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Short Communication

Cannabis and cue-induced craving in cocaine-dependent individuals: A pilot study

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ABSTRACT

Background: Cannabis consumption is common among cocaine users; however, little is known about its effect on cocaine craving. The objective of this study was to assess whether cannabis co-use is associated with lower cue-induced cocaine craving in non-treatment-seeking cocaine-dependent individuals.

Methods: Data from twenty-eight cocaine-dependent men were analyzed in this pilot study. Cocaine-dependent subjects (n = 12) were compared with cocaine-dependent subjects who also abused or were dependent on cannabis (n = 16). After at least 72 h of cocaine abstinence, verified using the Timeline Followback and a drug screening test, subjects participated in a functional magnetic resonance imaging session during which neutral and drug cue video sequences were presented. Each sequence comprised four video blocks alternating with resting blocks. We report here subjective craving measures that were collected using the Visual Analog Scale, administered before and after each video block as per standard craving measurement paradigms.

Results: Cocaine craving was successfully induced, with no significant difference in cue-induced craving between the two groups. However, post-hoc analyses revealed a significant increase in pre-video cocaine craving scores over time among individuals with cannabis use disorders.

Conclusion: We could not highlight significant differences in cocaine craving induction between groups, but we observed a possible deficit in craving decay in the cocaine and cannabis group. In light of this finding, methodology of craving assessment in non-treatment-seeking users, particularly when different substances are combined, should possibly include outcomes linked to craving decay. Studies examining the association between cocaine craving decay and other outcome measures, such as relapse, are also warranted.

1. Introduction

Cocaine dependence is a chronic disorder associated with various neurobiological changes and a long-term sensitivity to relapse. A number of factors such as anxiety and drug-related stimuli are known to induce an intense desire to use drugs (called craving) and to trigger relapse in cocaine-dependent subjects (Sinha, 2009a,b).

Accumulating evidence suggest that the endocannabinoid system (ECS) may be involved in cocaine addiction (Olière, Jolette-Riopel, Potvin, & Jutras-Aswad, 2015). Nevertheless, whether and how ECS modulation from cannabis use can alter cocaine craving remains controversial. In Brazilian studies observing crack users with concomitant cannabis use, participants reported that cannabis helped with reducing undesirable effects, subsiding cravings, and facilitating withdrawal from crack (Gonçalves & Nappo, 2015; Labigalini, Rodrigues, & Da Silveira, 1999). These results are in line with preclinical findings suggesting that delta9-tetrahydrocannabinol (delta9-THC) and cannabidiol (CBD) administration potentiated the extinction of cocaine-conditioned place preference in rats (Robinson & Berridge, 1993; Parker, Burton, Sorge, Yakiwchuk, & Mechoulam, 2004). However, other studies, mostly conducted in abstinent populations undergoing treatment in a controlled environment, highlighted that cannabis could contribute to cross-sensitization of craving in cocaine users (Fox, Tuit, & Sinha, 2013), to cocaine withdrawal and craving during detox-

Abbreviations: CHUM, Centre Hospitalier de l'Université de Montréal; ECS, endocannabinoid system; SCID-IV, Structured Clinical Interview DSM-IV; Delta9-THC, delta9-tetrahydrocannabinol; CBD, cannabidiol; CMG, cocaine + marijuana group; CG, cocaine only group; TLFB, Time Line Follow-Back self-report; VAS, Visual Analog Scale; BPRS, Brief Psychiatric Rating Scale; CCQ-brief, Cocaine Craving Questionnaire-brief version; MCQ, Marijuana Craving Questionnaire; CSSA, Cocaine Selective Severity Assessment; PANAS, Positive and Negative Affect Schedule; PRE-VAS, pre-video visual analog scale score; POST-VAS, post-video visual analog scale score; fMRI, functional magnetic resonance imaging

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ification (Viola et al., 2014), and to an increased risk of relapse and re-hospitalization after treatment (Aharonovich et al., 2005).

Intriguingly, little is known about the effect of cannabis in non-treatment-seeking cocaine-dependent individuals. Therefore, using a standard craving induction paradigm (Sayette et al., 2000; Sinha, 2009a,b), we conducted a pilot study to examine the effect of cannabis on cocaine cue-induced responses in non-treatment-seeking cocaine users. Here, we specifically report pilot data comparing craving induction and subjective craving outcome measures between cocaine-dependent subjects (CG) and cocaine-dependent subjects who also abused or were dependent on cannabis (CMG). We hypothesized that the CMG would report lower subjective cocaine craving scores compared to subjects with cocaine dependence only.

2. Methods

2.1. Participants

Participants were recruited at the Centre Hospitalier de l'Université de Montréal (CHUM) clinical and research programs as well as through flyers, web and community advertisements. Eligibility criteria included being at least 18 years old with a current cocaine dependence asserted using the Structured Clinical Interview DSM-IV (SCID-IV) (Lobbestael, Leurgans, & Arntz, 2011). 66 subjects were met for eligibility. Among those, 28 men fully met the eligibility and completion criteria for inclusion in the analyses. If the eligible participants also met the SCID-IV cannabis abuse/dependence criteria and reported cannabis consumption during the last three-months and at least 25 days/month, they were assigned to the CMG ($n = 16$). Eligible subjects not meeting the cannabis abuse/dependence and consumption criteria were assigned to the CG ($n = 12$). Except for nicotine, subjects were deemed not eligible if they had another substance dependence requiring pharmacological treatment during the study. Drug-screen and Time Line Follow-Back (TLFB) (Sobell, Toneatto, Sobell, Leo, & Johnson, 1992; Robinson, Sobell, Sobell, & Leo, 2014) were used to confirm eligibility. In addition, subjects were excluded if they reported a current psychotic or manic episode, elevated suicide-risk, history of neurological disease, contraindications to functional magnetic resonance imaging (fMRI), or if they reported the use of psychotropic medication that could alter craving. Subjects received 10$ for compensation during the first screening visit and 30$ with an additional 40$ gift card on the second visit. The study was approved by the CHUM institutional review board and only subjects who signed informed consent participated in the study.

2.2. Procedure and measures

During the initial visit, sociodemographic data was collected, subjects were screened for eligibility and the Severity of Dependence Scale (SDS) (Gossop et al., 1995) was administered to assess the severity of substance dependence. A 72-hour period of abstinence from cocaine and any substance other than nicotine was requested in both groups prior to the second study session. In the CMG only, cannabis was allowed up to the time of the second visit. Drug-screen and TLFB were administered during the second visit to reassess substance use. Mental health status, craving, cocaine withdrawal symptoms and affect were assessed using the Brief Psychiatric Rating Scale (BPRS) (Kay, Fiszbein, & Opler, 1987), the Cocaine Craving Questionnaire-brief version (CCQ-brief) (Paliwal, Hyman, & Sinha, 2008), the Marijuana Craving Questionnaire (MCQ) (Heishman et al., 2009), the Cocaine Selective Severity Assessment (CSSA) (Kampman et al., 1998), and the Positive And Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988). Subjects were then invited to participate in the fMRI cue-induced craving session.

Participants were instructed to lie down, watch the videos and answer the questions presented to them visually. All participants were presented the same two video sequences in pseudo-randomized order (Maas et al., 1998). One sequence depicted individuals in everyday life situations (neutral) while the other showed individuals preparing and using cocaine in multiple contexts (drug-cue). Each sequence, totaling 870 s, included four different 105-second video blocks alternating with four relaxation blocks representing clouds moving in the sky (rest). Resting blocks lasted 105 s. The sequence ended with a video block and the last 30 s were devoted to the last craving scoring. Relaxation techniques, comprising visualization and deep breathing, were used between sequences and at the end of the session to help with craving decay. Using the Visual Analog Scale (VAS), participants were asked to orally score their level of craving from 0 (representing no craving at all) to 10 (extreme craving) upon the visual presentation of the question once before (PRE-VAS) and once after (POST-VAS) each video block, for a total of eight times (PRE-VAS: blocks 1–4 and POST-VAS: blocks 1–4) per sequence.

2.3. Data analysis

Statistical analyses were conducted using the IBM SPSS statistics 24.0 software. The statistics included frequency distributions and mean ± standard deviation (± SD). For the descriptive sociodemographic and clinical data, group comparisons were performed using the Fisher test for categorical variables and the Mann-Whitney test for continuous variables. We calculated the delta (Δ) score change by subtracting the PRE-VAS from the POST-VAS craving scores for each video block and by calculating the mean of the entire acquisition for neutral and cocaine videos. Most craving induction studies use standard paradigms, comparing craving measurements immediately before and after cue exposure (Sayette et al., 2000; Sinha, 2009a,b). The Mann-Whitney/Wilcoxon tests were used to compare the mean Δ change in VAS craving scores within and between groups. The statistical significance threshold was set at an alpha value of 0.05 (two-sided). In both groups, the mean PRE-VAS craving scores were compared using a two-way analysis of variance for repeated measures (Two-way ANOVA-RM; factors: time and group) and a post-hoc Bonferroni test for multiple comparisons.

3. Results

A descriptive analysis of the sociodemographic and clinical characteristics of each group is presented in Table 1. Compared to CG, only the mean number of days since last cocaine use before fMRI was significantly higher in the CMG (CG: 5.6 vs CMG: 8.3, $P = 0.05$). There was no significant difference between groups for psychiatric symptoms, recent craving, cocaine withdrawal symptoms and affect (Table 1). The mean Δ changes in VAS craving scores during the cue-induced craving session are illustrated in Fig. 1A. Craving induction was significant within both groups (CG $Z = -2.91$, $P = 0.004$; CMG $Z = -2.77$, $P = 0.006$), but we found no significant difference between groups for the neutral or drug-cue videos. Since there was a pattern of increasing mean PRE-VAS craving scores over time during the drug video with a trend that was more evident in the CMG than in the CG (Fig. 1B), we conducted further analyses to examine the effect of cannabis use on PRE-VAS craving scores change over time. A two-way ANOVA-RM revealed a significant effect of time ($F_{3,\ 78} = 16.4$, $P < 0.001$) and time × group interaction ($F_{3,\ 78} = 3.3$, $P = 0.023$) for PRE-VAS craving scores, but the main effect of group was not statistically significant ($F_{1,\ 26} = 0.75$, $P = 0.394$). Importantly, a *post-hoc* analysis revealed a significant difference in craving scores mainly driven by the CMG when comparing PRE-VAS1 and PRE-VAS2 to 4 ($P \leq 0.001$), using Bonferonni adjustment for multiple comparisons. Among the CMG, PRE-VAS1 was significantly lower than PRE-VAS2 ($P = 0.040$), PRE-VAS3 ($P = 0.006$) and PRE-VAS4 ($P < 0.001$), while PRE-VAS2 was significantly lower than PRE-VAS4 ($P = 0.037$), again adjusting for multiple comparisons. By including the time since last cocaine use as