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The Impact of Psychological Stress on Neurocognitive Functioning and Decline in HIV-Positive Adults: A Systematic Review of the Literature

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Abstract

Adults infected with HIV have been living longer and healthier lives with the development of antiretroviral therapies. Aging with HIV, however, leads to a growing number of comorbidities. Evidence strongly supports that older HIV-positive (HIV+) adults are at increased risk for the development of HIV-Associated Neurocognitive Disorders (HAND). Currently, there is limited evidence on the etiological factors and mechanisms of this neurocognitive decline. Recent research suggests the potential interactive effects of psychological stress and HIV on decreased neurocognitive functioning. This systematic literature review seeks to examine existing research with the purpose of analyzing the relationship between psychological stress and neurocognitive outcomes in HIV+ adults. From an original search of 576 full-text and peer-reviewed articles, 11 were selected for investigation. A number of studies found combinative effects of stress and HIV on domains of neurocognition such as verbal learning, memory, delayed recall, executive functioning, memory retrieval and attention. These results help provide more insight into the mechanisms, such as psychological stress, contributing to and interacting with HAND. Conclusively, it is feasible that interventions for the prevention and treatment of HAND for this vulnerable population can potentially stem from HIV-related stress management techniques.

Introduction

The relationship between life stress, perceived stress, early life stress (ELS), and trauma on neurocognitive functioning in HIV+ adults has recently become and increasingly relevant and influential topic. With the development of highly active antiretroviral therapy (HAART) in 1996 and combination antiretroviral therapy (CART), HIV is now considered to be more of a chronic condition rather than an acute death sentence (Kirk & Goetz, 2009). The longer infection periods, however, are more likely to lead to increases in HIV-related disorders and diseases as well as increased healthcare costs (Krentz & Gill, 2015).

A disconcerting comorbid condition is HAND. Anywhere between 30-50% of people living with HIV (PLWH) meet the criteria for some level of HAND or neurocognitive decline (Tozzi et al., 2007). HAND can manifest itself in domains such as verbal and working memory, attention and concentration, executive functioning, fine motor skills and more. These deficits create challenges in the completion of everyday tasks such as going to the grocery store, focusing while at the movies or watching TV, or remembering names (Hopcroft et al., 2013). HAND is also a contributor to other HIV-related psychological and social support issues. For example, some older HIV+ adult males felt that their inability to retain information has kept them from keeping a job (Hopcroft et al., 2013). The inability to hold employment due to exhaustion and lack of memory, therefore, leads to less social support from coworkers and more social isolation (Rueda, Law & Rourke, 2014).

There are many theories on the development of neurocognitive impairment in the HIV/AIDS population. It is known that the virus has the ability to penetrate the blood-brain barrier. The broken barrier allows for the entrance of HIV cells or infected white blood cells. These cells can then aid in the production of inflammatory cytokines or lead to the infection

brain cells such as glial cells. These cytokines and infected brain cells subsequently contribute to neuroinflammation, which may lead to neurocognitive decline (Vance, Fazeli, Grant, Slater & Raper, 2013).

There are also suggestions indicating a co-existing relationship between immune health and brain health. With HAART or CART reducing viral load in the body, it may seem conceivable that these therapies will then also prevent the penetration of the blood-brain barrier and, consequently, decrease neuroinflammation (Vance, Fazeli, Grant, Slater & Raper, 2013). However, to date, there are no proven significant differences in neurocognitive impairment in patient groups with pre-CART and CART therapies. In a recent study by Heaton et al. (2011), 73.4% of the pre-CART and 76% of the CART groups experienced some form of HAND. The study also showed that some severe neurocognitive impairments were actually observed more frequently in the CART populations than the pre-CART ones.

Evidently, although advancing antiretroviral therapies have significant impacts on length and quality of life in HIV+ patients, they have not been shown to have significant positive effects on slowing the onset of neurocognitive decline. In summary, the exact etiology of the development of HAND is still unknown. A more comprehensive understanding of the etiological factors of HAND is essential in order to aid in the prevention and treatment of neurocognitive decline for the HIV+ population.

According to a systematic literature review of the interactive effects of childhood maltreatment, mental health outcomes, and HIV-status, rates of childhood maltreatment such as physical, sexual, or emotional abuse are consistently significantly higher in the HIV+ population as compared to the general population (Spies, Afifi, Archibald, Fennema-Notestine, Sareen & Seedat, 2012). Additionally, those with HIV, especially those with ELS or current life stress and

trauma, are significantly more likely to self-report or become diagnosed with post-traumatic stress disorder (PTSD) and persistent chronic stress (Spies, Afifi, Archibald, Fennema-Notestine, Saren & Seedat, 2012). The combined effects of increased stress and an HIV+ infection will likely lead to complications with neurocognitive functioning, the development and onset of HAND, and brain structure. This systematic literature review, therefore, seeks to gather evidence and compile data with the intention of contributing to the formidable goal of discovering some of the etiological mechanisms of HAND and neurocognitive decline in PLWH.

Methods

Search Strategy

Academic journal articles were searched through the electronic databases of PubMed and Ebscohost during the time period of January 23 through February 3, 2017. Ebscohost also reviewed the databases of PsycINFO, MEDLINE, and CINAHL. The search criteria included original peer-reviewed and full text research articles in the English language. Any secondary articles, reviews, systematic reviews, or meta-analyses were excluded. No limit on publication date was established in order to include all potentially relevant articles. No limitations were imposed based on type of original research study or sample size. From the articles selected for further detail, reference lists were also examined in order to discover any and all potentially relevant sources (see **Figure 1.)**

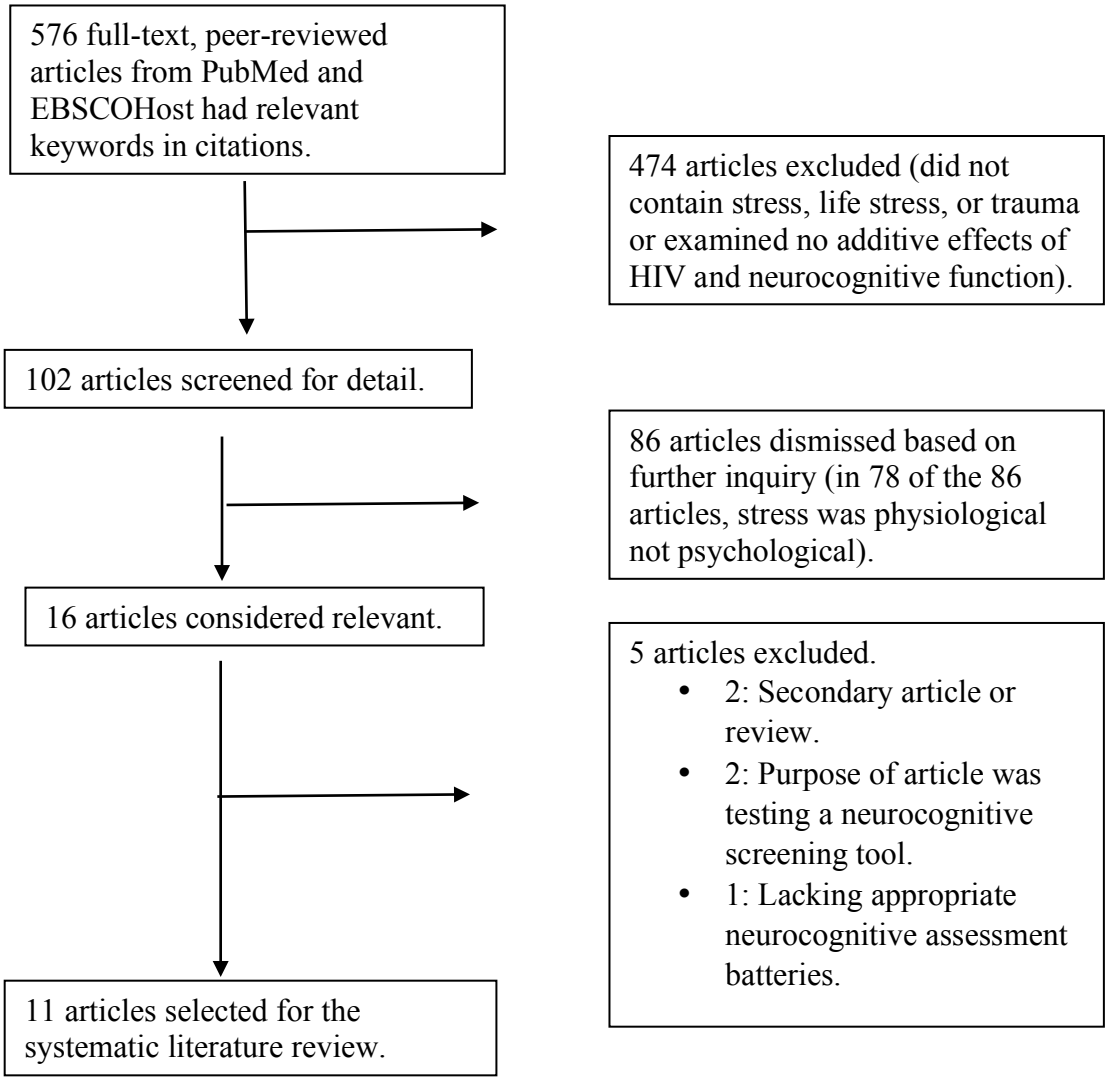
Selection Criteria

With a major variable being neurocognitive decline – a feature most strongly associated with aging, any articles referencing cognitive ability in children or adolescents under the age of 18 were excluded. There were no exclusions based on gender, sex, gender identity, or sexual

orientation. Articles without reference to HIV, HIV-1, HIV-positive, or HIV-infection in major headings were excluded.

In regard to the predictor variable of stress, the focus of this systematic review is to examine the effects psychological stress, trauma, PTSD, ELS, life stress, chronic stress, perceived stress, or persistent stress on neurocognitive outcomes in HIV+ participants. All of these terms were included. Any articles with a focus solely on physiological stress, such as oxidative stress, as a result, were excluded.

Figure 1. Flow diagram of literature review process.



Finally, the variable of neurocognition was screened. The domains of neurocognitive performance or impairment reviewed included verbal memory and learning, recall, processing speed, attention and working memory, verbal fluency, attention and concentration, executive functioning, psychomotor speed, and fine motor skills. All studies referencing neurocognitive assessment or batteries as related to one, some, or all of these measures were therefore included.

Results

An original search of 1,119 articles appeared with the initial keyword search of all relevant terminology. Of the 1,119 articles, only 576 remained after removal of articles that were neither full-text nor peer-reviewed. Of the 576 articles, 474 were immediately excluded, as they had no relevance to the interactive effects of HIV, neurocognitive functioning, or stress. These articles, generally, only included one or two of the relevant keywords in major headings and subject lines. With 102 articles remaining, 86 articles were dismissed based on further inquiry. The vast majority of articles (78 of the 86) were dismissed because the variable of stress referred only to physiological stress, such as oxidative stress. Other articles were excluded based on the fact that neurocognition was only utilized in a demographic sense, such as through a Mini Mental Status Exam, or they had no relevant statistical analyses performed on neurocognition. With 16 articles remaining, the rest were excluded because they were secondary reviews (2), studied the effectiveness of neurocognitive screening tools instead of measuring neurocognitive functioning (2), or did not utilize appropriate neurocognitive assessment batteries (1). 11 articles remained and exhibited the requirements of the inclusion criteria.

From the articles selected for review, the studies ranged from one article being completed in 2003 and the remaining 10 publications published between 2012 and 2017. Two of the 11 articles measured only HIV+ participants, while the remaining nine studies had comparisons

Table 1. Summary of 11 articles selected for review.

Study	Participants and Exclusion Criteria	Design and Procedure	Major Findings
Pukay-Martin, N. D., Cristiani, S. A., Saveanu, R. & Bornstein, R. A. (2003) The Relationship Between Stressful Life Events and Cognitive Function in HIV-Infected Men.	251 HIV+ participants and 82 HIV- participants. Participants with a history of intravenous drug use, head trauma, unconsciousness and neurologic or learning disorders were excluded.	Self-reported results from the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale was utilized to determine the amount of control participants felt over personal stressful life events in the past decade. Standard neuropsychological batteries were used to determine cognitive performance. Multiple linear regression analyses using the Pearson's r coefficient were performed to determine the partial correlational relationships between the types of life stress in HIV+ and HIV- sub groups.	More positive life events and less negative stressful triggers led to better cognitive performance. For HIV+ individuals only, negative life stressors led to worse performance in executive functioning, attention, and processing speed.
Clark, U. S., et al. (2012) Effects of HIV and Early Life Stress on Amygdala Morphometry and Neurocognitive Function.	49 HIV+ and 47 HIV- participants. The participants excluded were those with a history of substance abuse, developmental or learning disabilities, psychiatric illness, dementia, neurological or CNS illness, or traumatic head injury.	The Early Life Stress Quantification (ELSQ) measured histories of adverse life events such as abuse, neglect, bullying or family conflict before the age of 18. Participants were categorized based on high-ELS, with three or more adverse life events, or low-ELS, with less than three adverse life events. Standard neurocognitive batteries were used to determine psychomotor speed, executive functioning, fine-motor dexterity and verbal memory. Structural MRI and neuroimaging analyses were	Larger left and right amygdala volumes were seen in the HIV+ groups compared to the HIV- groups. The HIV+ and high-ELS group largely drove this significant difference. Left amygdala enlargement was significantly associated with poor performance on processing and psychomotor speed. High ELS was associated with poorest and slowest psychomotor and

		used to measure brain structure. ANOVA testing, post-hoc comparisons, and linear regression analyses measured for statistically significant differences in HIV-disease factors and ELS.	processing speeds in both HIV+ and HIV- groups.
Spies, G., Fennema-Notestine, C., Archibald, S. L., Cherner, M. & Seedat, S. (2012). Neurocognitive Deficits in HIV-Infected Women and Victims of Childhood Trauma.	83 HIV+ and 27 HIV- South African women with and without exposure to childhood trauma. Participants excluded were those with current or previous psychotic disorders, substance abuse, dementia, head trauma, seizure disorders or use of psychotropic medication.	The Childhood Trauma Questionnaire Short Form (CTQ-SF) was used to categorize the HIV+ and HIV- women into trauma and non-trauma groups. The 28-item questionnaire scores from 25-125. Those with scores of 41 or higher were considered to have moderate trauma and were placed in the trauma+ group. Those with scores less than 41 were placed in the trauma- groups. 17 individual batteries of neurocognitive assessment were utilized including a culturally revised Hopkins Verbal Learning Test-Revised (HVLT-R). Fish LSD post-hoc tests in combination with ANOVA and ANCOVA linear analyses aided in transcription of the data.	HIV+ status was a significant indicator of lower test scores in immediate and delayed learning, memory and executive functioning, with lower scores on the HVLT-R. Trauma was found to be associated with deficits in memory recall and in the delayed trial of the HVLT-R. There were no significant effects found for the combined interactive effects of HIV and trauma on performance in the neurocognitive battery assessments.
Moradi, A. R., Miraghaei, M. A., Parhon, H., Jabbari, H. & Jobson, L. (2013). Posttraumatic Stress Disorder, Depression, Executive	34 HIV+ and 34 controls (HIV-) participants. All participants were male. Those with other neurological problems, psychotic symptoms, PTSD symptoms from	The Impact of Event Scale-Revised (IES-R) was used to measure PTSD symptoms in response to the specified trauma of an HIV diagnosis. Beck's Depression and Anxiety Inventories. Autographical memory and	Autobiographical memory was significantly worsened with depression and PTSD symptoms. HIV groups showed significantly more PTSD and depression and significantly less

Functioning, and Autobiographical Remembering in Individuals with HIV and in Carers of Those with HIV in Iran – Study 1.	another trauma (not HIV), and other chronic illness. Healthy controls were to have no other chronic illness.	executive functioning were measured using the Autographical Memory Test (AMT), Autobiographical Memory Interview (AMI), Wisconsin Card Sorting Test (WCST), and the Tower of London (ToL). Two MANOVA tests using Wilks' lambda coefficients were used to analyze the differences in memory and functioning for the HIV+ and HIV- control groups.	episodic autobiographical and semantic recall.
Rubin, L. H. et al. (2015). The Association of Perceived Stress and Verbal Memory is Greater in HIV-Infected Versus HIV-Uninfected Women.	1009 HIV+ and 496 HIV- women from the Women's Interagency HIV Study (WIHS) longitudinal study of women with or at-risk of HIV. Women excluded were those with missing data from the Perceived Stress Scale, those with conditions such as impaired hearing or vision that could impact cognitive assessment performance, those with history of stroke/CVA/head trauma and those with a self-reported use of antipsychotic medication.	The Perceived Stress Scale (PSS-10) was used to measure stress with items being ranked on a five-point Likert scale. Total scores ranged from 0-40. Lower stress was categorized by PSS-10 scores in the bottom two tertiles (<18) and higher stress was categorized by PSS-10 scores in the top tertiles (>18). Verbal Memory was measured using the Hopkins Verbal Learning Test (HVLT). Other neurocognitive domains such as attention, executive functioning, and fine motor skills were measured using other neurocognitive assessment batteries. Multivariable linear regression analyses and ANOVA testing were used to perform the statistical analysis.	Women with combined effects of HIV and higher levels of perceived stress performed worse on tasks of verbal memory, verbal learning, and attention. Perceived stress did not differ significantly between HIV+ and HIV- groups. Regardless of HIV status, women with higher perceived stress performed worse on four neurocognitive tests in verbal memory, verbal learning, processing speed, and executive function.
Rubin, L. H., et. Al (2016a). Prefrontal Cortical	38 HIV+ Women enrolled in the Chicago Consortium of WIHS.	The Perceived Stress Scale (PSS-10). The PTSD Checklist-Civilian	HIV+ women with higher perceived stress (on the PSS-10 scale) performed worse on

Volume Loss Is Associated with Stress-Related Deficits in Verbal Learning and Memory in HIV-Infected Women.	The women excluded were those with a history of dementia, an open head injury, a self-reported diagnosis of psychosis, the use of medication known to affect cognition, an AIDS-related diagnosis, or current hospitalization. MRI exclusion criteria includes those with any metal in their body or claustrophobia.	Version (PCL-C). The Center for Epidemiological Studies Depression (CES-D) 20-item self-report was used to measure depressive symptoms. Verbal learning and memory was measured by the Hopkins Verbal Learning Test (HVLT) in three trials of verbal recall. Structural MRI and neuroimaging analyses were used to measure brain structure. Multivariable linear regressions were performed to determine differences in brain volume, verbal learning, and memory between HIV+ high and low stress groups, controlling for age.	the HVLT tasks of verbal memory and on tasks of retrieval and semantic clustering than women with lower perceived stress. There were no significant differences in attention, concentration, executive functioning, psychomotor speed and verbal fluency between the high and low perceived stress groups. High stress women with HIV had lower bilateral brain volumes in the inferior, middle and superior frontal gyri and in the parahippocampus. Smaller right hemisphere inferior frontal gyrus volume was found to be associated with poor verbal memory and learning performance.
Rubin, L. H., et al. (2016b). Post-Traumatic Stress is Associated with Verbal Learning, Memory, and Psychomotor Speed in HIV-Infected and HIV-Uninfected Women.	1500 women (1004 HIV+ and 496 HIV-) were analyzed from WIHS. Women excluded were those with missing data from the cognitive assessments, those with conditions such as impaired hearing or vision that could have impacted	The PTSD Checklist-Civilian Version (PCL-C). Hopkins Verbal Learning Test (HVLT) was used to measured verbal memory. Secondary cognitive domains including verbal learning, attention, memory, executive functioning, verbal fluency, psychomotor speed and fine motor skills were measured	Both HIV+ and HIV- groups with probable PTSD performed significantly worse on cognitive assessments than those without, especially in domains of verbal learning and memory and psychomotor speed. HIV+ women performed significantly

	cognitive assessment performance and those with a self-reported use of antipsychotic medication.	using standard neurological assessment batteries. Inverse probability weighted linear regression analyses were used, controlling for factors such as income, depressive symptoms and drug use, to determine significant associations between HIV status, PTSD, and cognitive domain scores.	worse on verbal learning and memory, and all HVLT indices than HIV- women. There was no significant difference in the HIV+ and HIV- probable PTSD groups in verbal learning, memory, and processing speed. HIV+ and PTSD probable group did perform significantly better than all other groups in the domain of fine motor skills.
Rubin, L. H., et al. (2016c) Elevated Stress is Associated with Prefrontal Cortex Dysfunction During a Verbal Memory Task in Women with HIV.	36 HIV+ women from the Chicago Consortium of the WIHS were selected. Women were excluded with current or previous head trauma, dementia, or psychotic disorders and those with use of psychiatric medication affecting cognitive function and illicit drugs or those with metal in the body, pregnancy or those with excessive body weight (contraindications for scanner use).	The Perceived stress scale (PSS-10). The PTSD Checklist-Civilian Version (PCL-C) measured the primary explanatory variable of DSM-IV symptoms of PTSD. Scores range from 17 to 85 with a score of 44 or above indicating a probable PTSD diagnosis. Functional MRI (fMRI) scans were used to analyze brain images. Participants completed an in-scanner verbal memory scan that is similar to the HVLT-R with five experimental and five control sessions. Using age as a covariate, multivariable linear regression analyses were performed.	Women with higher perceived stress performed worse on the in-scanner verbal memory task. Brain activation differences were found in the recognition portion of the in-scanner test. Significant atrophy in the right medial prefrontal cortex and posterior cingulate cortex was seen. This suggests the impact of perceived stress on memory retrieval rather than memory encoding.
Spies, G., Ahmed-Leitao, F. A., Fennema-	62 participants with an HIV+ status, 32 with a history of childhood	The Childhood Trauma Questionnaire Short Form (CTQ-SF).	HIV+ women with trauma performed significantly more

Notestine, C. F., Cherner, M. & Seedat, S. (2016). Effect of HIV and Childhood Trauma on Brain Morphometry and Neurocognitive Function.	trauma and 30 without. 62 participants were HIV-negative and 31 had a history of childhood trauma and 31 did not. All were women. The women excluded were those with pregnancy and metal in the body as contraindications to an MRI, those with history of schizophrenia, bipolar disorder, substance abuse, head trauma, those with demonstrated neurocognitive impairment, or those with a history of seizure disorders or use of psychotropic medication.	Neurocognitive performance was measured using 10 common battery assessments for learning, delayed recall, processing speed, working memory, verbal fluency and motor ability. Structural MRI and neuroimaging analyses were used to measure brain structure. ANOVA, ANCOVA, Fisher's LSD and Bonferroni post-hoc tests were utilized to determine significant differences between groups.	poorly on the neurocognitive battery assessments than all other three groups. Controlling for age, women in the HIV+ and trauma+ groups had significantly smaller brain volumes than the other three groups in the regional brain areas of bilateral hippocampi, corpus collosum, left and right caudate and left and right putamen.
Spies, G., Fennema-Notestine, C., Cherner, M. & Seedat. S. (2017). Changes in Cognitive Function with HIV-Infection and Early Life Stress.	67 HIV+ and 50 HIV- women recruited from community or local healthcare facilities in South Africa aged 18-65 years. Women excluded were those with a history of schizophrenia, bipolar disorder, significant head injury, CNS infections of neoplasms or a hepatitis B or C positive status and those with current substance abuse or using psychotropic medication.	The Childhood Trauma Questionnaire Short Form (CTQ-SF) Culturally-modified neurocognitive assessment batteries were used including the Hopkins Verbal Learning Test-Revised (HVLT-R) and the Controlled Oral Word Association Task (COWAT). Domains of learning, delayed recall, processing speed, attention/working memory, executive functioning, verbal fluency and motor ability were measured. ANOVA and ANCOVA	The combined effects of HIV and ELS led to significant poorer performance on semantic verbal fluency and abstract reasoning especially with verbal fluency, processing speed and executive functioning. Poorest performance in the group that was HIV+ and trauma+ compared to all other groups at baseline and at the 12-month follow-up. All HIV+ women

		statistical in combination with LSD post-hoc corrections were used to analyze the data.	(trauma+ and trauma-) performed worse at baseline and at follow-up. Individual effects of HIV led to lowest scores in processing speed in phonemic verbal memory.
Thames, A. D., et al. (2017). Effects of Social Adversity and HIV on Subcortical Shape and Neurocognitive Function.	70 HIV+ and 23 HIV- male and female participants aged 23-75. Those excluded were those with a current or previous substance use or abuse, a current or past psychiatric diagnosis, previous head trauma or any contraindications to an MRI machine.	Measures of social adversity (SA) included perceived racial/ethnic discrimination, perceived previous and current neighborhood socioeconomic (SES) statuses, financial strain, and perceived personal SES. Neurocognitive battery testing was performed for attention/ concentration, information processing speed, verbal memory, learning and memory and recall. Neurological imaging was analyzed from the results of structural MRI scans. Linear regression was performed to determine significant relationships in learning/memory and executive functioning as compared to HIV status.	The HIV+ and SA interaction showed a statistically significant decrease in verbal learning and memory functioning and no statistically significant impact on executive functioning. HIV and SA groups showed reductions in the size of left hippocampus and right amygdala while also showing the greatest deformity in subcortical ventricles. Greater SA scores were associated with decreased left amygdala size. The left hippocampus is significantly correlated with learning/memory, verbal fluency, executive functioning and motor functioning. The right amygdala is only significantly associated with verbal fluency.

between HIV+ and HIV- populations. Of the studies completed, two were male-only, while seven focused only on women. These findings contrast with the majority of academic literature for HIV participants, which tend to focus on males. However, it has been noted that HIV+ women may be more vulnerable to neurocognitive decline (Vance, Rubin, Valcour, Waldrop-Valverde & Maki, 2016). The remaining two studies had both male and female participants.

Findings in the Different Interpretations of the Primary Explanatory Variable of Stress

In this literature review, the primary explanatory variable, in addition to HIV status, was stress. Findings indicted that the variable of psychological stress, as it relates to neurocognitive functioning in HIV+ participants, was interpreted in numerous ways, including: ELS and childhood trauma, perceived or current stress, PTSD, and perceived social adversity (SA).

Early life stress and childhood trauma. Four of the 11 studies focused on ELS or childhood trauma as the main predictor variable. Spies, Fennema-Notestine, Archibald, Cherner & Seedat (2012), Spies, Ahmed-Leitao, Fennema-Notestine, Cherner & Seedat (2016) and Spies, Fennema-Notestine, Cherner & Seedat (2017) utilized the Childhood Trauma Questionnaire – Short Form (CTQ-SF), which is a 28 item self-report measure that screens for a history of abuse or neglect that includes, but is not limited to, physical, emotional, or sexual abuse. Scores may range 25-125 and are categorized as follows: no trauma (25-31), low to moderate trauma (31-51), moderate to severe trauma (56-68), and severe to extreme trauma (73-125). Throughout the three studies, the CTQ-SF was used in the same manner, with a score of 41 or higher placing participants in the trauma groups. Clark et al. (2012) utilized an Early Life Stress Questionnaire (ELSQ), which assessed 17 life occurrences of family abuse, conflict, bullying and neglect throughout childhood. Three or more adverse life events led to a categorization of high ELS, while less than three events led to a categorization of low-ELS.

Perceived stress, stressful life events or current stress. Another four studies interpreted stress as current life stress or current perceived stress, with no focus on childhood trauma. Rubin et al. (2015), Rubin et al. (2016a), and Rubin et al. (2016c) utilized the Perceived Stress Scale (PSS-10), which measures 10 personal situations in the past months that participants considered stressful. Using a five-point Likert scale, participants were categorized into lower-perceived stress (PSS-10 scores under 18) or higher perceived stress (PSS-10 scores 18 or higher). While Rubin et al. (2015) only utilized the PSS-10 to measure perceived stress, Rubin et al. (2016a) and Rubin et al. (2016c) also measured for PTSD using the PTSD-Civilian Checklist (PCL-C), which categorizes participants into a probable DSM-IV PTSD diagnosis with scores of 44 or above, or into a not probable DSM IV PTSD diagnosis with scores below 44. Finally, Pukay-Martin, Cristiani, Saveanu & Bornstein (2003) measured stressful life events using the self-reported results of the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale, which measures the amount of control participants feel over stressful life events that have occurred to them within the past decade.

Posttraumatic stress disorder (PTSD). The primary explanatory variable of two of the 11 studies was PTSD. Although Rubin et al. (2016a) and Rubin et al. (2016c) also measured for PTSD using the PCL-C, their primary variable was perceived stress. Rubin et al. (2016b), however, used only the outcomes of the PCL-C. Moradi, Miraghaei, Parhon, Jabbari & Jobson (2013) took another approach of measuring PTSD using the Impact of Event Scale-Revised (IES-R). This 22-item self-report measures PTSD symptoms in response to one specified trauma – in this case, the trauma of an HIV diagnosis.

Social adversity. Lastly, Thames et al. (2017) developed a comprehensive composite score of perceived social and socioeconomic (SES) adversity and its impact on neurocognitive

functioning. Perceived racial/ethnic discrimination, financial strain, perceived childhood neighborhood SES, perceived current neighborhood SES and current personal SES were the variables measured that aided in the development of the combined SA composite scores.

Neurocognitive Testing Results

All 11 studies selected for review used standard neuropsychological assessments to discover discrepancies in neurocognitive functioning. These batteries are commonly used in HIV research and cover the domains of learning, delayed recall, processing speed, attention/concentration, executive functioning/working memory, verbal fluency, fine motor ability, psychomotor skills utilizing tests such as the WAIS-II Digit Symbol Test, Hopkins Verbal Learning Tool-Revised (HVLT-R), the Wisconsin Card Sorting Test (WCST), Trial Making Tests (A and B), Stroop tests, and Category Fluency Tests. Rubin et al. (2016c), however, measured only for verbal memory using an in-scanner verbal memory task similar to the HVLT-R. Moradi, Miraghaei, Parhon, Jabbari & Jobson (2013) measured only for autobiographical memory and executive control using the autobiographic memory interview (AMI), WCST, and Tower of London (ToL) tests.

In the four studies that focused on either ELS or childhood trauma, Spies, Fennema-Notestine, Archibald, Cherner & Seedat (2012) revealed HIV+ status was a significant indicator of lower performance in immediate and delayed learning, memory, and executive functioning, and individual high ELS effects included deficits in memory recall and in the delayed trial of the HVLT-R. No significant combinative HIV and ELS effects were found. Clark et al. (2012) discovered a high ELS effect in both HIV+ and HIV- populations on worsened psychomotor and processing speed. Spies, Ahmed-Leitao, Fennema-Notestine, Cherner & Seedat (2016) inferred that the alterations in regional brain structure found could predict poorer neurocognitive

performance in processing speed, attention/working memory, executive functioning, motor skills and verbal fluency. Spies, Fennema-Notestine, Cherner & Seedat (2017) found significant interactive effects of HIV and stress on semantic verbal fluency and abstract reasoning, especially with verbal fluency, processing speed and executive functioning, in addition to finding individual HIV effects on processing speed in phonemic verbal memory.

The four studies that focused on life stress or perceived stress showed more consistency in their results. Rubin et al. (2015) reported that verbal memory, verbal learning, and attention were significantly worse in the combined HIV+ and high stress groups. Additionally, regardless of HIV status, women with higher perceived stress performed worse on four neurocognitive tests in verbal memory, verbal learning, processing speed, and executive function. Rubin et al. (2016a) reported that higher PSS-10 scores led to significant decreased performance on tasks of verbal memory and recall as well as semantic clustering. Yet, they failed to discover any significant combined HIV and stress results for attention and concentration, executive functioning, psychomotor speed or verbal fluency. Rubin et al. (2016c) reported that higher PSS-10 scores in HIV+ women led to significant worsening performance on assessments of verbal memory and decreased functional brain activity related to memory retrieval. Pukay-Martin, Cristiani, Saveanu & Bornstein (2003) revealed that for HIV+ men, negative stressful life events in family, residential and financial domains led to worsening performance on executive functioning, attention, processing speed and overall neurocognitive impairment.

For the two studies measuring the impact of PTSD on neurocognitive functioning, Rubin et al. (2016b) reported that individual HIV+ effects include significant declines in verbal learning and memory while individual PTSD effects include significant declines in verbal learning and memory as well as in psychomotor speed. The combined effects of PTSD and stress only led to a

significant difference in fine motor skills, with the probable PTSD/HIV+ groups performing better on tasks of fine motor skills as compared to the probable PTSD/HIV- groups. Moradi, Miraghaei, Parhon, Jabbari & Jobson (2013) showed that HIV+ men with PTSD had less specific memories and less semantic and episodic autobiographical recall.

Finally, Thames et al. (2017) revealed that there were significant effects of SA on learning and memory and executive functioning. There were, however, no significant effects on areas of attention or processing speed.

Neuroimaging Results

Of the 11 studies testing for neurocognitive impairment, five also measured brain activity and structure using magnetic resonance imaging (MRI) machines (see **Table 2**). Results of the MRIs varied. Clark et al. (2012) reported no significance in intracranial volumes for the HIV+ and HIV- groups but uniquely concluded that an HIV+ status and high ELS led to significant increases in left amygdala volume. Rubin et al. (2016a) reported that stress combined with HIV led to prefrontal cortical atrophy and lower bilateral brain volumes in the inferior, middle and superior frontal gyri and in the parahippocampi. Rubin et al. (2016c) reported that brain activity in an fMRI was significantly decreased in the right medial prefrontal cortex and the posterior coagulate cortex during the retrieval portions of a verbal memory task in HIV+ participants with higher levels of perceived stress. Spies, Ahmed-Leitao, Fennema-Notestine, Cherner & Seedat (2016) reported statistically significant reductions in brain volumes in the regional brain areas of bilateral hippocampi, corpus collosum, left and right caudate and left and right putamen in the HIV+ and high-ELS groups. Both right and left amygdala were smallest in this group, but the results were not significant. Thames et al. (2017), however, did report significant decreases in right amygdala volumes as well as in the left hippocampal volumes.

Table 2. Brain areas measured using neuroimaging.

Study	Type of Neuroimaging	Brain areas (Regions of Interest) Measured
Clark et al. (2012)	Structural MRI	Anterior cingulate cortex (AAC), left and right caudate, left and right putamen, bilateral hippocampi and left and right amygdala.
Rubin et al. (2016a)	Structural MRI	Medial temporal brain regions including parahippocampi and hippocampi, and prefrontal brain areas including the AAC, and inferior, frontal and superior internal gyri.
Rubin et al. (2016c)	Functional MRI (fMRI)	Total brain activity measured during an in-scanner verbal memory task similar to the HIVLT-R.
Spies, Ahmed-Leitao, Fennema-Notestine, Cherner & Seedat (2016)	Structural MRI	Brain volume, bilateral hippocampi, corpus callosum, left and right caudate, left and right putamen, frontal lobe, AAC, and left and right amygdala.
Thames et al. (2017)	Structural MRI	Bilateral hippocampi and left and right amygdala.

While Clark et al. (2012) noted a significant association between increased left amygdala size and poor performance on processing and psychomotor speed, Thames et al. (2017) reported an association between decreased left amygdala size and greater SA scores. Thames et al. (2017) also reported that reductions in the right amygdala significantly affect verbal fluency and the shape and size of the left hippocampus was significant correlated with learning/memory, verbal fluency, executive functioning and motor functioning. Rubin et al. (2016a) noted an association between the poorest verbal memory scores and prefrontal cortical atrophy in the superior, middle, and inferior frontal gyri and in parahippocampal areas. Rubin et al. (2016c) noted that poorest verbal memory retrieval was marginally significantly associated with the lower medial prefrontal cortical volumes. Lastly, Spies, Ahmed-Leitao, Fennema-Notestine, Cherner & Seedat (2016) concluded a potential effect of the left hippocampus, right AAC, corpus callosum, right and left amygdala, and left caudate may be associated with decreased neurocognitive functioning

because low regional brain volumes in these areas was strongly associated with poorer performance on the neurocognitive assessments.

Discussion

With the majority of the studies being published within the last five years (ten of 11), it is evident that the interactive effects of stress and HIV on neurocognitive performance is a new and emerging topic that is just beginning to be understood.

These studies were predominantly cross-sectional and comparative in nature. Eight of the 11 studies showed direct significant and negative interactive effects of stress and HIV on neurocognitive performance in all four areas of stress including ELS and childhood trauma, current or perceived life stress, PTSD, and SA. The areas significantly affected included verbal memory and learning, delayed recall, semantic verbal fluency, abstract reasoning, psychomotor speed, processing speed, executive functioning and attention. The remaining studies showed significant individual HIV or individual stress effects on neurocognition or significant correlations between brain structure and neurocognitive performance related to an HIV+ status and stress (see **Table 1**). With the studies achieving generally consistent results utilizing the same exclusion criteria and reliable neurocognitive batteries, there is evidence showing some of the interactive effects of HIV, stress, and neurocognition.

The most notable effect was the impact of HIV and stress on verbal memory and learning. Five studies concluded combinative HIV and stress effects on verbal memory and learning and two more studies concluded individual HIV or trauma effects on verbal learning. Specifically, Rubin et al. (2015), Rubin et al. (2016a) and Rubin et al. (2016c) utilized the same stress scale (PSS-10) and consistently reported statistically significant combinative HIV+ and life stress effects on declines in verbal memory performance in women. However, the

correlational nature of these studies makes it currently impossible to claim causality. More research should be conducted to determine if current and perceived stress and HIV leads to declines in verbal memory or if the declines in verbal memory caused by HIV leads to increased stress. Having more insight into this relationship can help researchers further understand the etiology of HAND and subsequently develop better interventional tools to prevent and slow the onset of HAND.

Although many of the results showed consistency, there were still some contradictory findings. For example, Spies, Fennema-Notestine, Cherner & Seedat (2017) reported significant combinative effects of HIV and high ELS on poorer performance on semantic verbal fluency and abstract reasoning, especially in domains of verbal fluency, processing speed and executive functioning using the CTQ-SF measure. In contrast, Spies, Fennema-Notestine, Archibald, Cherner & Seedat (2012) reported no statistically significant interactive effects of HIV and ELS using the same CTQ-SF scale. However, separate and individual significant effects of HIV and ELS were found in delayed learning, memory and recall, and executive functioning. Sample sizes and battery assessments were similar. Both studies screened South African HIV+ and HIV- women. Differences in the combinative effects could then potentially be due to variances in the sample population.

Another discrepancy lies in the domain of executive functioning. Rubin et al. (2016a) and Thames et al. (2017) however reported no significant combinative HIV and stress effects on executive functioning while Pukay-Martin, Cristiani, Saveanu & Bornstein (2003) and Spies, Fennema-Notestine, Cherner & Seedat (2017) did. It is interesting to note that Rubin et al. (2016a) and Thames et al. (2017) both reported on current life stressors or perceived life stress, while Pukay-Martin, Cristiani, Saveanu & Bornstein (2003) and Spies, Fennema-Notestine,

Cherner & Seedat (2017) looked at past negative life stress events and ELS respectively. Therefore, based on this literature, it is possible that current or perceived life stress combined with HIV does not affect executive functioning while past life stress or past life stress events combined with HIV, in fact, does. Evidently, more research should be discovered to review how the onset of stress potentially impacts the domain of executive functioning.

For the studies measuring PTSD, Moradi, Miraghaei, Parhon, Jabbari & Jobson (2013) showed differences in autobiographical memory while Rubin et al. (2016b) showed no combinative effects in HIV and PTSD except in the domain of fine motor skills. Rubin et al. (2016b) did, however, report individual probable PTSD effects on verbal learning and memory and psychomotor speed and individual HIV effects on verbal learning and memory. Outcome dissimilarities may be attributed to study differences. Moradi, Miraghaei, Parhon, Jabbari & Jobson (2013) studied males and the emergence of PTSD only as a result of an HIV diagnosis. On the other hand, Rubin et al. (2016b) studied women and used the PCL-C for probable PTSD symptoms of any origin. Therefore, it would be interesting to conduct more research on the different effects of HIV infections on neurocognitive performance as it compares to gender and to the varying origins of PTSD, whether it be the emergence of PTSD related to an HIV diagnosis or the emergence PTSD related to life events such childhood trauma or abuse experiences, which are unrelated to the diagnosis of HIV.

In regard to neuroimaging, it was most intriguing to note the discrepancies in amygdala volumes. Clark et al. (2012) concluded significant increases in amygdala volumes while Thames et al. (2017) found significant decreases in amygdala volume in HIV+ and high stress groups. Clark et al. (2012) then proceeded to conclude that increases in amygdala volume were significantly related to decreases in processing and psychomotor speed. In contrast, Thames et al.

(2017) reported a significant relationship between decreased amygdala volumes and decreased verbal fluency. Since Clark et al. (2012) focused on ELS and Thames et al. (2017) focused on current perceived SA, it is possible that the onset and development of stress exposure could have a relationship with amygdala structure. In the remainder of the studies that examined brain structure, results consistently reported atrophies in the regions of interest including hippocampal volumes, general brain volumes, or prefrontal cortices in relation to either HIV, stress, or combined HIV and stress groups. These results, therefore, provide increased insight into the combinative effects of HIV and stress on brain structure in addition to the effects on neurocognitive functioning.

Strengths and Limitations

This review seeks to identify and analyze the new and growing body of literature relating HIV, stress, and neurocognition in the adult population. Strengths of this review include the comprehensiveness of the search in two different databases. Explicit exclusion criteria limited the HIV+ adult research to studies that were primary and peer-reviewed in nature. The broad inclusion criteria, on the other hand, allowed for the review of studies of adult men and women inside and outside of the United States. Lastly, the comprehensive definition of stress allowed for the analysis of the effects ELS and childhood trauma, current or perceived life stress, PTSD, and SA. Many of the studies also utilized similar or the same explanatory variable assessments as well as many of the same reliable neurocognitive testing batteries. This consistency allows for an increase in reliability of the review and a decrease in confounding factors that could have resulted from differences in assessment tools.

There are, however, some limitations to this literature review. Exclusion criteria excluded those adults with previous head trauma, seizure disorders, or substance abuse. Although these

variables many have acted as compounds, adults who have experienced severe stress related to severe physical abuse or physical trauma, neurological disorders, or substance abuse were not studied. Children, adolescents, and young adults were also not included. Studies not written in English were unable to be reviewed. Additionally, any studies such as conference abstracts or presentations without full-text articles were unable to be categorized.

Implications for Further Research

According to this literature review, it is apparent that there are interactive effects of stress and HIV on neurocognitive impairment. Other factors, however, may also impact cognition. Although significant correlations were made between stress and HIV in this review, the comparisons are unable to discern causality. Variables including gender, types of stress or abuse, current antiretroviral therapies or mental health and stress-related drug therapies, or levels of inflammation could also lead to changes in neurocognitive function and should be analyzed.

Some research areas of interest include the potential interrelatedness of HIV, stress, and neuroinflammation. PLWH face chronic physiological inflammation due to inflammatory cytokines crossing the blood-brain barrier. The inflammation combined with psychological stress can further result in neurocognitive decline (Valdez, Rubin & Neigh, 2016). It may be beneficial also to study this inflammation and physiological distress in addition to brain structure and function to help determine another potential mechanism of HAND. Additionally, a study conducted by Maki et al. (2015) shows the additive effect of demographic characteristics, socioeconomic status, and reading level in combination with HIV as it relates to declines in delayed memory, verbal learning, delayed recall and recognition. Therefore, it may be interesting to also compare these variables to psychological stress for PLWH as well.

Furthermore, there were some areas of contradiction in this review. However, the claims of the variables leading to these discrepancies are merely speculations. There are many avenues for future research that could help differentiate the etiological mechanisms for the development of HAND in HIV+ and high stress populations. Because many of the neurocognitive batteries were the same or similar, the type and onset of stress and the variations in population and sample characteristics may, in fact, have significant effects on the onset of neurocognitive decline and the domains of neurocognition affected.

Additionally, although common neurocognitive batteries are used to help diagnose abnormal neurocognitive decline, it may be beneficial to continue reviewing new screening tools specifically for PLWH. For example, the Montreal Cognitive Assessment (MoCA) has shown significant positive comparisons with other "gold standard" neurocognitive batteries (Fazeli, Casaletto, Paolillo, Moore, Moore & The Hnrp Corp, 2017). These new measures may help tailor to growing needs of the aging HIV population in the diagnosis of HAND.

Finally, and arguably most importantly, further research is necessary to understand the mechanisms of the neurocognitive impairment in order to more effectively provide interventions to slow the onset of HAND. Presently, there is extremely limited information on successful neurocognitive intervention measures for PLWH. This gap in knowledge can likely be attributed to a lack of understanding of the etiology of HAND. Comprehensive research on predictors of neurocognitive decline, such as continued research of the effects of HIV and stress, will have positive implications. For example, healthcare practitioners in the practice setting will be able to better educate PLWH on potential neuroprotective measures. (Fazeli, Marceaux, Vance, Slater & Long, 2011). Based on the results of this review, these measures may now begin to include stress reduction techniques for overall health and wellbeing for PLWH to prevent HAND.

Conclusion

This systematic literature review is a starting point for the discovery some of the etiological factors contributing to HAND. Results of this review provide insight into potential HAND interventions that stem from therapeutic measures tackling underlying past or current life stress. These prospective interventions may not prevent the development of HAND completely, but they can at least help decrease the powerful interactive effect of psychological stress and HIV on neurocognition.

In summary, with a growing number of aging HIV+ adults, it is necessary that researchers look to not just increase the quantity of life and longevity of this population but to also increase the quality of life. Declines in neurocognition related to stress and an HIV status evidently negatively impacts quality of life. According to the World Health Organization, health is defined as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmary" (World Health Organization, 1946). Although it is impossible to avoid the physical manifestations of HIV, the health of a person with HIV should not just be defined by a prolonged asymptomatic period or increased white blood cell counts. A more holistic perspective of health in aging HIV+ adults that includes neurocognitive health, stress management and mental health and should be taken. By increasing our understanding of the comprehensive challenges for PLWH, we can create more effective interventions and improve quality of life for this vulnerable population.

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