Original Research

Selective executive impairments as neuroimmunological manifestations of the human immunodeficiency virus

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Executive processes that predominantly effect people living with human immunodeficiency virus remain to be understood. In the present case-control study, components summarizing executive functions were empirically determined to clarify the nature of executive difficulties observed in individuals with human immunodeficiency virus. One hundred and five seropositive and 62 seronegative healthy adults without comorbidities underwent a comprehensive executive function assessment. Test data were reduced via principal components analysis and component scores were used to investigate whether seropositive adults exhibit selective difficulties in specific executive processes. A three-component solution was found, consisting of updating, inhibition and set-shifting. Group differences between seropositive and seronegative participants were observed only in the updating component. In the present exploratory analyses, significant findings emerged that suggest a selective executive impairment associated with the updating/working memory process in young to middle adulthood seropositive individuals without comorbidities.

Keywords

Executive functions; Human Immunodeficiency Virus; HIV-associated neurocognitive disorder; Principal components analysis; Neuropsychology

1. Introduction

The Central Nervous System (CNS) is affected by human immunodeficiency virus (HIV) with changes seen in frontal and subcortical brain areas, as well as in frontostriatal circuits [1–3]. Neurocognitive impairment occurs in approximately 40–50% of adults living with HIV (ALWH) [4], despite the advent of combined antiretroviral therapy (cART). Although prevalence rate of diagnosed HIV-associated neurocognitive disorder is decreased among those who receive early antiretroviral treatment (20–30%) [5], asymptomatic neurocognitive impairment (ANI) and minor neurocognitive disorder (MND), the two milder forms of HIV-associated neurocognitive disorder (HAND), remain common and can be observed at any stage of HIV infection.

The profile of HAND has changed considerably since the pre-cART era, but still remains to be fully determined. Compared to cognitive domains predominantly affected in the pre-cART era, such as motor and information processing speed, in the cART era impairment in Executive Function (EF) is a prevalent symptom that predicts functional capacity and is related to medication adherence and risky decision-making [6–12]. In spite of research efforts to describe the exact nature of EF impairment observed in ALWH, the specific executive processes that are predominantly or selectively affected remain to be understood. Impaired performance has been previously observed in tests tapping the domains of working memory [13–15], while others have documented shifting mental deficits [16–18] and yet others, disinhibition [19]. Moreover, low performance was found in tasks that estimated more complex executive processes, such as planning [6, 18, 20] and decision making [10, 21, 22].

Various definitions have been proposed for EF, which describes a complex cognitive system encompassing a set of abilities necessary for purposeful behavior and adaptive functioning [23]. Even early studies in the field of EF supported the existence of multiple cognitive processes [24–28] that are not solely related to frontal brain areas [23, 29–31] but also posterior [32, 33] and subcortical regions [34–36]. Among the existing conceptual approaches to EF, the 3-factor model described by Miyake and colleagues is most influential [25]. According to this model, three basic executive abilities, namely updating/working memory, mental flexibility and inhibitory control are basic and likely underlie most other executive processes. Updating/working memory describes the ability to keep information in an active state, while simultaneously processing it. Mental flexibility refers to the ability to effectively alternate/shift between mental criteria or mental sets. Inhibition refers to the ability to inhibit a dominant, or prepotent response that is incompatible with one's goals [25, 37].

Delineating the exact nature of executive impairments in ALWH is critical. First, impairment in EF can emerge early in the disease course [38] and can be detected even in its

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medically asymptomatic stage [2, 3, 7, 10]. Second, executive dysfunction has been characterized as a central neurocognitive deficit. Findings from several studies suggest that impaired performance of ALWH in non-executive neuropsychological measures is attributed to EF impairment. More specifically, visuospatial perception deficits and poor verbal fluency performance have been linked to impaired EF [39–42]. Moreover, HIV infection is characterized by deficits in memory processes that place demands on the executive system, such as retrieval [7, 43–45] and prospective memory [46–48]. Finally, but not least, executive impairment seems to have selective characteristics as recently published meta-analytical data indicates that HIV infection affects discrete executive processes differently [49]. Selective executive decline has not only been observed in normal aging [50],but also in other clinical populations, such as patients with mild cognitive impairment [51, 52].

Several known methodological issues that limit understanding of EF difficulties in ALWH need to be addressed. Many studies included individuals with HIV and additional pathological or confounding conditions, such as co-infections (e.g., hepatitis C), substance abuse, psychiatric history and age-related disorders. All of these conditions are known to affect cognitive performances. Thus, the "pure" effect of HIV infection on the CNS and EF, in particular, remains unknown. A second limitation is that, in most studies, EF ability was determined *a priori* by a single test (or even few measures). Thus, a single measure, such as the N-back test was used to assess working memory, the Stroop test for inhibition etc. However, any such test may draw upon other cognitive abilities and their validity had not been empirically tested on the samples of interest. Consequently, the limited assessment of EF abilities in combination with the problem of "task specificity" constitute a major limitation, when trying to determine the nature of EF deficits in individuals living with HIV. This was acknowledged in a recent meta-analysis [49]. Finally, most studies assessed a single aspect of E, thus, the comparability of EF findings across studies may be confounded by the characteristics of a specific sample [49]. In the present study, three conceptually different executive domains, updating, inhibition and set-shifting, were assessed with an extended battery of EF tests. Subsequently, an attempt was made to reduce test data via principal components analysis and the derived component scores were used to investigate whether participants with HIV present *selective* deficits in *specific* executive processes.

2. Materials and methods

2.1 Participants

Young to middle adulthood seropositive and seronegative individuals participated in this study. Participants with HIV were recruited from a single site, operating in an Infectious Diseases Unit of a University Hospital in Greece. HIV status was confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot. Participants with HIV were on self-administered combined antiretroviral therapy (cART). More specifically, most participants with HIV received cART regimens that contained one (n = 74, 70.5%), two (n = 12, 11.4%) or three (n = 19, 18.1%) pills per day. HIV plasma viral load (VL) was at undetectable levels in 86 (81.9%) ALWH. Only qualitative recordings for VL (i.e., detectable/undetectable) were systematically available in patient records for all participants with HIV and exact VL values were not available due to limited resources associated with non-systematic evaluation and recording. Inclusion criteria were: (1) no history of psychiatric disorder, (2) no history or current substance abuse, (3) absence of medical condition affecting CNS related to HIV, (4) at least six years of formal education in Greek School, (5) absence of any pathological condition affecting cognition (e.g., neurological disorder, traumatic brain injury, chronic medical conditions such as cardiovascular disease and hypothyroidism) and co-infections (e.g., hepatitis C). The same criteria were applied for the inclusion of participants in the non-clinical control group, but with the third criterion substituted by the criterion of absence of HIV infection. Psychiatric history and medical conditions affecting the CNS were determined through clinical interview and medical records. Demographic and clinical variables of participants are presented in Table 1.

2.2 Measures

Table 1 summarizes overall cognitive status (Clock Drawing Test score, CDT) and scores on the short form of Depression, Anxiety and Stress Scale (DASS) of the two groups. The Greek Word Intonation and Synonyms tasks were administered for premorbid cognitive function evaluation. Tasks were selected that are representative of the domains assessed (updating, inhibition, set-shifting) based on previous studies (Table 2, Ref. [53–57]). This categorization was only preliminary and served to guide test selection. Generally, few traditional paper-and pencil tests were included in the research protocol. Instead, mainly computerized tasks were used as they are considered measures of high accuracy sensitive to and appropriate for timed EF evaluation. The tasks were part of a battery developed by the National Institutes of Health in collaboration with the University of California-San Francisco [53].

Specific measures were carefully selected offering indexes and scores appropriate for the assessment of the above executive domains. Updating was assessed with two computerized tasks, the Dot Counting (DOT) and the N-back test (NB) [53], together with two traditional paper-and-pencil tests, the Digit Span (DST) and the Letter-Number Sequencing (LNS) [54]. Shifting ability was assessed with three measures, the Trail Making Test (TMT) [57], the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test (STsh) [55] and the Set-Shifting Test (SS) [53]. Finally, the Continuous Performance Test (CPT) and the Flanker (FL) task [53], as well as the Hayling Sentence Completion Test (HSCT) [56] and the D-KEFS Color-Word Interference Test (STin) [55] were administered to assess the ability to in-

Table 1. Demographic and clinical characteristics of participants.

	ALWT (n = 105)		Control group (n = 62)		
	Mean (*SD*) (%)	Range	Mean (*SD*)	Range	p
Age (*years*)	33.9 (7.0)	22–50	32.2 (8.1)	21–49	0.190
Education (*years*)	14.1 (2.5)	9–20	14.7 (2.6)	12–22	0.116
Word intonation	39.2 (5.2)	27–48	39.2 (4.7)	29–47	0.986
Synonyms	31.1 (5.5)	16–40	31.0 (5.8)	20–50	0.993
CDT	14.8 (0.5)	13–15	15.0 (0.7)	13–15	0.079
DASS	13.4 (10.4)	0–48	6.8 (7.1)	0–34	<0.001
Disease duration (*months*)	55.9 (52.0)	2–269	-	-	-
CD4 count	727.4 (283.2)	134–1800	-	-	-
Nadir CD4 count	395.6 (200.3)	10–1534	-	-	-
cART duration (*months*)	36.2 (42.4)	6–198	-	-	-
CDC stage					
A1	24.8				
A2	50.5				
A3	4.8				
B1	1.9				
B2	8.6				
B3	3.8				
C1	1.9				
C2	1.0				
C3	2.9				

Note. ALWH, Adults living with HIV; CDT, Clock Drawing Test/Free Drawn; DASS, Depression, Anxiety and Stress Scale/short form; CD4 count, cells/μL; cART, combined antiretroviral therapy; CDC, Center for Disease Control and Prevention.

hibit prepotent responses. Table 3 summarizes performance on executive measures administered in the study.

The Psychometric properties of the NIH-EXAMINER battery of tests have been previously described [58, 59]. Regarding individual tasks, Cronbach's α indexes are available in the instrument's manual, suggesting acceptable (Continuous Performance Test) to excellent (Flanker and Set-Shifting tasks) internal consistency.

2.3 Procedures

Participants with HIV were recruited from the outpatient clinic of an Infectious Diseases Unit in Northern Greece. This public clinic is located in a large metropolitan area and attracts persons from a broad range of urban and rural regions in Northern Greece. From May 2016 to October 2017 adults living with HIV who visited the outpatient clinic for their routine examination and fulfilled the study inclusion criteria were recruited for this study. Participants of the non-clinical control group were recruited via social media or from family members and close friends of participants with HIV. All participants gave their informed consent to participate and the study was conducted according to the ethical standards set forth in the Declaration of Helsinki. As the present investigation did not involve clinical trials of medication or other interventional procedures, there was no requirement for institutional review board approval.

Participation took place after personal communication with the first author (EK) and included the administration of clinical and experimental neuropsychological measures. NIH-EXAMINER authors kindly granted permission and provided the necessary software for the computerized tasks. When asked, no participant had previous experience with the EF measures or other neuropsychological procedures administered in the present study.

2.4 Data analysis

Log-transformations were applied to obtain achieve normal distributions for the TMT and the STsh test variables, which were highly skewed or presented extreme kurtosis. Principal Components Analysis (PCA) of the 11 test variables was performed to obtain empirical data reduction and derive components, so as to best summarize executive test performance. As the primary aim was to identify scores that distinguish ALWH from seronegative adults, a PCA was conducted for the data from the total study sample. The resulting components were subjected to oblique rotation using the direct oblimin rotation method (Delta = 0). The number of components retained was determined according to the scree plot criterion and parallel analysis [60]. Reliability of the extracted component scores was estimated using Cronbach's alpha coefficient.

Finally, significant differences between the two groups of participants in component scores summarizing performance on tests of EF were explored via one-way analysis of variance (ANOVA, α = 0.05). Demographic and clinical characteristics, overall cognitive status and DASS score of the two

Table 2. Summary of tests and test variables.

Test	Variable
Dot Counting	Total recall score [53]
Digit Span	Total backward score [54]
Letter-Number Sequencing	Total score [54]
N-back	Total accuracy score, 1-back [53]
Continuous Performance Test	Accuracy score, non-target stimuli [53]
Flanker	Total accuracy score [53]
D-KEFS Color-Word Interference Test	Total correct, Inhibition trial [55]
Hayling Sentence Completion Test	Inhibition error score, 2nd part [56]
Trail Making Test	Time on Part B minus time on Part A [57]
Set-Shifting	Mean response time on Shifting trial minus mean response time on Non-Shifting trial [53]
D-KEFS Color-Word Interference Test	Time on Shifting trial minus mean time on Color and on Word trials [55]

Table 3. Performance of the two groups of participants on tests of EF.

	ALWH	Control group		
Test index	Mean (SD)	Mean (SD)	*p*	*d*
DOT	17.2 (4.4)	19.2 (4.6)	0.010	0.434
DS	6.6 (2.1)	7.9 (2.4)	0.001	0.579
LNS	11.3 (2.5)	12.8 (3.1)	<0.001	0.557
NB	25.8 (2.4)	27.0 (1.8)	0.015	0.558
CPT	18.8 (1.2)	19.1 (0.9)	0.163	0.234
FL	47.5 (0.7)	47.5 (0.8)	0.727	0.026
STin	48.9 (1.4)	49.3 (1.2)	0.026	0.312
HSCT	3.0 (2.3)	2.3 (2.1)	0.159	0.304
TMT	38.6 (24.0)	34.2 (20.7)	0.357	0.198
SS	0.16 (0.14)	0.2 (0.1)	0.701	0.029
STsh	37.0 (17.5)	30.4 (10.1)	0.039	0.461

Note. ALWH, Adults living with HIV; DOT, Dot Counting; DS, Digit Span; LNS, Letter-Number Sequencing/Total score; NB, N-back; CPT, Continuous Performance Test; FL, Flanker; STin, Color-Word Interference/Inhibition; HSCT, Hayling Sentence Completion Test; TMT, Trail Making Test; SS, Set-Shifting; STsh, Color-Word Interference/Shifting.

groups of participants were also compared by ANOVA. All statistical analyses were performed with the SPSS software (version 25.0, IBM Corp., NY, USA).

3. Results

One hundred and five adults with HIV (98 males, 93.3%) and 62 seronegative healthy adults (53 males, 85.5%) participated in the study. PCA of the 11 executive measure variables revealed four components with eigenvalues greater than 1.0, accounting for 59.3% of the variance. Further inspection of the scree plot indicated three reliable components that accounted for 50.2% of the variance. The three-factor solution was also supported from parallel analytic results, which indicated that only eigenvalues extracted for the first three components were larger than the corresponding random eigenvalues, based on the sample size and the number of variables entered in the analysis. A second PCA restricted to data from the participants with HIV revealed similar results (three components that accounted for 52% of the variance).

All measures loaded predominantly on one of the three factors identified (loadings >4) (Table 4). Five test indexes loaded on the first factor. Three were measures that assess updating or manipulating of verbal information in working memory (DOT, DS, LNS). Thus, this factor was labeled updating/working memory. Additionally, two more tests that had been initially selected to tap inhibition and set-shifting loaded predominantly on this working memory factor (HSCT, TMT). In turn, three executive measures that assessed the ability to inhibit prepotent responses loaded on the second factor, which was labeled inhibition (CPT, FL, STin). Finally, two executive tests assessing response shifting, namely the SS and STsh, as well as the NB loaded on the third factor. This factor was named set-shifting. Cronbach's α values were 0.711, 0.774 and 0.682 for updating, inhibition and set-shifting components respectively. The correlation between the updating and set-shifting components was low, but significant ($r = 0.254$, $p = 0.001$). Correlation between inhibition and set-shifting was even lower and almost reached statistical significance ($r = 0.150$, $p = 0.056$), whereas a non-significant ($r = 0.048$, $p = 0.544$) correlation was observed between updating/working memory and inhibition component scores.

The mean score on the three executive components for each group of participants is shown in Fig. 1. Because of their possible impact on neuropsychological test performance, group differences in EF components were explored while accounting for possible differences in other factors, such as demographic and clinical characteristics, mood state and premorbid functioning. There were no significant differences in demographic characteristics (age, years of education, gender) between the two groups of participants. Moreover, the two groups did not differ either with respect to the CDT score, which was used in the present study as a measure of overall cognitive functioning, or in the Test of Greek Word Intonation and Synonyms scores, which were administered for premorbid cognitive functioning evaluation. However, the mean score of participants with HIV on the DASS scale

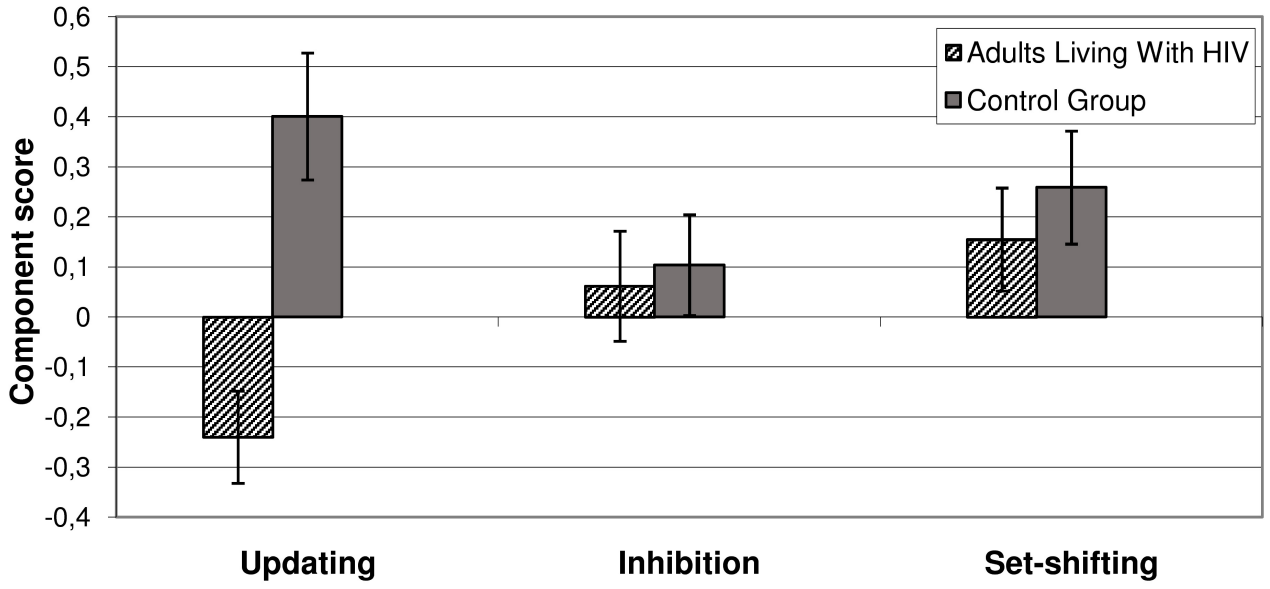

Fig. 1. Scores of the two groups of participants on three executive functioning summary scores derived from principal components analysis. *Means + standard errors.*

Table 4. Rotated solution and component loadings of the eleven executive test indexes in the total sample of participants.

	Component		
Test index	1	2	3
DOT	0.766	0.186	0.075
DS	0.714	–0.057	–0.120
LNS	0.699	0.190	–0.11
HSCT	–0.522	0.248	–0.129
TMT	–0.434	–0.160	0.240
CPT	0.157	0.697	–0.031
FL	–0.029	0.662	0.160
STin	0.011	0.572	–0.160
NB	0.024	–0.086	–0.761
SS	0.129	–0.127	0.763
STsh	–0.260	0.151	0.663
Eigenvalue	2.91	1.37	1.25
% Variance	26.43	12.41	11.32

Note. DOT, Dot Counting; DS, Digit Span; LNS, Letter-Number Sequencing/Total score; NB, N-back; CPT, Continuous Performance Test; FL, Flanker; STin, Color-Word Interference/Inhibition; HSCT, Hayling Sentence Completion Test; TMT, Trail Making Test; SS, Set-Shifting; STsh, Color-Word Interference/Shifting.

was significantly higher than that of the control group [t (165) = 4.454, $p < 0.001$].

Three analyses (ANOVA) were conducted with executive component scores as the dependent variables. Since significant difference was found on DASS between the two groups of participants, this variable was entered as a covariate into the analyses. Results showed that the two groups of participants differed significantly only in the updating component score [F (1, 160) = 14.032, $p < 0.001$, $\eta^2 = 0.081$]. Further investigation of effect size indicated a medium to large effect (d = 0.667, 95% CI [0.36–0.98]). For the components of inhibition [F (1, 160) = 0.948, $p = 0.332$, $\eta^2 = 0.006$] and set-shifting [F (1, 160) = 3.333, $p = 0.070$, $\eta^2 = 0.020$], the observed differences were not significant, with a small (d = 0.173, 95% CI [–0.13–0.48]) and a small to medium (d = 0.43 95% CI [0.12–0.74]) effect, respectively.

4. Discussion

Executive dysfunction is a prominent deficit in ALWH [61] that emerges at the initial disease stage [38] and becomes more apparent as the disease progresses [62]. Notably, the pattern of cognitive deficits has changed from the pre- to the cART era and the frequency of EF deficits has increased [6, 7]. In this study, a data reduction approach was employed to extract component scores from a group of traditional and experimental tests of EF and to identify differences in EF between the HIV and the non-clinical control groups. Test variables were selected based on their conceptual relevance for basic executive processes (updating, set-shifting, inhibition). The methodology applied for investigation of those executive domains was similar to the methodological design of the original study of Miyake *et al.* [25]. Their model, encompassing the ideas of both unity and diversity of EF, has been broadly and successfully applied in previous studies providing insight into the nature of EF.

Three components that summarized executive processes emerged in the present study. They supported the diversity of the executive processes of updating, inhibition and set-shifting. A closer observation of test loadings showed that three tests were required by a subject to successfully update or

manipulate verbal or visual information in working memory loaded on the first component (DST, LNS, DOT). Thus, this component was defined by the term *Updating/working memory*. Three tests measuring inhibition of prepotent response (CPT, STin, FL) loaded on the second, *Inhibition* component. Finally, two measures (SS, STsh) that had been chosen to tap set-shifting ability loaded on the third, *Set-shifting* component. However, two measures that are traditionally used for the assessment of inhibition and set-shifting executive processes in clinical and research settings (HSCT and TMT, respectively), loaded on the first, updating component. The NB on the contrary, a measure that is believed to assess the ability to update information in working memory, loaded on the third, set-shifting component. The three executive components extracted from the analyses were labeled from the main executive ability assessed from most of the tests that loaded on the respective factor. Undoubtedly, others could assume different or more complex labeling of these three components. Of interest, only a weak significant correlation was observed between updating and set-shifting components, whereas the correlation between inhibition and set-shifting components was near significant. Results from previous studies examining the factor structure of EF support that executive components are to some extent related, but are also separable or independent from each other, since their intercorrelations are usually of low or medium magnitude [25, 63–66].

There are many potential explanations when trying to interpret the pattern of test loadings observed in the present study. For example, the HSCT was found to load on the updating component, even though it measures the ability to inhibit verbal prepotent responses (incongruent answers should be provided, while congruent avoided). However, apart from inhibiting prepotent responses, successful performance on the HSCT requires activation, preservation and processing of verbal information in working memory. On the other hand, the TMT, which was also found to load on the updating component, taps many cognitive processes [67, 68]. For example, the second part of TMT is a dual task which has high demands on monitoring and updating visual information. Thus, the TMT loadings on the updating component can be partially explained.

A major finding of the present study is that executive abilities are affected in ALWH without comorbidities and suggest a prominent selective symptom in the form of updating difficulties. The group of ALWH tested consisted of young to middle adulthood participants (<50 years old) without psychiatric and/or substance abuse history, not meeting the criteria for ANI. However, even in the "cognitively intact" group of ALWH, compromised ability to successfully update information in working memory was evident. Thus, this study indicates a selective executive difficulty in young to middle adulthood individuals living with HIV, associated with information updating, whereas inhibition and set-shifting abilities remain comparable to those individuals without HIV.

Previous studies have shown working memory deficits are repeatedly observed in samples of seropositive drug-users [13, 15], predict participants' cognitive complaints [14] and are not specific to the verbal or visuospatial aspects of working memory [69]. Thus, they seem to be a "central executive deficit" in ALWH, similar for verbal and visuospatial information [69]. More recently, a meta-analysis of HIV-associated executive dysfunction showed that, in comparison to decision-making, inhibition and set-shifting; working memory is more severely affected in the era of cART [49]. Interestingly, the clinical characteristics of people living with HIV, such as recent or current substance abuse, were associated with more pronounced deficits on inhibition and set-shifting, but not with working memory. Thus, the findings reported here are consistent with this recent metanalysis, indicating that updating deficits are disproportionally affected. Moreover, since our sample included only ALWH without comorbidities the current findings raise the possibility that updating difficulties most likely constitute a direct effect of HIV infection.

A three-component solution of EF has been observed in several studies that included young and middle-aged healthy adults [25, 37, 66]. However, other research findings indicate that components summarizing executive processes may vary in individuals with CNS pathology and in the elderly. For example, studies with frontal lobe patients [70] or older participants [64, 65, 71, 72] reported one or two-factor solutions, while others suggest the existence of more than three executive components [73–75]. In the present study, a "typical" three-component solution was observed in the total sample, as well as in the sample of participants with HIV. Three executive components have also been noted in a sample of patients with Mild Cognitive Impairment [52], although there they were labeled differently, as planning/problem solving, working memory and judgment. The labeling of components extracted from Principal Components Analysis is, to some extent, arbitrary and the interpretation of components depends on what researchers perceive as common among the different tests that anchor each factor.

Several factors complicate the comparability of findings from different studies investigating component solutions and factor structure derived from groups of EF measures. First, different methodological approaches in test selection may account for differences in the number of components revealed. The present study followed the methodological approach suggested in the original study of Miyake *et al.* [25]. Components extracted from a group of tests were carefully selected before they were examined to measure specific executive processes. Second, the selection of test indexes as representative measurements of specific executive processes (i.e., set-shifting), that are also unaffected from other executive (i.e., updating, inhibition) and non-executive processes (i.e., visual perception, information of processing speed), is a challenging task. *Task specificity* is a common problem in understanding and measuring EF. To maximize test specificity, total scores provided from EF measures were avoided

and only single test indices were included as variables in the reported analyses. Moreover, cognitive measures were carefully selected offering "pure" indexes and scores appropriate for the assessment of the executive domains under investigation. Third, the characteristics of the population being investigated, such as health status (i.e., healthy participants/non-clinical groups, clinical groups) or age, may account for the variability in the number of executive components revealed by different studies [65, 72, 76–78].

Generalization of the findings reported here may be limited by several factors. First, the stability of the three-component solution found in the present study should be ensured along with the selective updating difficulties observed in a more heterogeneous sample (i.e., older individuals or in advanced disease stages), since alteration of EF structure remains a possible scenario for individuals who present some form of neurocognitive impairment. The small subgroup of female participants also restricts the generalization of the present findings. However, the large sample of ALWH examined in the present study was homogeneous with respect to demographic (age, gender, ethnicity) and clinical characteristics (disease status, absence of comorbidities, treatment), minimizing the potential impact of such confounding factors on cognitive functioning. Of note, participation of young to middle adulthood persons living with HIV excludes, or at least minimizes, the possibility of cognitive changes due to normal aging or even age-related disorders, whereas many previous studies investigated cognition in older ALWH, typically over 50 years old [3, 79]. Consequently, the present study attempts to provide evidence regarding the impact of HIV infection on EF *per se*. The possibility is acknowledged that the administration of more or different EF tests may result in a different or more complex component solution, potentially revealing deficits in other executive processes. However, multi-dimensional components representing complex abilities make conceptualizations more difficult. In the present study, pure test indexes were used in the analyses, since total or composite scores of EF measures usually offer no insight into the specific executive processes assessed. A further consideration is that in the PCA conducted, unequal size of the two groups of participants may have influenced variance partition. Finally, it should be noted that the present investigation is rather exploratory.

5. Conclusions

The results of the present study highlight the presence of EF difficulty in young to middle-aged ALWH without comorbidities, which is typically selective and is associated with the ability to update and manipulate verbal and visual information in working memory.

Abbreviations

ALWH, adults living with human immunodeficiency virus; ANI, asymptomatic neurocognitive impairment; ANOVA, analyses of variance; cART, combined antiretroviral therapy; CDT, clock drawing test; CNS, central nervous system; CPT, continuous performance test; DASS, depression, anxiety and stress scale; DOT, dot counting test; DST, digit span test; EF, executive functions; FL, Flanker test; HAND, human immunodeficiency virus-associated neurocognitive disorder; HIV, human immunodeficiency virus; HSCT, hayling sentence completion test; LNS, letter number sequencing test; MCI, mild cognitive impairment; NB, N-back test; NCI, neurocognitive impairment; MND, minor neurocognitive disorder; PCA, principal components analysis; SS, set-shifting test; STin/sh, Color-Word Interference Test inhibition/shifting; TMT, trail making test.

Author contributions

EK and EA designed the research study. EK performed the research, collected the data and wrote the manuscript. PI contributed to data collection and provided advises in clinical diagnosis. GK performed the statistical analyses. EA performed editorial changes in the manuscript. EK, EA, PI and GK read and approved the final manuscript.

Ethics approval and consent to participate

Participation in the study was obtained with the informed consent of all participants. The institutional review board of the Aristotle University of Thessaloniki does not require approval for studies not involving clinical trials of medication and/or invasive techniques.

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Conflict of interest

The authors declare no conflict of interest.

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