

# Recent scientific data

## Recent scientific data on the consequences of cannabis use (20/10/2003)

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In this paper the data is presented in the following context:

- A description of the areas with high cannabinoid receptor density and their neuropsychological function.
- Findings in Brain imaging studies.
- Differences in short term use - long term use.
- The effect of the cannabinoids on the cognitive input and output process in a neuropsychological perspective.
- The influence on the cognitive functions used in daily life.

First, a word from an unknown spokesman of the Assyrian society, 4000 BC. Cannabis, called GAN-ZI-GUN-NU, is "the drug that takes the mind away". In 1860 Charles Baudelaire gave us this observation: "What hashish gives with one hand it takes away with the other: that is to say, it gives you power of imagination and takes away the ability to profit by it."

Rarely are the consequences of cannabis use described so eloquently by its users as in this extract from Baudelaire writing in the mid-nineteenth century. After euphoria, the acute cognitive effects of cannabis are among those that are most often sought by those who use the drug. Loosening of associations, the intensification of ordinary experience, a heightening of humour, pleasant imaginative reverie, are all cognitive effects that provide users with a welcome relief from tedium of everyday life. It has long been suspected that the price paid for the regular elicitation of these diverting cognitive effects of cannabis may be some type of enduring, cognitive impairment, and thus the loss of the ability to profit by its use. There is a prima facie case to support this suspicion.

## The cannabis receptor and endogenous ligand

The discovery of the cannabinoid receptor and its endogenous ligand revolutionised previous conceptions of the mode of action of the cannabinoids, and the localisation of cannabinoid receptors in brain helps in understanding of cannabis' pharmacology.

High densities in the hippocampus and cortex suggest roles for the cannabinoid receptor in cognitive functions. In fact, in humans the dominant effects of cannabis are cognitive. Highest densities in the basal ganglia and cerebellum suggest a role for the cannabinoid receptor in movement control, and probably in giving the system an "attitude", sometimes called the amotivational syndrome in cannabis users. The cannabinoids probably interfere with the

normal processing of sensory information by interrupting the transmission of neural activity between the hippocampus, cortex and other brain regions, causing a fragmentation of the neuropsychological network.

Given the wide distribution of cannabinoid receptors in brain, it is not surprising that the behavioural and physiological actions of cannabinoids are so diverse.

Further, it is necessary to understand the mechanisms concerning Anandamide, the endogenous ligand for the cannabinoid receptor. Anandamide is probably involved in psychologically important processes like control of psychomotor activity and subjective perception. The aftermath of long term use of cannabis includes sleeping anomalies and feelings of emptiness. Recent findings in the field of neurochemistry give us reasons to suggest that this may be a result of the role of anandamide as a neurotransmitter and neuromodulator. Clinical observations indicate that these symptoms may remain for months after cessation of use.

### **Frontal cortex**

A few words about that region of the brain that is most sensitive to cannabis exposure, the frontal cortex.

The function of the frontal cortex is to exhibit the overall control and planning functions, allows the individual to form the structures at the highest levels of behavioural hierarchy and helps the bridging of temporal discontinuities within them.

Executive function is thought to serve as a marker of frontal lobe function and thus it may be that this part of the central nervous system may be particularly vulnerable to cannabis exposure. The executive function is noted to be negatively associated with cannabis exposure, and involve self-regulatory abilities, the ability to maintain attention, and the ability to act on accumulated knowledge.

An example of executive functioning. You all know the alphabet of your own language. This is a test of your executive capacity, reading this paper.

1. Please say the alphabet silently for yourself.
2. Please say it loud
3. Please say every second letter loud.

You are now aware of your own executive capacity. This is the function that is extremely sensitive to the effects of the cannabinoids. When this function is negatively affected, the rest of the cognitive network will be affected.

The prefrontal cortex makes the decision how the individual should act and allocates the cognitive and motoric efforts needed for the specific event. It involves:

- planning and control,
- organisation and behavioural temporal co-ordination.
- problem solving and social intentions.

- autonomy. The source to autonomy or independence is the inner control, the attitudes, motives, and plans.
- feelings. It is through the processes in the frontal cortex that we become aware of the impulses, and permit them to influence the behaviour. The dysfunction causes emotional shallowness, listlessness, and lack of emotions.

### **Brain Imaging results**

Recent neuroimaging research has begun to address the question of metabolic changes secondary to long-term chronic cannabis use, and acute intoxication due to cannabis smoke or injection of delta-9 tetrahydrocannabinol solution. We have come a bit closer to identify brain regions responsible for the behavioural changes associated with drug intoxication. Today we have 15 published studies in this field.

In summary,

- cannabis produces various metabolic changes in the brain.
- Long-term cannabis users appear to have lower resting levels of cerebral blood flow (CBF), compared with non-smokers.
- Administration of cannabis increases CBF and brain metabolism in experienced users,
- while it decreases CBF in non-users.
- These effects have been particularly apparent in the frontal lobes, which are responsible for the cognitive functions of everyday life.
- 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.

### **recreational and long-term users**

O'Leary and colleagues (2002) assessed 12 recreational users. Smoking marijuana (moderate dose, 20 mg) did not change mean global CBF significantly.

- Increased rCBF was observed in orbital and mesial frontal lobes, insula, temporal poles, and anterior cingulate, as well as in the cerebellum. The increases in rCBF in anterior brain regions were predominantly in "paralimbic" regions that may be related to marijuana's mood-related effects.
- Reduced rCBF was observed in temporal lobe auditory regions, in visual cortex, and brain regions that may be part of an attentional network (parietal lobe, frontal lobe and thalamus).

These rCBF decreases may be the neural basis of perceptual and cognitive alterations that occurs with acute marijuana intoxication.

- The auditory activation paradigm did not show rCBF increases in temporal lobe auditory regions that were significantly different from a baseline condition.

Additionally, marijuana decreased rCBF in comparison to the baseline condition in brain regions that have been found in a number of studies to be involved in attentional modulation of sensory processing.

- Whereas rCBF increases were localised to ventral forebrain and cerebellum,
- decreases in rCBF were localised to brain regions that mediate sensory processing and attention.
- These findings suggest that it may be possible to isolate the mood-enhancing effects of marijuana (rCBF increases in ventral forebrain) from cannabis' effect on perception, attention and behaviour (decreased rCBF in sensory regions and attention-related brain systems).

The second study focus on the residual effects after cessation of long-term use.

Lundqvist and colleagues (2001) measured brain blood flow levels in 14 long-term cannabis users 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.

It is unclear to what extent the lower level of flow values found corresponds to individual cognitive capacity. However, in a study by Lundqvist (1995), the same group displayed weaknesses in cognitive functions. Thus, the reduced blood flow may be a reflection of the passivity and bluntness seen in long-term users not being acutely intoxicated. The increased blood flow observed after acute administration in other studies may reflect the reason to continue the habit. The subject gets an impression of compensating cognitive impairment.

In a small pilot study the subjects were challenged with a frontal activation task. The subjects were assessed three times with controlled abstinence, at admission, after 1 month and after three months. An increase in rCBF levels in right dorsolateral area was seen first after three months of abstinence, compared to controls.

## Surveys

There have been several surveys in the last 100 years. Recent surveys (House of Lords, England 1998, Addiction Research Foundation, Canada, 1999) conclude in an overall appraisal on:

acute effects, that cannabis induce

- anxiety, dysphoria, panic and paranoia, especially in naive users; loss of internal control.
- cognitive impairment, especially of attention and memory, for the duration of intoxication;
- psychomotor impairment, and probably an increased risk of accident if an intoxicated person attempts to drive a motor vehicle, or operate machinery;
- an increased risk of experiencing psychotic symptoms among those who are vulnerable because of personal or family history of psychosis;
- an increased risk of low birth weight babies if cannabis is used during pregnancy.

The major health and psychological effects of chronic heavy cannabis use, especially daily use over many years, remain uncertain. On the available evidence, the major probable adverse effects appear to be:

- Respiratory diseases associated with smoking as the method of administration, such as chronic bronchitis, and the occurrence of histopathological changes that may be precursors to the development of malignancy.
- Development of a cannabis dependence syndrome, characterised by an inability to abstain from or to control cannabis use;
- Subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversible after prolonged abstinence from cannabis.

In general, acute effects are better studied than those of chronic use. It is essential for the understanding of the diversity of symptoms shown in cannabis use to look for differences in short-term and long-term use, and in intensity and amount used, and to recognise that there are two kinds of influences on cognitive functions, an acute and an additional chronic effect.

Initially or with recreational use,

- the input process is affected, that is, the area of the Hippocampus,
- which will cause a disturbance in concentration, attention, and the storage and elaboration of new information, the so called tephphone effect.

The effect on the hippocampal area is similar to turn up the volume on a radio, i.e. an intensification of ordinary experience.

Regular long-term use of cannabis for about two years (sometimes once a week is sufficient),

- may impair a person's ability to efficiently process complex information, which will influence the output process, a dorsolateral task.

Additional consequences may be

- an inability to make plans,
- difficulties in temporal integration of the behaviour,
- not inclined to interpret opinions and motives of other people, little self-criticism, and emotional superficiality (apathy, listless).

Several studies confirm that long term cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use. The brain imaging studies focusing on the acute intoxication reported reduced rCBF both during resting as activated conditions in brain regions that may be part of an attentional network (parietal lobe, frontal lobe and thalamus).

Neuropsychological studies concerning long-term cannabis use and attention conclude that:

- While basic attentional processes appear to remain intact,
- long-term cannabis users are less efficient when performing complex cognitive tasks and attempting to resist distraction.
- Long-term users are less efficient at performing complex tasks that require cognitive flexibility, recognition planning strategies, and learning from experience, functions that have been clinically associated with the frontal area of the brain.

The ability of long-term users to efficiently process information declines more rapidly under a moderate cognitive load compared with controls or short duration users.

- Because language and verbal intellectual abilities appear to be unaffected, long-term cannabis users may do reasonably well coping with routine tasks of everyday life, although they may have difficulties with verbal tasks that are novel and/or which cannot be solved by automatic application of previous knowledge.

Thus, the adverse effects during the chronic influence are similar to the acute effects of cannabis.

Solowij et al found in a study focusing on clients seeking treatment that "Long term cannabis users (23.9 years) differed significantly from short term users ( 10.2 years) and controls on tests of memory, attention and time estimation, but were unrelated to measures of recent cannabis use, withdrawal symptoms or other confounds.

In recent years, clinicians have sought to characterise the specific deficits observed in chronic cannabis users, by integrating these into cognitive theory and evidence from empirical research.

Using a conceptual framework of cognitive categories in the I.Q. test weaknesses are found in general verbal ability; logical-analytic ability (making accurate inferences); psychomotility (flexibility of thought); memory (short-term and long-term recall); analytic-synthesis (ability to synthesise); psychospacial ability (perceiving environmental patterns), and gestalt memory (holistic memory).

These psychological qualities are not independent of each other. On the contrary, an interaction among them is necessary. They are different aspects of one theme: cognitive control and management of behavioural patterns. The focus is on the level of processing information.

A few examples of weaknesses observed

- Vocabulary appropriate to chronological age, finding exact words with which to express oneself,
- Critical and logical self-examination, correcting errors and mistakes logically, thinking before answering,
- establish a correct focus of attention,
- maintaining the theme of a story.
- poor recollection of the past, which refers to become aware of one's identity and existence in subjective time that extends from the past through the present to the future.
- classifying information in a correct way and understanding shades of meaning.
- being aware of one's social position relative to others, structuring the daily life.
- Creating patterns and pictures of the visual world

The clinical observations together form a psychological and behavioural profile, which seems unique to cannabis users, and the profile is, so far, reversible. The transition into such a profile occurs very slowly, which makes it difficult for instance for family members or relatives to note. This emergence of a new pattern of thinking as part of what can be

considered a cannabis state-dependent set of cognitive processes seems to be the result of, on the one hand, an individual's inborn need to explore reality in his or her own way, or the need for an identity, and, on the other hand, a deficiency in the correct structuring of the outer and inner world.

## **Conclusion**

Cognitive deficits associated with the acute and chronic use of cannabis have important theoretical and clinical significance. Brain imaging techniques do reveal neurotoxic effects of cannabis. Thus, the deficits reflect changes to the underlying cortical, sub-cortical and neuromodulatory mechanisms that underpin cognition. The main effect is on information processing which implies a deficiency to utilise your cognitive capacity.

The epidemiological literature provides uneven coverage of the possible health and psychological effects of cannabis. However, the research has helped to clarify the role that cannabis plays in impairing educational performance, mainly through the negative effect of cannabis on prefrontal functions as Executive Functioning. A third negative effect is the drugrelated self-knowledge based on difficulties in storing adequate information in the episodic memory.

I am well aware of the immense diversity of influence cannabis has on cognitive functions in humans. I do not claim that this is a complete or definitive depiction. However, it may fill in some more pieces of the seemingly infinite puzzle.

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