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## Marijuana effects on changes in brain structure and cognitive function among HIV+ and HIV– adults

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### Abstract

**Background**—The current study examined the independent and interactive effects of HIV and marijuana (MJ) use on brain structure and cognitive function among a sample of HIV-positive (HIV+) and HIV-negative (HIV–) individuals.

**Methods**—Participants (HIV+, n = 48; HIV–, n = 29) individuals underwent cognitive testing, questionnaires about substance use, and brain MRI. The HIV+ group was clinically stable based upon current plasma CD4 count, 50% had undetectable viral load (i.e., < 20 copies/mL), and all were on a stable regimen of cART.

**Results**—For HIV+ and HIV– participants, higher levels of MJ use were associated with smaller volumes in the entorhinal cortex and fusiform gyrus. HIV status (but not MJ use) was associated with cingulate thickness, such that HIV+ participants evidenced smaller thickness of the cingulate, as compared to HIV-controls. Regarding neurocognitive functioning, there was a HIV\*MJ interactive effect on global cognition, such that when the amount of MJ use was less than 1.43 g per week, the HIV– group displayed significantly better neurocognitive performance than the HIV

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### Conflict of interest

The authors report no conflict of interest.

### Contributors

Dr. April Thames designed the study, wrote the protocol assisted with the statistical analysis and wrote the first draft of the manuscript. Dr. Kuhn assisted with the statistical analysis of the data, and equally contributed to the writing of the first draft of the manuscript. Mr. Timothy Williamson undertook the statistical analyses of the data and assisted in the writing of the results. Dr. Jones participated in the write-up of the manuscript and provided scientific input into the data analysis. Ms. Zanjbeel Mahmood managed the literature searches and summaries of previous related work and assisted with the write-up of the introduction. Ms. Andrea Hammond assisted with the managing of the literature searches and assisted with tables and write-up of the discussion. All authors contributed to and have approved the final manuscript.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2016.11.007>.

+ group ( $t = 3.14, p = 0.002$ ). However, when MJ use reached 1.43 g per week, there were no significant HIV group differences in global cognitive performance ( $t = 1.39, p = 0.168$ ).

**Conclusions**—Our results show independent and interactive effects of HIV and MJ on brain structure and cognition. However, our results do not support that HIV+ MJ users are at *greater* risk for adverse brain or cognitive outcomes compared to HIV– MJ users.

### Keywords

HIV; Magnetic resonance imaging; Cognition; Marijuana; Cannabis

## 1. Introduction

People living with HIV (PLWH) constitute one of the largest groups that consume marijuana (MJ) for medicinal (e.g., pain; 27–34.7%) as well as recreational purposes (43–55.7%; Fogarty et al, 2007; Robson, 2014; Woolridge et al., 2005). Considering that approximately 50% of PLWH present with HIV-associated neurocognitive disorder (HAND; Heaton et al., 2011), there are legitimate concerns about the cognitive consequences of MJ use in this population.

Studies of medically healthy populations have documented acute as well as non-acute effects of marijuana across multiple cognitive domains (Battisti et al., 2010; Crean et al., 2011; Gonzalez et al., 2012; Lisdahl and Price, 2012; Morrison et al., 2009; Schuster et al., 2012; Solowij et al., 2002; Thames et al., 2014). However, some studies have reported minimal effects of MJ use on cognitive function (Grant et al., 2003; Jager et al., 2006). These disparate findings may be a function of sample differences involving degree of MJ exposure, tolerance and other neuroadaptations resulting from long-term MJ use. Studies of medical/neurologic populations have been mixed. In studies of patients with Multiple Sclerosis, MJ use was associated with cognitive impairment, particularly impairments in memory and processing speed (Honarmand et al., 2011; Pavisian et al., 2014; Romero et al., 2015). In contrast, among patients with Tourette's Syndrome, there was no effect of a single dose administration of THC on neurocognitive functioning (Muller-Vahl et al., 2001).

The relationship between morphometric changes in gray matter regions associated with MJ use has resulted in conflicting findings across a number of studies of healthy individuals (Battistella et al., 2014; Demirakca et al., 2011; Yücel et al., 2008; Zalesky et al., 2012). For example, Battistella et al. (2014) found that independent of usage duration, anatomical differences in the temporal pole, parahippocampal gyrus, and left insula between occasional users and regular users, with regular users showing decreased volume. Furthermore, a number of neuroanatomical differences between MJ users and non-users were reported in gray matter volume, with users showing reduced volume in bilateral orbitofrontal region and higher functional connectivity in the orbitofrontal network (i.e., bilateral orbitofrontal and bilateral temporal gyri) during resting states, suggesting compensatory mechanisms (Filbey et al, 2014). In contrast, a study of 11 users and 8 non-users of MJ reported greater gray matter tissue density in the left precentral gyrus, thalamus and right dorsomedial nucleus among users compared to non-users. In the same study, MJ participants were found

to have decreased hippocampal volume suggesting that increases and decreases in gray matter may be regionally specific (Matochik et al., 2005).

Few studies have examined the combined effects of MJ and HIV-infection on brain structure and cognition. A study by Cristiani et al. (2004) found that frequent marijuana use (i.e., at least once per week) was associated with greater memory impairment among individuals with symptomatic HIV, but not HIV-negative or asymptomatic HIV+ marijuana users. Chang and colleagues (2006) found independent and combined effects of routine MJ use and HIV on brain metabolites. There were no observed additive or interactive effects of MJ use and HIV on cognitive performance, a finding that was attributed to the relatively asymptomatic status of the HIV+ sample. Among a group of polysubstance users, main and additive effects for HIV and MJ were found on tasks of complex motor skills, but not procedural learning (Gonzalez et al., 2011). However, no significant HIV\*MJ interactive effects were found on any of the tasks.

Our group found that moderate-to-heavy MJ use among HIV+ participants was associated with lower performance in learning and memory in comparison to HIV+ non-users, HIV+ light users, and HIV-negative moderate-to-heavy users (Thames et al., 2015). However, this study was limited by its inability to determine the precise amount of moderate-to-heavy MJ use that contributed to poor cognitive outcomes. The degree of MJ use (i.e., frequency, amount, duration) within any “user” group is important when examining its impact on cognitive and brain outcomes.

There are studies to suggest both neuroprotective and neurotoxic effects of MJ compounds that may have direct relevance to HAND. Briefly, compounds that stimulate CB2 on macrophages have been found to effectively reduced HIV viral replication and inflammation in the brain (Persidsky et al., 2015), inhibit migration of microglial cells toward HIV Tat protein (Fraga et al., 2011), and down-regulate active forms of integrins that increase permeability of the blood-brain barrier (BBB; Ramirez et al., 2012). Additionally, stimulation of CB<sub>1</sub> receptors can have a neuroprotective effect via blocking lipid mediators that induce apoptosis (Maccarrone and Finazzi-Agro, 2003). However, chronic marijuana use downregulates CB<sub>1</sub> receptors, and is linked to decreased protection against oxidative stress (Goncharov et al., 2005). This is particularly relevant to HIV, as oxidative stress has been proposed as a significant mechanism in the pathogenesis of HAND (Sacktor et al., 2004). Therefore, it is possible that chronic marijuana use may increase susceptibility to neuro-inflammation among individuals with HIV. Indeed there is initial evidence that marijuana use in HIV+ individuals is associated with metabolic brain changes, particularly in brain regions important for cognitive functioning, including the basal ganglia and thalamus (Chang et al., 2006).

Several questions remain with regard to the effects of MJ use on cognitive functioning in the context of HIV-infection. Previous studies have relied upon vague/non-specific categorical groups to classify marijuana use (i.e. a dichotomous frequent user versus non-frequent/never used; Chang et al., 2006; Cristiani et al., 2004; Gonzalez et al., 2011; Thames et al., 2015). Classifying the precise amount of use is critical to when evaluating potential adverse effects of MJ. This method of quantification has been linked to cognitive performance and brain-

based outcomes in other populations (Crane et al., 2015; Gonzalez et al, 2015; Jacobus et al., 2015; Roebke et al., 2014; Schuster et al., 2015).

The purpose of the current study was to examine the independent and interactive effects of HIV status and MJ use on neuroanatomical and cognitive outcomes using precise quantification of MJ use. We hypothesized both independent and interactive effects of HIV and MJ on brain structure and cognitive performance, such that HIV and MJ would show independent relationships with brain volume and thickness in selective structures as well as lower cognitive performance. Specific to interactive effects, we expected that the adverse effects of MJ on brain structure and cognitive performance would be greater in the HIV+ group.

## 2. Methods

### 2.1. Participants

This study consisted of 77 participants including HIV+ MJ using (n = 24), HIV+ non-using (n = 24), HIV- MJ using (n = 13) and HIV-non-using (n = 16) adults recruited from local HIV clinics, participant social networks (e.g., friends), and community advertisements in the Greater Los Angeles area. The UCLA Institutional Review Board (IRB) approved study procedures. All participants provided written informed consent and results from serologic testing were used to confirm HIV status. The Structured Clinical Interview (SCID) for DSM-IV (First et al., 1995), Mini-mental Status Exam (Folstein et al., 1975) and questionnaires about neurological, medical history, and MRI contraindications were used to screen for neurological, psychiatric and medical confounds as well as MRI contraindications. Participants were excluded if they reported a history of head injury with a loss of consciousness (>30 min), neurological insult (e.g., seizures), HIV-associated CNS opportunistic infections (e.g., CNS lymphoma), current or past dependence on stimulants, current or past diagnosis of psychotic-spectrum disorder (per SCID).

### 2.2. Substance use

The Drug Use History Form (DHQ) created by the University of California, Los Angeles' Center for Advanced Longitudinal Drug Abuse Research was used to collect detailed information about marijuana use, frequency, amount and time since last use. Participants underwent urine toxicology screening using Integrated E-Z Split Key (Innovacon, Inc., San Diego, CA). Participants were excluded from the study if they reported current use (within past 12 months) or past abuse or dependence of other substances aside from marijuana, alcohol, tobacco, opiates or sedatives (e.g., methamphetamine). Amount of MJ use was quantified based on participant's report of the average amount (in grams) smoked per day multiplied by the number of days per week of reported MJ use over the past month. Of the 37 participants who reported "no use" (i.e., MJ = 0) within the past month, 51% (n = 19) of the sample was MJ naïve (HIV+ = 33%; HIV- = 84%), with 35% (n = 13) reporting past experimental use (no more than 3 occasions), and the remaining 14% (n = 5) reported use 10+ years ago (range 10–30), but denied a history of moderate/heavy use (defined as 3+ days per week) of MJ. Participants were asked to abstain from MJ on the day of testing and none reported use or appeared intoxicated based on examiner behavioral observations.

Participants reported a median of 2 days since last MJ use. Self-reported MJ use was corroborated by urinalysis on day of testing. Data about the frequency of participant's alcohol and tobacco use was also collected to characterize the use of these substances across HIV groups. For statistical analyses, substance use variables were log-transformed because of skewed distributions that violated parametric assumptions.

### 2.3. Neurocognitive functioning and clinical measures

Participants were administered a brief cognitive test battery used in prior studies (Thames et al., 2014,2015). Briefly, this battery included tests of premorbid intellectual ability (Wechsler Test of Adult Reading [WTAR]), attention/working memory (Trail Making Test – Part A; Stroop Test [Color and Word conditions]; Wechsler Adult Intelligence Scale – IV [WAIS-IV] Letter-Number Sequencing subtest), speed of information processing (WAIS-IV Digit Symbol and Symbol Search subtests), verbal fluency (Controlled Oral Word Association Test), learning and memory (Brief Visual Memory Test-Revised [BVM-T-R]; Hopkins Verbal Learning Test-Revised [HVLT-R] Immediate and Delayed subtests), and executive functioning (Trail Making Test – Part B; Stroop Test [Color-Word condition]). Domain specific (e.g., learning, memory) and global neuropsychological performance composite scores were calculated by averaging *t* scores from individual cognitive tests (Heaton et al., 1991; Miller and Rohling, 2001). HIV+ participants underwent a blood draw for laboratory testing of CD4 and HIV viral load.

### 2.4. Neuroimaging acquisition and processing

T1-weighted images were collected using a 3T Siemens Trio scanner (Siemens, Germany) located at the UCLA Center for Cognitive Neuroscience (CCN). Structural MP-RAGE T1-weighted scans were acquired with 208–1.0 mm sagittal slices, FOV = 256mm (A–P) × 192 mm (FH), matrix =256-192, TR= 1900.0 ms, TE = 2.41 ms, Flip Angle = 9, voxel size = 1.0 mm × 1.0 mm × 1.0 mm. All MR images were visually inspected and quality controlled prior to being preprocessed and analyzed. T1-weighted images underwent cortical reconstruction and volumetric segmentation using Freesurfer (<http://surfer.nmr.mgh.harvard.edu>) image analysis software. This involved standard Freesurfer preprocessing procedures, which resulted in automated parcellation of cortical surfaces and subcortical structures (Desikan et al., 2006; Fischl et al., 2004) and extraction of regional volume and cortical thickness (Fischl and Dale, 2000). To reduce the number of regional comparisons, composite volume and thickness values for the frontal lobe, temporal lobe, basal ganglia, and occipito-parietal lobe were generated by summing and averaging the regions of interest (e.g., temporal lobe volume included the inferior temporal, middle temporal, temporal pole, and superior temporal volume). Other regions of investigation included the hippocampus, perirhinal volume, cingulate gyrus, cuneus, entorhinal cortex, fusiform, and insula.

### 2.5. Statistical analyses

Hierarchical regressions were conducted to determine the relationships between gray matter volume and thickness in aforementioned regions and cognitive function. Age, log-transformed intracranial volume and recent MJ use (i.e., days since last use) were entered as covariates in the first step for analyses of gray matter volume. Age and recent MJ use was

entered as a covariate in analyses of gray matter thickness. Given that age was accounted for in the process of standardizing neurocognitive test scores, we did not include age as a covariate for analyses of cognitive outcome, but included years of education and recent MJ use. HIV status was dummy coded and MJ use, a log-transformed continuous variable reporting the quantity of MJ use per week, were included as predictors in the second step. In the final step, the interaction term (i.e., HIV\*MJ) was entered. A subset ( $n = 40$ ) of participants in the current study underwent cognitive testing and MRI 1 year after the initial visit. In an exploratory manner, we conducted analyses to investigate associations between MJ use and changes in brain structure and/or cognitive functioning as a function of HIV-status (see Supplementary materials)

To decompose significant interactions, simultaneous simple effects analyses were used to determine the levels of MJ use at which our HIV status groups differed.

Below, we report findings from analyses in which MJ use (treated as a continuous variable), HIV status or their two-way interaction significantly predicted the dependent variable, after controlling for confounding variables. These overall models for the analyses were significant after controlling for multiple comparison corrections using Bonferroni adjustment (Weissstein, 2004).

### 3. Results

#### 3.1. Demographic comparisons

Table 1 reports the statistics of demographic comparisons between HIV status groups and descriptive statistics for significant outcomes of interest (reported below). Results demonstrated that the HIV status groups did not significantly differ on age or education ( $p$ 's  $> 0.05$ ). Among those who reported current MJ use, the HIV+ and HIV- group did not differ in the average amount (in grams) used (HIV+: Mdn = 4.08 [0–21] versus HIV- Mdn = 2.18 [0–15.75]); age of first MJ (HIV+:  $M = 18.27$ ;  $SD = 6.43$  versus HIV-:  $M = 15.9$ ;  $SD = 1.70$ ), and recency/days since last use (HIV+: Mdn = 1 [1–10] versus HIV-: Mdn = 2 [1–13], and frequency of use/days per week (HIV+: Mdn = 3.5 [0–7] versus HIV-: Mdn = 3.75 [0–7]). However, there were significantly more HIV+ participants who met criteria for past MJ dependence (14%) than HIV- participants (0%). HIV groups did not differ on race/ethnicity, past alcohol use/dependence, past opiate or sedative dependence, or current alcohol use. However, there were significantly more women in the HIV- group than the HIV+ group, and more transgendered (male-to-female) participants in the HIV+ group than the HIV- group. HIV- participants reported greater tobacco use than HIV+ participants. We did not observe that tobacco or gender group was significant related to MJ use, neuroimaging and cognitive outcome variables of interests (all  $p$ 's  $> 0.10$ ). Therefore, gender and tobacco use were not included as covariates in statistical analyses. There were no statistically significant relationships between MJ use and HIV-related clinical variables such as CD4 count, nadir CD4 count, or viral load (all  $p$ 's  $> 0.10$ ). Our HIV+ group was clinically stable based upon current plasma CD4 count, and 50% had undetectable viral load (i.e.,  $< 20$  copies/mL), and all were on a stable regimen of cART.

We conducted additional demographic comparisons between individuals who reported MJ use versus those who reported no use collapsed across HIV status. There were no significant difference between those who currently used MJ and those who do not in years of education and race/ethnicity (all  $p$ 's > 0.10). MJ users were younger ( $M = 45.0$ ;  $SD = 12.05$ ) than non-users ( $M = 50.50$ ;  $SD = 10.36$ ); however, when stratified by HIV status, there were no age differences between HIV+ MJ users and HIV- MJ users. There was a statistical trend ( $p = 0.06$ ) toward gender differences, with a greater number of male users versus non-users (83.8% versus 65%) as well as transgender (male-to-female) users versus non-users (2.7% versus 0). There were no differences between users versus non-users on current tobacco and alcohol use, current opiate or sedative use, or past dependence on alcohol, opiates, or sedatives (all  $p$ 's > 0.20). None of the participants reported past or current intravenous drug use.

### 3.2. Gray matter volume and thickness

Overall model statistics for significant regressions are reported in Table 2. Education or recency of MJ use did not significantly predict outcome variables. In separate analyses, higher levels of MJ use (but not HIV status) were associated with smaller volumes in the entorhinal cortex ( $b = -78.12$ ,  $SE = 33.61$ ,  $p = 0.03$ ) and fusiform gyrus ( $b = -226.19$ ,  $SE = 121.81$ ,  $p = 0.04$ ). Additionally, HIV+ participants evidenced reduced thickness of the cingulate ( $b = -0.09$ ,  $SE = 0.05$ ,  $p = 0.04$ ), as compared to HIV- controls. There was no interaction between HIV status and MJ use on these outcomes (Fig. 1).

### 3.3. Cognitive performance

There was a significant interaction between HIV status and MJ use on neurocognitive performance ( $b = 0.89$ ,  $SE = 0.34$ ,  $p = 0.011$ ; Fig. 2). This interaction was analyzed using the method of Aiken and West (1991). Simple slopes indicated that higher levels of MJ use were associated with lower scores on global cognition for HIV-controls ( $b = -0.81$ ,  $SE = 0.25$ ,  $p = 0.002$ ), but there was no effect of MJ on cognition for HIV+ participants ( $b = 0.06$ ,  $SE = 0.22$ ,  $p = 0.79$ ).

Simultaneous simple effects analyses were used to determine the levels of MJ use at which our HIV-serostatus groups differed (Potthoff, 1964; Bauer and Curran, 2005). When the amount of MJ use was zero, the HIV- group displayed significantly better baseline neurocognitive performance than the HIV+ group ( $t = 3.14$ ,  $p = 0.002$ ). However, when MJ use reached 1.43+ grams per week, there were no significant HIV group differences in global cognitive performance ( $t = 1.39$ ,  $p = 0.17$ ).

Investigation into which cognitive domains were driving our global cognitive effects revealed that the HIV by MJ status interaction only was related to the domains of processing speed ( $b = -0.44$ ,  $SE = 0.19$ ,  $p = 0.02$ ) and memory ( $b = -0.34$ ,  $SE = 0.15$ ,  $p = 0.04$ ). Therefore the domains of processing speed and memory were the strongest contributors to this relationship. Memory performance was significantly correlated with fusiform volume,  $r(77) = 0.31$ ,  $p = 0.007$ . There was a non-significant trend towards an inverse relationship between processing speed and volume of the cingulate gyrus,  $r(77) = -0.21$ ,  $p = 0.08$ .

## 4. Discussion

Our primary interest was in quantifying the amount of self-reported MJ use that was associated with abnormalities in brain structure and cognitive performance for both HIV status groups. Considering that findings from most investigations have been comprised of medically healthy adults, and MJ use is common among people living with various chronic diseases, it is important to assess whether previous findings generalize to medical populations. Consistent with previous reports (Küper et al., 2011), HIV status (regardless of MJ use) significantly predicted cingulate thickness, whereby HIV+ individuals demonstrated reduced thickness, as compared to HIV- controls. We additionally found that heavier MJ use (independent of HIV status) was associated with reduced volume of the entorhinal cortex and fusiform gyrus. The interactive effects of HIV\*MJ were found on our global measure of cognition. Overall, the HIV+ group had lower global cognitive scores until reported MJ use increased beyond 1.43 g per week. At this point, there were no HIV group differences in global cognition, suggesting that HIV-negative MJ users demonstrated similar cognitive performance levels as HIV+ users.

Current findings are consistent with our previous study showing that HIV- individuals who reported no use demonstrated greater cognitive performance scores than their HIV+ MJ using counterparts. In our prior study however, global cognitive performance was similar among HIV+ and HIV- light users (Thames et al, 2015). Together, our results do not provide support that HIV+ MJ users are at greater risk for adverse brain or cognitive outcomes compared to HIV- MJ users. Instead, our results suggest that the adverse effects of MJ on neurocognitive performance are more observable in HIV-users.

Regarding a possible mechanism for the HIV by MJ interaction, the HIV+ group showed reduced volume and thickness in various brain structures (although only the cingulate survived multiple comparisons correction), which may explain why we were unable to detect MJ-related adverse effects in the HIV+ group. While the HIV+ group showed reduced volume in the cingulate, MJ use was related to entorhinal cortex and fusiform gyrus. These regions have been implicated in important cognitive processes, particularly memory (Hornberger et al., 2012; Kirchoff et al., 2000), and our results showed that volume of the fusiform was significantly correlated with memory performance. It is possible that damage to overlapping neural systems may reduce the ability to detect incremental/additional cognitive changes due to MJ among individuals with HIV. Certainly, this idea is speculative and requires further examination. Further, our smaller sample size may have contributed to our failure to detect statistically significant interactive effects.

Our results from the HIV- group are consistent with previous reports about the effects of heavy MJ use among medically healthy populations and provide insight into neural structures that are associated with heavy use. Considering that the temporal lobe contains an abundance of CB1 receptors (Herkenham et al., 1990) and has been found to be a key structure in other studies of marijuana use in humans (Cousijn et al., 2012; Koenders et al., 2016; Rocchetti et al, 2013) as well as studies of animal models (Abush and Akirav, 2012; Castellano et al., 2003; Navakkode and Korte, 2014), it is not surprising that this region was found to be most sensitive to changes over the course of 1 year (see Supplemental material).



It is important to note that both HIV groups in this study evidenced intact global neurocognitive functioning. This indicates that MJ use did not result in “global cognitive impairment” per se, but the significant relationships found between MJ use and reduced brain structure and function suggest adverse effects. It is possible that these effects would be exacerbated in patients with moderate-to-severe cognitive impairment. Therefore, the results highlight the effects of persistent MJ use in both PLWH and in non-HIV MJ users in light of intact cognitive functioning.

There are limitations to the current investigation that are worth noting. First, we had a relatively small sample size for characterizing such factors as polydrug use (e.g., MJ + tobacco). Also, as with most studies that use self-report, there may have been inaccurate reporting of the amount of MJ used. Further, we had a disproportionate amount of HIV+ compared to women, which limits the generalizability of the study. Importantly, we did not find gender group differences in our outcomes of interest, which increases our confidence that the gender imbalance in our groups did not affect our findings. Further, this was a cross-sectional study and thus we cannot make inferences about the direction of predicted effects. For example, it could be possible that in our sample, lower cognitive functioning drives heavy MJ use.

Finally, a large proportion of our HIV+ participants spontaneously report that they use MJ for medicinal purposes, with some reporting that they obtained MJ from a medical marijuana dispensary. Although we did not collect data on where MJ was obtained, different preparations of MJ (e.g., different ratios of THC vs. CBD concentrations) may contribute to differential effects in brain structure.

#### 4.1. Conclusions and future directions

The findings presented coincide with prior investigations of morphometric changes that were found as a function of MJ use. This study provides an important contribution to the literature on MJ use in both HIV+ and HIV- populations, as it precisely quantified the degree of use associated with prospective changes in brain structure. Although this study sheds some light with respect to HIV and MJ use, there are several questions that remain for future investigations. One question is whether or not the brain and cognitive changes that result from MJ use change over a longer duration of time, and the degree to which these effects reverse with abstinence. If these effects do reverse, is the degree of recovery somehow different for HIV+ versus HIV- individuals? Considering that the development of cannabimimetic drugs is of particular relevance to HAND, further investigations are needed to determine whether or not CB<sup>2</sup> agonists could reduce inflammation in the human brain such that has been found in animal models (see Kurihara et al., 2006; Montecucco et al., 2008).

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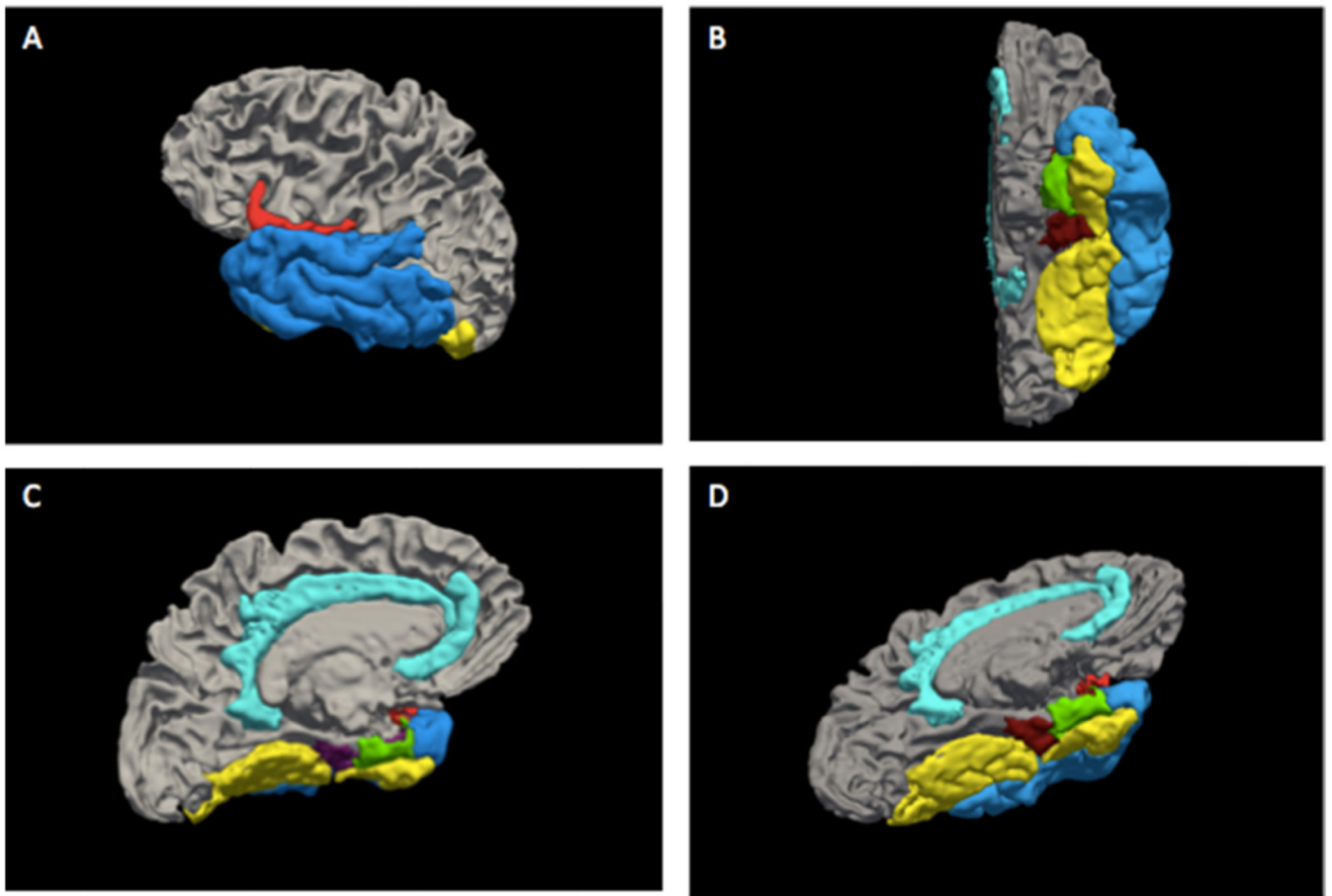
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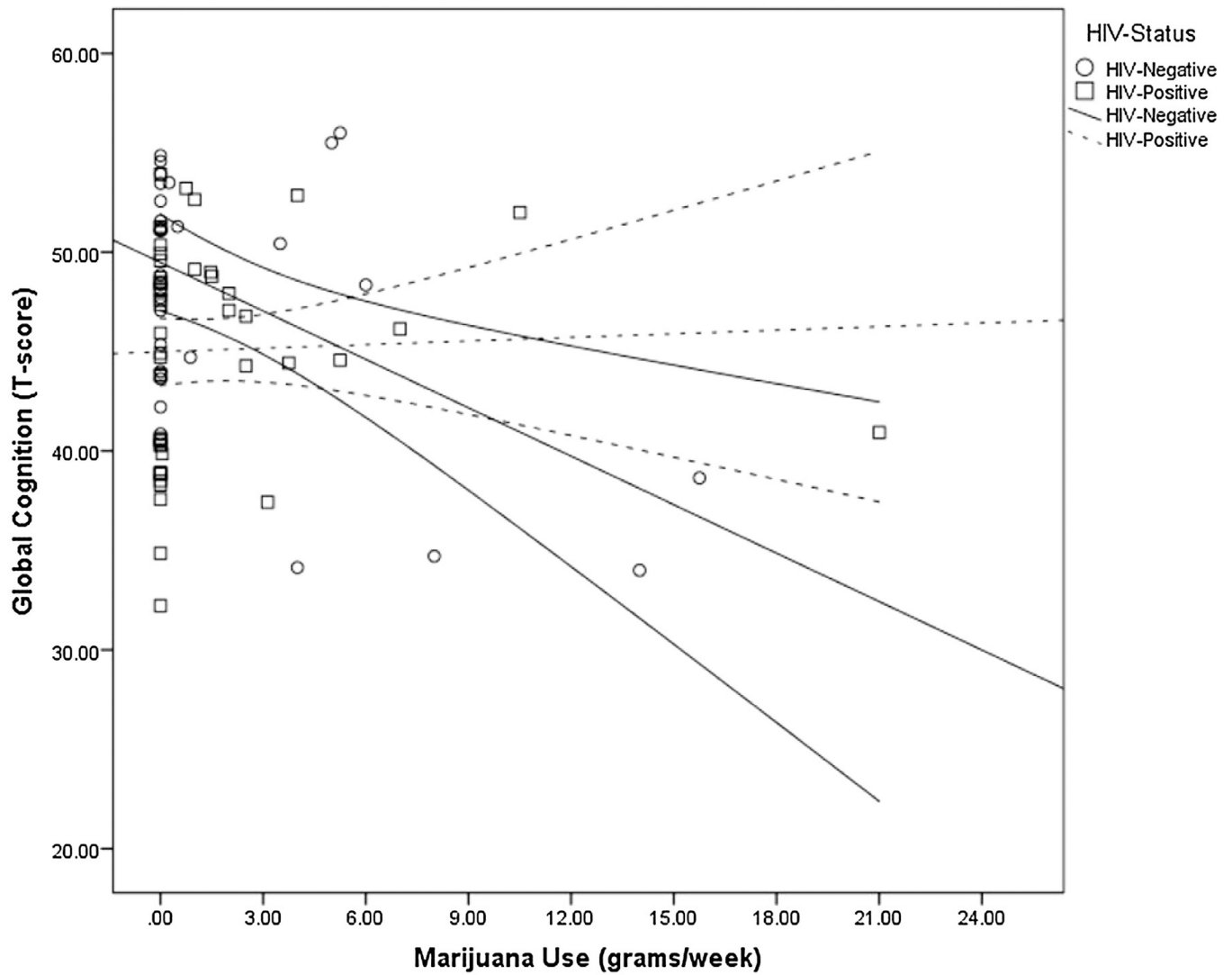
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**Fig. 1.** ROI's shown in (a) sagittal view, (b) lateral view, (c) medial view (d) rotated medial view. At baseline increased MJ associated with reduced volume in Entorhinal Cortex (shown in purple) and Fusiform Gyrus (shown in yellow). HIV status (at  $MJ=0$ ) associated with reduced volume of the Cingulate Gyrus (shown in turquoise). At 12-month follow-up (see supplement data), HIV\*MJ interactive effects found in Temporal volume (shown in blue) and Perirhinal thickness (shown in green).



**Fig. 2.** Regression model predicting global neurocognitive performance as a function of MJ use for both HIV status groups. Statistically significant (i.e.,  $p < 0.05$ ) differences between groups were no longer found after MJ use reached 1.43 g/wk of MJ.

**Table 1**

Participant Demographics by HIV Status (Baseline Sample).

	<b>HIV+ Mean/% (SD) (n = 48)</b>	<b>HIV- Mean/% (SD) (n = 29)</b>	<b>Test statistic, p-value</b>
Age	48.46 (10.23)	46.62 (14.43)	$t = 0.60, p = 0.72$
Education	13.56 (1.99)	14.34 (2.29)	$t = -1.52, p = 0.07$
Gender (% male)	83.33%	51.72%	$\chi^2 = 14.842, p = 0.001^a$
Trans (male to female)	6.25%	0	–
Race/ethnicity (%)			$\chi^2 = 2.0, p = 0.16$
AA-Black	64.58%	48.28%	–
NH-White	35.42%	51.72%	–
Nadir CD4	253.65	N/A	N/A
CD4 count	615.84 (279.20)	N/A	N/A
Viral load (% detectable)	50%	N/A	N/A
Cognitive Performance			
Global Cognition	45.08 (5.32)	47.72 (6.48)	$t = -1.94, p = 0.05^a$
Verbal Fluency	50.94 (9.33)	49.18 (6.74)	$t = 0.956, p = 0.34$
Executive Function	48.22 (6.37)	50.31 (7.39)	$t = -1.30, p = 0.19$
Processing Speed	46.49 (7.14)	49.16 (9.41)	$t = -1.40, p = 0.16$
Attention/WM	46.79 (7.83)	47.79 (6.46)	$t = -0.579, p = 0.56$
Learning/Memory	38.34 (10.33)	45.89 (11.6)	$t = -2.95, p = 0.004$
Gray Matter Volume			
Entorhinal	3873.20 (607.42)	3683.59 (684.68)	$t = 1.25, p = 0.22$
Fusiform	20157.76 (2383.63)	19302.93 (2365.89)	$t = 1.51, p = 0.14$
Gray Matter Thickness			
Cingulate	2.58 (0.12)	2.63 (0.12)	$t = -1.70, p = 0.093$
MJ use	<b>(n = 24)</b>	<b>(n = 13)</b>	
Age of onset	18.27 (6.43)	15.91 (1.70)	$t = 1.81, p = 0.25$
Avg. grams per week over past 4 weeks [Range]	4.08 [0–21]	2.18 [0 – 15.75]	$t = 0.68, p = 0.54$
Days since last use (past 12 months)	1 [1–10]	2[1–13]	$t = 0.75, p = 0.64$
% Past dependence			
Alcohol	17%	10%	$\chi^2 = 0.65, p = 0.42$
Opiates	2%	0%	$\chi^2 = 0.625, p = 0.42$
Sedatives	4%	0%	$\chi^2 = 1.267, p = 0.26$
Marijuana	14%	0%	$\chi^2 = 4.757, p = 0.03^a$
Alcohol use	<b>(n = 21)</b>	<b>(n = 15)</b>	
Avg # drinks past 4 weeks	17.66 (22.22)	18.87 (21.10)	$t = -1.02, p = 0.92$
Tobacco use	<b>(n = 13)</b>	<b>(n = 8)</b>	
Avg # of tobacco products used in the past 4 weeks.	95.31 (88.58)	219.50 (129.37)	$t = -2.621, p = 0.02^a$
Sedative use past 4 weeks	1 (OTC Sleep aid)	0	<i>NS</i>
Opiate use past 4 weeks	4 (Hydrocodone)	2 (Hydrocodone)	<i>NS</i>



	<b>HIV+ Mean/% (SD) (n = 48)</b>	<b>HIV- Mean/% (SD) (n = 29)</b>	<b>Test statistic, p-value</b>
Injection Drug Use past 4 weeks	<b>0</b>	<b>0</b>	<i>NS</i>

<sup>a</sup>Statistical significance p = 0.05

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Regression Statistics of Models Assessing the Main and Interactive Effects of Marijuana Use and HIV Status on Cognitive Performance, Gray Matter Volume and Gray Matter Thickness.

**Table 2**

Dependent Variable	Intercept	Model R <sup>2</sup>	F	df	p
Cognitive Performance					
Global Cognition	49.84	0.17	5.02	3,73	0.003
Gray Matter Volume					
Entorhinal	3952.91	0.40	11.47	4,73	<0.0001
Fusiform	20300.73	0.52	18.60	4,73	0.002