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Subjective Memory Complaints are Associated with Poorer Cognitive Performance in Adults with HIV

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Abstract

With successful antiretroviral therapy (ART) in the US, HIV-positive adults now routinely survive into old age. However, increased life expectancy with HIV introduces the added complication of age-related cognitive decline. Aging with HIV has been associated with poorer cognitive outcomes compared to HIV-negative adults. While up to 50% of older HIV-positive adults will develop some degree of cognitive impairment over their lifetime, cognitive symptoms are often not consistently monitored, until those symptoms are significant enough to impair daily life. In this study we found that subjective memory complaint (SMC) ratings correlated with measurable memory performance impairments in HIV-positive adults, but not HIV-negative adults. As the HIV-positive population ages, structured subjective cognitive assessment may be beneficial to identify the early signs of cognitive impairment, and subsequently allow for earlier interventions to maintain cognitive performance as these adults continue to survive into old age.

Keywords

HIV-1; Aging; Memory; Cognition; Subjective Memory Impairment

Introduction

Nearly 50% of Human Immunodeficiency Virus (HIV)-positive individuals in the US are now aged 50 or older (Vance, McGuinness, Musgrove, Orel, & Fazeli, 2011). Both older age and HIV increase the risk of cognitive dysfunction, though it's unclear whether or not the two interact (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Becker, Lopez, Dew, & Aizenstein, 2004; Bhatia, Ryscavage, & Taiwo, 2011; Iudicello, Paul Woods, Deutsch, Grant, & Group, 2012; Manly et al., 2011; Morgan et al., 2012). Additionally, older age is associated with higher risk of depression and anxiety (Kohler, Thomas, Barnett, & O'Brien,

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2010), which can further worsen cognition (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Lockwood, Alexopoulos, & van Gorp, 2002; Wang et al., 2008). Identifying markers of cognitive vulnerability would allow intervention before symptoms significantly affect daily life.

Subjective memory complaints (SMCs) may have particular clinical value in adults undergoing pathological aging processes. SMCs were shown to correlate with informants' memory rating in adults diagnosed with Mild Cognitive Impairment (MCI) or dementia (Abner, Kryscio, Caban-Holt, & Schmitt, 2015; Buckley et al., 2015; Salem, Vogel, Ebstrup, Linneberg, & Waldemar, 2015), and to correlate with subjective mood (Yates, Clare, Woods, & Matthews, 2015). SMCs have also been associated with poorer verbal episodic memory performance (Gifford et al., 2015). However, previous studies in HIV have found stronger association between SMCs and mood (Au et al., 2008; van Gorp et al., 1991) rather than with cognitive performance.

We examined if SMC ratings correlated with objective memory performance in HIV-positive and -negative adults. We hypothesized that SMC ratings would correlate with objective impairments more significantly in HIV-positive adults than controls.

Methods

Participants

We enrolled 35 HIV-positive and 21 HIV-negative adults (n=56). Groups were similar with respect to race, sex, age, and education (Table 1). Participants endorsing current substance abuse (alcohol, cocaine, opiates) or HIV-positive participants not on Anti-Retroviral Therapy were excluded. Participants gave informed consent, approved by the Vanderbilt Institutional Review Board and Human Research Protection Program.

Memory and Mood Measures

The Memory Functioning Questionnaire (MFQ) is a 64-item subjective survey of current memory problems, rated from 1-7. (Gilewski & Zelinski, 1988). The Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) are 21-item self-report questionnaires, measuring incidence and severity of current depressive/anxiety symptoms, rated from 0-3 (Beck, Epstein, Brown, & Steer, 1988; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). For the MFQ, BDI and BAI, participants answered regarding the previous 30 days, including their study day.

Cognitive Tasks

Tasks were chosen for reliability in accurately assessing episodic and working memory, executive functioning and attention. The Selective Reminding Task (SRT) measures episodic verbal memory (Buschke, 1973). Participants are read a list of sixteen (16) words and asked to recall as many as possible. Participants completed eight (8) immediate recall trials. Before each trial, experimenter re-reads only the words that the participant failed to recall. Recall and Recall Consistency (words recalled in two (2) sequential trials without reinforcement)

were recorded. Participants completed a Delayed Recall trial after approximately 25 minutes.

Participants completed four (4) CogState tasks (Fredrickson et al., 2010) previously used in HIV-positive adults (Boivin et al., 2010; Cysique, Maruff, Darby, & Brew, 2006; Thiagarajan et al., 2010; Winston et al., 2012): Groton Maze (executive functioning), Detection (psychomotor functioning), Identification (visual attention), and One-Card Learning (working memory).

Data Analysis

Group means were calculated for age, BDI/BAI Scores, MFQ Score, and cognitive performance measures, and compared using independent samples t-tests. In the HIV-positive group, mean CD4+ T-cell nadir and current CD4+ counts were obtained from medical records (Ellis et al., 2011). For the SRT, Total Recall and Recall Consistency were calculated for the full 8-trial task (SRT-T), as well as for first four (SRT-F) and last four (SRT-L) trials.

“Accuracy” on the CogState tasks was defined as an arcsine transformation of the proportion of correct to incorrect responses. Pearson Correlations (2-tailed) were calculated between MFQ score, age, BDI/BAI score, SRT-T, SRT-F and SRT-L performance measures, CogState accuracy measures; and in the HIV-positive group, CD4+ nadir. Multiple regression analysis was conducted to evaluate the relationship of MFQ and BDI scores to Total Recall on the SRT-T.

Results

Group means and standard deviations for the descriptive, behavioral, and cognitive data can be found in Table 1. There were no significant group differences in age or education. Mean BDI, BAI, and MFQ scores were not significantly different between groups.

HIV-negative participants had significantly higher Total Recall on the SRT-T compared to HIV-positive participants ($t=4.270$, $p<0.001$), while SRT-T Recall Consistency was not significantly different between groups. HIV-negative participants also showed significantly higher Delayed Recall compared to HIV-positive participants ($t=3.330$, $p=0.002$).

When SRT immediate performance was split between the first four (SRT-F) and last four (SRT-L) trials, Recall and Recall Consistency were significantly different between groups on the first four (SRT-F Recall $t=4.026$, $p<0.001$; SRT-F Consistency $t=-4.21$, $p<0.001$) and last four (SRT-L Recall $t=4.218$, $p<0.001$; SRT-L Consistency $t=4.275$, $p<0.001$) trials, shown in Figure 1. Paired t-tests revealed that differences in Recall Consistency between SRT-F and SRT-L were significantly different in the HIV-positive group ($t=10.340$, $p<0.001$), but not in the HIV-negative group.

HIV-positive participants showed significantly lower accuracy on the One Card Learning (OCL) Task than HIV-negative participants ($t=4.07$, $p<0.001$). The HIV-positive group completed the Groton Maze (GML) significantly slower than the HIV-negative group ($t=-3.848$, $p<0.001$), with significantly fewer moves per second ($t=4.182$, $p<0.001$). No other CogState measures were significantly different between groups.

MFQ score was significantly correlated with BDI and BAI ratings in both the HIV-negative (MFQ $\times$ BDI corr = -0.618, $p=0.003$; MFQ $\times$ BAI corr = -0.466, $p<0.001$) and HIV-positive (MFQ $\times$ BDI corr = -0.579, $p=0.03$; MFQ $\times$ BAI corr = -0.630, $p<0.001$) groups. MFQ score was significantly correlated with SRT-T Recall in both the HIV-negative (MFQ $\times$ SRT-T corr = 0.499, $p=0.021$) and HIV-positive (MFQ $\times$ SRT-T corr = 0.432, $p=0.012$) groups. Delayed Recall performance was significantly correlated with MFQ score in the HIV-positive (MFQ $\times$ SRT-T Delay corr = 0.548, $p=0.002$), but not the HIV-negative group.

There were no significant correlations between mood ratings or MFQ and age, in either group. Age was significantly correlated with SRT-T Recall and Delayed Recall in the HIV-negative group (age $\times$ SRT-T corr = -0.492, $p=0.024$; age $\times$ SRT-T Delay corr = -0.546, $p=0.010$), but not the HIV-positive group. There were no sex differences in MFQ scores in either group, or correlations between current or nadir CD4+ count and any cognitive measures.

MFQ score was significantly correlated with OCL accuracy in the HIV-positive group (MFQ $\times$ OCL corr = 0.414, $p=0.025$) but not in the HIV-negative group. No other measures of the CogState were significantly different between serostatus groups, or correlated with SMCs.

Despite statistically insignificant differences in BDI score between groups, regression analysis showed that in a model including MFQ and BDI scores, BDI explained a significant portion of performance variance on the SRT-T Recall in the HIV-negative group ($F(2,18)=6.36$, Sig = 0.008, BDI beta = -0.516, MFQ beta = 0.180), whereas in the HIV-positive group, MFQ explained a significant portion of variance in SRT-T Recall ($F(2,30)=3.45$, Sig = 0.045, BDI beta = 0.23, MFQ beta = 0.446).

Discussion

The HIV-positive participants in this study had significantly lower scores on verbal episodic memory (SRT) and recognition working memory (OCL) tasks compared to HIV-negative participants. Previous studies have linked episodic memory failures in HIV to the loss of fronto-striatal white matter and hippocampal volume (Castelo, Sherman, Courtney, Melrose, & Stern, 2006; Pfefferbaum et al., 2014), impairing memory storage and retrieval, which may be the underlying mechanisms in this HIV-positive group. On the SRT, differences in Recall Consistency between early and late trials of the task may reflect impairment in transferring encoded information from short- to long-term storage.

Prior studies have shown strong correlations between SMCs and mood ratings (van Gorp et al., 1991). However in this study, SMC scores accounted for a greater portion of SRT performance variance. This may indicate that in HIV-positive adults, SMCs may be a more salient marker of actual cognitive deficits than in HIV-negatives, and may deserve closer monitoring. A unique property of this sample was similar depression ratings between groups. Because of the higher proportion of mood disorders in HIV-positive adults, it may be more clinically relevant to compare HIV-positive populations to controls with higher mood ratings, to examine the effects of serostatus alone.

Our results support the use of SMCs as a marker to identify memory impairments in adults experiencing pathological aging processes, versus “normal” age-related cognitive changes. This is an important distinction, since studies of cognitively normal adults have found little to no correlation between SMCs and performance (Abner et al., 2015; Dalla Barba, La Corte, & Dubois, 2015; Fritsch, McClendon, Wallendal, Hyde, & Larsen, 2014; Howieson et al., 2015; Huler, Hertzog, Pearman, Ram, & Gerstorf, 2014). Our positive results may also be due to the more thorough SMC measure used versus other common SMC instruments. The MFQ's more detailed query of memory may more accurately portray deficits in memory function.

Our design was insufficient to explore biochemical factors of HIV infection and treatment that may affect cognition and mood. Relative CNS penetrance of different ARTs (Declodt, Rosenkranz, Maartens, & Joska, 2015; Skinner, Adewale, DeBlock, Gill, & Power, 2009), ART neurotoxicity (Akay et al., 2014; Underwood, Robertson, & Winston, 2015), mood disorders (Dal-Bo et al., 2015; Silveira et al., 2012), substance abuse history (Byrd et al., 2011) and length and severity of HIV infection (Heaton et al., 2015) can all negatively affect cognitive performance in aging HIV-positive adults, and fluctuate over time (Dawes et al., 2008). Accounting for these differences in disease and treatment are necessary to further specify individual risk factors for cognitive changes.

Conclusions

This study showed that memory performance was significantly different between HIV-negative and -positive adults, and that in HIV-positive adults, SMCs correlated with episodic and working memory performance. Differences in SMCs and memory performance were not explained solely by depressive symptoms. This data indicate that measuring SMCs may have clinical value, to monitor cognitive changes in HIV-positive adults. Adding structured SMC measures to routine assessments may help identify those who should be more closely monitored for HAND symptoms, leading to earlier, more effective interventions for adults aging with HIV.

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Figure 1. SRT-F and SRT-L Recall and Recall Consistency, by Serostatus Groups. (**: significant at $p < 0.001$ level). There were significant differences between Recall in the first four (SRT-F) and last four (SRT-L) trials in both serostatus groups. Recall Consistency between SRT-F and SRT-L was significantly different in the HIV-positive, but not HIV-negative group.

Table 1

Descriptive, Behavioral and Cognitive Results, HIV-Positive and HIV-Negative Groups. Data presented as Mean (St. Dev).

	HIV-Positive	HIV-Negative	
	N=35	N=21	p-value
Gender (% Male)	57.1	47.6	0.584
Race (% White)	42.9	61.9	0.270
Years of Education	14.0	15.61	0.083
Age	49.1 (11.5)	46.6 (13.5)	0.459
Minimum-Maximum Age	26-76	23-69	-
CD4 Nadir	395.6 (209.6)	-	-
CD4 Current	754.3 (494.8)	-	-
MFQ Score	275.1 (87.6)	286.4 (54.9)	0.600
BDI Score	18.6 (11.0)	13.7 (8.1)	0.081
BAI Score	18.2 (13.3)	12.9 (14.4)	0.165
Detection Accuracy	1.38 (0.25)	1.48 (0.11)	0.087
Identification Accuracy	1.30 (0.25)	1.37 (0.14)	0.344
One-Card Learning Accuracy	0.88 (0.07)	0.98 (0.09)	** < 0.001
Groton Maze Duration (s)	11456 (6416)	56.92 (22.52)	** < 0.001
Groton Maze (moves per second)	0.34 (0.18)	0.56 (0.20)	** < 0.001
SRT-Total Recall	49.18 (16.44)	75.00 (28.06)	** < 0.001
SRT-Total Recall (Delay)	5.61 (3.37)	9.52 (5.06)	*0.002
SRT-Total Consistency	7.00 (0.79)	7.38 (0.81)	0.098
SRT-First 4 Recall	20.96 (6.03)	31.52 (12.08)	** < 0.001
SRT-Last 4 Recall	28.21 (11.09)	43.47 (15.50)	** < 0.001
SRT-First 4 Consistency	10.47 (1.73)	7.35 (3.69)	** < 0.001
SRT-Last4 Consistency	440 (1.93)	7.40 (3.23)	** < 0.001

* : significant at p<0.05 level

** : significant at p<0.001 level