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Subjective cognitive decline disrupts aspects of prospective memory in older adults with HIV disease

Jennifer L. Thompson[1], **David P. Sheppard**[2], **Anastasia Matchanova**[1], **Erin E. Morgan**[3], **Shayne Loft**[4], **Steven Paul Woods**[1,4]

[1]Department of Psychology, University of Houston, Houston, TX 77004, USA

[2]Mental Illness, Research, Education, and Clinical Care (MIRECC), Veterans Affairs Puget Sound Health Care System, Seattle, WA 98108, USA

[3]Department of Psychiatry, University of California San Diego, San Diego, CA 92103, USA

[4]School of Psychological Science, University of Western Australia, Perth, WA 6009, Australia

Abstract

Subjective cognitive decline (SCD) is a risk factor for incipient dementia that may occur at higher rates in people with HIV (PWH) disease. Prospective memory (PM; i.e., remembering to remember) is an ecologically relevant aspect of cognition that may help us better understand how SCD impacts daily life. The study sample included 95 adults ages ≥ 50 years with (n=62) and without (n=33) HIV disease. SCD was operationalized as normatively elevated cognitive symptoms in daily life on standardized questionnaires, but with normatively unimpaired cognition in the laboratory and no current affective disorders per a semi-structured interview. PM was measured with the Comprehensive Assessment of Prospective Memory (CAPM), the Cambridge Test of Prospective Memory (CAMPROMPT), and an experimental computerized time-based PM task. A logistic regression covarying for medical comorbidities revealed that older PWH had a three-fold increased likelihood for SCD as compared to older individuals without HIV (46.8% vs 18.2%, respectively). Among the PWH, SCD was associated with more frequent PM symptoms in daily life, particularly in the encoding phase. PWH with SCD also demonstrated poorer accuracy on the time-based scale of the CAMPROMPT, which was marked by omission errors and intact recognition performance. Taken together, these findings suggest that HIV is a risk factor for SCD, which is associated with elevated PM symptoms in daily life and moderate time-based PM performance deficits in the laboratory among older PWH. Future work may examine whether assessing PM improves the diagnosis of SCD in older adults and persons with HIV disease.

Keywords

aging; everyday functioning; future thinking; infectious disease; neuropsychological assessment; subjective cognitive impairment

Corresponding author: Steven Paul Woods, Psy.D. spwoods@uh.edu. Address: 126 Heyne Building, Suite 239D, Houston, TX 77004-5022. Phone: 713-743-6415.

Introduction

The combination of longer life expectancies due to effective antiretroviral treatment and a rising incidence of HIV among persons ≥50 years old has increased the number of older people with HIV disease (PWH; CDC, 2021). Older PWH are at risk for a variety of age-related health challenges (Blanco et al., 2012), including higher rates of medical comorbidities (e.g., Rodriguez-Penney et al., 2013), polypharmacy (Back & Marzolini, 2020), and frailty (Jones et al., 2022), as well as lower quality of life (e.g., Moore et al., 2014). There is also evidence for poorer long-term brain health outcomes in older PWH. In general, age and HIV appear to have additive effects on brain structure and function (e.g., Thomas et al., 2013). Older PWH may demonstrate both accelerated and accentuated cognitive aging (Sheppard et al., 2017); moreover, older PWH can experience steeper trajectories of pathological cognitive aging (e.g., dementia; Alisky, 2007) and HIV-associated Neurocognitive Disorders (HAND; Valcour et al., 2004). In an effort to facilitate early identification of cognitive disorders in older PWH, investigators have borrowed diagnostic concepts from the cognitive aging spectrum, which posits that the transition from cognitive health to dementia is marked by intermediate stages involving Subjective Cognitive Decline (SCD; Jessen et al., 2014) and Mild Cognitive Impairment (MCI; Petersen et al., 1999). Data thus far suggest that HIV is associated with an increased risk of MCI, which is separable from HAND diagnoses and is associated with mild difficulties in activities of daily living (Sheppard et al., 2015; Sundermann et al., 2021).

We know less about the frequency and correlates of SCD in PWH. SCD is a pre-clinical stage of cognitive impairment (i.e., MCI or dementia) that is characterized by the experience of worsening cognitive difficulties in daily life that are not better explained by mood and are not detectable by standard cognitive assessments (Jessen et al., 2014). SCD is nevertheless associated with an increased risk of objective cognitive declines and incident dementia (Mitchell et al., 2014). Individuals with SCD demonstrate biomarker profiles associated with Alzheimer's disease, including phosphorylated tau and amyloid-β (Jessen et al., 2018; Wolfsgruber et al., 2017), as well as alterations in temporal and frontal system structures (e.g., Perrotin et al., 2017) and functions (Erk et al., 2011; Rodda et al., 2009). In 2019, Sheppard and colleagues demonstrated that HIV was associated with a nearly five-fold increased risk of SCD in 188 PWH (ages 22 to 75) as compared to 133 individuals without HIV. Within the PWH group, those with SCD demonstrated more problems with activities of daily living (ADLs) and lower (but clinically normal) scores on measures of verbal learning and memory (i.e., list and story recall), which has also been observed in samples without HIV (Crumley et al., 2014). Thus, it is plausible that the earliest stages of cognitive aging in PWH may involve a disruption of declarative memory that adversely affects daily life but may not be readily detectable by typical clinical tools. These memory failures might occur in the context of daily life pressures (e.g., forgetting to return to an intended task after being interrupted). Such memory failures may not be apparent in a quiet laboratory environment where persons with SCD can provide optimal effort in the absence of naturalistic distractions.

Prospective memory (PM), or "remembering to remember," is an ecologically relevant aspect of declarative memory defined as the execution of a planned intention and may be

of relevance to SCD (Einstein & McDaniel, 1990). Theoretical accounts of PM generally agree that PM involves: (1) forming/encoding of an intention, (2) associating the intention with a cue (e.g., the passage of a certain amount of time, or an expected event in the environment), (3) retaining the cue-intention pairing in the context of ongoing tasks that preclude continuous rehearsal, (4) identifying the cue signaling execution of the intended action, (5) retrieving the intended action from memory, and (6) correctly enacting the intended action (Rummel & Kvavilashvili, 2019). The demands on cognitive resources during the six stages of PM can vary from relatively low, automatic processes that depend on retrospective memory and medial temporal lobe function (e.g., Gordon et al., 2011) to highly strategic processes that tax executive functions and prefrontal-parietal systems (Scullin et al., 2013). One example of this can be found in the distinction between cues that are based on time (e.g., take a medication at 2pm) versus an event (e.g., take a medication after breakfast). Time-based PM tasks tend to require more cognitive resources for monitoring and detecting the appropriate temporal cue (Kliegel et al., 2001), whereas event-based PM tasks tend to involve more salient environmental cues that allow the intention to more easily "pop into mind," thus placing fewer demands on strategic monitoring. PWH show much larger deficits in time-based PM versus event-based PM, which follows from the known fronto-striatal pathogenesis of HIV disease (Avci et al., 2018). Older PWH are particularly susceptible to deficits in the strategic aspects of PM in the laboratory (Woods et al., 2010; 2020) and in daily activities (Avci et al., 2016; Woods et al., 2021), which can affect medication adherence (e.g., Sheppard et al., 2016) and quality of life (e.g., Doyle et al., 2012). In fact, HIV-associated deficits in PM may be a harbinger of cognitive decline among older adults (Sheppard et al., 2015). As such, it is reasonable to hypothesize that older PWH with SCD might experience PM symptoms in their daily lives and demonstrate impairment on performance-based measures of PM.

A small literature on SCD and PM in otherwise typically aging adults provides further support for the hypothesis that SCD may disrupt PM in older PWH. Rabin and colleagues (2014) were the first to describe deficits in PM among persons with SCD. Subsequent research shows that SCD is associated with worse performance on measures of time-based PM as compared to healthy adults (e.g., Hsu et al., 2015), although they perform better than persons with MCI (Hsu et al., 2019). SCD has not been reliably associated with deficits in either focal or non-focal event-based PM as measured in the laboratory (Chi et al., 2014; Lee et al., 2018; Rabin et al., 2014), which may be a function of increased mnemonic strategy use among SCD (Aronov et al., 2015). Outside of the laboratory, however, SCD has been associated with worse naturalistic PM in both cross-sectional (e.g., Lee et al., 2018; Rabin et al., 2014) and longitudinal (Kamberis et al., 2021) studies. These cross-sectional samples involved seronegative adults over the age of 65 (Lee et al., 2018; Rabin et al., 2014), which is notable given that seronegative older adult samples with lower age limits (e.g., 50 years old, 60 years old) have failed to demonstrate a significant association between SCD and naturalistic PM (McAlister & Schmitter-Edgecombe, 2016; Nurdal et al., 2020). Among persons with SCD, individual differences in PM are associated with white matter integrity (Hsu et al., 2019), executive functions and retrospective memory (Lee et al., 2018), and informant-rated ADL dependence (McAlister & Schmitter-Edgecombe, 2016). We are unaware of any prior studies examining PM symptoms in the daily lives of people with SCD.

The present study aimed to extend previous findings by examining the association of SCD with poorer prospective memory among older PWH. First, we aimed to provide a conceptual replication of the Sheppard et al. (2019) finding of elevated rates of SCD in PWH. We extend that study by focusing specifically on older adults with HIV disease and by including a more comprehensive assessment of subjective cognitive symptoms. Second, we examined whether SCD was associated with elevated self-perceived PM symptoms and lower objectively-measured PM performance among older PWH. It was hypothesized that SCD would be associated with more frequent PM symptoms in daily life and poorer PM performance, particularly on measures of strategically demanding time-based PM.

Methods

Participants

The study sample included 95 cognitively unimpaired adults ages 50 and older (age range = 50 to 75) with (n=62) and without (n=33) HIV disease. Individuals were enrolled via the University of California San Diego's (USCD) HIV Neurobehavioral Research Program and were recruited via community-based organizations, regional advertisements, and local clinics. All participants were part of a larger study cohort of 203 individuals described in Woods et al. (2020). The parent study excluded individuals with history of serious psychiatric disorders (e.g., schizophrenia), color blindness, intellectual disability, neurological conditions not due to HIV disease (e.g., non-HIV-related dementia, seizure disorders), head injury with loss of consciousness greater than 30 minutes, current substance dependence, or positive urine toxicology screen/breathalyzer for illicit drugs on the day of testing. Given the current study's focus on SCD, we further excluded participants who had: 1) cognitive impairment based upon age-adjusted global deficit scores ≥ 0.5 (Carey et al., 2004) on either the Cogstate Research battery (www.cogstate.com, see also Woods et al., 2016) or the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function (Casaletto et al., 2015); or 2) current diagnoses of major depressive disorder (MDD) or generalized anxiety disorder (GAD) based on the Composite International Diagnostic Interview (CIDI, version 2.1; WHO, 1998). Lifetime history of MDD, GAD, and substance use disorder (SUD) were also assessed using the CIDI. Affective disorders (i.e., MDD and/or GAD) and SUD were considered as separate variables from general medical co-morbidities given their unique effects on cognitive functioning and other health outcomes (Alford & Vera, 2018; Bruce & Altice, 2007). Ethical approval for the study was obtained by the Institutional Review Board at UCSD.

Procedures and Measures

All participants provided written, informed consent and completed a blood draw and an extensive research assessment of their cognitive, psychological, and medical status (see Woods et al., 2020). The medical assessment was conducted by a research nurse who obtained pertinent information related to HIV disease (e.g., infection duration), medication regimen (e.g., antiretrovirals), and medical comorbidities (e.g., hypertension). The basic cognitive assessment was conducted by a research assistant and included a semi-structured interview (i.e., CIDI) for mood and substance use disorders, self-report mood, cognition, personality, and everyday functioning questionnaires, a computerized cognitive battery, and

performance-based tests of everyday functioning. This study was hypothesis-driven, but the analyses were not pre-registered.

SCD Classification

We drew from current diagnostic systems (Jessen et al., 2014) to retrospectively classify participants into study groups with and without SCD (SCD+ vs. SCD-). SCD was determined by self-report of cognitive symptoms in the absence of normatively impaired cognition or current affective disorders. Cognitive symptoms were assessed using four self-report measures, including the Executive Dysfunction (Cronbach's alpha=.84) and Disinhibition (Cronbach's alpha=.77) scales of the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001), the Confusion & Bewilderment scale (Cronbach's alpha=.81) of the Profile of Mood States (POMS; McNair et al., 1981; Nyenhuis et al., 1999), and Retrospective Memory scale (Cronbach's alpha=.83) of the Prospective and Retrospective Memory Questionnaire (PRMQ; Crawford et al., 2003; Smith et al., 2000). Participants with elevated cognitive symptoms as defined by scores ≥1.5 SDs above the normative mean on at least one of the four measures were classified as SCD+. This criteria aligns with clinical cut-points and prior classification approaches used in aging and HIV (Aarsland et al., 2010; Jessen et al., 2020; Sheppard et al., 2019). Persons who were within normal limits on all four measures of cognitive symptoms were classified as SCD-. Among the entire sample of 95 participants with and without HIV, 35 individuals were classified as SCD+ and 60 were classified as SCD-. Relevant demographic, social, health, and HIV disease characteristics for the sample are displayed in Table 1.

Prospective Memory

The Comprehensive Assessment of Prospective Memory (CAPM; Waugh, 1999) is a self-report measure that was used to evaluate different dimensions of PM symptoms in daily life. The CAPM Section A (CAPM-A) is a 39-item scale that assesses the frequency of PM failures (e.g., "forgotten to buy an item at the grocery store") over the past month. Participants rated items on a scale from 1 "never" to 5 "very often-daily," whereby higher scores indicated greater frequency of PM failures (Cronbach's alpha=.97, sample range = 1.0 to 3.7). The CAPM Section B (CAPM-B) is a 39-item scale that measures frustration or concern regarding the same PM failures assessed on the CAPM-A. Participants rated their responses on a scale from 1 "no problem at all" to 5 "a very serious problem," where higher scores indicated greater frustration and concern (Cronbach's alpha=.96, sample range = 0.0 to 3.2). The CAPM Section C (CAPM-C; Roche et al., 2007) is a 15-item scale that measures attributions for why PM failures occur. Participants rated responses on a scale from 1 "strongly disagree" to 4 "strongly agree" (Cronbach's alpha=.85, sample range = 15 to 45). The CAPM-C is broken down into four subscales based upon Ellis' (1996) model of PM which includes stages of encoding (e.g., "I rely on other people to remind me when I have to remember to do things"), retention interval (e.g., "I tend to forget to do things if there is a long delay before they need to be done, [e.g., in three weeks' time]"), performance interval (e.g., "If I am engrossed in another task, I find it difficult to remember to do things"), and outcome evaluation (e.g., "I do not usually need to check whether I have done something because I am confident of my own memory"). Items assessing attributions for PM successes (e.g., "I do not need to rely on aids…when I have to remember to do things") were

reverse coded and then raw scores were summed for each respective subscale and for the total CAPM-C scale, such that greater scores indicated greater attributions of PM problems in each subscale and in overall PM problems.

The Cambridge Test of Prospective Memory (CAMPROMPT; Wilson et al., 2005) was used to assess objective PM performance. The CAMPROMPT is comprised of three time-based PM trials (e.g., “in 7 minutes stop whichever task you’re on and change to another task”) and three event-based PM trials (e.g., “when I say the test is over, remind me I have hidden objects, what they are, and where they are hidden”). Puzzles completed via pencil and paper were used as ongoing tasks throughout CAMPROMPT administration. Each of the six PM trials was scored ranging from 0 (fail item after two prompts) to 6 (correctly recall item without prompt and respond to correct cue). Items were summed for the time-based and event-based scales separately to generate total raw scores for each scale, with higher scores indicating better performance (sample ranges = 0 to 18). Omission errors, defined as failing to respond to the PM cue at any point during the evaluation, were also summed for time-based and event-based tasks (sample ranges = 0 to 3). The recognition task consisted of six questions asking participants to identify one of three multiple-choice options that was associated with each of the time- and event-based PM intentions.

An experimental laboratory time-based PM task was examined to provide a second objective measure of PM performance (see Woods et al., 2020). This measure was designed for the parent study, which was focused specifically on enhancing time-based PM in older PWH. HIV-associated deficits in time-based PM are more common in older adults (Avci et al., 2016), in whom the downstream functional implications are particularly noticeable (Avci et al., 2018). Only data from the control trials of this time-based PM task were used in this study (see Woods et al., 2020). Participants were told to press a white response button in the center of the screen at minutes 2, 5, and 9 during an ongoing language task (i.e., randomly assigned to either word category judgment task or lexical decision-making task condition). Responses were scored as correct if participants pressed the center white response button within ±20 seconds of the instructed time. Performance on the experimental task was scored as the percentage of accurate PM hits (sample range = 0 to 100%). A blue response button was displayed on the screen that allowed participants to check a clock, though they were instructed to limit their use of this option (Huang et al., 2014). Total number of clock checks were summed for each participant during the experimental task (sample range = 0 to 37).

Data Analysis

The critical alpha was .05 for all analyses, which were conducted in JMP 16.0 (SAS). A logistic regression analysis was used to determine whether HIV was associated with the frequency of SCD in the full study sample. We used a data-driven approach (Field-Fote, 2019) to determine covariates whereby any sociodemographic or clinical variable listed in Table 1 that significantly related to both the independent and dependent variable in each analysis were included as a covariate. Wilcoxon rank sums tests, Spearman’s rho correlations, and chi-square analyses were conducted to identify potential covariates. A retrospective power analysis was conducted to show that our sample size (N=95) afforded

adequate power (1-*B*=.92) to detect a medium effect size (i.e., odds ratio=3.47; Chen et al., 2010) for a logistic regression.

The remaining analyses were examined exclusively within the PWH (*n*=62) to compare the PM variables between PWH with (*n*=29) and without (*n*=33) SCD. The same data-driven approach was used to determine covariates for the analyses within the PWH sample, whereby any variables that were significantly associated with both SCD and the PM outcomes were included as covariates. The distributions were significantly non-normal for the variables CAPM-A (W=0.86, *p*<.001), CAPM-B (W=0.91, *p*<.001), experimental PM accuracy (W=0.68, *p*<.001), and time-based (W=0.95, *p*=.01) and event-based CAMPROMPT (W=0.89, *p*<.001) according to Shapiro-Wilk tests. Thus, non-parametric analyses were conducted. A retrospective power analysis identified adequate power (1-*B*=.86) to detect a large effect size (e.g., Cliff's delta=.45; Romano et al., 2006) for a Wilcoxon rank sums analysis within the sample size of PWH (n=62). Cliff's delta was used as a measure of effect size for the non-parametric group comparisons, where approximate values of 0.15, 0.30, and 0.45 were interpreted as small, medium, and large effect sizes, respectively (see Romano et al., 2006; Vargha & Delaney, 2000). Given the relatively small sample sizes of PWH with and without SCD, multiple efforts were taken to achieve balance between the risks of Type I and Type II error. First, all analyses were hypothesis driven, which increases the conceptual power and helps to mitigate the risk of Type I error. Second, analyses were restricted to the primary scales and outcomes from these established PM measures, which also helps to limit the risk of Type I error. Finally, the primary analyses were complemented with reporting and interpretation of effect sizes.

Results

Determining Covariates

In the full study sample (N=95), Wilcoxon rank sums tests revealed the HIV serostatus groups (i.e., the independent variable) differed in age (X^2=7.95, *p*=.005) and medical comorbidities (X^2=6.63, *p*=.01), and chi-square analyses revealed significant group differences in gender (X^2=4.59, *p*=.032) and lifetime affective disorder (X^2=5.51, *p*=.019; see Table 1). The HIV serostatus groups did not differ on any other variable (*ps*>.05). SCD classification (i.e., the outcome) was significantly related to medical comorbidities (X^2=7.98, *p*=.005), but not age (X^2=0.03, *p*=.862), gender (X^2=0.51, *p*=.475), or lifetime affective disorder (X^2=3.67, *p*=.055). Therefore, only medical comorbidities was included as a covariate in the logistic regression model.

For the PM analyses related to SCD in the PWH sample (*n*=62), the SCD groups differed in lifetime substance use disorder (X^2=4.61, *p*=.032) but were comparable on every other variable shown in Table 1 (all *ps*>.05). A Wilcoxon rank sums test showed that lifetime substance use disorder was not significantly related to any of the PM outcomes (all *ps*>.05). Therefore, no covariates met criteria for inclusion in the PM analyses among PWH.

SCD Frequency by HIV Groups

A logistic regression was conducted to compare the frequency of SCD in PWH versus individuals seronegative for HIV, covarying for number of medical comorbidities. Figure 1 displays the frequency of SCD by HIV serostatus. The overall regression model was significant (X^2(2, N=95)=15.08, p<.001). HIV disease was a significant predictor (X^2(1, N=95)=5.32, p=.021), such that HIV seropositivity was associated with a 3-fold increase in likelihood for SCD (odds ratio=3.70, 95% CI=1.22, 11.22). Medical comorbidities also emerged as a significant predictor (X^2(1, N=95)=5.12, p=.024), whereby the odds of SCD increased with a larger number of medical comorbidities.

Prospective Memory Symptoms

Table 2 displays the relationship between SCD and PM outcomes within the PWH sample only. Among PWH, Wilcoxon rank sums tests were conducted to examine SCD group differences in self-reported PM symptoms on the CAPM subscales. SCD+ persons endorsed a higher frequency of PM symptoms on the CAPM-A (X^2=4.54, p=.033, Cliff's d=.32). However, the two SCD groups did not differ significantly on their ratings of frustration with PM symptoms on the CAPM-B (X^2=2.82, p=.093) and the effect size was small-to-medium (Cliff's d=.25). Findings revealed the SCD+ and SCD− groups significantly differed on overall attributions of PM problems on the CAPM-C (X^2=5.74, p=.017, Cliff's d=.35), which were driven by greater problems during the encoding stage of PM in SCD+ individuals (X^2=7.29, p=.007, Cliff's d=.40). The groups differed on one item in the retention interval subscale related to forgetting tasks in the immediate future, such that the SCD+ group endorsed greater problems (X^2=4.37, p=.037). The groups did not differ on attributions of PM problems during stages of PM characterized by retention interval, performance interval, and evaluation of outcome scales (ps>.05, Cliff's ds range=.03 to .28).

Performance-Based (Objective) Prospective Memory

A Wilcoxon rank sums test was conducted to compare performance on the CAMPROMPT between the SCD+ and SCD− groups in the HIV sample. A significant group difference was observed for the time-based CAMPROMPT scale (X^2=7.10, p=.008, Cliff's d=.39), such that the SCD+ group exhibited worse PM performance than SCD− (see Figure 2). Omission errors on the time-based CAMPROMPT task also differed by group (X^2=4.80, p=.029, Cliff's d=.31), whereby the SCD+ group had more omission errors. However, the groups did not differ for performance on the ongoing task (i.e., puzzles completed; X^2=1.80, p=.179, Cliff's d=.20) or post-test recognition of the prescribed intentions (X^2=0.17, p=.678, Cliff's d=.06). Furthermore, the SCD+ and SCD− groups did not differ on the event-based CAMPROMPT scale (X^2=1.21, p=.272, Cliff's d=.16).

On the simple experimental PM task, the groups did not significantly differ in PM performance accuracy (X^2=0.08, p=.775, Cliff's d=.04) or frequency of clock checks (X^2=0.36, p=.548, Cliff's d=.09). There were no group differences in performance accuracy for the ongoing language distractor task (ps>.05).

Discussion

SCD is a risk factor for cognitive decline in older adults (Jessen et al., 2020; Mitchell et al., 2014) that may occur at higher rates in the context of HIV disease (Sheppard et al., 2019). The current study provides further support for the elevated frequency of SCD among older adults with HIV disease; specifically, older PWH in this study had a three-fold greater risk of SCD than the comparison sample without HIV. Our findings parallel the results of Sheppard and colleagues (2019) who observed an odds ratio of 4.5 (CI=1.6, 15.4) for HIV infection in predicting SCD. Moreover, our findings extend those of Sheppard and colleagues to an older sample assessed with an overlapping yet broader battery of measures to define SCD. One notable area of divergence is that we observed a 47% rate of SCD in PWH in this study versus 17% reported by Sheppard et al. (2019). The present results also showed a higher prevalence of SCD in 18% of persons seronegative for HIV compared to 5% in the study by Sheppard et al. (2019), despite the two studies using the same clinical cut-points (i.e., classification approaches). The higher frequency of SCD in the current sample may relate to older age (i.e., mean overall age for current study = 58 vs. mean age = 43.1 (HIV−), 46.1 (HIV+) in Sheppard et al., 2019). In populations seronegative for HIV, the prevalence of SCD slowly increases throughout late middle age and early older adulthood (Röhr et al., 2020). Though the age range of the current sample was quite broad (i.e., ages 50 to 75), future studies might examine whether different age bands for young-old (e.g., ages 50–65), older adults, and the oldest old (e.g., 80s) influence the relationship between SCD and PM. Other possible reasons for the divergent SCD frequencies might include the use of more measures of cognitive symptoms and the inclusion of executive functions (i.e., FrSBe), or simple sampling variability. Nevertheless, both studies reveal that SCD occurs at higher rates among PWH compared to persons without HIV. Whether the presence of SCD confers an increased risk for incident HAND or other cognitive disorders among older PWH remains to be determined by longitudinal studies.

Of clinical relevance, SCD was associated with elevated frequency of perceived PM failures in daily life among older PWH. This association was observed at a medium effect size and was not better explained by mood or other sociodemographic factors (Avci et al., 2018; Yoo-Jeong et al., 2018). Although HIV itself is associated with elevated PM failures in daily life (e.g., Woods et al., 2007), our findings suggest that PWH who also have SCD may be at elevated risk for greater PM difficulties. The only prior study to date on this topic reported that older adults with SCD had less frequent PM symptoms compared to persons with MCI (Hsu et al., 2019). Therefore, the current study is the first to our knowledge to indicate that SCD is associated with an increased prevalence of self-reported PM symptoms. These elevated problems have important implications given that older PWH endorse greater frequency of PM symptoms (Kordovski et al., 2020) and such problems are reliable predictors of medication mis-management (e.g., Woods et al., 2008a) and lower quality of life (e.g., Doyle et al., 2012) in PWH, above and beyond the influences of mood and cognitive factors.

In terms of component process, we observed that the perceived PM failures in PWH with SCD were driven by reported problems with the encoding stages of PM as defined by CAPM-C, but not with aspects of the retention or performance intervals, nor evaluation

of the outcome. For example, the encoding scale includes items such as, “When I forget to do something I had planned to do…it is usually because I forgot when I had to do it” (Roche et al., 2007). This finding is consistent with prior studies that reveal older adults with HIV have difficulty linking the PM cue to the intention (Woods et al., 2010) and benefit from strategic encoding supports to increase success in PM tasks (Faytell et al., 2017; Woods et al., 2020). Although the formation and encoding subscale of the CAPM-C demonstrates reasonable internal consistency in this sample (Cronbach’s alpha=.77), it nevertheless includes several items with content that may reflect failures along the PM continuum (Kliegel et al., 2008). For example, it includes items related to task importance and deployment of compensatory mnemonic strategies, both of which are also known to relate to PM accuracy among older adults (Matchanova et al., 2020; Woods et al., 2014). Thus, these cognitive processes which occur during the initial stages of encoding PM intentions may drive subjective problems for older PWH with SCD and highlight targets for clinical intervention. Experiments that allowed external strategy use (e.g., write notes, use personal digital assistant) revealed that persons with SCD tended to utilize these strategies during PM tasks more than healthy controls, and that strategy use can be reliably associated with better PM performance (Aronov et al., 2015). In addition, visualization of accurate task performance and implementation intention strategies (e.g., verbalizing intent and details of PM task to be completed) can facilitate better performance for time-based PM among PWH (Woods et al., 2020). Future studies may examine the efficacy of additional methods including elaboration and spaced retrieval-practice during encoding to improve PM in SCD and HIV populations.

Surprisingly, the current sample of older PWH with SCD did not differ from their counterparts without SCD in their experienced frustration related to PM symptoms. Although the SCD group had quantitatively more frustration at a small-to-medium effect size, the group difference did not reach statistical significance in the current sample. This finding was unexpected given that PM symptoms are associated with greater frustration than retrospective memory problems (Smith et al., 2000), and logically speaking one might expect greater frustration to correlate with greater frequency of perceived PM symptoms. Prior findings revealed that frustration did not map onto PM performance in SCD (Chi et al., 2014). However, PM failures can result in significant difficulties in daily life that are themselves frustrating, irrespective of how often they might occur. It is possible that persons with SCD are attuned to their cognitive symptoms but experience normalization of these lapses in daily life (e.g., attribute to normal aging). Furthermore, persons with SCD might be more likely to use compensatory strategies (Aronov et al., 2015), which may alleviate associated frustration and allow persons to adjust to these minor PM lapses in daily life. On the other hand, perceived PM and cognitive failures may result in other negative emotional states (e.g., embarrassment, anxiety, negative self-talk) rather than frustration for people with SCD (Buckley et al., 2015). Taken together, subjective PM symptom frequency, regardless of frustration levels, may be a potentially sensitive indicator to highlight the risk for poorer functional outcomes in older PWH with SCD.

The PM difficulties evident in the daily lives of PWH with SCD were also observed on objective measures of PM performance in the laboratory setting. In line with study hypotheses, SCD was associated with moderately poorer performance on the CAMPROMPT

time-based PM task. This reduced performance was explained by greater omission errors (i.e., no response to the PM cue), but no group differences were observed on the ongoing task or on post-test recognition, suggesting that impaired cue monitoring and detection may be the mechanism for poorer PM performance, rather than differences between groups in the relative allocation of attention to the PM task versus ongoing task, or differences in retrospective memory. These findings provide additional support for established associations between SCD with poorer time-based PM performance (Hsu et al., 2015) and poorer declarative memory in HIV (Sheppard et al., 2019). These time-based PM tasks, that theoretically require more strategic processing than event-based PM tasks, may be sensitive to detect subtle cognitive failures in persons with SCD. Moreover, PM skills are associated with antiretroviral medication adherence (Sheppard et al., 2016), online health navigation (Matchanova et al., 2021), and functional independence (Hering et al., 2018; Woods et al., 2008b). Therefore, understanding PM capacity failures may help explain some of the lapses in daily life that people with SCD and PWH complain about.

On the other hand, the SCD groups did not differ on performance for the computer-based experimental laboratory PM task among older PWH. This time-based PM task was designed to be strategically demanding, particularly because clock checking was discouraged and target times were staggered to reduce the likelihood of becoming habitual and potentially reducing demands on cognitive resources. Thus, the null finding of similar performance between the SCD groups on the experimental computerized time-based task was unexpected in the context of significant group differences for the CAMPROMPT time-based task in the current study, as well as previous literature that suggests strategically demanding PM task performance is lower in persons with HIV or SCD alone (Avci et al., 2018; Hsu et al., 2015). One possible explanation for the null finding could be that the SCD+ group compensated more by checking the clock more frequently than their SCD− counterparts. However, the results revealed there was no group difference in clock checking and thus this is an inadequate explanation. Perhaps it was the case that the SCD+ group neglected the ongoing language task more in order to compensate for greater difficulty with the PM task. However, follow-up analyses indicated the groups performed similarly during the ongoing language distraction tasks. The computer-based PM task involved a limited retrospective memory load and this could perhaps explain why the SCD groups differed significantly on the CAMPROMPT, which places a greater load on retrospective memory, but not on the computer-based task. Lastly, prior work identified that persons with HAND performed similarly to individuals seronegative for HIV after a 2-minute PM delay, but significantly worse at a 15-minute delay, accompanied by a medium effect size (Avci et al., 2016; Morgan et al., 2012). Thus, it is plausible that longer delay time-based PM tasks may be more sensitive to PM problems in cognitively unimpaired PWH who are noticing subjective changes in cognition.

Event-based PM performance (CAMPROMPT) was also assessed among the older PWH sample and no meaningful differences were observed between the SCD groups. Among HIV seronegative older adult populations with SCD, null to trend-level findings at small-to-medium effect sizes, respectively, have been reported for event-based PM (Hsu et al., 2015; McAlister & Schmitter-Edgecombe, 2016). A review of the HIV literature revealed that significant associations between HIV and event-based PM performances tend to occur for

such tasks with greater cognitive demand (i.e., more strategic event-based PM tasks) and are observed at smaller effect sizes than the relationship between HIV and time-based PM (Avci et al., 2018). Indeed, the event-based task in the current study was likely highly automatic given that environmental prompts were salient and participants were permitted to take notes (i.e., external strategy) to support PM. Aronov and colleagues (2015) demonstrated that external strategies were associated with better overall PM and persons with SCD utilized external strategies more than their healthy counterparts. In the current study, both SCD groups used notetaking strategies at similar rates (X^2=1.06, p=.30). As such, in line with the existing literature and study hypotheses, event-based PM tasks with automatic processing, high cue salience, and which permit external strategy use may not be negatively impacted in older PWH who experience subjective memory complaints in daily life.

There are some limitations to the current study which might inform the interpretation of the findings and future lines of research. First, the lack of a full factorial design for the current study precludes the examination of whether SCD and HIV combine to have more detrimental effects on PM above and beyond SCD alone. Future studies may wish to compare groups across both SCD and HIV serostatus to better understand the interaction and main effects of HIV and SCD on PM outcomes. Additionally, the current sample was obtained from an urban region of Southern California and comprised of reasonably well-educated, White men, which may limit the generalizability of the current findings to underserved populations that are highly affected by HIV (e.g., Southern U.S.). Future studies might increase community-based recruitment strategies and collaborate with HIV research centers in affected parts of the country to examine SCD and PM in a more representative sample of older PWH. The use of laboratory-based PM tasks confer greater constraints on the environment than may exist in daily life (e.g., unexpected distractions), and future studies may employ naturalistic PM tasks (e.g., smart home technology) to capture different aspects of PM failures in the home environment. Given that the CAPM-C measure evaluates steps of PM on a continuum rather than discrete stages, future studies might explore the effects of explicit PM stages to understand where PM performance fails in various clinical samples (e.g., PWH, healthy older adults, SCD). Furthermore, the current study did not examine PM delays longer than 15 minutes. Future investigations into longer delay PM tasks (e.g., 24-hour delays) may illuminate potential problems associated with SCD among PWH for tasks with longer retention intervals. Finally, studying clinical samples (e.g., Asymptomatic Neurocognitive Impairment in HIV) may illuminate differences in PM task performance at different stages of cognitive declines. Taken a step further, longitudinal studies may inform the progression of PM changes among older PWH with SCD to examine risks for converting to a clinically detectable cognitive disorder.

Current findings of poorer objective and subjective PM outcomes in SCD among older PWH provide important clinical implications for identifying persons at risk for functional problems including medication adherence, medical appointment attendance, health-related Internet use, and independent functioning in ADLs (Avci et al., 2018). This may support implementation of intervention and prevention efforts to preserve functional capacity and quality of life for these patients.

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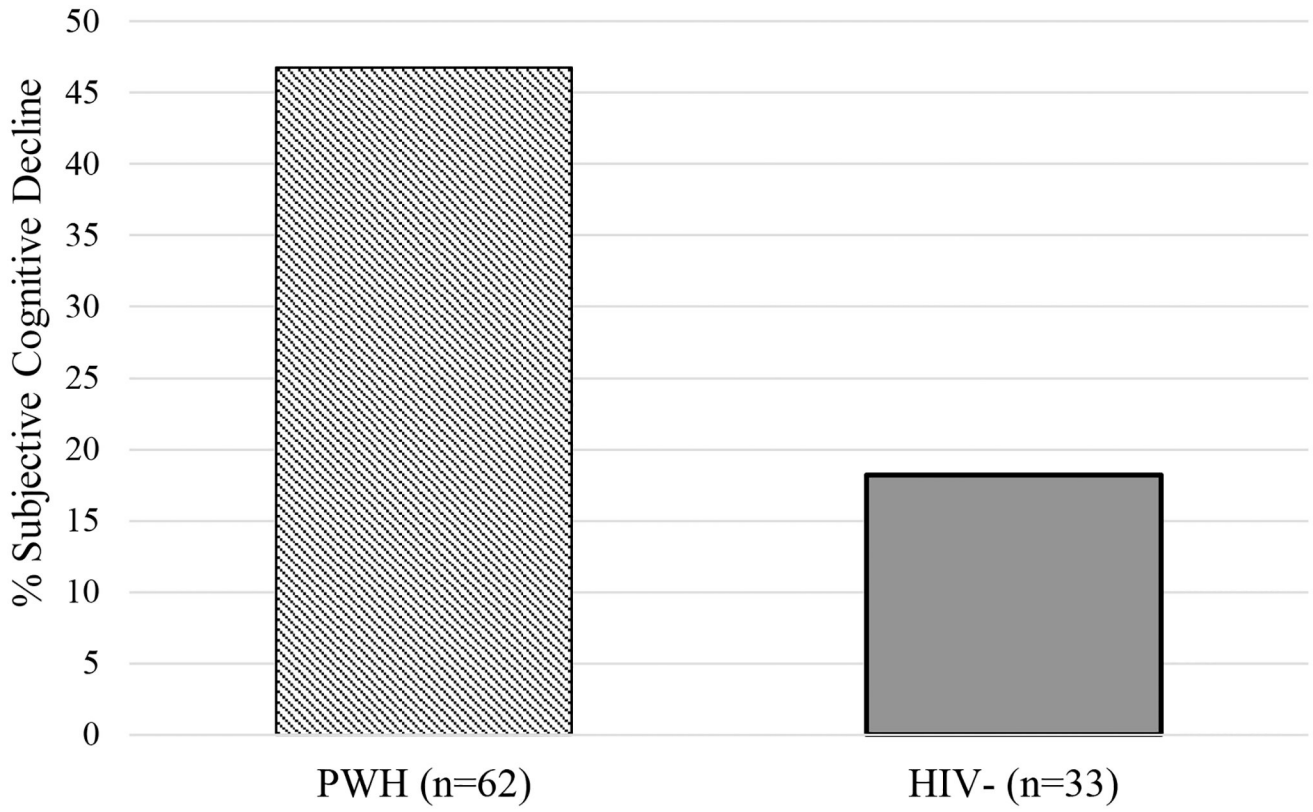

Figure 1.
Bar graph demonstrating rates of subjective cognitive decline (SCD) in persons with HIV (PWH) and HIV− individuals.

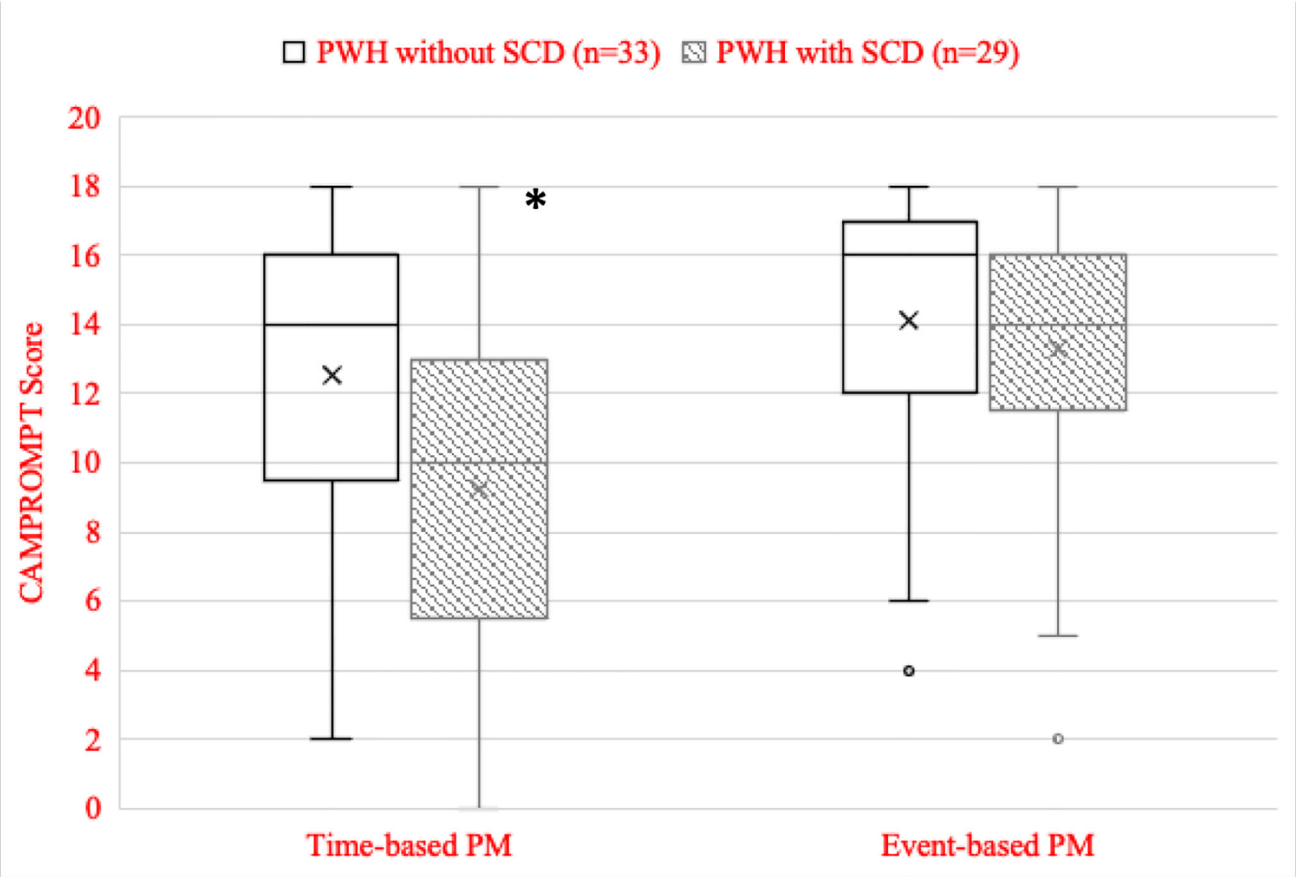

Figure 2.

Box and whisker plot showing the differences on time-based and event-based prospective memory (PM) tasks on the Cambridge Prospective Memory Test (CAMPROMPT) among persons with HIV (PWH) with subjective cognitive decline (SCD) and PWH without SCD. Prospective memory is defined as the ability to remember and carry out an intention in the future. ***p*<.05

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Table 1.

Descriptive table of sociodemographic and clinical information for the study sample (*N*=95).

Variable	HIV−	HIV+	HIV+		HIV+ SCD Group Differences *p*-value
	Total (*n*=33)	Total (*n*=62)	With SCD (*n*=29)	Without SCD (*n*=33)	
Sociodemographic					
Age (years)	60.9 (6.6)*	57.0 (5.9)*	58.0 (6.1)	56.1 (5.7)	.18
Gender (% men)	66.7*	85.5*	86.2	84.9	.88
Handedness (% right)	87.9	90.3	82.8	97.0	.06
Education (years)	14.8 (2.2)	14.1 (2.6)	13.7 (3.1)	14.5 (2.0)	.19
Hollingshead Index	46.3 (10.6)	43.3 (11.9)	40.7 (12.4)	45.5 (11.2)	.10
Race/Ethnicity (%)					.75
Caucasian/White	72.7	58.1	62.1	54.6	
Black/African American	15.2	24.2	24.1	24.2	
Hispanic/Latin@	9.1	16.1	13.8	18.2	
Other	3.0	1.6	0.0	3.0	
Psychiatric					
Affective Disorder (%)					
Current	0.0	0.0	0.0	0.0	--
Lifetime	39.4*	64.5*	75.9	54.6	.08
Substance Use Disorder (% Lifetime)	51.5	69.4	82.8	57.6	**.03**
Medical					
Comorbidity Burden (no. conditions)	1.3 (1.2)*	2.1 (1.5)*	2.5 (1.5)	1.7 (1.3)	.06
Estimated duration of infection (years)	--	20.3 (8.9)	19.0 (8.8)	21.5 (9.0)	.23
Plasma HIV RNA (% detectable)	--	4.9	0.0	9.4	.24
Current CD4 count (cells/μL)	--	594.6 (258.1)	609.3 (261.3)	581.7 (258.5)	.69
Nadir CD4 count (cells/μL)	--	192.1 (183.0)	174.2 (187.3)	207.8 (180.5)	.28
AIDS (%)	--	64.5	69.0	60.6	.49
Antiretroviral therapy (% prescribed)	--	87.1	93.1	81.8	.43
Subjective Cognitive Symptoms					
Number of elevated SCD scales (of 4)	0.3 (0.8)*	0.9 (1.1)*	1.9 (0.8)	0.0 (0.0)	**<.01**

Variable	HIV−	HIV+	HIV+		HIV+ SCD Group Differences *p*-value
	Total (*n*=33)	Total (*n*=62)	With SCD (*n*=29)	Without SCD (*n*=33)	
FrSBe Disinhibition (of 75)	23.4 (6.4)*	27.3 (6.8)*	30.6 (7.3)	24.4 (4.7)	**<.01**
FrSBe Executive Dysfunction (of 85)	30.7 (8.8)*	35.6 (9.4)*	42.3 (8.1)	29.7 (5.9)	**<.01**
POMS C&B (of 28)	5.6 (3.7)*	8.1 (5.0)*	10.8 (5.6)	5.8 (2.9)	**<.01**
PRMQ Retrospective Memory (of 40)	14.0 (4.5)*	16.2 (5.5)*	18.6 (6.6)	14.2 (3.0)	**.01**

Note. Data represent Mean (SD) or valid population % values. HIV = Human Immunodeficiency Virus; SCD = Subjective Cognitive Decline; Affective Disorder = Major Depressive Disorder and/or Generalized Anxiety Disorder; RNA = Ribonucleic acid; CD4 = Cluster of differentiation 4; AIDS = Acquired Immunodeficiency Syndrome; FrSBe = Frontal Systems Behavior scale; POMS C&B = Profile of Mood States Confusion & Bewilderment scale; PRMQ = Prospective and Retrospective Memory Questionnaire. Comorbidity Burden is constructed from Hepatitis C virus, Hepatitis B virus, diabetes, chronic pulmonary disease, malignancy, peptic ulcer disease, cerebrovascular accident, myocardial infarction, renal disease, congestive heart failure, metastatic solid tumor, liver disease, peripheral vascular disease, rheumatologic disease, hemiplegia/paraplegia, hypertension, hyperlipidemia, head injury, and seizures.

* indicates HIV− (n=33) and HIV+ (n=62) groups significantly differed on that variable at $p<.05$.

Bold indicates the HIV+ groups with and without SCD significantly differed on a variable at $p<.05$. For the primary logistic regression analysis, medical comorbidity burden was the only variable included as a covariate, given that was significantly related to both HIV and SCD status. For the analyses within the HIV+ sample only, although lifetime Substance Use Disorder significantly differed by SCD status, it did not significantly relate to any prospective memory outcomes and thus no covariates were included for those analyses.

Table 2.

Prospective memory measures among persons with HIV (PWH; *n*=62).

Variable	PWH with SCD (*n*=29)	PWH without SCD (*n*=33)	*p*	Effect size (Cliff's delta)
Experimental Time-based PM				
Accuracy (%)	77.0 (34.6)	80.8 (30.1)	.775	.04
Total Clock Checks	11.6 (7.5)	10.5 (7.1)	.548	.09
CAPM				
A- Frequency Average (of 5)	1.8 (0.7)	1.5 (0.3)	**.033**	.32
B- Frustration Average (of 5)	1.3 (1.0)	0.9 (0.6)	.093	.25
C- Attributions Total (of 60)	35.3 (6.3)	31.2 (6.6)	**.017**	.35
Encoding (of 36)	20.4 (4.1)	17.5 (3.9)	**.007**	.40
Retention Interval (of 12)	7.3 (1.7)	6.5 (1.9)	.117	.28
Performance Interval (of 8)	4.8 (1.3)	4.8 (1.4)	.827	.03
Evaluation of Outcome (of 4)	2.7 (0.9)	2.3 (0.7)	.059	.26
CAMPROMPT				
Time-based Total (of 18)	9.2 (4.9)	12.5 (4.5)	**.008**	.39
PM Proper errors	2.1 (1.0)	1.5 (1.0)	**.029**	.31
Event-based Total (of 18)	13.3 (3.8)	14.1 (3.7)	.272	.16
Ongoing Task Puzzles Completed	5.0 (1.8)	5.7 (2.4)	.179	.20
Recognition Total (of 6)	4.8 (1.3)	4.9 (1.4)	.678	.06

Note. Data represent M (SD). HIV = Human Immunodeficiency Virus; SCD = Subjective Cognitive Decline; PM = Prospective memory; CAPM = Comprehensive Assessment of Prospective Memory; CAMPROMPT = Cambridge Prospective Memory Test. **Bold** indicates $p<.05$. Cliff's delta effect sizes were used for the non-parametric group comparisons, where approximate values of 0.15, 0.30, and 0.45 were interpreted as small, medium, and large effect sizes, respectively.