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Random Number Generation in HIV Disease: Associations with Neuropsychological Functions and Activities of Daily Living

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Abstract

Objective: HIV is associated with frontostriatal dysregulation and executive dysfunction. This study evaluated whether HIV-infected individuals evidence deficits in random number generation (RNG), which is a strategic task requiring paced, rule-guided production of digits.
Method: In total, 74 HIV+ adults and 54 seronegative comparison participants completed a comprehensive research neuropsychological battery. Participants produced a random digit sequence by avoiding any order and using numbers 1 through 10 for 100 s at a pace of 1 digit/s. Outcomes included intrusions, repetitions, seriation (1-2-3-4), and cycling (median length of gaps between repeating digits).
Results: HIV disease was associated with higher levels of seriation and cycling ($ps < .05$) but not intrusions or repetitions ($ps > .10$). Among HIV+ individuals, higher seriation was associated with neuropsychological performance including poorer auditory attention, verbal learning, and delayed memory, whereas higher cycling scores were associated with poorer delayed memory and verbal fluency ($ps < .05$). Higher seriation also was independently associated with self-reported declines in activities of daily living (ADLs) in the HIV+ group.
Conclusions: Individuals living with HIV disease evidence moderate difficulties in inhibiting statistically unlikely non-random sequences, which showed medium associations with higher order verbal abilities and may contribute to greater declines in everyday functioning outcomes. Future studies might examine RNG's role in health behaviors such as medical decision-making or medication adherence.

Keywords: Verbal fluency; Executive functions; Attention; Verbal learning; Everyday functioning

Introduction

HIV disease is associated with a 30%–50% prevalence of neurocognitive impairment in the era of combined antiretroviral therapies (Heaton et al., 2010). The direct and indirect neural effects of HIV disease are commonly observed in frontostriatal circuitry (Ipser et al., 2015), which often manifests as executive dysfunction (Woods, Moore, Weber, & Grant, 2009). Because executive dysfunction interferes with health behaviors (Thames et al., 2011) and independent living in HIV (Heaton et al., 2004), investigating novel assessment approaches in this population is valuable (Gorman, Foley, Ettenhofer, Hinkin & van Gorp, 2009).

Random number generation (RNG) is an executively demanding task, which requires participants to produce single digits in a paced, rule-guided manner. RNG requires the inhibition of statistically unlikely non-random sequences, output monitoring, and switching of response strategies (Jahanshahi, Saleem, Ho, Dirnberger, & Fuller, 2006). Abnormal RNG output occurs in other populations with prefrontal systems injury, including individuals with Parkinson's disease (Spatt & Goldenberg, 1993). RNG deficits commonly manifest as a tendency towards serial counting (Peters, Giesbrecht, Jelicic, & Merckelbach, 2007). Studies on the neuropsychological correlates of RNG are limited, but most have focused almost exclusively on

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executive functions such as prepotent response inhibition as measured by Stroop and verbal fluency (Maes, Eling, Reelick, & Kessels, 2011).

In a prior review, Woods and coworkers (2009) articulated the potential benefits of drawing from the cognitive neuropsychology literature in order to enhance outcomes in neuro-AIDS, including identifying ecologically relevant neurocognitive constructs that could improve detection of central nervous system problems and their effects on daily life. RNG is a viable candidate in this regard. Although the associations between neurocognitive impairment and everyday functioning are significant and promising (Blackstone et al., 2012), these effect sizes tend to be fairly small, suggesting that there remains room for improvement in the detection and classification of HIV-associated neurocognitive disorders (HAND) and its effects on daily life. For example, even though there is substantial evidence showing that executive functions predict everyday functioning outcomes in HIV (Chernoff, Martin, Schrock, & Huy, 2010; Heaton et al., 2004; Scott et al., 2011), the amount of variance explained is quite modest and we still have much work to do. One approach is to draw constructs from cognitive literature that may also be relevant to everyday functions, such as RNG. This novel task has cognitive demands of relevance to daily life, such as strategy application (Levine, Dawson, Boutet, Schwartz, & Stuss, 2000), development of novel task completion with a time-pressure element (Kramer et al., 2014), or multitasking (Scott et al., 2011). RNG is a short task and conceptually could provide additional information regarding the broad construct of executive functions and their role in daily life, which are not assessed by more traditional clinical measures. Although RNG has been studied extensively, no studies have examined its ecological relevance much less than its incremental ecological validity. Thus this study contributes to the overall literature by examining the potential associations of RNG with everyday functioning in HIV disease.

With this rationale and literature review in mind, the purpose of this study was to: (1) examine the possible effects of HIV serostatus on RNG, (2) describe the cognitive architecture involved in RNG in a novel neuropsychological sample of HIV+ individuals, and (3) to look at the general ecological relevance of RNG in a sample with established executive dysfunction and activity of daily living (ADL) relationships. Given the preferential effects of HIV-associated neural injury on frontostriatal systems, we hypothesized that HIV disease would be associated with difficulties generating random sequences of numbers as compared to an HIV-negative comparison group. Within the HIV+ group, we expected that RNG performance would be directly related to neuropsychological domains of executive functions, verbal fluency, and attention/working memory, as well as other domains that may be affected by frontal systems injury and are commonly impaired in HIV such as learning or information processing speed. Given the previous literature suggesting that RNG tasks are particularly dependent on executive processing and because executive dysfunction is considered to be one of the strongest predictors of difficulties with everyday functioning complications (Heaton et al., 2004), we conducted an exploratory investigation into whether RNG is independently associated with self-reported declines in ADLs.

Materials and Methods

Participants

This study was approved by UC San Diego's human research protections program. Participants included 74 adults with HIV disease and 54 seronegatives with broadly comparable demographics (Table 1) who completed the RNG task at a 1-year follow-up visit of a longitudinal study on the effects of aging and HIV on memory. This study utilized retrospective data collected during the second time point of a longitudinal parent study that examined the effects of aging and HIV on prospective memory. Individuals included in this study were enrolled between 2008 and 2013. The data reported herein used the same basic inclusion and exclusion criteria as the parent study's baseline entry criteria. Inclusion criteria consisted of confirmation of HIV serostatus and the ability to provide informed consent on the day of evaluation. Given the focus of the parent study on aging and memory, the inclusion criteria across both serostatus groups also included being ≥50 ("Older") or ≤40 ("Younger") years, which was necessary for recruitment purposes for the parent study. Across all participants ages ranged from 23 to 72 years and the median (Q1, Q3) age was 53 (39.3–60) years. In the HIV+ group, ages ranged from 23 to 72 years and the median (Q1, Q3) age was 52 (40–60) years. In the HIV− group, ages ranged from 24 to 69 years and the median (Q1, Q3) age was 54 (39–60) years. Exclusion criteria included the presence of a psychotic disorder (e.g., schizophrenia), neurological complications known to adversely affect cognition (e.g., seizure disorder, active opportunistic infection), or a verbal IQ estimate of <70 (based on the Wechsler Test of Adult Reading [WTAR]; Psychological Corporation, 2001). Because neurocognitive impairment was an important outcome for the parent study, the parent study did *not* exclude individuals with neurocognitive disorders with the exception of frank neurological complications other than HIV known to adversely affect cognition such as seizure disorders or active opportunistic infection. Additionally, participants were excluded if they met DSM-IV criteria (American Psychiatric Association, 2000) for substance dependence (including alcohol) within

Table 1. Mean (standard error) demographic and clinical information for HIV-seronegative and HIV-seropositive groups

Variable	HIV-seronegative ($n = 54$)	HIV-seropositive ($n = 74$)
Age (years)	50.4 (1.7)	50.1 (1.5)
Gender (% men)	66.7	79.7
Education (years)	14.2 (0.3)	13.6 (0.3)
Ethnicity		
Caucasian (%)	63.0	63.5
African American (%)	16.7	20.3
Hispanic (%)	18.5	13.5
Other (%)	1.9	2.7
Estimated verbal IQ (WTAR)	105.0 (1.2)*	101.2 (1.3)*
Neuropsychological Impairment[a] (%)	7.4*	29.7*
Lifetime major depressive disorder[b] (%)	44.4*	66.2*
Lifetime generalized anxiety disorder[b] (%)	5.6*	28.8*
Current affective disorder[c] (%)	21.7*	78.3*
POMS total (of 200)	44.2 (2.8)*	55.4 (3.3)*
Substance dependence[d] (%)	55.6	58.1
Activities of daily living (number of declines)	0.87 (0.4)*	2.4 (0.3)*
Medical HCV (%)	11.1*	29.7*
Estimated duration of infection (years)	—	14.3 (0.9)
Duration of regimen (months)	—	31.2 (3.5)
CPE rank	—	7.54 (0.2)
Current CD4 count (cells/μl)	—	629.7 (38.3)
Nadir CD4 count (cells/μl)	—	189.6 (18.9)
AIDS (%)	—	57.5
Plasma viral load (% detectable)	—	8.7

Note: WTAR = Wechsler Test of Adult Reading; POMS = Profile of Mood States total mood disturbance score; HCV = hepatitis C virus; CPE Rank = CNS Penetration-Effectiveness Rank; CD4 = cluster of differentiation.

[a]Indicated by performance > 1 SD below the mean of demographically adjusted normative scores in at least two cognitive domains, per Frascati criteria.

[b]Lifetime diagnosis.

[c]Diagnosis of major depressive disorder, generalized anxiety disorder or panic disorder within 1 month of evaluation.

[d]Any lifetime diagnosis of dependence on alcohol or illicit substances.

*$p < .05$.

1 month of evaluation (as determined by the Composite International Diagnostic Interview, version 2.1; World Health Organization, 1998), had a urine toxicology screen positive for illicit drugs (e.g., cocaine and methamphetamine) on the day of evaluation (excluding marijuana), or a breathalyzer test that was positive for alcohol.

Materials and Procedure

After providing written, informed consent, all participants completed psychiatric, neuropsychological, and standardized medical research evaluations, for which they received nominal financial compensation.

Random number generation. All participants were instructed to verbally produce a sequence of digits between 1 and 10 in a random fashion by avoiding any order for 100 s at a steady pace of 1 digit per second. Participants were asked to avoid using any specific systems, such as repeating the same number repeatedly or saying numbers in any order (1-2-3-4, 2-4-6-8, etc.). To illustrate the idea of RNG and as consistent with prior RNG studies (Jahanshahi et al., 2006), participants were instructed to imagine that they have placed 10 pieces of paper into a hat, with each piece of paper having a number between 1 and 10, and to imagine repeatedly drawing 1 piece of paper out of the hat, reading the number aloud, and then placing it back into the hat and drawing again. Participants were instructed to keep pace with a metronome, which provided a beat rate of 1 digit per second; if participants fell behind the metronome, they were instructed to stop and carefully listen to the rhythm and start again. After receiving instructions of the task, each participant completed a 10-s practice trial. If the test administer noted any errors, including repetitions, intrusions, or seriation (1-2-3-4, 10-8-6-4, etc.) of >3 seriated digits, participants were reinstructed and asked to complete the 10-s practice trial until it was clear that the participant understood the task.

As described by Spatt and Goldenberg (1993), the RNG scoring criteria included four outcome variables for each participant: (1) intrusions, (2) repetitions, (3) seriation, and (4) cycling. Intrusions included the total number of non-1-10 digits

(0, 11, etc.) generated by the participant. Repetitions included any two consecutive identical digits (1–1). Seriation was measured by considering each increasing or decreasing sequence of ones or twos (1–2; 2–4) that contained at least two digits. The number of digits within each seriated sequence minus 1 was squared to produce a seriation score for that series (3–4 received a score of $1^2 = 1$; 1-2-3-4 received a score of $3^2 = 9$; etc.), and the total score was summed for each participant (higher scores indicated more deviation from randomness). Cycling was computed by counting the number of intervening numbers between each occurrence of a given digit. The cycling score was computed as the median length of gaps between occurrences of identical digits, with extremely high scores (1-2-3-…10) or extremely low scores (1-2-1-2-1) indicative of more deviation from randomness. Although task instructions prompted participants to maintain a steady beat of one digit per second, there was substantial variation in the total number of digits between participants. Notably, a Wilcoxon rank sum test revealed that the HIV+ group (mean [standard deviation] = 76.39 [20.66]) generated significantly fewer total digits than the HIV− group (86.83 [15.38]), $X^2 = 9.64$, $p = .002$, Hedge's $g = .56$. Therefore, each RNG outcome variable described earlier was divided by the total number of digits generated for each participant in order to minimize the effect of total digit production on performance.

Neuropsychological assessment. In order to examine the potential underlying neuropsychological functions supporting efficient RNG performance, domain scores were constructed using raw average composites by computing z-scores derived from mean scores within the HIV+ group only. The domains and associated measures included (a) verbal fluency: total number of correct switches in the fruits–furniture category switching subtest from the Delis–Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) and total words generated for phonemic fluency (Letter L; because the parent study included a verbal fluency experiment that precluded us from using traditional FAS letters, we chose Letter L, which also is a commonly used as part of the CFL fluency protocol); (b) executive functions: time to complete Trail Making Test, Part B (Army Individual Test Battery, 1944) and the Total Moves score from the Tower of London Test (Drexel Version; Culbertson and Zillmer, 1999); (c) attention/working memory: the Digit Span subtest from the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler, 1997) and Trial 1 from the California Verbal Learning Test, second edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000; NB. the CVLT-II manual indicates that trial 1 may be utilized as a measure of auditory attention span [p. 28]); and (d) learning: the Logical Memory I subtest from the WMS-III and Total Trials 1–5 from the CVLT-II. In addition, we diagnosed HAND, meaning that cognitive impairment was at least partially attributable to HIV disease, per Frascati criteria (Antinori et al., 2007). HAND designations were derived from the broader battery using established procedures (Doyle et al., 2015) for descriptive purposes (Table 1) and for inclusion as a covariate in the planned ADL analyses. Specifically, we included the domains as detailed earlier (except verbal fluency) and additionally included measures of delayed memory (Logical Memory subtest from the WMS-III and the long-delay free recall trial of the CVLT-II), speed of information processing (Trail Making Test, Part A and the Total Execution Time from the Tower of London Test), and motor skills (Grooved Pegboard dominant and non-dominant total time; Heaton et al., 2004; Kløve 1963). HAND was determined using Frascati criteria utilizing global deficit scores (GDS; Carey et al., 2004). See Appendix A for a detailed description of generating GDS.

In order to compare RNG indices between HIV+ and the seronegative groups for Fig. 1, sample-based z-scores were calculated by using the mean RNG performance across all participants in the study. For these analyses, all indices were first corrected for total digit output by dividing each RNG score by the total number of digits generated. For these sample-based z-scores, higher z-scores indicate a larger deviation from "randomness," although it is noted that previous studies have concluded that repetitions are grossly underrepresented even in healthy control RNG (Peters et al., 2007), while extremely low cycling scores also could indicate less random responding.

Everyday functioning. All participants completed a modified version of the Lawton and Brody ADL scale (Lawton & Brody, 1969). Appendix B provides a full description and listing of the ADL domains considered by the Lawton and Brody ADL scale. We elected to utilize the Lawton and Brody ADL scale (1969) because it is a well-validated scale that assesses functional domains highly relevant to HIV disease and is widely used in the neuro-AIDS literature. Participants rated their ability to perform each ADL both currently and at their highest level of performance in the past. An ADL domain was considered to have declined if a participant rated their current level of functioning as less independent compared to their previous highest level of independence, and the total number of ADL domains with a decline was summed (range 0–16). Thus, the ADL sum represents the total number of ADL domains that have declined for each participant; this metric represents an index for the broad level of everyday functioning declines from a previous level of functioning and indicates the severity of overall everyday functioning dependence.

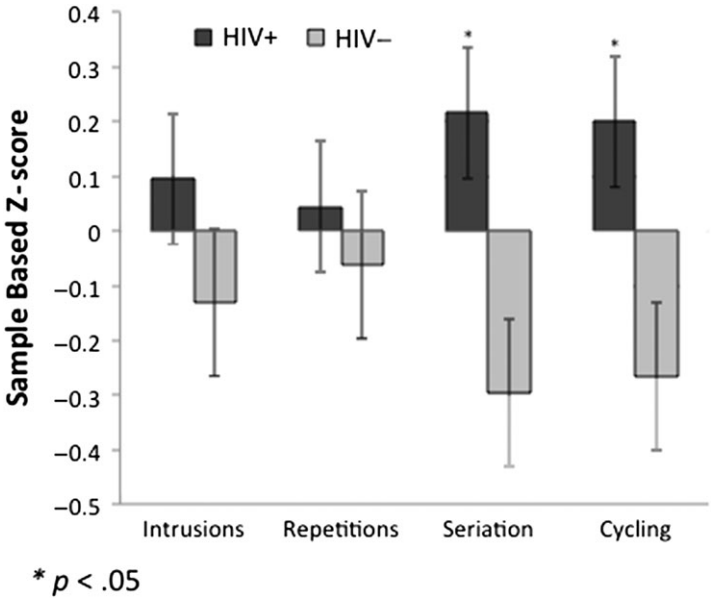

Fig. 1. Sample-based z-scores for intrusions, repetitions, seriation, and cycling (each divided by total number of digits generated) in HIV+ and HIV− groups. Error bars represent standard errors.

Statistical Analyses

Statistical analyses included a series of multiple linear regressions to examine the association between HIV serostatus and RNG while accounting for relevant confounds. Because each of the four RNG outcome variables were non-normally distributed as determined by Shapiro-Wilks tests of normality (all *p*s < .05), we performed transformations on each of the RNG variables. A log transformation of each of the RNG variables was performed, which resulted in only the seriation variable as being non-normal ($p = .105$). Next, a more liberal inverse ($1/x$) transformation of the remaining variables was conducted, which resulted in only the cycling variable being non-normal ($p = .229$). Due to the low rate of individuals who produced intrusions or repetitions, transformation of these data were not possible, with skewness values of 2.43 (standard error [*SE*] = 0.001) for repetitions and 8.13 ($SE = 0.047$) for intrusions. Thus, we elected to dichotomize these data using a yes/no categorization scheme for both repetitions and intrusions, and as such logistic regressions were used for the outcomes of repetitions and intrusions. We examined each of the variables in Table 1 as possible covariates by including any variables that significantly differed between HIV+ and HIV− groups and concurrently were significantly related to any of the four RNG outcome variables. Of the variables listed in Table 1, only WTAR met these criteria and thus was included as a covariate. Pearson *r* coefficients were used to examine the correlations between neuropsychological domain scores and RNG performance within the HIV+ group. Finally, multiple linear regression was used to examine the independent association between RNG and ADL in the HIV+ group, with three covariates selected on an *a priori* basis to include AIDS, lifetime affective disorder, and HAND. In an effort to control for Type I error, the neuropsychological correlations and ADL regressions were conducted only on RNG scores that differed by HIV serostatus. We report Hedge's *g* due to the relatively smaller size of our samples ($n = 54$ [HIV−], 74 [HIV+]), which allows for a more conservative effect size and more accurately reflects the magnitude of associations in such smaller samples. Critical alpha was set to .05 for all analyses.

Results

Random Number Generation

The overall model with HIV serostatus predicting RNG seriation scores reached statistical significance, $F(2,125) = 4.12$, $p = .019$, R^2 adjusted = .047. Within this model, HIV serostatus was the only significant predictor, $\beta = 2.48$, $p = .015$, whereby HIV+ individuals evidenced higher seriation scores compared to seronegatives (Hedge's $g = .48$, Fig. 1). The overall model predicting RNG cycling scores also was significant, $F(2,123) = 8.31$, $p < .001$, R^2 adjusted = .105, with HIV serostatus ($\beta = -2.88$, $p = .005$) and WTAR ($\beta = 2.32$, $p = .022$) emerging as significant independent predictors. Fig. 1 shows that

HIV+ individuals had higher cycling scores compared to seronegative adults (Hedge's $g = -.60$). Neither of the overall models with HIV serostatus predicting digit intrusions or digit repetitions were significant ($ps > .10$). Neither seriation nor cycling scores were associated with HIV disease factors or Hepatitis C virus (all $ps > .10$).

Neuropsychological correlates of RNG in the HIV+ group. Seriation scores were significantly negatively correlated with composite scores of auditory attention ($r = -.30$, $p = .010$), verbal learning ($r = -.43$, $p < .001$), and delayed memory ($r = -.42$, $p < .001$), whereas cycling scores were significantly negatively correlated with performances on delayed memory ($r = .24$, $p = .046$) and verbal fluency ($\rho = .39$, $p < .001$). No other correlations were significant (all $ps > .05$).

RNG predicting everyday functioning in the HIV+ group. The overall model with seriation predicting ADL declines reached statistical significance, $F(4,67) = 11.75$, $p < .001$, R^2 adjusted = .377. Seriation was a significant independent predictor, $\beta = 3.10$, $p = .003$, with higher seriation scores associated with greater ADL declines. In addition, each of the model covariates were significant independent predictors of declines in ADLs (all $ps < .003$). The overall model with cycling predicting ADL declines reached statistical significance, $F(4,66) = 7.76$, $p < .001$, R^2 adjusted = .279. However, cycling was not an independent predictor, $\beta = -1.43$, $p = .159$; rather, each of the other model covariates was significant independent predictors of declines in ADLs (all $ps < .008$).

Discussion

Although there are established associations between executive dysfunction and disability among persons living with HIV disease, clinical prediction of functional problems remains challenging thereby highlighting the need to develop and test novel neuropsychological methods for use in neuro-AIDS. RNG is a promising candidate in this regard, as it has shown sensitivity to frontal systems populations and has task demands that parallel aspects of daily life (e.g., rapid verbal strategy application). Therefore, the aims of this study were to: (a) examine the possible effects of HIV serostatus on RNG, (b) describe the cognitive architecture involved in RNG in a neuropsychological sample of HIV+ individuals, and (c) determine the incremental ecological relevance of RNG in a sample with established executive dysfunction and ADL problems. Overall findings from this study suggest that RNG is adversely affected by HIV disease and may provide some added value in detecting declines in ADLs.

Because non-random patterns of responding during RNG can be separated into multiple possible metrics, our data provide possible clues regarding the profile of non-random responding in HIV. Individuals infected with HIV were more likely to generate digit responses in seriated order as well as higher median gap scores when cycling between digits than were seronegative adults. These HIV-associated aberrations from "randomness" were accompanied by medium effect size and were not confounded by estimated premorbid verbal IQ, demographic factors, or medical comorbidities. The HIV+ group did not produce elevated rates of repetitions and intrusions, suggesting that the overall RNG deficit is not being driven by very basic attentional processes, a fundamental misunderstanding of the rule-guided generation task nor gross perseverative tendencies. Instead, there was evidence of elevated cycling, meaning the HIV+ group produced wider gaps between identical numbers, which suggests a potentially maladaptive approach to randomness that simply focuses on avoiding repetitions. Interestingly, cycling difficulties have not previously been reliably detected in other neuropsychological populations (Peters et al., 2007) and therefore may be a unique feature of HIV disease. Furthermore, HIV+ individuals evidence larger cycling gaps, which may reflect a tendency to invest the limited available cognitive resources on separating identical digits for extended periods of time as opposed to maintaining a truly "random" script. In other words, HIV+ individuals with high cycling scores may be impaired in their ability to generate truly random sequences and may be compensating by imposing a strategy that results in wider gaps between numbers but is still strategic (and thus not random). One may infer that this strategy would require better executive function or working memory processes; however, our data suggest that individuals who may have been avoiding recently generated numbers, and therefore had higher cycling scores, did not relate to executive functions. In further support of this hypothesis, cycling scores were related to neuropsychological composites of episodic memory, as well as verbal fluency, which suggest that elevated cycling may be related more purely to rule-guided generation from semantic memory stores (note that verbal fluency had the largest effect size, $r = .39$) and the ability to implement learned task rules and retain task-specific instructions.

The higher seriation scores observed in HIV, however, are indicative of patterning and producing stereotyped or ordered responses. Such difficulties would be expected only with poor inhibition of prepotent responses or a broader inability to maintain learned task rules, such as randomness. In support of this hypothesis, a study by Peters et al. (2007) examined seriation in healthy adults and found that seriation was positively correlated with Stroop interference, which the authors suggested was due to higher RNG seriation reflecting difficulties in inhibiting stereotype responses. Interestingly, seriation and cycling scores were not correlated ($r = .02$, $p = .848$). Thus, participants with higher cycling scores or those individuals imposing strategic

structure to their responding were not the same participants producing patterned sequences of ordered digits. It is possible that seriation reflects a more severe impairment in broader neuropsychological functioning. Indeed, seriation was related to auditory attention, verbal learning, and delayed memory. Auditory attention as well as verbal learning and memory may each contribute to individuals' ability to (a) maintain a sustained focus on the pattern of previously produced digits and (b) continue to work with a novel construct in "randomness." In other words, given the assumed uniqueness of the RNG task, individuals may be required to work with their own construct of randomness and simultaneously focus cognitive resources on keeping previously produced digits online in order to continue to guide digit generation. In general, previous studies examining RNG tasks have concluded that such tasks are multifaceted in nature and require multiple online response demands such as auditory working memory, monitoring output, interference avoidance, and verbal fluency (see Jahanshahi et al., 2006), many of which also are affected in HIV disease (Doyle et al., 2015; Heaton et al., 2010; Woods et al., 2009). As such, the complex, multifaceted nature of RNG tasks underscore their utility in characterizing patterns of cognitive performance often observed in HIV disease.

To our surprise, RNG was not related to performance with the executive functions composite, which comprised visual planning and cognitive flexibility measures. Previous studies have indicated that neuropsychological domains associated with RNG are not limited to executive functions (Maes et al., 2011). One obvious limitation of this study is that our executive functions domain did not include a test of inhibition (Maes et al., 2011). *Post hoc* analyses examining the tests within the executive functions composite score did reveal, however, that the Trail Making Test Part B time was related to seriation (ρ = .28, p = .016), which indicates that sequencing and shifting may play a role. Also, we included fruits–furniture category switching task in the fluency domain instead of in the executive functions domain. Therefore, our verbal fluency domain may be considered to be somewhat influenced by executive processes (see also Iudicello et al., 2008). Furthermore, the modality in which executive functions were assessed, specifically visual planning and switching, may have reduced the likelihood of detecting a potential correlation between the predominantly verbal RNG task and the presently utilized visual planning and switching tasks comprising the executive functions domain. Intact inhibition also may aid RNG performance through the avoidance of any one structured (and therefore non-random) strategic pattern of responding such as avoiding repetitions, whereas shifting may allow for individuals to employ highly executively demanding strategies such as switching between ascending and descending counting or even mimic random responding by switching between multiple strategies.

The specific indices of RNG utilized in this study were derived from the available literature examining RNG tasks in other clinical populations, such as schizophrenia (Peters et al., 2007). However, the presently utilized indices are not without their limitations. For example, other studies examining RNG have utilized indices that assess the distribution of specific responses (e.g., the variance of generating each possible pair of digits), which has been previously utilized as a supplement to measures of cycling and seriation but has not shown reliable predictive validity in distinguishing clinical populations and control (Brown, Soliveri, & Jahanshahi, 1998). Given our study's aims of identifying whether individuals living with HIV are more likely to respond in a non-random manner and to examine the potential cognitive architecture of RNG in HIV disease beyond executive functions as studied previously (Peters et al., 2007), we felt it is important to choose indices that parallel previous investigations of RNG in clinical populations and to utilize indices shown to be dependent on specific cognitive processes. Finally, although we did not include *a priori* covariates known to affect cognition (such as current depression) and no other variables in Table 1 (other than estimated premorbid IQ) were related to RNG indices and differed by HIV serostatus groups, future studies should determine whether variables such as current substance use (excluded from this study) affects RNG performance.

Of clinical relevance, elevated RNG seriation—but not cycling—was independently associated with greater self-reported decline in ADLs in the HIV+ group. Thus, individuals who had difficulty inhibiting patterned responding were more likely to require greater support in completing daily activities such as household and medication management. The previously established (Chernoff et al., 2010; Heaton et al., 2004; Scott et al., 2011) association between executive functions and everyday functioning outcomes in HIV has been generally modest. Thus, there is a need to further examine ways to improve clinical predictive power of executive functions in the context of daily life. This study utilized an established approach to this end, which adapts constructs from the cognitive literature that may also be relevant to clinical outcomes (Woods et al., 2009), as our laboratory has previously done with some success with constructs such as action fluency (Woods et al., 2005) and prospective memory (Woods et al., 2008). Our data suggest that RNG may provide incremental ecological validity in predicting ADL declines in persons living with HIV. In some ways, RNG may more closely parallel task demands sometimes encountered in daily life (e.g., rapid verbal strategy application), which are not captured by traditional paper and pencil tasks used in clinic. Indeed, to our knowledge, this is the first study to evaluate the ecological relevance of RNG in a neuropsychological population. Future studies may examine its ability to predict functional problems in other groups, such as Parkinson's disease, aging, and schizophrenia. This is relevant because the association between RNG seriation was not simply an artifact of global neuropsychological impairment, because HAND status was included as a covariate in the model, which suggests that RNG provides incremental ecological validity beyond that of global impairment. Note that, *post hoc* analyses confirmed that using

a continuous demographically adjust T-score average or the executive function domain score alone instead of the dichotomous impairment outcome produced an identical pattern of results. In contrast, the absence of an effect of cycling on ADLs may reflect the notion that non-random responding due to the utilization of a strategic process may relate to a higher likelihood of performing similar compensatory processes in the real world. To our knowledge, these data are the first to investigate the relationship between RNG and everyday functioning. One important limitation of our examination of ADLs is the self-report measure used to assess ADLs, which by virtue of being subjective could potentially be biased due to limited insight. Future studies should aim to investigate other functional outcomes associated with RNG performance, including performance-based measures of everyday functioning in the laboratory as well as manifest everyday functioning in the real world such as medication adherence and compensatory strategy use.

Despite these encouraging results, this study has a few limitations worth noting. Given the older age of our sample, future investigations should aim to stratify data across the aging spectrum in order to examine RNG and its potential associations with everyday functioning across the lifespan. An additional limitation is that our sample comprised a primarily non-Hispanic white cohort. Future research should aim to elucidate whether the currently observed results regarding RNG and everyday functioning might also be generalized to more ethnically diverse populations. RNG and its separable metrics may be particularly useful clinical tools for differentiating between multiple gradations and patterns of cognitive impairment—and possibly manifest everyday functioning—in HIV. Furthermore, RNG may be particularly practical due to its minimal practice effects (Jahanshahi et al., 2006) and resistance to the effects of education (Brugger, 1997), which is consistent with our findings of group-level differences in RNG even considering premorbid IQ levels.

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Conflict of Interest

None declared.

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Appendix A

For each participant, raw scores on neuropsychological tests were converted to T-scores utilizing demographically corrected normative data. Next, these individual T-scores were converted to deficit scores (range = 0 [normal] to 5 [severe]) in

order to attribute a clinical rating to neuropsychological test performance as described by Carey and coworkers (2004). Next, each of the global deficit scores (one for each neuropsychological test) was averaged to generate neurocognitive domain scores and a GDS (Carey et al. 2004). A GDS of ≥0.50 was used as a cutoff for HAND per published recommendations (Antinori et al., 2007). This is a widely accepted and well-validated procedure in the neuro-AIDS literature.

Appendix B

The current version of the Lawton and Brody (1969) ADL was modified by Heaton et al. (2004) in order to assess for current level of functioning and the previous highest level of functioning. Items currently used were identical to those outlined by Heaton et al. (2004) and included 13 items assessing individual domains of activities of daily living: financial management, home repair, medication management, laundry, transportation, buying groceries, comprehension of TV/reading materials, shopping, housekeeping, cooking, bathing, dressing, and telephone use (Heaton et al., 2004). For each domain, participants rated their level of independence compared to their previous highest level of independence. Ratings of each domain was specific to each domain depending on content for that domain but generally ranged from: (0) complete independence (I manage all of my finances by myself), (1) needing minor assistance with tasks (I manage routine small purchases, but need help with banking, checking, and balancing accounts), and (2) complete dependence (I am not able to handle money accurately). In addition, there was a separate option for each domain if a participant was able to complete an ADL accurately but elected to have someone else complete that activity (I am able to handle my own finances, but someone else does them for me), which was considered to be identical with complete independence in this study. An ADL domain was considered to have declined if participant rated their current level of functioning as less independent compared to their previous highest level of independence. The total number of domains considered to have declined were summed to create the ADL score (range 0–13). Although the Lawton and Brody (1969) ADL scale is typically utilized with older adults, given the inclusion of individuals with cognitive impairment, which often has downstream effects on everyday functioning, we elected to utilize the Lawton and Brody (1969) ADL scale.

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