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REVIEW

Human Neuroimaging of Acute and Chronic Marijuana Use: Implications for Frontocerebellar Dysfunction

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The effects of cannabis use on the human brain are not well understood. Recently neuroimaging research has begun to address the question of metabolic changes secondary to (1) long-term chronic cannabis use, and (2) acute intoxication due to cannabis smoke or injection of delta-9-tetrahydrocannabinol (Δ^9-THC) solution. A comprehensive review of the neuroimaging literature was performed. To further interpret and understand this research, literature addressing animal receptor and neurochemical models were also surveyed. Neuroimaging findings have concluded that abstinence from smoking results in depressed cerebral metabolism in chronic users, while acute exposure reverses this condition, producing higher cerebral blood flow in chronic users compared to controls. These changes are hypothesized to be associated with alterations of cannabinoid receptors secondary to chronic exposure. Findings from animal models are consistent with the proposition that adaptation to chronic exposure results in adjustment of normal neurotransmitter levels. The frontopontocerebellar network is implicated as a site sensitive to cannabinoid-induced alterations in the levels of dopaminergic activity derived through the medial forebrain bundle, which projects from the ventral tegmental area. This network is involved in the modulation of a range of human behavior that is clearly altered by use of cannabis. The combined neuroimaging and animal data suggest that metabolism of component regions of the frontopontocerebellar network are altered by acute and chronic exposure to cannabis through modulation of both the cannabinoid and the dopamine system.

KEY WORDS — marijuana; positron emission tomography; magnetic resonance imaging; dopamine; frontal lobes; cerebellum

INTRODUCTION

Despite the prevalence and long history of cannabis use by man, the neural mechanisms underlying its influence on the brain are not well understood. Although considerable research into the effects of cannabis on the central nervous system was initially reported in the 1960s, numerous neuroscientific advances have been made since then. For example, more than 60 cannabinoids have been discovered in *Cannabis sativa* (Turner, 1985), while more recently, two receptors which show high affinity for cannabinoids have been characterized and cloned, the CB_1 receptor in rats and humans (Matsuda *et al.*, 1990; Gerard *et al.*, 1991) and the CB_2 receptor in humans (Munro *et al.*, 1993). The former seems to be responsible for most of the psychoactive effects of cannabis. The most studied cannabinoid present in marijuana is Δ^9-THC (Razdan, 1986). The effects of this chemical have been documented to be present on nearly every neurotransmitter system, on multiple steroidal systems, and on cerebral vasculature (Harclerode, 1984; Mendelson and Mello, 1984; Dewey, 1986; Gardner and Lowinson, 1991; Ellis *et al.*, 1995; Navarro *et al.*, 1995).

To date the majority of investigations aimed at clarifying the neurological mechanisms of cannabinoids have primarily been based on the

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rat model, with a few studies in non-human primates. Human research has been limited by moral and legal issues which have slowed the completion of studies based on the implementation of controlled substances to determine the brain behavior correlates of marijuana (Voelker, 1997). The advent of non-invasive brain imaging techniques have now made testing hypotheses of neural responses to cannabis possible in the human brain. This paper will review recent neuroimaging research addressing the effects of marijuana on the human brain. These findings will be considered in view of receptor changes secondary to acute and chronic marijuana exposure. These findings suggest that chronic marijuana use results in changes at the receptor level, which subsequently influence major neurotransmitter systems, mainly dopamine. This alteration of the dopamine system leads to a global reduction in brain metabolism, particularly in the frontal lobe and cerebellar cortex, which is reversed upon acute exposure to marijuana.

STRUCTURAL IMAGING

Studies examining structural brain changes as a consequence of cannabis use have been sparse, and those that are done are often complicated by including subjects with polysubstance abuse. The first attempt to describe the existence of cerebral atrophy in chronic marijuana users was a pneumoencephalography study of 10 patients admitted for general neurological testing and drug abuse patients (Campbell *et al*., 1971). They found cerebral atrophy in their users as evidenced by enlarged ventricles. However, this study was biased in that it was undertaken after the authors noticed that a routine pneumoencephalograph showed these changes in a number of their drug abuse patients. They also selected their controls without being blind to ventricular size. Subsequently, computerized axial tomography (CAT) applied to similar populations found no evidence of atrophy (Co *et al*., 1977; Kuehnle *et al*., 1977). These results are surprising because the subjects used were polysubstance abusers. A number of electroencephalographic (EEG) studies consisting of sleep and waking EEGs have not found differences between groups of heavy long-term marijuana users and controls (Rodin *et al*., 1970; Rubin and Comitas, 1975; Karacan *et al*., 1976; Stefanis *et al*., 1977). A more recent study using magnetic resonance imaging (MRI) technology, which has higher spatial resolution and the ability to examine differences in gray and white matter more precisely than CAT scans, has shown a higher frequency of atrophy, smaller cerebellar vermis area, and more focal white matter abnormalities in long-term marijuana users with a history of polysubstance abuse (Aasly *et al*., 1993). The authors point to alcohol as the most likely causative agent. The ideal method of quantifying structural brain abnormalities secondary to exposure to a neurotoxic agent is to use high resolution MRI and software that segments and allows regional volume measurements to be made. Findings using this technique have not been reported on subjects who solely use marijuana on a regular chronic basis. Because of this lack of definitive information, it is not possible to determine if and what long-term changes, such as specific cell-loss, may occur following chronic marijuana exposure.

FUNCTIONAL IMAGING

Chronic exposure

The majority of neuroimaging data is derived from studies of brain imaging during acute marijuana exposure (see Table 1). However, a number of studies have either imaged the brain of chronic users and compared the results to control subjects, or performed a baseline scan prior to acute marijuana exposure. The common result in these instances is lower cerebral blood flow (CBF) during a washout period observed in chronic smokers as compared to controls. In one of the first experiments, which utilized ^{133}Xenon inhalation with 32 scalp detectors, Mathew and colleagues studied right-handed males with a history of smoking for at least the previous 6 months (Mathew *et al*., 1986). CBF was measured during a 10 minute clearance period and no significant differences were found between subjects who smoked marijuana regularly, and age-, sex-, and handedness-matched control subjects who had never smoked marijuana. In a later review article, Mathew and Wilson note that there was a trend in the data toward lower CBF values in the smokers (Mathew and Wilson, 1991).

A similar study by Tunving *et al*. (1986), using nearly identical methods to those used by Mathew *et al*. (1986), reported large differences in CBF. All subjects had a minimum duration of 3 months of regular marijuana use. One notable difference between this group of smokers and the subjects in the Mathew *et al*. study was that the men in the Tunving study had voluntarily admitted themselves

Table 1. Brain imaging studies of the effects of acute and chronic cannabis use in humans

Study	Subjects[a]	Controls[a]	Ages (years)	No. of doses of marijuana[b]	Abstinence period[c]	Excluded for psychiatric history[d]	Exclusion for[e] alcohol	Exclusion for[e] other drugs
Mathew *et al.* (1986)	17 M	17 M	25·5 ± 8	4650 ± 2410	12 h	Yes	No	No
Tunving *et al.* (1986)	9 M	9 M	24·2 ± 5	5500 ± 3900	5·8 ± 3·7 days	S: No C: Yes	No	No
(follow-up)	4 M: subset from above	0			9, 14, 15, or 60 days after first study			
Mathew *et al.* (1989)	ES: 7 M, 2 F IES: 10 M, 7 F	9 M, 5 F	ES: 25·9 ± 4 IES: 28·3 ± 8 C: 26·9 ± 8	ES: at least 1560 IES: NR C: NR	ES: 12 h IES: 3 y	Yes	NR	No
Volkow *et al.* (1991)	8 M	0	34 ± 8	NR	2 weeks	NR	No	No
Mathew *et al.* (1992)	10 M	0	25·9 ± 6	NR	3 months	Yes	No	No
Mathew and Wilson (1993)	35 M	0	21·7 ± 8	NR	2 weeks	Yes	No	No
Volkow *et al.* (1996)	8 M	8 M	ES: 31 ± 6 C: 35 ± 7	3700 ± 1400	3 days	Yes	No	No
Mathew *et al.* (1997)	20 M, 12 F	0	32·5 ± 8	NR	2 weeks	Yes	No	Yes, if heavy
Solowij *et al.* (1991)	6 M, 3 F	6 M, 3 F	29·4 ± 9	2800 ± 670	12 h	Yes	No	Yes, if heavy

Study	Toxic screen[f]	Dose	Global changes	Regional changes	Result
Mathew *et al.* (1986)	No	None	No	NR	No difference in CBF from controls
Tunving *et al.* (1986) (follow-up)	Yes	None	Yes	NR	9 per cent lower global CBF than controls 12 per cent increase from initial values
Mathew *et al.* (1989)	S: Yes C: No	2·2 per cent cigarette or placebo	Yes	NR	ES: lower baseline CBF; increases in both conditions IES: larger decreases after THC
Volkow *et al.* (1991)	No	2 mg i.v.	Yes	Yes	Global CBF increased in 3 subjects, decreased in 4, no change in 1; total 4 per cent increase; consistent increase in cerebellum
Mathew *et al.* (1992)	Yes	3·5 per cent cigarette or placebo	Yes	NR	Increases during smoking THC lasted full 60 min period
Mathew and Wilson (1993)	Yes	1·75 or 3·55 per cent cigarette or placebo	Yes	NR	Increases after both THC conditions
Volkow *et al.* (1996)	Yes	2 mg i.v.	Yes	Yes	Baseline cerebellar CBF lower than controls; regional increases after THC
Mathew *et al.* (1997)	Yes	3 or 5 mg i.v. or placebo	Yes	Yes	CBF increased in most regions by 30 min with the high dose, and 60 min with the low dose
Solowij *et al.* (1991)	Yes	None	NR	NR	ERP early processing negativity indicating poor attentional focus and filtering

[a]M, male; F, female; ES, experienced smokers; IES, inexperienced smokers.
[b]Mean number of times subjects had used marijuana in their lives.
[c]Mean duration from last time using marijuana to testing.
[d]Yes, an attempt was made to exclude subjects with a past history of a major psychiatric disorder; No, subjects were included despite significant past or current psychiatric history; NR, not reported/ambiguous.
[e]Yes, indicates that some attempt was made to exclude subjects with prior or current use of alcohol or other drugs; No, indicates that investigators did not exclude subjects with prior or current use of alcohol or other drugs; NR, not reported/unknown.
[f]Yes, at the time of testing, subjects gave a urine or blood sample that was screened for psychotropic substances; No, no screen was performed.

to a detoxification unit secondary to problems associated with the cannabis use, e.g., sleep disturbances, anxiety, and irritability. The scanning data indicated that the smokers had global CBF values that were 11 per cent lower than those of the matched control subjects. When examined by region however, the smokers had higher frontal than posterior flow values. Four of the smokers were available for a follow-up scan either 9, 14, 15, or 60 days later. The result of the second scan showed a 12 per cent increase in CBF. This change matched the improvement in cerebral dysfunction which occurred in all patients within 2–4 weeks after entering the program. These findings suggest that a return to baseline CBF occurs within the first 2 weeks of abstinence.

Following their earlier ^{133}Xenon inhalation protocol, Mathew and colleagues performed a study of both chronic and acute effects of marijuana exposure on experienced and naive smokers (Mathew *et al*., 1989). Experienced smokers were defined as people who had smoked a minimum of 10 marijuana cigarettes a week for 3 years. These subjects were asked not to smoke for 12 h prior to the imaging study. Inexperienced smokers included individuals that had not smoked marijuana for at least 3 years. Scans were performed before and after smoking. As described by Tunving *et al*., the experienced smokers had a pre-smoking baseline CBF that was lower than the other groups.

In a later study addressing the effects of chronic marijuana exposure, Volkow *et al*. (1996) utilized 2-deoxy-2-^{18}F-fluoro-D-glucose (2DG) and positron emission tomography (PET) scanning. Measures were done on a cohort of chronic marijuana users and control subjects. No drugs were to be used 3 days prior to the imaging study. Measures of local metabolism relative to global brain metabolism were reported because of a calibration error that prevented the use of absolute values. Comparison of their pre-injection measures revealed that baseline cerebellar metabolism was lower in chronic marijuana users compared to controls.

Acute exposure

Acute exposure to marijuana has consistently resulted in increases in CBF measures. In the first study of this kind, Mathew *et al*. (1989) continued beyond the baseline measurements with the study cohort described above and acquired scans after each of two conditions. The first treatment condition required that subjects smoke a cigarette with a Δ^9-THC content of 2·2 per cent during a 15 min period with nine full inhalations held for 15 s each. This attempt to standardize the delivery of smoke was problematic in that smokers claimed they inhaled more smoke than the amount to which they were accustomed. The second treatment condition required smoking a placebo cigarette from which the Δ^9-THC was extracted. Comparison of CBF measurements acquired 60 min after smoking marijuana with measurements acquired pre-smoking showed that the inexperienced smokers had significant global decreases in CBF, the experienced smokers demonstrated bilateral frontal and left temporal increases in CBF that were significant, while no significant differences were evident in the control group.

A subset of the experienced and inexperienced smokers were scanned before and after smoking the placebo cigarette. The inexperienced smokers had decreased CBF following the placebo cigarette, but the decreases after smoking marijuana were significantly greater. The experienced smokers showed increased CBF after smoking the placebo cigarette which did not differ significantly from the increases seen after smoking marijuana. The authors suggest that differences in response to marijuana in the two smoking groups is due to anxiety and sympathetic arousal accompanying this reaction. The inexperienced smokers experienced increased anxiety and a higher pulse rate following marijuana smoking, while the experienced smokers reported decreased anxiety with a smaller increase in pulse-rate. Another consideration is the long half-life of Δ^9-THC in the body and that 12 h may not be long enough to provide an accurate baseline CBF measurement in the heavy smokers.

The first study of acute exposure utilizing the 2DG-PET method was done by Volkow *et al*. (1991). These investigators administered 2 mg of Δ^9-THC intravenously to experienced smokers. Scanning was performed prior to administration of Δ^9-THC and for 20 min beginning at 40 min post-administration. For the first time in an experiment of this kind, plasma levels of Δ^9-THC and its metabolite THC-COOH were collected at 20 and 40 min. The levels of Δ^9-THC were 17 ± 12 ng/ml and 6 ± 2 ng/ml at those two times. A detailed study of levels during and after smoking marijuana cigarettes with 1·75 per cent or 3·55 per cent Δ^9-THC have shown that levels reach 7·0 and 18·1 ng/ml after the first inhalation respectively (Huestis *et al*., 1992). They peak at 9 min prior to

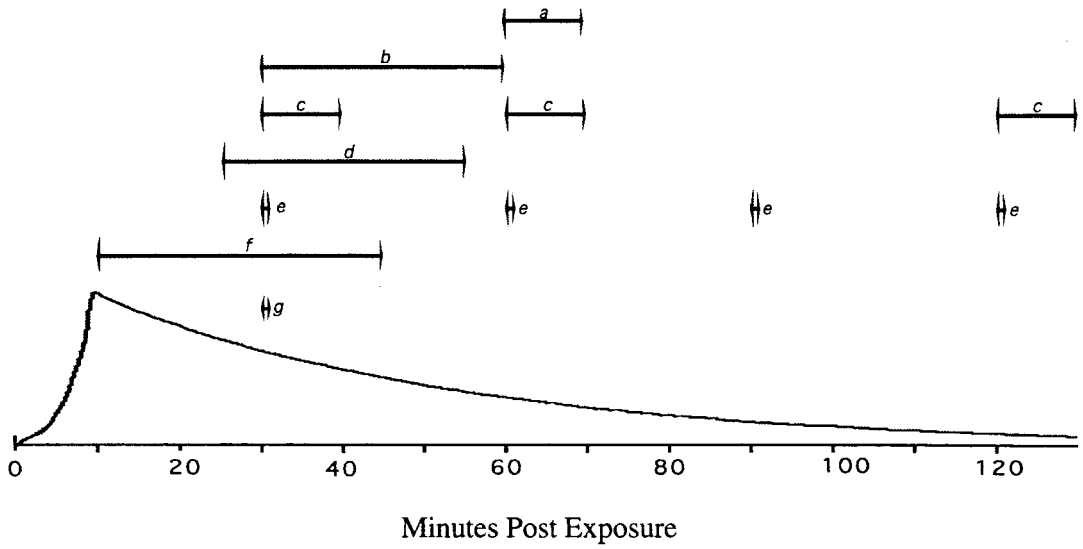

Figure 1. Time course of data collection for acute exposure experiments relative to average plasma-Δ^9-THC levels. [a]Mathew *et al.* (1989); [b]Volkow *et al.* (1991); [c]Mathew and Wilson (1993); [d]Volkow *et al.* (1996); [e]Mathew *et al.* (1997); [f]Margulies and Hammer (1991); [g]Bloom *et al.* (1997). The curve is representative of average plasma levels as presented in the currently reviewed articles

cessation of smoking at about 79 and 150 ng/ml. The levels drop precipitously after the peak and reach 17 and 30 ng/ml by 30 min, fall below 5 ng/ml by 2 h and are just detectable at 12 h. The levels reported by Volkow *et al.* (1991) are compatible with smoking a low dose marijuana cigarette. A schematic showing a curve representing average plasma Δ^9-THC and the data collection times for acute exposure experiments is depicted in Figure 1. Of further note is the fact that there is controversy over the time of peak psychological effects. Some studies have reported peak effects 30 min–1 h following smoking. Huestis *et al.* (1992) in the same study determined that the peak was present as soon as 15 min following smoking. Volkow *et al.* (1991) report that peak effects occur in a range from 10 min to 1 h, reflecting the fact that there are individual differences not only in psychological responses, but also in physiologic factors. These investigators found that following Δ^9-THC administration, three subjects had increased global cerebral metabolism, four had decreased, and one had no change. The overall average was a 4 per cent increase, but this is not a very informative number. Of the 13 anatomical regions studied, the values for cerebellar metabolism normalized to whole brain metabolism were the only values that showed a statistically significant increase. Interestingly, the relative metabolic measures of the cerebellum correlated with the subjective sense of intoxication. This measure of intoxication also correlated with plasma Δ^9-THC levels. These levels were positively correlated with cerebellar metabolism and negatively with prefrontal metabolism.

Mathew *et al.* (1992) studied changes in the brain with transcranial doppler ultrasonography following acute marijuana exposure. They measured middle cerebral artery (MCA) velocity in subjects with a history of marijuana use, but who had not used it in the last 3 months. Measurements were made at 1 min intervals starting with the 10 min period in which the subjects smoked either a marijuana cigarette with a 3·55 per cent Δ^9-THC, or a placebo cigarette, and for the subsequent 50 min. Standardized smoking was not used due to the difficulties described earlier. MCA velocity increased during the 10 min smoking period and maintained this elevated level for the duration of the 60 min recording session. The placebo cigarette had no effect, an unexpected finding given the results from their earlier study. The authors conclude that the increase following marijuana is likely the result of increased cerebral metabolism and thus CBF, although other mechanisms are discussed. Changes in perfusion pressure are excluded as a cause of increased blood velocity since this measure did not change during smoking, and cerebral vasculature is auto-regulated. Although, intracranial pressure increases could

cause increased blood velocity, there are no indications that marijuana increases intracranial pressure. Effects of sympathetic stimulation are ruled out on the basis that (1) marijuana does not activate the superior cervical ganglion, which innervates intracranial vasculature, and (2) this would decrease cerebral perfusion. Furthermore, the effect of end-tidal CO_2 or CO production are also ruled out on the basis that they were the same for marijuana and placebo conditions. One mechanism that cannot be definitively excluded is the dilation of cerebral resistance arterioles as it is known that marijuana dilates muscle capillaries and conjunctival vessels. As will be discussed below, it has recently been found that Δ^9-THC directly applied to rabbit cerebral arterioles causes vasodilation (Ellis *et al*., 1995).

In a later ^{133}Xenon inhalation study, Mathew and Wilson (1993) measured CBF in experienced marijuana smokers who had not smoked for 2 weeks prior to the study. They also used a urine screen to ensure compliance. Each subject participated in a low dose (1·75 per cent Δ^9-THC), high dose (3·55 per cent Δ^9-THC), and placebo condition. Measurements were made before and at 30, 60, and 120 min post-smoking. Plasma Δ^9-THC levels were also measured at 5, 10, 20, 40, 130, and 170 min. The results of this latter analysis were nearly identical to that published by Huestis *et al.* (1992), with only a slightly slower decline in CBF following the peak. Significant global increases in CBF were recorded following both low and high dose conditions. These increases were larger in the anterior portion of the brain. Using a correlation analysis, the investigators showed that CBF changes in frontal and temporal regions, particularly on the right side, correlated with a pattern of psychological changes as assessed with self-rated measures of feeling 'high', depersonalization, confusion, and temporal disintegration. The left parietal region was more weakly correlated with these measures.

As an extension of the Volkow *et al.* (1996) study, the authors studied changes in cerebral glucose metabolism following intravenous administration of 2 mg of Δ^9-THC to their subjects. Plasma Δ^9-THC levels were collected at 30 and 60 min post-injection and were $11{\cdot}13 \pm 5$ and $6{\cdot}1 \pm 2$ ng/ml in the marijuana users and $18{\cdot}42 \pm 9$ and $7{\cdot}2 \pm 1$ ng/ml in the control subjects. These levels were not different between the two groups. The metabolite THC-COOH was non-significantly higher in chronic users. Subjective responses were stronger in the control subjects. Comparison of baseline to Δ^9-THC conditions showed an increase in relative metabolism in the prefrontal cortex, left and right frontal cortices, right temporal cortex, and the cerebellum. Comparison of chronic users to control subjects showed that metabolism was higher for chronic users in the prefrontal cortex, orbitofrontal cortex, and basal ganglia, while it decreased or remained unchanged in controls. Correlations between plasma Δ^9-THC concentration and paranoid symptoms were positive for both groups. There was no correlation between plasma Δ^9-THC concentration and metabolic changes. Subjective sense of intoxication and metabolic measures were significantly correlated with the cerebellum only. The authors conclude that because of the high concentration of cannabinoid receptors in the cerebellum (Herkenham *et al.*, 1991; Glass *et al.*, 1997), decreased baseline metabolism in chronic users may reflect changes at the receptor level. They also note other regions which contain high concentrations of cannabinoid receptors but were too small to be measured with this PET technique, namely hippocampus, substantia nigra pars reticulata, and globus pallidus. They also mention that animal studies have shown self-stimulation in the cerebellum. Limitations cited are the lack of absolute measures, possible effects of withdrawal, and uncertainties in pattern and accuracy of reported drug-use.

The most recent study has been done by Mathew *et al.* (1997) and utilizes ^{15}O-water and PET. They randomized their subjects, all chronic users, to one of three groups, placebo, low dose and high dose. PET scans were performed for 1 min at 30, 60, 90, and 120 min following a 20 min infusion of either 0·15 mg Δ^9-THC/min, 0·25 mg Δ^9-THC/min, or human albumin. Mean plasma levels of Δ^9-THC at 30 and 60 min were $16{\cdot}61 \pm 6{\cdot}63$ and $7{\cdot}99 \pm 3{\cdot}15$ ng/ml for the low dose group and $26{\cdot}29 \pm 10{\cdot}03$ and $15{\cdot}70 \pm 6{\cdot}57$ ng/ml for the high dose group. These levels are consistent with expected values based on earlier reports. PET images were co-registered with T2-weighted MRI images and regions of interest were defined on these same MRI images using Talairach & Tournoux coordinates. In the high dose group most regions showed increased CBF at 30 min. By 60 min, increased CBF was measured bilaterally in the frontal, temporal, and parietal lobes, the cingulate gyrus, insula, basal ganglia, and thalamus. However, the right amygdala and hippocampus demonstrated significant increase in CBF at 30 min but not at 60 min. In contrast, at 30

min, the low dose group had increases in the right frontal lobe and cingulate and left insula, whereas by 60 min, all regions had increased CBF except the occipital region. The placebo group had a slight decrease in overall CBF compared to baseline at both time points. An anterior/posterior effect was detected in the low and high dose groups both within the cingulate and for the whole brain, reflecting the finding that frontal flow increased while occipital flow remained the same. The CBF in the cerebellum was calculated separately and although it appeared to increase following Δ^9-THC with a similar magnitude as reported by Volkow *et al*. (1996), the variation across individuals and treatment groups was great. The CBF in the cerebellum did not correlate with plasma Δ^9-THC levels or intoxication ratings. In contrast, these measures did correlate with frontal CBF, with a stronger correlation evident for the right frontal and the left anterior cingulate. Intoxication ratings only were negatively correlated with left parietal lobe and bilateral hippocampal CBF.

One complementary area of research which also addresses CBF changes secondary to exposure to cannabis is the application of autoradiographic methods to rat brain slices (Margulies and Hammer, 1991; Bloom *et al*., 1997). Margulies and colleagues examined 24 male rats weighing 220–250 g after Δ^9-THC was administered intravenously at 0, 0·2, 0·5, 2·0, or 10 mg/kg. Ten minutes after drug administration ^{3}H-2-deoxy-D-glucose was injected. At 45 min post-drug the rats were sacrificed and their brains were frozen. Nearly all limbic and cortical areas showed a biphasic dose-response, with increased glucose usage or uptake at 0·2 mg/kg, no change at 0·5 mg/kg, and decreased usage at higher doses. Very little change was observed in diencephalic and brainstem structures. This biphasic response closely mirrors the effect of injection of Δ^9-THC on global cyclic adenosine 3′,5′-monophosphate (cAMP) levels in mouse brain (Dolby and Kleinsmith, 1974). At doses of 0·1–1 mg/kg, cAMP levels increased by 50–160 per cent, while doses from 2 to 10 mg/kg resulted in a decrease of 30–60 per cent in cAMP levels. Others have described biphasic changes in electrophysiological measures with neuronal activity increasing after low doses of Δ^9-THC and decreasing after high doses (Foy *et al*., 1982; Turkanis and Karler, 1987). A subsequent autoradiography study done by Bloom *et al*. (1997) used 30 slightly older rats (weighing 275–300 g). Instead of ^{3}H-2-deoxy-D-glucose, they used ^{14}C-iodoantipyrine which requires only 30–60 s to develop an adequate signal for the measurement of CBF. Rats were administered Δ^9-THC intravenously at doses of either 0, 0·5, 1, 4, or 16 mg/kg. ^{14}C-iodoantipyrine was injected 30 min after treatment with Δ^9-THC and the animals were sacrificed a minute later. Decreased CBF was found in about half of the regions measured, while the other regions had no change. The authors note that they did not replicate the biphasic response of Margulies and Hammer (1991), although they did not use the 0·2 mg/kg dose which was reported to cause increases in glucose utilization measures. In addition, Bloom *et al*. (1997) report that increases of more than 10 per cent, although not statistically significant, were observed in 15 of 37 brain regions at a dose of 0·5 mg/kg.

One reason for discrepancies between these rat studies and the previously described research on humans may be the amount of Δ^9-THC administered in each instance. In the rat studies, the dose ranged from 0·5 to 5 mg, whereas in the human studies, subjects were given from 2 to 5 mg of Δ^9-THC, depending on the experiment. It has been reported that an oral dose of 20 mg/kg results in peak plasma levels of 150 ng/ml Δ^9-THC within 1 h in the rat (Scallet *et al*., 1987). Given that oral administration delivers about 6 per cent of the drug to the blood stream (Ohlsson *et al*., 1980), this dose amounts to 1·2 mg/kg, comparable to the lower intravenous doses in the rat studies. Others have made considerably smaller estimates as to the dose given to a rat that corresponds to smoking a single marijuana cigarette (Gardner and Lowinson, 1991). It remains that Bloom *et al*. (1997) found decreased CBF even at their lowest dose of 0·5 mg/kg, whereas Margulies and Hammer (1991) reported increased metabolism, a finding similar to the human studies, at their lowest dose. Perhaps the non-significant CBF increases Bloom *et al*. (1997) recorded at 0·5 mg/kg would have been greater had they injected their tracer earlier as done by Margulies and Hammer. This and other methodological differences may account for the discrepancies between studies. Another substantive reason for expecting that responses to Δ^9-THC would be different in human versus rat brain is the significant type and number of psychological changes experienced by humans. These global behavioral changes are known to be associated with regional cellular activity distributed throughout the brain.

Despite the current capacity of PET and functional MRI to study cognitively mediated brain

activity, thus far no such experiments have been published. A recent finding from analysis of event-related potentials (ERP) in chronic users performing an auditory selective attention task suggested focal cortical changes (Solowij *et al*., 1991). In this study the subject population used marijuana for at least 3 years, and controls were matched for age, sex, years of education, and alcohol consumption. The main difference in the EEG of the two groups was an enhanced early processing negativity in the marijuana users. The authors interpreted this as a difficulty in accurately focusing attention which resulted in unnecessary processing and poor filtering of the stimuli. In a follow-up case report, Solowij *et al*. (1995) found that this abnormal ERP was present in a 35 year old male with an 18 year history of cannabis use, and no change was observed throughout a 6 week period of abstinence. Furthermore, in an intoxicated state, this ERP abnormality disappeared.

Cognitive dysfunction after marijuana use has also been reported by a number of investigations (Pope *et al*., 1995). In a recent report by Pope and Yurgelun-Todd (1996), neuropsychological performance was compared for two groups of college students after an overnight period of abstinence from marijuana. These groups included subjects with a history of heavy or light marijuana use. Overall, the findings suggested that heavy marijuana use is associated with impairment of the attentional/executive system and reduced verbal learning. However, the ability to retain newly-learned information after a temporal delay appeared relatively unimpaired in the heavy users, as shown by the lack of decay between immediate and delayed recall conditions. Thus, the results suggest that, although marijuana use may produce some residual impairment in memory function, the principal effect of the drug appears to be on the attentional/executive system. These results suggest that there are subtle abnormalities in particular cognitive networks that may be missed by these structural and functional imaging experiments, but may be observed with functional imaging methods applying focal measurement strategies including cognitive challenge paradigms (Yurgelun-Todd *et al*., 1998).

RECEPTOR BINDING

One additional area of research which contributes to our understanding of the neuroimaging data is receptor binding studies. Insofar as changes in CBF are mediated through the CB_1 receptor system, we would expect to see changes in receptor binding with chronic exposure to Δ^9-THC. In one study, four groups of 8–10 week old rats were given either 0, 5, 10, or 20 mg/kg Δ^9-THC intravenously Monday through Friday. A fifth group received 20 mg/kg Monday through Thursday and 60 mg/kg on Friday. This procedure was carried out for 3 months, after which the animals were given 2 months of no-exposure prior to being sacrificed. No changes in receptor binding were found between any treatment group and those animals having received vehicle (Westlake *et al*., 1991). In this same study, periadolescent rhesus monkeys were exposed to either one marijuana cigarette (2·6 per cent Δ^9-THC) a day for 7 days a week for 1 year, or a sham cigarette from which the Δ^9-THC had been extracted. Seven months after the last exposure the monkeys were sacrificed and receptor binding analysis performed. Again, no differences were found between the marijuana exposed and the sham exposed animals (Westlake *et al*., 1991). In an earlier experiment, this same group reported on the effect of neurotransmitter concentrations and receptor binding in rats gavaged with 10 or 20 mg/kg Δ^9-THC for 3 months and then sacrificed either 24 h or 2 months after the last exposure (Ali *et al*., 1989). On the basis of this study, no significant changes on measures of concentration or binding were evident for dopamine, serotonin, acetylcholine, GABA, benzodiazepine, or opioids.

In a more recent study, positive findings of receptor alteration have been reported. Three groups of adult rats were either given 10 mg/kg Δ^9-THC intraperitoneally and sacrificed 20 min later, given this same dose for 5 days and then sacrificed 20 min after the last treatment, or treated with vehicle (Romero *et al*., 1997). Decreased cannabinoid receptor binding was found in nearly all brain regions in the animals treated for 5 days compared to vehicle treated animals. There were no differences in binding in the acutely treated animals. Changes in animals with five-day exposure paralleled a tolerance phenomenon described as less motor inactivity with successive treatments. Levels of mRNA were found to increase in the striatum presumably as a compensatory mechanism, this was not observed in any other region. Thus it appears that tolerance due to repeated exposure to marijuana results from a combination of compensatory mechanisms including changes in receptor binding and sensitivity. Another study looked at changes in rat CB_1 receptor mRNA and

cannabinoid-stimulated GTPγS, a measure of receptor sensitivity in animals injected with 10 mg/kg/day Δ^9-THC (Zhuang *et al*., 1998). Animals were sacrificed after 6 h, 1, 2, 3, 7, 14, and 21 days. Levels of mRNA in the hippocampus and cerebellum initially dropped sharply, but then increased above control levels by day four. At the same time, measures of receptor sensitivity decreased in these regions and continued to do so through day 21, while mRNA levels approached control values by day 21. Unlike the hippocampus and cerebellum, mRNA in the striatum remained below control values throughout the study, while receptor sensitivity decreased by a significantly smaller amount compared to the other regions. Furthermore, the time course of these changes suggest that acute exposure to marijuana leads to a rapid decline in receptor number and density at the same time that receptor sensitivity decreases. With continued exposure, mRNA levels increase to compensate for the changes in receptor sensitivity. In the striatum, where decreased sensitivity is not as great, mRNA levels return to normal without ever going above control levels. By day 21, mRNA levels are near normal, while receptor sensitivity is significantly lower than controls. These animal studies have important implications for interpreting human neuroimaging data. For example, the identified receptor changes may play a role in the lower CBF and metabolism seen in chronic marijuana smokers when subjects are scanned during a brief washout period. In all but one study reported above subjects were actively smoking.

DISCUSSION

Most of the reviewed neuroimaging studies have reported increased CBF upon acute exposure to marijuana (Volkow *et al*., 1991, 1996; Mathew *et al*., 1992, 1997; Mathew and Wilson, 1993). The one conflicting study found regional increases in experienced smokers after smoking both marijuana and placebo, but decreases in inexperienced smokers (Mathew *et al*., 1989). The authors concluded that differences in anxiety between the two groups following marijuana smoking accounted for the CBF results with higher anxiety in inexperienced smokers. In support of this conclusion, their indicators of anxiety were negatively correlated with CBF measurements. The design of this study is unusual in that the investigators employed a fixed smoking method and experienced smokers reported receiving more smoke that they usually would. This, in addition to the idea that tolerance exists in experienced smokers and that inexperienced smokers had increased anxiety, suggests that plasma Δ^9-THC and intoxication levels were higher than other studies and thus those factors responsible for reduced cerebral metabolism at high doses in the rat study may have emerged. The main mechanism may be as the authors suggest, anxiety. In general, imaging data indicate a trend for chronic marijuana users to have lower CBF measures than non-smokers at baseline (Tunving *et al*., 1986; Mathew *et al*., 1989; Volkow *et al*., 1996). The negative finding of Mathew *et al*. (1986) was weakened by two later publications in which the authors report that there was a trend toward lower CBF in their subjects (Mathew and Wilson, 1991) and that their subjects were high functioning and infrequent smokers (Mathew *et al*., 1989). In addition, the washout period of 12 h is clearly too short for proper drug clearance. The half-life of Δ^9-THC after it first enters the body and distributes into the tissues is 30 min, due to its high lipophilicity. The time course for its redistribution out of the tissues and clearance is much slower at 56 h (Lemberger *et al*., 1970). Therefore, a washout period of 3 days is the minimum required in order to have negligible levels in the body.

There are numerous difficulties in reducing the findings reviewed here to a single definitive theory. In acute experiments, different routes of administration can produce differential effects such that smoking a marijuana cigarette versus injection of a Δ^9-THC solution will result in exposure to different types of cannabinoids, as well as different blood plasma levels. Standardization of exposure has been attempted through fixed timing of inhalations and exhalations (Mathew *et al*., 1989). However, in this study there was no control for differing lung capacities, and thus subjects experienced different volumes, as well as more inhaled smoke than what they would have during their normal patterns of use. This variance is a problem with studies using the smoking method, nevertheless one strength of this method is that the exposure is more like normal marijuana use, and the chemicals introduced to the subject include the full-range occurring naturally in the plant, as opposed to only the extracted Δ^9-THC. In the human studies that deliver Δ^9-THC solution intravenously, the doses are fixed and do not take into account body weight, while in general animal studies give weighted doses.

This results in varying amounts of drug across study subjects.

Inherent differences also exist among the methods that have been used for measuring CBF. ^{133}Xenon inhalation is used to measure CBF through scalp scintillation counters placed over large cortical areas with a 10 min time-course. Using a PET scanner, the 2DG method measures CBF in more discrete brain regions with a time-course of 20 min, while ^{15}O-water was used with a 1 min measurement period. Furthermore, the human brain imaging studies share the common characteristic of uncertainty in the history of the subject's exposure to marijuana, as well as other potentially neurotoxic drugs, and tobacco use. Receptor binding studies have shown that there are changes that occur over short periods of regular exposure to marijuana. These changes appear to be reversible, although the time-course in humans has yet to be clarified. Thus the measures obtained via recent imaging technology are probably dependent upon total lifetime, as well as recent amounts of drug exposure. Another methodologic problem is the small number of subjects studied with any individual protocol. The largest study involved 35 experienced smokers participating in each of three conditions (Mathew and Wilson, 1993). This study, however, did not include a control group of marijuana-naive subjects.

It is noteworthy that when Δ^9-THC or anandamide, the first endogenous cannabinoid to be characterized (Devane *et al*., 1992), was applied directly onto rabbit cerebral arterioles, the vessel diameter increased (Ellis *et al*., 1995). This effect was observed for concentrations of Δ^9-THC in the range of 10^{-13}–10^{-3} M. In the studies performed by Mathew *et al*. and Volkow *et al*., scans are usually acquired when plasma levels are approximately 20 ng/ml, a level which corresponds to a concentration of 10^{-7} M. Vasodilation was blocked by indomethacin, a cyclo-oxygenase inhibitor which prevents the formation of prostaglandins. The authors state that preliminary evidence suggests that vasodilation occurs via the cannabinoid receptor (Ellis *et al*., 1995). More recently, a review of vasodilation experiments carried out on vessels throughout the body has suggested that endocannabinoids are endothelium-derived hyperpolarizing factors with resistance vessels as a primary site of action (Randall and Kendall, 1998). Because the PET studies found the same results as the ^{133}Xenon and arterial velocity experiments, it can be assumed that psychological sequelae of marijuana smoking is in part due to alteration of synaptic activity in neural circuits. Thus the literature supports the view that there are two mechanisms by which marijuana increases CBF. On one level, the interaction of Δ^9-THC with CB_1 receptors in neural tissue leads to global alterations in the activity of all neurotransmitter systems with which cannabinoids interact. On the other, direct effects on vasculature independent of neuronal metabolism may influence the measurements made in the reviewed imaging studies. Both of these will be altered by chronic stimulation and possible down-regulation of CB_1 receptors.

In summary, there are clear metabolic changes in the brains of chronic marijuana users. The literature indicates that depressed CBF and thus cerebral metabolism are the end result. Given that CBF shows consistent increases upon acute exposure and that animal models suggest down-regulation of receptors with chronic use, reduced CBF during short periods of drug washout appear to be the result of metabolic changes occurring because of events at the receptor level that are a natural compensatory response to over-stimulation with exogenous cannabinoids. Whatever the mechanism behind the changes in CBF, an important aspect of the marijuana–brain interaction remains untouched: what are the correlates to regional neuronal activation? Previous research has shown an emphasis on frontal changes. For instance, comparison of responses to acute exposure in chronic smokers versus naive controls revealed increased metabolism in multiple frontal regions in chronic users, but not in controls (Volkow *et al*., 1996). Interestingly, recent findings applying cognitive challenge paradigms and functional MRI have found that chronic marijuana users display a pattern of decreased dorsal lateral prefrontal cortex and increased anterior cingulate activation compared with naive controls after a 28-day washout period (Yurgelun-Todd *et al*., 1998). Additionally, Mathew *et al*. have reported a larger anterior to posterior effect in multiple acute exposure studies (Mathew and Wilson, 1993; Mathew *et al*., 1997). An analogous gradient is reported in the rat receptor binding studies (Herkenham *et al*., 1991), while in the human receptor binding study, the gradient increases from primary sensory cortices to secondary sensory, to association cortices (Glass *et al*., 1997). Finally, CBF in right frontal and cingulate regions evidenced increases by 30 min following low doses of marijuana, indicating their sensitivity to Δ^9-THC (Mathew *et al*., 1997).

Further support for a frontal dominance in humans comes from the literature examining the changes in dopamine levels with marijuana use. Markianos and Stefanis (1982) report that in long-term users, dopamine levels dropped and norepinephrine rose during a 3 day deprivation period, while the opposite effect was seen following smoking on the fourth day. Rat studies have shown multiple times that treatment with cannabis increases firing of dopamine neurons of the substantia nigra pars compacta, the ventral tegmental area (VTA), and medial forebrain bundle projections (Gardner and Lowinson, 1991; Chen *et al*., 1993; French *et al*., 1997; Gessa *et al*., 1998). On the contrary, chronic exposure results in decreased firing of VTA neurons projecting to the nucleus accumbens (Diana *et al*., 1998) and reduced dopamine metabolism in medial prefrontal cortex, but not the striatum or accumbens (Jentsch *et al*., 1998). The VTA makes widespread connections throughout the brain, but these are heavily weighted in anterior brain regions (Williams and Goldman-Rakic, 1998). This anatomy allows it to be an important system through which acute marijuana use elicits behavioral changes and, by its downregulation, produces noticeable differences between chronic marijuana users and controls.

The other brain region consistently identified with changes due to marijuana exposure is the cerebellum. The data show depressed cerebellar metabolism in chronic marijuana smokers and correlations between self-rated intoxication measures and increases of cerebellar metabolism (Volkow *et al*., 1991, 1996). This finding corresponds well with recent theorizing that the cerebellum is active during such non-motor cognitive behaviors as language generation (Leiner *et al*., 1993; Fiez *et al*., 1996), dynamic state-estimation (Ito, 1993; Paulin, 1993), timing of behavioral responses (Ivry, 1996), fine-tuning the acquisition of sensory data (Bower, 1997), attention (Courchesne *et al*., 1994), and maintaining behavioral homeostasis (Schmahmann, 1996). There is an abundance of literature addressing the possible roles of cerebellar function (Thach *et al*., 1992; Schmahmann, 1997; Schmahmann *et al*., 1998). In addition, there is anatomical support for these functional theories as there are strong feedback and feedforward connections between the cerebellum and prefrontal cortical regions (Middleton and Strick, 1994; Schmahmann and Pandya, 1995, 1997).

The hypothesis proposed is arrived at through the convergence of data from independent neurobiological modalities, imaging, receptor binding and pharmacologic studies. These findings implicate dysregulation of frontopontocerebellar networks as a consequence of acute and chronic marijuana use. Although other brain regions may be involved to a lesser extent, firm conclusions cannot be drawn based upon current human neuroimaging data. Thus far, studies have been limited in spatial resolution, sample size, matching for clinical profile and history of past and recent substance use. Moreover, the absence of challenge paradigms has prevented previous studies from identifying functional brain changes, which may not be apparent with baseline measurement techniques. If demands are not placed on those functional networks mediating specific cognitive processes, dysfunction of these systems may not be revealed. Recently developed fMRI technology is just beginning to be applied to this field of research and is ideally suited for testing activation of specific brain areas during such cognitive challenges. This type of research is essential to understanding the precise mechanisms behind both the chronic and acute effects of cannabis use in humans. Future studies are needed to evaluate the proposed hypothesis of cannabis induced alteration of the frontopontocerebellar network. Application of neuroimaging modalities in combination with cognitive challenge paradigms provide powerful techniques to pursue these questions.

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