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Research report

Combined effects of marijuana and nicotine on memory performance and hippocampal volume

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HIGHLIGHTS

- Examined drug effects of tobacco, marijuana and combined marijuana + nicotine use.
- Hippocampal volumes were smaller in marijuana users (with or without nicotine).
- Abnormal brain-behavior relationships in combined marijuana + nicotine users.

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ABSTRACT

Combined use of marijuana (MJ) and tobacco is highly prevalent in today's population. Individual use of either substance is linked to structural brain changes and altered cognitive function, especially with consistent reports of hippocampal volume deficits and poorer memory performance. However, the combined effects of MJ and tobacco on hippocampal structure and on learning and memory processes remain unknown. In this study, we examined both the individual and combined effects of MJ and tobacco on hippocampal volumes and memory performance in four groups of adults taken from two larger studies: MJ-only users ($n = 36$), nicotine-only (Nic-only, $n = 19$), combined marijuana and nicotine users (MJ + Nic, $n = 19$) and non-using healthy controls ($n = 16$). Total bilateral hippocampal volumes and memory performance (WMS-III logical memory) were compared across groups controlling for total brain size and recent alcohol use. Results found MJ and MJ + Nic groups had smaller total hippocampal volumes compared to Nic-only and controls. No significant difference between groups was found between immediate and delayed story recall. However, the controls showed a trend for larger hippocampal volumes being associated with better memory scores, while MJ + Nic users showed a unique inversion, whereby smaller hippocampal volume was associated with better memory. Overall, results suggest abnormalities in the brain-behavior relationships underlying memory processes with combined use of marijuana and nicotine use. Further research will need to address these complex interactions between MJ and nicotine.

1. Introduction

Marijuana (MJ) and tobacco products remain two of the most widely used substances worldwide. In the U.S., combined use of both substances is upwards of 60–70% in MJ users and more than five times as likely as measured by past month use in tobacco users [1,2]. Moreover, in some countries, smoked MJ joints are almost exclusively mixed with tobacco [3]. Despite the widespread prevalence of MJ and tobacco co-use, interactive effects of marijuana and nicotine are scantly characterized in the existing literature and lacking direct comparisons of separate (MJ-only, Nicotine-only) and combined uses (MJ + Nicotine) is a limitation in most studies of marijuana use.

Individually, MJ and tobacco are associated with changes to brain structure and function. Structural neuroimaging studies in MJ users have indicated that volumes of several brain areas are smaller in heavy MJ users [4–8], especially in areas enriched with cannabinoid type I (CB1) receptors such as medial temporal lobe structures [9]. Of these structures, the hippocampus appears to be particularly sensitive to heavy marijuana use. Delta9-tetrahydrocannabinol (THC), the primary psychoactive component in marijuana, which binds to CB1 receptors, is associated with

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cell shrinkage and damage to DNA strands in THC-treated hippocampal neuron cultures [10]. The association of these alterations, such as smaller hippocampal volume with greater lifetime duration of use and cumulative amount [4,8] as well as with recent use [11], suggest that these changes are consequences of exposure to MJ. A recent study by Smith et al. [12] examined the interaction between cannabis use and schizophrenia on hippocampal morphology and found a main effect of cannabis use such that altered hippocampal shape was found in both cannabis users with and without schizophrenia. Moreover, these hippocampal differences were related to poorer episodic memory performance emphasizing the relationship between hippocampal morphology and memory. Taken together, smaller brain volumes in MJ users may reflect potential neurotoxic influence of exogenous cannabinoid exposure.

Relative to MJ, less is known about structural brain changes specific to chronic nicotine use. However, existing studies report lower gray matter densities across widespread areas (e.g., prefrontal cortex, cingulate gyrus, parietal lobe, cerebellum, thalamus, striatum and medial temporal lobe) in tobacco smokers [13–15]. Animal models of rats exposed to nicotine show reduced cell numbers, increased markers of apoptosis and alterations in synaptic activity in these regions [16,17]. These regions express dense levels of acetylcholine receptors that are primary binding targets for nicotine, which further supports the potential for nicotine-related brain changes. Thus, it is likely that similar to MJ's effects, reported morphometric changes result from nicotine-related neurotoxicity.

In addition to structural changes, MJ and tobacco have also been individually associated with declines in cognitive function. Existing studies suggest that tobacco use is associated with impaired working memory, attention, and verbal abilities [18,19] that map on to brain structures that undergo changes due to tobacco use (e.g., frontal and parietal cortices, striatum and hippocampus). In terms of MJ's effects on cognition, studies have reported widespread deficits across various domains such as memory [20], attention [21], and learning [22] that are dependent on CB1 receptor activation [23]; however, deficits in working memory appear to be the most consistent [24–27]. While individual studies provide evidence for neurocognitive consequences of MJ and nicotine, the independent drug effects may not generalize to the context of combined use. Interactions between the two substances have been described at the cellular level wherein CB1 and nicotinic acetylcholine (nACH) receptors are densely co-localized in hippocampal regions and both are involved in a diverse set of modulatory processes (for review see Viveros et al., 2006 [28]). For example, chronic nicotine treatment in rats results in altered endocannabinoid levels in the brain [29]. There is also pharmacological evidence that cannabinoids alter nicotinic-acetylecholinergic receptor response [30]. Moreover, Valjent, et al. [31] noted altered fear, withdrawal, and tolerance behaviors in rats co-treated with THC and nicotine, suggesting functional-biochemical interactions. Taken together, there is convergent evidence from human, animal and pharmacological studies supporting the potential for additional consequences on the integrity of the hippocampal structure and function with combined MJ and nicotine use. However, to date, this has not yet been directly examined. In this study, we aimed to characterize the differential and combined impact of marijuana (MJ) and nicotine (Nic) on hippocampal morphometry and memory function among marijuana-only users, nicotine-only users, and comorbid marijuana and nicotine users (MJ + Nic) with a non-using comparison control group. As a primary aim, we compared groups on hippocampal volume. To then further characterize any difference found in hippocampal volumes, we also compared groups on memory performance and examined relationships between morphometry, memory and substance use patterns. Given findings from existing literature, we anticipated that MJ and nicotine individually and in combination would be associated with smaller hippocampal volumes and poorer memory scores that are inversely related to substance use patterns [4,8,24–27].

2. Materials and methods

2.1. Participants

Participants were recruited through flyers and advertisements in the Albuquerque, New Mexico metro area. The community subsample used for this study originated from two larger studies conducted at the University of New Mexico (UNM; see [32]). Informed consent was provided by all of the participants in accordance with the Institutional Review Board (IRB) at UNM. Participants were compensated for their time. To be eligible for the study, all individuals had to meet the following criteria: (a) be between the ages of 18 and 50 years; (b) be right-handed; (c) have no magnetic resonance imaging (MRI) contraindications (e.g., no metallic implants, pregnancy, claustrophobia, etc.); (d) have no symptoms of psychosis (via SCID psychosis screen) and (e) be fluent in both oral and written English. Furthermore, individuals with fewer than 10 years of education, IQs less than 75, or illicit drug use (other than marijuana) were excluded from our sample. We were interested in differences resulting from regular, heavy marijuana and nicotine use rather than from recreational marijuana and nicotine use. To that end, the marijuana users were also required to report using marijuana (verified by urinalysis) at least 4 times per week over the past six months. Nicotine users were included if they reported nicotine use (verified by carbon monoxide breath monitor) of 10 or more times daily and had less than three months of abstinence in the past year. Controls were included if they reported no marijuana use occasions and no tobacco use occasions in the preceding three months, and did not meet criteria for any drug or alcohol abuse or dependence according to the Structured Clinical Interview for DSM-IV disorders.

For our study, participants were categorized into four groups based on substance use: MJ (marijuana users), NIC (nicotine users), MJ + NIC (marijuana and nicotine users), and non-using controls (Table 1). The combined chronic marijuana and nicotine smoking group (MJ + NIC) was derived from the two studies, with participants having to meet criteria for both chronic marijuana and frequent nicotine use to be part of this group.

2.2. Study procedures

The study took place over two separate visits. The first visit included assessments of substance use history and neuropsychological tests. The second visit was scheduled three days after the first visit and consisted of an MRI scan. Participants were required to abstain from MJ and illicit drugs between the two visits so that MRI and cognitive measures did not reflect effects of acute intoxication. This resulted in a ~72-hour abstinence period confirmed by self-report. To promote compliance with the 72-hour abstinence from marijuana, we followed a bogus pipeline by collecting a urine cannabis toxicity screen before and after abstinence (visit 1, visit 2). While the urinalysis is insensitive to 72-hour abstinence, this method has been shown to increase accuracy of self-report (17). Only those who reported 72-hour abstinence were included in the study.

Participants were also asked not to use caffeine or tobacco for two to four hours prior to their brain scan and neither were permitted during their MRI appointment. During session two, each participant had a head MRI scan and each was administered a brief