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Synergistic effects of marijuana abuse and HIV infection on neural activation during a cognitive interference task

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Abstract

Marijuana use, which is disproportionately prevalent among HIV-infected persons, can alter activity in fronto-parietal regions during cognitively demanding tasks. While HIV is also associated with altered neural activation, it is not known how marijuana may further affect brain function in this population. Our study examined the independent and additive effects of HIV infection and regular marijuana use on neural activation during a cognitive interference task. The sample included 93 adults who differed on marijuana and HIV statuses (20 MJ+/HIV+, 19 MJ+/HIV–, 29 MJ–/HIV+, 25 MJ–/HIV–). Participants completed a counting Stroop task during a functional magnetic resonance imaging scan. Main and interactive effects on neural activation during interference versus neutral blocks were examined using a mixed-effects analysis. The sample showed the expected Stroop effect for both speed and accuracy. There were main effects of MJ in the right and left inferior parietal lobules, with the left cluster extending into the posterior middle temporal gyrus, and a main effect of HIV in the dorsal anterior cingulate cortex. There was an interaction in the left fronto-insular cortex, such that the MJ+/HIV+ group had the largest increase in activation compared to other groups. Among MJ+, signal change in this cluster correlated positively with cumulative years of regular marijuana use. These results suggest that comorbid HIV and marijuana use is associated with complex neural alterations in multiple brain regions during cognitive interference. Follow-up research is needed to determine how marijuana-related characteristics may moderate HIV neurologic disease and impact real-world functioning.

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Author Contributions

CSM, N-KC, and SAH were responsible for study concept and design. RPB performed the functional magnetic resonance imaging analyses. CSM and SLT assisted with data analysis and interpretation. CSM drafted the manuscript. All authors critically reviewed content and approved the final version for publication.

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Keywords

marijuana; cannabis; HIV; Stroop; inhibitory control; functional magnetic resonance imaging (fMRI)

Introduction

Marijuana, the most commonly abused drug in the United States, is disproportionately prevalent in HIV-infected (HIV+) persons. Across different HIV+ populations, 20–60% currently use marijuana, with 30–50% of users reporting daily use (D'Souza et al., 2012; Mimiaga et al., 2013; Okafor et al., 2017a; Okafor et al., 2017b). As of January 2018, nine states and the District of Columbia have legalized recreational marijuana use and an additional 20 states have legalized medical marijuana. In states with medical marijuana laws, HIV/AIDS or HIV-related symptoms such as cachexia, nausea, and pain are listed as qualifying conditions. Despite the high prevalence of marijuana use, there is little research on how it may impact HIV neurologic disease.

HIV can indirectly damage the brain by infiltrating the central nervous system and triggering an inflammatory cascade (Valcour et al., 2011). Nearly half of HIV+ Americans have neurocognitive impairments that have real-world impacts on daily functioning, including driving ability, employment, and medication adherence (Cattie et al., 2012; Heaton et al., 2010; Thames et al., 2013). These neurocognitive impairments are predictive of increased morbidity and mortality (Vivithanaporn et al., 2010). In the era of combination antiretroviral therapies, impairments are most prominent in the domains of learning, executive functioning, and working memory (Heaton et al., 2011). In particular, HIV+ persons consistently perform more poorly than HIV– controls on the color-word Stroop task, which assesses cognitive interference (Cohen et al., 2017; Crystal et al., 2012; Martin et al., 2004).

Co-occurring marijuana use may exacerbate HIV-associated neurocognitive impairments. An early study found an interactive effect on neurocognitive impairment for marijuana use and HIV disease state, such that weekly marijuana users with symptomatic HIV had the greatest overall impairment (Cristiani et al., 2004). A more recent study reported an interaction effect for frequency of use, with HIV+ persons who were moderate-to-heavy users performing worse than all other groups on learning/memory tasks (Thames et al., 2016). In contrast, another study found that HIV+ persons had worse global cognitive function compared to HIV– controls only when marijuana use was low (Thames et al., 2017). Taken together, these seemingly conflicting results suggest that the neurocognitive effects of marijuana in HIV+ persons are complex.

HIV-associated neurocognitive impairment has been linked to alterations in neural activation observed during task-based functional magnetic resonance imaging (fMRI). Studies using attention, working memory, and executive control paradigms have found greater activation in prefrontal, cingulate, striatal, and parietal regions despite comparable task performance, but less activation and diminished accuracy for the most difficult trials (Hakkers et al., 2017). This pattern of hyperactivation within task-relevant regions and engagement of additional regions has been interpreted as a compensatory mechanism to preserve cognitive

performance in the context of neural injury, which can only be maintained up to a certain level of difficulty (Hakkers et al., 2017). Additional studies focused on cocaine suggest that drug abuse may further exhaust neural resources in HIV+ persons, as evidenced by hypoactivation in task-relevant regions (Meade et al., 2018; Meade et al., 2017; Meyer et al., 2014). However, the effects of marijuana abuse on neural activation patterns have not been examined.

Chronic marijuana use, independent of HIV, can produce deficits in executive control functions that are mediated by a fronto-parietal network. Two systematic reviews reported that chronic marijuana use is associated with deficits across executive functions such as cognitive interference, problem solving, and decision making, though several studies have also reported null findings (Broyd et al., 2016; Crean et al., 2011). Neuroimaging studies suggest that marijuana users have altered activity in fronto-parietal regions when performing cognitively demanding tasks, which is generally expressed as hyperactivity despite comparable behavioral performance (Batalla et al., 2013; Brumback et al., 2016; Martin-Santos et al., 2010). However, studies using the Stroop paradigm, which requires conflict monitoring and inhibitory control, have yielded inconclusive results. In one fMRI study, healthy controls (n=34) showed robust activation in the posterior cingulate cortex during interference trials, while marijuana users (n=50) had more diffuse activity in the anterior cingulate cortex (ACC); however, a statistical comparison of the groups was not presented (Sagar et al., 2015). In another fMRI study of 20 cannabis-dependent men entering outpatient treatment and 20 age-matched controls, the marijuana group had less activation during interference trials in the bilateral dorsolateral prefrontal cortex (dlPFC) and striatum, as well as the right anterior insula, superior and middle temporal gyri, and frontal pole (Kober et al., 2014). Finally, in a positron emission tomography study, recently abstinent marijuana users (n=11) compared to healthy controls (n=11) showed hyperactivity in the hippocampus but hypoactivity in the dlPFC and rostral ACC (Eldreth et al., 2004). Each of these studies used a color-word Stroop, which is not optimized for the constraints of the MRI environment (Bush et al., 2006). While there have been additional studies, group sizes were too small (n < 10) to confidently interpret results (Gruber and Yurgelun-Todd, 2005; Hatchard et al., 2014). In sum, there remains a need to systematically examine the effects of marijuana use on cognitive interference tasks.

Given the high prevalence of marijuana use for both recreational and medical purposes among HIV+ persons, it is important to understand how marijuana may impact neural functioning in this vulnerable population. The present study focused on conflict monitoring and inhibitory control, which was assessed using the counting Stroop. This variant of the classic color-word Stroop test captures both accuracy and reaction time using a button-press instead of speech to minimize head motion during fMRI scanning, and it reliably activates a network of regions involved in attention, response selection, and motor planning (Bush et al., 2006; Matthews et al., 2004; Mayer et al., 2013; Rahm et al., 2013). During interference compared to neutral trials, there is typically increased activation in several regions of the executive control system, including dlPFC, ACC, and posterior parietal cortex (PPC). We hypothesized that HIV infection and marijuana use would each be independently associated with hyperactivity in these executive control regions. Furthermore, we expected HIV to

potentiate the effects of marijuana on neural activation, with greater hyperactivation in task-relevant regions among HIV+ compared to HIV– participants.

Materials and Methods

Participants

The sample included 93 adults aged 18–55 years who were active marijuana users with HIV (MJ+/HIV+, n= 20) and without HIV (MJ+/HIV–, n= 19) or non-marijuana users with HIV (MJ–/HIV+, n= 29) and without HIV (MJ–/HIV–, n= 25). The MJ+ groups met the following criteria: 4 days of marijuana use in the past month and 1 year of regular marijuana use [i.e., consistent use at a frequency of 3 or more days per week (McLellan et al., 1992)]. The MJ– groups met the following criteria: no lifetime cannabis use disorder, no history of regular marijuana use, 0 days of marijuana use in the past 90 days, and a THC-negative drug screen. Alcohol and nicotine use were permitted in all groups, but participants could not have current alcohol dependence. Participants also could have no history of abusing other drugs, including cocaine, amphetamine, benzodiazepines, and opioids, as defined by any of the following: history of regular use, lifetime dependence, use in the past 30 days, or positive drug screen. HIV-negative status was verified by an OraQuick© rapid test, and self-reported HIV-positive status was verified by medical record review.

Additional exclusion criteria were: English non-fluency or illiteracy; <8th grade education; severe learning disability; serious neurological disorders not due to HIV; acute opportunistic brain infections or history of such infections without return to normal cognition; severe head trauma with loss of consciousness >30 minutes and persistent functional decline; severe mental illness; current use of antipsychotic or mood stabilizing medications; MRI contraindications; and impaired mental status.

Procedures

Data were collected as part of two concurrent neuroimaging studies on drug abuse and HIV that had shared sampling and assessment procedures. Participants were recruited via advertisements in local newspapers, websites, community-based organizations, and infectious diseases clinics. After passing a brief pre-screener, individuals completed an in-person screening. Eligible participants returned for the MRI scan and additional assessments. Participants were asked to abstain from marijuana use for >4 hours prior to the scan; the mean number of hours since last use was 23.36 (SD= 13.44). All study groups were represented in each protocol. Although not statistically significant ($X(3)^2= 7.27$, $p= .06$), MJ+/HIV– was underrepresented (8% vs. 25%) and MJ–/HIV+ was overrepresented (50% vs. 25%) in the first protocol. Therefore, protocol was controlled for in analyses. Procedures were approved by the institutional review boards at Duke University and University of North Carolina at Chapel Hill.

Measures

Participants completed clinical interviews, questionnaires, urine drug screening, and pregnancy tests. Module E of the Structured Clinical Interview for DSM-IV-TR identified current and past substance use disorders (First et al., 1996), and the Addiction Severity

Index-Lite assessed history of substance use and associated impairments (McLellan et al., 1992). Timeline follow-back methodology was used to assess substance use in the past 90 days at both the screening and MRI visits (Robinson et al., 2014). The Wechsler Test of Adult Reading estimated premorbid verbal IQ (Wechsler, 2001). The Stroop Color and Word Test was used to assess executive functioning (Golden, 1978), and published norms were used to convert raw interference scores to demographically corrected T-score (Norman et al., 2011). An audio computer-assisted self-interview assessed demographics, smoking behavior, and medical history. Healthcare records were reviewed to confirm no exclusionary neurologic, psychiatric, or medical conditions. For HIV+ participants, we abstracted HIV disease indicators, including date of diagnosis and CD4 cell counts.

fMRI counting Stroop Task

The counting Stroop is a cognitive interference task that was designed for administration during MRI (Bush et al., 1998). Participants were presented alternating blocks of neutral and interference trials. During each trial, the same word was listed vertically 1–4 times, and participants were instructed to indicate as quickly as possible the number of words using a response pad. Interference trials consisted of number words (one, two, three, or four), while neutral trials consisted of animal words (dog, cat, mouse, and bird); the conditions were balanced for word length. Each block contained six randomly selected trials that were presented for 1.5s, and there was a 0.75s fixed interval between trials during which a crosshair was displayed. The single 4-minute run consisted of 16 alternating interference and neutral blocks, with the initial block type randomized across participants. Prior to the fMRI session, participants were trained on the task to ensure comprehension.

MRI data acquisition

MRI data were acquired using a 3.0T GE MR750 scanner with an 8-channel head coil. High-resolution T 1-weighted structural images were acquired with the following parameters: TR= 8.1ms; TE= 3.18ms; FOV= 25.6cm; matrix= 256*256; slice thickness= 1mm; voxel size= 1mm³; and number of slices= 172. Whole-brain blood-oxygen-level-dependent (BOLD) images were collected using high-throughput T2*-weighted echo-planar imaging in the axial plane. Parameters for the two protocols were the same (TR= 2000ms; FOV= 240; matrix= 64*64; slice thickness= 3.8mm; voxel resolution= 3.75mm × 3.75mm × 3.79mm), except there were slight differences for TE (27ms vs. 25ms) and number of slices (35 and 39). Interleaved images covered the entire brain. There was no difference in signal-to-fluctuation noise ratio (SFNR) between protocols [141.33 ± 33.13 vs. 142.57 ± 22.48 ; $t(91) = 0.21$, $p = .84$]. This measure of temporal intensity stability reflects factors like scanner and electronics noise, head motion, and physiological changes.

Quality control

From 99 study completers, 3 were excluded for poor task performance indicative of inattention across multiple blocks (defined as mean accuracy of <67% on neutral blocks). Three additional participants were excluded for SFNR <75. In the final sample (N=93), all participants had a relative mean displacement of <0.20mm (M= 0.053mm, SD= 0.035). DVARS, an index of the rate of change of BOLD signal across the brain at each frame of data, was also calculated using the motion outliers tool in FMRIB's Software Library (FSL)

v6.00. A 2×2 between-subjects ANOVA revealed no main effects of HIV [$F(1,89) = 0.04$, $p = .84$] or MJ [$F(1,89) = 0.18$, $p = .68$] and no interaction effect [$F(1,89) = 0.04$, $p = .84$] for DVARS. Six motion parameters calculated using FSL's MCFLIRT were included as regressors of no interest in first level analyses to control for linear movement across the run, and DVARS was included in third level analyses to control for individual differences in motion.

fMRI Data Analysis

The functional and anatomical data were pre-processed and analyzed using FSL's FEAT (Smith et al., 2004). Preprocessing steps included: motion correction with MCFLIRT; slice-timing correction using Fourier-space time-series phase-shifting; spatial smoothing with a Gaussian kernel of 5mm full-width at half-maximum; high-pass temporal filtering (Gaussian-weighted least squares straight line fitting with $\sigma = 50$ s); grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and skull stripping of structural images with BET. Registration of functional data to the T1-weighted anatomical slices and registration of structural images to the 2mm Montreal Neurological Institute (MNI) standard-space template were done with FLIRT using a 12-parameter affine transformation.

Individual time-series statistical analysis was carried out using FILM with local autocorrelation correction. The interference blocks, serving as the regressor, were convolved with a double-gamma hemodynamic response function. Statistical contrasts of the interference condition compared to the implicitly modeled neutral condition were conducted using a fixed-effects analysis. For visualization, task activation maps for all participants combined were generated using FSL's Local Analysis of Mixed Effects (FLAME 1+2) with a stringent cluster threshold of $Z > 3.5$ and $p < .05$, corrected over the entire brain using Gaussian random field theory (Worsley et al., 1992).

A 2-factor between-subjects general linear model (GLM), implemented using FLAME 1+2, was used to identify main and interaction effects of marijuana and HIV. Age, education, DVAR, and protocol were entered as covariates. In FSL, the interaction is modeled as a 2-group comparison; in this case, the combined effects of MJ+/HIV+ and MJ-/HIV- were compared to the combined effects of MJ+/HIV- and MJ-/HIV+. This model was cluster thresholded at $Z > 2.3$ and a corrected cluster significance level of $p < .05$ (Worsley et al., 1992). For all analyses, the Harvard-Oxford cortical and subcortical structural atlases were used to identify regions within significant clusters (Desikan et al., 2006).

For each significant cluster identified in the ANOVA, percent signal change was extracted using Featquery. Further analyses were conducted in SPSS 24.0. Group averages were examined to determine the direction of effects. Pearson partial correlation tests were run to examine the relation of signal change to clinical variables (cumulative years of marijuana use among MJ+ participants and nadir CD4 count among HIV+ participants). These correlations controlled for age, education, DVAR, and protocol.

Results

Participant characteristics

Table 1 summarizes the sample by group. Overall, participants were 71% male and ranged in age from 20 to 54 years ($M = 37.80$, $SD = 9.30$). The majority were non-Hispanic (96%) and Black (65%). Most had at least a high school diploma or GED certificate (97%), with a mean of 14.30 ($SD = 2.07$) years of education. The groups were comparable on gender and race, but there were significant differences on age and education. Tukey's HSD posthoc tests revealed that MJ-/HIV+ were older than MJ+/HIV+ and MJ+/HIV- (both $p < .01$), and that MJ-/HIV- had significantly more years of education than each of the other groups (all $p < .05$). Age and education were controlled for in all subsequent analyses. There were no significant group differences on premorbid IQ or color-word Stroop interference score (both $p > .05$), suggesting comparable cognitive function.

Among MJ+, participants had used marijuana regularly for 1–30 years, with a mean of 12.36 years ($SD = 7.29$). All participants reported smoking as their primary route of administration, generally as blunts, and none reported oral ingestion in the past 30 days. They had used on an average of 24.41 days the past 30 ($SD = 8.82$, range: 4–30); 62% were daily users. Nearly half (44%) endorsed criteria for current cannabis dependence. There were no significant differences between HIV+ and HIV- on any marijuana use characteristics.

As per inclusion criteria, participants could have no history of abuse of any other illicit drugs or prescription medications. Only thirty percent had used alcohol to intoxication in the past 30 days, with no difference by MJ status [$X^2(1) = 2.57$, $p = .11$]. The frequency of use among drinkers was low ($M = 3.21 \pm 3.07$ days in the past 30). Approximately half of the sample reported daily cigarette use, and MJ+ were more likely than MJ- to smoke cigarettes [$X^2(1) = 17.93$, $p < .001$].

All HIV+ participants were currently in HIV care and receiving antiretroviral therapy. They had been diagnosed with HIV for an average of 9.20 years ($SD = 7.68$, range: 1–29 years), and all initiated care within 6 months of diagnosis. Nadir CD4 cell counts ranged 3–1,037 (Median = 264, IQR = 389), and 41% of participants had a nadir CD4 count < 200 (indicative of progression to AIDS). Current CD4 cell counts ranged 36–1,477 (Median = 705, IQR = 417), and 90% had a suppressed HIV viral load of < 50 copies/mL. There were no significant differences between MJ+ and MJ- on any of these HIV characteristics.

Behavioral performance

The sample demonstrated a significant Stroop effect for both speed [$t(92) = 10.89$, $p < .001$] and accuracy [$t(92) = -3.22$, $p = .002$]. Mean reaction time was slower for interference compared to neutral blocks [0.74 ($SD = 0.12$) vs. 0.70 ($SD = 0.11$)], and proportion correct was lower for interference compared to neutral blocks [0.94 ($SD = 0.07$) vs. 0.96 ($SD = 0.06$)]. Table 2 shows reaction times and accuracy by group. In a series of ANCOVAs controlling for age and education, there were no main or interactive effects of HIV and marijuana (all $p > .05$).

Task-related brain activation

Figure 1 shows the pattern of activation during the counting Stroop task in the sample, and Supplementary Table 1 describes the clusters. For the interference > neutral contrast, there was increased BOLD signal (positive activation) bilaterally in the lateral PFC (middle and inferior frontal gyri); motor cortices (precentral gyrus, superior frontal gyrus, and supplementary motor area); dorsal ACC (primarily paracingulate gyrus); PPC (inferior and superior parietal lobules); and posterior inferior temporal gyrus (ITG). There was also negative BOLD signal (deactivation) in bilateral clusters that encompassed the precuneus; visual cortex (cuneus, lingual gyrus, and occipital pole); posterior cingulate cortex; medial PFC (including rostral ACC, frontal medial cortex, and frontal pole); and anterior middle temporal gyrus (MTG).

Group-level effects (Table 3)

The GLM revealed main effects of marijuana in two clusters centered in the left and right supramarginal gyrus of the PPC (Figure 2a). In both clusters, MJ+ had robust positive activation, while MJ− had minimal signal change. Among MJ+, cumulative years of use was unrelated to percent signal change (partial $r = -0.17$ and 0.15 for left and right clusters, respectively; both $p > .05$).

There was a main effect of HIV in one large cluster encompassing the anterior portion of the dorsal ACC (Figure 2b). While HIV− had robust deactivation, HIV+ had positive percent signal change. Among HIV+, signal change was unrelated to nadir CD4 count (partial $r = 0.14$, $p > .05$).

There was a MJ*HIV interaction effect in one cluster centered in the left anterior insula that extended into the amygdala, orbitofrontal cortex, and inferior frontal gyrus (Figure 2c). Consistent with the modeling of the interaction effect, the MJ+/HIV+ and MJ−/HIV− groups had larger increases in activation compared to the MJ−/HIV+ and MJ+/HIV− groups. To further probe this interaction, we examined the effect of MJ on percent signal change within this cluster separately by HIV status. Among HIV+, there was a strong MJ effect [$F(1,43) = 21.135$, $p < .001$], with MJ+/HIV+ having larger increases in activation compared to MJ−/HIV+ (0.11 vs. -0.04 , respectively). Among HIV−, there was no MJ effect [$F(1,43) = 0.39$, $p = .54$]. Percent signal change was correlated with cumulative years of use (partial $r = 0.38$, $p = .02$). As shown in Figure 3, this correlation was stronger in HIV+ than in HIV−.

Discussion

The results of this study show that regular marijuana users with co-occurring HIV infection are at risk for altered neural activation within multiple brain regions during cognitive interference processing. In the sample overall, we observed the expected increases in BOLD signal during interference compared to neutral trials in regions involved in executive control (lateral PFC, dorsal ACC, and PPC), motor functions (pre-, primary, and supplementary motor cortices), and complex visual processing (ITG). There was also “deactivation” in default mode regions (posterior cingulate, medial PFC, and precuneus), as well as rostral ACC, limbic regions, and visual cortex. While HIV and marijuana were independently

associated with hyperactivity in discrete portions of the executive control system, only persons with co-occurring HIV and marijuana demonstrated hyperactivation in the left fronto-insular cortex. These differences in neural activation were observed despite comparable task performance.

Independent of HIV status, marijuana use was associated with alterations in the PPC. In response to interference compared to neutral trials, marijuana users had larger increases in activation in the right and left supramarginal gyrus, with the left cluster extending into the posterior MTG. These findings are consistent with prior studies on the effects of chronic marijuana use, which generally report alterations in frontal, parietal, and temporal regions during cognitive tasks (Batalla et al., 2013; Brumback et al., 2016; Martin-Santos et al., 2010). Such hyperactivity may serve as a mechanism to compensate for decreased efficiency and neural capacity due to marijuana use (Brumback et al., 2016). Compensatory theories posit that, in order to preserve cognitive function, additional regions that are not typically activated for a specific task must be engaged to maintain performance (Barulli and Stern, 2013). Neural activation in the inferior parietal lobule, and in particular the supramarginal gyrus, is critical to successful inhibitory control (Simmonds et al., 2008), while the left posterior MTG is part of a semantic control network that plays an important role in capturing context-sensitive meaning (Davey et al., 2016; Noonan et al., 2013). Thus, it may be that marijuana users must employ additional neural resources in regions related to cognitive and semantic control to perform the Stroop task at the same level as non-marijuana users.

As expected, we observed a main effect of HIV that encompassed a large portion of the dorsal ACC. As a core region of the executive control system, the dorsal ACC is believed to allocate attentional resources to mediate response selection in the face of competing information-processing streams (Shenhav et al., 2016). While the sample overall had increased BOLD signal in the dorsal ACC, HIV+ participants also showed increased activation in ventral and rostral portions of the ACC that deactivated in HIV- participants. This effect was evident in both marijuana and non-marijuana users. HIV-associated hyperactivity has also been conceptualized using compensatory models (Hakkers et al., 2017). Given the role of the dorsal ACC in supporting optimal allocation of executive control, it may be that HIV+ persons need to engage this region to achieve similar task performance. Surprisingly, there was no relationship between nadir CD4 count, a clinical marker of HIV neurologic disease (Ellis et al., 2011), and signal change. Structural and functional brain alterations are known to occur early in HIV infection (Cao et al., 2015; Wang et al., 2011), but prompt initiation of combination antiretroviral therapies may minimize further damage.

In addition to the independent effects of marijuana and HIV, their co-occurrence appears to be associated with complex alterations in neural functioning. We identified an interaction in the left fronto-insular cortex, such that the effect of marijuana was evident in HIV+ but not HIV- persons. Signal change in this cluster correlated with cumulative years of use, and this effect was more pronounced in HIV+ persons. Prior studies have found that chronic marijuana use is associated with hyperactivity in the insula during attention and response inhibition tasks (O'Leary et al., 2007; Tapert et al., 2007), as well as higher resting-state

functional connectivity in the orbitofrontal network and between insula and executive control regions (Filbey et al., 2014; Harding et al., 2012; Lopez-Larson et al., 2015). Altogether, our results suggest that HIV+ persons are more vulnerable to the long-term effects of regular marijuana use and accumulated exposure to cannabis. While mechanistic studies are needed, HIV infection may reduce neural reserve via chronic low-grade neuroinflammatory processes, resulting in compensatory activation to sustain cognitive function.

Our study has multiple strengths, including the use of a factorial design and comprehensive substance use assessment to isolate the effects of HIV and marijuana. Importantly, participants could have no history of abuse of drugs other than marijuana. However, to ensure generalizability, nicotine and non-problematic alcohol use were permitted. As expected, the MJ+ group was more likely than the MJ- group to smoke cigarettes, and most marijuana users smoked the drug in the form of blunts containing nicotine. As a result, we were unable to control for the independent effects of nicotine. It is possible that our results may be partially driven by co-occurring nicotine use. Future studies should stratify groups by cigarette status and assess nicotine exposure during marijuana administration. Finally, nearly all members of our MJ+ group were characterized by chronic and heavy marijuana use, limiting our ability to examine the potential effects of quantity and frequency of current use. In addition, the sample was predominantly male. Therefore, our results may not generalize to women or individuals with occasional or previous marijuana use.

There are several additional limitations to consider. First, since our version of the counting Stroop task did not include an inter-block interval, we were unable to quantify the degree of activation from baseline. This would more directly test hypotheses related to neural efficiency and capacity in response to increasing cognitive load. Second, the data are from one 4-minute run, which may have limited power to detect group differences. However, this is the duration recommended for the counting Stroop task (Bush et al., 1998), and the task evoked robust activity within expected regions. Third, despite the large overall sample, the sub-groups ranged in size from 19–29, limiting our ability to detect small effects, although we identified robust effects of marijuana and HIV in multiple regions. Finally, since the study was cross-sectional, causality cannot be inferred. It is possible that group differences in neural function preceded the onset of marijuana use and/or HIV infection. Longitudinal studies that track the course of HIV disease and substance use patterns over time are needed.

In conclusion, this study provides evidence that co-occurring HIV infection and marijuana use is associated with complex alterations in neural activation patterns. The effects of marijuana on parietal regions of the executive control network affected HIV+ and HIV- participants similarly. In contrast, alterations in the left fronto-insular cortex were evident only in HIV+ marijuana users. Despite performing the counting Stroop with equivalent speed and accuracy, HIV+ marijuana users had exaggerated hyperactivations in this cluster. Given the role of the component regions in emotional and reward decision making, HIV+ marijuana users may be more prone to impulsive behaviors. Future studies should examine how these alterations may affect real-world functioning, such as employment and medication adherence. Given the high prevalence of marijuana use in HIV+ persons - both

for recreational and medical purposes - more research is needed to determine if factors such as age of onset and quantity/frequency of use moderate neural activation patterns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Mean activation and deactivation maps for the counting Stroop task.

Overall task activation across all participants for: (A) interference > neutral stimuli, and (B) interference < neutral stimuli. Cluster information is described in Supplementary Table 1.

Activation maps were thresholded using clusters determined by $Z > 3.5$ and a corrected cluster significance threshold of $p = 0.05$. The underlying image is the MNI152 2mm standard-space T1-weighted structural template. Images are in radiological orientation (left = right, right = left).

Figure 2. Effects of marijuana use and HIV infection on neural activation during the counting Stroop task.

On the left, images show the clusters that exhibited significant F-values in the 2 (MJ status) by 2 (HIV status) between-subjects general linear model for the interference > neutral contrast. The Z-statistic images were thresholded at 2.3 with a cluster p threshold of 0.05. The underlying image is the MNI152 2mm standard-space T1-weighted structural template, and images are in radiological orientation (left = right, right = left). The four significant clusters are characterized further in Table 3. On the right, bar graphs show the percent BOLD signal change by group (error bars represent standard error from the mean).

Figure 3. Association between neural activation during the counting Stroop task and years of regular marijuana use.

BOLD signal change was extracted from the fronto-insular cluster where the ANOVA identified an HIV*Marijuana interaction effect. The standardized residuals from the partial correlations controlling for age, education, protocol, and DVAR are plotted. These analyses were restricted to MJ+ participants, and HIV+ and HIV- groups are shown separately. The r-values represent the partial correlation coefficients. * $p < .05$, ** $p < .01$.

Table 1.

Sample characteristics of the four study groups (N=93)

General characteristics	MJ+/HIV+ N=20	MJ+/HIV- N=19	MJ-/HIV+ N=29	MJ-/HIV- N=25	Statistic
Male, %	75%	68%	72%	68%	$\chi^2(3)=0.35$
Age in years, M (SD)	33.30 (9.43)	33.63 (6.57)	42.62 (7.68)	38.96 (10.00)	F(3,89)=6.57***
Education in years, M (SD)	13.25 (1.94)	13.95 (1.68)	14.14 (2.22)	15.60 (1.68)	F(3,89)=6.09**
Race, %					$\chi^2(6)=10.24$
African American	65%	68%	72%	52%	
White	35%	16%	28%	32%	
Other/Mixed	0%	16%	0%	16%	
Premorbid IQ, M (SD)	92.95 (18.37)	95.63 (14.63)	93.24 (20.53)	105.40 (15.88)	F(3,89)=2.68
Color-Word Stroop interference, M (SD)	56.47 (15.07)	52.80 (7.15)	51.08 (12.12)	58.27 (11.59)	F(3,89)=1.95
<u>Marijuana use characteristics</u>					
Age initiated regular use, M (SD)	19.40 (4.37)	18.58 (3.44)	N/A	N/A	t(37)=0.65
Years of regular use, M (SD)	12.70 (8.97)	12.00 (5.21)	N/A	N/A	t(37)=0.76
Days of use in past 30 days, M (SD)	24.35 (8.59)	24.47 (9.29)	N/A	N/A	t(37)=0.96
Current marijuana dependence, %	40%	47%	N/A	N/A	$\chi^2(1)=0.22$
Hours since last use at MRI, M (SD)	22.74 (13.90)	22.95 (13.33)	N/A	N/A	t(37)=0.78
<u>Other substance use in past 30 days</u>					
Any alcohol to intoxication, %	40%	37%	17%	32%	$\chi^2(3)=3.66$
Days of use, M (SD) [/]	2.63 (1.85)	4.71 (5.16)	2.80 (1.64)	2.75 (2.38)	F(3,24)=0.72
Regular cigarette use, %	60%	53%	17%	12%	$\chi^2(3)=18.34$ ***
Cigarettes per day, M (SD) [/]	12.42 (6.02)	9.90 (5.47)	12.75 (6.08)	10.00 (5.00)	F(3,25)=0.48
<u>HIV characteristics</u>					
Years since HIV diagnosis, M (SD)	8.30 (8.11)	N/A	9.83 (7.46)	N/A	t(47)=0.50
Nadir CD4 count, Median (IQR)	275.50 (478)	N/A	195.00 (405)	N/A	U=209.00
Current CD4 count, Median (IQR)	685.50 (386)	N/A	705.00 (579)	N/A	U=262.00
Suppressed HIV viral load, %	95%	N/A	86%	N/A	$\chi^2(1)=0.32$

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Table 2.

Behavioral performance on the counting Stroop task across the study groups (N=93)

	MJ+/HIV+ N=20	MJ+/HIV- N=19	MJ-/HIV+ N=29	MJ-/HIV- N=25
<u>Reaction time</u>				
Neutral blocks	0.686 (.026)	0.713 (.026)	0.719 (.022)	0.669 (.024)
Interference blocks	0.731 (.027)	0.754 (.028)	0.774 (.023)	0.704 (.025)
Stroop effect ^I	0.045 (.009)	0.042 (.009)	0.055 (.008)	0.035 (.008)
<u>Accuracy</u>				
Neutral blocks	0.963 (.015)	0.953 (.015)	0.955 (.013)	0.955 (.013)
Interference blocks	0.952 (.015)	0.936 (.015)	0.949 (.013)	0.933 (.014)
Stroop effect ^I	-0.010 (.009)	-0.017 (.010)	-0.006 (.008)	-0.022 (.009)

The reported values are estimated marginal means and standard errors from analysis of covariance (ANCOVA) models controlling for age and education.

^IInterference – Neutral

Table 3.
Effects of marijuana use and HIV infection on BOLD activation during the counting Stroop task

Anatomical region at center of gravity	Other anatomical regions in cluster	MNI coordinates (x, y, z)	Number of voxels	Max Z-score
<u>Main effect of Marijuana</u>				
L supramarginal gyrus	L middle and inferior temporal gyri (temporo-occipital), lateral occipital cortex (inferior division)	-60, -49, 13	1055	3.98
R supramarginal gyrus	none	56, -38, 36	873	4.51
<u>Main effect of HIV</u>				
B anterior cingulate gyrus	B paracingulate gyrus	0, 33, 23	1113	5.13
<u>HIV*Marijuana interaction</u>				
L anterior insula	L amygdala, frontal operculum, frontal orbital cortex, central operculum, precentral gyrus, inferior frontal gyrus	-40, 15, -5	579	3.78

Abbreviations: R= right hemisphere, L= left hemisphere, and B= bilateral

Anatomical labels are from the Harvard-Oxford cortical and subcortical structural atlases in FSL.