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HIV-associated Deficits in Action (Verb) Generation May Reflect Astrocytosis

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Abstract

Commensurate with the hypothesized neural dissociation between verb and noun generation, research in HIV infection shows that, relative to noun fluency, action (verb) fluency is disproportionately impaired, more strongly related to executive dysfunction, and more sensitive to declines in everyday functioning. However, whether the neurobiological correlates of HIV-associated deficits in verb and noun generation are separable have not heretofore been investigated. The present study examined the biomarker correlates of action and noun fluency in 74 participants with HIV infection. Biomarkers of viral burden, neuroaxonal damage, macrophage activation, neuroprotection, inflammation, and astrocytosis were measured in plasma and cerebrospinal fluid (CSF). Deficits in action, but not noun generation, were significantly associated with higher CSF levels of S100 β , a marker of astrocyte activation, even after controlling for antiretroviral therapy, current immune compromise, and general cognitive impairment. Concurrent validity for the frontal systems hypothesis of verb generation was provided by post-hoc analyses demonstrating that S100 β was also associated with measures of executive functions, but not semantic memory or psychomotor speed. Overall, these findings suggest that HIV-associated impairment in action fluency, and executive dysfunction more generally, may reflect astrocytosis (i.e., elevated S100 β). Complementing the literature in HIV and other clinical populations with frontal systems involvement, these data also support the possible neurobiological dissociation of noun and verb generation.

Keywords

Human immunodeficiency virus; cognitive processes; verbal fluency; verbs; frontal lobe

The human immunodeficiency virus (HIV) is capable of crossing the blood-brain barrier and altering the structure and function of several neural systems, most notably the fronto-striato-thalamo-cortical loops (e.g., Ellis et al., 2007). Although HIV does not productively infect neurons, it can replicate in brain parenchyma (i.e., macrophages and microglia) and can lead to neuropathological changes (e.g., synaptodendritic injury and astrogliosis) in approximately 50% of cases (Budka, 2005). The mechanisms of these HIV-associated neuropathologies are not fully understood, but may involve both direct (e.g., viral proteins, such as Tat) and indirect (e.g., inflammatory chemokines and astrogliosis) factors (González-Scarano & Martín-García, 2005). Neural injury can lead to the development of HIV-associated neurocognitive disorders, which are estimated to occur in 30-50% of persons living with HIV infection (Antinori et al., 2007). The neurobehavioral profile of HIV-associated neurocognitive disorders most often involves deficits in the areas of executive functions, episodic memory, psychomotor skills, and verbal fluency (Reger et al., 2002).

Recent forays into verbal fluency paradigms have suggested that HIV infection is particularly associated with deficits in action (verb) fluency (Cysique et al., 2008; Woods et al., 2005a), which requires an individual to generate as many verbs (i.e., “things... that people do”) as possible in 60 seconds. Extending research in Parkinson's disease (e.g., Piatt et al., 1999b) and other conditions with frontal systems involvement (e.g., Friedreich's ataxia; de Nóbrega et al., 2007), HIV-associated action fluency deficits may be more prevalent and severe than impairment in noun (i.e., animal) fluency (Woods et al., 2005a). In fact, research in healthy adults has demonstrated a dissociation between the neural systems responsible for generating nouns and verbs (Damasio & Tranel, 1993). More specifically, considerable research now supports the notion that the frontostriatal loops are critical for retrieving verbs, a process that has been linked to executive functions and motor planning (Piatt et al., 1999b). In contrast, the temporoparietal region and associated semantic memory networks are more strongly linked to noun generation (Cappa & Perani, 2003). Given the relative prominence of frontostriatal systems pathology in HIV, the disproportionate impairment in action versus animal fluency is commensurate with the hypothesized dissociation between verb and noun generation. In addition, the underlying cognitive mechanisms that have been associated with action and noun fluency further support a possible dissociation. Specifically, HIV-associated action fluency deficits are more strongly associated with motor incoordination and executive dysfunction than are the relatively milder deficits in noun fluency (Woods et al., 2005b). Of clinical relevance, action fluency is also more sensitive to HIV-associated declines in the independent performance of instrumental activities of daily living than are measures of noun and letter fluency (IADLs; Woods et al., 2006). In summary, action (verb) generation may be dissociable from noun (animal) generation in HIV infection, as evidenced by its relatively stronger relationships with serostatus, cognitive markers, and everyday functioning outcomes.

To our knowledge, however, the possible neural correlates of verb and noun generation deficits in HIV infection have not yet been explored (e.g., biomarkers of central nervous system injury). Indeed, although the current literature provides cognitive evidence in support of the observed noun-verb dissociation in HIV, no prior studies have linked action fluency directly to biological markers of neural injury or examined whether a neurobiological dissociation may underlie the differential HIV-associated impairment in action versus noun fluency. Accordingly, the primary aim of this study was to examine the neural dissociability of HIV-associated deficits in action and noun fluency using biomarkers representing the most common pathways of neural injury in HIV infection. A subsequent aim was to examine the specificity and concurrent validity of these neurobiological associations using conceptually related tasks of executive functions, psychomotor speed, and semantic memory.

Method

Participants

Participants included 74 individuals with HIV infection who provided both plasma and CSF samples at the UCSD HIV Neurobehavioral Research Center. Individuals with histories of severe psychiatric disorders (e.g., psychosis), substance dependence within 6 months of evaluation, or neurological conditions known to adversely impact cognitive functions (e.g., seizure disorders, stroke, head injury with loss of consciousness in excess of 30 minutes) were excluded. The demographic, neuropsychological, HIV disease, and psychiatric characteristics of this sample are displayed in Table 1. No participant met diagnostic criteria for HIV-associated dementia, but 22 individuals (29.7%) met criteria for other HIV-associated neurocognitive disorders (HAND; Antinori et al., 2007), including 16 persons (21.6%) with Asymptomatic Neurocognitive Impairment (ANI) and 6 persons (8.1%) with Minor Neurocognitive Disorder (MND).

Procedure

Neuropsychological evaluation—After providing written, informed consent, each participant was administered a comprehensive neuropsychological evaluation, which included standardized measures of action and noun (i.e., animal) fluency. On the action fluency task, participants were asked to rapidly generate as many verbs (i.e., “things...that people do”) as possible within 60 seconds (see Piatt et al., 1999a and Woods et al., 2005b for further details). In brief, participants were instructed to generate only single verbs and to avoid repeating earlier generated verbs with a different ending (e.g., eat, eating, and eaten). For the animal fluency task, participants were asked to rapidly generate as many animals as they could within 60 seconds (see Benton et al., 1983). Participants were instructed not to use proper nouns (e.g., Snoopy) or to generate the same word with a different ending (e.g., dog, dogs). Raw scores on both fluency tasks were converted to demographically-adjusted T-scores ($M = 50$, $SD = 10$) using published normative standards (Heaton et al., 2004; Woods et al., 2005b).

To evaluate the specificity and concurrent validity of the action fluency results, we also conducted analyses of other neuropsychological domains from the larger test battery. To minimize our risk of Type I error, we only examined domains that are conceptually linked to verb generation (i.e., executive functions, psychomotor speed, and semantic memory) and limited those analyses to biomarkers that were significantly related to action fluency. Tests of *psychomotor speed* included Trail Making Test, Part A (TMT; Reitan & Wolfson, 1985), total execution time from the Tower of London – Drexel (ToL-DX; Culbertson & Zillmer, 2001), and total scores from the Grooved Pegboard test (Kløve, 1963). Measures of *executive functions* included TMT Part B-A, Digit Span backward from the Wechsler Adult Intelligence Scale – Third Edition (The Psychological Corporation, 1997), and the ToL-DX rule violations score. Finally, tests in the *semantic memory* domain included the total scores from the Boston Naming Test (BNT; Goodglass, Kaplan, & Barresi, 2001) and the Famous Faces subtest of the Kaufman Adult and Adolescent Intelligence Test (KAIT; Kaufman & Kaufman, 1993). Raw scores were converted to population-based z-scores and then averaged within each ability area to create summary z-scores for use in the regression analyses.

Biomarkers—Participants also underwent a standardized neuromedical evaluation, which included venipuncture and lumbar puncture. A panel of biomarkers was measured in both plasma and CSF when possible and included HIV RNA (viral burden), total tau (neuroaxonal damage), monocyte chemoattractant protein-1 (MCP-1; macrophage activation), erythropoietin (EPO; a neuroprotectant), interferon induced protein-10 (IP-10; innate immunity), and S100 β (S100 β ; astrocytosis). Since neuronal and astrocyte proteins are present primarily within the nervous system, total tau and S100 β were measured only in CSF. HIV

RNA was quantified by RT-PCR (Roche Amplicor®, lower limit of quantitation 50 copies/mL). Other biomarkers were measured using commercial enzyme-linked immunosorbent assays (Quantikine; R&D Systems, Minneapolis, MN).

Statistical Analyses—Exploratory correlational analyses were conducted using Spearman's rho tests due to non-normal distributions of the data (Shapiro-Wilk W test, $p_s < 0.05$). Next, standard least regression analyses were used to assess the relative associations between the biomarkers and action and animal fluency. Given the necessarily exploratory nature of this study, several steps were taken to reduce our risk of Type I error. First, we limited the panel of biomarkers *a priori* to include only single representatives from each of the major neuropathogenic pathways of HIV infection (González-Scarano & Martín-García, 2005). Second, we employed a critical alpha level of .01 for the initial series of exploratory correlational analyses between the various biomarkers and action and animal fluency. Third, only biomarkers that significantly correlated with action and animal fluency at the univariate level were included in a follow-up linear regression that also statistically controlled for current antiretroviral treatment (i.e., current cART), immune status (i.e., current CD4 lymphocyte count), and global cognitive functioning (i.e., HDS total score). Although the study variables were slightly non-normal, the distributions of the residuals from the linear regression evidenced no serious departures from normality and were therefore deemed appropriate.

Results

A paired-sample Wilcoxon signed rank test revealed significantly lower performance on action fluency as compared to animal fluency ($N = 74$; $p < 0.05$, Cohen's $d = -0.21$). These data are displayed in Table 1. The results of the correlational analyses between action and noun fluency and the panel of HIV biomarkers are displayed in Table 2. These analyses revealed that worse performance on action fluency (i.e., lower T-scores) was significantly associated with higher levels of S100 β in CSF (Spearman's rho = -0.30 ; $p = 0.009$). A trend-level association was found between poorer animal fluency and higher levels of Tau (Spearman's rho = -0.27 ; $p = 0.022$). No other biomarker was significantly correlated with action or animal fluency (all $p_s > 0.05$). Next, a standard least squares regression revealed that S100 β remained a significant ($p = 0.007$) independent predictor of action fluency, even when cART, current CD4 count, and the HDS total score were included in the statistical model (adjusted $R^2 = 0.14$, $p = 0.009$). However, either Tau or S100 β was significantly associated with animal fluency when examined individually in a linear regression model that included cART, current CD4 count, and the HDS total score (both adjusted $R^2 = 0.04$, $p = 0.191$, and adjusted $R^2 = 0.04$, $p = 0.191$). Identical regressions with S100 β , cART, CD4 count, and the HDS were conducted to predict the executive, psychomotor speed and semantic memory domain scores. Results showed that S100 β was a unique predictor of executive functions (S100 β $p = 0.004$; adjusted $R^2 = 0.17$, overall model $p = 0.003$). In contrast, S100 β was not uniquely predictive of either psychomotor speed (S100 β $p = 0.75$; adjusted $R^2 = 0.17$, overall model $p = 0.004$) or semantic memory (S100 β $p = 0.06$; adjusted $R^2 = 0.13$, overall model $p = 0.014$), despite the fact that the overall regression models were significant. Including lifetime major depressive disorder and substance use disorders in the statistical models did not alter the results of any of the above-described regression analyses.

Discussion

The present study provides the first insights into the possible neuropathogenesis of HIV-associated impairment in verb generation. Among a panel of biomarkers reflecting the primary mechanisms of neural injury in HIV infection (e.g., neuroaxonal injury, macrophage activation, neuroprotective factors, and neuroinflammation), only higher levels of S100 β (i.e., a marker of astrocytosis) were significantly associated with deficits in action (verb) fluency. Follow-up

multiple regression analyses demonstrated that the robustness of this small-to-medium association between S100 β and action fluency was independent of current cART, immune status, and general cognitive status. As such, these data suggest that elevated S100 β , which is a calcium binding protein that is expressed almost exclusively by astrocytes in the brain and is a marker of astrocytosis (Gonçalves et al., 2008), may play a critical role in HIV-associated impairment in verb generation.

Once believed to function largely as support cells, astroglia are now being recognized as playing a critical, interactive role in the information processing functions that have long been ascribed exclusively to neurons (Seth & Koul, 2008). Astrocytosis (i.e., a proliferation of astrocytes) is a commonly recognized pathological sequelae of HIV infection (e.g., Zhou et al., 2006) and may be associated with more rapid progression of HIV-associated neurocognitive disorders (Pemberton & Brew, 2001). Although HIV does not productively infect astrocytes, HIV proteins and macrophage activation can lead to astrocytosis, which promotes neuronal damage by facilitating monocyte trafficking across the blood-brain barrier, upregulating inflammatory chemokines, altering brain homeostasis (e.g., reducing glutamate-glutamine shuttling, leading to accumulation of neurotoxic glutamate), and interfering with neural repair processes (González-Scarano & Martín-García, 2005; Zhou et al., 2004). Although astrocytes are plentiful and widely distributed throughout brain parenchyma, HIV-associated astrocytosis (i.e., an increase in the number and size of astrocytes) is most frequently observed in subcortical white matter (Vanzani et al., 2006). Such data converge with the hypothesis that rapid verb generation is strongly, although not exclusively (e.g., Ostberg et al., 2007), related to frontostriatal systems pathophysiology (Damasio & Tranel, 1993).

This study also lends further support to the possible dissociation between action (verb) and noun fluency in HIV disease by providing preliminary evidence that the neural mechanisms of impairment are separable. Specifically, action (verb), but not animal (noun) fluency was associated with a biomarker of astrocytosis (i.e., elevated S100 β). These findings extend prior research on the dissociation between verb and noun fluency, showing that, as compared to animal (noun) fluency, action (verb) fluency is disproportionately impaired in HIV infection (Woods et al., 2005a), demonstrates stronger HIV-associated impairment in executive functions, working memory, and processing speed (Woods et al., 2005b), and is more sensitive to declines in everyday functioning (Woods et al., 2006). Consistent with this prior HIV research, as well as that in other conditions with frontal systems involvement (e.g., Piatt et al., 1999), participants in the present study scored significantly lower on action versus noun fluency (even though both tasks were analyzed using T-scores that were adjusted for demographics).

In addition, the observed neural dissociation between impairment in verb and noun fluency in HIV is commensurate with the prominent role of frontostriatal systems in the neurobehavioral pathogenesis of HIV infection (Ellis et al., 2007) and verb processing (Damasio & Tranel, 1993). Concurrent validity for this hypothesis was provided by post-hoc analyses demonstrating that S100 β was associated with measures of executive dysfunction, but not with tests of semantic memory or psychomotor speed. These results provide strong evidence that the association between S100 β and action fluency was not a chance finding, especially when considered alongside the various methodological and statistical protections against Type I error that were described above in detail. Furthermore, this evidence of concurrent validity and specificity argues against the alternate hypothesis that the action fluency finding is an artifact of general cognitive impairment, particularly considering the non-significant relationship between S100 β and animal fluency and the inclusion of the HIV Dementia Scale in the statistical models. Thus, the association between astrocytosis and action fluency impairment may reflect a broader deficit in executive functions that are predominately mediated by fronto-striato-thalamo-cortical loops (e.g., Alexander & Stuss, 2000). Further supporting this interpretation, action fluency relates strongly to measures of executive functions in healthy

adults (e.g., Woods et al., 2005b), as well as in individuals with HIV infection (Woods et al., 2005a) and Parkinson's disease (e.g., Piatt et al., 1999a). It is nevertheless important to note that the lack of association between S100 β and semantic memory and processing speed may also be an artifact of the tasks that were available to measure these constructs in the current study. In particular, our assessment of processing speed would have benefited from the inclusion of more traditional tasks commonly used in neuroAIDS research, such as the WAIS-III Processing Speed Index.

Despite the intriguing nature of these preliminary data, they must be interpreted in the context of the limitations of our study methodology. For example, the current panel of biomarkers does not afford adequate anatomical specificity. Indeed, HIV-infected persons may show astrogliosis (i.e., GFAP+ cells) in the hippocampus and entorhinal cortex, albeit to a lesser extent than deep white matter (Vanzani et al., 2006). We therefore cannot rule out the possible contribution of temporolimbic systems, as these networks also play an important role in word generation (Tranel et al., 2001) and are susceptible to HIV-associated neuropathologies, including astrogliosis (e.g., Vanzani et al., 2006). Future research using structural (e.g., volumetric and diffusion tensor) and functional neuroimaging (e.g., blood oxygen level dependent functional MRI) may more clearly delineate the precise neural systems involved in HIV-associated action and noun fluency impairment. Clinico-pathological studies may also be useful in further clarifying the role of astrogliosis and frontostriatal systems in the expression of verb generation deficits in HIV disease. There are also limitations to the interpretation of CSF elevations in S100 β , which despite being a well-validated marker of astrogliosis may also reflect damage to oligodendrocytes, microglia, or cholinergic neurons (see Gonçalves et al., 2008). Furthermore, action fluency was not associated with IP-10 or MCP-1, each of which may be considered as markers of astrogliosis in HIV (González-Scarano & Martín-García, 2005); however, these two biomarkers are arguably less specific to astrogliosis than S100 β . Since these data are cross-sectional and derived from a relatively immunocompetent, non-demented sample with a low prevalence of HIV-associated neurocognitive disorders, the reliability and generalizability of these findings remain to be determined. Examination of the predictive power of S100 β as a marker of incident declines in action (verb) fluency (e.g., Pemberton & Brew, 2001) may be useful in identifying individuals in need of targeted therapies, especially considering that impairment on action fluency has been associated with a five-fold risk of IADL dependence in HIV (Woods et al., 2006).

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Table 1
Participants' Demographic, Cognitive, HIV Disease, and Psychiatric Characteristics

Variable	Value (N = 74)
Demographics	
Age	45.1 (9.0)
Education	13.5 (2.7)
Sex (% female)	12.2%
Ethnicity (% Caucasian)	63.5%
Neuropsychological	
Action Fluency (T-score) ^a	45.5 (39.0, 56.0)
Animal Fluency (T-score) ^a	49.0 (43.0, 57.3)
WTAR Verbal IQ	105.9 (12.6)
HIV Dementia Scale (range = 0 – 16) ^a	16.0 (14.0, 16.0)
HAND (%)	29.7%
HIV Disease and Treatment	
Current CD4 lymphocyte count ^a	533.0 (361.0, 826.3)
Nadir CD4 lymphocyte count ^a	217.5 (46.5, 360.3)
Detectable plasma HIV RNA (%)	39.2%
Detectable CSF HIV RNA (%)	18.9%
AIDS (%)	47.2%
cART (%)	74.3%
Psychiatric	
Lifetime Major Depressive Disorder (%)	58.9%
Lifetime Generalized Anxiety Disorder (%)	9.7%
Lifetime Substance Dependence (%)	54.8%

Note. Data represent means and standard deviations or population percentages unless otherwise indicated.

^aData are presented as the median value, with the interquartile range in parentheses. HAND = HIV-associated neurocognitive disorder (Antinori et al., 2007). WTAR = Wechsler Test of Adult Reading. CSF = cerebrospinal fluid. AIDS = acquired immunodeficiency syndrome. cART = combination antiretroviral therapy.

Table 2
Correlations Between Action Fluency and Biomarkers of HIV Disease (N = 74)

HIV Biomarkers	Actions	p	Nouns	p
Plasma Biomarkers				
CD4 lymphocyte count (c/ml)	-0.17	0.16	-0.07	0.55
HIV RNA (log 10)	0.03	0.83	-0.05	0.65
Erythropoietin (EPO)	-0.11	0.37	-0.02	0.87
Interferon induced protein (IP-10)	0.07	0.55	0.18	0.14
Monocyte chemoattractant protein-1 (MCP-1)	0.06	0.63	-0.20	0.09
CSF Biomarkers				
HIV RNA (log 10)	-0.04	0.75	-0.04	0.75
Erythropoietin (EPO)	0.05	0.70	0.11	0.34
Interferon induced protein (IP-10)	-0.18	0.13	-0.02	0.90
Monocyte chemoattractant protein-1 (MCP-1)	0.19	0.10	-0.11	0.34
Tau (total)	-0.05	0.65	-0.27 [†]	0.02
S100β	-0.30 ^{**}	0.009	-0.20	0.09

Note. Data represents Spearman's rho coefficients

[†] $p < 0.05$,

^{**} $p < 0.01$