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Basal ganglia structures differentially contribute to verbal fluency: Evidence from Human Immunodeficiency Virus (HIV)-infected adults

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Abstract

Background—The basal ganglia (BG) are involved in executive language functions (i.e., verbal fluency) through their connections with cortical structures. The caudate and putamen receive separate inputs from prefrontal and premotor cortices, and may differentially contribute to verbal fluency performance. We examined BG integrity in relation to lexicosemantic verbal fluency performance among older HIV infected adults.

Method—20 older (50+ years) HIV+ adults underwent MRI and were administered measures of semantic and phonemic fluency. BG (caudate, putamen) regions of interest were extracted.

Results—Performance on phonemic *word generation* significantly predicted caudate volume, whereas performance on phonemic *switching* predicted putamen volume.

Conclusions—These findings suggest a double dissociation of BG involvement in verbal fluency tasks with the caudate subserving word generation and the putamen associated with switching. As such, verbal fluency tasks appear to be selective to BG function.

Keywords

Basal ganglia; Verbal fluency; Magnetic resonance imaging; Human Immunodeficiency Virus; Neuropsychology; Aging

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Conflict of interest

None of the authors have any financial relationships that could be interpreted as a conflict of interest.

1. Introduction

The caudate nucleus (CN) and putamen are primary structures within the basal ganglia-thalamo-cortical loop that synthesize information from widespread cortical regions (Alexander, Del Long, & Strick, 1986; Mega & Cummings, 1994). The BG is implicated in higher-level cognitive functions via five parallel frontal-subcortical circuits (i.e., skeletomotor, oculomotor, dorsolateral prefrontal, orbitofrontal, and anterior cingulate) (Alexander et al., 1986; Cummings, 1993). In primate models, retrograde labeling of neurons have demonstrated that 1/3 of BG output is directed to prefrontal areas (i.e., BA regions 9, 46, and lateral aspect of 12), including multiple areas of the prefrontal cortex (PFC) that are critical to functions such as language production (Crescentini, Lunardelli, Mussoni, Zadini, & Shallice, 2008). Understanding the neuroanatomical correlates of selective language functions is the first step to improving the assessment and identification of language disturbances that may arise from neurological insult to the basal ganglia (BG), or from diseases that preferentially target BG functions (e.g., Human Immunodeficiency Virus-Type 1 [HIV-1], Huntington's, and Parkinson's).

1.1. Dissociable neural systems and executive-mediated language task performance

Verbal fluency measures the efficiency of lexical access and is recognized as an important component of the executive system (Fisk & Sharp, 2004; Lezak, Howieson, & Loring, 2004). Phonemic word fluency requires the participant to retrieve words that begin with a particular phoneme or letter (e.g., F), while semantic word fluency requires the participant to name words that belong to a particular category (e.g., Animals). Successful performance on word fluency tasks requires executive functions such as inhibiting words that do not conform to task rules (Anderson, Zink, Xiong, & Gendleman, 2002).

It is generally thought that word generation within a specified phonemic or semantic category relies upon verbal memory storage; whereas switching relies more upon frontally mediated processes such as strategic search processes, cognitive flexibility, and shifting (Troyer, Moscovitch, & Winocur, 1997). Underlying neural systems commonly identified in verbal fluency performance include the left inferior frontal gyrus, anterior cingulate cortex, and supramarginal gyrus (Hirshorn & Thompson-Schill, 2006; Paulesu et al., 1997; Phelps, Hyder, Blamire, & Shulman, 1997).

Cognitive neuroscience has provided evidence that the lateral PFC is important for higher-level cognitive tasks that involve retrieval and maintenance of task rules and representations. An fMRI study examining the role of PFC in executive control identified anatomically separable sub-regions within lateral PFC. Dorsolateral regions were involved in monitoring and selecting goal-relevant representations, whereas ventrolateral regions were involved in maintaining these representations (Wagner, Pare-Blagoev, Clark, & Poldrak, 2001).

In contrast, the medial PFC is important for task switching (Crone, Wendelken, Donohue, & Bunge, 2006). The medial PFC includes pre-supplementary motor area (pre-SMA), supplementary motor area (SMA), cingulate motor area, and superior parietal cortex that have been activated during task-switching (DiGirolamo et al., 2001; Paus, 2001; Rushworth, Hadland, Paus, & Sipila, 2002; Wager, Jonides, & Reading, 2004). As it relates to verbal fluency performance, word generation requires that the individual maintain a cognitive phoneme or category representation while retrieving novel words. Explicit task switching requires that the individual switch between phonemes (e.g., F & S) or categories (e.g., Animals & Things People do).

The caudate and putamen receive differential projections from the PFC. Projections from the lateral PFC terminate at the central strip of the caudate (Fuster, 2008). Primary putaminal

projections involve the supplementary and primary motor cortex. During executive-mediated language tasks, BG structures have also demonstrated activation during word-generation and task switching (Fu et al., 2002), suggesting that the BG and prefrontal areas work in tandem while performing executive-mediated language tasks.

1.2. Basal ganglia dysfunction and verbal fluency

Studies using voxel-based morphometry have found atrophy of the BG among patients with HIV-1 infection (Aylward et al., 1995; Küper et al., 2011), and abnormalities of the CNS dopaminergic system, found particularly in the BG of HIV-1 infected individuals have been associated with deficits in neurocognitive functions abnormalities (Berger & Arendt, 2000; Kumar, Ownby, Waldrop-Valverde, Fernandez, & Kumar, 2011). While general language functions (i.e., expressive, receptive ability) appear to remain preserved in HIV, deficits in verbal fluency are observed in approximately 40% of patients (Rippeth et al., 2004). Hence, the HIV-1 infected population may provide critical insights into the underlying neural correlates of selective aspects of verbal fluency performance. Using structural neuroimaging, Hestad et al. (1993) found that poorer verbal phonemic fluency scores were associated with reduced caudate volume among patients with HIV-associated dementia. Nevertheless, it is unclear whether the association between caudate volume and verbal fluency was independent of global neuropsychological functioning. A meta-analysis of 68 studies with a total of 4644 participants with Parkinson's disease found that both phonemic and semantic fluency were moderately impaired relative to healthy controls (Henry & Crawford, 2004). Among Huntington's disease and Parkinson's disease patients, verbal fluency abnormalities have been associated with degeneration of the caudate nucleus (Benke, Delazer, Bartha, & Auer, 2003; Lawrence, Sahakian, & Robbins, 1998). A neurology case study of a patient with primary putaminal damage demonstrated difficulties switching between subcategories on fluency tasks, but not generating words within subcategories (Troyer, Black, Armilio, & Moscovitch, 2004). Although these studies utilized different patient populations, results were consistent with our knowledge of BG and PFC anatomy and function, thereby suggesting that separate aspects of fluency performance involve differential BG pathways.

The purpose of this study was to use structural MRI to examine the association between verbal fluency performance and basal ganglia integrity among a convenience sample of HIV infected individuals. We hypothesized that caudate and putamen volumes would be differentially associated with aspects of phonemic and semantic word generation such that performance on word generation would be associated with caudate volume, whereas phonemic and semantic switching would be associated with putaminal volume. We also expected that separate aspects of verbal fluency performance would continue to predict basal ganglia integrity after controlling for neuropsychological performance given its sensitivity to frontal-striatal dysfunction. To our knowledge, this is the first study to assess whether the caudate and putamen are differentially involved in verbal fluency performance in an HIV-positive population.

2. Materials and methods

UCLA and VA Institutional Review Board (IRB) approval was obtained prior to implementing study procedures. Written informed consent was obtained from all participants in the study.

2.1. Participants

This was a convenience sample of 20 HIV+ adults (age $M = 53.25$, $SD = 4.2$ years; education $M = 13.5$, $SD = 2.0$ years) who were recruited for neuroimaging (MRI) from an

existing pool of HIV+ participants enrolled in a large project examining the interaction between advancing age and HIV on neurocognitive and functional outcomes. Prior to study entry, participants received explanation of study procedures and provided informed consent.

Inclusion criteria—(1) HIV positive – Status confirmed based upon serologic testing for HIV antibody [screening ELISA, confirmed by Western blot if positive]; (2) willing and able to comply with study procedures; (3) willing and able to provide written informed consent; (4) demonstrated at least 6th grade English reading level.

Exclusionary criteria—(1) Unable to provide informed consent; (2) presented with neurologic disorder, such as moderate-severe head injury, seizure disorder, demyelinating illness, or CNS neoplasm, or have history of an HIV-associated CNS opportunistic infection (e.g., toxoplasmosis) or neoplasm; (3) presented with a current psychotic spectrum disorder or mood disorder; (4) presented with substance abuse/dependence within the past year, or (5) if MRI was contraindicated (e.g., due to claustrophobia or metallic inclusions). Thirty participants were screened, of which 10 were excluded due to current drug use ($n = 3$), metallic inclusions ($n = 5$), and claustrophobia ($n = 2$).

2.2. MRI acquisition

Structural MRI images were obtained using a 1.5 T Magnetom Sonata scanner (Siemens AG, Erlangen, Germany), using a single-shot, echo-planar acquisition sequence (TR/TE = 10,000/88 ms; four $b = 0/b = 750$ s/mm²; 4 averages; matrix = 128 × 128, 256 mm × 256 mm field of view; slice thickness = 2 mm). The protocol included an initial multiplanar scout, axial-oblique, proton density-/T2-weighted double spin-echo, and sagittal whole-brain high-resolution T1-weighted MRI sequences. Scans planes were oriented perpendicular to the AC-PC line.

2.3. ROI segmentation

Basal ganglia (caudate, putamen) regions of interest (ROIs) (see Fig. 1) were extracted from the T1 weighted scans using the UCLA Laboratory of Neuroimaging (LONI) BrainParser. The LONI Brain Parser software is an automated learning-based algorithm that efficiently performs whole brain image segmentation to parse an input MRI image into 56 anatomical structures of interest (see Tu et al., 2008) for methodological review) (Table 1).

2.4. Neuropsychological assessment

Participants were administered a standard neuropsychological (NP) battery (see Table 2 for description). Raw scores were converted to demographically corrected *T* scores. Global neuropsychological performance represented average performance across cognitive domains of attention, information processing speed, learning and memory, motor functioning, and executive functioning (not including verbal fluency).

2.5. Verbal fluency

Verbal fluency was assessed using the Controlled Oral Word Association Test (COWAT; Benton, 1983), which requires subjects to produce words beginning with a particular letter of the alphabet (F, A, S), in three respective 60-s trials. In semantic/category fluency, participants are asked to generate words belonging to a specific category in a 60-s trial. Switching abilities have been suggested to contribute to verbal fluency performances (Troyer et al., 1997), therefore, we employed an experimental manipulation, forced switching, that was initiated after standard word fluency trials were completed. In the forced switching trials, participants were asked to switch between specified categories following the generation of each word (e.g., ‘animals’ and ‘F’ & ‘S’).

2.6. Data analysis

2.6.1. Demographics—Bivariate correlations were used to examine relationships between demographic/disease related variables (age, education, current CD4 count, nadir CD4 count) and the primary study variables of verbal fluency performance scores, global neuropsychological performance score, and BG volume. We used *t*-test and Analysis of Variance (ANOVA) to examine whether ethnicity and presence of viral load accounted for differences in verbal fluency performance and BG volume.

2.6.2. BG volume data—Caudate and putamen values were corrected for whole brain volume. Distributions of volumetric data, global neuropsychological performance (NP) scores, and verbal fluency scores were inspected to ensure that statistical assumptions were met. Multiple regression analyses were then used to examine whether word generation and correct switches (for both phonemic and semantic fluency conditions) predicted basal ganglia volume after controlling for performance on other NP measures that represent frontal–striatal function (see Section 3.1). Regression models included frontal–striatal NP performance in the first step and verbal fluency performance data in the second step. We examined the statistical significance of change in R^2 between models to determine the additive predictive value of verbal fluency performance.

3. Results

3.1. Demographics and primary study variables

Demographic and disease related variables such as age, education, ethnicity, recent CD4 count, and viral load were not significantly related to verbal fluency performance or BG volume. Nadir CD4 count was significantly correlated with total basal ganglia volume, $r(18) = .452$, $p = .032$. Global neuropsychological performance (NP) and total basal ganglia volume were significantly correlated $r(19) = .759$, $p < .0001$. In order to determine whether verbal fluency was uniquely sensitive to striatal dysfunction, we decided to statistically control for performance on Global NP.

3.2. Verbal fluency variables and BG volume

Considering that language is typically lateralized to the left-hemisphere for right-handed individuals, analysis of verbal fluency predictors were conducted for both right and left hemispheres. After controlling for frontal–striatal function, phonemic ($\Delta r^2 = .16$, $p = .02$) word generation significantly predicted left caudate volume, but not right caudate volume ($\Delta r^2 = .04$, $p = .39$). Semantic word generation did not predict left ($\Delta r^2 = .08$, $p = .18$) or right caudate ($\Delta r^2 = .001$, $p = .91$) volume. Phonemic and semantic correct task switches were not predictive of left or right caudate volume.

Phonemic task switching significantly predicted left putamen volume ($\Delta r^2 = .26$, $p = .03$), but not left caudate volume ($\Delta r^2 = .02$, $p = .53$). Semantic task switching was not predictive of left putamen volume ($\Delta r^2 = .02$, $p = .52$). Phonemic and semantic task switching performances were not predictive of right putamen or right caudate volumes. Please see Table 3 for additional detail.

4. Discussion

In this study, we examined the utility of executive mediated language tasks (i.e., verbal fluency) as predictors of basal ganglia (BG) integrity among a sample of HIV-infected patients. In general, our findings support the role of BG involvement in verbal fluency, which is consistent with prior studies suggesting that subcortical structures work in concert with frontal lobe during performance of these tasks. More importantly, however, phonemic

verbal fluency performance predicted BG integrity above and beyond other NP measures that are linked to BG function. This suggests the additive utility of such measures when evaluating basal ganglia dysfunction in HIV, and perhaps among other extrapyramidal conditions with prominent basal ganglia dysfunction (e.g., Parkinson's disease). Despite functional similarities between the caudate and putamen, these findings suggest a double dissociation such that the caudate (word generation/retrieval) and putamen (switching) play different, but complementary roles in verbal fluency. Right-sided BG did not predict executive-language function performances, which is consistent with prior fMRI studies of language lateralization (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 2002).

4.1. Caudate volume and word generation

As hypothesized, we found that caudate volume was associated with phonemic word generation, but not with phonemic correct switches. This is consistent with studies associating tasks of verbal fluency and caudate volume in a variety of populations (Beglinger et al., 2005; Levitt et al., 2002; Rosas et al., 2008) and in studies assessing the relationship between caudate lesions and verbal fluency (Petty, Bonner, Mouratoglou, & Silverman, 1996). These findings are also consistent with those of Hestad et al. (1993) that implicated the caudate in verbal fluency and extend their work by demonstrating that caudate volume is associated with both phonemic and semantic word generation independent of frontal striatal performance.

The lack of association between task switching and caudate volume suggests that the caudate may be primarily involved in regulating frontally mediated behaviors such as initiating goal-directed behavior and maintaining task representations. This is consistent with our understanding of the neuroanatomical connections between the caudate and lateral PFC, which has repeatedly demonstrated PFC involvement in executive processes. Although the lack of association may initially appear to contradict studies linking task-switching difficulties with the caudate (Cools, Clark, & Robbins, 2004; Gu et al., 2008), we believe that discrepancies in results can best be explained by the type of neuroimaging method employed in our study. Many studies linking the caudate to task switching have employed fMRI, whereas our study used MRI volumetric data to predict task performance. As such, it is possible that functional relationships exist between the caudate and task switching; however, putaminal volume may actually be more predictive of optimal performance in task switching. Perhaps hyperactivation of the caudate is a marker of putaminal dysfunction and vice versa, as these structures are closely linked and may compensate for one another in degenerative diseases.

4.2. Putaminal volume and correct switches

In contrast to caudate findings, the putamen was associated with phonemic and semantic task switching, but not with word generation. Prior work has also demonstrated that putaminal damage results in task switching difficulties (Troyer et al., 2004) and hypoactivation of the putamen during attentional switching tasks (Kübler, Murphy, Garavan, 2005).

It should be noted, however, that in the study conducted by Troyer et al. (2004) switching deficits were only found on a task of phonemic fluency (as opposed to semantic). Methodological differences between the current study and the study conducted by Troyer and colleagues likely explain the differences observed. In the current study, we found associations between putamen volume and explicit switching (as opposed to the implicit switching measure used in by Troyer and colleagues). Hence, our results may only generalize to performance on explicit switching measures.

4.3. Basal ganglia dissociation and verbal fluency

The dissociation found in the current study may best be understood in the context of the cognitive underpinnings of switching in particular and the differential interconnections from the PFC to the caudate and putamen. Cognitive switching requires two separate processes regulated differentially by the PFC (Crone et al., 2006). One aspect of switching consists of actively retrieving or selecting currently relevant cues (rule representation), whereas the second aspect requires the act of overriding previously relevant stimulus responses (rule reconfiguration). As mentioned previously, the caudate and the putamen are differentially connected to the frontal lobes. The caudate connects to the frontal lobes primarily through the dorsolateral prefrontal and lateral orbitofrontal circuitry, whereas the putamen is connected primarily through the motor cortices (Cummings, 1993). On tasks of verbal fluency, words generation may be akin to rule representation whereas switching may be more akin to rule reconfiguration. Given the considerable amount of task-related overlap in word generation and switching, it is not surprising that studies have found that implicit switching largely accounts for the verbal fluency deficits in HIV (Iudicello et al., 2008; Milliken, Trepanier, & Rourke, 2004; Woods et al., 2004).

Although we expected to find a similar dissociation with tasks of semantic fluency, our null findings suggest that basal ganglia structures play a less important role in semantic fluency compared to phonemic fluency. Among Alzheimer's patients, impairments in semantic fluency are often linked to a breakdown of semantic knowledge (Chan, Butters, Salmon, 1997; Martin, Wiggs, Lalonde, & Mack, 1994). Furthermore, semantic fluency involves a more widely distributed neural system than phonemic fluency (Wallesch, Curio, Galazky, Jost, & Synowitz, 2001) with primarily temporal lobe involvement. Hence, our failure to link semantic fluency performance with BG integrity supports the assertion that phonemic fluency may be more restricted to functions of the basal ganglia and inferior frontal lobe.

Our results are also consistent with studies that have suggested that HIV-associated verbal fluency deficits involve impaired switching (Iudicello et al., 2008; Milliken, Trepanier, & Rourke, 2004; Woods et al., 2004). We recognize that our sample is limited due to size (i.e., $n = 20$), HIV status, and restricted age (>50), particularly to healthy, younger cohorts. It is possible that our sample may also be undergoing normal age-associated neurological changes that may partially explain our current findings. Nevertheless, the effect sizes of our predictor variables ranged from moderate to large (phonemic word generation [$F^2 = .58$], phonemic switching [$F^2 = 1.12$] which demonstrates the robust nature of our findings and enhances the likelihood of replication in a larger sample.

Considering that relationships between verbal fluency and BG have been documented in a number of patient and non-patient populations, including the HIV population, we do not believe that HIV status confounded our study results. Rather, our results support the contention that BG plays a role in verbal fluency, and that dysfunction in selective areas of the BG can give rise to specific deficits in verbal fluency performance.

Future studies should focus on using multimethod approaches (e.g., structural and functional neuroimaging, examining implicit vs. explicit task switching performance, using longitudinal design to examine the predictive validity of verbal fluency performance.

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Fig. 1. ROI segmentation of basal ganglia using LONI BrainParser (axial and coronal view). Regional volume of caudate and putamen determined by Brain-Parser, an automated segmentation program correcting for whole brain volume.

Table 1Sample characteristics ($n = 20$).

Age in years	53.2 (4.2)
Years of education	13.5 (2.0)
% Male	60
Ethnicity	
% African American	60.0
% Caucasian	16.7
% Hispanic	15.0
% Asian	0
% Other	8.3
Median recent CD4 count	399 (I.Q. range – 307)
Nadir CD4 count	123 (I.Q. range – 173.5)
% AIDS diagnosis ^a	77
% on ARV	100
Length of ARV	
% 0–11 months	10
% 1–3 years	5
% over 3 years	85
% Past substance abuse/dependence	45
% HIV neurocognitive disorder ^b	50
Global NP <i>T</i> score	45.39 (4.98)
% Right handed	95

^aBased upon CD4 < 200 or opportunistic infection.^bBased upon Clinical Ratings classification.

Table 2

Neuropsychological battery.

Domain	Test name and citation	Variable used	Normative data
Executive functioning	Trail Making Test	Part B	Heaton, Miller, Taylor, and Grant (2004)
	Wisconsin Card Sorting Test	Perseverative Errors	Heaton, Chelune, Talley, Kay, and Curtiss (1993)
	Stroop Color and Word Test	Interference	Golden (1978)
Information processing speed	Trail Making Test	Part A	Heaton et al. (2004)
	WAIS-III	Digit Symbol Coding	Taylor and Heaton (2001)
	WAIS-III	Symbol Search	Taylor and Heaton (2001)
	Conners' Continuous Performance Test-2 (CPT-II)	Reaction Time	Conners and MHS Staff (2000)
Attention and working memory	Paced Auditory Serial Addition Test (PASAT)	Total Score	Diehr et al. (2003)
	CPT-II	Omissions and Comissions	Conners and MHS Staff (2000)
	WAIS-III	Letter-Number Sequencing	Taylor and Heaton (2001)
Learning and memory	Hopkins Verbal Learning Test-Revised (HVLTR)	Total Learning Score and Recall	Brandt and Benedict (2001)
	Brief Visual Memory Test-Revised (BVMT-R)	Total Learning Score and Recall	Benedict (1997)
Motor functioning	Grooved Pegboard	Dominant and Non-Dominant Hand Score	Heaton et al. (2004)

Table 3
Phonemic & Semantic word generation and caudate and putamen volumes^a ($n = 20$).^b

	Left caudate volume				Right caudate volume			
	R^2	Δr^2	B	p -Value	R^2	Δr^2	B	p -Value
Phonemic word generation								
Global NP ^c	.21	.21	.31	.04 *	.10	.10	.29	.18
# FAS words generated	.37	.16	.43	.02 *	.11	.004	.07	.78
Semantic word generation								
Global NP	.21	.21	.48	.04 *	.10	.10	.32	.18
# of animals generated	.29	.08	-.29	.18	.10	.001	-.03	.91

	Left putamen volume				Right putamen volume			
	R^2	Δr^2	B	p -Value	R^2	Δr^2	B	p -Value
Phonemic switching								
Global NP ^b	.27	.27	.34	.02 *	.06	.06	.26	.34
F & S correct switches generated	.53	.26	.36	.03 *	.06	.00	.04	.84
Semantic switches								
Global NP ^b	.27	.27	.34	.02 *	.06	.06	.26	.34
Animals and things people do correct switches	.29	.02	.13	.52	.09	.03	-.18	.50

* Statistically significant at $p < .05$.

^a Results for switching and caudate volume not illustrated. Findings were non-significant. See Section 3.

^b Results are based upon 20 participants who underwent MRI and performed verbal fluency. Ten participants who completed verbal fluency were excluded from MRI. See Section 2 for more details.

^c NP, neuropsychological performance.