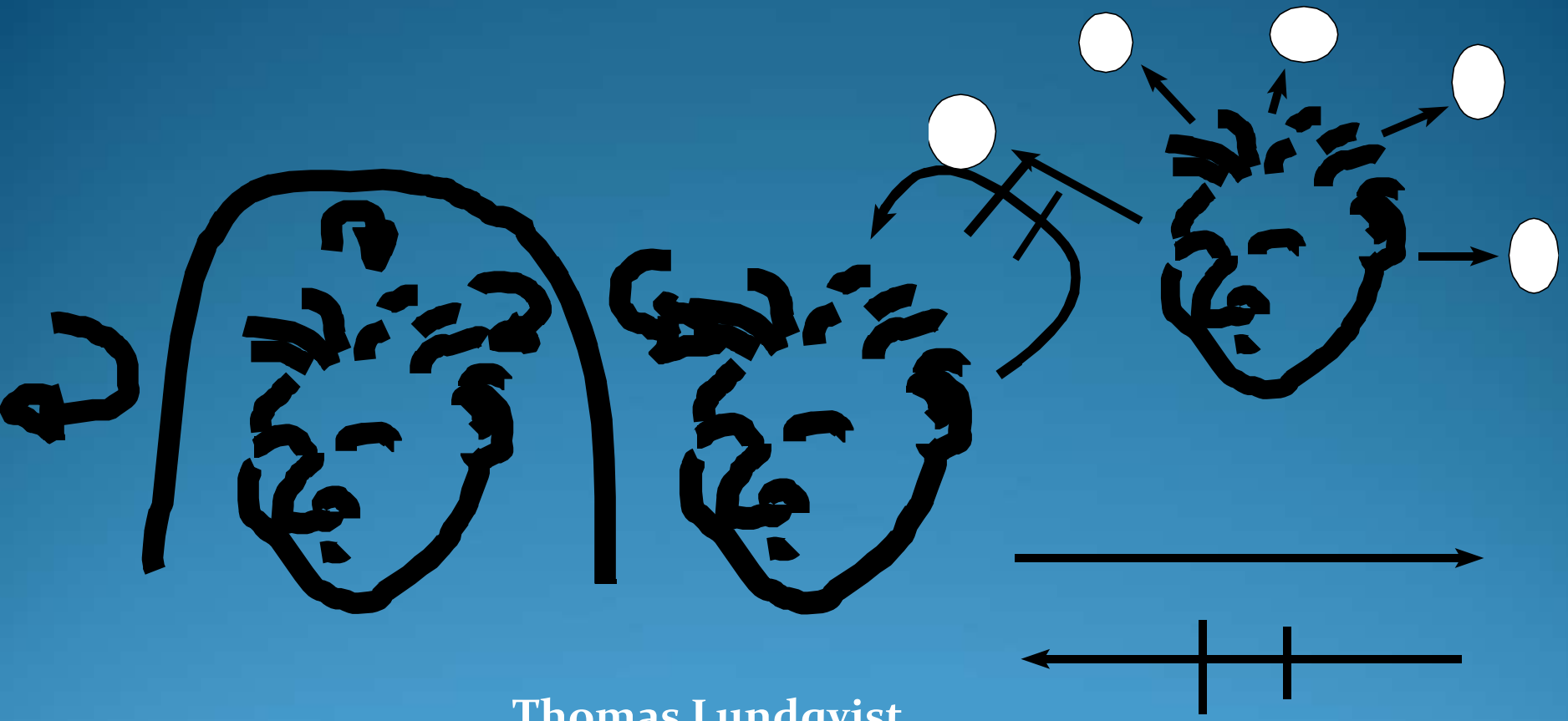
Treatment of cannabis dependance according to HAP



Thomas Lundqvist
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Drug Addiction Treatment Centre, Skåne University hospital Lund, Sweden

Brest 19 and 20 feb

www.droginfo.com

How cannabis acts on the human brain and behavior.

Dense binding of cannabinoid receptors

- hippocampus, (cognitive functions)
- cerebral cortex, (cognitive functions)
- the basal ganglia, (movement control)
- and cerebellum, (movement control)

- The localisation of the cannabinoid receptor with high densities in basal ganglia, cerebral cortex and hippocampus (Herkenham et al., 1990) is an indication of cannabinoid involvement in attentional and memory processes.

- 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.

Cannabis influence on the brain

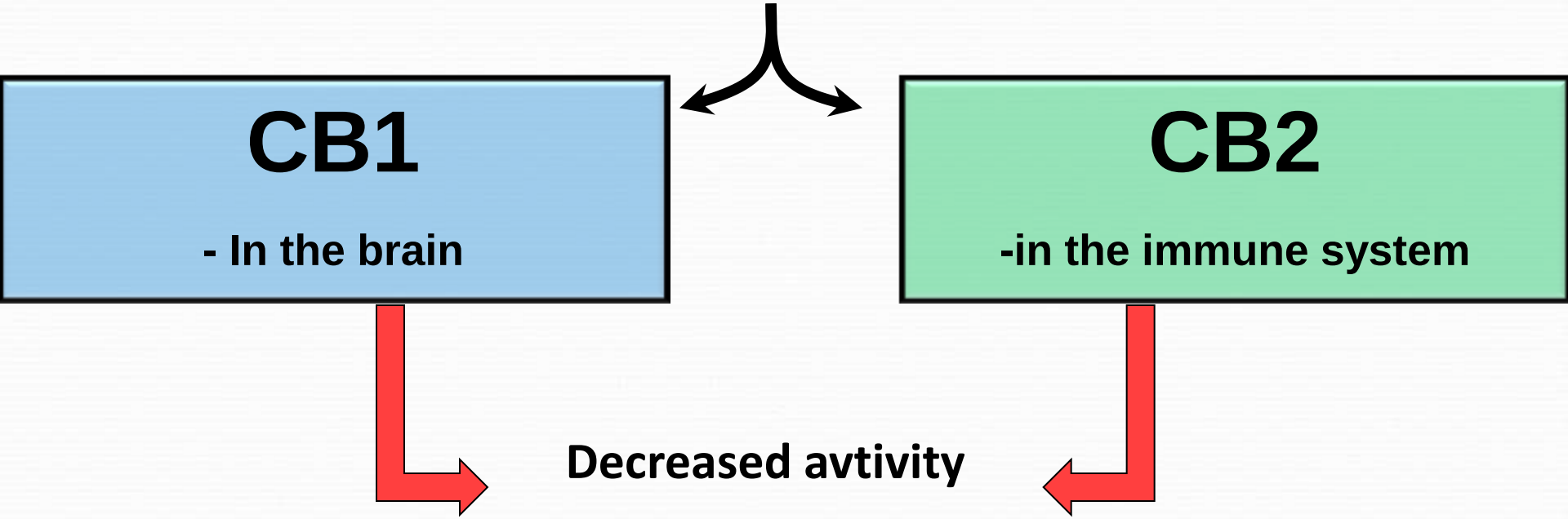
”What hashish gives with one hand it takes away with the other: that is to say, it gives you power of imagination and takes away the ability to profit by it” (Baudelaire 1860).

THC

endocannabinoids

synhtetic cannabinoids CB1 and CB2 agonister

Binds to cannabinoidreceptor



Endocannabinoids are blocked by cannabinoids and synthetic cannabinoids

- Anandamide is involved in the regulation of
- mood,
- memory,
- appetite,
- pain,
- cognition and
- emotion and
- to consolidate fine moments.
- The research has identified additional 9 pcs. endocannabinoids.

Mol Neurobiol. 2007 Aug;36(1):92-101. Epub 2007 Aug 17.

The endocannabinoid system and extinction learning.

Lutz B.

The endocannabinoid system as a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD).

Trezza V, Campolongo P

The endocannabinoid system in anxiety, fear memory and habituation.

Ruehle S, Rey AA, Remmers F, Lutz B.

J Psychopharmacol. 2012 Jan;26(1):23-39.

- The normal way to use cannabis, is to smoke it, but it can also be eaten or drunk [Bhang].
- The systemic bioavailability of oral administration is only about 6%, one third from that of smoking.
- The efficiency of delivery of a dose by smoking has been estimated to be about 18%, but frequent smokers obtain 23%, while infrequent users obtain only 10% (Hollister, 1986).

Three Phases of the intoxication process

1The Primary (Acute) intoxication

2.The secundary(Acute) intoxication

3.The tertiary(chronic) intoxication

Acute intoxication

Phase 1: (extrovert) 15-45 minutes, aktive in mind, giggling, talkative, red eyes, sensitive to lighgt, enhanced heartbeat, dryness in mouth and throat

Phase 2 (introvert) active in mind – introspective music listening, letting a film pilot your thoughts, hoovering around, great ideas, thoughts and plans. Enhanced perception of colours and smells

(about 3 hours, for regular users only 1 hour)

3. The chronic prolonged intoxication

Long-Term use

- not inclined to interpret opinions and motives of other people.
- hardly any self criticism.
- emotional superficiality (apathy, listless)

Experimental or Recreational use

Short-term

The cognitive input process is affected (Hippocampus):

- **a disturbance in concentration, attention, and storing and elaborating information.**
- **psychologically the individual will experience enhanced subjective perception**

An overall appraisal
Acute effects

- anxiety, dysphoria, panic and paranoia, especially in naive users;
- cognitive impairment, especially of attention and memory, for the duration of intoxication;
- psychomotor impairment,
- an increased risk of experiencing psychotic symptoms among those who are vulnerable
- an increased risk of low birth weight babies if cannabis is used during pregnancy.

Long-Term use

In addition the cognitive process is influenced

- may impair the ability to efficiently process complex information, due to a prefrontal dysfunction.
- inability to make plans.
- difficulties in temporal integration of behaviour.

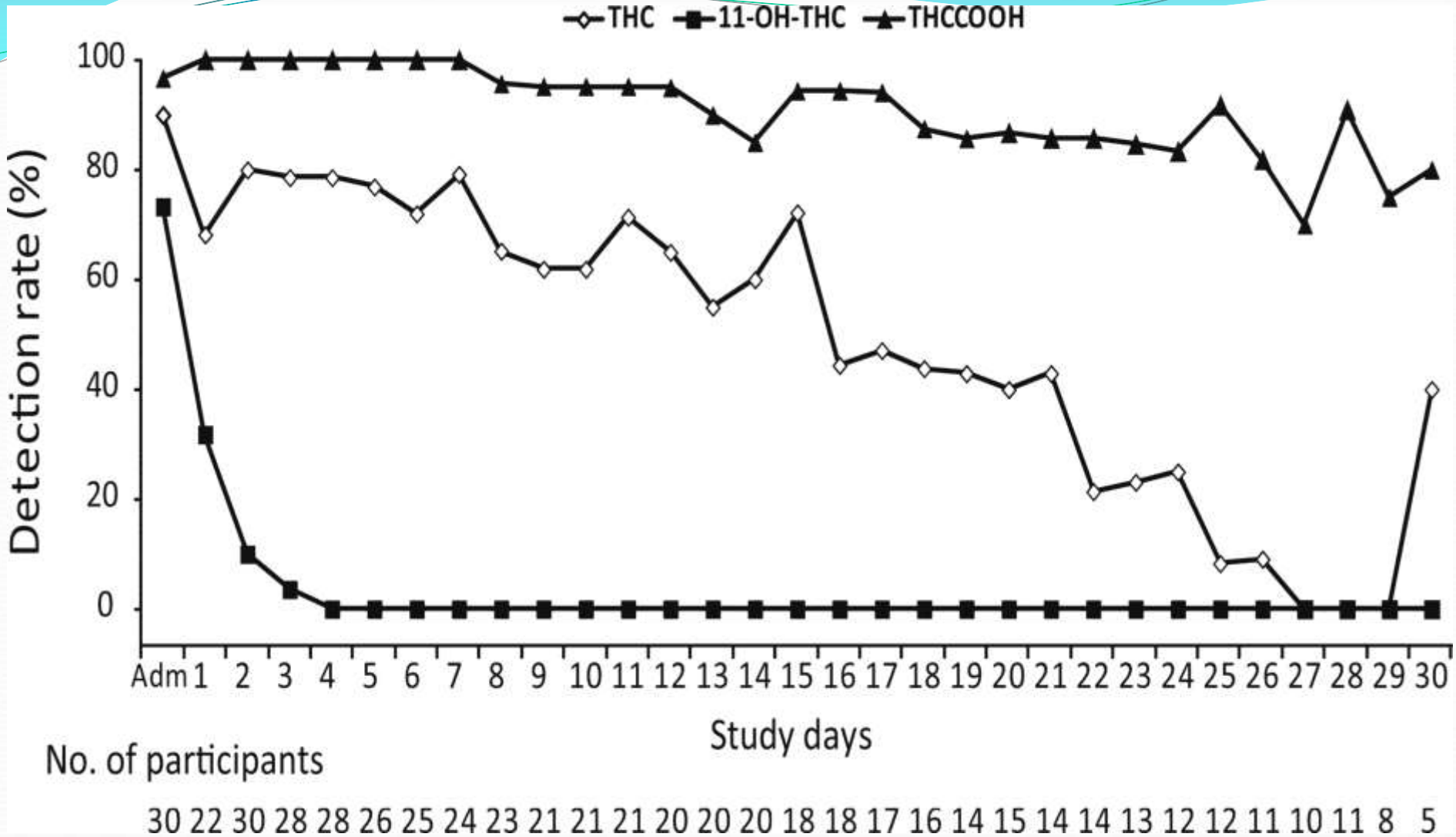
An overall appraisal
Chronic effects

- respiratory diseases such as chronic bronchitis

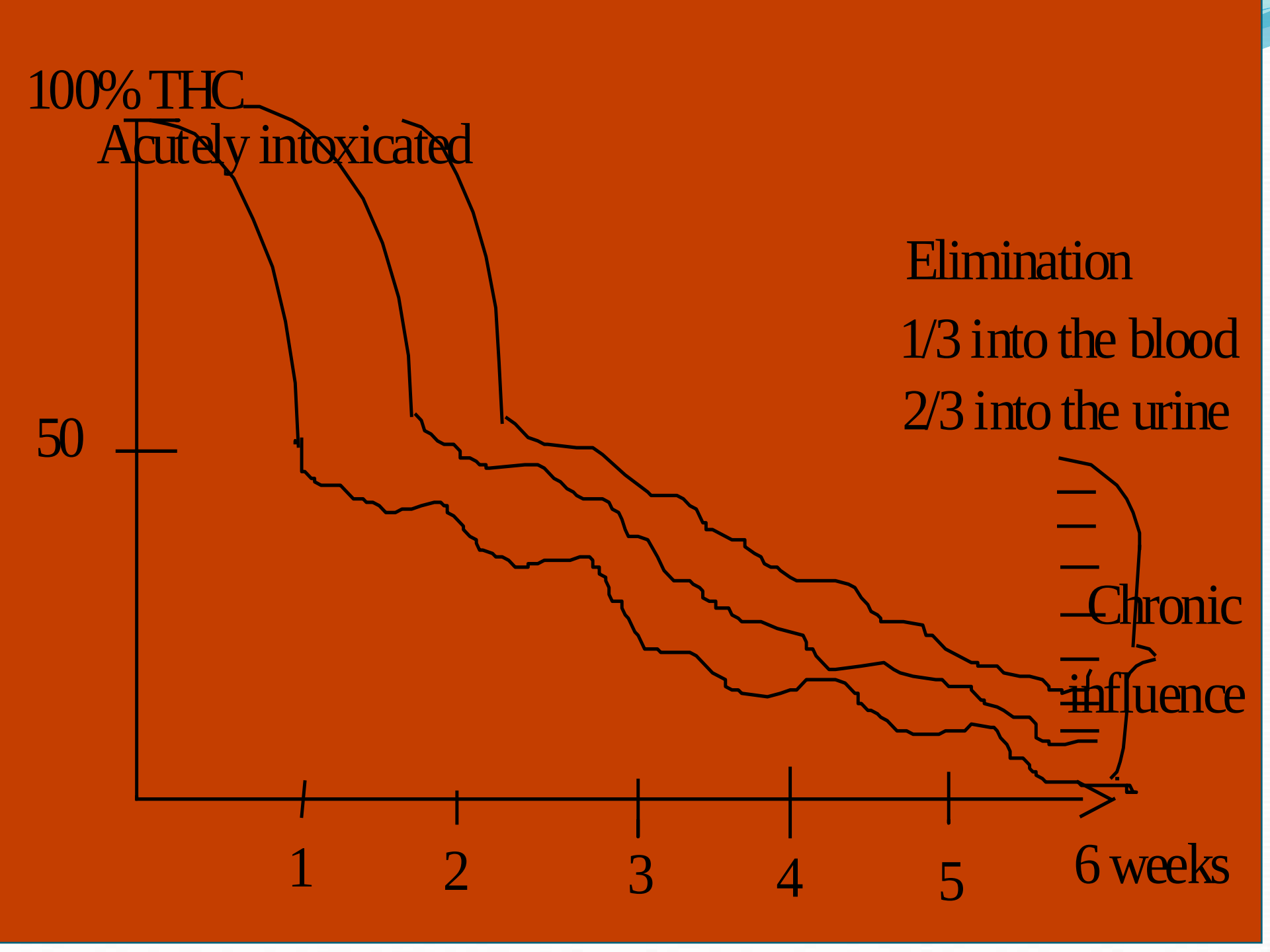
- development of a cannabis dependence syndrome

- subtle forms of cognitive impairment, most particularly of attention and memory.

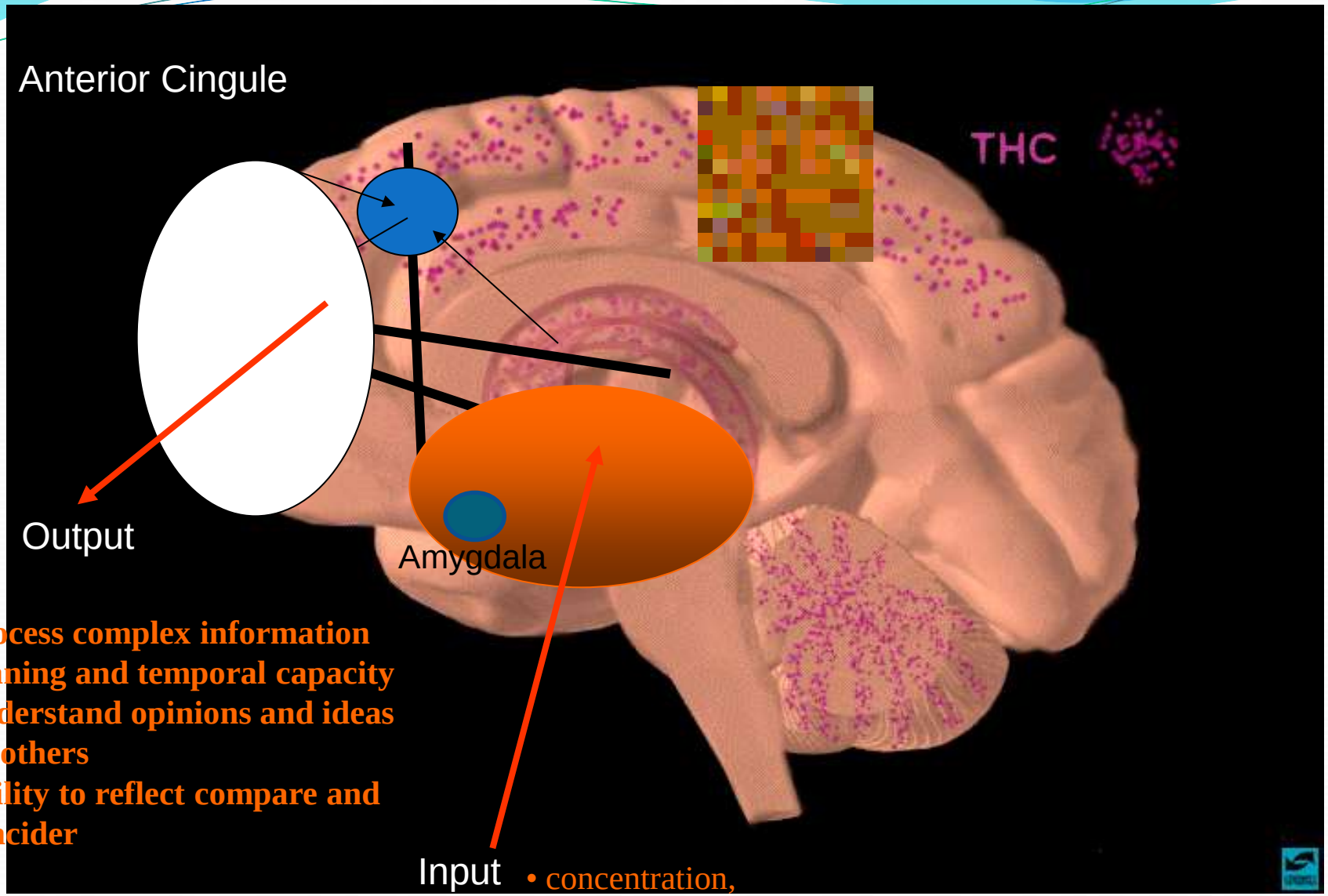
Impact of Prolonged Cannabinoid Excretion in Chronic Daily Cannabis Smokers' Blood on Per Se Drugged Driving Laws



Bergamaschi MM et al *Clinical Chemistry*. 2013 Mar;59(3):519-26.


100% THC
Acutely intoxicated
Elimination
1/3 into the blood
2/3 into the urine
50
Chronic
influence
1
2
3
4
5
6 weeks

Fragmenting the neuropsychological network.



- **process complex information**
- **planing and temporal capacity**
- **understand opinions and ideas of others**
- **ability to reflect compare and concider**

- concentration,
- attention,
- ability to elaborate and store new information

Precuneus

A high CB1 activity decreases the activity in precuneus

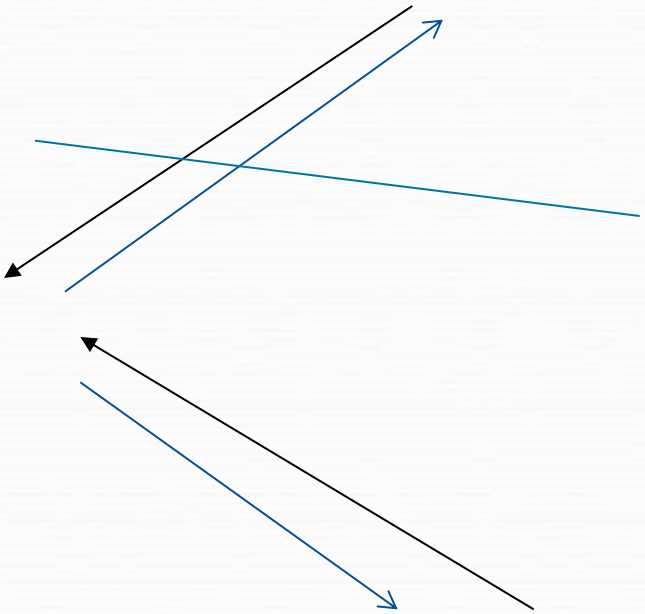
Self
Functional imaging has linked the precuneus to the processes involved in self-consciousness, such as reflective self-awareness, that involve rating ones own personality traits compared to those judged of other people.

Empathy and forgiveness
Together with the superior frontal gyrus and orbitofrontal cortex, the precuneus is activated when people make judgments that requires understanding whether to act out of empathy and forgiveness.

Episodic memory and visuospatial processing
Is involved with episodic memory, visuospatial processing, reflections upon self, and aspects of consciousness.

Executive functions- attention, impulse of control mental flexibility, structuring incoming stimuli and temporal integration

= Internal control



Emotions created by inner and outer stress

Social context, rules, principles, attitudes

= External control

Cannabis use before age 15 and subsequent executive functioning

BJP 2011, 198:442-447. Maria Alice Fontes, Karen I. Bolla, Paulo Jannuzzi Cunha,

Results

The early-onset group showed significantly poorer performance compared with the controls and the late-onset group on tasks assessing sustained attention, impulse control and executive functioning.

Conclusions

Early-onset chronic cannabis users exhibited poorer cognitive performance than controls and late-onset users in executive functioning.

Chronic cannabis use, when started before age 15, may have more deleterious effects on neurocognitive functioning.

Cannabis Use is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users. Jodi M. Gilman et al.,
The Journal of Neuroscience, April 16, 2014 • 34(16):5529 –5538

Nucleus Accumbens is a part of the Brainreward system and it is involved in drugaddiction and is believed to be involved in feelings expressed in faciel muscles and Body language.

Amygdala is a part of the limbic system and is believed to be involved in arising of fear and pleasure. It has thereby an important role in patological conditions as aggression, anxiety, autism , depression, narcolepsy, panic disorder, posttraumatic stress and diffirent kinds of phobia.

These data suggest that marijuana exposure, even in young recreational users, is associated with exposure-dependent alterations of the neural matrix of core reward structures and is consistent with animal studies of changes in dendritic arborization (förgreningar).

1 time per week

Cannabis is emotional imitative

Infatuation – love – marriage – divorce, and living with the ex.

A logistic framework of seven cognitive functions

1. Verbal Ability (quantitative and qualitative)
2. Logical-Analytic Ability (to make correct conclusions)
3. Psychomotility (flexibility in thought)
4. Memory (working and long-term memory)
5. Analytic-Synthetic Ability (to synthesis and create an entity from perceived information)
6. Psychospatial Ability (orientation in space and time continuum)
7. Gestalt Memory (to create patterns and pictures of perceived information)

The effect on the human cognitive functioning

To understand the observed effects of chronic intoxication induced by cannabis, it is necessary to examine the specific dysfunctions in each area on cognitive function.

Chronic users who have consumed high doses over long time periods can be expected to show almost all of the symptoms that are listed. Those having consumed lower doses can be expected to show fewer of these symptoms.

1. Verbal Ability

- An ability to know many words,
- which is a semantic memory process (quantitatively), associated with noetic (knowing) consciousness.

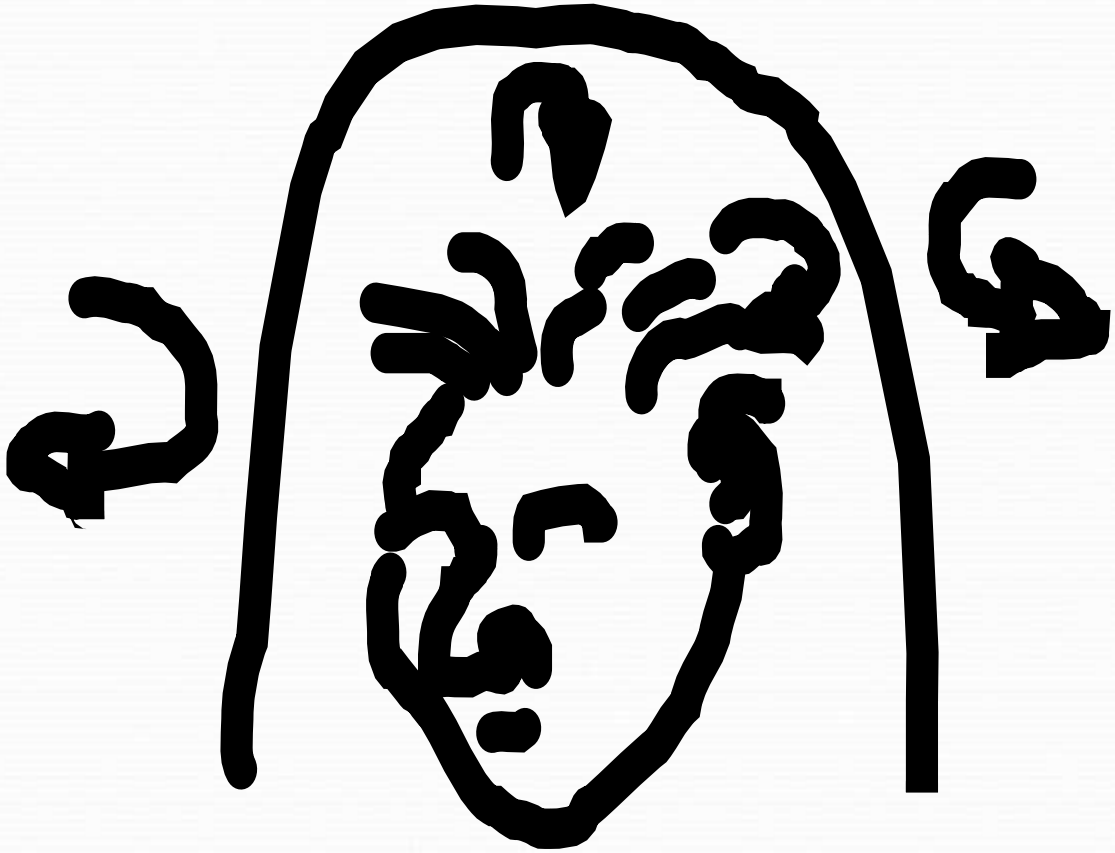
- An ability to express thoughts and feelings so that others understand the meaning of the communication.

- This implies that the words get a qualitative sense to yourself.

- This ability is dependent on access to the episodic memory and its correlate autonoetic (self-knowing) consciousness and is influenced by emotions.

Weaknesses are observed in the following:

- vocabulary appropriate to chronological age,
- finding exact words with which to express oneself,
- understanding what other people mean,
- abstract thinking and engaging in concrete thinking.
- These symptoms lead the patient to feel misunderstood and lonely.



2.Logical-Analytic Ability

We have an ability of

- logical reasoning,
- to critically examine what is being communicated,
- to use logical thought to correct errors and mistakes,
- and to make logical analyses of the behaviour of self and others.

This ability is dependent on an appropriate process of elaboration.

Weaknesses are observed in the following:

- critical and logical self-examination,
- correcting errors and mistakes logically,
- thinking before answering,
- abstract and logical solution of problems e.g., socio-analytic, understanding of casual relationships.

- These symptoms lead the patient to feel inadequate and unsuccessful.

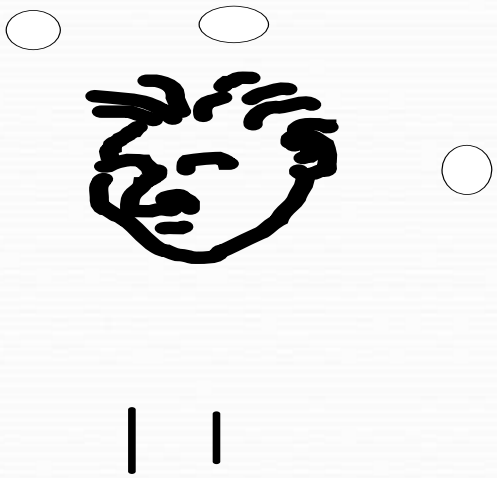
The figure illustrates the impairments in self-examination which normally enables us to correct errors and mistakes.

3. Psychomotility (Flexibility of thought)

This ability makes it possible for us to

- shift attention from one stimulus/task to another,
- to maintain a train of thought in a complex situation,
- to carry on a dialogue in conversation,
- to see different sides of an issue, social situation or problem,
- and to establish an adequate focus of attention.

Weaknesses are observed in the following:



- establish a correct focus of attention,
- maintaining attention,
- shifting attention,
- understanding the points of view of others,
- changing opinions,
- changing mental set in problem solving and social perception.

- The effect will be intensified feelings of loneliness and to not belonging to society.

Cannabis and attention I

- **Basal basic attentional processes appear to be intact**
- **Long-term cannabis users are less efficient when performing complex cognitive tasks**
- **less efficient to resist distraction**

Cannabis and attention II

- Long-term users ability to process information efficiently declines more rapidly under a moderate cognitive load compare to non users and short-term users.

Cannabis and attention III

- Long-term users are inefficient in:
- to perform complex tasks that require cognitive flexibility
- to identify of unproductive planning strategies
- to learn from experience.

Cannabis and attention IV

- Long-term users may well cope with everyday routine tasks
- difficulties with verbal tasks that are novel and which cannot be solved by automatic application of previous knowledge.

4. Memory
Short-term/Working memory;

- refers to an active system of memory in which information is assembled and organized prior to recall.

- It is a working space for several cognitive processes, and it provides us with a temporal integration.

- It has an immediate function, and enables us to read books with pleasure.

Long-term memory;

consists of *episodic memory*,

- which refers to knowledge about episodes and events, to entities that are marked as happening at a particular time, and it has a autobiographical flavour, and

semantic memory,

which refers to our de-contextualised memory for facts about entities, and to relations between entities in the world.

Precuneus

Weaknesses are observed in the following:

Short-term/working memory;

- remembering meetings, promises, and so on, e.g. prospective memory (remember to remember),
- estimating of the passage of time,
- imagining long time spans and maintaining the theme of a story.

Long-term memory weaknesses include

- 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.
- These symptoms lead the patient to exhibit a lack of patience.

Precuneus

A high CB1 activity decreases the activity in precuneus

Self
Functional imaging has linked the precuneus to the processes involved in self-consciousness, such as reflective self-awareness, that involve rating ones own personality traits compared to those judged of other people.

Empathy and forgiveness
Together with the superior frontal gyrus and orbitofrontal cortex, the precuneus is activated when people make judgments that requires understanding whether to act out of empathy and forgiveness.

Episodic memory and visuospatial processing
Is involved with episodic memory, visuospatial processing, reflections upon self, and aspects of consciousness.

5. Analytic-Synthesic Ability

This ability is based on a synthesis of the other six items and therefore is dependent on normal functioning of them.

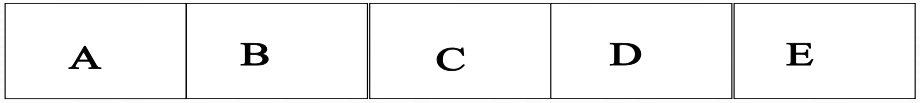
The result of this process is an identity.

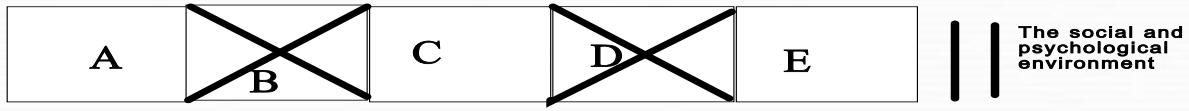
It makes it possible for us to form points of views, moral, set of values that make up the self, and to synthesize and see the whole.

Weaknesses are observed in the following areas:

sorting out information,
synthesizing from parts to whole e.g. classifying information in a correct way and understanding shades of meaning.
These symptoms lead the patient to feel different and unique.

The upper picture symbolizes the natural way of perceiving an entity, or creating a notion.
The lower picture illustrates the disrupted process in chronic cannabis users. The loss of or neglect of adequate information, is depicted by the crossed squares.





This disrupted processing contributes to the emergence of a new pattern of thinking that can be viewed as a cannabis state-dependent set of cognitive processes.

These changes lead to a mental and behavioral profile that seems quite unique to cannabis use. We call it a *cannabis pattern*.

Cannabispattern

In this cognitive pattern,

- new views and sets of values will be created which differ from what would have been created in a non-intoxicated state.

- Concepts (points of view) created under these circumstances cannot be questioned due to an inability of critical examination.

- To the user they are real. After a while the myths thus become truths.

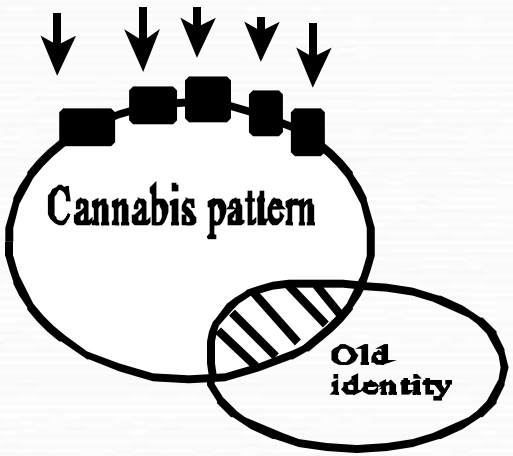
- Attitudes, fantasies, concepts, and interests created in the cannabis pattern are superficial, that is, they are seldom the effects of an adequate contact with the social environment.

- The chronic user is always planning a new project, but seldom follows through with it.

Cont.

- The continuous planning of these so-called projects creates a feeling of being active.
- This pattern also produces pat or fictional answers for every conceivable situation deriving from any kind of problem.
- This cannabis pattern is based upon newly learned schemes, as a result of the cognitive dysfunction caused by the chronic use of cannabis, mainly as a result of the impaired process of attention and elaboration.

The picture symbolizes the emerging identity based on the disrupted cognitive functions. When you talk to the user (arrows) his/her pat answers will emerge (black boxes). This new identity is superficial and has very little in common with his old identity (striped area).



6. Psychospatial Ability

It makes it possible for us to locate oneself and function in the time and space continuum.

Weaknesses are observed in the following:

- differentiating the time of the year and/or time of the day,
- maintaining routines of the day or the week,
- having interest in what is going on,
- being aware of one's social position relative to others,
- having an accurate perception of the immediate environment and mental representation of localization in space (e.g., having a mental map of surroundings),
- structuring the daily life.

These symptoms lead the patient to feel that he or she does not belong to the society.

7. Gestalt memory (Holistic memory)

It helps us to create patterns and pictures of what we see, and to have a correct sense of direction.

Weaknesses are observed in the following:

- creating patterns and pictures of the visual world and remembering the relations between others,
- putting names to faces.

These symptoms lead patients to feel as if they are living in a world of their own.

A typical client profile

- has problems finding exact words to describe what he really mean.
- has limited ability to enjoy reading, motion picture, theatre, music, etc.
- has feelings of boredom and emptiness in daily life, loneliness, being misunderstood.
- externalizes problems and avoid accepting blame.
- is certain that he functions adequately.
- is not able to examine his own behaviour critically.
- has feelings of being incapable and unsuccessful.
- is unable to maintain a dialogue.
- has difficulties with concentration and attention span.
- has fixed opinions and pat answers to questions.
- makes statements like, "I am different, other people don't understand me, I don't belong to the community".
- doesn't plan the day.
- thinks that he is active because he has many ongoing projects, which are seldom finished.
- has no daily or weekly routine.

It is important to note that this is a typical "picture" of a chronic user.

Many individual differences have been observed,

but the elements of the clinical picture are similar to the skilled observer.

The sense of coherence

- is a global orientation that expresses the extent
- to which one has a pervasive, enduring though dynamic feeling of confidence that:

Aaron Antonovsky, 1987

- 1) the stimuli deriving from ones internal and external environments in the course of living are structured, predictable, and explicable (comprehensibility);
- the resources are available to one to meet the demands posed by these stimuli (manageability);
- 3) these demands are challenges, worthy of investment and engagement (meaningfulness).

CONCLUSION; chronic cannabis users

- has a mean at admission to treatment, which is considerable lower than control.
- to a very low extent experience inner and outer stimuli as comprehensible in a rational way.
- are convinced that they have the ability to handle all kinds of problems.
- has a low emotional and cognitive motivation.

Four processes observed in chronic use of cannabis

1 a: Experimenting with cannabis you will get an acute intoxication and experience the significance of this state in comparison to your normal state of consciousness.

1 b: Smoking cannabis more often than every six weeks creates a shift in consciousness toward being passive, unreflecting, and blunt. The user will gradually adjust to this and it will be a new normal state of consciousness. The significance of the acute intoxication will then be experienced in comparison to this altered state of consciousness.
The cannabis user will get a feeling of capacity and a sense of being normal and thereby enabling him to perform different tasks.

In the beginning you smoke to get stoned, but after a while (individually) you have to smoke to be normal and to get a nice feeling.

Four processes observed in chronic use of cannabis continued

2. The influence of the chronic use affects the cognitive processes in such a way that you can't question or criticize your behaviour and will therefore be unable to change it if necessary. This will create a "cannabis pattern", a new identity, which is a continuous ongoing process, so the longer the use continues the stronger the cannabis pattern will grow. We have noticed that it will take around two years of regular use to fully establish a cannabis pattern.

3. Cannabis magnifies negative feelings which the cannabis user can't cope with because of his concrete way of thinking, and this causes anxiety. The only solution left is to smoke cannabis again, in order to get rid of the bad feelings. These feelings do not disappear, they will reappear, and thereby enforcing the urge to continue smoking.

Four processes observed in chronic use of cannabis continued

4. During an overall negative puberty crisis cannabis helps the teenager to screen of the environment. A pseudodevelopment will replace the natural maturity. He will not continue to mature until he ceases cannabis smoking.

Cognitive neuropsychology and Cannabis

Imaging cognitive deficits in cannabis users

From a clinicians perspective

- Resting paradigm
- Cognitive challenge paradigm
- Extended washout period
- Focus on the growing adolescent brain, neuroadaptation, stress and dysfunction of hippocampus and amygdale
- Associative memory

Thomas Lundqvist
Psychologist & associate professor
AddictionTreatment Centre
Lund Sweden

Resting conditions

- subnormal cerebral blood flow (CBF) (Tunving et al. 1985; Mathew et al. 1986; Mathew et al. 1989)
- or lower cerebellar metabolism (Volkow et al. 1996; Amen and Waugh 1998) in long-term cannabis users who were assessed within one week of cessation of use.
- significantly lower mean hemispheric blood flow values and significantly lower frontal values (Lundqvist 2001)

Resting conditions continued

- Acute exposure to marijuana has resulted in dose related increases in CBF measures among experienced users (Mathew and Wilson 1991; Mathew et al. 1993).
- regional metabolic increases in orbitofrontal cortex (OFC), prefrontal cortex (PFC), and basal ganglia compared to the normal group.
- regional flow increases that reached statistical significance in frontal regions, insula, cingulate gyrus, and subcortical regions. (Mathew et al. 1997, 1999).
- Block et al. (1999) found that chronic marijuana use was related to a decrease in memory related activation

Cognitive challenge paradigm

- Yurgelun-Todd et al. (1999) assessed chronic marijuana smokers twice with fMRI, after 24 h and 28 days of abstinence using a visual working memory task with known sensitivity.
- 24 h of washout showed diminished activation in the dorsolateral prefrontal cortex (DLPFC) during the challenge paradigm. This effect remained diminished after 28 days of washout.
- The results indicate that even after an extended washout period, specific deviating patterns of cortical activation exist.

Cognitive challenge paradigm continued

- Marijuana disrupted both sustained and transient attention processes resulting in impaired memory task performance. (Ilan et al. 2004)
- The greatest differences between users and controls occurred in brain activity related to episodic memory encoding, which may infer with the individual subjective history. (Block et al. 2002).
- Increased rCBF after inhalation of cannabis in orbital and mesial frontal lobes, insula, temporal poles, and anterior cingulate cortex (ACC), 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 moodrelated effects. (O’Leary et al. 2000, 2002)

Cognitive challenge paradigm continued

- Reduced rCBF was observed both during resting as in activated conditions, acutely intoxicated, in brain regions that may be a part of an attentional network (parietal lobe, frontal lobe and thalamus).
- Reduced rCBF was observed in temporal lobe auditory regions, and in visual cortex.
- Decreased rCBF in comparison to baseline in brain regions known to be involved in attentional modulation of sensory processing. (O'Leary et al. 2000, 2002)

Extended washout period

- A washout period of 3 days is the minimum required in order to show negligible levels of metabolites. (Yurgelun-Todd 1999) even after an extended washout period (28 days).
- Residual (after 28 days) diminished brain activation is still observed in motor cortical circuits after discontinuing cannabis use. (Pillay et al. 2008).
- Hypoactivity in the left perigenual ACC and the left lateral prefrontal cortex and hyperactivity in the hippocampus bilaterally (Eldreth et al. 2004).
- Persistent metabolic alterations in brain regions responsible for ECF. Marijuana users may recruit an alternative neural network as a compensatory mechanism.

Extended washout period continued

- Heavy long-term cannabis abusers display greater and more widespread brain activation than normal subjects attempting to perform a spatial working memory task.
- Heavy long-term cannabis abusers may experience subtle neurophysiological deficits, and that they compensate for these deficits by "working harder" – calling upon additional brain regions to meet the demands of the task. (Kanayama et al. 2004).
- Sneider et al. (2008) suggest that while CBV levels begin to normalize with continued abstinence from cannabis, specifically in frontal areas, other temporal and cerebellar brain regions show slower CBV decreases.
- Yücel et al (2008) conclude that heavy daily cannabis use across protracted periods exerts harmful effects on braintissue and mental health.

Brain Imaging Studies

- Cannabis produces various metabolic changes in the brain.
- Long-term users appear to have lower resting levels of CBF.
- Administration of cannabis increases CBF and brain metabolism in experienced users.
- Administration of cannabis decrease CBF in inexperienced users.
- The effects have been particularly apparent in frontal cortical areas.
- Cessation of long-term use leads to a decrease in the frontal lobes.

The prefrontal cortex and executive function

- Planning and control
- Behavioural temporal co-ordination
- Problem solving
- Autonomy
- Feelings

Executive functions

- Attention
- Control of impulse
- Mental flexibility
- Structuring incoming stimuli
- Temporal integration

Adolescent cortical development: A critical period of vulnerability for addiction

Fulton Crews, Jun He, Clyde Hodge

Pharmacology, Biochemistry and Behavior 86 (2007) 189–199. Review

The prefrontal cortex (PFC) and the limbic system, which includes

- the hippocampus,
- amygdala,
- nucleus accumbens (NAc),
- prefrontal, frontal and orbital frontal cortices and the
- hypothalamus,

undergo prominent reorganization during adolescence.

Focus on the growing adolescent brain, neuroadaptation, stress and dysfunction of hippocampus and amygdale

- Li et al. (2005) used fMRI to examine subjects abstinent for at least 15 days and they found that recent cannabis abuse is associated with decreased activation in the frontal cortex during an emotional stress task.
- Phan et al. (2008) found that THC significantly reduced amygdala reactivity to social signals of threat, but did not affect activity in primary visual and motor cortex.

Focus on the growing adolescent brain, continued

- Padula et al. (2007) collected fMRI data from adolescent marijuana users aged 16–18 years after 28 days' monitored abstinence suggesting a different approach to a spatial working memory task via altered neural pathways.
- Chang et al. (2006) studied the reversibility of cognitive deficits (attention and memory). The result suggest neuroadaptive processes or alteration of brain development in chronic marijuana users.

Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use
Manzar Ashtari et. al (2008)

Hypothesis: Individuals with heavy cannabis use (HCU)

would have brain structure abnormalities in similar brain regions that undergo development during late adolescence, particularly the fronto-temporal connection.

Conclusions:

- The results support the hypothesis that heavy cannabis use during adolescence may affect the trajectory of normal brain maturation.

Early onset substance use may affect

- the development of fronto-temporal white matter circuits,
- potentially resulting in disturbed memory,
- and deficits in executive and affective functioning.

The impact of early-onset cannabis use on functional brain correlates of working memory
Benjamin Beckera, et al 2010

Functional magnetic resonance imaging was used to examine cortical activation during verbal working memory challenge in
(1) early-onset (onset before the age of sixteen; *n* = 26) and
(2) late-onset cannabis users (age at onset at least sixteen; *n* = 17).

Early-onset users showed increased activation in the left superior parietal lobe. Correlational analyses confirmed the association between an earlier start of use and increased activity.

Contrariwise neither cumulative dose, frequency nor time since last use was significantly associated with cortical activity.

Our findings suggest that an early start of cannabis use is associated with increased cortical activation in adult cannabis users,
possibly reflecting suboptimal cortical efficiency during cognitive challenge.

The maturing brain might be more vulnerable to the harmful effects of cannabis use.

Cannabis Use and Memory Brain Function in Adolescent Boys:
A Cross-Sectional Multicenter Functional Magnetic Resonance Imaging Study
Gerry Jager Ph.D., 2010

Results
Cannabis users performed normally on both memory tasks. During WM assessment, cannabis users showed excessive activity in prefrontal regions when a task was novel, whereas automatization of the task reduced activity to the same level in users and controls. No effect of cannabis use on AM-related brain function was found.

Conclusions
In adolescent cannabis users, the WM system was overactive during a novel task, suggesting functional compensation.
Inefficient WM recruitment was not related to a failure in automatization but became evident when processing continuously changing information.

The results seem to confirm the vulnerability of still developing frontal lobe functioning for early-onset cannabis use.

Padula (2007)

Cannabis prevent the neurological restructuring of the teenage brain to an adult brain.

Essentially the problem on a neuropsychological level of

- a underdeveloped executive function which reduces the ability to
- inner will and thus causes a difficulty to withstand emotional and
- stress-related impulse breakthrough
- and thus the individual must rely on external control.

Associative memory

- Jager et al. (2007) studied non-acute effects of frequent cannabis use on hippocampus-dependent associative memory, investigated with fMRI in frequent cannabis users. Cannabis users displayed lower activation than non-users in brain regions involved in associative learning.
- Jager et al. (2006) assessed brain function in frequent but relatively moderate cannabis users in the domains of working memory and selective attention. Cannabis users and controls performed equally well during the working memory task and the selective attention task.

Cannabis induces loss of internal control and cognitive impairment, especially of attention and memory, for the duration of intoxication.

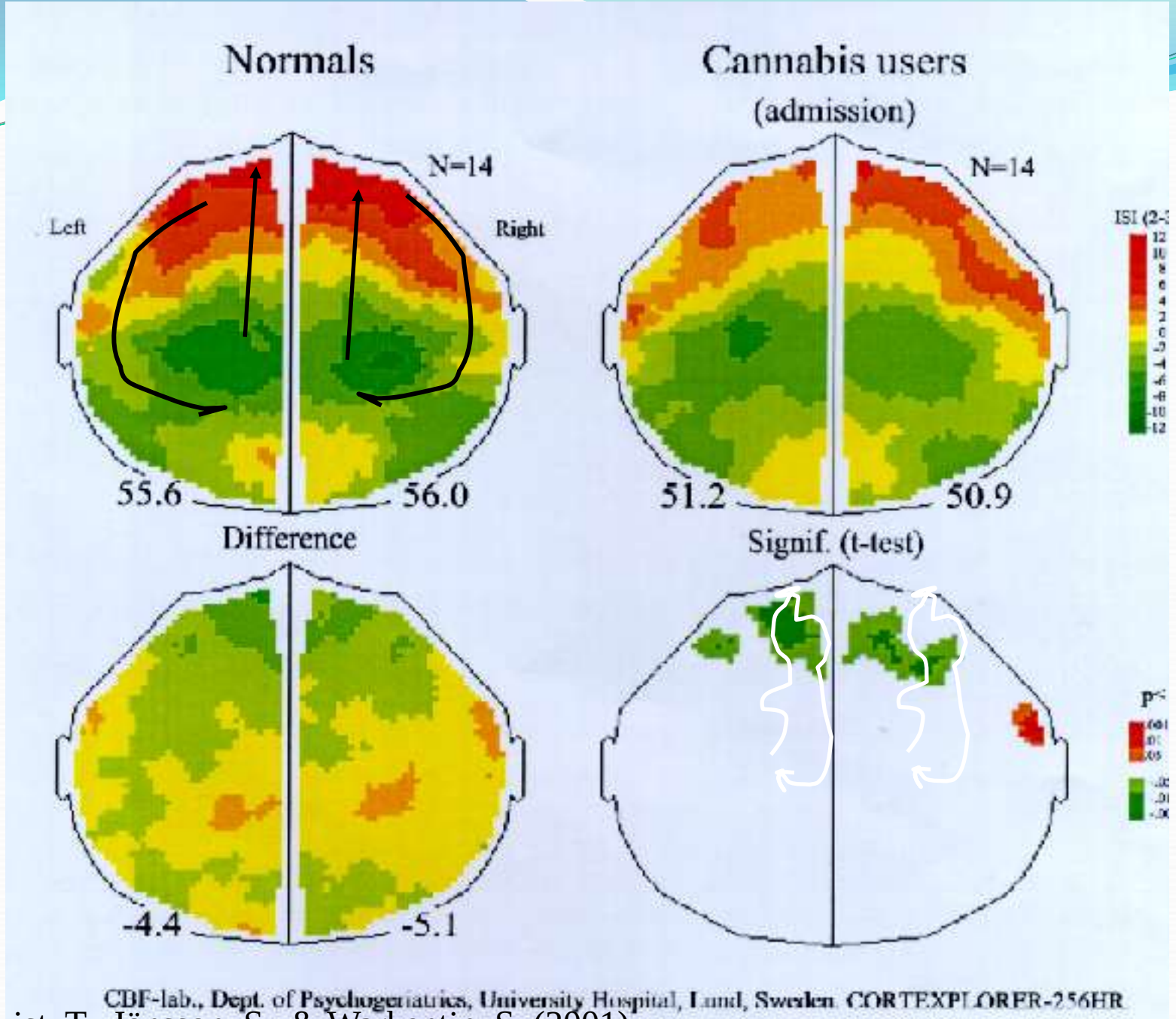
Heavy cannabis use is associated with reduced function of the

- attentional/executive system, as exhibited by
- decreased mental flexibility,
- increased perserveration, and
- reduced learning,
- to shift and/or sustain attention.

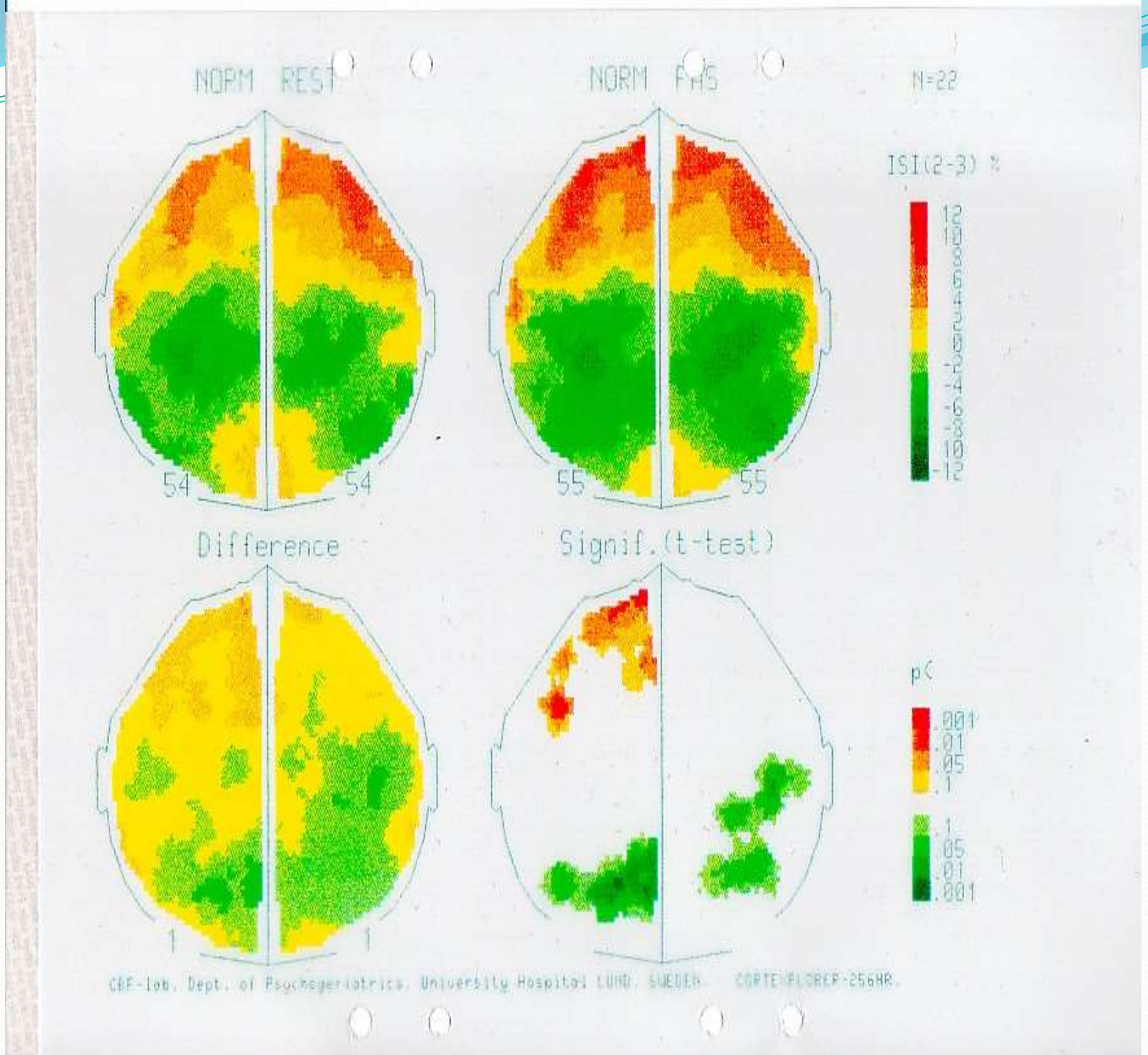
Cannabis reduces the ability to interpret social signal of threat
Chan et al (2008).

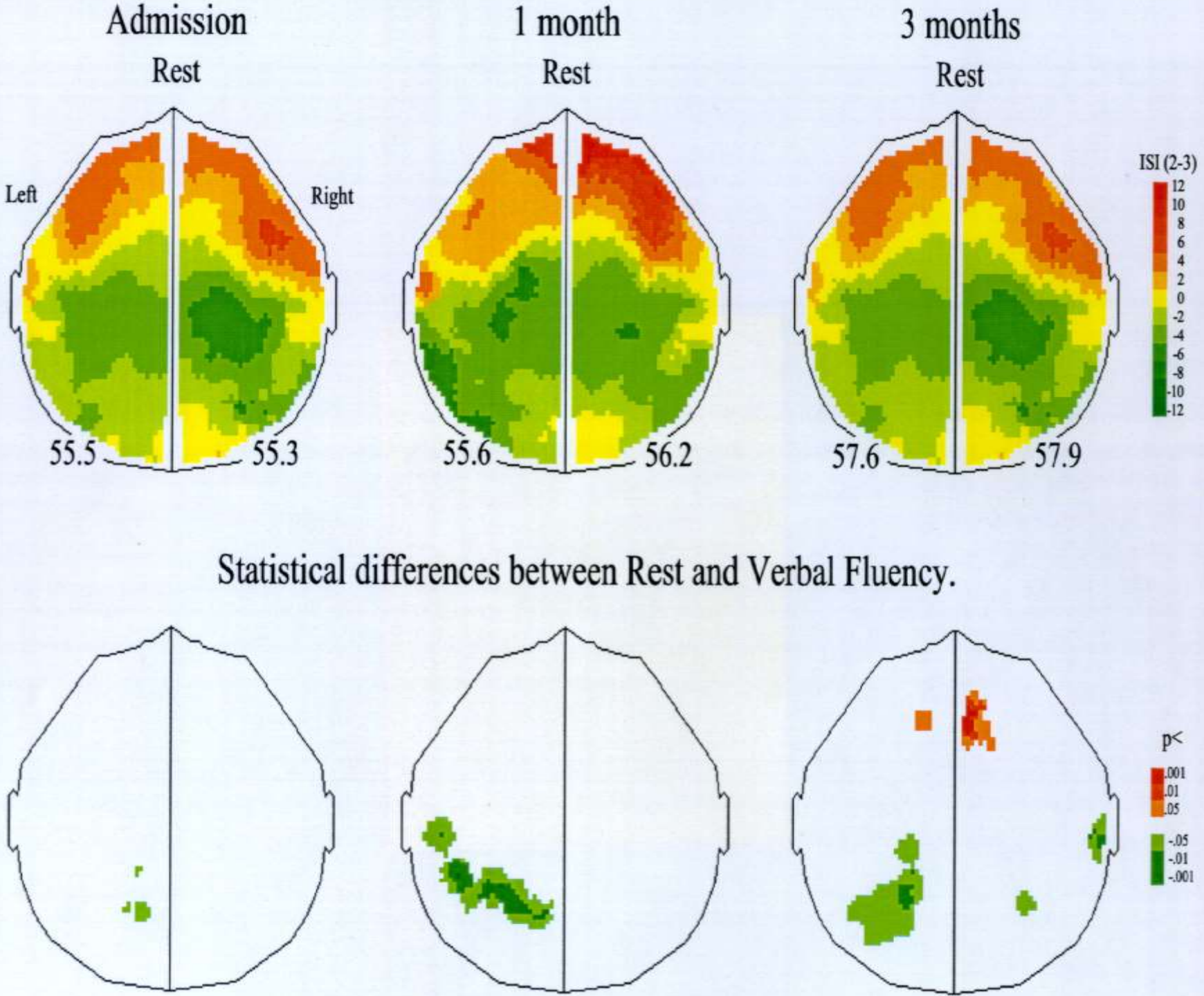
Cannabis reduces the possibility of creating lasting qualitative memories.
(Yücel et al 2008)

Teens, 16-18 years, shows after 28 days of abstinence, a reduction in the function the data related to the ability to "orient themselves in space".
Padula et al (2007).



Lundqvist, T., Jönsson, S., & Warkentin, S. (2001).
Frontal lobe dysfunction in long-term cannabis users. *Neurotoxicology & Teratology, 23(5),* 437-443


NORM REST
NORM PHS
N=22
ISI(2-3) %
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
54
54
55
55
Difference
Signif.(t-test)
p<
.001
.01
.05
.1
.1
.05
.01
.001
1
1
CBF-Lab. Dept. of Psychogeriatrics. University Hospital LUND, SWEDEN


Admission
Rest
1 month
Rest
3 months
Rest
Left
Right
55.5
55.3
55.6
56.2
57.6
57.9
ISI (2-3)
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
Statistical differences between Rest and Verbal Fluency.
p<
.001
.01
.05
-.05
-.01
-.001

It can be assumed that addicts recruits alternative neural network, as a compensatory mechanism.

Eldreth DA, Matochik JA, Cadet JL, Bolla KI. (2004)

Cannabis users are recruiting regions that are not typical of spatial working memory,
i.e. they compensate by working harder.

This independent of the individuals age, IQ, years of abuse or metabolites

Kanayama, Rogowska, Pope, Gruber, Yurgelun-Todd. (2004)

- Cannabis smoking affects working memory and impairs monitoring function in acute intoxication and in the emerging chronic effects.

- It becomes vague and slow.

- It becomes more difficult to identify and process important information,
- partly it to be stored in memory for self-knowledge (episodic memory)
- secondly, it will be retrieved out of memory so that it controls the focus in attention

Ilan AB, Smith ME, Gevins A. (2004)
(Gruber et al., Drug and alcohol dependence, 2009)

Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. Eldreth DA, Matochik JA, Cadet JL, Bolla KI. (2004)

Despite the lack of performance differences, the marijuana users showed hypoactivity in the left perigenual anterior cingulate cortex (ACC) and the left lateral prefrontal cortex (LPFC) and hyperactivity in the hippocampus bilaterally, when compared to the comparison group.

These results suggest that marijuana users display persistent metabolic alterations in brain regions responsible for executive functions.
It may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task.
These differences in brain activity may be a common denominator in the evolution of maladaptive behaviors.

Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. Smith AM, Fried PA (2006)

The results suggest that prenatal marijuana exposure alters neural functioning during visuospatial working memory processing in young adulthood.

In older cannabis abuser this may contribute to the socio-phobic reaction seen in SCL-90.