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The impact of marijuana use on memory in HIV-infected patients: a comprehensive review of the HIV and marijuana literatures

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Abstract

Background—The most robust neurocognitive effect of marijuana use is memory impairment. Memory deficits are also high among persons living with HIV/AIDS, and marijuana is the most commonly used drug in this population. Yet research examining neurocognitive outcomes resulting from co-occurring marijuana and HIV is limited.

Objective—The primary objectives of this comprehensive review are to: (1) examine the literature on memory functioning in HIV-infected individuals; (2) examine the literature on memory functioning in marijuana users; (3) synthesize findings and propose a theoretical framework to guide future research.

Method—PubMed was searched for English publications 2000–2013. Twenty-two studies met inclusion criteria in the HIV literature, and 23 studies in the marijuana literature.

Results—Among HIV-infected individuals, memory deficits with medium to large effect sizes were observed. Marijuana users also demonstrated memory problems, but results were less consistent due to the diversity of samples.

Conclusion—A compensatory hypothesis, based on the cognitive aging literature, is proposed to provide a framework to explore the interaction between marijuana and HIV. There is some evidence that individuals infected with HIV recruit additional brain regions during memory tasks to compensate for HIV-related declines in neurocognitive functioning. Marijuana use causes impairment in similar brain systems, and thus it is hypothesized that the added neural strain of marijuana can exhaust neural resources, resulting in pronounced memory impairment. It will be important to test this hypothesis empirically, and future research priorities are discussed.

Keywords

AIDS; cannabis; drug use; cognitive effects; neuropsychological functioning; neurocognitive

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

1. INTRODUCTION

Cannabis use among HIV-infected individuals is disproportionately common. In a recent study of >3000 patients receiving HIV care in four cities in the United States (US), 24.3% reported marijuana use in the past 3 months [1]. In comparison, a national prevalence study of adults aged 26 or older in the general population reported 5.6% used marijuana in the past month [2]. In addition, the CHARTER study, a large multi-site study of HIV-infected adults enrolled between 2003 and 2007, reported >25% met criteria for a lifetime marijuana use disorder [3]. Some HIV-infected individuals report smoking marijuana to alleviate HIV-related symptoms by stimulating appetite and reducing nausea, but many also use for recreational purposes [4]. Given the legalization of medicinal marijuana in 23 U.S. states and the District of Columbia, with most explicitly citing HIV/AIDS as a condition appropriate to manage with medicinal marijuana [5], it is important to understand the effects of regular marijuana use in this population.

The neurocognitive consequences of marijuana use among HIV-infected individuals are not well known. HIV infiltrates the central nervous system [6], and the CHARTER study found 52% of HIV-infected persons to have neurocognitive impairment with the greatest deficits in learning, memory, attention/working memory, and executive functioning [3, 7]. Among the general population, the most robust effect of marijuana use is memory impairment, which is also the most frequently reported cognitive complaint [8, 9]. One study provides preliminary evidence that marijuana use may accelerate cognitive impairment among HIV-infected marijuana users who are already experiencing memory decline due to their disease [10]. Comparing the neurocognitive performance of HIV-positive and HIV-negative individuals, stratified by disease stage and frequency of marijuana use, Cristiani and colleagues (2004) found that current marijuana use was associated with greater global neurocognitive impairment among individuals with symptomatic HIV infection. Furthermore, they found that this effect was primarily driven by impaired performance on a delayed memory task.

This comprehensive review is motivated by the need to understand how marijuana use impacts memory among HIV-infected individuals. An initial literature search revealed that research on this topic is scarce. Since Cristiani and colleagues published their findings in 2004, no subsequent studies could be identified that examine memory outcomes resulting from co-occurring marijuana use and HIV infection. A broader literature search to identify articles examining the impact of co-occurring marijuana and HIV on *any* cognitive domain produced two additional articles. The first study found past marijuana dependence and HIV infection to be independently and additively associated with slower performance on complex motor tasks [11]. The second, a neuroimaging study utilizing MR spectroscopy, examined the combined effects of past marijuana use and HIV, revealing both independent and additive effects on brain metabolites [12]. The dearth of literature in this area underscores the need for research examining how marijuana use may impact neurocognitive functioning among individuals already experiencing HIV-associated decline.

To pave the way for integration of two currently independent fields, separate reviews of the HIV and marijuana literatures were conducted, and then findings were synthesized into a hypothesis regarding how co-occurring marijuana use and HIV infection may impact

episodic memory. While there have been several excellent review papers written about the impact of marijuana use on neurocognitive functioning across multiple domains [13–16], this review provides an in-depth focus specifically on memory functioning. A recent meta-analysis reported negative residual effects of marijuana use on short- and long-term recall within the first 25 days of abstinence [14], and our review extends these findings by examining verbal, visual, and prospective tasks separately. This review focuses specifically on episodic memory, which encompasses the acquisition, retention, and retrieval of facts and events that took place, or will take place, in a particular context [17, 18]. The vast majority of memory research conducted in marijuana-using and HIV-infected samples examines episodic memory, arguably because it is essential for daily functioning and independent living [19, 20]. Furthermore, since episodic memory is the memory system most vulnerable to neural injury [21], the combined effects of marijuana and HIV may impact this system most prominently.

2. METHODS

2.1. Review procedure

PubMed was searched for English publications 2000–2013. Variations of the following terms were used in the search: cannabis, marijuana, HIV, memory, and neurocognitive. A secondary search involved checking the reference section of relevant review papers to identify any articles that may have been missed.

2.2. Eligibility criteria

Inclusion criteria were: (1) sample of HIV-infected individuals or marijuana users; (2) adults aged ≥18 years; (3) administration of an objective episodic memory task; (4) minimum sample size > 10 per group; (5) when applicable for the study design, inclusion of appropriate “controls” (i.e., HIV-negative participants for HIV studies or infrequent/non-drug users for marijuana studies). Exclusion criteria were: (1) sample composed entirely of participants with severe neurological impairment (e.g., multiple sclerosis); (2) acute administration of marijuana to participants during the testing session as part of the study protocol; (3) failure to report outcome of memory tasks or whether performance by experimental and control groups were significantly different from each other; (4) study conducted in non-Western country where neurocognitive norms may not be established yet.

3. RESULTS

3.1. HIV infection and memory

3.1.1. Overview of studies—Twenty-two empirical studies of HIV-infected persons met inclusion criteria. Characteristics of reviewed studies are presented in Table 1. Effect sizes for neurocognitive task performance were calculated when authors reported raw mean scores and standard deviations. The majority of studies reported predominantly male samples, with 77% having >80% men. Most studies (77%) also included participants with an average age of 35–49. Only two studies (9%) included patient groups with average CD4 counts under 200 [22, 23].

Researchers had diverse inclusion/exclusion criteria with regards to substance use. Two studies specifically recruited substance-using populations [24, 25]. While the majority of studies excluded individuals with indications of substance abuse, several made exceptions for marijuana [26–30]. Although one of these studies [29] did conduct statistical tests to confirm there were no differences in performance between participants whose urine tested positive for marijuana and those who did not, most of the other studies either did not report this, nor did they specify how many participants screened positive for marijuana [26–28]. Given that marijuana use is generally higher among HIV-infected individuals, it is unclear to what extent memory performance differences between groups were caused directly by HIV infection or by the combined effects of HIV infection and marijuana.

3.1.2. Verbal and visual memory—Poorer memory performance in HIV-infected persons compared to persons without HIV was observed in immediate and delayed recall of word lists [28, 30–37] and stories [28]. Five studies provided enough information to calculate effect sizes, which ranged from 0.45 to 1.12 [32, 33, 35–37]. Despite impaired recall, individuals infected with HIV often demonstrated intact recognition abilities [31–33]. There is also evidence of HIV-associated deficits in visual memory [24, 30, 31, 33, 34] with similar effect sizes ranging from 0.64 to 1.03 [24, 31, 33]. Two additional studies finding HIV-related memory impairment created a composite score that included performance on both visual and verbal memory tasks, and so the specific contributions of each domain is unclear [30, 34].

3.1.3. Prospective memory—All seven studies examining prospective memory found impairment on some tasks [24, 26, 27, 37–40]. On time-based prospective memory tasks, effect sizes ranged from 0.40 to 0.68 [24, 27, 38–40]. Morgan and colleagues (2012) found that HIV-infected individuals demonstrated impairment in the long delay but not the short delay trial, suggesting that HIV-related impairment may be more pronounced as delays increase. On event-based tasks, HIV-infected participants also demonstrated impairment [26, 38], but findings were less robust. Several studies reported time-based impairment in the context of intact event-based prospective memory [24, 39, 40], suggesting that decline in performance may be more easily observed on tasks that are more challenging and require more cognitive resources. Further, recognition remained intact despite impaired recall in all studies [26, 38–40].

3.1.4. Influence of HIV disease progression—There is evidence that difficulties with relatively easier tasks of recognition and event-based prospective memory develop in the context of advanced HIV disease progression, suggesting memory functioning is associated with disease severity. Although among HIV-infected samples in which half or fewer had a diagnosis of AIDS, event-based prospective memory was intact despite time-based deficits [24, 40], a patient sample with more severe HIV disease progression (more than three-fourths diagnosed with AIDS) demonstrated event-based prospective memory impairment [38]. Further, researchers found that individuals with acute/early HIV demonstrated less impairment than patients chronically infected with HIV. Several studies examined specific markers of HIV disease progression [24–26, 29, 33, 41], but results were inconsistent.

3.1.5. Regional neural activity—Only one study utilizing functional magnetic resonance imaging (fMRI) to examine neural activity during a memory task met our inclusion criteria (e.g., >10 participants per group) [42]. A comparison of remembered versus forgotten scenes found that the HIV-infected group demonstrated less neural activation in medial temporal regions, including the right posterior hippocampus and portions of the prefrontal cortex, and increased activation in neighboring frontal areas and posterial parietal regions, compared to the control group. These results suggests that even when task performance is equivalent, associated neural activity in HIV-infected participants may be disrupted.

3.2. Marijuana use and memory

3.2.1. Overview of studies—Twenty-three empirical studies examining the impact of marijuana use on memory met inclusion criteria (Table 2). Nearly half (48%) were conducted on marijuana users with an average age of <25 years old, which contrasts with the HIV studies that were predominantly conducted with samples 35–49 years old. About a fifth (22%) of the marijuana studies included a predominantly male (>80%) sample of marijuana users. There was significant variability in how marijuana use was measured, but the most common measures were the mean or median number of times (or joints) used in past week or month, or the total number of lifetime uses.

3.2.2. Verbal and visual memory—Across studies, marijuana users demonstrated verbal memory deficits immediately and up to 7 days after stopping use compared to controls [43–52]. The effect size of marijuana impairment on recall tasks ranged from 0.41 in a sample including both current and past marijuana users to 2.29 among current long-term users who averaged 16 years of use [46, 50].

Extant studies provide inconsistent evidence on whether deficits persist over longer periods. Evidence that cessation from marijuana use does not restore neurocognitive functioning comes from the Dunedin Study, a birth cohort of 1,037 individuals that assessed marijuana use five times over the course of their lives and neurocognitive functioning at age 13, before they began to use marijuana, and then again at age 38 [49]. Participants with more persistent marijuana dependence demonstrated a broad decline in performance across multiple neurocognitive domains, including both verbal and visual memory. Furthermore, although the specific effect of abstinence on memory was not reported, global neurocognitive decline remained even after a year of very infrequent use among participants who initiated marijuana in adolescence. In contrast, a longitudinal study in which participants were assessed three times over an 8-year period found that memory improved with abstinence [53]. Differences between these two studies may be because Tait and colleagues (2011) categorized marijuana users as “heavy” if using at least once per week whereas the Dunedin Study examined individuals who met diagnostic criteria for dependence, which would be consistent with greater frequency and quantity of use.

Four cross-sectional studies with average abstinence periods ranging from 2 weeks to 20 years concluded that former marijuana users did not demonstrate memory problems compared to controls [53–56]. A fifth cross-sectional study reported that impaired

performance on verbal memory tasks persisted after 1 month of abstinence [57], but there were no checks to verify that that participants maintained abstinence.

Marijuana users also experience visual memory impairments [47, 49, 56, 58–60]. Of the ten studies that reported verbal and visual memory results separately, six found verbal memory impairment in the context of intact visual memory abilities [50–53, 57, 61], whereas none found impaired visual memory in the context of intact verbal memory. Two of the three studies that found both visual and verbal impairment in marijuana users compared to controls were conducted in heavy marijuana users [49, 59], suggesting casual or moderate marijuana users may not experience visual memory problems.

3.2.3. Prospective memory—Of the four studies that examined prospective memory, two found evidence of impairment [58, 62]. McHale and colleagues (2008) found marijuana users performed significantly worse than participants who did not use drugs on both event- and time-based tasks and Bartholomew et al. (2010) reported similar event-based impairment among marijuana users. The other two studies did not find event- or time-based performance differences between marijuana users and controls [56, 63]. In one of the studies, however, several of the memory tasks were created by the researchers, and neither reliability nor validity data is available [63].

3.2.4. Parameters of marijuana use affecting memory functioning—Several studies found that the age at which a person first begins to use marijuana is an important variable in its impact on cognitive functioning [48–50], suggesting that early use is problematic if the threshold age is approximately 18. In the Dunedin Study birth cohort, participants who began to use marijuana before age 18 demonstrated a broad decline in cognitive performance whereas those who started using after age 18 did not [49]. These results were corroborated with cross-sectional studies. Pope and colleagues (2003) reported that only individuals who began using marijuana before age 17 exhibited memory impairment, and Battisti and colleagues (2010) found age of first marijuana use to be correlated with brain alterations measured by event-related potentials, despite no impact on task performance. The two studies that did not find an effect of age of first use were both limited by minimal variability in this factor [53, 64]. In one study, participants were split at the median into two subgroups with the “late-onset” group having a mean initiation age of 17 [64], and in the other study all participants had begun using before age 18 [53].

Memory deficits also are correlated with longer duration of regular marijuana use [44–46, 49] and frequency of use. Specifically, greater memory impairment correlates with a higher number of total lifetime uses [50, 56, 61, 65] in the past week [59], month or 30 days [53, 56], or year [65]. This association between frequency of use and memory is robust, and there is evidence that it persists even after 28 days of abstinence [50, 59].

3.2.5. Regional neural activity—Four studies that utilized brain imaging technology to examine neural activity while participants were engaged in memory tasks met criteria to be included in this review, and all of these studies reported marijuana-related alterations in neural activity. Across all studies, marijuana-related alterations were observed in the parahippocampal gyrus or hippocampus. Nestor and colleagues (2008) found

hyperactivation in the right parahippocampal gyrus compared to controls. Similarly, Becker and colleagues (2010) reported a positive correlation between higher frequency of marijuana use and greater activation in the left parahippocampal gyrus. In contrast, Jager and colleagues (2007) found less activation in the parahippocampal area among marijuana users compared to controls, particularly in the left hippocampus and parahippocampal gyrus. Use of different visual cues (i.e., faces vs. object) may explain variable activation patterns in similar regions associated with marijuana use. The one PET study reported altered lateralization in the hippocampus [43]. Most studies also found corresponding marijuana-related decreases in frontal regions [43, 60, 65]. During associative learning tasks, marijuana users demonstrated hypoactivation in the dorsolateral prefrontal cortex [65], prefrontal cortex [43], as well as the right superior frontal gyrus, right middle frontal gyrus, and left superioral frontal gyrus [60].

4. DISCUSSION

4.1. HIV, marijuana, and episodic memory: Summary

There is substantial evidence that marijuana use and HIV infection are independently associated with episodic memory disturbance. HIV-infected individuals demonstrate greater impairment in tasks with higher cognitive demand such as verbal and visual recall, whereas they often perform comparably to controls on easier recognition tasks. Similarly, HIV-associated memory deficits are more pronounced in difficult time-based prospective memory tasks compared to easier event-based tasks. However, as HIV disease progresses, overall memory functioning worsens and performance even on easier tasks declines. In addition to duration and frequency of marijuana use, one of the strongest indicators of memory impairment in marijuana users appears to be earlier age of first use. Consistent with prior reviews [66, 67], this suggests that during periods of cognitive vulnerability (i.e., adolescence when the brain is still in the process of developing), the deleterious effects of marijuana use are most pronounced. Findings also suggest that marijuana users experience verbal and visual memory impairment for up to a week after last marijuana use, but more research is needed to know how long this period of impairment lasts, which may depend on frequency, duration, and age of first use. Heavy users who began smoking in adolescence may continue to experience prolonged memory impairment even after a year of abstinence, whereas among less frequent users cognitive functioning may restore within several weeks. Contradictory findings between studies may be attributable to variability in assessment and inclusion of these marijuana use parameters, and including these variables in analyses may lead to greater consensus in the literature.

The results of this review, however, must be understood in the context of several limitations. First, while conducted a careful search of the literature, it is possible that we missed studies. Second, to maximize the number of studies available for review, we did not exclude studies where the information to calculate effect sizes was not reported. Effect sizes were calculated when authors reported means and standard deviations, but many studies did not provide this information. As a result, we were not able to conduct a meta-analysis. Third, we only included studies with sample sizes of >10 participants per group, which resulted in the exclusion of some interesting studies (e.g. the fMRI substudy including 7 HIV-infected and

4 controls by Maki et al., 2009). Fourth, several studies were conducted by the same research group, which may bias findings. Although we were unable to determine whether there was overlap in subject recruitment for these studies, we noted geographic region in Tables 1 and 2 in order to highlight this limitation. Fifth, there was great diversity in how researchers reported marijuana use characteristics (e.g. duration, frequency, age of first use), and often several of these variables were not reported at all, making it difficult to compare across studies and to understand fully how these characteristics may moderate memory function. Additionally, study samples were diverse with regards to participant demographics, which is relevant because older HIV-infected adults may already be experiencing age-related neurocognitive impairment [68, 69] and recent evidence suggests that marijuana differentially impacts women compared to men [16]. Therefore, it will be important to understand the impact of potential moderators in order to identify subsets of HIV-infected marijuana users who may be at greater or lesser risk for memory impairment before generalizing findings more broadly.

4.2. HIV, marijuana, and episodic memory: Compensatory hypothesis

Because the brain of an individual infected with HIV is particularly susceptible to neural injury, the effects of marijuana on memory functioning may be more pronounced in this population. In one of the few studies utilizing imaging technology to examine brain functioning during memory processing in persons with HIV infection, Castelo and colleagues (2006) observed disrupted neural activation. The pattern of underactivation in task-specific regions typically activated in healthy individuals coupled with a greater recruitment of frontal regions is strikingly similar to neural activation patterns observed as the brain ages [70, 71].

A “compensatory hypothesis” has been posited to explain age-related changes in neural activation [70, 71]. During cognitive tasks, older adults demonstrate neural activation in brain regions similar to their younger counterparts, but with different degrees of activation. Specifically, the older brain demonstrates decreased neural activity in regions typically activated during cognitive tasks, which is thought to reflect age-related deficits in brain functioning [70]. At the same time, older adults engage additional frontal and prefrontal regions that are not typically utilized by their younger counterparts. This overactivation is thought to be adaptive, reflecting the brain’s attempt to compensate for cognitive impairment by engaging additional neural circuits. In fact, there is evidence that successfully engaging in these neural compensatory strategies can be associated with comparable task performance and that older adults can effectively compensate for age-related cognitive decline by engaging additional neural networks [70, 71].

This hypothesis maps well onto the HIV-infected brain. The virus causes neuronal death and loss of hippocampal functioning, which is crucial to memory functioning [72, 73]. Castelo and colleagues (2006) observed normal performance on memory tasks among HIV-infected individuals despite altered neural activation in the hippocampal-prefrontal circuitry. Their sample had relatively high CD4 counts, which may indicate that in early stages of the disease the brain is able to effectively compensate for hippocampal damage through compensatory strategies. However, there may be a threshold beyond which the brain is

unable to provide sufficient resources to compensate for impairment, and then performance suffers. This decline in performance could occur when the task requires more cognitive resources than the brain is able to provide, either because the task is overly difficult or because impairment it too significant for the brain to fully compensate for it.

Marijuana most prominently affects frontal-limbic neurocircuitry [74], which includes the hippocampus and associated structures, with molecular models reporting particularly large concentrations of cannabinoid receptors in the hippocampus [75]. When engaged in a neurocognitive memory task, marijuana users demonstrate altered neural activation compared to non-drug users [43, 60, 64, 65], which may be the consequence of marijuana-related hippocampal damage. Results of this review suggests that the burden of marijuana use is most severe when an individual has used for a longer duration, at greater frequency, and began using during adolescence when the brain was undergoing maturation. In healthy individuals, marijuana use may not be associated with memory impairment [60, 65] if the brain is able to compensate for neural damage through compensatory strategies. It is hypothesized, however, that the added neural strain caused by co-occurring marijuana use and HIV-infection is likely to exhaust neural resources, resulting in more significant memory impairment.

This hypothesis is consistent with the Cristiani et al. study (2004), which found that marijuana use was associated with significant memory impairment only in the context of symptomatic HIV infection. Interpreting these results through the compensatory hypothesis suggests that marijuana users who are in the early stages of HIV are able to draw upon neural reserves to compensate for marijuana-related impairment. As HIV disease progresses and HIV-related impairment exhausts neural resources, however, the brain may no longer able to compensate for marijuana-related brain injury. Consequentially, the cognitive effects of marijuana on memory functioning are exacerbated in in the context of advanced HIV disease progression.

4.3. Critique of the current literature and future research priorities

While the compensatory hypothesis provides a theoretical framework, empirical research is the essential next step. Research focused specifically on the additive and interaction effects of marijuana use and HIV infection on memory is needed. Further, there is still work to be done in understanding the independent impacts of these conditions on memory function. Researchers examining this question would benefit from the following research priorities and methodological improvements.

First, it will be important for future studies to clarify the unique contributions and interactive impact of different parameters of marijuana use on memory. There is evidence that several parameters, including age of first use, duration, and frequency, impact memory functioning, but many prior studies did not measure or include all these variables in analyses. Including all relevant predictors can be a significant challenge because obtaining sufficient power and variability requires large, diverse samples. To tease apart the relative contributions of these variables and how they may interact, a thorough drug use history that assesses each of these parameters must be obtained. Multiple assessment strategies with established validity are recommended, including utilization of Timeline Follow-Back methodology to assess use

frequency [76] and a biological measure, such as a urine toxicology screen, to confirm self-report. It may also be beneficial to utilize Audio-Computer Assisted Self-Interviewing technology given that some individuals may be more honest reporting sensitive and potentially stigmatizing behaviors such as drug use when using a computer [77, 78].

In examining the impact of age of first marijuana use, gender is an important moderator to consider. A recent review highlighted differences in cannabinoid receptor densities and brain maturation patterns with female brains developing earlier than males, suggesting that there will be an interaction between gender and age of first use [16]. Specifically, it may be that marijuana use causes the most severe neurocognitive damage in men who begin using in early- to mid-adolescence but that women's brains are most vulnerable at a younger age.

Identifying marijuana use parameters that are associated with greater memory impairment may have two significant clinical implications. First, it may be possible to determine a maximum threshold for marijuana consumption that would have minimal impact on memory. This information would allow healthcare providers who prescribe medicinal marijuana to provide more precise recommendations to patients, which is urgently needed because currently there are no guidelines regarding appropriate doses for managing symptoms associated with HIV infection [79]. Second, there is evidence that initiation of marijuana use in adulthood may not be associated with the same memory deficits as when initiation occurs in adolescence, but these findings need to be replicated. If future research confirms these findings, patients with health conditions such as HIV may feel more confident that managing symptoms with marijuana will not have iatrogenic effects on memory.

Second, research needs to examine the effects of specific markers of HIV disease progression within the same study sample in order to determine the precise mechanisms by which HIV infection impacts memory functioning. Objective sources of data such as medical chart review or blood tests should be utilized whenever possible. Length of HIV diagnosis and viral suppression were associated with neurocognitive impairment in the pre-HAART era (prior to 1995), but recent studies have failed to find a significant relationship [3]. This highlights also the importance of addressing HIV medication regimens, which can influence the course of HIV disease and improve neurocognitive functioning [80].

Third, it will be important to examine comorbid characteristics that potentially have confounding effects on neurocognition. Both HIV-infected individuals and marijuana users have higher rates of psychopathology [81–83], which can impact neurocognitive functioning [84–86]. Further, alcohol and other drug use is high among HIV-infected individuals, with the only national prevalence study of HIV-infected adults in the US reporting that 26% were using illicit drugs other than marijuana without meeting criteria for dependence, and another 13% met criteria for drug dependence (including marijuana) within the last 12 months [87]. In a more recent multisite study of nearly 1,000 HIV-infected individuals, 40% reported cocaine or heavy alcohol use and 25% reported use of two or more illicit drugs (excluding alcohol or marijuana) in the past year [88]. Some studies in this review sought to account for these confounds by reporting mental health diagnoses or attempting to exclude individuals currently using other drugs, and this matching is important when making group

comparisons. However, given that other drug use and psychiatric conditions are widespread among HIV-infected marijuana users, as this body of literature grows it will be critical not to exclude participants with these comorbidities but instead to understand how they may interact with marijuana use to impact brain functioning.

Fourth, researchers should consider how antiretroviral medications may be impacting functioning. One systematic review reported that HAART can improve cognition among HIV-infected individuals [89], but a subsequent review suggested that antiretroviral therapy did not improve memory functioning and may even have a negative impact [90]. Thus, it will be important to clarify the impact that these medications have on neurocognitive functioning in order to tease out the unique contributions of marijuana use. In considering the role of these medications, it will be crucial for investigators to take into account adherence because being prescribed an antiretroviral medication does not necessarily mean an individual is taking is regularly. Research is limited and findings are mixed as to whether marijuana use lowers adherence or increases it potentially by reducing unpleasant side effects [91], and it may be that dependent individuals are negatively impacted whereas casual users are not [92].

Fifth, more nuanced understanding of mechanisms underlying memory impairment may be attained through the use of neuroimaging. Remarkably, investigations using fMRI have been able to detect cognitive brain changes associated with both HIV infection and marijuana use that are not observable on behavioral tasks [42, 60, 65, 93]. These techniques have been underutilized despite their potential to advance our understanding of mechanisms, which may be due to the significant cost and advanced training needed to utilize this technology. Neuroimaging studies will allow us to examine changes in activation patterns, including compensatory strategies, which can help to establish a definitive theory of the interaction between marijuana use and HIV infection as they pertain to cognitive functioning.

5. CONCLUSION

Existing research suggests that marijuana and HIV are independently associated with episodic memory impairment. Studies that rigorously assessed substance use histories and HIV disease progression provide a more nuanced understanding of how severity of marijuana use and HIV infection affect memory, although future research is needed to draw firm conclusions. A compensatory hypothesis was proposed that suggests the effects of marijuana use will be more pronounced among HIV-infected individuals whose cognitive resources are already limited due to their disease. Future research is needed to test this hypothesis empirically. The prevalence of marijuana use among this population is already high, and given increased legalization of this drug to manage HIV, understanding how it affects cognitive functioning should be a public health priority.

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Table 1

Studies examining episodic memory in HIV-infected populations (n = 22)

Authors & Region	Sample Size	Mean Age; % Male	Current CD4 M(SD) or Median[IQR]	Memory Domain (Measure Used)	Illicit Drug Use	Neurocognitive Task Performance	HIV-related Correlations
Cross-sectional studies (n=21)							
Durvasula et al., 2001 Los Angeles, CA	HIV 91 HIV/AIDS 45 Con 91	HIV 36; 0 HIV/AIDS 38; 0 Con 35; 0	HIV 540 (279); HIV/AIDS 173 (139)	Verbal (WHO/UCLA-AVLT)	No drug use exclusions Of note, secondary analysis eliminated participants who reported any illicit drug use in past year and results did not change	No significant differences on overall verbal memory score in multivariate model	Not reported
Richardson et al., 2002 Los Angeles, CA & Chicago, IL	HIV 108 HIV/AIDS 41 Con 31	HIV 36; 0 HIV/AIDS 37; 0 Con 35; 0	HIV 534 (257) HIV/AIDS 99 (55)	Verbal (WHO/UCLA-AVLT); Visual (Visual Reproduction subtest of WMS-R)	No drug use exclusions 44% of HIV, 20% of HIV/AIDS, & 24% of con group had “high” lifetime drug use index (i.e., sum of years using marijuana, opiates, cocaine, or abusive alcohol totaled 31–121 years)	No significant differences	Not reported
Waldrop et al., 2004 South Florida	HIV/IDU 59 IDU 50 Con 38	HIV/IDU 40; 64 IDU 39; 64 Con 31; 45	Not reported	Verbal (RAVLT)	No drug use exclusions Both IDU groups were primarily polysubstance abusers, predominantly heroine, cocaine, and marijuana	Con > HIV/IDU on overall (d= 0.99) & delayed recall (d= 0.77) Con > IDU on overall (d= 0.94) & delayed recall (d= 0.83) No significant differences between HIV/IDU & IDU groups	No associations with viral load
Rippeth et al., 2004 San Diego, CA	HIV 50 HIV/Meth 43 Meth 47 Con 60	HIV 39; 84 HIV/Meth 37; 91 Meth 38; 74 Con 34; 50	HIV 410 (244) HIV/Meth 388 (240)	Verbal (HVLT-R); Visual (BVMT-R)	Excluded if any of the following: 1) dependent on alcohol within past year, 2) abused illicit drugs within past year, 3)	HIV > Con on visual/verbal composite rates of impairment for immediate (34% vs. 17%) & delayed recall (40% vs. 15%) HIV/Meth > Con on visual/verbal composite for immediate (44% vs. 17%) & delayed recall (54% vs. 15%)	Not reported

Authors & Region	Sample Size	Mean Age; % Male	Current CD4 M(SD) or Median[IQR]	Memory Domain (Measure Used)	Illicit Drug Use	Neurocognitive Task Performance	HIV-related Correlations
					"significant" length of alcohol dependence during lifetime (determined on case-by-case basis), or 4) dependent on illicit drug other than marijuana within past 5 years. If urine toxicology screen positive, participants were rescheduled for another day.	Meth > Con on visual/verbal composite for delayed recall (51% vs. 15%) Comparing T scores, Con > HIV/ Meth on visual immediate recall (d= . 72)	
Justice et al., 2004 Atlanta, GA, Bronx, Brooklyn and Manhattan, NY, Houston, TX, and Los Angeles, CA	HIV 28 Con 22	HIV 51; 93 Con 49; 100 (reported median age)	Not reported	Verbal (HVLT-R); Visual (BVMT-R)	No drug use exclusions Heavy alcohol use (HIV 43%; Con 45%) and drug use (HIV 64%; Con 54%) was relatively common	No significant differences	Not reported
Woods et al., 2005 San Diego, CA	HIV 42 Con 29	HIV 44; 81 Con 29; 72	450 [263, 608]	Verbal (HVLT-R)	Excluded for any current substance use disorder	Con > HIV on total recall (d= 0.71), delayed recall (d= 0.79), & percent retained (d= 0.57)	Not reported
Castelo et al., 2006 Boston, MA	HIV 14 Con 14	HIV 39, 100 Con 40, 100	690 (370)	Verbal (Logical Memory subtest of WMS-R & CVLT-R); Visual (fMRI task involving visual memorization of landscape pictures)	Excluded if history of substance abuse or dependence within the past 6 months, or history of IV drug use	No significant differences	Not reported
Carey et al., 2006 San Diego, CA	HIV 42 Con 29	HIV 44; 81 Con 44; 72	450 [263, 608]	EB & TB ProM (MIST); Visual (BVMT-R)	Excluded if history of a substance use disorder within the past two years or a positive urine toxicology screen for any drug	Con > HIV on MIST summary score (d= 0.92), EB cues (d= 0.84), TB cues (d= 0.68), & 24-hour delay (12% complete vs. 38%).	Not reported
Scott et al., 2006 San Diego, CA	HIV 50 HIV/HAD 16 Con 50	HIV 40; 88 HIV/HAD 41; 94	HIV 415 [251, 583] HIV/HAD 235 [22, 397]	Verbal (HVLT-R)	Excluded if current substance use disorder	HIV > HIV/HAD on total recall (d= 2.72), delayed recall (d= 2.05), & percent retained (d= 0.79)	Not reported

Authors & Region	Sample Size	Mean Age; % Male	Current CD4 M(SD) or Median[IQR]	Memory Domain (Measure Used)	Illicit Drug Use	Neurocognitive Task Performance	HIV-related Correlations
		Con 40; 86				Con > HIV/HAD on total recall (d= 2.89), delayed recall (d= 2.59), & percent retained (d= 1.01) Con > HIV on delayed recall (d= 0.59)	
Martin et al., 2007 Chicago, IL	HIV 31 Con 35	HIV 44; 84 Con 43; 89	508 (full range 36–2,040)	EB & TB ProM (MIST); Verbal (Logical Memory & Verbal Paired Associate Learning subtests of WMS-R); Visual (Visual Reproduction subtest of WMS-R)	All diagnosed with current or previous substance dependence (90% cocaine, 70% alcohol, 66% opiates) Excluded if urine toxicology screen positive for cocaine or opiates	Con > HIV on TB ProM (d = 0.52), WMS-R immediate visual reproduction (d= 0.70), & delayed visual reproduction (d= 0.60)	No associations with AIDS diagnosis, detectable viral load, or current HAART treatment
Woods et al., 2007 San Diego, CA	HIV 75 Con 60	HIV 45; 95 Con 43; 57	524 [325, 801]	ProM (MIST); Verbal (Long delay recall subtest of CVLT-II)	Excluded if history of substance dependence within the past 6 months or urine toxicology screen positive for any illicit drug.	Con > HIV on CVLT-II long delay recall (d= 0.45) & MIST total score (d= 0.54)	Not reported
Maki et al., 2009 Chicago, IL	HIV 51 Con 12	HIV 43; 0 Con 43; 0	443 (316)	Verbal (HVLT); Visual (ROCF)	Excluded if evidence of intoxication or withdrawal at testing	Con > HIV on HVLT immediate (d= 0.87) & delayed recall (d= 0.68), and ROCF immediate (d= 0.67) & delayed (d= 0.64) recall	Viral load inversely correlated with ROCF immediate recall score
Schiller et al., 2009 South Florida	HIV 22 Con 22 LD 22 Depressed 22	HIV 48; 100 Con 40; 100 LD 39; 73 Depressed 40; 74	Not reported	Verbal & Visual (WMS-III); yielding 7 index scores: auditory immediate memory, visual immediate memory, immediate memory, auditory delayed memory, visual delayed memory, general memory, & auditory recognition delayed	Excluded if history of any substance use disorder	Con > HIV on auditory delayed memory, visual delayed memory, visual immediate memory, immediate memory, & general memory. No differences between HIV and LD or depressed groups	Not reported
Woods et al., 2010 San Diego, CA	Younger/HIV 35 Older/HIV 48 Younger/Con 20 Older/Con 15	Younger/HIV 35; 86 Older/HIV 56; 79 Younger/Con 32; 35 Older/Con 56; 67	Younger/HIV 547 [303, 879] Older/HIV 512 [253, 693]	EB ProM (MIST; AAIM)	Excluded if history of substance disorder within 6 months or positive urine toxicology screen for any illicit	Among younger participants, Younger/Con > Younger/HIV on EB ProM task (MIST only) (d= 1.01). Among older participants, Older/Con > Older/HIV on EB ProM task (AAIM only) (d= 0.79)	Lower nadir CD4 counts associated with worse performance on EB ProM (AAIM) in HIV/Older group No associations with duration of infection, current CD4 count, or viral load

Authors & Region	Sample Size	Mean Age; % Male	Current CD4 M(SD) or Median[IQR]	Memory Domain (Measure Used)	Illicit Drug Use	Neurocognitive Task Performance	HIV-related Correlations
					drug except marijuana		
Moore et al., 2011 San Diego, CA	Acute/early HIV 39 Chronic HIV 63 Con 63	Acute/ early HIV 32; 92 Chronic HIV 35; 92 Con 35; 84	Acute/early 538 (287) Chronic HIV 570 (299)	Verbal (HVLT-R); Visual (BVMT-R)	Excluded if positive urine toxicology screen for any illicit drug except marijuana Participants reported no use of illicit substances in the past wk	Significant monotonically increasing trend in domain deficit score among the three groups in the order of Con, Acute/Early HIV, and Chronic HIV on verbal/visual composite for immediate and delayed recall Acute/early HIV & Con > Chronic HIV on verbal/visual composite domain deficit score for immediate and delayed recall	Not reported
Scott et al., 2011 San Diego, CA	Younger/HIV 24 Older/HIV 48 Younger/Con 24 Older/Con 20	Younger/HIV 34; 83 Older/HIV 56; 79 Younger/Con 30; 33 Older/Con 57; 60	Younger/HIV 640 [299, 916] Older/HIV 512 [253, 693]	Verbal (Logical Memory subscale of WMS-3; CVLT-II)	Excluded if history of substance dependence within 6 months or a positive toxicology screen for any illicit drug except marijuana	Combining all groups, main effect of HIV status on WMS-3 (Total I, Total II, Recognition, percent retained) & CVLT-II (Total 1–5, Total Cued Recall Intrusions, Long Delay Free Recall, Recognition Discriminability)	Not reported
Weber et al., 2011 San Diego, CA	Younger/HIV 53 Older/HIV88 Younger/Con 59 Older/Con 54	Younger/HIV 32; 83 Older/HIV 56; 82 Younger/Con 30; 61 Older/Con 56; 65	Younger/HIV 559 [404, 840] Older/HIV 512 [308, 738]	TB ProM (MIST)	Excluded if history of substance dependence within 1 month or a positive toxicology screen for any illicit drug except marijuana	Combining all groups, main effects of HIV status (d= .40) and aging on TB ProM impairment (d= 0.86) No differences on 24-hour delay task	AIDS diagnosis associated with successfully completing the 24-hour trial across both age groups
Wright et al., 2011 Los Angeles, CA	HIV/Good Adh 33 HIV/Poor Adh 42 Con 25	HIV/ Good-Adh 48; 79 HIV/Poor-Adh 42; 83 Con 43; 44	HIV/Good-Adh 449 (318) HIV/Poor-Adh 356 (215)	Verbal (CVLT)	Excluded if current substance use disorder	Con > HIV/Good-Adh on total recall (d= 0.95), short-delay (d= 0.70), & long-delay (d= 0.68) Con > HIV/Poor-Adh on total recall (d= 1.12), short-delay (d= 0.92), & long-delay recall (d= 0.83). No differences between two HIV groups	Not reported
Zogg et al., 2011 San Diego, CA	HIV 143 Con 43	HIV 46; 87 Con 43; 54	536 [326, 783]	TB & EB ProM (MIST)	Excluded if history of substance dependence within 6 months or positive urine toxicology for any drug	Con > HIV on TB ProM (d= 0.43)	Not reported

Authors & Region	Sample Size	Mean Age; % Male	Current CD4 M(SD) or Median[IQR]	Memory Domain (Measure Used)	Illicit Drug Use	Neurocognitive Task Performance	HIV-related Correlations
Morgan et al., 2012 San Diego, CA	HIV/HAND 49 Con 78	HIV/ HAND 45; 88 Con 43; 91	637 (364, 936)	TB & EB ProM (MIST)	Excluded if history of substance dependence within 6 months.	Con > on long-delay TB ProM (d= 0.56)	Not reported
Woods et al., 2013 San Diego, CA	HIV 50 Con 50	HIV 55; 88 Con 55; 78	506 (374, 750)	Visual (temporal order memory task)	HIV: Excluded if current substance dependence or positive urine toxicology for any drug except marijuana Con: Excluded if history of alcohol or other substance abuse	Con > HIV across all temporal separations	No associations with between current CD4 count, nadir CD4 count, viral load, or duration of infection
Longitudinal study (n=1)							
Fama et al., 2009 Palo Alto, CA	Baseline: HIV 40 Alc 47 HIV/Alc 38 Con 39	Baseline: HIV 42; 70 Alc 43; 63 HIV/Alc 45; 81 Con 40; 56	Baseline: HIV 258 (264) HIV/Alc 437 (216)	Verbal (address and paragraph recall from MicroCog: Assessment of Cognitive Functioning)	HIV, Alc, & Alc/ HIV: Excluded if history of substance dependence within 3 months except alcohol Con: Excluded if history of alcohol or other substance use disorder	HIV, Alc, & Con > HIV/Alc on immediate recall	Within HIV/Alc group, higher CD4 cell counts correlated with greater improvements in percent memory retention over time No associations with change in CD4 count over time

Con – control group; *WHO/UCLA AVLT* – WHO/UCLA Auditory Verbal Learning Test; *WMS-R* – Weschler Visual Memory Scale-Revised; *IDU* – injection drug user; *RAVLT* – Rey Auditory Verbal Learning Test; *Meth* – methamphetamine; *HVLT-R* – Hopkins Verbal Learning Test-Revised; *BVMT-R* – Brief Visuospatial Memory Test-Revised; CVLT-R – California Verbal Learning Test-Revised; *TB* – time-based; *EB ProM* – event-based; *ProM* – prospective memory; *MIST* – Memory for Intentions Test; *HAD* – HIV-associated dementia; *CVLT-II* – California Verbal Learning Test 2nd edition; *ROFC* – Rey Osterrieth Complex Figure Task; *LD* – learning disabled; *AAIM* – Abbreviated Assessment of Intentional Memory; *WMS-3* – Weschler Memory Scale, 3rd edition; *Good-Adh* – Adherence to HAART medication ≥ 90%; *Poor-Adh* – Adherence to HAART medication < 90%; *HAND* – HIV associated neurocognitive disorder; *Alc* -- alcohol

Table 2

Studies examining episodic memory in marijuana users (n = 23)

Authors & Region	Sample Size	Mean Age, % male	Frequency or Amount of Use	Duration in Years	Age of 1st Use	Abstinence Period	Memory Domain (Measure Used)	Neurocognitive Task Performance (Effect Size)	Marijuana-related Correlations
Case-controlled studies (n = 18)									
Rodgers et al., 2000 United Kingdom	MJ 15 Con 15 Ecstacy/MJ 15	MJ 30; 47 Con 32; 40 Ecstacy/MJ 31; 47	MJ: M= 4 days/wk Ecstacy/MJ: M= 4 days/wk	MJ: M=11 Ecstacy/MJ: M=10	Not reported	≥ 1 month	Verbal (WMS-R); Visual (WMS-R)	Con > MJ on Logical Memory I (d= 2.60) & Logical Memory II (d= 1.99) Con > Ecstacy/MJ on Logical Memory I (d= 2.69), Logical Memory II (d= 1.82), Verbal Paired Associates II (d= 0.88) & Visual Paired Associates II (d= 1.25 Can > Ecstacy/MJ on Verbal Paired Associates II (d= 1.24) & Visual Paired Associates II (d= 0.94)	Not reported
Pope et al., 2001 Belmont, MA	MJ 63 Past MJ 45 Con 72	MJ 36; 55 Past 41; 30 Con 40; 61	MJ: required ≥ 5,000 lifetime episodes and currently 7x/wk Past: required ≥ 5,000 lifetime episodes and ≤ 12 episodes in past 3 months	MJ: M=19, range 15–24 Past: M= 15, range 11–19	Not reported	0, 1, 7, & 28 days monitored abstinence, but baseline abstinence not reported	Verbal (BSRT on days 0,1,7, & 28; WMS on day 28); Visual (BRVRT on days 0, 7, 28); WMS on day 28)	Con > MJ on BSRT total recall (day 0, d= 0.58; day 1, d= 0.54; day 7, d= 0.63) & delayed recall (day 1, d= 0.94; day 7, d= 0.65; day 28, d= 0.49) Adjusting for Verbal IQ, Con > MJ on BSRT total recall (day 7) & delayed recall (day 7) only	THCCOOH-creatinine ratios at baseline inversely associated with BSRT total recall at day 1 & delayed recall at day 28. Adjusting for Verbal IQ, THCCOOH-creatinine ratios at baseline inversely associated with BSRT total recall at day 1 only No associations with lifetime episodes of use
Block et al., 2002 Iowa City, IA	MJ 18 Con 13	MJ 22; 50 Con 23; 46	Required ≥ 7 times/wk; M= 18 times/wk	3.9±0.4	Not reported	M= 15.7 hours prior to monitored abstinence for ≥ 26 hours (M=27.8)	Verbal (BSRT)	Marijuana users required more presentations to learn initial word list in both learning and relearning trials	Not reported
Solowij et al., 2002 Seattle, WA, Farmington, CT, & Miami, FL	Long-term MJ 51 Short-term MJ 51 Con 33	LT 42; 76 ST 29; 71 Con 35; 67	LT: Mdn = 27 days/ month ST: Mdn =28 days/month	LT 23.9±4.1, range 17.3–31.7 ST 10.2±3.8, range 2.7–17.0	Among whole sample, M=17.5±3.2 (began regular use)	Mdn= 17 hours, range 7–240 hours	Verbal (RAVLT)	Con > LT on RAVLT sum (d=0.80), recognition A (d=0.82), & recognition B (d=0.95) ST > LT on RAVLT sum (d= 0.68)	Controlling for age and IQ, duration of marijuana use inversely associated with RAVLT sum
Pope et al., 2003 Belmont, MA	Early-onset MJ 69 Late-onset MJ 53 Con 87	EO 36; 75 LO 44; 62 Con 40; 70	Required ≥ 7x/wk OR ≥ 5,000 lifetime episodes and ≤ 12 episodes in past 3 months	Not reported	EO ≤ 17 LO > 17	28 days monitored abstinence, but baseline abstinence not reported	Verbal (BSRT; WMS); Visual (BRVRT; WMS)	Controlling for age, sex, ethnicity, and five family-of-origin variables, Con > EO on BSRT total recall (d= 0.41) and delayed recall (d= 0.47)	Controlling for age of first use, lifetime episodes inversely associated with BSRT total recall and WMS total score

Authors & Region	Sample Size	Mean Age, % male	Frequency or Amount of Use	Duration in Years	Age of 1st Use	Abstinence Period	Memory Domain (Measure Used)	Neurocognitive Task Performance (Effect Size)	Marijuana-related Correlations
								When additionally controlling for Verbal IQ, no significant group differences	
Lyons et al., 2004 United States (Vietman Era Twin Registry)	MJ 54 Con 54	MJ 46; 100 Con 46; 100	Required ≥ 1x/day for ≥ 1 year (past acceptable); M= 916 days/lifetime	M=5.8±5.3, range 1–22	21.3±3.8, range 17–38	M= 27.1±6.0 years, range: 19–43 years	Verbal (WMS-R; CVLT); Visual (WMS-R; ROCFT)	Con > MJ on CVLT long delay free recall (d= 0.31) and cued recall (d= 0.28) but non-significant due to authors' conservative statistical criteria	No associations with total days of marijuana use
Messinis et al., 2006 Athens, Greece	Long-term MJ 20 Short-term MJ 20 Con 24	LT 33; 55 ST 24; 70 Con 28; 54	LT M= 20 days/month, range: 16–28 ST M=21 days/month, range: 16–28	LT: M=15.6±4.8 range 10–25 ST: 7.0±1.5, range 5–9	Not reported	LT: M= 126.3±78.3 hours, range 36–240 hours ST: M= 122.8±76.3 hours, range 36–240 hours	Verbal (RAVLT)	Con > LT on delayed recall (d= 2.29), recognition (d= 1.38), & sum trials 1–5 (d= 1.63) Con > ST on delayed recall (d= 0.95) & recognition (d= 0.98)	Collapsing ST and LT groups, duration of marijuana use inversely correlated with delayed recall and sum trials 1–5
Wadsworth et al., 2006 United Kingdom	MJ 34 Con 85	MJ 24; 65 Con 27; 33	M= 3.35 days/wk	M= 7.63±4.72, range 1–21	Not reported	Not reported	Verbal list task (computer-based) to assess immediate recall, delayed recall, and recognition. Administered pre- and post-work day at beginning and end of wk	Con > MJ on delayed recall in pre-work testing sessions (d= 1.05)	Duration of use inversely associated with delayed recall at pre-work, beginning of wk testing session No associations with frequency of use
Hermann et al., 2007 Germany	MJ 13 Con 13	MJ 22; 100 Con 23; 100	M= 25 days/last month; M=300/last year	5.6	16.2±1.6	M= 29±29.4 hours, range: 3–84	Verbal (TME); Visual (Benton Visual Retention Test)	Con > MJ on TME 1 (d= 1.11), TME 2 (d= 1.21), Benton Test number correct (d= 1.16) & Benton Test total errors (d= 1.06)	No associations with THC & CBD ratios
Jager et al., 2007 The Netherlands	MJ 20 Con 20	MJ 25; 65 Con 24; 65	Mdn= 333 joints/last year; range 10–1,450 joints/last year	M= 8.4±4.8	Not reported	≥ 7 days	Visual (pictorial memory fMRI paradigm)	No differences	Number of joints smoked in lifetime and in last year were negatively correlated with recall accuracy
McHale et al., 2008 United Kingdom	MJ 18 Con 20	MJ 22; 56 Con 21; 50	M= 3x/wk & two joints per session	Not reported	Not reported	Requested ≥ 24 hours	EB ProM (Belonging subtest of RBMT); TB ProM (researcher created); Visual (Doors Test, Shapes Test)	Con > MJ on the visual recognition Doors task (d=1.37), delayed visual recall Shapes Test (d=0.99), short-delay TB ProM task (d=0.95), & long-delay TB ProM task	Not reported
Nestor et al., 2008 (exper. 1) Ireland	MJ 35 Con 38	MJ 22; 91 Con 22; 76	M= 23 days/past 30, range: 7–30	M= 5.7±0.6, range 1.5–17	16.5±0.4	M=15 hours, range: 2–45	Visual (Face-name association task)	Con > MJ on short & long-term recall No differences on recognition	No associations with length of abstinence, duration, or frequency of use
Nestor et. al., 2008 (exper. 2) Ireland	MJ 14 Con 14	MJ 24; 86 Con 24; 86	M= 19.1 days/past 30, range: 1–30	M= 7.2±1.1, range 2–16	17±0.9	M= 80.8 hours, range: 3–686 hours	Visual (Face-name association task)	No differences	No associations with length of abstinence, duration, or frequency of use

Authors & Region	Sample Size	Mean Age, % male	Frequency or Amount of Use	Duration in Years	Age of 1st Use	Abstinence Period	Memory Domain (Measure Used)	Neurocognitive Task Performance (Effect Size)	Marijuana-related Correlations
Bartholomew et al., 2010 United Kingdom	MJ 45 Con 45	MJ 19 (Mdn); 44 Con 19 (Mdn); 38	Mdn= 2 joints/wk	Mdn = 3, range 6	Not reported	Required ≥ 24 hours; Mdn= 10.5 days, range 211.9 days	EB ProM (video-based task)	After controlling for alcohol and tobacco use, Con > MJ on recall of location-action combinations (d= 0.67)	Not reported
Battisti et al., 2010 Australia	MJ 24 Con 24	MJ 36; 54 Con 36; 46	Mdn = 30 days/month, range: 4–30	17±9.3	Mdn= 17, range 13–42	Mdn= 13 hours, M=20 hours, range: 9–108	Verbal (short delay recall of word lists)	Con > MJ on total number of words recalled (d= 0.74)	Longer history of regular use associated with greater number of correctly recalled words
Hadjiefthyvoulou et al., 2011 United Kingdom	MJ 12 Con 18 Ecstasy/MJ 29	MJ 22; 42 Con 20; 11 Ecstasy/MJ 21; 59	MJ: M=22 joints last/30 days, M= 2x/wk Ecstasy/MJ: M= 26 joints/last 30 days, M= 2x/wk	Not reported	Not reported	MJ: M=73.3±113.7 wks Ecstasy/MJ: M=20.3±37.1 wks	Verbal (RAVLT); EB & TB ProM (CAMPROMPT)	Con > Ecstacy/MJ on EB ProM (d= 1.33) & TB ProM (d= 1.25) MJ > Ecstacy/MJ on EB ProM (d= 0.87)	Among the whole sample, frequency of use inversely correlated with TB & EB ProM
Cuttler et al., 2012 Vancouver, Canada	MJ 48 Exp 48 Con 48	MJ 20; 52 Exp 21; 40 Con 20; 21	≥ 3x/wk required	≥ 1 required	Not reported	Not reported	EB ProM (Fruit Test; Reminder Test); TB Pro (Call In Test)	No differences	No associations with quanity of marijuana consumed
Lisdahl et al., 2012 Cincinnati, OH	MJ 23 Con 35	MJ 21; 44 Con 21; 50	M= 208 joints/past year, range: 10–728	Not reported	15±2.0, range 11–19	M=50±109 days, range 7–407 days	Verbal (CVLT-II)	No differences	No associations with length of abstinence or frequency of use
Cross-sectional studies examining dose-related effects without inclusion of a control group (n= 3)									
Bolla et al., 2002 Baltimore, MD	22	22; 86	M= 49 joints/wk, range 2–117	4.8±3.1, range 2–15	Not reported	28 days	Verbal (RAVLT; Logical Memory subtest of WMS-R); Visual (ROCF; Symbol Digit Paired Associate Learning Test)	Not applicable	Joints/wk correlated with lower performance on RAVLT delayed recall & Symbol-Digit Paired Associate Learning
Indlekofer et al., 2009 Germany	284	26; 64	43% never used marijuana; 39% ≤ 365 lifetime occasions; 18% > 365 lifetime occasions	Not reported	Not reported	≥ 1 wk required	Verbal (Logical Memory subtest of WMS-R; RAVLT); Visual (ROCF)	Not applicable	Controlling for verbal IQ, frequency of lifetime consumption negatively correlated with immediate & delayed recall on WMS-R.
Becker et al., 2010 Germany	42	23; 79	M=14 days/month; M=2.4 joints/day	51.3±37.8 months	15.1±2.0	M= 86.5±235.7 days	Visual (Face-profession association paradigm)	Not applicable	No associations with age of first use, duration, and frequency of use
Longitudinal studies (n= 2)									
Tait et al., 2011 Australia	1,517	Age 20–24 baseline; assessed again 4 and 8 years later		“Light” ≤ 1x/month; “Heavy” ≥ 1x/wk			Verbal (CVLT)	There were baseline differences on immediate and delayed recall between light and heavy users. The “never”, “always former”, and both the “light” & “heavy” former users improved CVLT immediate recall scores at each assessment visit, while those who remained users declined from the 2nd to the 3rd assessment.	

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Meier et al., 2012 New Zeland	1,037	Memory assessed age 13 & 38; marijuana use assessed age 18, 21, 26, 32, & 38		Never (n=242); Used/not dependent (n=479); 1 diagnosis (n=80); 2 diagnoses (n=35); 3+ diagnoses (n=38)			Verbal (RAVLT; WMS); Visual (CANTAB)	Controlling for childhood IQ, more persistent marijuana dependence associated with declines on RAVLT total recall & delayed recall, & CANTAB Visual Paired Associates Learning First Trial Memory Score	

MJ – Marijuana*; Con* – control group; *M* – mean; *Wk* – week; *WMS-R* – Weschler Visual Memory Scale-Revised; *Past* – Used marijuana in past, but not currently; *LT* - Long-term marijuana users; *ST* – Short-term marijuana users; *BSRT* – Buschke Selective Reminding Test; *Mdn* – median; *RAVLT* – Rey Auditory Verbal Learning Test; *EO* – Early-onset marijuana users; *LO* – Late onset marijuana users;; *WMS* – Weschler Memory Scale; *BRVRT* – Benton Revised Visual Retention Test; *WMS-R* – Weschler Visual Memory Scale-Revised; *CVLT* – California Verbal Learning Test-Revised; TME – Tempoleistung und Merkfähigkeit Erwachsener; *THC* – Delta-9-tetrahydrocannabinol*; CBD* – Cannabidiol; *EB* – Event-based; *TB* – Time-based; *ProM* – Prospective memory; *RBMT* – Rivermead Behavioural Memory Test; *CAMPROMPT* – Cambridge Prospective Memory Test; *Exp* – Experimenter group who had tried marijuana five times or fewer; *ROCF* – Rey-Osterrieth Complex Figure Test; *CANTAB* – Cambridge Neuropsychological Test Automated Battery