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Frontal lobe dysfunction in long-term cannabis users

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Abstract

This study examined the neurophysiological effects of cannabis. Cerebral blood flow (CBF) was measured in 12 long-term cannabis users shortly after cessation of cannabis use (mean 1.6 days). The findings showed significantly lower mean hemispheric blood flow values and significantly lower frontal values in the cannabis subjects compared to normal controls. The results suggest that the functional level of the frontal lobes is affected by long-term cannabis use. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Cannabis; Marijuana; Long-term; Cessation; Cerebral blood flow; Verbal fluency

1. Introduction

Although many studies have reported behavioural alterations and cellular effects in connection with cannabis (see reviews in Refs. [15,31]), relatively little is still known about the neurophysiological effects of cannabis on brain function. Neuroimaging data have been derived from studies focusing both on chronic users and on acute marijuana exposure. A summary of neuroimaging studies is shown in Table 1. These studies suggest that abstinence from smoking results in depressed cerebral metabolism in chronic users, while acute exposure reverses this condition [13].

The initial study by Tunving et al. [32] showed subnormal cerebral blood flow (CBF) in long-term cannabis users who were assessed within 1 week of cessation of use. No significant regional flow differences were noted in comparison to normal age- and sex-matched healthy controls. In four of the subjects, CBF returned to normal levels after the washout period, that is, after allowing time for cannabinoid residues to be eliminated from the body. Contemporaneously, Mathew et al. [16] assessed chronic users after 12 h of abstinence and found no difference in CBF between chronic marijuana users and normal subjects, but there was a trend toward lower CBF values in the cannabis group [22], and in an acute study, experienced smokers had a lower presmoking baseline than controls [22]. In a study using positron emission tomography (PET), Volkow et al. [34] injected chronic marijuana users and nonusers with 2 mg Δ-9-tetrahydrocannabinol (THC). Comparison of their preinjection measures revealed that baseline cerebellar metabolism was lower in chronic marijuana users compared to controls. In a single photon emission computed tomography (SPECT) study, Amen and Waugh [2] found that 25 of 30 (83%) marijuana users with attention deficit/hyperactivity disorders (AD/HD) showed a decreased perfusion in the prefrontal cortex compared to a non-marijuana-using AD/HD control group. However, the marijuana group also demonstrated marked decreased activity in the right and left temporal lobes.

Yurgelun-Todd et al. [36] assessed chronic marijuana smokers twice with functional magnetic resonance imaging (fMRI) after 24 h and 28 days. A visual working memory task with known sensitivity was used as a cognitive challenge paradigm. The control subjects produced significant activation in the dorsolateral prefrontal cortex (DLPFC) during the challenge paradigm. Smokers who completed 24 h of washout showed diminished activation in this region. The effect remained diminished after 28 days of washout, although some increase in the DLPFC activation was noted relative to the 24 h time point. In contrast, smokers produced increased activation in the cingulate during both washout conditions, whereas controls did not.

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

	Method	Number of subjects/age	Frequency of use	Cannabis effect studied	Total duration of use	Total abstinence	No other drugs	THC potency/ administration	Testing conditions[a]
Tunving et al. [32]	^{133}Xe[b]	9/24.2 years	Minimum daily use for 6 months	Chronic	9.8 years	5.8 days (range 3–12 days)	3 months	Not reported/none	Rest
Mathew et al. [16]	^{133}Xe[b]	17/25.5 years	Minimum six joints per week for 6 months	Chronic	2.3 years	12 h	2 weeks	Not reported/none	Rest
Mathew et al. [18]	^{133}Xe[b]	26/25.9 years	Minimum 10 joints per week for 3 years	Acute/chronic	3 years/not 3 years	12 h	1 month	2.2%, 0.004%/smoke	Rest
Volkow et al. [33]	PET[c], FDG[d]	8/34.0 years	Minimum one joint every 2 months	Acute	Not reported	2 weeks	2 weeks	2.0 mg/intravenous	Rest
Mathew et al. [18]		10/26 years				3 months		3.5%	
Mathew et al. [19]	^{133}Xe[b]	35/27.1 years	No marijuana <2 weeks	Acute	Not reported	2 weeks	1 year	3.58% 1.75%/smoke	Rest
Volkow et al. [34]	PET, FDG	8/31 years	No marijuana <18 months	Acute/chronic	5.5 years	18 months	72 h	2.0 mg/intravenous	Rest
Mathew et al. [20]	PET, ^{15}O[e]	32/32.5 years	No marijuana <6 months	Acute	Not reported	2 weeks	6 months	0.15 mg/min, 0.25 mg/min/ intravenous	Rest
Amen et al. [2]	Spect	30/28 years	Weekly	Chronic/AD/HD	1 year	24 h	Not reported	Not reported	Rest
Mathew et al. [21]	PET, ^{15}O MRI	46/NR	147 ± 165 joints per year			2 weeks	24 h		Rest
Yurgelun-Todd et al. [36]	fMRI	8/NR	Daily	Chronic	5000 times in life	24 h, 28 days	Not reported	Not reported	Activation
Mathew et al. [22]	PET, ^{15}O	59/31.8 years	Not reported	Acute	Not reported	2 weeks	6 months	0.15 mg/min, 0.25 mg/min/ intravenous	Rest
Block et al. [6]	MRI	18/NR	Seven or more per week	Chronic	2 years	24 h	30 days	Not reported	Rest
Block et al. [5]	PET, ^{15}O	18/24 years	Seven times per week for 2 years	Chronic	2 years	24 h	Not reported	Not reported	Activation
Block et al. [7]	PET, ^{15}O	17/22.4 years	Seven times per week for 2 years	Chronic	2 years	33.5 h	30 days	Not reported	Rest

[a] Rest = the subject was instructed to rest, to relax, and not to think. Activation = measurements during a cognitive challenge paradigm.
[b] $^{133}Xenon$ inhalation technique.
[c] Positron emission tomography.
[d] ^{18}F-2-fluoro-2-deoxyglucose.
[e] ^{15}O-water.

These results indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use. Using PET and a cognitive challenge paradigm, Block et al. [6] found that chronic marijuana use was related to decreased memory-related activation in users relative to controls. The results revealed a number of between group differences in prefrontal regions. Using PET in a resting paradigm, the same authors [7] found that after 26 h of controlled abstinence, 17 young frequent marijuana users showed hypoactivity relative to controls in a large region of bilateral posterior cerebellar hemispheres, vermis, and in left and right ventral prefrontal cortex (Brodmann's area 11). Compared with average whole brain activity in controls, marijuana users showed 9% lower values. Block et al. [5] also used MRI to investigate brain structure in 18 young, currently frequent marijuana users. The users showed no evidence of cerebral atrophy or global or regional changes in tissue volumes compared to controls.

Acute exposure to marijuana has consistently resulted in increases in CBF measures among users. Mathew et al. [18] reported that administration of marijuana cigarettes to inexperienced users lead to a reduction of CBF compared to the baseline values, 60 min after smoking marijuana. On the other hand, administration to experienced users produced an increase of CBF (compared to the baseline) that reached significance in the frontal regions bilaterally and left temporal regions. In a successive study, Mathew et al. [20] gave marijuana cigarettes of different potencies to subjects with a history of cannabis use. The results showed a dose-related increase in CBF, with the highest increase in the high-potency cigarettes. In a PET study, Volkow et al. [33] administered THC intravenously to eight male volunteers with a history of cannabis use. Three of the subjects showed an increase in brain metabolism compared to baseline, whereas three showed a decrease and two showed no change. The results suggested different individual responses to the drug. In a subsequent study [34], chronic marijuana users and normal subjects were injected with 2 mg THC. Besides an increase in the global metabolism, the users also showed regional metabolic increases in orbitofrontal cortex, prefrontal cortex, and basal ganglia, which were not seen in the normal group. Mathew et al. [19] also reported an increase in blood flow after intravenous infusion of THC to subjects with a history of marijuana use. The regional flow increases reached statistical significance in frontal regions, insula, cingulate gyrus, and subcortical regions. The same authors in a recent study [21] also reported similar regional findings of increased blood flow after cannabis administration to experienced users.

In summary, cannabis produces various metabolic changes in the brain. Long-term cannabis users appear to have lower resting levels of CBF compared with non-smokers. Administration of cannabis increases CBF and brain metabolism in experienced users, while it decreases CBF in nonusers. These effects have been particularly apparent in frontal cortical areas. Cessation of chronic use is hypothesised to lead to a decrease in the functional level of the frontal lobes in experienced users shortly after cessation. The washout period is important to consider. The results from one study with a challenge paradigm [36] indicate that even after an extended washout period (28 days), specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use. Loeber and Yurgelun-Todd [13] postulate that a washout period of 3 days is the minimum required in order to have negligible levels of metabolites in the body. In the present exploratory study of 14 long-term cannabis users assessed within 5 days of cessation of cannabis use, CBF was measured during resting conditions using the same ^{133}Xe-inhalation method as previously described by Tunving et al. [32] and Mathew et al. [16,18].

2. Materials and method

2.1. Subjects

The characteristics of the cannabis group are shown in Table 2. Fourteen subjects (mean age 29.8 years, S.D. 5.0) were recruited from a detoxification unit (11 subjects) and an outpatient clinic at St. Lars Hospital, Lund, Sweden between 1987 and 1995. All subjects applied voluntarily to the units for detoxification of cannabis. The cannabis users had daily cannabis consumption estimated between 0.5 and 5–10 g (mean 2.4 g, S.D. 1.7) of mainly Moroccan hashish with a content of about 6–8% THC [35]. The preceding period of abuse was between 6 months and 21 years (mean 8.3 years, S.D. 5.6), with a total duration of abuse between 7 and 21 years (mean 12.3 years, S.D. 4.5). Users were assessed within 5 days (mean 2 days) after cessation. All had cannabis metabolites in urine at admission. All users were right handed. Handedness was assessed by the Edinburgh Handedness Inventory [26]. Subjects with signs of brain damage or history of psychiatric illness were excluded based on a detailed medical history and a thorough somatic-neurological examination. We also excluded subjects with a history of alcohol or other drug use. All subjects were cigarette smokers and met all seven criteria of Cannabis Dependence according to Diagnostic and Statistical Manual (DSM-IV) [3].

2.2. The reference group

An age-matched control group ($n = 14$) served as a reference in this study. Individuals were recruited among right-handed, nonsmoking male university students. The mean age of the sample was 27.8 years (S.D. 5.2, range 22–39). They were found healthy based on the results of an extensive medical questionnaire. Handedness was assessed by the Edinburgh Handedness Inventory [26]. All subjects were informed in detail about the measurement procedure

Table 2
Characteristics of the cannabis group

Age (years)	Case	Cannabis consumption (g/day)	Frequency of use	Duration of preceding period of abuse (years)	Total duration of abuse (years)	Time between end of abuse and measurement (days)
Male, 39	1	2	Daily	2	19	2
Male, 33	2	2–4	Daily	7	7	1
Male, 24	3	2	Daily	8	9	3
Male, 35	4	3–4	Daily	21	21	2
Male, 23	5	2	Daily	4	8	1
Male, 28	6	1	Daily	0.5	14	1
Male, 34	7	0.5	Daily	14	14	3
Male, 36	8	1–2	Daily	15	15	2
Male, 29	9	4	Daily	11	12.5	2
Male, 23	10	1	Daily	7	7	1
Male, 29	11	1	Daily	10	10	1
Male, 30	12	5–10	Daily	9	15	1
Female, 27	13	2	Daily	4	7	2
Female, 27	14	3–4	Daily	3.5	14	5

and purpose of the study before acceptance to participate by requirements of the ethical committee. The Ethics Committee and the Radiation Safety Committee at Lund University, Sweden approved the study.

2.3. Urine tests

Emit[8]ll SB3 [4] was used in the routine clinical assessment of substances in urine. This assessment was done at admission to the detoxification unit. All patients showed high or very high concentration of cannabis metabolites (80–100 g/l). Absolute values above 100 g/l were not reported as they are of no clinical value. No evidence of central stimulants, opiates, barbiturates, and tranquilisers was seen in the subjects' urine. Urine sampling was supervised for authenticity.

2.4. CBF measurements

Measurements were made by the ^{133}Xe inhalation technique using a high-resolution system (Cortexplorer 256 HR; Ceretronix, Randers, Denmark) with 254 stationary detectors [10 × 10 mm Nal(Tl) crystals] mounted in a pneumatically controlled helmet. The system adjusts for differences in head size and shape, and the position of the head is standardised in relation to bony landmarks (nasion and ear channels) by means of light crosses [28]. This makes it possible to reposition the subject accurately in successive measurements. A minute of ^{133}Xe inhalation (70–100 MBq/l) was followed by 10 min of normal air breathing according to the standard procedure [24]. Before the administration of the isotope, the background activity was measured (30 s for the first measurement and 5 min for the repeated measurement) [27]. The measurement procedure was carefully explained before the study and the subjects were instructed to keep their eyes closed under the eye pads and to relax without falling asleep. Noise levels from various mechanical sources were kept at a minimum. The Initial Slope Index (ISI), a predominantly grey matter flow parameter [29], was chosen as a measure of cortical blood flow due to its high stability and reliability [25].

Arterial $PaCO_2$ was estimated from recordings of end-tidal CO_2 concentrations (Ohmeda gas-analyser), and the variation in $PaCO_2$ was corrected to a level of 40 mmHg using the standard procedure [23]. To ensure that subjects were relaxed during the measurement procedure, heart rate and respiratory rate were monitored during each measurement.

2.5. Statistical analysis

The raw values of each probe were used to compute the mean hemispheric flow values (CBF). Between-group differences in CBF values were analysed by Mann–Whitney *U*-test after a correction to a standard $PaCO_2$ level of 40 mmHg [23]. In addition, the raw values were transformed into distribution-normalised values (in percentage of the hemispheric mean). Thus, the analyses were based on both raw values and distribution-normalised values. To reduce the probability of type I errors, the 254 probes were combined into 14 regions of interest, seven for each hemisphere (see Tables 3 and 4). The

Table 3
Regional cerebral blood flow (percentage of hemispheric mean)

	Cannabis users ($n=12$)		Normal controls ($n=14$)	
Region	Right	Left	Right	Left
Prefrontal	104.7 ± 2.1	104.3 ± 2.4	107.0 ± 4.6	105.3 ± 3.2
Superior frontal	100.7 ± 1.6*	100.7 ± 1.5	102.0 ± 1.6	101.6 ± 2.0
Frontotemporal	104.0 ± 2.3	102.6 ± 1.5	103.9 ± 2.2	103.0 ± 2.3
Temporal	100.8 ± 1.3**	100.0 ± 1.8*	98.6 ± 2.0	97.9 ± 2.1
Central	97.1 ± 1.8	96.9 ± 1.8	98.1 ± 1.7	97.2 ± 2.0
Parietotemporal	98.1 ± 1.5	98.0 ± 1.6	98.4 ± 1.8	97.9 ± 2.0
Occipital	98.7 ± 3.1	99.3 ± 3.3	96.9 ± 3.1	97.7 ± 3.3

Figures denote means and standard deviation.
* $P<.05$.
** $P<.01$ (Mann–Whitney *U*-test).

Table 4
Regional cerebral blood flow (absolute values)

	Cannabis users ($n=12$)		Normal controls ($n=14$)	
Region	Right	Left	Right	Left
Prefrontal	55.3 ± 7.8*	55.2 ± 8.4†	62.4 ± 8.0	61.4 ± 7.4
Superior frontal	53.4 ± 7.6*	53.4 ± 7.3†	59.5 ± 6.5	59.3 ± 6.7
Frontotemporal	55.0 ± 8.2†	54.3 ± 7.7†	60.5 ± 6.2	60.1 ± 6.6
Temporal	53.3 ± 7.1	52.9 ± 7.0	57.5 ± 5.5	57.2 ± 5.7
Central	51.6 ± 7.1*	51.4 ± 6.9†	57.3 ± 6.2	56.8 ± 6.4
Parietotemporal	52.1 ± 6.9†	51.8 ± 6.7†	57.5 ± 6.0	57.2 ± 6.1
Occipital	52.5 ± 7.1	52.5 ± 6.8	56.6 ± 5.4	57.0 ± 5.6

Figures denote means and standard deviation.
* $P<.05$ (Mann–Whitney U-test).
† $P<.10$.

mean of the probe distribution values for each region was determined, and these values were used in the regional analysis. Spearman's coefficient was used to discern patterns of regional intercorrelation.

3. Results

3.1. Mean hemispheric blood flow (CBF)

The $PaCO_2$-uncorrected flow values in the cannabis group [50.9 (0.1) and 51.2 (10.5) for the right and left hemispheres, respectively] were significantly lower ($P<.03$) than in the normal reference group [56.0 (5.6) and 55.6 (5.7)]. However, the arterial $PaCO_2$ value for the cannabis group [34.4 (4.0)] was lower than in the normal reference group [36.5 (3.1), $P<.13$]. Thus, we calculated the CBF values after a standard correction procedure to 40 mmHg [23]. The corrected mean hemispheric flow values were not significantly different between groups: 55.4 (9.2) and 55.2 (8.8) for the cannabis group and 58.5 (6.0) and 58.2 (6.2) for the normal subjects. Since women have been shown to have higher CBF than men [30], the two women were excluded from the cannabis group. The control group exclusively consisted of men. After this correction, the mean hemispheric values in the cannabis group decreased to 53.1 (7.3) and 52.9 (7.1), respectively, and there was a trend towards a significant group difference ($P<.06$) for both hemispheres. It is interesting to note that the difference in mean CBF between the cannabis users and the normal subjects (9%) was similar to that reported by Tunving et al. [32] who also investigated male subjects.

3.2. Regional distribution values

When regional CBF was expressed in terms of percentages of the respective hemispheric means, a highly significant augmentation in flow could be observed bilaterally in the temporal lobe in the cannabis users as well as a significant hypofrontality restricted to the right superior frontal lobe (Table 3).

On the other hand, when the same comparisons were based on absolute blood flow levels, the temporal augmentation in flow disappeared. Instead, a significant reduction or trend ($P<.10$) toward a reduction in blood flow could be seen in the cannabis users in all regions but the temporal and occipital lobe. Differences in comparisons with controls were more prominent in the right hemisphere (Table 4).

The augmentation in flow detected in the temporal lobes of cannabis users when data are presented in percentages thus appears to be an artefact and the result should rather be interpreted as preservation or a not so drastic reduction as seen in other regions of the cerebral cortex. Also, the occipital region seems relatively resistant to long-term cannabis use according to these measurements.

No significant correlation was seen between the regional flow values and the preceding or total duration of cannabis use or cannabis consumption.

4. Discussion

This study supports previous findings of decreased CBF values with lower regional flow in frontal regions after long-term cannabis use. Before discussing the findings, some limitations of the present study must be considered. The sample was small and may not be representative of cannabis users overall. The majority of the subjects included in our study were motivated to abstain from cannabis and chose hospitalisation to succeed. Thus, we do not know whether cannabis users who were not motivated to apply for help or who had a shorter duration of abuse would differ to those included in the present study. There may be a number of confounding factors, which could have influenced our findings. Tobacco smoking is a clear confound as all of the cannabis users smoked tobacco while our reference group consisted only of nonsmokers. However, in contrast to our findings, Hagstadius and Risberg [10] reported no significant difference in mean CBF between tobacco smokers and nonsmokers. The regional differences observed here between cannabis users and nonusers have also been related to high levels of anxiety [12] which were not measured in this study.

4.1. Mean hemispheric flow

In this study, we measured CBF in cannabis subjects shortly after cessation of use. The results showed a trend toward reduced flow for both hemispheres in the cannabis group compared with normal control subjects. These results are consistent with previous research (e.g. Tunving et al. [32], Mathew et al. [18], and Volkow et al. [34]).

4.2. Regional CBF

We also found significantly lower regional flow values in the right prefrontal, superiorfrontal, and central areas. This

is consistent with Mathew et al.'s [18] findings but not with Tunving et al.'s [32]. The reason for this discrepancy between studies is unclear. The variation in findings cannot be explained by differences in cannabis consumption, frequency of use, or the total duration of use. Thus, the cannabis groups were clinically similar to each other in terms of abuse. One possible explanation may pertain to methodological differences between Tunving's and our study. The spatial resolution of the 32 detector system for two-dimensional measurements used in Tunving's study was relatively poor (in the order of 3–5 cm). This may have limited the possibility of describing more narrowly localised cortical blood flow changes compared to the high-resolution system used in our study (1 cm). More importantly, however, we believe that an explanation might be found in the fact that subjects were studied at different time points after cessation of use. The mean duration between the last cannabis use and measurements in Tunving's study was 5.8 (range 1–12) days, whereas we assessed our subjects after a mean period of 1.6 (1–3) days after cessation. This difference in time of assessment after cessation may be an important factor because the terminal half-life of THC is between 1 and 7 days with an average of 2–5 days [1]. Thus, it might well be the case that if subjects are assessed within the terminal half-life of THC, brain imaging findings will reflect the lingering effects of drug residues to a higher degree than when subjects are assessed at a later stage of abstinence. Consistent with this hypothesis, Mathew et al. [18] reported lower frontal values in experienced cannabis users who were assessed within 12 h of cessation. A washout period of 3 days should be the minimum in order to have negligible levels of cannabinoid metabolites in the body [13].

The interpretation of findings from previous studies and reduction to a single definitive theory is difficult because of a number of factors aside from the time of assessment after cessation. Changes in brain function may also relate to different models of administration. Thus, the effects of cannabis on brain function and metabolism might differ according to whether effects of detoxification are studied, whether cannabis is administered to inexperienced or to experienced users, and whether subjects are given THC in experimental doses, either orally or intravenously. Taken together, the results of most studies suggest that the acute effects of cannabis or THC differ in inexperienced and experienced subjects. These differences in response to the drug might relate to variations in the brain's adaptation to the exposure of cannabis.

It has recently been reported that cannabis may have an effect on the cerebral vasculature. Hillard [11] reports from a review of endocannabinoids and vascular function that in the cerebral circulation, cannabinoids reduce vascular smooth muscle cell calcium influx and cause vasodilatation directly through CB1 receptors. This finding is consistent with evidence reported by Mathew et al. [17] that marijuana produces an increase in CBF in humans that is not due to changes in sympathetic regulation of the cerebral circulation. It may also be the mechanism by which marijuana impairs cerebral autoregulation in response to changes in posture. This vasodilatory effect confirms previous findings by Ellis et al. [8] who reported that low concentrations of cannabinoid increase the diameter of cerebral vessels and thus increases blood flow. It is possible that blood flow increases, which have been reported after acute administration of THC, could reflect vasodilatory properties of the drug rather than primary functional changes in the brain's neurones. To what extent hemodynamic factors may play a role in this context is still not understood. Gebremedhin et al. [9] showed that the maximum increase in CBF was seen after 90 min, which is well within limits of most experimental studies. However, it seems unlikely that such hemodynamic effects could have influenced our findings, as we assessed the subjects after a mean period of 1.6 days and found decreased blood flow.

It is unclear to what extent the lower level of flow values found in this study corresponds to individual cognitive capacity. Cannabis-induced cognitive dysfunction was found in the same group of cannabis users in another study [14] and was likened to a prefrontal impairment. The reduced blood flow, as seen in this study, may be a reflection of the passivity and bluntness seen in long-term users not being acutely intoxicated, and the increased blood flow observed after acute administration in other studies may reflect an effort to compensate for the impairing effects of cannabis and overt attempts to improve in cognitive functioning.

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References

[1] S. Agurell, M. Halldin, J.-E. Lindgren, A. Ohlsson, M. Widman, H. Gillespie, L.E. Hollister, Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man, Pharmacol. Rev. 38 (1) (1986) 21–43.

[2] D.G. Amen, M. Waugh, High resolution brain SPECT imaging of marijuana smokers with AD/HD, J. Psychoact. Drugs 30 (1998) 209–214.

[3] American Psychiatric Association, Quick Reference to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), American Psychiatric Association, Washington, DC, 1994.

[4] Behring Diagnostics, Syva and Behring Diagnostics Products, Cupeclino, CA 95014, USA, 1997.

[5] R.I. Block, D.S. O'Leary, J.C. Ehrhardt, J.C. Augustinack, M.M. Ghoneim, S. Arndt, J.A. Hall, Effects of frequent marijuana use on brain tissue volume and composition, NeuroReport 11 (2000) 491–496.
[6] R.I. Block, D.S. O'Leary, R.D. Hichwa, J.C. Augustinack, L.L. Boles Ponto, M.M. Ghoneim, et al., Effects of chronic marijuana use on regional cerebral blood flow during recall, Soc. Neurosci. Abstr. 25 (1999) 2077.
[7] R.I. Block, D.S. O'Leary, R.D. Hichwa, J.C. Augustinack, L.L. Boles Ponto, M.M. Ghoneim, S. Arndt, J.C. Ehrhardt, R.R. Hurtig, G.L. Watkins, J.A. Hall, P.E. Nathan, N.C. Andreasen, Cerebellar hypoactivity in frequent marijuana users, NeuroReport 11 (2000) 749–753.
[8] E.F. Ellis, S.F. Moore, K.A. Willoughby, Annadamide and delta 9-THC dilation of cerebral arterioles is blocked by indomethacin, Am. J. Physiol. 269 (1995) H1859–H1864.
[9] D. Gebremedhin, A.R. Lange, W.B. Campbell, C.J. Hillard, D.R. Harder, Cannabinoid CB1 receptor of cat cerebral arterial muscle functions to inhibit L-type Ca^{2+} channel current, Am. J. Physiol. 276 (1999) H2085–H2093.
[10] S. Hagstadius, J. Risberg, Regional cerebral blood characteristics and variations with age in resting normal subjects, Brain Cognit. 10 (1989) 28–43.
[11] C.H. Hillard, Endocannabinoids and vascular function, J. Pharmacol. Exp. Ther. 294 (1) (2000) 27–32.
[12] A. Johansson, Neuropsychological Studies of Dementia and Anxiety, Academic Thesis Lund, Lund University Press, 1991.
[13] R.T. Loeber, D.A. Yurgelun-Todd, Human neuroimaging of acute and chronic marijuana use: Implications for frontocerebellar dysfunction, Hum. Psychopharmacol. Clin. Exp. 14 (1999) 291–301.
[14] T. Lundqvist, Cognitive Dysfunctions in Chronic Cannabis Users Observed During Treatment, an Integrative Approach, Almqvist & Wiksell International, Stockholm, 1995.
[15] B.R. Martin, E.J. Cone, Chemistry and pharmacology of cannabis, in: H. Kalant, W. Corrigal, W. Hall, R. Smart (Eds.), The Health Effects of Cannabis, Addiction Research Foundation, Centre for Addiction and Mental Health, Toronto, 1999, pp. 19–68.
[16] R.J. Mathew, S. Tant, C. Berger, Regional cerebral blood flow in marijuana smokers, Br. J. Addict. 81 (1986) 567–571.
[17] R.J. Mathew, W.H. Wilson, T.G. Turkington, R.E. Coleman, Cerebellar activity and disturbed time sense after THC, Brain Res. 797 (1999) 183–189.
[18] R.J. Mathew, W.H. Wilson, S.R. Tant, Acute changes in cerebral blood flow associated with marijuana smoking, Acta Psychiatr. Scand. 79 (1989) 118–128.
[19] R.J. Mathew, W.H. Wilson, R.E. Coleman, T.G. Turkington, T.R. DeGrado, Marijuana intoxication and brain activation in marijuana smokers, Life Sci. 60 (23) (1997) 2075–2089.
[20] R.J. Mathew, W.H. Wilson, D. Humphreys, J.V. Lowe, K.E. Weithe, Depersonalization after marijuana smoking, Biol. Psychiatry 33 (1993) 431–441.
[21] R.J. Mathew, W.H. Wilson, N.Y. Chiu, T.G. Turkington, R.E. Coleman, Regional cerebral blood flow and depersonalization after tetrahydrocannabinol administration, Acta Psychiatr. Scand. 100 (1999) 67–75.
[22] R.J. Mathew, W.H. Wilson, Substance abuse and cerebral blood flow, Am. J. Psychiatry 148 (1991) 292–305.
[23] V.A. Maximilian, I. Prohovnik, J. Risberg, The cerebral hemodynamic response to mental activation in normo- and hypercapnia, Stroke 11 (1980) 342–347.
[24] W.D. Obrist, H.K. Thompson Jr., H.S. Wang, W.E. Wilkinson, Regional cerebral blood flow estimated by 133xenon inhalation, Stroke 6 (1975) 246–256.
[25] W.D. Obrist, W.E. Wilkinson, Stability and sensitivity of CBF indices in the noninvasive ^{133}Xe method, in: A.H. Hartmann (Ed.), Cerebral Blood Flow and Metabolism Measurement, Springer-Verlag, Berlin, 1985, pp. 30–36.
[26] R.C. Oldfield, The assessment and analysis of handedness: The Edinburgh Inventory, Neuropsychologia 9 (1971) 97–113.
[27] J. Risberg, Regional cerebral blood flow measurements by ^{133}Xe-inhalation: Methodology and applications in neuropsychology and psychiatry, Brain Lang. 9 (1980) 9–34.
[28] J. Risberg, Development of high-resolution two-dimensional measurement of regional cerebral blood flow, in: J. Wade, S. Knezevic, V.A. Mubrin, Z. Mubrin, I. Prohovnik (Eds.), Impact of Functional Imaging in Neurology and Psychiatry, John Libbey and Co., London, 1987, pp. 35–43.
[29] J. Risberg, J.H. Halsey, E.L. Wills, E.M. Wilson, Hemispheric specialization in normal man studied by bilateral measurement of the regional cerebral blood flow, Brain 98 (1975) 511–524.
[30] G. Rodriguez, S. Warkentin, J. Risberg, G. Rosadini, Sex differences in regional cerebral bloodflow, J. Cereb. Blood Flow Metab. 8 (1988) 783–789.
[31] N. Solowij, Long-term effects of cannabis on the central nervous system. Brain function and neurotoxicity: II. Cognitive functioning, in: H. Kalant, W. Corrigal, W. Hall, R. Smart (Eds.), The Health Effects of Cannabis, Addiction Research Foundation, Centre for Addition and Mental Health, Toronto, 1999, pp. 195–265.
[32] K. Tunving, O. Thulin, J. Risberg, S. Warkentin, Regional cerebral blood flow in long-term heavy cannabis use, Psychiatr. Res. 17 (1985) 15–21.
[33] N.D. Volkow, H. Gillespi, N. Mullani, L. Tancredi, C. Grant, M. Ivanovic, L. Hollister, Cerebellar metabolic activation by delta-9-tetrahydrocannabinol in human brain: A study with positron emission tomography and ^{18}F-2-fluoro-2-deoxyglucose, Psychiatr. Res.: Neuroimaging 40 (1991) 69–78.
[34] N.D. Volkow, H. Gillespie, N. Mullani, L. Tancredi, C. Grant, A. Valentine, L. Hollister, Brain glucose metabolism in chronic marijuana users at baseline and during intoxication, Psychiatr. Res.: Neuroimaging 67 (1996) 29–38.
[35] A.M. Von Wachenfelt, Personligt medellande, in: J. Ramström J. (Ed.), Skador av hasch och marijuana, Stockholm Socialstyrelsen, SoS-rapport, 1997, p. 16.
[36] D.A. Yurgelun-Todd, S.A. Gruber, R.A. Hanson, A.A. Baird, P.F. Renshaw, H.G. Pope, Residual effects of marijuana use: A fMRI study, in: L.S. Harris (Ed.), Problems of Drug Dependence 1998: Proceedings of the 60th Annual Scientific Meeting of the College on Problems of Drug Dependence, NIDA Res. Monogr. vol. 179, National Institute on Drug Abuse, Bethesda, MD, 1999, p. 78.