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HIV-associated executive dysfunction in the era of modern antiretroviral therapy: A systematic review and meta-analysis

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Abstract

Objective: While some reports suggest that HIV+ individuals continue to display executive function (EF) impairment in the era of cART, findings have been contradictory and appear to differ based on the aspect of EF being measured. To improve the understanding of how discrete executive abilities may be differentially affected or spared in the context of HIV-infection, we conducted a systematic review and meta-analysis to (a) determine whether and to what extent HIV + adults experience deficits in EFs, and (b) understand how demographic and clinical characteristics may modify the associations between HIV-infection and executive abilities.

Method: Studies comparing HIV+ and HIV-uninfected groups on measures of working memory, set-shifting, inhibition, decision-making, and apathy between 2000 and 2017 were identified from three databases. Effect sizes (Cohen's *d*) were calculated using inverse variance weighted random effects models. Meta-regression was used to examine the moderating effect of demographic and clinical variables.

Results: Thirty-seven studies (*n* = 3,935 HIV+; *n* = 2,483 HIV-uninfected) were included in the meta-analysis. Pooled effect sizes for deficits associated with HIV-infection were small for domains of set-shifting (*d* = −0.34, 95% CI: −0.47, −0.20) and inhibition (*d* = −0.31, 95% CI: −0.40, −0.21), somewhat larger for measures of decision-making (*d* = −0.41, 95% CI: −0.53, −0.28) and working memory (*d* = −0.42, 95% CI: −0.59, −0.29), and largest for apathy (*d* = −0.87, 95% CI: −1.09, −0.66). Meta-regression demonstrated that age, sex, education, current CD4 count, and substance dependence differentially moderated the effects of HIV-infection on specific EFs. However, lower nadir CD4 count was the only variable associated with greater deficits in nearly all EF domains.

Conclusions: Our results suggest that discrete domains of EF may be differentially affected by HIV-infection and moderating demographic and clinical variables. These findings have implications for the development of targeted cognitive remediation strategies.

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Keywords

HIV/AIDS; HIV-associated neurocognitive disorder; Executive functioning; Neuropsychological functioning; Frontal lobe

Introduction

Despite the advent of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) continue to persist in a significant subset of infected individuals (Heaton et al., 2011; McArthur et al., 2003). As many as 50% of HIV+ individuals in the era of cART continue to experience some degree of cognitive impairment, and this is often associated with negative functional outcomes (Heaton et al., 2004; Hinkin et al., 2004). Of the multiple domains of cognition affected by HIV-infection, executive function (EF) has been found to be among the most commonly and severely impaired in previous cohort and meta-analytic studies (Cysique, Maruff, & Brew, 2006; Heaton et al., 2011; Reger, Welsh, Razani, Martin, & Boone, 2002). Briefly, EF can be defined as the collection of cognitive processes required to effectively initiate, monitor, and regulate thoughts and actions, thereby allowing one to respond in an adaptive manner in novel situations (Friedman & Miyake, 2004; Lezak, Howieson, Bigler, & Tranel, 2012). The utility of EF as a neuropsychological construct is underscored by studies that have identified EF as a predictor of functional capacity, vocational status, risky sexual behavior, and medication adherence among HIV+ individuals (Heaton et al., 2004; Hinkin, et al., 2002; Hinkin et al., 2004).

There has been a considerable diversity in the manner in which EF is defined and measured in individuals infected with HIV. This may reflect the diversity of theories put forth to define EF and the failure of the field to agree upon the manner by which EF should be conceptualized and measured. Modern theories have conceptualized EF as several distinct, yet related, abilities which can be differentially affected or preserved in the context of specific neuropsychiatric syndromes (Friedman et al., 2008; Hull, Martin, Beier, Lane, & Hamilton, 2008; Lehto, Juuja, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000; Stuss, 2011). For example, evidence from a seminal study by Miyake et al., (2000) and a number of subsequent studies (see Friedman et al., 2008; Hull, Martin, Beier, Lane, & Hamilton, 2008; Lehto, Juuja, Kooistra, & Pulkkinen, 2003) supports the existence of three distinct, yet related, domains of EF (i.e., updating and working memory, set-shifting, and inhibition). However, other conceptualizations of EF include a broader set of cognitive and non-cognitive processes carried out by frontal-subcortical and frontal-limbic brain structures, such as planning and decision-making, volition, energization, and obversely, apathy (Bechara, Damasio, Tranel, & Anderson, 1998; Lezak et al., 2012; Stuss, 2011). Apathy, in particular, is discussed in current treatises on executive function (Suchy, 2009, 2015). Each of these executive abilities is believed to be facilitated, at least in part, by a series of frontostriatal brain networks (Alexander, DeLong, & Strick, 1986; Mega & Cummings, 1994) known to be especially vulnerable to pathological structural and functional changes that occur as a result of HIV-infection (Jernigan et al., 1993; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008; Ortega, Brier, & Ances, 2015). Currently, it is unclear whether

each of these frontostriatal networks, and the executive abilities which they contribute to, is equally affected by neuropathological changes resulting from HIV-infection. However, previous work suggests that specific neural networks and selective neuronal populations (e.g., dopaminergic-rich neurons) can be selectively vulnerable to specific forms of neurologic injury (McColgan et al., 2015; Seeley, Crawford, Zhou, Miller, & Greicius, 2009), including that which accompanies HIV-infection (Nath et al., 2000; Ortega et al., 2015; Thomas, Brier, Snyder, Vaida, & Ances, 2013).

Although evidence suggests that individuals infected with HIV can experience deficits in executive abilities, findings from individual studies which examined the effect of HIV-infection on specific aspects of EF in the era of cART have been inconsistent. In our review of the literature, we have found no previous attempts to systematically aggregate and quantify the findings from this relatively large body of work. Consequently, there is still no consensus as to whether specific executive abilities might be preferentially affected or spared in the context of HIV infection. Likewise, there is little understanding of the degree to which demographic and clinical variables, such as age, sex, immunological status, and ART use modify the effect of HIV infection on components of EF. An improved understanding of the degree to which HIV-infection affects a relatively diverse set of executive abilities will lead to a more accurate conceptualization of HIV-related neurobehavioral deficits in the era of cART and inform the development of targeted interventions such as cognitive remediation.

The purposes of this systematic review and meta-analysis are (1) to determine whether and to what extent HIV-infected adults experience deficits in EF relative to HIV-uninfected controls in the era of cART by deriving pooled effect size estimates (Cohen's *d*) for distinct domains of EF; (2) to determine whether study-level demographic and clinical characteristics modify the associations between HIV-infection and executive abilities; and (3) to contextualize these findings within a broader qualitative review of neuropsychological, neuroimaging, biomarker, and genetic literature. Taking the lead from modern theories and influential taxonomies in cognitive neuroscience (Friedman et al., 2008; Hull, Martin, Beier, Lane, & Hamilton, 2008; Lehto, Juuza, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000; Stuss, 2011), the current analysis makes distinctions between discrete EFs rather than treating EF as a unitary construct. Although numerous executive abilities have been examined within the HIV literature, we limit the scope of this paper to five components of EF that have received considerable attention in the HAND literature thus far: working memory, inhibition, set-shifting, decision-making, and apathy.

Methods

Protocol and registration

Study inclusion criteria and methodology for this systematic review and meta-analysis were described in advance and documented in a protocol, consistent with PRISMA guidelines (Liberati et al., 2009).

Eligibility criteria

Eligible studies were human studies comparing HIV+ adults to HIV-uninfected adults on measures of working memory, inhibition, set-shifting, decision-making, or apathy. A priori, each neuropsychological test was categorized as a measure of a specific component of EF based on domain definitions from widely-used neuropsychological test compendiums (Lezak et al., 2012; Strauss, Sherman, & Spreen, 2006). We excluded studies that only reported findings from multi-measure EF composite scores if the measures that were included in the EF composite score were judged by both reviewers to assess dissimilar domains of EF. We retained studies that reported results from fully overlapping samples only if the studies reported on distinct domains of EF. We excluded studies that enrolled perinatally infected participants, and we excluded conference abstracts, unpublished material, and reports that were not peer-reviewed. We did not limit the review to HIV+ groups with documented HAND. To ensure that the findings were generalizable to the current HIV+ population, we only included studies conducted in the era of cART. Although no clear distinction between the pre-cART and cART-era exists, the year 2000 was chosen as the cutoff for this study. As such, only studies published between January 2000 and January 2017 were included.

Information sources

Studies were identified by screening paper titles and abstracts using electronic databases, by conducting a full-text review of the references lists of relevant articles, and by consulting experts in the field of HAND research. We did not apply language restrictions. The EMBASE, PubMed, and PsycINFO electronic databases were each searched separately using specific subject heading terms in an iterative fashion.

Search

Title and abstract search terms included ‘executive functioning,’ ‘working memory,’ ‘set-shifting,’ ‘response inhibition,’ ‘inhibitory control,’ ‘Stroop,’ ‘decision-making,’ and ‘apathy’ combined with ‘HIV’ or ‘human immunodeficiency virus.’ The last search was conducted on 19 January 2017.

Study selection

The primary author (K.W.) was responsible for identifying articles that met the paper’s eligibility criteria and conducting quality assessments to ensure adherence to the predefined protocol. The co-author (G.B.) reviewed the list of articles that were identified as meeting the study inclusion criteria and identified any missing articles.

Data collection process & Data items

The following information was collected from each study: year of publication, country, sample size, sample demographic characteristics (i.e., age, sex, race, education), sample clinical characteristics, including ART and cART use, current CD4 count, nadir CD4 count, proportion of participants with current or recent (within one year of neuropsychological testing) substance dependence, and hepatitis C infection. The name of each neuropsychological measure of interest, group raw scores, standard deviations, and available

effect size data was also collected. When unadjusted and covariate-adjusted results were reported, we chose to calculate standardized effect sizes using data from unadjusted or minimally-adjusted models in order to maintain consistency in effect size calculation across studies. Additionally, using data from minimally adjusted models allowed for the unbiased examination of moderator effects using meta-regression techniques. For purposes of the systematic review, information about neuroimaging modality used, biomarkers collected, and relevant genetic data was also obtained from each study when available.

Planned Methods of Analysis

Cohen's d effect sizes (Cohen, 1988) were calculated for each study based on group differences between HIV+ and HIV-uninfected control groups on measures of EF. Pooled effect size estimates (Cohen's d) were calculated for each domain of EF using random-effects models weighted using inverse variance. Random-effects models were chosen because these models account for between-study heterogeneity in the estimate of pooled effect sizes (Hedges & Vevea, 1998). Given study level differences in participant demographic and clinical characteristics known to affect EF, we expected significant between-study heterogeneity. In the instance in which no between-study heterogeneity was found, effect sizes were estimated using a fixed-effects model. Individual and pooled effect sizes were reported using forest plots. To examine the effect of HIV-infection on individual EF measures, pooled effect estimates were also calculated for the neuropsychological measure used most commonly to assess each EF domain.

Heterogeneity between studies was evaluated using a chi-square test (Cochran's Q), and the degree of variation among study effect sizes was estimated using I^2 . Statistically significant Q tests and I^2 values above 50% were considered indicators of heterogeneity (Higgins & Thompson, 2002). Heterogeneity is suggestive of study level variation in effect sizes in excess of that which would be expected due to chance alone. Publication bias was assessed by visual inspection using funnel plots and more formally using Egger's regression asymmetry test (Egger, Davey Smith, Schneider, & Minder, 1997). If evidence of publication bias was found, pooled effect sizes were re-estimated after adjusting for bias using the trim-and-fill method (Duval & Tweedie, 2000).

Random-effects meta-regression was used to examine the effect of study level demographic (i.e., age, sex, education) and clinical (i.e., ART use, current or recent substance dependence, CD4 count, and nadir CD4 count) characteristics on pooled effect size estimates. Meta-regression was used to examine whether one or more predictor variables accounted for significant variance among study level effect sizes (Thompson & Higgins, 2002). The moderating effect of demographic variables was examined simultaneously in a single meta-regression model to reduce residual confounding. Separate meta-regressions were performed for each clinical variable to ensure an optimal ratio of studies to predictor variables, as recommended by Bornstein, Hedges, Higgins, and Rothstein (2011).

Results

Study selection

Displayed in Figure 1 is a flow diagram which describes the article selection process in detail. A total of 47 studies published between January 2000 and January 2017 were identified for inclusion as part of the systematic review. The search on Embase, PubMed, and PsychINFO yielded a total of 1,490 citations. After screening out duplicates, 1,099 citations remained. Of these, 842 were excluded after a title and abstract review because it was apparent they did not meet the search criteria, leaving 257 articles for a full-text review. From the full-text review, 215 articles were excluded, and five additional articles were identified through a review of references. Of the 47 studies included in the systematic review, 37 were included in the meta-analysis. Studies were excluded from the meta-analysis for not directly comparing HIV+ and HIV-uninfected individuals on measures of interest, failing to report statistics needed to calculate effect sizes, using EF impairment as a criterion for study inclusion, and for using the same sample and reporting on the same results as a study already included.

Risk of bias in individual studies

Each study included in the meta-analysis was assessed for risk of bias, which included an assessment of the comparability of the HIV+ and HIV-negative groups, the representativeness of the sample, and the use of statistical methods to adequately adjust for potentially confounding variables. Systematic differences between HIV+ and HIV-uninfected groups on potentially confounding participant characteristics were found in a subset of studies. Statistically significant group differences in age, education or literacy, and rates of current or recent substance dependence were observed in 14%, 24%, and 23% of studies, respectively. Forty-three percent of these studies reported findings that statistically adjusted for these factors. Although the effects of these potentially confounding variables on pooled effect size estimates were explored using meta-regression, we were unable to correct for bias at the individual study level.

Study Characteristics

A total of 3,935 HIV+ and 2,483 HIV-uninfected individuals were included in the meta-analysis. Study samples were largely made up of middle-aged participants in their third, fourth, and fifth decade of life. HIV+ groups had a mean age between 40 and 50 in 73% of studies. Thirty-two percent of studies used HIV+ samples made up entirely of male participants, 52% used majority male samples, and 8% used exclusively female samples. Whereas 5% of studies enrolled only patients who were naïve to ART, 11% required that all participants be active ART or cART users. In the majority (73%) of the studies, a subset of the HIV+ participants was not prescribed or taking any form of ART. The majority of studies were cross-sectional in nature (97%); only one study (3%) reported on longitudinal data from a prospective cohort. Data from the baseline visit was used for the meta-analysis. The majority (86%) of studies were conducted within the United States, 5% were conducted in Canada, 3% in South Africa, and 3% in Iran, and 3% in Brazil. A qualitative synthesis of study characteristics, study findings, and associated imaging and genetic biomarkers is

presented in Table 1 and Table 2. Studies included in the meta-analysis are identified with an asterisk after the author name.

Pooled Effect Size Estimates for Executive Functions

Working memory—Fifteen studies included in this meta-analysis assessed the effect of HIV-infection on measures of working memory ($n = 1,622$ HIV+, and $n = 1,015$ HIV-uninfected). HIV+ individuals performed significantly worse than HIV-uninfected comparison groups on measures of working memory; the pooled effect estimate was in the medium range ($d = -0.42$, 95% confidence interval (CI): $-0.59, -0.29$; Figure 2a). Evidence for between-study heterogeneity was found ($Q(14) = 34.34, p = .002; I^2 = 51.21\%$). Working memory was most commonly measured using a variant of the 2-back test ($k = 4$). The pooled effect estimate for studies that used the 2-back test was in the medium to large range ($d = -.70$, 95% CI: $-1.00, -0.41$). There was no evidence of between-study heterogeneity among studies using the 2-back ($Q(3) = 0.99, p = .803; I^2 = 0\%$).

Set Shifting—Fourteen studies included in this meta-analysis assessed the effect of HIV-infection on measures of set-shifting ($n = 2,849$ HIV+, and $n = 1,552$ HIV-uninfected). On measures of set-shifting, HIV+ individuals performed significantly worse than their HIV-uninfected counterparts; the pooled effect estimate was small ($d = -0.34$, 95% CI: $-0.47, -0.20$; Figure 2b) and evidence of heterogeneity was observed ($Q(13) = 32.22, p = .002, I^2 = 59.65\%$). The Trail Making Test – B (TMT-B) was used most frequently to assess set-shifting ($k = 10$). The pooled effect estimate for studies using the TMT-B was similar in magnitude to that of set-shifting overall ($d = -0.34$, 95% CI: $-0.51, -0.17$). Significant heterogeneity across studies using the TMT-B was observed ($Q(9) = 26.92, p < .001; I^2 = 71.89\%$).

Inhibition—Nine studies included in this meta-analysis assessed the effect of HIV-infection on measures of inhibition ($n = 1,377$ HIV+, and $n = 705$ HIV-uninfected). Although the pooled effect estimate was small ($d = -0.31$, 95% CI: $-0.40, -0.21$; Figure 3a), HIV+ individuals performed significantly worse than HIV-uninfected persons. There was only marginal evidence for between-study heterogeneity ($Q(8) = 12.33, p = .137; I^2 = 35.14$). The incongruent trial of the Stroop task (i.e., Stroop Interference) was used most commonly to assess inhibition ($k = 6$). The pooled effect estimate for Stroop Interference was similar in magnitude to that of inhibition overall ($d = -0.27$, 95% CI: $-0.37, -0.18$), with HIV+ individuals performing worse than their HIV-uninfected counterparts. Statistical tests for heterogeneity were non-significant ($Q(5) = 6.40, p = .270; I^2 = 21.84$).

Decision-Making—Eleven studies included in this meta-analysis assessed decision-making ($n = 629$ HIV+, and $n = 513$ HIV-uninfected). HIV+ individuals were found to perform significantly worse than HIV-uninfected individuals on measures of decision-making; the pooled effect estimate was in the medium range ($d = -0.41$, 95% CI: $-0.53, -0.28$; Figure 3b). No evidence for heterogeneity across studies was found ($Q(10) = 9.67, p = .475; I^2 = 0.00$). The pooled effect estimate was similar in magnitude ($d = -0.43$, 95% CI: $-0.62, -0.25$) for studies using the Iowa Gambling Task (IGT), the most frequently-used

measure of decision-making ($k = 6$). There was no evidence for between-study heterogeneity ($Q(5) = 7.09, p = .214; I^2 = 17.92$).

Apathy—Six studies evaluating apathy among HIV+ individuals were included in the current meta-analysis ($n = 240$ HIV+, and $n = 164$ HIV-uninfected). A comparison of self-reported apathy found that HIV+ participants reported significantly greater levels of apathy compared to HIV-uninfected individuals; the pooled effect estimate was large ($d = -0.87$, 95% CI: $-1.09, -0.66$; Figure 3c). Statistical tests for heterogeneity were non-significant ($Q(5) = 6.08, p = .305; I^2 = 0.00$). Apathy evaluation scale (AES; $n = 2$) and the Apathy subscale of Frontal Systems Behavior Scale (FrSBe; $n = 2$) were the two most commonly used rating scales to assess apathy. Whereas the pooled effect estimate for the AES was in the medium range ($d = -0.65$, 95% CI: $-1.01, -0.30$), the pooled effect estimate for the FrSBe was large ($d = -1.00$, 95% CI: $-1.41, -0.60$). There was no evidence for heterogeneity across results using AES or FrSBe measures (p 's > 0.05 ; I^2 's $= 0.00$).

Publication Bias

Visual inspection of the funnel plot and Egger's test ($t = -5.65, p < .001$) suggest that publication bias exists among the studies which assessed working memory. After using the nonparametric trim-and-fill method to adjust for possible publication bias, the effect size for working memory did not change substantively ($d = -0.51$, 95% CI: $-0.64, -0.38$). Evidence for publication bias was also found among studies which assessed inhibition (Egger's test: $t = 3.24, p = .014$). Adjustment using the trim-and-fill method yielded a similar pooled effect estimate for inhibition ($d = -0.24$, CI: $-0.23, -0.25$). Overall, our assessment of publication bias suggested that smaller studies with smaller effect sizes may have been less likely to be published or ascertained for the current meta-analysis. Evidence for publication bias was not observed for other domains of EF.

Moderator Analysis

Demographic Variables—Random-effects meta-regression models were used to examine the effects of the age, sex, and education of the HIV+ group on study effect sizes. Greater age was associated with more pronounced differences between HIV+ and HIV-uninfected groups on measures of working memory ($z = -12.97, p < .001$) and set-shifting ($z = -22.65, p < .001$), but not on measures of other EFs. A higher proportion of males was associated with greater differences between HIV+ and HIV-uninfected participants on measures of working memory ($z = -12.81, p < .001$), set-shifting ($z = -17.46, p < .001$), and inhibition ($z = -3.55, p < .001$), but not on measure of decision-making or apathy. Lower education was only associated with greater between group differences on measures of set-shifting ($z = 9.40, p < .001$).

Clinical Variables—The effects of substance dependence (current or recent), ART use, current CD4 count, and nadir CD4 count on executive abilities were also examined using random-effects meta-regression models. A greater proportion of HIV+ participants with current or recent substance dependence was associated with more pronounced deficits on measures of set-shifting ($z = -7.16, p < .001$) and inhibition ($z = -8.73, p < .001$), but not on measures of other executive abilities. Whereas a lower current CD4 count among HIV+

individuals was only associated with larger deficits on measures of decision-making ($z = 2.41$, $p = .016$), a lower nadir CD4 count was associated with more pronounced working memory ($z = 20.18$, $p < .001$), set-shifting ($z = 4.87$, $p < .001$), and inhibition ($z = 5.10$, $p < .001$) deficits, and greater levels of apathy ($z = 5.21$, $p < 0.001$) among HIV+ individuals. There was no significant association between the percentage of HIV+ participants on ART and study level effect sizes for any domain of EF.

Discussion

Summary of the Evidence

To our knowledge, this is the first systematic review and meta-analysis to examine to what degree discrete executive abilities are differentially affected or preserved in the context of HIV-infection. Performance decrements were found among HIV+ individuals in all domains of EF; however, the extent of HIV-associated deficits differed across domains. Overall, we found that the effect of HIV-infection was large and most prominent on measures of apathy. Decrements in functioning associated with HIV-infection were small for set-shifting and inhibition, and only somewhat larger (in the medium range) for decision-making and working memory. Working memory studies that used a variant of the 2-back test found between-group differences that were substantively larger, suggesting that this measure may be more sensitive to the effects of HIV-infection than other measures of working memory. Although the estimated effect of HIV-infection differed across EF domains, in many cases these differences were small and the confidence intervals of the pooled effect size estimates overlapped. Imprecision in pooled effect size estimates may be a result of within-domain study heterogeneity resulting from study level differences in sample demographic and clinical characteristics. Nonetheless, HIV-infection appeared to have a larger effect on measures of apathy and on working memory, as measured by the 2-back task, than on the other components of EF we examined.

The results of our meta-regression analyses indicate that HIV's effect on discrete domains of EF is influenced by multiple demographic and clinical factors. First, our finding that working memory and set-shifting deficits are more prominent in studies of older HIV+ groups suggest that executive abilities such as these, which are believed to rely largely on dorsolateral prefrontal cortex (dlPFC) circuitry, may be most vulnerable to the effects of aging in the context of HIV-infection. This idea is in agreement with evidence from studies of seronegative aging individuals (Chen & Li, 2007; Perry et al., 2009), which demonstrate the vulnerability of the dlPFC network to the aging process. A pattern of accelerated physiological aging has been previously described in HIV+ individuals, who tend to show an increased rate of cognitive decline with increasing age (Ding et al., 2017). It is possible that the increased age-related deficits in executive and other cognitive abilities may be a manifestation of the disproportionate burden of cardiovascular disease and cortical amyloid beta pathology found within the aging HIV+ population (Achim et al., 2009; Currier et al., 2008). Second, we found that studies with a higher proportion of HIV+ males show greater HIV-associated deficits on the *cognitive* aspects of EF (i.e., working memory, set-shifting, and inhibition). Currently, it is unclear whether these findings are due to confounding by characteristics overrepresented in males (e.g., greater lifetime substance use), true

neurobiological sex differences, or publication bias. With regard to the latter, two large all-female studies, which reported on data from the Women's Interagency HIV Study (WIHS), found relatively small effect sizes on measures of EF. It is possible that studies made up of all- or majority-male participants with similarly small effect sizes were not published. Few studies included in this review examined the effect of sex using stratification or interaction terms, and only one study found evidence of effect modification by sex: greater decision-making deficits among HIV+ women (Martin et al., 2016). The mechanisms driving the sex-specific effects observed in this meta-analysis warrant further investigation.

With regard to clinical variables, nadir CD4 count was found to be inversely associated with performance in all domains of EF, with the exception of decision-making, which was inversely associated with current CD4 count. These results are consistent with previous findings which suggest that nadir CD4 count is among the most robust predictors of cognitive impairment in the cART-era (Heaton, 2011). The current findings are in agreement with the notion that severe immunosuppression may cause irreversible damage to frontal systems responsible for both cognitive and limbic aspects of EF. In contrast to other executive abilities, decision-making may stand alone as being sensitive to one's current immunological status. The effects of current or recent substance dependence, on the other hand, appear to be restricted to domains of set-shifting and inhibition. These findings coincide well with models of addiction, which posit that poor inhibitory control may constitute an endophenotype associated with increased vulnerability for substance use behaviors (Kim-Spoon et al., 2016; Nigg et al., 2006), and reduced set-shifting ability, a cognitive sequelae of heavy substance use (Lundqvist, 2005; Verdejo-Garcia & Perez-Garcia, 2007). We found no evidence for a reduced effect of HIV-infection on EF among HIV+ groups with greater rates of reported ART use. However, many studies did not report the number of participants using *combined* or *highly active* ART, so the neuroprotective effects of these potentially more effective therapeutics could not be assessed.

Qualitative Review of the Literature

Working Memory—Our results suggest that working memory is perhaps the most significantly affected *cognitive* component of EF among cART-era HIV-infected individuals. A review of individual studies suggests that HIV preferentially disrupts working memory *processing* (i.e., the mental manipulation and re-ordering of information), while leaving working memory *storage* (i.e., mentally holding information for an extended time) relatively intact (Martin et al., 2001; Martin et al., 2003). Evidence from functional neuroimaging studies largely supports the behavioral findings, and in doing so, links HIV-associated working memory deficits to abnormalities in frontostriatal and frontoparietal circuitry (Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Tomasi, Chang, De Castro Caparelli, Telang, & Ernst, 2006). Specifically, among HIV+ individuals, fMRI has shown abnormal hyperactivation within and outside of the working memory network, particularly in the lateral PFC, even before tasks performance is affected (Chang et al., 2001; Ernst et al., 2002). HIV-related fMRI abnormalities during a working memory task have been associated with abnormal levels of glial functioning markers (i.e., choline-containing compounds and myo-inositol) in frontal white matter and the basal ganglia (Ernst, Chang, & Arnold, 2003). Also, reduced working memory performance has been associated with

elevated levels of serum inflammatory cytokines in HIV+ individuals (Cohen et al., 2011). Based on such findings, some have proposed a model of HIV-related working memory dysfunction in which inflammation leads to glial metabolic abnormalities, which in turn disrupt neural processing needed for working memory. However, HIV-related deficits in working memory have also been associated with the availability of dopamine transporters (DAT), dopamine receptor 1 (DRD1) genotype (Jacobs, Murray, Byrd, Hurd, & Morgello, 2013), and presence of the *APOE* ϵ 4 allele (Chang et al., 2014), implicating additional biological pathways. Future multimodal studies are needed to further understand how these distinct neurobiological processes may interact with HIV infection to disrupt brain regions necessary for working memory.

Set-Shifting—Whereas the findings from studies examining the effect of HIV-infection on set-shifting ability have been mixed, deficits in this domain of EF have only been consistently demonstrated among HIV+ individuals with co-occurring substance use disorders (Bousman et al., 2010; Rippeth et al., 2004). This is consistent with our findings that larger deficits in set-shifting are found among studies with relatively high proportions of substance-dependent HIV+ participants. While measurable set-shifting deficits were not found in the majority of individual studies, neuroimaging studies have demonstrated that structural and functional brain abnormalities in the basal ganglia and medial frontal regions (e.g., dorsal anterior cingulate cortex) are associated with poorer performance on set-shifting measures in HIV+ individuals (Corrêa et al., 2016; Jiang, Barasky, Olsen, Riesenhuber, & Magnus, 2016). With regard to biomarkers, HIV-associated set-shifting deficits have been associated with magnetic resonance spectroscopy (MRS) markers of abnormal astrocytic glutamate processing, reduced oxygen and glucose metabolism in frontal white matter structures (Mohamed et al., 2010), and elevated levels of circulating cytokines (Cohen et al., 2011). Furthermore, possession of an *APOE* ϵ 4 allele has been associated with set-shifting deficits among HIV+, but not HIV-uninfected, individuals (Chang et al., 2011; Chang et al., 2014).

Inhibition—Evidence suggests that inhibitory control deficits occur in HIV+ individuals with co-occurring alcohol or stimulant use disorders (Rippeth et al., 2004; Schulte, Müller-Oehring, Sullivan, & Pfefferbaum, 2011); however, as with set-shifting, there is little evidence that HIV-infection alone contributes to measurable deficits in inhibition. Although the overall estimated effect of HIV-infection on measures of inhibition was small, there is evidence that HIV may functionally alter brain regions involved in inhibitory control processes (du Plessis et al., 2015). Specifically, on a measure of reactive response inhibition (i.e., withholding a response following a “stop” signal), HIV+ individuals were found to display a pattern of hypoactivation in the right and left putamen. Moreover, MRS markers of glial functioning (i.e., myo-inositol and creatine) within the frontal white matter have also been found to correlate with reduced inhibitory control, suggesting a possible etiological basis for striatal abnormalities (Chang et al., 2002). Given the potential link between inhibitory control and risky decision-making, future efforts should continue to examine how HIV-related disruption to brain networks implicated in inhibitory control relates to real-world risk-taking and impulsive behavior.

Decision-making—Decision-making has received considerable attention in the HIV literature over the last two decades. This is in large part due to the idea that faulty decision-making may predispose individuals to enact unsafe sexual practices or substance use behaviors, thus increasing the likelihood of HIV transmission. Overall, there is strong support for the relationship between HIV infection and decision-making deficits among HIV+ individuals with (Hardy, Hinkin, Levine, Castellon, & Lam, 2006; Martin et al., 2013; Martin et al., 2004) and without co-occurring or recent substance dependence (Fama, Sullivan, Sasso, Pfefferbaum, & Zahr, 2016; Iudicello, Woods, Cattie, Doyle, & Grant, 2013; Thames et al., 2012) using measures such as the Iowa Gambling Task (IGT) (Bechara, 2007) and the Cambridge Gambling Task (Sahakian & Owen, 1992). Decision-making under ambiguity, when risk and reward contingencies are not explicitly known, appears to be particularly impaired among HIV+ individuals compared to decision-making under specified conditions (Brand, Grabenhorst, Starcke, Vandekerckhove, & Markowitsch, 2007; Martin et al., 2016; Martin et al., 2013). Functional imaging studies suggest that HIV infection is associated with abnormal activation in several brain regions known to support decision-making processes, including the medial PFC, the dorsal striatum, the ventral striatum, and the insula (Connolly et al., 2014; Meade et al., 2016). In agreement with our findings demonstrating a relationship between current immunologic status and decision-making ability, lower current CD4 cell count has been associated with greater activation of prefrontal brain regions during a decision-making task (Connolly et al., 2014). Whether additional biomarkers or genetic factors are associated with impaired decision-making in the context of HIV infection warrants future research.

Apathy—Evidence from cART-era studies suggests that apathy is a relatively common neurobehavioral syndrome among HIV+ individuals, although estimated prevalence rates vary significantly (Kamat et al., 2014; Rabkin et al., 2000). Previous reports suggest that apathy occurs early following seroconversion (Kamat et al., 2016) and tends to correlate with performance on EF measures, suggesting that this symptom may arise as a direct result of structural or functional neurological changes to frontostriatal networks (Castellon, Hinkin, & Myers, 2000; Paul et al., 2005; Shapiro, Mahoney, Zingman, Pogge, & Verghese, 2013). Our results indicate that deficits in goal-directed behavior (i.e., apathy) among cART-era HIV+ individuals are on average more severe than deficits in other domains of EF. Apathy among HIV+ individuals has been linked to disruption to the white matter pathways that project to the superior and ventromedial regions of the PFC (Hoare et al., 2010; Kamat et al., 2014). Volume loss in the nucleus accumbens, which is known to be involved in reward processing and (Hikida, Morita, & Macpherson, 2016), has also been associated with apathy among HIV+ individuals (Paul et al., 2005). Apathy has been most consistently associated with disruption to the functioning of frontostriatal networks, which innervate the medial frontal and anterior cingulate cortex and subcortical limbic structures, such as the nucleus accumbens (Hoare et al., 2010; Kamat et al., 2014; Paul et al., 2005). Given our findings indicating that goal-directed behavior is among the aspects of EF most vulnerable to HIV-infection, it is possible that this medial frontostriatal network may be especially vulnerable to the pathophysiology of HIV infection. This idea is supported by structural and functional neuroimaging studies, which demonstrate abnormalities in the anterior cingulate

region among individuals in the earliest phase of HIV infection (Küper et al., 2011; Wang et al., 2015).

Limitations

While the current study provides novel insights into the relationship between HIV-infection and executive dysfunction, several limitations need to be acknowledged. First, evidence of publication bias was found for studies of working memory and inhibition. Although publication bias may have reduced our ability to estimate accurate pooled effect sizes, statistical correction for publication bias using the trim and fill method did not substantially change these estimates. Second, as was described in the assessment of individual study bias, several studies included in this review have used HIV+ and control groups which differ significantly on potentially confounding variables, including age, education, literacy, and substance use characteristics. Because each of these variables is known to independently correlate with executive and frontostriatal functioning (Castellon, Hinkin, & Wood, 1998; Manly et al., 1999; Manly et al., 2011; Rohit et al., 2007; Ryan et al., 2005; Weiss, Reed, Kligman, & Abyad, 1995), these studies may have provided biased effect sizes. Third, we have treated EF as a group of distinct, yet related, cognitive processes. Although many of the neuropsychological measures included in this study are purported to assess discrete executive functions, all of these measures likely also draw upon other executive and non-executive cognitive processes. This issue of task impurity may limit the conclusions that can be drawn about HIV's impact on specific domains of EF. Relatedly, we recognize that because of task impurity, there may be some disagreement as to which domains of EF specific neuropsychological tests are believed to primarily assess. Future studies may benefit from making greater use of laboratory measures adapted from the field of cognitive neuroscience, which are often better suited to assess discrete executive processes with greater specificity.

Fourth, with regard to the assessment of apathy, all of the cART-era studies reviewed here have used self- or informant-report apathy measures, which in some cases do not correlate with objective symptoms (Donders, Oh, & Gable, 2015). Given this distinction between objective and subjective measures, it is unclear whether it is appropriate to compare the effect estimates for apathy with those of other domains of EF. An improved understanding of how motivationally based frontostriatal processes are disrupted by HIV infection may result from making use of task-based measures of goal-directed behavior and initiation, such as the *rewarded CPT*, in conjunction with structural and functional neuroimaging (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Lastly, it is important to mention that we limited the scope of the current review to components of executive and frontostriatal functioning that have been included in recent conceptual theories and taxonomies of EF (Banich, 2009; Lezak et al., 2012; Miyake, Akira; Friedman, 2012; Stuss, Binns, Murphy, & Alexander, 2002; Suchy, 2015) and have received substantial attention in the HIV literature. It is important to note that there are other executive and frontostriatal processes believed to be affected by HIV-infection, such as reaction time variability and verbal fluency, which were not directly addressed here. A number of these cognitive processes have been the subject of previous reviews (e.g., Iudicello et al., 2007; Stéfan Du Plessis et al., 2014).

Conclusions

In addition to confirming the widely-held notion that HIV-infection is associated with deficits in EF, the current systematic review and meta-analysis has quantified the extent to which HIV-infection differentially affects discrete domains of EF and has shed light on the moderating effects of relevant demographic and clinical variables. It is our hope that this initial attempt to summarize and quantify the relatively large body of literature will inform the current understanding of frontal systems dysfunction in the context of HIV-infection and highlight the most relevant targets for cognitive remediation and pharmacologic intervention for patients with HAND.

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Figure 1.
A flowchart diagram of the article selection process used for the current systematic review and meta-analysis

Figure 3.

Forest plots depicting individual and pooled effect size estimates (Cohen's *d*) and 95% confidence intervals for measures of (a) inhibition, (b) decision-making, and (c) apathy are shown. The dotted line represents the pooled effect size estimate. Negative effect sizes reflect poorer performance among the HIV+ groups. LCL = lower confidence level; UCL = upper confidence level; WGHT= weight.

Table 1.

Studies comparing HIV+ and HIV-uninfected groups on measures of working memory, set-shifting, and inhibition in the era of combined antiretroviral therapy

Working Memory	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Farinpour et al., (2000) *	Listening Span Self-Ordered Pointing Task	30 HIV+, 30 HIV- Age: 41.7 100% Male	57%		Listening Span: HIV+ < HIV- Self-Ordered Pointing Task: HIV+/Sym < HIV+/Asym, HIV-HI
Chang et al., (2001) *	2-Back 2-Increment	11 HIV+, 11 HIV- Age: 41 (4.8) 100% Male	91%	fMRI: lateral PFC and supplementary motor area more active in HIV+ group during 2-back	2-Back: Data lost due to error 2-Increment: HIV+ = HIV-
Martin et al., (2001) *	Modified Letter-Number Span task	41 HIV+, 37 HIV- Age: 44.1 (6.0) 100% Male	73%, 22%		Modified Letter-Number Span task: HIV+ < HIV-
Hinkin et al., (2002) *	2-Back, Verbal 2-Back, Visual	50 HIV+, 23 HIV- Age: 43.5 (7.5) 82% Male	100%, 100%		2-Back, Verbal: HIV+ < HIV- 2-Back, Visual: HIV+ < HIV-
Ernst et al., (2002)	2-Back	10 HIV+, 10 HIV- Age: 36.3 (7.9) 100% Male	100%	fMRI: lateral PFC activated more in HIV+ group during the 2-back	2-Back: HIV+ = HIV-
Martin et al., (2003) *	DNM	50 HIV+, 35 HIV- Age: 47 100% Male	90%, 80%		DNM: HIV+ < HIV-
Ragin et al., (2005)	Digit Span	11 HIV+, 11 HIV- Age: 49.4 (7.3) 82% Male	100%	DTI: Putamen FA positively correlated with digit span performance	
Tomasi et al., (2006)	2-Back with 'soft' and 'loud' acoustic noise	10 HIV+, 15 HIV- Age: 37.1 (2.7) 100% Male	80%, 80%	fMRI: Cerebellum and superior prefrontal cortex hypoactive in HIV+ group during the 2-back	2-Back: HIV+ = HIV-
Chang et al., (2008) *	2-Back	35 HIV+, 14 HIV- Age: 43.0 (11.9) 60% Male	96%	PET: Lower dopamine transporter (DAT) in putamen associated with worse 2-Back	2-Back: HIV+ < HIV-
Caldwell et al., (2014) *	2-Back	34 HIV+, 28 HIV- Age: 45.6 69% Male	79%, 79%	fMRI: Brain activation during task did not differ between HIV+ and HIV- groups	2-Back: HIV+/HCV- = HIV+/HCV+ = HIV-/HCV-
Chang et al., (2014) *	Working Memory Composite TMT-B	80 HIV+, 97 HIV- Age: 47.4 (1.1) 82% Male	93%	MRS: Relationship between MRS and TMT-B association not reported	Interaction found between APOE $\epsilon 4$ allele and HIV on TMT-B, but not working memory composite score.
Set-Shifting	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings

Working Memory	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Rippeth et al., (2004) *	TMT-B WCST HCT Working Memory Composite	93 HIV+, 107 HIV- Age: 38.3 84% Male	Not reported		TMT-B: All groups equal WCST: HIV+/Mt+ < HIV-/Mt- HCT: All groups equal Working Memory Composite: All groups equal
Bousman et al., (2010) *	TMT-B WCST HCT	130 HIV+, 99 HIV- Age: 38.7 100% Male	Not reported		TMT-B: HIV+/Mt+ < HIV-/Mt- WCST: All groups equal HCT: HIV+/Mt+ < HIV-/Mt-
Manly et al., (2011) *	TMT-B	1,142 HIV+, 511 HIV- Age: 42.4 (8.5) 100 % Female	Not reported		TMT-B: HIV+ = HIV-
Chang et al., (2011) *	TMT-B Working Memory Composite	69 HIV+, 70 HIV- Age: 47.0 (1.2) 91% Male	80%	MRI: Relationship between brain volume and TMT-B not reported	TMT-B: Interaction found between APOE e4 and HIV on TMT-B
Byrd et al., (2013) *	Set-Shifting Composite Working Memory Composite	30 HIV+, 30 HIV- Age: 46.4 50% Male	63%, 63%		EF Composite: HIV+ = HIV-
Kesby et al., (2015) *	TMT-B WCST HCT Stroop, Interference	60 HIV+, 61 HIV- Age: 39.8 100% Male	58%		TMT-B: HIV+ < HIV- WCST: HIV+ = HIV- HCT: HIV+ = HIV- Stroop: HIV+ HIV-
Tang et al., (2015) *	TMT-B Intra/Extra Dimensional Shift	21 HIV+, 22 HIV- Age: 37.5 (9.0) 67% Male	71%	DTI: Left anterior internal capsule FA positively correlated with TMT-B, and CC FA positively correlated with IED	TMT-B: HIV+ < HIV- Intra/Extra Dimensional Shift: HIV+ = HIV-
Fama et al., (2016) *	TMT-B Intra/Extra Dimensional Shift Cambridge Gambling Test	75 HIV+, 70 HIV- Age: 49.8 Sex not reported	78%, 78%		TMT-B: HIV+/ALC- < HIV-/ALC- Intra/Extra Dimensional Shift: HIV+/ ALC- < HIV-/ALC- Cambridge Gambling Test: HIV+/ALC- < HIV-/ALC-
Jiang et al. (2016)	Task Switching Paradigm	9 HIV+, 5 HIV- Age: 55-57 100% Male	100%, 100%	fMRI: dorsal ACC activation positively correlated with task switching costs in HIV+ group	Task Switching Paradigm: HIV+ = HIV-
Corréa et al., (2016)	WCST	47 HIV+, 19 HIV- Age: 52.5 (7.4) 76% Male	100%, 100%	MRI: WCST deficits associated with reduced caudate, putamen, globus pallidum, and accumbens volumes in HIV+. WCST performance was not related to measures of cortical thickness.	
Spies et al., (2016) *	WCST HCT Color Trails 2 Stroop, Interference	67 HIV+, 50 HIV- Age: 36 (6) 100 % Female	69%		WCST: HIV+ = HIV- HCT: HIV+ = HIV- Color Trails 2: HIV+ = HIV- Stroop: HIV+ = HIV-

Working Memory	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Inhibition	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Chang et al., (2002) *	Stroop, Interference TMT-B	45 HIV+, 25 HIV- Age: 35.7 (1.4) 84% Male	0%	MRS: Stroop correlated with MI, CHO, and CR in HIV group	Stroop: HIV+ < HIV- TMT-B: HIV+ < HIV-
Martin et al., (2004)	Stroop, Interference	67 HIV+, 89 HIV- Age: 43.1 100% Male	73%		Stroop: HIV+ < HIV-
Cohen et al., (2011)	Stroop, Interference TMT-B LNS	30 HIV+, 37 HIV- Age: 44.8 (9.1) 63% Male	80%, 80%	Cytokine Assay: HIV+ associated with INF- γ , IL-1 β , IL-6, IP-10, MCP-1, MIP-1 β , and TNF- α levels. Stroop associated with IL-18, MCP-1, MIP-1 β , and TNF- α . TMT-B associated with IL-10 and IL-16. LNS associated IL-10 and TRAIL.	
Schulte et al., (2011) *	Stroop matching task	42 HIV+, 36 HIV- Age: 48.0 25% Male	82%, 82%		Stroop matching task: HIV+/ALC+ < HIV-/ALC- HIV+/ALC-, HIV-/ALC+ = HIV-/ALC-
du Plessis et al., (2015) *	Stop Signal Anticipation Task	17 HIV+, 18 HIV- Age: 31 (4.1) 14% Male	0%	fMRI: HIV+ show putamen hypoactivation during stop signal task	Stop Signal Anticipation Task: HIV+ = HIV-
Maki et al., (2015) *	Stroop, Interference TMT-B LNS	1,019 HIV+, 502 HIV- Age: 47.5 (8.8) 100% Female	76%, 76%		Stroop: HIV+ = HIV- TMT-B: HIV+ = HIV- LNS: HIV+ = HIV-

Note: Age and sex of HIV+ group displayed; bolded measures assess the executive function of interest; ACC = anterior cingulate cortex; ALC = alcohol; Asym = asymptomatic; CHO = choline compounds; CR = total creatine; DNM = Delayed Nonmatch-to-Sample; FA = fractional anisotropy; HCT = Halstead Category Test; HCV = hepatitis C; LNS = Letter Number Sequencing; MI = myo-inositol; Mt = methamphetamine; PFC = prefrontal cortex; Sym = symptomatic; TMT-B = Trail Making Test- Part B; WCST = Wisconsin Card Sorting Task

* Study included in meta-analysis

Table 2.

Studies comparing HIV+ and HIV-uninfected groups on measures of decision-making and apathy in the era of combined antiretroviral therapy

Decision Making & Risk Taking	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Martin et al., (2004) *	IGT	46 HIV+, 47 HIV- Age: 46.2 (4.4) 100% Male	80%, 50%		IGT: HIV+ < HIV-
Gonzalez et al., (2005)	IGT Stroop, Interference DNM	109 HIV+, 154 HIV- Age: 44.6 (6.1) 100% Male	82%, 41%		IGT: HIV+ = HIV- Stroop: HIV+ = HIV- DNM: HIV+ = HIV-
Hardy et al., (2006) *	IGT Stroop, Interference Digit Span Backward TMT-B PASAT errors	67 HIV+, 19 HIV- Age: 43.8 (8.1) 66% Male	100%, 100%		IGT: HIV+ < HIV- Stroop: HIV+ = HIV- Digit Span Backward: HIV+ = HIV- TMT-B: HIV+ = HIV- PASAT: HIV+ < HIV-
Thames et al., (2012) *	IGT	100 HIV+, 26 HIV- Age: 43.8 (7.3) 76% Male	Not reported		IGT: HIV+ < HIV-
Iudicello et al., (2013) *	IGT	146 HIV+, 51 HIV- Age: 43.3 91% Male	79%		IGT: HIV+/HAND+ < HIV- HIV+/HAND- = HIV-
Martin et al., (2013) *	IGT Cups Task	56 HIV+, 23 HIV- Age: 47.6 (5.1) 100% Male	93%		IGT: HIV+ < HIV- Cups Task: HIV+ = HIV-
Connolly et al., (2014) *	Risky-Gains Task	21 HIV+, 19 HIV- Age: 40.8 (2.6) 90% Male	71%	fMRI: Caudate, ACC, dorsolateral prefrontal cortex, insula more activated on Risky-Gains Task in HIV+	Risky-Gains Task: HIV+ = HIV-
Fujiwara et al., (2015) *	Game of Dice Task	20 HIV+, 20 HIV- Age: 48.2 (9.9) 75% Male	90%, 90%		Game of Dice Task: HIV+ < HIV-
Martin et al., (2016) *	Game of Dice Task	92 HIV+, 134 HIV- Age: 47.1 65% Male	94%		Game of Dice Task: HIV+ < HIV-
Meade et al., (2016) *	Intertemporal Choice Task	18 HIV+, 17 HIV- 41.0 (9.5) 57% Male	100%	fMRI: Left parietal, superior PFC, and ACC regions more active during task in HIV+	Intertemporal Choice Task: HIV+ = HIV-
Payday et al., (2016) *	IGT Balloon Analogue Risk Task	60 HIV+, 60 HIV- Age: 36.4 100% Male	Not Reported		IGT: HIV+ = HIV- Balloon Analogue Risk Task: HIV+ < HIV-

Decision Making & Risk Taking	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Apathy	Executive Functioning Measure(s)	Sample Size Age Sex	ART, cART/HAART	Imaging/Biomarker	Behavioral Findings
Castellon et al., (2000) *	NPI, Apathy Stroop, Interference	65 HIV+, 21 HIV- Age: 39.4 93% Male	71%		NPI Apathy: HIV+/Asym > HIV- HIV+/Sym > HIV- Stroop: HIV+/ Sym + < HIV-
Tate et al., (2003)	AES Apathy	45 HIV+, 22 HIV- Age: 42.7 (5.7) 36% Male	100%		AES Apathy: HIV+ > HIV-
Paul et al., (2005) *	AES Apathy TMT-B	45 HIV+, 22 HIV- Age: 42.7 (5.7) Sex not reported	100%		AES Apathy: HIV+ > HIV- TMT-B: HIV+ < HIV-
Bogdanova et al., (2010) *	AES Apathy Toronto Alexithymia Scale-20	34 HIV+, 34 HIV- Age: 47.5 (6.0) 73% Male	Not Reported		AES Apathy: HIV+ > HIV- Toronto Alexithymia Scale-20: HIV+ > HIV-
Hoare et al., (2010)	AES Apathy LNS	26 HIV+, 10 HIV- Age: 33.7 Sex not reported	100%	DTI: Compared to HIV+/AP+, HIV +/AP- had higher FA in the CC, superior and anterior corona radiata, and anterior thalamic radiation	Spatial Span: HIV +/AP+ = HIV+/AP- = HIV- LNS: HIV+/Ap.+ = HIV+/Ap.- = HIV-
Kamat et al., (2013) *	Beck Depression Inventory-II, Apathy Items	43 HIV+, 29 HIV- Age: 42.4 (9.5) 51% Male	70%		Beck Depression Inventory-II, Apathy Items: HIV+ > HIV-
Kamat et al., (2014) *	Frontal Systems Behavioral Scale, Apathy	19 HIV+, 19 HIV- Age: 42.9 (11.4) 84% Male	75%	DTI: Apathy was negatively correlated with FA in anterior and superior corona radiata, genu, vmPFC in HIV+	Frontal Systems Behavioral Scale, Apathy: HIV+ > HIV-
Kamat et al., (2016) *	Frontal Systems Behavioral Scale, Apathy	34 HIV+, 39 HIV- Age: 32.7 (10.0) 97% Male	32%		Frontal Systems Behavioral Scale, Apathy: HIV+ > HIV-

Note: Age and sex of HIV+ group displayed; bolded measures assess the executive function of interest; ACC = anterior cingulate cortex; AES = Apathy Evaluation Scale; AP = apathy; Asym = asymptomatic; DNM = Delayed Nonmatch-To-Sample; FA = fractional anisotropy; HAND = HIV associated neurocognitive disorder; LNS = Letter Number Sequencing; NPI = Neuropsychiatric Inventory; PASAT = Paced Auditory Serial Addition Test; PFC = prefrontal cortex; Sym = symptomatic; TMT-B = Trail Making Test- Part B; vmPFC = ventral medial prefrontal cortex

* Study included in meta-analysis