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Differences in regional blood volume during a 28-day period of abstinence in chronic cannabis smokers

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Abstract

Cerebral blood volume (CBV) studies have provided important insight into the effects of illicit substances such as cannabis. The present study examined changes in regional blood volume in the frontal and temporal lobe, and the cerebellum during 28 days of supervised abstinence from cannabis. Dynamic susceptibility contrast MRI (DSCMRI) data were collected on 15 current, long-term cannabis users between 6 and 36 h after the subjects' last reported cannabis use (Day 0), and again after 7 and 28 days of abstinence. Resting state CBV images were also acquired on 17 healthy comparison subjects. The present findings demonstrate that at Day 7, cannabis users continued to display increased blood volumes in the right frontal region, the left and right temporal regions, and the cerebellum. However, after 28 days of abstinence, only the left temporal area and cerebellum showed significantly increased CBV values in cannabis users. These findings suggest that while CBV levels begin to normalize with continued abstinence from cannabis, specifically in frontal areas, other temporal and cerebellar brain regions show slower CBV decreases.
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1. Introduction

Cannabis research remains an important area of investigation since it is the most widely used illicit drug in the United States (NIDA, 2005; SAMHSA, 2004). One area of interest has focused on the effects of cannabis on the neurovascular system. Specifically, the quantitative measurement of cerebral perfusion is critical for the study of both normal and impaired human brain function; cerebral blood volume (CBV) and cerebral blood flow (CBF) studies have provided important insight into the acute and chronic neurobiologic effects of illicit drugs. Previously, we reported that recently abstinent cannabis users demonstrated significantly increased blood volumes relative to comparison subjects in the right frontal region, left temporal region and

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cerebellum (Sneider et al., 2006). However, no studies, to our knowledge, have examined the effects of chronic heavy cannabis use on the cerebral vasculature after an extended period of abstinence.

A number of prior investigators have focused on the acute effects of cannabis on cerebral blood flow. These studies used either ^{133}Xenon inhalation or ^{15}O-water and Positron Emission Tomography (PET) to measure cerebral blood flow both before and after intravenous infusion of delta-9-tetrahydrocannabinol (Δ^9-THC) or after smoking marijuana cigarettes or placebo (for review, see Quickfall and Crockford, 2006). In particular, work from Mathew and colleagues found increased CBF, predominantly in frontal regions, the insula, cingulate gyrus and the right hemisphere, after an acute challenge with marijuana or Δ^9-THC (e.g., Mathew et al., 1997; Mathew et al., 1992; Mathew et al., 2002). In addition, alterations in the neurovascular system have been shown to be associated with behavioral changes in chronic cannabis users. For instance, Mathew et al. (1992) found increased ratings of tension and anger after smoking marijuana but not placebo cigarettes as measured by the Profile of Mood States. Another relevant study (Volkow et al., 1996) examined regional brain glucose metabolism; it found that at baseline cannabis users demonstrated lower cerebellar metabolic values than comparison subjects. While cerebellar metabolism was increased in both cannabis users and comparison subjects during Δ^9-THC intoxication, only the cannabis users exhibited increased glucose metabolism in the prefrontal cortex, orbitofrontal cortex, and basal ganglia after the acute Δ^9-THC challenge. These findings suggest that chronic cannabis users demonstrate differential regional brain metabolic responses in response to an acute cannabis challenge (Volkow et al., 1996); however the duration of these effects was not assessed.

Blood flow changes have been examined during cognitive challenge tasks. Specifically, PET studies have demonstrated decreased regional blood flow in the prefrontal cortex, increased CBF in the cerebellum, and altered lateralization in the hippocampus during performance of an episodic memory task in recently abstinent cannabis users (Block et al., 2002). The effect of smoking cannabis on CBF during auditory attention task was also examined using PET (O'Leary et al., 2002). The findings showed decreased CBF in areas associated with sensory processing and attention (e.g., auditory areas of the temporal lobe, visual cortex, parietal lobe, frontal lobe, and thalamus); however CBF increased in paralimbic regions, which may be associated with the mood-enhancing effects of cannabis. Overall, these findings suggest that cannabis use may affect brain activation in brain regions important for memory, attention and cognition (Block et al., 2002; O'Leary et al., 2002).

In addition to blood flow studies, cerebrovascular perfusion has been examined by measuring blood flow velocity (e.g., systolic velocity and pulsatility index) with transcranial Doppler sonography in light, moderate, and heavy cannabis users after 3 days, and again after 28 to 30 days of supervised abstinence (Herning et al., 2005). Both systolic velocity and pulsatility index, a measure of cerebrovascular resistance, were increased in cannabis users compared with control subjects. Further, this increase remained essentially unchanged in heavy cannabis users for the entire month of abstinence, yet began to decrease in the light users. The authors suggested that these persistent alterations in vascular hemodynamics might possibly be due to changes in the blood vessels or the density of CB1 receptors in the brain (Herning et al., 2005).

Neuroimaging data have provided evidence of alterations in patterns of brain activity after an extended period of abstinence in heavy marijuana users (e.g., Bolla et al., 2005; Eldreth et al., 2004). For example, Bolla et al. (2005) demonstrated deficits in decision-making ability during the Iowa Gambling Task, as well as alterations in brain activity using Positron Emission Tomography (PET), in heavy marijuana users abstinent for 25 days. Results from this study demonstrated that marijuana users exhibited less activation in the right lateral orbitofrontal cortex and the right dorsolateral prefrontal cortex and greater activation in the left cerebellum compared to the control group. Further analyses dividing the marijuana group into heavy and moderate users revealed more pronounced deficits in performance and brain activity in the heavy marijuana group. In a PET investigation, Eldreth et al. (2004) examined 25-day abstinent marijuana smokers during the performance of a modified Stroop test; they found hypoactivity of the ACC and lateral PFC and increased activity in the hippocampus relative to control subjects despite a lack of performance differences between the groups (Eldreth et al., 2004). The authors suggested that marijuana smokers may recruit alternative networks as a compensatory strategy for the completion of their version of the Stroop task. More recently, Jager et al. (2006), using functional magnetic resonance imaging (fMRI), found no overall differences in the patterns of brain activity between 7-day abstinent moderate users of cannabis and controls during a working memory task and a selective attention task. However, these authors did report altered brain activity in the left superior parietal cortex in the cannabis users during the working memory task suggesting possible region-specific effects of cannabis on brain function after 1 week of abstinence. Further, a study from the same investigators used fMRI to examine the effects of frequent cannabis use on a hippocampal-dependent associative memory task (Jager et al., 2007). The findings revealed hypoactivity in 7-day abstinent cannabis users in the left and right parahippocampal regions and the right dorsolateral prefrontal cortex specifically during the associative learning component of the task. Thus, despite similar behavioral performance, activational differences are evident in abstinent cannabis users during hippocampal-associative memory. Chang et al. (2006) examined activation using BOLD (blood oxygenation-level dependent) fMRI during a visual-attention task in abstinent chronic marijuana smokers (the majority abstinent for less than 2 months), active marijuana smokers and control subjects. Both marijuana groups exhibited altered activation patterns during the visual-attention tasks. The investigators found that marijuana users demonstrated decreased activation in the right prefrontal, medial and dorsal parietal areas, and medial cerebellar regions, but greater activation in frontal, parietal, and occipital regions. Notably, there was a positive correlation between duration of abstinence and BOLD activation in the right prefrontal area and the cerebellum suggesting normalization of brain activation with continued abstinence (Chang et al., 2006). Overall, the majority of the above studies suggest that altered neural activity patterns still persist even after a week of abstinence from cannabis. However, after longer durations of abstinence (i.e., over 1 month) brain activation patterns may begin to normalize.

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