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Combined effects of HIV and marijuana use on neurocognitive functioning and immune status

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ABSTRACT

The current study examined the independent and combined effects of HIV and marijuana (MJ) use (no use, light use, and moderate-to-heavy use) on neurocognitive functioning among a convenience sample of HIV-positive (HIV+) and HIV-negative (HIV−) individuals recruited from HIV community care clinics and advertisements in the Greater Los Angeles area. MJ users consisted of individuals who reported regular use of MJ for at least 12 months, with last reported use within the past month. Participants included 89 HIV+ ($n = 55$) and HIV− ($n = 34$) individuals who were grouped into non-users, light users, and moderate-to-heavy users based on self-reported MJ use. Participants were administered a brief cognitive test battery and underwent laboratory testing for CD4 count and viral load. HIV+ individuals demonstrated lower performance on neurocognitive testing than controls, and moderate-to-heavy MJ users performed more poorly on neurocognitive testing than light users or non-users. Moderate-to-heavy HIV+ users performed significantly lower on learning/memory than HIV− moderate-to-heavy users ($M_D = -8.34$; 95% CI: −16.11 to −0.56) as well as all other comparison groups. In the domain of verbal fluency, HIV+ light users outperformed HIV− light users ($M_D = 7.28$; 95% CI: 1.62–12.39), but no HIV group differences were observed at other MJ use levels. HIV+ MJ users demonstrated lower viral load ($M_D = -0.58$; 95% CI: −1.30 to 0.14) and higher CD4 count than non-users ($M_D = 137.67$; 95% CI: 9.48–265.85). The current study findings extend the literature by demonstrating the complex relationship between HIV status and MJ use on neurocognitive and clinical outcomes.

1. Introduction

Approximately, 23–56% of HIV+ individuals report using marijuana (MJ) to alleviate disease-related symptoms and medication side effects (Fogarty et al., 2007), indicating potential benefits of MJ. However, the cognitive consequences remain highly debated (Chang, Cloak, Yakupov, & Ernst, 2006; Lundqvist, 2005). Some studies of healthy populations have not found adverse cognitive effects following abstinence (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Jager, Kahn, Van Den Brink, Van Ree, & Ramsey, 2006), whereas others have reported acute as well as long-term effects on cognition when compared to non-users (Abdullaev, Posner, Nunnally, & Dishion, 2010; Battisti et al., 2010; Gonzalez et al., 2012; Grant, Chamberlain, Schreiber, & Odlaug, 2012; Lisdahl & Price, 2012; Solowij et al., 2002; Thames, Arbid, & Sayegh, 2014; Tapert, Granholm, Leedy, & Brown, 2002). Furthermore, animal studies of Alzheimer's disease and neuroinflammation-induced cognitive damage support the neuroprotective effects of cannabinoids (Fishbein-Kaminietsky, Gafni, & Sarne, 2014; Ramírez, Blázquez, Gómez del Pulgar, Guzmán, & de Ceballos, 2005).

While the adverse effects of MJ on cognitive functioning are still unclear, HIV-associated cognitive compromise is well-documented (Becker, Thames, Woo, Castellon, & Hinkin, 2011; Heaton et al., 2011). However, few investigations have examined the interactive effects of MJ and HIV status on cognitive functioning. One study found that self-reported frequent MJ use was associated with greater memory impairment, but only among symptomatic patients (Cristiani, Pukay-Martin, & Bornstein, 2014). Chang and colleagues (2006) found no additive effects on a measure of reaction time, a finding that was attributed to the relatively asymptomatic status of the HIV+ sample.

For the current study, we examined the combined effects of HIV status and MJ use on neurocognitive and immune functioning among a sample with varying degrees of use.

2. Method

HIV+ ($n = 55$) and HIV− ($n = 34$) participants recruited from HIV clinics and advertisements in the Greater Los

Angeles area. All procedures received institutional approval and participants provided written informed consent. Screeners and questionnaires about neurological and medical history assessed for neurological, psychiatric, and medical confounds (see Thames et al., 2014). We grouped participants based upon their reported MJ use using a similar classification as outlined in Bolla, Brown, Eldreth, Tate, and Cadet (2002): light users [i.e., 2–14 times per week ($n = 42$)], moderate-to-heavy users [i.e., 18–90 times per week ($n = 21$)], and non-users [reported never using MJ ($n = 26$)]. Users had to report using MJ for at least 12 months for inclusion.

2.1. Measures

2.1.1. Drug use

The Brief Drug Use History Form (DHQ; UCLA's Center for Advanced Longitudinal Drug Abuse Research) was used to collect information about drug use. Participants underwent urine toxicology screening using Integrated E–Z Split Key (Innovacon, Inc., San Diego, CA). Participants were excluded if they reported MJ use within 24 hours of cognitive testing or regular use of other substances aside from MJ and alcohol.

2.1.2. Neurocognitive functioning and immune status

Participants were administered a brief cognitive test battery used in prior studies (Thames et al., 2014). Global neuropsychological performance was calculated by averaging t scores from individual cognitive tests (Heaton, Grant, & Matthews, 1991; Miller & Rohling, 2001). Participants provided a blood sample for CD4 and HIV viral load testing.

3. Statistical analyses

3.1. Group comparisons

3.1.1. HIV and MJ use groups

MJ groups did not significantly differ in age, years of education, or race/ethnicity (all $ps > .10$). However, there were significant differences in gender [χ^2 (4, $N = 89$) = 10.81, $p = .03$] and estimated premorbid IQ (WRAT-4 performance) [F (2, 86) = 3.29, $p = .04$], with significantly greater proportion of males in the MJ use groups (light and moderate-to-heavy) than females, and significantly lower WRAT-4 scores among moderate-to-heavy MJ users. There were no significant differences between MJ use groups on alcohol use variables (all $ps > .10$). We included WRAT-4 as a covariate

given its association with overall neurocognitive performance, r (89) = .52, $p < .001$. HIV status groups did not significantly differ in age, education, estimated premorbid IQ, or race/ethnicity (all $ps > .10$). There was no statistically significant interaction between MJ use and HIV on age and education ($ps > .10$). Please see Table 1 for a summary of group differences.

3.1.2. Statistical procedures

We used analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) to examine the independent and interactive effects of MJ use and HIV status on global neurocognitive functioning and individual cognitive domains.

4. Results

4.1. HIV status and MJ use effects on neurocognitive performance

ANOVA demonstrated a significant main effect of MJ use [F (2, 82) = 9.08, $p < .0001$, $\eta_p^2 = .18$] and a non-significant statistical trend towards a main effect of HIV status [F (1, 82) = 3.77, $p = .05$, $\eta_p^2 = .05$] on global neurocognitive performance. There was no significant interaction between HIV status and MJ use on global neurocognitive performance [F (2, 82) = .519, $p = .59$]. Moderate-to-heavy MJ users demonstrated lower global neurocognitive performance than light users and non-users.

MANCOVA demonstrated a main effect for HIV status [F (5, 78) = 3.708, $p = .005$, $\Lambda = .81$, $\eta^2 = .19$], MJ use [F (5, 78) = 2.84, $p = .003$, $\Lambda = .71$, $\eta_p^2 = .16$], and an HIV × MJ interaction effect [F (5, 78) = 2.53, $p = .04$, $\Lambda = .92$, $\eta_p^2 = .08$] on individual cognitive domain scores. Main MJ effects were in the domains of processing speed [F (2, 82) = 6.12, $p = .003$, $\eta^2 = .05$], learning/memory [F (2, 82) = 3.46, $p = .03$, $\eta_p^2 = .07$], and executive functioning [F (2, 82) = 7.22, $p = .01$, $\eta_p^2 = .15$], such that moderate-to-heavy users performed significantly lower in these domains than light users and non-users. There were no significant differences between non-users and light users across these domains. HIV+ individuals performed lower in cognitive domains of learning/memory [F (1, 82) = 15.65, $p < .001$, $\eta_p^2 = .16$], and executive functioning [F (1, 82) = 3.23, $p = .03$, $\eta_p^2 = .07$] than HIV– individuals. There was a significant HIV × MJ interactive effect in learning and memory [F (2, 82) = 8.82, $p = .004$, $\eta_p^2 = .07$], such that HIV+ moderate-to-heavy users demonstrated significantly lower learning and memory performance than all other comparison groups. There was also a significant HIV × MJ interactive effect such that HIV+ light users

Table 1. Participant demographics and group statistics.

HIV/MJ groups

	(a) HIV–/MJ none Mean/% (Std) (n = 12)	(b) HIV+/MJ none Mean/% (Std) (n = 14)	(c) HIV–/MJ light Mean/% (Std) (n = 12)	(d) HIV+/MJ light Mean/% (Std) (n = 30)	(e) HIV–/MJ mod Mean/% (Std) (n = 10)	(f) HIV+/MJ mod Mean/% (Std) (n = 11)
Age	43.16 (3.43)	52.35 (3.17)	53.5 (2.17)	48.6 (3.43)	53.7 (3.71)	48.7 (3.52)
Education	15.08 (2.23)	13.07 (0.82)	13.33 (2.21)	14.27 (2.13)	12.96 (1.66)	12.27 (1.72)
Gender (% male)	45%	85%	75%	95%	100%	54%
Race/ethnicity (%)						
AA-Black	50%	57%	58%	66%	30%	72%
NH-White	36%	42%	41%	33%	70%	27%
Nadir CD4	N/A	233.09 (1.70)	N/A	281.72 (172.92)	N/A	176.75 (132.03)
CD4 count	N/A	490.4 (275.71)	N/A	609.64 (265.11)	N/A	646.50 (258.80)
Viral load (log)	N/A	2.46 (1.36)	N/A	1.79 (.85)	N/A	1.97 (1.18)
Length of HIV	N/A	10.1 (3.4)	N/A	12.13 (1.9)	N/A	12.98 (2.2)
Global NP	46.79 (4.45)	45.35 (4.74)	49.52 (4.26)	46.12 (4.05)	42.72 (4.07)	41.46 (5.89)
Attention	44.42 (2.38)	42.52 (2.04)	46.22 (2.20)	44.95 (1.42)	43.67 (2.48)	43.73 (2.36)
Processing speed	50.18 (2.15)	50.31 (1.84)	51.29 (1.98)	47.53 (1.28)	43.96 (2.24)	42.53 (2.13)
Learning/mem	41.48 (2.58)	39.90 (2.21)	49.66 (2.38)	38.13 (1.34)	41.26 (2.69)	32.92 (2.56)
Executive	50.04 (1.99)	46.95 (1.73)	50.70 (1.84)	47.32 (1.19)	42.39 (2.08)	42.06 (1.97)
Fluency	49.85 (2.76)	51.08 (2.37)	48.78 (1.55)	56.06 (1.65)	46.68 (2.88)	47.41 (2.73)
BDI-II	6.56 (2.20)	7.50 (5.99)	8.0 (4.97)	9.43 (9.08)	10.43 (4.67)	13.45 (8.5)
%Past dependance						
Alcohol	0	0	50%	14%	75%	18%
Stimulants	0	0	0	0	0	0
Opiates	0	14%	0	7%	0	0
Sedatives	0	0	0	7%	0	0
Alcohol use						
# Days past 4 weeks	3.5	1.2	3.2	8.3	10	4.8
# Drinks per day	2.0	1.5	2.0	2.5	2.0	2.8

outperformed HIV– light users in verbal fluency, but no HIV group differences were found at other MJ use levels in the domain of verbal fluency [$F (2, 82) = 10.24$, $p = .001$, $\eta_p^2 = .09$]. See Figure 1.

4.1.1. MJ use group differences on HIV-disease markers

There were no statistically significant differences between MJ use groups on Nadir CD4 [$F (2, 52) = 1.13$, $p = .32$]. Non-users demonstrated significantly lower current CD4 than light or moderate-to-heavy users [$F (2, 52) = 3.14$, $p = .04$]. Higher viral load was found among non-users compared to light and moderate-to-heavy users, $F (2, 52) = 3.76$, $p = .03$.

5. Discussion

The current study found main effects for both HIV status and MJ use on neurocognitive functioning. HIV+ moderate-to-heavy users performed significantly worse on

learning/memory than other comparison groups, whereas HIV+ light users performed significantly better on verbal fluency than HIV– light users. HIV+ MJ users (light and moderate-to-heavy) evidenced higher plasma CD4 and lower viral load than HIV+ non-users, suggesting healthier immune functioning. This is consistent with a recent investigation by Costantino et al. (2012) that found a 40% reduction in HIV-1-infected CD4+ cells that were pretreated with a cannabinoid receptor 2 agonist.

Nevertheless, there was a trend for moderate-to-heavy MJ use to be associated with worse performance on cognitive functioning for HIV+ and HIV– individuals, which is consistent with previous reports (Bolla et al., 2002; Cristiani et al., 2014; Solowij et al., 2002). Light users on average demonstrated better performance than heavy users, but it is unclear why HIV+ light users outperformed HIV– light users in the domain of verbal fluency. We should note that although the performance differences were statistically significant, from
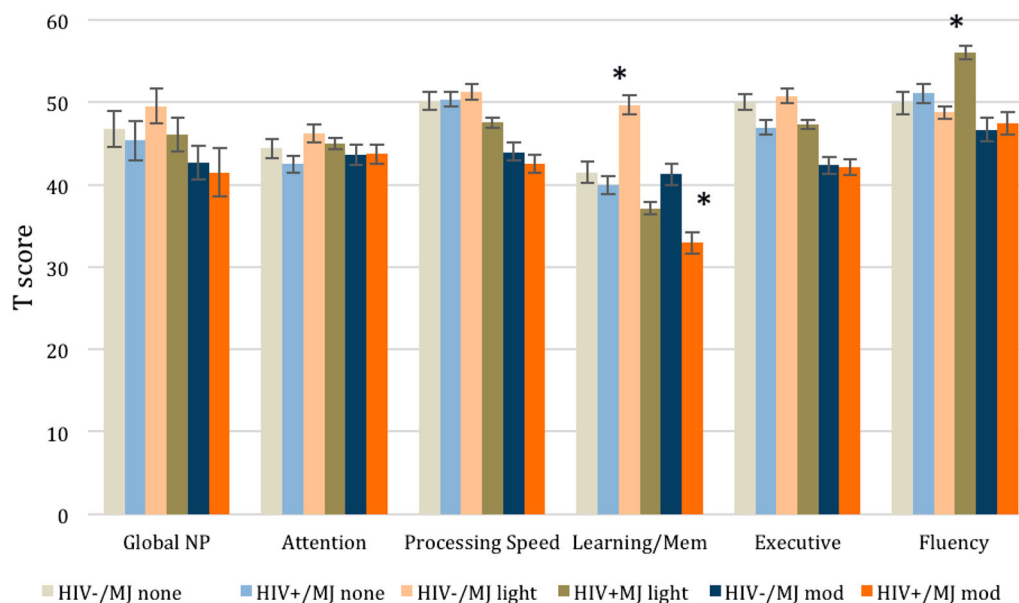
Figure 1. HIV status and MJ use effects on neurocognitive performance. *Significant at FDR corrected $p < .05$.

a clinical standpoint, the scores obtained from the HIV+ light users ($T = 56.06$; 73rd %ile) and HIV− light users ($T = 48.78$; 47th %ile) fall well within the average range.

These results highlight the complex relationship between MJ use and neurocognitive functioning as a function of chronic disease. If light or occasional MJ use protects against disease progression or helps with maintaining adequate immune functioning (perhaps through reducing inflammation) without associated cognitive compromise, such use may have a neuroprotective role in several neuroinflammation related diseases (Klein, 2005).

However, the mechanisms by which MJ act upon immune and neurocognitive functioning cannot be determined from the current study. Further, our sample was from a region that has legalized the use of medical MJ. Perhaps there is more variability in the sources and preparations of MJ used among our sample in comparison to prohibited areas. Finally, we were unable to gather information about age of onset of MJ use and our abstinence period was very short (24 hours). This limits our interpretation as we cannot determine if moderate-to-heavy smokers performed worse on cognitive testing as a function of starting at an earlier age, or if the observed effects would remain after a prolonged period of abstinence. In a previous study, we found that individuals who abstained from smoking cannabis for four weeks continued to demonstrate deficits in executive functioning, although most other performances were similar to non-users (Thames et al., 2014).

In sum, based on the needs of this population and the rapidly advancing legislation of medicinal cannabis use,

there is a pressing need for future investigations to isolate the benefits for medicinal purposes. There is a mix of low-quality and moderate-quality evidence supporting the therapeutic effects of cannabinoids across clinical trials (Whiting et al., 2015). As more studies adhere to CONSORT guidelines, appropriate dosage levels (based upon CB receptor effects), formulations, and delivery mechanisms may be established.

Disclosure statement

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