Published in final edited form as:

J Neurovirol. 2016 December ; 22(6): 840–851. doi:10.1007/s13365-016-0446-3.

Elevated stress is associated with prefrontal cortex dysfunction during a verbal memory task in women with HIV

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Abstract

HIV-infected women may be particularly vulnerable to verbal learning and memory deficits. One factor contributing to these deficits is high perceived stress, which is associated with prefrontal cortical (PFC) atrophy and memory outcomes sensitive to PFC function, including retrieval and semantic clustering. We examined the association between stress and PFC activation during a verbal memory task in 36 HIV-infected women from the Chicago Consortium of the Women's Interagency HIV Study (WIHS) to better understand the role of the PFC in this stress-related impairment. Participants completed standardized measures of verbal learning and memory and stress (Perceived Stress Scale-10). We used functional magnetic resonance imaging to assess brain function while participants completed encoding and recognition phases of a verbal memory task. HIV-infected women with higher stress (scores in top tertile) performed worse on all verbal memory outcomes including strategic encoding ($p < 0.05$) compared to HIV-infected women with lower stress (scores in lower two tertiles). Patterns of brain activation during recognition (but not encoding) differed between women with higher versus lower stress. During recognition, women with higher stress demonstrated greater deactivation in medial PFC and posterior cingulate cortex compared to women with lower stress ($p < 0.05$). Greater deactivation in medial PFC marginally related to less efficient strategic retrieval ($p = 0.06$). Similar results were found in analyses focusing

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Conflict of Interest/Financial Disclosure: The authors declare that they have no conflicts of interest.

on PTSD symptoms. Results suggest that stress might alter the function of the medial PFC in HIV-infected women resulting in less efficient strategic retrieval and deficits in verbal memory.

Keywords

HIV; stress; verbal memory; fMRI; prefrontal cortex

Introduction

Negative life stressors are highly prevalent in HIV-infected individuals, particularly women who encompass 24% of HIV cases in the United States. Negative life stressors include unemployment, low socioeconomic status, a single parent household, childhood trauma, adult sexual assault, and physical violence (Brief *et al*, 2004; Machtinger *et al*, 2012; Spies *et al*, 2012). A recent meta-analysis indicated that among HIV-infected women the prevalence of childhood sexual abuse is 39%, adult sexual abuse is 35%, and physical violence is 54% (Machtinger *et al*, 2012). In HIV-infected men, stressful life events are related to worse cognitive functioning including decreased attention, executive functioning, and processing speed but not memory (Pukay-Martin *et al*, 2003). In contrast, in HIV-infected women, we recently reported that higher levels of perceived stress are associated with decreased verbal memory but not attention, executive function, or processing speed (Rubin *et al*, 2015a). Notably, in HIV-uninfected women higher levels of perceived stress were not associated with verbal memory deficits (Rubin *et al*, 2015a). Among HIV-infected women, the association between perceived stress and verbal memory was particularly robust among women with higher levels of HIV RNA in blood (Rubin *et al*, 2015a). Taken together, these findings suggest that stress may have a unique cognitive impact that is manifested by deficits in verbal memory among women with HIV infection.

Understanding the neural basis of these stress-related impairments in memory can help to elucidate targets for future intervention studies in HIV-infected women to lower stress and possibly improve memory. The hippocampus and prefrontal cortex (PFC) are brain regions critical to verbal memory performance (Buckner *et al*, 2000; Dickerson and Eichenbaum, 2010) and show structural and functional alterations in relation to stress in healthy individuals (Lupien *et al*, 2009) as well as in patients with psychiatric disorders such as major depression and Post-Traumatic Stress Disorder (PTSD) (Bremner *et al*, 2003; Hayes *et al*, 2012; O'Doherty *et al*, 2015; Zhao *et al*, 2014). Critically, there are structural and functional abnormalities in the hippocampus in HIV (Maki *et al*, 2009) that might make HIV-infected individuals differentially vulnerable to stress. For example, the hippocampus is hypoactive during verbal encoding and hyperactivate during recognition in HIV-infected women compared to HIV-uninfected women (Maki *et al*, 2009). This functional alteration related to behavioral measures of memory such that hypoactivation during encoding and hyperactivation during recognition were each associated with worse performance on a standardized measure of verbal memory administered outside of the scanner (Maki *et al*, 2009).

Whether HIV-infected women show alterations in PFC activation during a memory task is unknown. However, compared to HIV-uninfected men, HIV-infected men show decreased recruitment of the right inferior and middle frontal gyrus during episodic memory tasks (Castelo *et al*, 2006). New evidence links decreases in PFC volume but not hippocampal volume to stress and memory deficits in HIV-infected women (Rubin *et al*, 2015b). Specifically, compared to HIV-infected women with lower levels of perceived stress, HIV-infected women with higher levels showed greater atrophy in prefrontal regions including the inferior frontal, middle frontal, and superior frontal gyri (Rubin *et al*, 2015b). Behaviorally, prefrontal volume loss (but not hippocampal volume loss) was associated with worse verbal memory retrieval and semantic clustering.

The purpose of the present study was to better understand the role of PFC function in stress-related memory impairments in HIV-infected women. Here we examined the effects of perceived stress on activation of the PFC during a verbal memory task in HIV-infected women. Based on our initial work, we hypothesized that HIV-infected women with higher levels of perceived stress versus lower levels of perceived stress would show decreased activation in the PFC during a verbal memory task. We expected that this decreased activation would be related to decreased performance on behavioral measures of verbal memory and strategic encoding and retrieval, particularly, semantic clustering. We also wanted to examine the extent to which comorbid symptoms of PTSD and depression affected patterns of brain activation and how those patterns related to behavioral measures of verbal memory.

Methods

Participants

Thirty-six HIV-infected female participants from the Chicago Consortium of the Women's Interagency HIV Study (WIHS) were enrolled in the study. The WIHS is the largest longitudinal, study of health outcomes among HIV-infected women (Bacon *et al*, 2005; Barkan *et al*, 1998). At the time of these studies (2010–2011), WIHS participants completed neurocognitive testing once every two years in conjunction with regular semiannual core study visits (Maki *et al*, 2015). The 36 women participated in an ancillary, single-site MRI study where a number of previous findings have previously been published (Meyer *et al*, 2014; Rubin *et al*, 2015b; Sundermann *et al*, 2015). The neuroimaging assessment occurred within 3 months on average ($M=2.92$, $SD=2.17$) of their scheduled semiannual WIHS visits which for these women included their biannual neurocognitive and stress assessments. Written informed consent was obtained by each site IRB, in this case Cook County Health & Hospitals System (CCHHS), and the University of Illinois at Chicago (UIC). As in our previous studies (Meyer *et al*, 2014; Rubin *et al*, 2015b), exclusionary criteria were the following: first language other than English; history of dementia; a positive toxicology test for illicit substance use; uncontrolled diabetes; open head injury of any kind or closed head injury with loss of consciousness; currently pregnant; eight years or less of formal education; diagnosis of schizophrenia; history of any clinical AIDS-defining disorders; endocrine, systemic disease, or seizure disorder; current use of psychiatric medication

known to influence cognitive functioning; metal in the body, claustrophobia, or weight greater than 250 pounds because of the scanner dimensions.

Functional MRI Procedure

Brain activation was measured by way of Blood oxygen level-dependent (BOLD) fMRI on a General Electric 3.0-Tesla Signa HDx scanner (General Electric Healthcare, Waukesha, WI) with 8-channel head coil. All scans took place at the Center for MR Research at the University of Illinois at Chicago. As described in Meyer *et al.* (2014), images were acquired with 30 axial, 4-mm slices with no gap using a standard T2*-sensitive echo planar image sequence (1.5-s repetition time; 25-ms echo time; 64×64 matrix; 20-cm field of view; flip angle 90°). The duration of the scan session was approximately 1 hour and, in addition to the verbal memory test, included a simple reaction time, a working memory task and structural scans that were examined as part of previous studies (Rubin *et al.*, 2015b; Sundermann *et al.*, 2015).

In-scanner verbal memory task

During fMRI scans, participants completed a verbal memory task that was adapted from previous fMRI studies (Maki *et al.*, 2009; Sperling *et al.*, 2002) and was designed to be similar to the Hopkins Verbal Learning Test (see below). The task as previously described in Meyer *et al.* (2014) included two conditions during which BOLD imaging was performed – encoding and delayed recognition – as well as a free recall condition during which BOLD imaging was not performed. During encoding, participants viewed a series of words and were instructed to remember them for a subsequent memory task. Participants were instructed to press a button on a response remote to indicate that they had seen each item. The button press ensured sustained attention. The encoding condition consisted of 5 experimental blocks, each comprised of 6 unique concrete nouns presented one time each. To facilitate semantic clustering, the 30 concrete nouns presented during the experimental blocks were frequently generated exemplars from five different semantic categories including body parts, insects, fruits, furniture, and natural formations. These 5 experimental blocks were interspersed with 5 control blocks, each also comprised of 6 concrete nouns, but these nouns were either always “sailboat” or “ballet”. The repeated presentation of the same two nouns controlled for the visual and motor demands of the encoding task but made very minimal demands on encoding processes. Each encoding block lasted 27 seconds and included six 4.5-second trials whereby each stimulus was presented for 3 seconds and the interstimulus interval was 1.5 seconds. The total scan time for the encoding phase was five minutes.

After the encoding phase, structural scans were acquired for 12 minutes. After the 12-minute delay, participants were asked to state aloud all words from the encoding task that they remembered. No scans were acquired during this free recall condition. Immediately following the free recall condition, the recognition condition began. Participants were shown one word at a time and were told to press one button to indicate that they remembered that item from the encoding phase and to press a different button to indicate that they did not recognize the word from the encoding phase. The recognition condition consisted of 10 experimental blocks of 6 trials each interspersed with 10 control blocks of 6 trials each. The

experimental blocks comprised 30 target stimuli from the encoding phase and 15 novel semantically related or 15 unrelated distractor stimuli. The control blocks involved the repeated presentation of “sailboat” and “ballet”. Each recognition block lasted approximately 20 seconds, including six 3.3-second trials whereby each stimulus was presented for 2.7 seconds and the interstimulus interval was 0.6 seconds. The total scan time for the recognition condition was seven minutes. Primary behavioral measures measured accuracy and included total words recalled during free recall, percent correct during the recognition task, and semantic clustering during free recall. As in our previous study (Meyer *et al*, 2014), a semantic cluster was defined by two or more semantically-related target items that were given in sequence (1 point for a cluster comprised of two words, 2 points for a cluster comprised of three words, 3 points for a cluster comprised of 4 words).

Hopkins Verbal Learning Test-revised (HVLTR)

The HVLTR (Benedict *et al*, 1998) assesses verbal learning and memory. A total of twelve words from three semantic categories are read aloud during each of three learning trials and the participant is asked to recall the list after each of the learning trials and again after a 20–25 minute delay. A yes/no recognition trial consisting of 12 targets, 6 semantic distractors, and 6 unrelated distractors follow. We computed three composite indices – verbal learning, verbal memory, and semantic clustering. In the present sample, z-scores were first computed for each test from raw scores and then averaged to create each composite index. The verbal learning domain score was computed by averaging z-scores for Trial 1 (single trial learning) and for the total words recalled across the three learning trials (total learning) (Rubin *et al*, 2015a; Valcour *et al*, 2015). The verbal memory domain score was computed by averaging z-scores for the total words recalled after a 25-minute delay (delayed recall) and by dividing the delayed recall score by the highest single trial learning score on trials 2 or 3 (percent retention) to assess verbal learning and memory (Rubin *et al*, 2015a; Valcour *et al*, 2015). The semantic clustering domain score was calculated by averaging z-scores for the semantic clustering score on Trial 1, clustering across three learning trials, and clustering on the delayed free recall trial (Rubin *et al*, 2015b). Semantic clustering is an executive functioning strategy whereby words belonging to a semantic category are grouped together to enhance performance on a word list memory test (Delis *et al*, 1988; Stricker *et al*, 2002). Secondary outcomes included recognition and retrieval. Recognition scores were computed by taking the total number of hits (correctly responding “yes” to a presented word) and subtracting the number of false positives (incorrectly responding “yes” to a non-presented word). A retrieval index (Woods *et al*, 2005) was computed by taking the number of correct words recalled during recognition (higher is worse retrieval) and subtracting the total number of words recalled during delayed recall.

Perceived Stress Scale (PSS-10)

The PSS-10 (Cohen *et al*, 1983; Cohen and Williamson, 1988) is a well-validated self-report tool comprised of 10 items that measure the extent to which personal situations in the past month are considered stressful. Each item was rated on a five-point Likert scale (0=never, 4=very often) depending on the degree to which participants deemed their lives uncontrollable, unpredictable, and overloaded. All items were summed to create a total score ranging between 0 and 40; higher scores indicate greater perceived stress. In the present

study, the Cronbach Alpha = 0.88 which indicates excellent internal consistency. Consistent with our WIHS-wide epidemiologic study in 1505 women (Rubin *et al*, 2015a), perceived stress was categorized as lower when PSS-10 scores were <18 (bottom two tertiles in WIHS) and higher when PSS-10 scores were ≥18 (top tertile in WIHS).

PTSD Checklist-Civilian version (PCL-C)

The PCL-C (Weathers *et al*, 1991) is a well-validated 17-item self-report measure of PTSD symptoms as defined by the DSM-IV and queries how symptoms relate to “stressful experiences”. Symptoms assessed included re-experiencing symptoms of trauma (5 items), avoidance of thoughts or feelings associated with the trauma (7 items), and hyperarousal such as difficulty concentrating or insomnia (5 items). A total symptom severity score was computed by summing the scores from all 17 items (range = 17–85). A Cronbach Alpha of 0.90 in the present study indicated excellent internal consistency.

Center for Epidemiological Studies Depression (CES-D) scale

Our self-report measure of depressive symptoms was the 20-item CES-D (Radloff, 1977), which has demonstrated excellent reliability and validity and is commonly used in studies in HIV-infected women (Cook *et al*, 2002; Maki *et al*, 2012; Rubin *et al*, 2011). The CES-D total score (range =0–60) was obtained by reverse scoring the appropriate items and adding the scores from each of the 20 items. The total score ranged from 0 to 60 with higher scores indicating more depressive symptoms.

Statistical analysis

Behavioral analyses—Differences between groups (HIV-infected higher stress; HIV-infected lower stress) in socio-demographic characteristics were examined using independent t-tests for continuous variables and Chi-square tests for categorical variables. Similar to our previous study (Rubin *et al*, 2015b), group differences (HIV-infected higher stress; HIV-infected lower stress) on the in-scanner and HVLt were examined using multivariable linear regression with age as a covariate. When group differences existed, a series of additional analyses were conducted to determine whether these differences remained after accounting for HIV-related disease characteristics including CD4 nadir (or current CD4 count), crack/cocaine use, and hepatitis C virus. Significance was defined as $p < 0.05$ (two-sided) and Cohen’s d effect sizes (small= 0.2; medium= 0.5; large= 0.8) were computed using estimated means adjusted for age and pooled standard deviations (Cohen, 1992). Analyses were performed with SAS (version 9.4, SAS Institute Inc, Cary, NC).

Neuroimaging analyses—fMRI images were preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>). Pre-processing steps included slice timing correction, motion correction, image normalization, resampling at a $2 \times 2 \times 2 \text{ mm}^3$ voxel size, and Gaussian spatial smoothing with 8mm FWHM. For first-level (within-subject) analysis, a general linear model (GLM) was conducted with novel words and repeated words as the two regressors of interest. Six additional nuisance regressors (motion parameters) were also included in the model to correct for artifact due to motion. For each participant, contrast images of brain activity that was greater in the unique target words condition (experimental) compared to the repeated control words condition (control)

for encoding and for recognition respectively, were generated in order to remove any motor component from BOLD signal. For second-level (between-subject) analysis, whole-brain voxelwise two-sample t-tests were conducted to examine possible differences in brain activations (experimental vs. control) between HIV-infected women with higher and lower stress levels. Individual recent CD4 counts (treated continuously) were input as a covariate for the second level analyses. To clarify the functional significance of group differences and to examine correlations between brain activity and behavior performances (i.e., in-scanner and out-of-scanner verbal memory and semantic clustering outcomes), parameter estimates (β weights, arbitrary units [a.u.]) were extracted and averaged from individual contrast map (experimental vs. control) with a 5-mm spherical region of interests (ROIs) centered at voxels showing peak group effect.

Results

The age range of participants was 27 to 59 years ($M=43.72$, $SD=7.02$) and 97% of participants were African American. The majority of women (48%) had recent CD4 lymphocyte counts >500 cells/ μ l, 14% of participants had AIDS-defining (<200) CD4 counts, 78% were on highly active antiretroviral therapy (HAART), and 68% were on HAART with 95% adherence (self-reported usage of prescribed medication). Recent plasma viral load was undetectable for 56%. Recent CD4 count was lower among women with higher compared to lower perceived stress ($p=0.04$; Table 1). Consistent with our previous publication (Rubin *et al*, 2015b), on the HVLT after controlling for age, women with higher compared to lower perceived stress performed worse on the verbal memory domain and its indices as well as on the clustering domain z-score and the delayed clustering score (p 's <0.05 ; Table 2; Cohen's d 's ranged 0.67–0.9469). On the in-scanner verbal memory task, after controlling for age, women with higher compared to lower perceived stress performed worse on delayed free recall and on the delayed clustering score (p 's <0.05 ; Table 2; Cohen's d 's ranged 0.68–0.69). The same pattern of associations remained after adjusting for HIV-related disease factors including CD4 nadir (or recent CD4 count). Additionally, controlling for crack/cocaine use and hepatitis C virus did not change the pattern of results.

We first examined the pattern of brain activation during encoding for HIV-infected women across stress groups ($n=36$). For the contrast of unique target words minus repeated control words during encoding, we found diffuse activation of bilateral parahippocampi and deactivation of default mode network (DMN) regions (Raichle, 2015; Raichle *et al*, 2001) including the medial PFC and posterior cingulate cortex (value set at $p<0.05$ and $k=10$, Figure 1). There were no significant group differences in patterns of brain activation during encoding. Next, we examined the pattern of brain activation during recognition for HIV-infected women across stress groups ($n=36$). For the contrast of unique target words minus repeated control words, we found diffuse activation of bilateral ventrolateral PFC, dorsolateral PFC, hippocampus, supplementary motor area, motor area, and occipital vision regions and deactivation of DMN regions including the medial PFC and posterior cingulate cortex (value set at $p<0.001$ and $k=10$, Figure 2). During recognition, women with higher stress demonstrated greater right medial PFC and posterior cingulate cortex deactivation compared to women with lower stress after controlling for recent CD4 count (p 's <0.05 ;

Figure 3). Greater deactivation in the medial PFC marginally related with less efficient clustering on the HVL semantic clustering outcomes including the clustering z-score ($p=0.06$; Figure 4A), total clustering on trials 1–3 ($p=0.05$; Figure 4B), and on total clustering on trial 1 ($p=0.05$). No associations were noted between verbal memory performance on the HVL and medial PFC activation. No associations were demonstrated between deactivation in either the medial PFC or posterior cingulate cortex and the in-scanner verbal memory task.

To determine the specificity of this pattern of findings, we examined the association of depressive symptoms and PTSD symptom burden (both assessed continuously due to the small proportion of participants meeting elevated symptoms), with patterns of brain activation during encoding and recognition. For second-level analyses, post-traumatic stress and depressive symptoms were entered as a continuous regressor to examine the association between each factor and brain activation after controlling for recent CD4 count. To clarify the functional significance of these variables and to examine correlations between brain activity and behavior performance, parameter estimates were extracted and averaged from individual contrast map (experimental vs. control) with a 5-mm spherical ROI centered at voxels showing peak associations between these variables and brain activation. Depressive symptoms were associated with decreased activation in the medial PFC during encoding after controlling for recent CD4 count ($p<0.01$). However, depressive symptoms were not associated with brain activation during recognition. Decreased activation in the medial PFC was not associated with either verbal memory or clustering. Parallel to the perceived stress findings, PCLC scores were not associated with brain activation during encoding, but higher PCLC scores were associated with greater deactivation in the medial PFC during recognition after controlling for recent CD4 count ($p<0.01$). Greater deactivation in the medial PFC was associated with less efficient clustering on the HVL semantic clustering outcomes including the clustering z-score ($r=-0.33$, $p=0.04$), total clustering on trials 1–3 ($r=-0.32$, $p=0.06$), and total clustering on trials 1–3 ($r=-0.31$, $p=0.07$). No association was noted between verbal memory performance on the HVL or on the in-scanner memory task and medial PFC activation.

Discussion

An earlier report from 1499 women in the WIHS showed that higher levels of perceived stress are related to greater deficits in verbal memory in HIV-infected women compared to HIV-uninfected women (Rubin *et al*, 2015a). To our knowledge, we are the first to use fMRI to examine the neural basis of the stress-related verbal memory impairment in HIV-infected women. Specifically, we compared brain activation patterns during a word list-learning task between HIV-infected women with higher and lower perceived stress and found activation differences during word recognition but not encoding. HIV-infected women with higher stress demonstrated greater deactivation of the medial PFC and posterior cingulate cortex during recognition after controlling for recent CD4 count.

In the present study, 83% of women reported a history of traumatic events, including childhood sexual abuse and all physical, sexual, or coercive violence, and 28% of women had a high total symptom severity score indicative of probable PTSD based on PCL-C.

Additionally, women with higher perceived stress were also more likely to report higher PTSD and depressive symptoms. Thus, we also examined patterns of brain activation in relation to PTSD and depressive symptoms after controlling for recent CD4 count. PTSD symptoms, but not depressive symptoms, were associated with greater deactivation of the medial PFC and posterior cingulate cortex during recognition. In line with our previous structural imaging finding of an association between lower volumes in the frontal cortex and poorer verbal memory retrieval and clustering during retrieval in women with HIV (Rubin *et al*, 2015b), we found that that greater medial PFC deactivation was marginally associated ($p = 0.06$) with lower clustering. The combination of our structural and functional imaging finding implicate alterations in PFC structure (Rubin *et al*, 2015b) and function in stress-related verbal memory deficits in HIV-infected women. The fact that activation differences were found between HIV-infected stress groups during recognition, but not encoding suggests that the negative effects of overall perceived stress and post-traumatic stress symptom severity more specifically may impact retrieval more than encoding processes in HIV, which is consistent with the broader stress and memory literature (Chen *et al*, 2009; Geuze *et al*, 2008; Jenkins *et al*, 1998; Lanius *et al*, 2001; Yehuda *et al*, 1995).

During verbal recognition, HIV-infected women with higher stress demonstrated greater deactivation (or less activation) of the medial PFC and posterior cingulate cortex compared to HIV-infected women with lower stress. The medial PFC and posterior cingulate are core components of the brain's default mode network (DMN; Raichle, 2015; Raichle *et al*, 2001). The DMN is most active when the brain is at rest or in the absence of cognitive demands and is suppressed during the performance of goal-oriented or cognitively demanding tasks. Thus, suppression of DMN is thought to reflect a reallocation of cognitive resources from more passive mental explorations to the external goal-oriented tasks (e.g., verbal memory task). Connectivity within the DMN and between the DMN and other brain networks is critical for cognitive functioning (e.g., salience network, executive control network) and may be compromised among individuals with HIV (Ortega *et al*, 2015), PTSD (Bluhm *et al*, 2009), or among individuals exposed to early life or chronic stress (Graham *et al*, 2015; Soares *et al*, 2013). In the present study, HIV-infected women with higher stress showed greater deactivation of the DMN compared to HIV-infected women with lower stress and this greater deactivation was marginally correlated with decreased semantic clustering. Thus, our data suggest that there may be an optimal level of DMN deactivation and reallocation of cognitive resources during memory tasks and high stress levels in HIV may be associated with supraoptimal levels of DMN deactivation and resource reallocation. Supraoptimal levels of DMN deactivation in HIV-infected women with stress may reflect a compensatory, although ineffective, strategy, whereby the adverse effects of HIV and stress on the brain requires greater allocation of passive cognitive resources to support cognitive demands. Alternatively, HIV women with high stress particularly those with high levels of PTSD symptoms may reallocate less efficiently so that cognitive resources are more dispersed and less concentrated in the neural networks underlying verbal memory. This might be a necessary effective strategy for dealing with stress and PTSD symptoms in order to function more optimally in other everyday life tasks. It is also possible that HIV-infected women with high stress may be unable to effectively turn off and on the DMN and fluidly switch to using more functionally relevant brain networks important for verbal memory performance

compared to HIV-infected women with lower stress. Future resting state fMRI studies are needed to examine the effects of HIV and stress on the integrity of the DMN and its functional connectivity and how these effects relate to cognitive dysfunction.

Consistent with our findings, studies in individuals with PTSD or other stress-related disorders demonstrate hypoactivity in the medial PFC and posterior cingulate cortex during cognitive tasks (Bremner, 2007; Bremner *et al*, 1999; Patel *et al*, 2012; Ramage *et al*, 2013; Shin *et al*, 2006). In contrast to studies of individuals with PTSD (Bremner, 2007; Chen *et al*, 2009; Geuze *et al*, 2008; Shin *et al*, 2004), we did not find stress-related differences during recognition in the medial temporal lobe or in other PFC regions including the dorsolateral PFC, inferior frontal gyrus, and anterior cingulate. We also did not find stress-related differences during encoding in either the medial temporal lobe or in prefrontal regions (Bremner *et al*, 2003; Chen *et al*, 2009; Geuze *et al*, 2008). One possibility is that we were underpowered to find differences during the encoding condition compared to retrieval as the encoding condition was comprised of half of the blocks of the recognition condition. Such differences might be evident only when comparing those with and without PTSD; we examined PTSD symptoms on a continuous scale because only 23% of participants met probable PTSD criteria on the PCL-C.

The medial PFC in particular has also been implicated in memory retrieval, decision making, and consistent with semantic clustering mechanisms, in learning associations between context (Euston *et al*, 2012). Indeed, greater deactivation in the medial PFC was marginally related to less semantic clustering. The same pattern of results was also noted when examining PTSD but not depressive symptoms. Overall, our results suggest that hypoactivation of the PFC, particularly the medial PFC, may contribute to verbal memory deficits in HIV-infected women with high stress.

This study has several limitations. First, given the cross-sectional design, it is not possible to determine the temporal associations among stress, HIV, and memory problems. Early life adversity is highly prevalent in HIV-infected women and may contribute to lasting alterations in the stress response system and in the function and structure of the PFC (Lupien *et al*, 2007; Lupien *et al*, 2009). Results from our epidemiological behavioral study in 1499 women demonstrated that stress was related to verbal memory deficits in HIV-infected women but not seronegative controls (Rubin *et al*, 2015a). Thus, early stress-related brain effects may be amplified by HIV infection or by syndemic factors (e.g., substance abuse, transactional sex, poverty, low psychosocial resources) leading to greater memory dysfunction. Future studies in the WIHS could compare the subset, albeit small, of those who did not experience early life trauma. Alternatively, HIV-related brain vulnerabilities might lead to verbal memory difficulties which consequently could lead to increased levels of stress. The effects of HIV and stress on brain regions such as the PFC which subserve memory functioning are likely bidirectional (Lupien *et al*, 1998). In the present study, although recent CD4 count significantly differed across group and was associated with our outcomes of interest, controlling for CD4 count did eliminate the stress-related behavioral and imaging associations. Larger-scale, longitudinal studies are needed to further explore these associations in HIV-infected women. Second, while it is possible that other covariates may have an influence on the pattern of results such as substance use and HCV status, such

effects could not be teased out in the small sample. Notably, in our early study of 1499 women, the stress-related memory impairment in HIV-infected women was not accounted for by relevant socio-demographic (age, race, education, annual household income), behavioral (depressive symptoms, substance use including heavy alcohol use, smoking, marijuana, crack, cocaine and/or heroin), or clinical characteristics (HCV status, antidepressant use, combination antiretroviral therapy, recent/nadir CD4 count, viral load) (Rubin *et al*, 2015a). Third, we did not include HIV-uninfected controls so we could not investigate the interactive effects of HIV status and stress on brain functioning. Given our previous finding that stress was related to verbal memory only in the context of HIV (Rubin *et al*, 2015a), we only focused on HIV-infected women in this study.

Conclusions

In the context of HIV, high stress may alter the function of the medial PFC resulting in less efficient retrieval and deficits in verbal memory. Understanding the role of the PFC in stress-related memory impairments will be particularly important for women aging with HIV as the PFC is vulnerable to neurodegeneration associated with age and HIV. Regardless of stress group, we found bilateral activation of the PFC during the verbal memory tasks in our total sample of HIV-infected women. As opposed to the hemispheric asymmetry model of PFC activation during episodic memory in healthy individuals (Tulving *et al*, 1994), the observed bilateral PFC activation generates the hypothesis that the effects of HIV and stress on the brain may similarly evoke the compensatory strategy of bilateral PFC neural recruitment for memory processes (Cabeza, 2002) that is associated with aging. This hypothesis could be further examined in a study with HIV-infected women and HIV-uninfected controls. Future studies should address whether interventions that lower stress can ameliorate the negative effects of stress on brain structure and function. Improving PFC function may help HIV-infected women to cope adaptively to acute stress or stressful life events and thus lessen the risk of sustained negative affect (depression, anxiety) as well as improve capacity to engage in cognitively demanding treatments such as cognitive behavioral therapy (e.g., problem solving therapy) which may improve HIV treatment adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Data in this manuscript were collected by the Chicago site of the Women's Interagency HIV study (WIHS) and is funded by National Institute of Allergy and Infectious Diseases (NIAID) grant U01 A1034993 (PI: Mardge Cohen, M.D.) and co-funded by National Cancer Institute (NCI) and National Institute of Drug Abuse (NIDA). L. Rubin's effort was supported by grant number 1K01MH098798-01 from the National Institute of Mental Health (NIMH) and grant number K12HD055892 from the National Institute of Child Health and Human Development (NICHD), and the National Institutes of Health Office of Research on Women's Health (ORWH). This grant was also supported by the Chicago Developmental Center for AIDS Research (D-CFAR), an NIH funded program (P30 AI 082151), which is supported by the following NIH Institutes and Centers (NIAID, NCI, NIMH, NIDA, NICHD, NHLBI, NCCAM). V. Meyer's effort on this project was supported by the National Institute on Drug Abuse (1F31DA028573). E. Sundermann's effort on this project was supported by the National Institute of Mental Health (1F31MH083537). This work was previously presented in part as part of an oral presentation at the 6th

International Workshop on HIV and Aging on October 5th in Washington, DC and as part of a poster presentation at the 13th International Symposium on Neurovirology on June 3 in San Diego, California.

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Figure 1.

Typical pattern of activation during encoding for the combined sample of HIV-infected women (n=36).

Note. Activation reflects activation during encoding of unique target words (experimental condition) minus the repeated control words (control condition), $p < 0.05$, cluster threshold: $k = 10$.

Figure 2.

Typical activation during recognition for the combined sample of HIV-infected women (n=36).

Note. Activation reflects activation during the recognition of unique target words (experimental condition) minus the repeated control words (control condition), $p < 0.001$, cluster threshold: $k = 10$.

Figure 3. Mean medial prefrontal cortex (PFC) deactivation during recognition (unique target words minus repeated control words) in HIV-infected women as a function of perceived stress.

Figure 4.

Greater deactivation in the right medial prefrontal cortex (PFC) during recognition relates to decreased semantic clustering.

Note. Same pattern seen for HVLIT trial 1 ratio cluster score and deactivation in the right medial PFC during recognition, $r = -0.33$, $p = 0.05$. Same pattern of associations are noted after controlling for age and recent cd4 count.

Table 1

Demographic and clinical characteristics for HIV-infected women as a function of perceived stress.

Variables	Perceived Stress		p-value
	Lower (n=18)	Higher (n=18)	
Socio-demographic factors			
Age, <i>M (SD)</i>	42.56 (6.32)	44.89 (7.67)	0.33
WRAT-R, <i>M (SD)</i>	87.44 (20.31)	83.17 (16.89)	0.50
Years of Education, <i>M (SD)</i>	12.94 (2.15)	12.14 (2.26)	0.28
Black, non-Hispanic	18 (100)	17 (94)	0.32
Risky health behaviors			
Currently smoking	8 (44)	7 (39)	0.74
Recent ^I use			
Heavy alcohol use	3 (17)	2 (11)	0.79
Marijuana use	3 (17)	3 (17)	1.00
Crack use	1 (6)	4 (22)	0.15
Cocaine use	1 (6)	0 (0)	0.32
Heroin use	1 (6)	3 (17)	0.29
Psychological profile			
Perceived stress (PSS-10), <i>M (SD)</i>	10.89 (3.89)	22.00 (3.74)	<0.001
Depressive symptoms (CES-D 16)	3 (17)	7 (39)	0.14
PTSD symptoms (PCL-C 44)	1 (6)	9 (50)	0.003
Abuse ever	16 (89)	14 (78)	0.38
Clinical characteristics			
Hepatitis C virus antibody (HCV)	3 (17)	6 (33)	0.25
Nadir CD4 count (cells/μl), <i>Median (IQR)</i>	315 (209)	311 (249)	0.53
CD4 Count (cells/μl), <i>Median (IQR)</i>	782 (730)	392 (271)	0.03
CD4 Count (cells/μl)			0.04
> 500	12 (70)	5 (28)	
200 and < 500	3 (18)	10 (55)	
< 200	2 (12)	3 (17)	
Viral Load (HIV RNA (cp/ml))			0.34
Undetectable	12 (67)	8 (44)	
< 10,000	4 (22)	5 (28)	
10,000	2 (11)	5 (28)	
Medication Use			1.00
No cART or cART+ < 95% medication adherence	6 (33)	6 (33)	
cART+ 95% medication adherence	12 (67)	12 (67)	

Note.

¹“Recent” refers to within 6 months of the most recent WIHS visit; IQR=Interquartile range. WRAT-R = Wide Range Achievement Test Standard Score; CES-D= Center for Epidemiologic Studies Depression Scale; PSS-10=Perceived Stress Scale. PCL-C=PTSD Checklist-Civilian Version. Heavy alcohol use = >7 drinks per week or > 4 drinks at a sitting; Undetectable=<48copies/ml; cART = combination antiretroviral therapy; Abuse ever=any childhood sexual abuse and all physical, sexual, and coercive violence.

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Table 2

Verbal memory performance for HIV-infected women as a function of perceived stress.

Domain	Perceived Stress		β	p-value	Cohen d (95%CI)
	Lower (n=18) M (SE)	Higher (n=18) M (SE)			
In-scanner memory task					
Recognition percent correct	0.64 (0.02)	0.65 (0.02)	0.05	0.74	0.12 (−0.54 to 0.77)
Free-recall total	5.37 (0.75)	3.18 (0.74)	−0.33	0.04	−0.69 (−1.36 to −0.02)
Free-recall cluster ratio score	2.15 (0.47)	0.79 (0.47)	−0.32	0.04	−0.68 (−1.35 to −0.01)
Hopkins Verbal Learning Test (HVLT)					
Verbal learning domain z-score	0.06 (0.23)	−0.14 (0.22)	−0.11	0.52	−0.21 (−0.44 to 0.86)
Trial 1	6.17 (0.40)	5.83 (0.40)	−0.09	0.55	−0.20 (−0.85 to 0.45)
Total Learning	23.91 (1.03)	22.97 (1.02)	−0.11	0.53	−0.22 (−0.87 to 0.44)
Verbal memory domain z-score	0.26 (0.21)	−0.37 (0.21)	−0.33	0.04	−0.72 (−1.39 to −0.04)
Delay free recall	8.63 (0.56)	7.03 (0.56)	−0.32	0.04	−0.67 (−1.34 to −0.01)
Retention	91.17 (4.55)	78.04 (4.47)	−0.32	0.04	−0.69 (−1.36 to −0.01)
Retrieval index	2.36 (0.47)	4.21 (0.46)	−0.42	0.006	−0.94 (−1.63 to −0.25)
Recognition	9.95 (0.61)	10.45 (0.59)	0.10	0.56	0.20 (−0.46 to 0.85)
Clustering domain z-score	0.19 (0.17)	−0.32 (0.17)	−0.32	0.03	−0.71 (−1.38 to −0.03)
Trial 1 cluster score	1.67 (0.25)	1.15 (0.25)	−0.23	0.14	−0.63 (−1.30 to 0.04)
Immediate total cluster score	7.03 (0.86)	5.29 (0.88)	−0.23	0.15	−0.47 (−1.13 to 0.19)
Delay cluster score	3.58 (0.51)	2.01 (0.54)	−0.34	0.03	−0.70 (−1.38 to −0.03)

Note. All models control for age. CI=Confidence Interval.