographic variables (e.g., ethnicity, IQ, and socioeconomic status) were not possible due to the lack of consistent data reporting across studies. The current study results must be interpreted cautiously because the aforementioned factors are prevalent in HIV-infected cohorts and may exert an adverse influence on neuropsychological functioning (Woods & Grant, 2005). In particular, the predominantly well-educated and male samples from which these data were derived represent a significant limitation to the generalizability of these findings, especially considering the growing HIV epidemic in women and minorities (CDC, 2005). Investigators are, therefore, encouraged to include these important, descriptive variables in all future studies of cognition in HIV.

In summary, this meta-analysis expands our understanding of HIV-associated neurocognitive disorders by providing the first systematic review of the verbal fluency literature in HIV infection. Results revealed generally small and comparable deficits in letter and category fluency. Although the observed deficits were small, these findings may be of clinical relevance, particularly for persons with advanced disease who are at risk for more severe verbal fluency impairment. HIV-infected individuals with deficits in verbal fluency, as well as in other tests with strong processing speed and executive function demands, may be more likely to experience poor health-related quality of life and problems with instrumental activities of daily living (IADLs), such as treatment adherence, automobile driving, and employment (e.g., Heaton et al., 2004). The development of novel verbal fluency tasks may be worthwhile in this regard; for example, action (verb) fluency, which was recently developed based on the hypothesized dissociation between noun and verb processing, may be a particularly useful predictor of IADLs in HIV. In fact, action fluency may be more sensitive to HIV-associated neurocognitive impairment (Woods et al., 2005) and provide incremental ecological validity in predicting IADL dysfunction relative to traditional letter and animal fluency tasks (Woods et al., 2006). Additional research is needed to more comprehensively examine the functional implications of HIV-associated deficits on both traditional and novel verbal fluency tasks, as well as the efficacy and ecological relevance of targeted pharmacological and neuropsychological remediation strategies.

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