UNIVERSITÀ DEGLI STUDI FIRENZE

DSS
Dipartimento di
Scienze della Salute

URITON

UNITÀ DI RICERCA ED INNOVAZIONE IN TOSSICOLOGIA FORENSE E NEUROSCIENZE DELLE DIPENDENZE E NUOVE DROGHE

Delibera Consiglio DSS 22/08/2015 Verb. n. 7/2015

“Addiction” e Identificazione di Nuove Sostanze Psicoattive

Firenze, 6 aprile 2016
Aula Magna NIC pad. 3 didattica, largo Brambilla 3, Firenze

ADDICTION NEUROSCIENCE AND FORENSIC TOXICOLOGY

Giovanni Serpelloni

Firenze, 6 aprile 2016

Giovanni Serpelloni – M.D.

serpelloni@giovanniserpelloni.it

Addiction Neuroscience and Forensic Toxicology: a New Opportunity

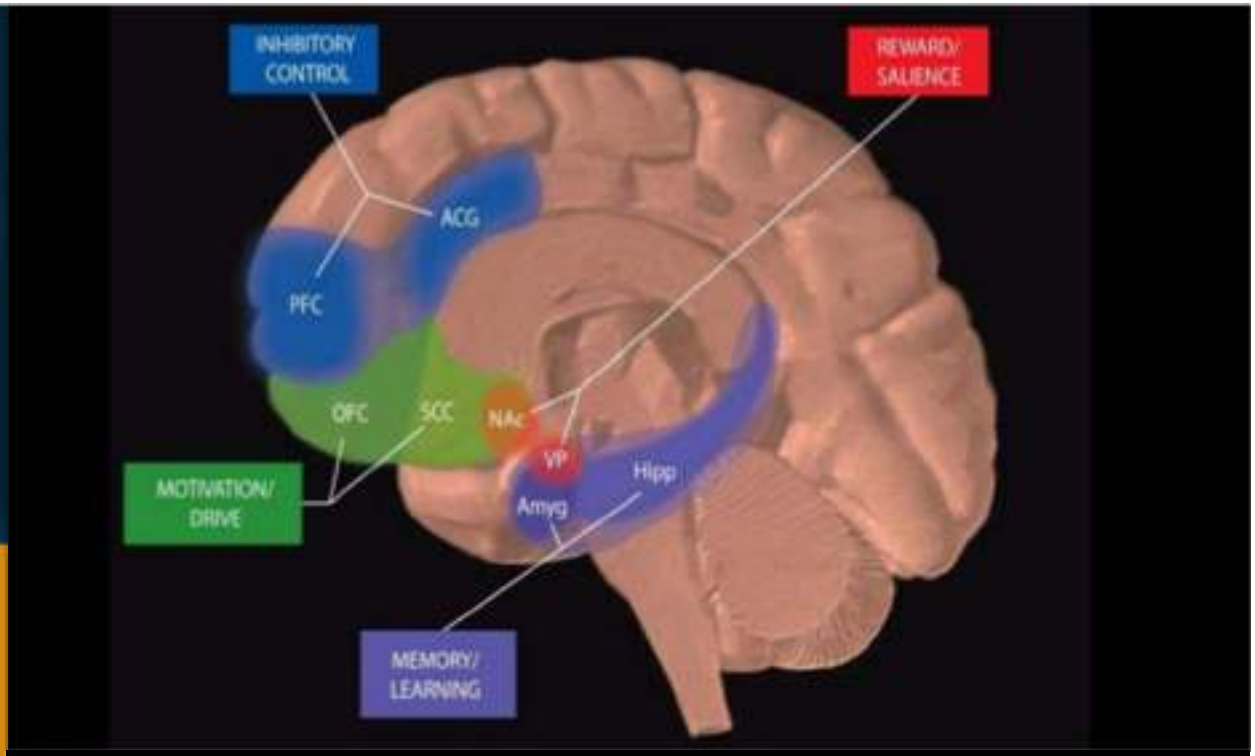
Agenda

1. Introduction
2. Most relevant Brain Structures and Systems for Forensic Toxicology
3. Cognitive functions and behaviours, coordination funtions…
4. Forensic consequences and interest
5. Advanced Assessing methods
6. Conclusions

Circuits Involved in Drug Use & Addiction

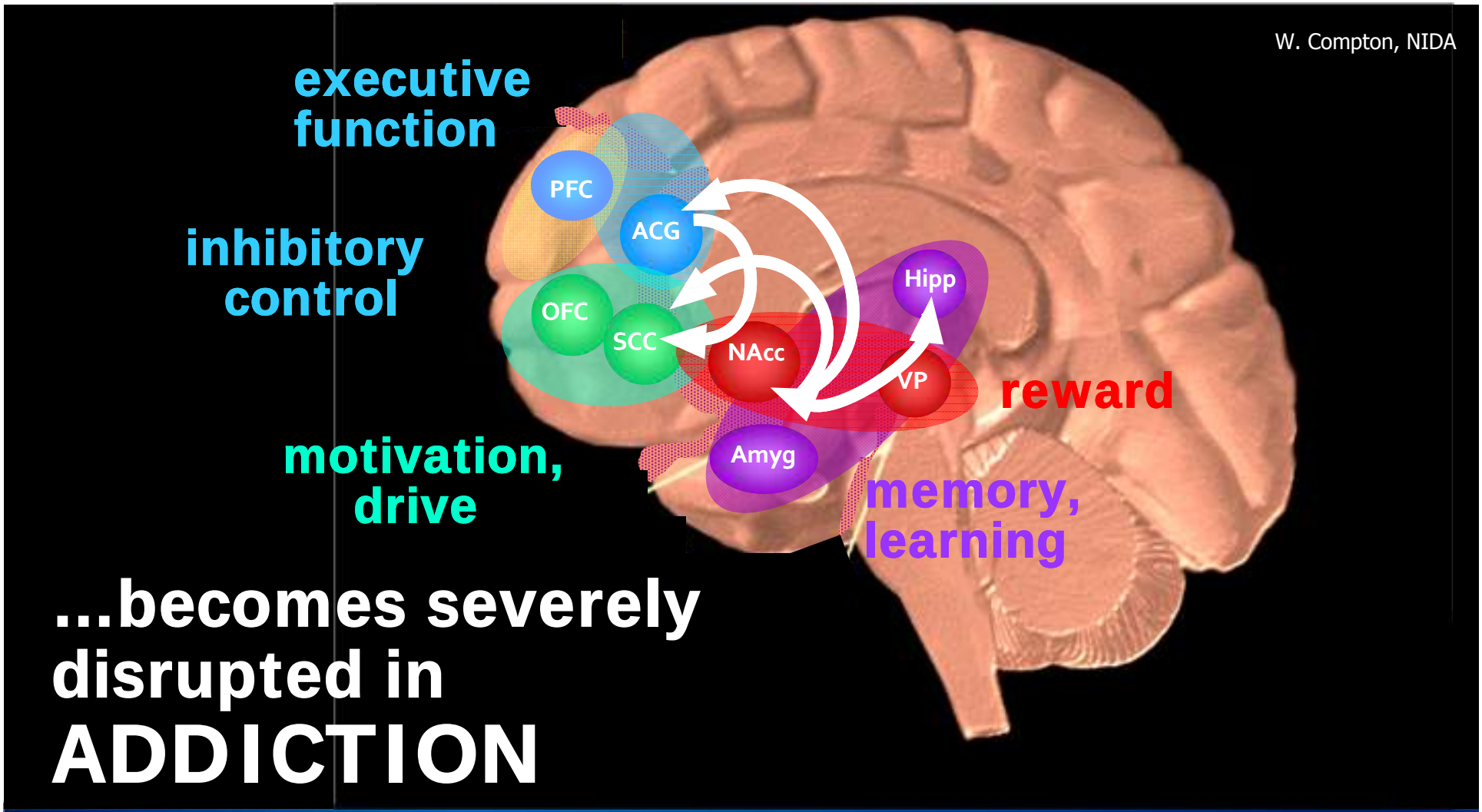
All drugs work

by imitating or over-producing neurotransmitters, the brain's "reward circuit," interfering with normal brain function.

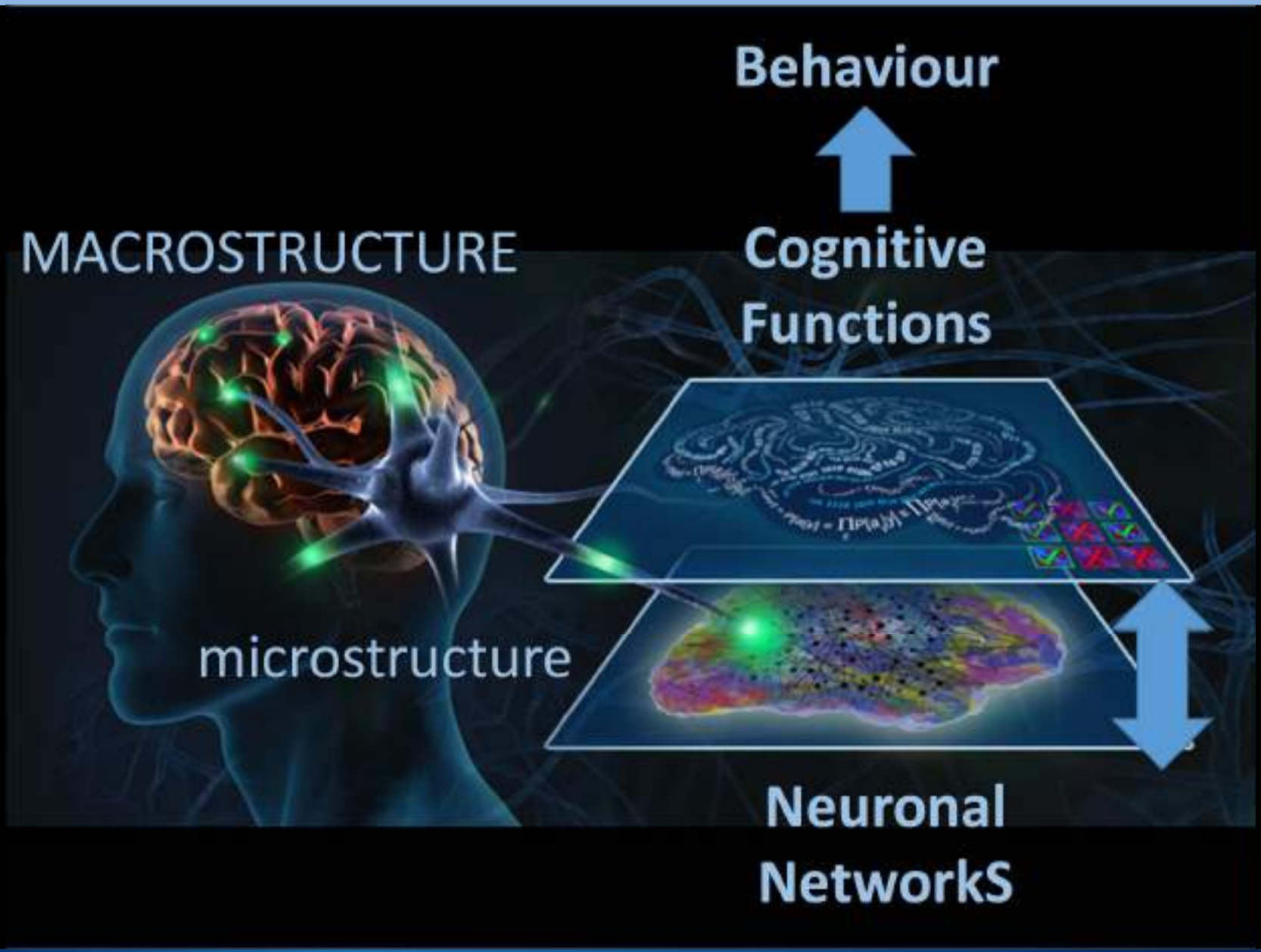


PFC – prefrontal cortex; ACG – anterior cingulate gyrus; OFC – orbitofrontal cortex; SCC – subcallosal cortex; NAc – nucleus accumbens; VP – ventral pallidum; Hipp – hippocampus; Amyg – amygdala

The fine balance in connections that normally exists between brain areas active in reward, motivation, learning and memory, and inhibitory control...

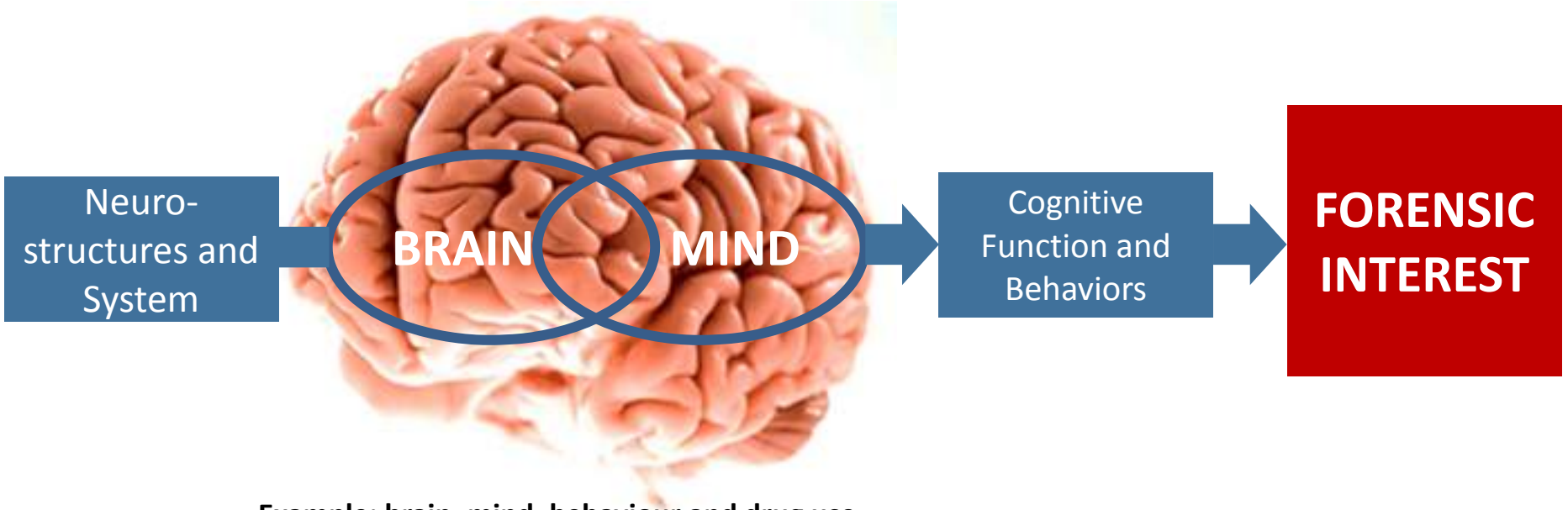


...becomes severely disrupted in ADDICTION


Behaviour
MACROSTRUCTURE
Cognitive
Functions
microstructure
Neuronal
NetworkS

Main presentation aim

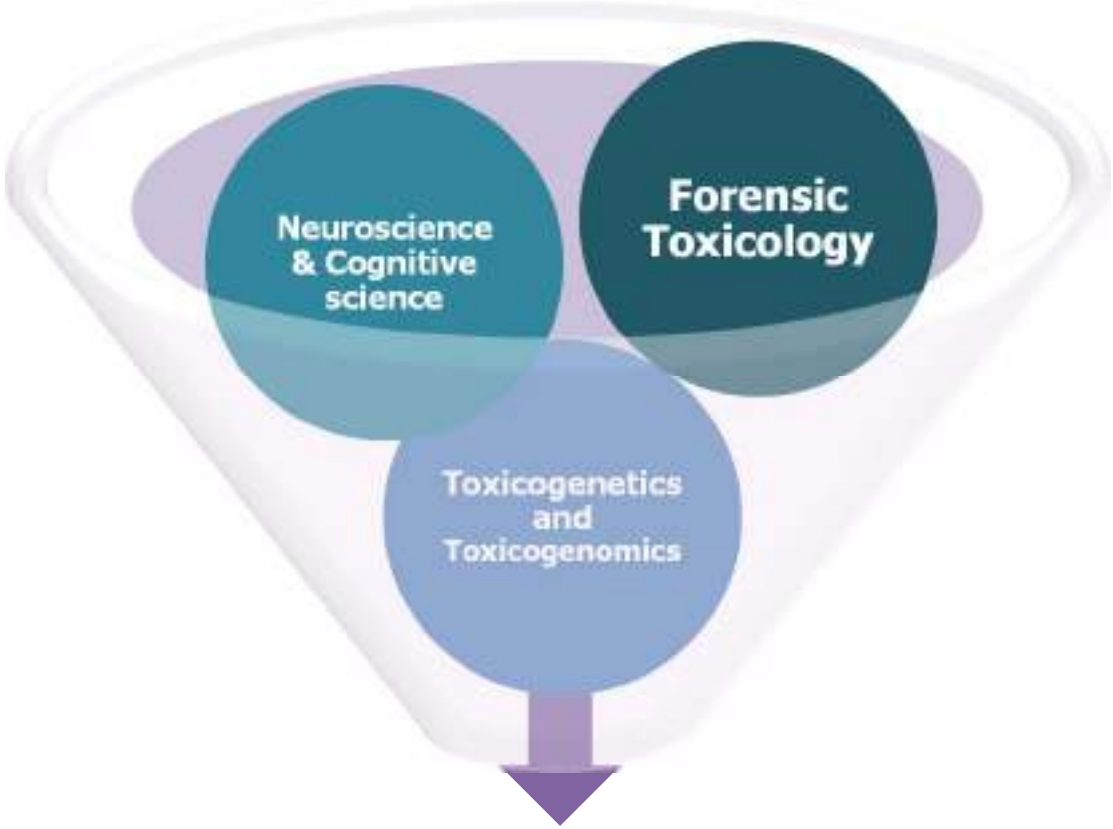
to start to clarify the relation between **brain structures**, **cognitive function and behaviours** (in particular functional mechanisms of the brain under the influence of substance abuse) and underline the **forensic interest.**



Example: brain, mind, behaviour and drug use

"Reactive" Amygdala	More Impulsivity	Aggressive behaviour	Criminal behavior
Empaiment Pre Frontal Cortex	Less self control	Easy Lack of self control	Imputability (?)

WE CAN CREATE A NEW SCIENTIFIC SYNERGY



TO CREATE A BETTER TOXICOLOGICAL EVIDENCE

Neuroscience & Neuroimaging in forensic toxicology can have also a deep impact on the justice process:

1. During Investigation Procedures

2. During Evidence collection and validation

3. Sentencing and penalty application (determine level of direct responsibility and imputability)

Neuroscience and Neuroimaging

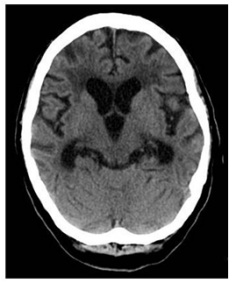
can provide more evidence of brain malfunctions and the causes of this, that make the person more likely to commit violent or sexual offenses (due to mental illnesses and disorders, or drug use, etc.).

These abnormalities affect the person's ability to choose and raise the issue of "free will" and, therefore, **accountability** and **imputability**.

THEORETICAL MEDICINE AND BIOETHICS
Theor Med Bioeth. 2010 Dec; 31(6): 429–443. Published online 2010 Oct 8. doi: 10.1007/s11017-010-9158-5. PMCID: PMC2975916. **Free will and mental disorder: Exploring the relationship.** Gerben Meynen

Neuroscience and Neuroimaging can bring a scientific contribute in forensic:

- Study and define the way in which **structural and functional** abnormalities of the brain and the mind can influence behaviors & responsa**bi**lity:



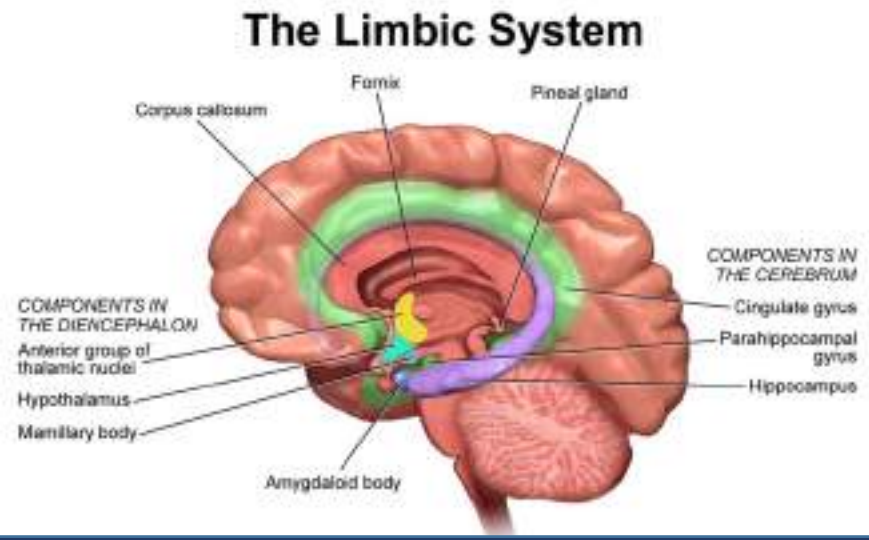
- **MORPHOLOGICAL EXAMINATION** (ex. CAT - Computerized axial tomography scan): Check presence of structural lesions of the brain areas that control and/or generate behaviors

- **FUNCTIONAL ANALYSIS** (eg. F-MRI): Check impairment of the areas that control and/or generate behaviors

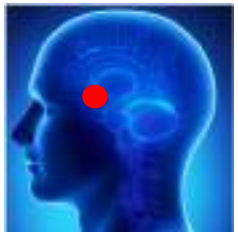
Using a unified approach "mind & brain": neuro-psychological approach

1. List of Most Relevant Brain Structures and Systems, for forensic toxicologists

- Genotype: DRD4 7R (dopamine receptors system), CNR 1, MAOA-L and brain development
- Limbic system:
  - Amygdala
  - Insula (iperactivity)
  - Nucleus accumbens
  - Hippocampus, temporal lobe
  - Thalamus – ventral striatus
- PFC Prefrontal Cortex
- Cerebellum
- Gray Matter - neurons -
  White Matter - dendritic arborization, intra lobes connections ….)
- Visual motor cortex
- Broca's & Wernicke's areas
- Neuronal systems and Receptor:
  - dopaminergic system
  - serotoninergic system
  - endorphine system
  - endocannabinoid system
  - GABA system
- Neurotransmitters/neurohormons (es. Glutamate)
- Glucose metabolism in the brain



Two main important Brain Structures <u>to be fit to plead</u>



Prefrontal Cortex

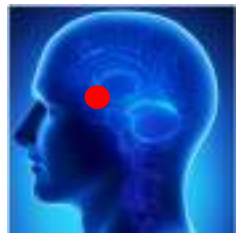
Amygdala

«rational CONTROLLER»

- Cortical area responsible for the control of voluntary behavior and rational choices.
- It controls & inhibits <u>aggressive</u> impulses generated by the amygdala.

«emotional DRIVER»

- Subcortical area responsible for impulsivity and emotions
- It generates fear and aggressiveness



Prefrontal cortex

Amygdala

«rational CONTROLLER»

«emotional DRIVER»

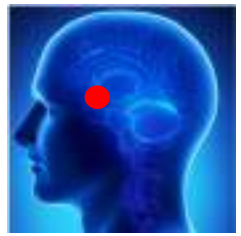
Higher

Lower

NORMAL BALANCE CONDITION

NORMAL BEHAVIOURS

LEGAL RESPONSABILITY



Genetic → **Impairment** ← Disease/Drugs

Inhibition
Low activity

Activation
Hyperactivity

Prefrontal cortex

«rational CONTROLLER»

Amygdala

«emotional DRIVER»

- Low activity
- Low moral sense
- No distinction between good and evil

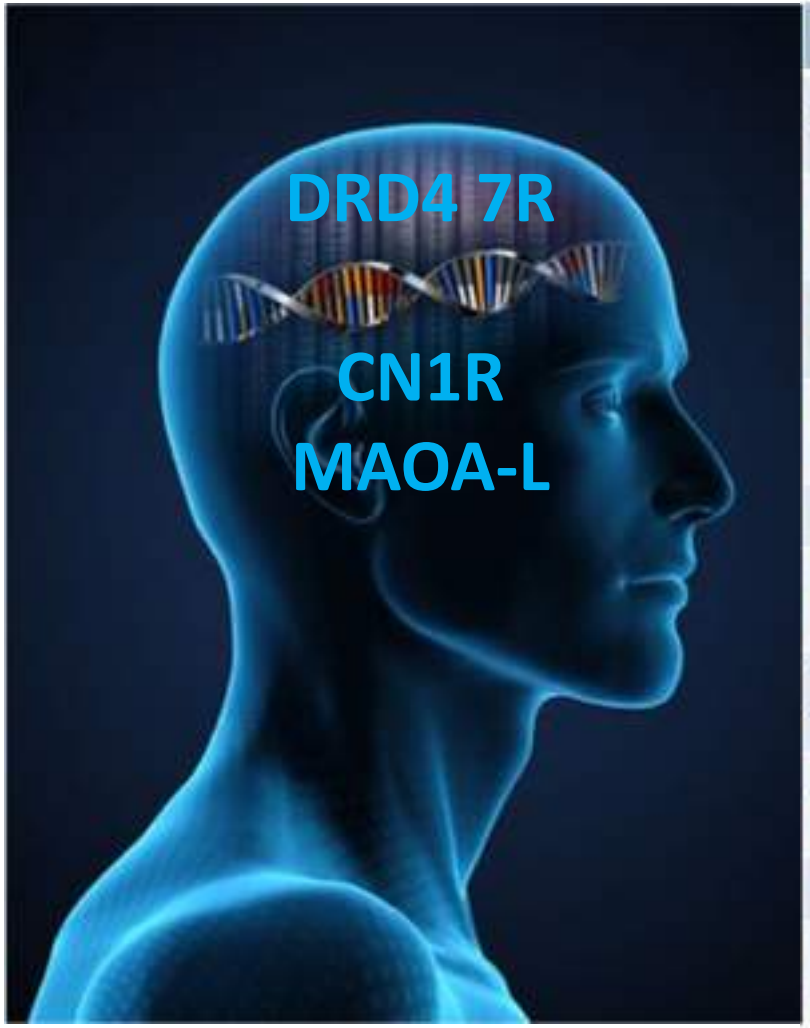
- High activity
- High impulsivity

UNBALANCE CONDITION

VIOLENT BEHAVIOURS

IS THERE DIRECT LEGAL RESPONSIBILITY ?

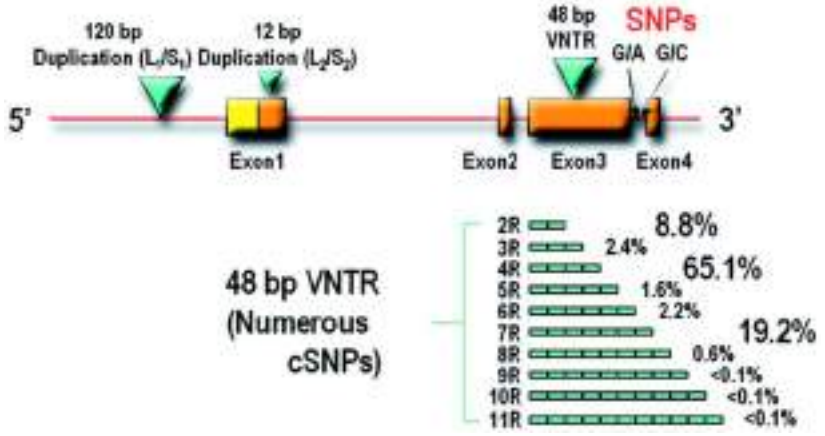
Genetic setting and Epigenitic expression: important genes →DRD4-7L, CN1R, MAOA-L …

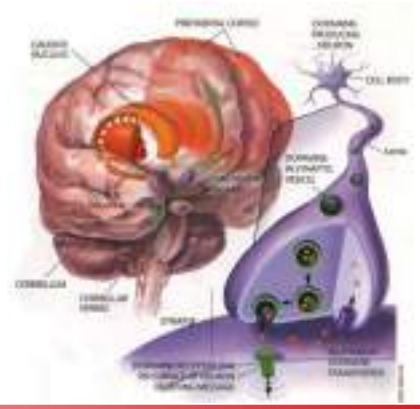


Genes & Dopamine
SLC64A Transporter gene 5-HT
D2A1 – Allele Faq – A1 Dopamine receptor gene D2
DRD4 Dopamine receptor gene
DRD1 Dopamine receptor gene D1
DRD2
DAT1 Dopamine transporter gene
TPM Triptofano Gene
ADMA2C Receptor Gene
NMDA1
PS1 Gene

DRD4 gene & Deficit of brain dopamine receptor D4...

→ Novelty Seeking Temperament ...
→ High Risk Behaviors Expression ...
→ High Risk of Drug Use and Addiction.



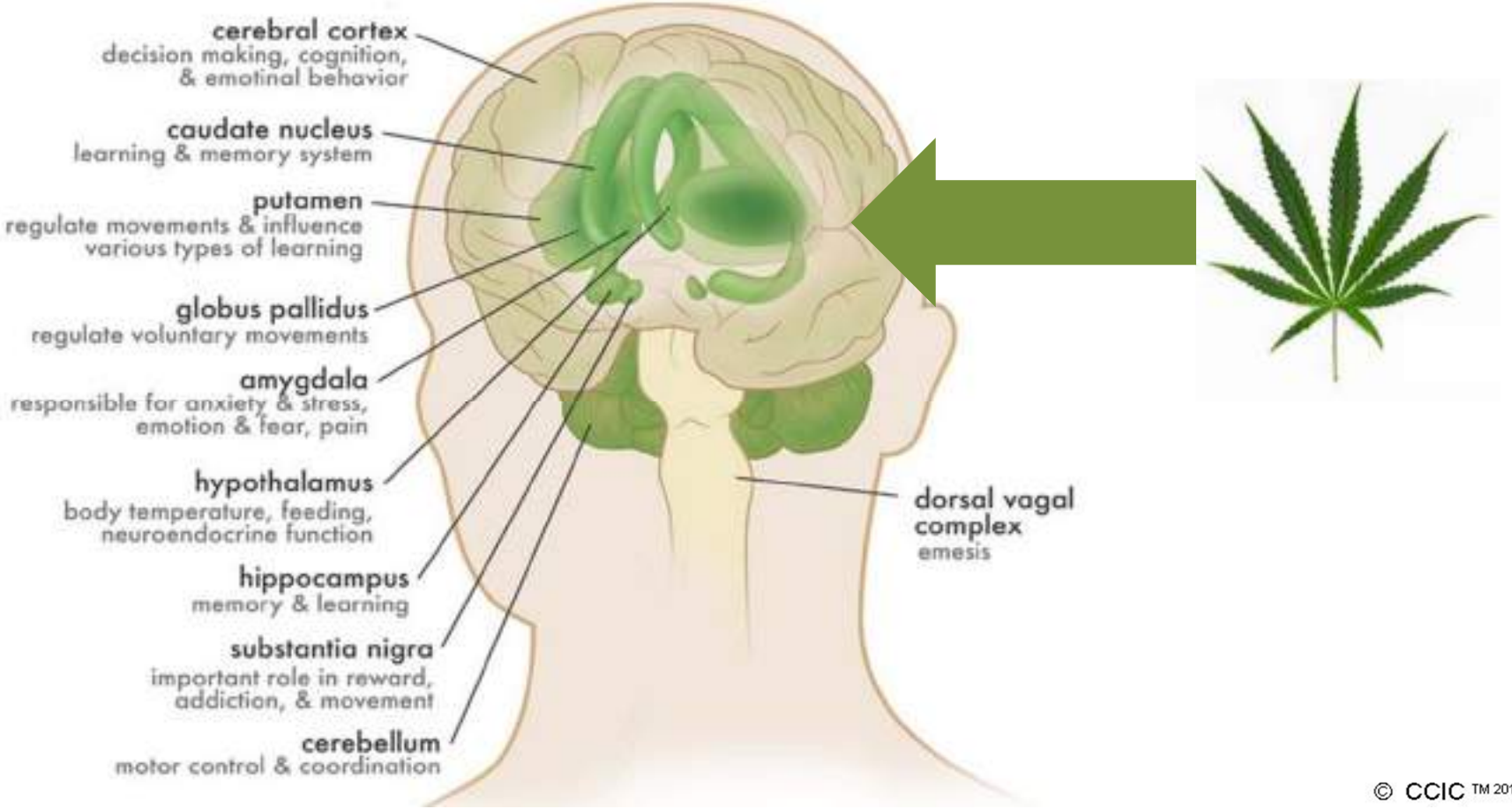


Novelty Seeking Temperament

Cloninger, C. Robert -
Biosocial Theory of Personality

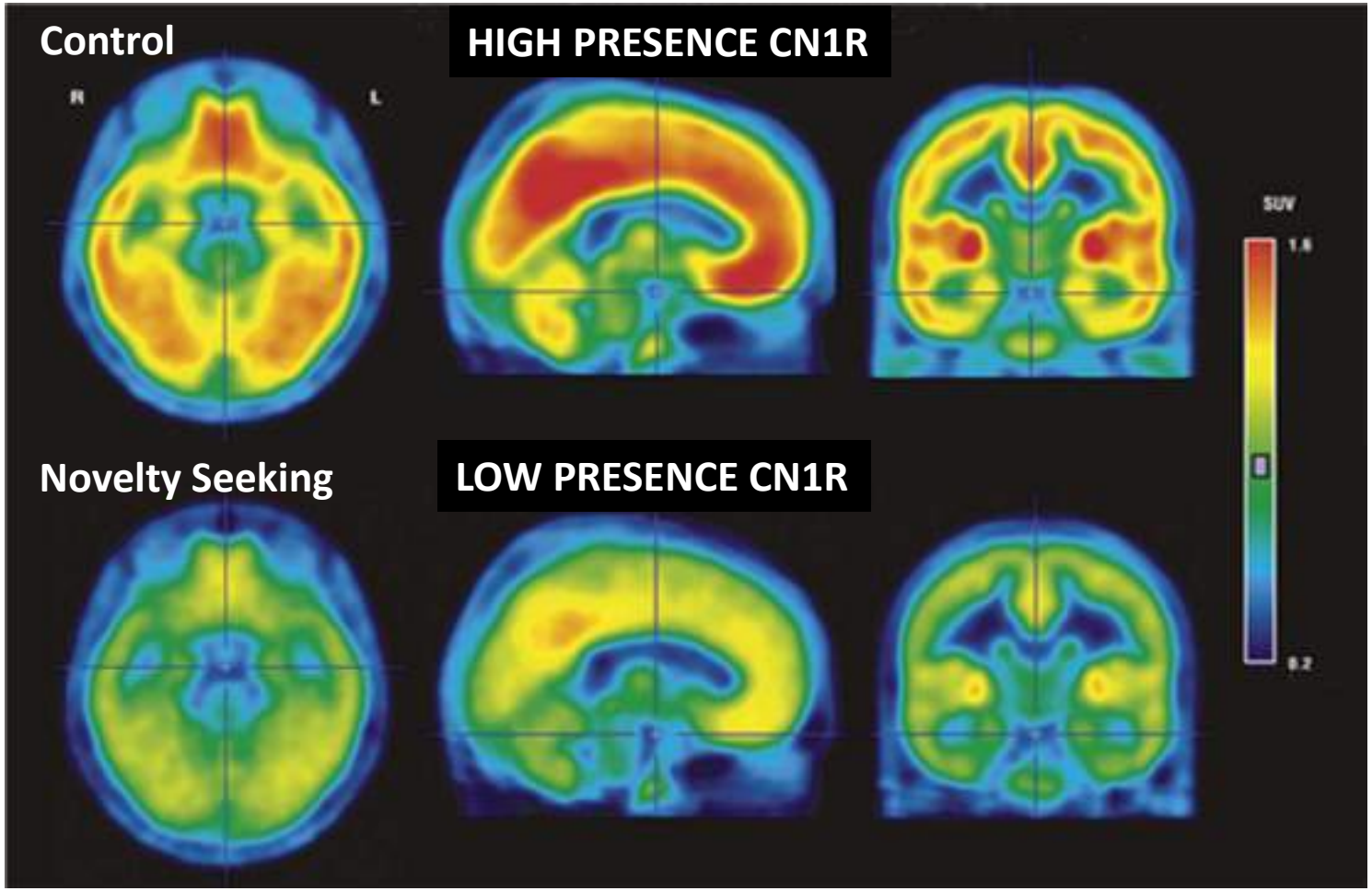
High risk behaviours

CN1R gene and large distribution of CB1 Receptors in the brain. They are involved in the regulation of many body functions



CN1R gene encodes cannabinoid receptors 1.

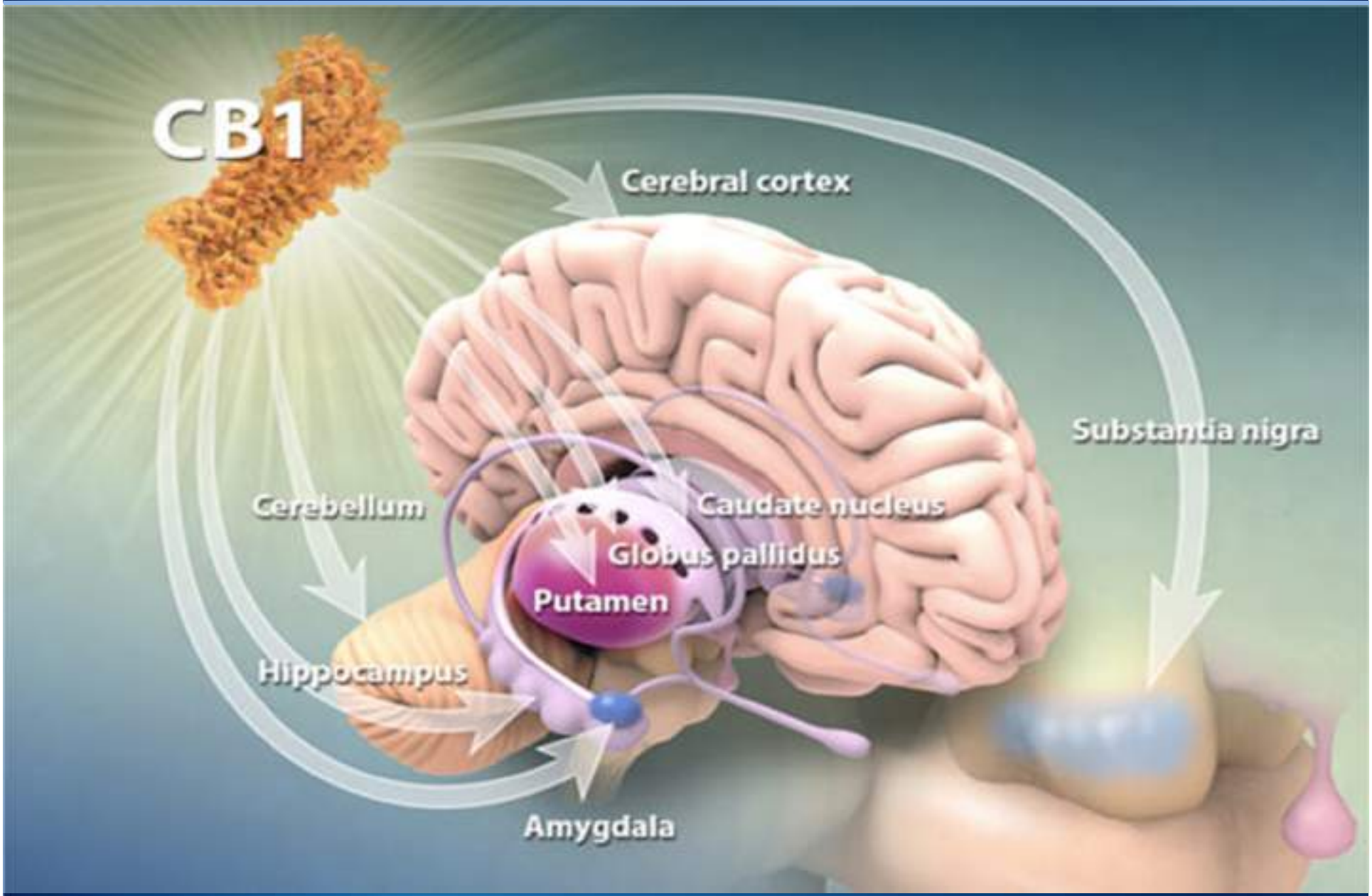
There is a Relationship of Low presence of Type 1 Cannabinoid Receptor in the Human Brain to Novelty-Seeking Temperament



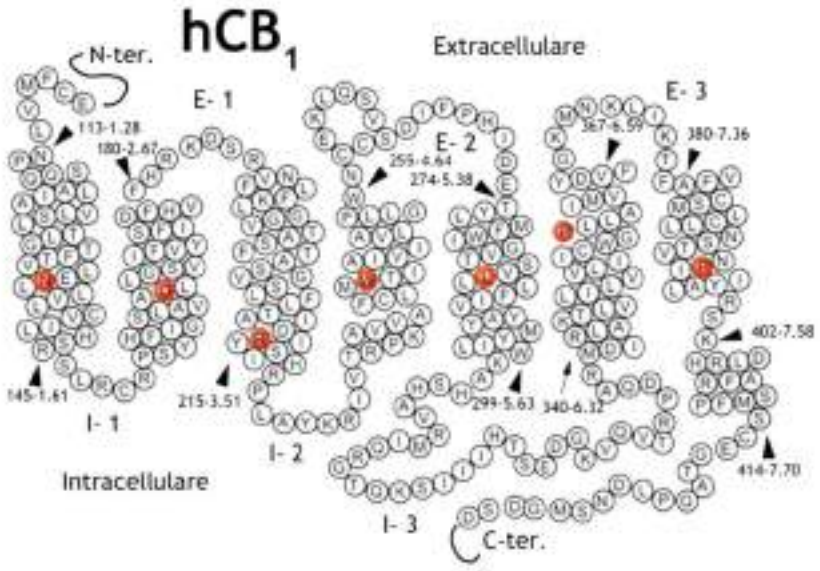
Arch Gen Psychiatry. 2009;66(2):196-204. doi:10.1001/archgenpsychiatry.2008.530.

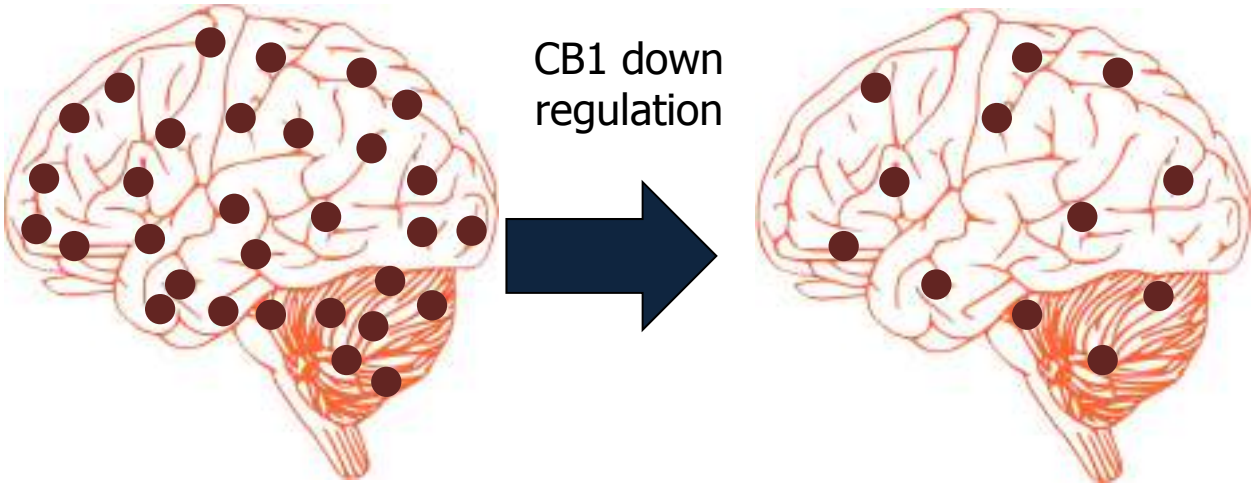
NCBI. Gene ID: 1268, updated on 24-Aug-2015

the difference is most pronounced is in the Amygdala


CB1
Cerebral cortex
Substantia nigra
Cerebellum
Caudate nucleus
Globus pallidus
Putamen
Hippocampus
Amygdala

CANNABIS use & Decrease of CB1 number



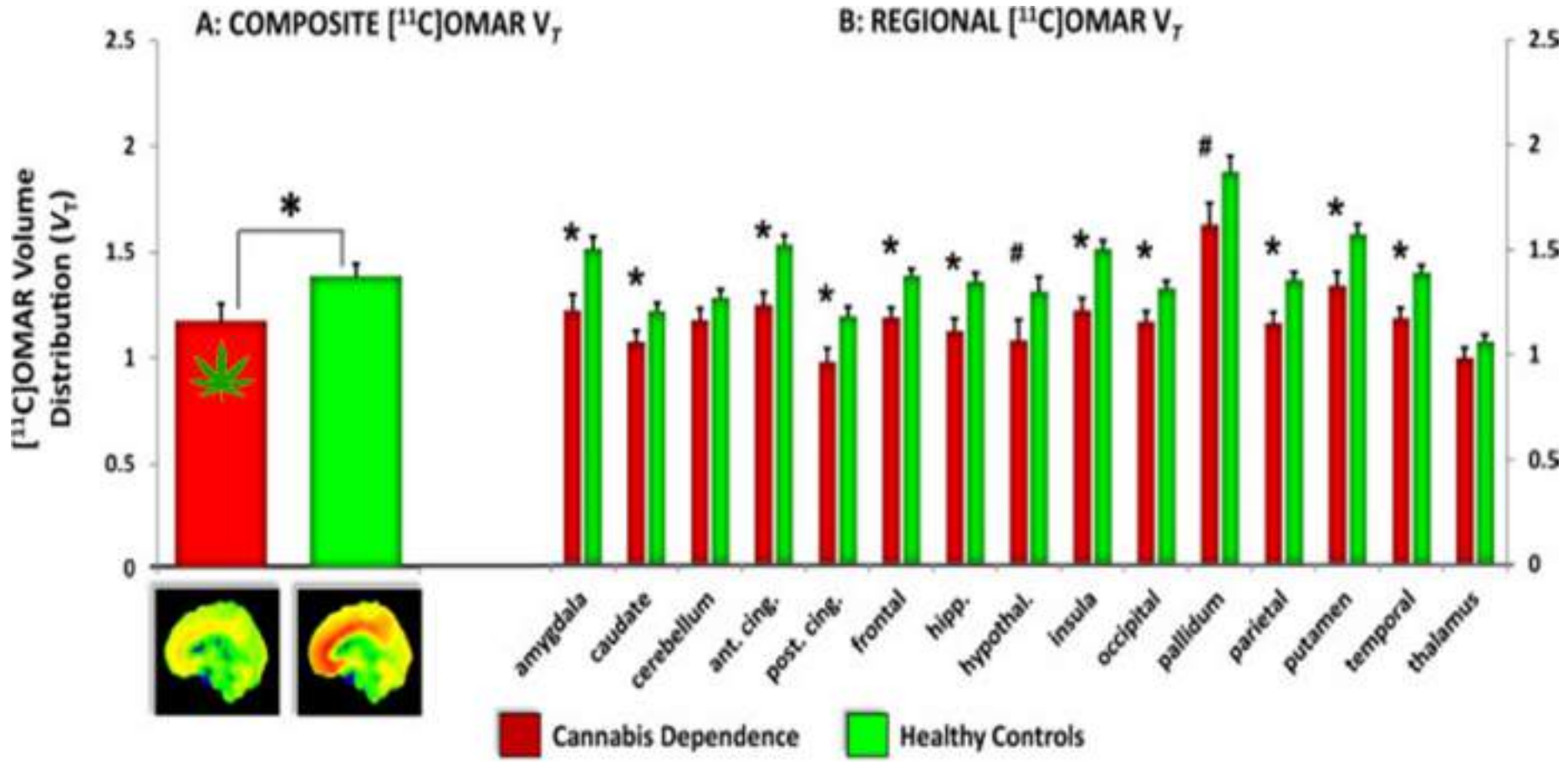


Brain functions impairment

Cannabinoid 1 receptor availability

Biological Psychiatry CNNI Cognitive Neuroscience and Neuroimaging

Deepak Cyril D'Souza 2016



Composite and regional cannabinoid 1 receptor availability in cannabis-dependent (CD) subjects compared with healthy control (HC) subjects at baseline.

PNAS

Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation

Rose McDermott[a,1], Dustin Tingley[b,1], Jonathan Cowden[c], Giovanni Frazzetto[d], and Dominic D. P. Johnson[e,2]

[a]Department of Political Science, Brown University, 36 Prospect Street, Providence, RI 02912; [b]Department of Politics, Princeton University, Princeton, NJ 08544; [c]Department of Political Science, University of California, Santa Barbara, CA 943106; [d]Research Centre for the Study of Bioscience, Biomedicine, Biotechnology, and Society, London School of Economics, Houghton Street, London WC2A 2AE, United Kingdom and European Molecular Biology Laboratory, I-00015 Monterotondo (Rome), Italy; and [e]Politics and International Relations, University of Edinburgh, 15a George Square, Edinburgh EH8 9LD, Scotland

Edited by Raghavendra Gadagkar, Indian Institute of Science, Bangalore, India, and approved December 11, 2008 (received for review September 2, 2008)

LOW ACTIVITY
Monoamine Oxidase A Gene

NORMAL ACTIVITY
Monoamine Oxidase A Gene

PROVOCATION

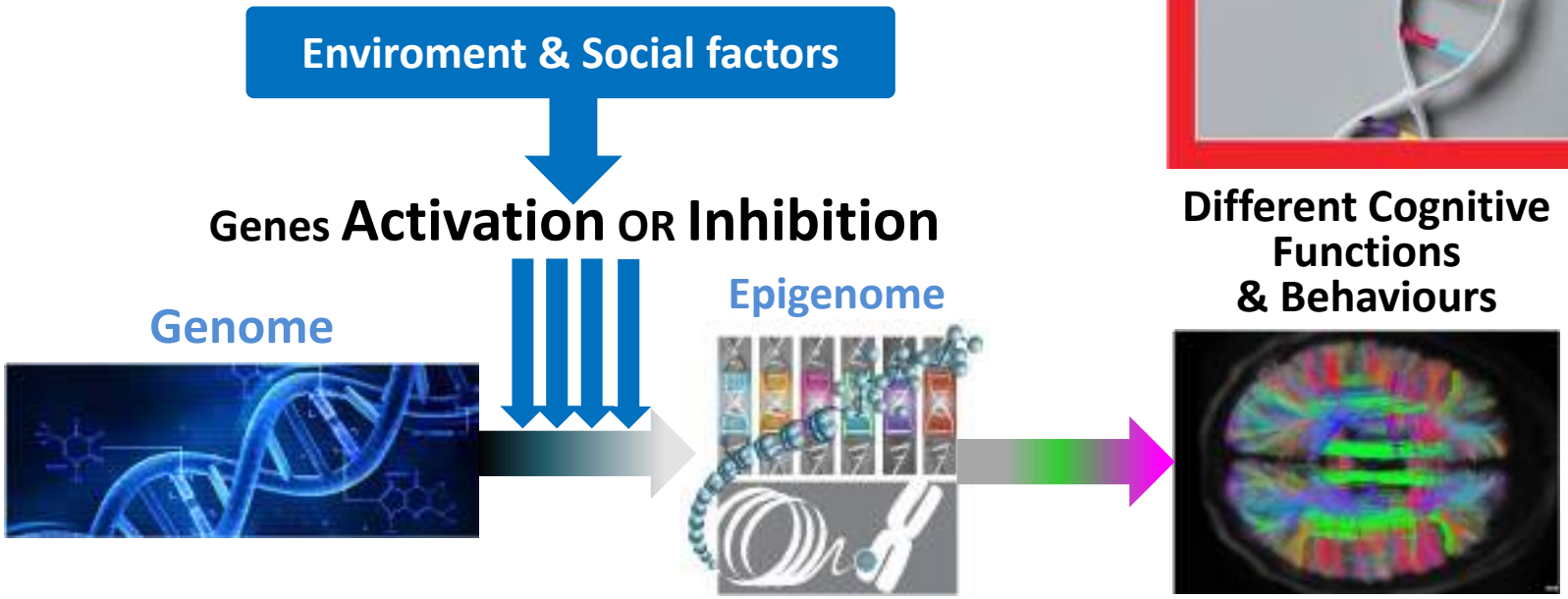
PROVOCATION

HIGH AGGRESSIVE BEHAVIORS

LOW AGGRESSIVE BEHAVIORS

But Genetics isn't a «destiny» → Epigenetics

The human genome contains about 25,000 genes, but the number of patterns of epigenetic marks is likely to be 50 to 100 times as large



HERE IS HOW IT DEVELOPS →

1.0. GENOTYPE
- DRD4
- CN1R
- MAOA-L
- ……..

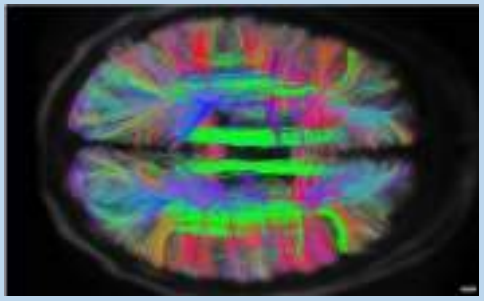
1.1. ORIGINARY NEUROTYPE (brain):
- PFC (controller), - Amigdala
- Reward system, - Memory system
- …..

1.2. ORIGINARY COGNITYPE (mind)
- psychic functioning
- attitudes
- motivational system
- problem analisys and solving
- decision making process

1.3. ORIGINARY BEHAVIORAL FENOTYPE

First part of the life

CONSTANT NEUROPLASTICITY



EXTERNAL DEVELOPMENT FACTORS:
Time, Social and envoirmental factors, educational factors, positive and negative experiencies, knowledges, **substance abuse**, behaviours feedback….

EPIGENETIC INFLUENCE

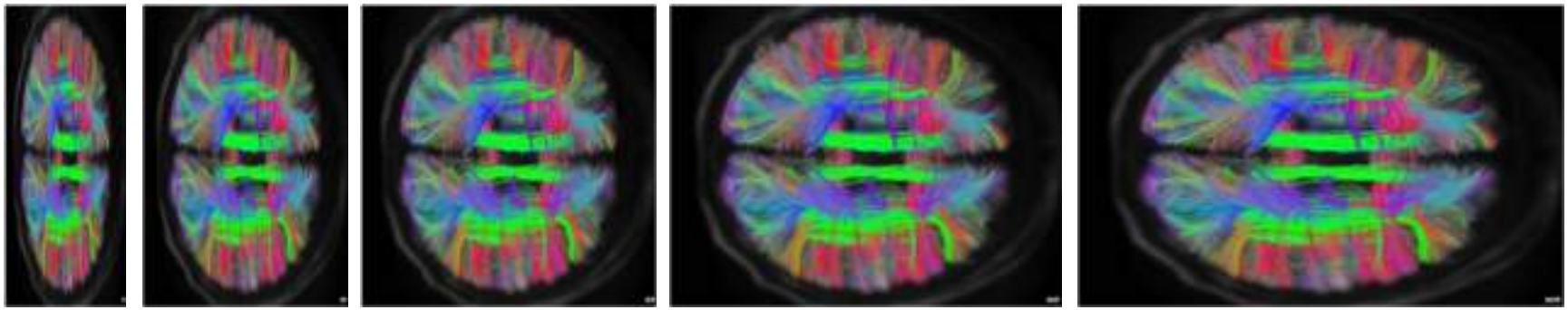
Second part of the life

2.1 SECONDARY NEUROTYPE
Advanced/Expert/Adult

2.2 SECONDARY COGNITYPE
Advanced/Expert/Adult

2.3 «ADVANCED» BEHAVIORAL FENOTYPE
Secondary - different types for different genotypes, experiences and cognitive development

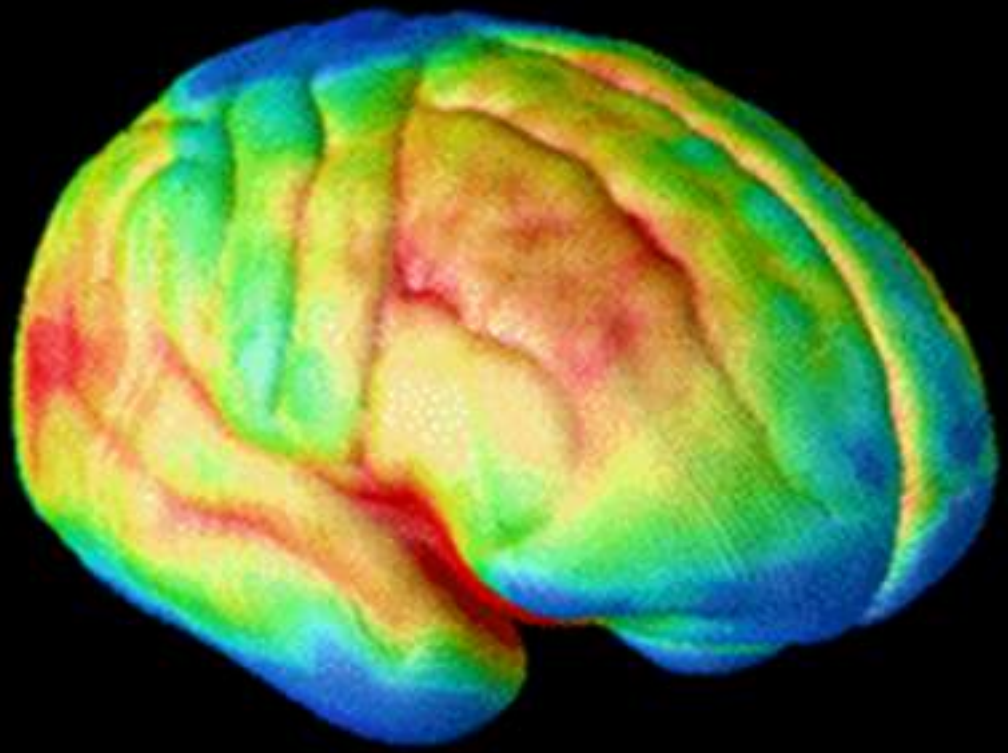
Neuro-fenotipic development of the brain and its cognitive funtions is a **long continuous process of neuroplasticity**



Brain development **changes its structures and functions over time:** from genetic bases to behaviours BUT underlining **the importance of neuroplasticity and of the social, educational and environment factors to change the "destiny to addiction " of a vulnerable person to a low probability of negative evolution.**

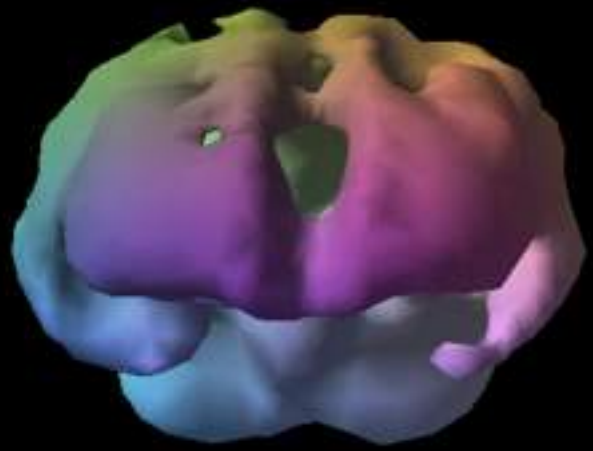
Brain development from 0 to 25 age:

Gray matter maturation

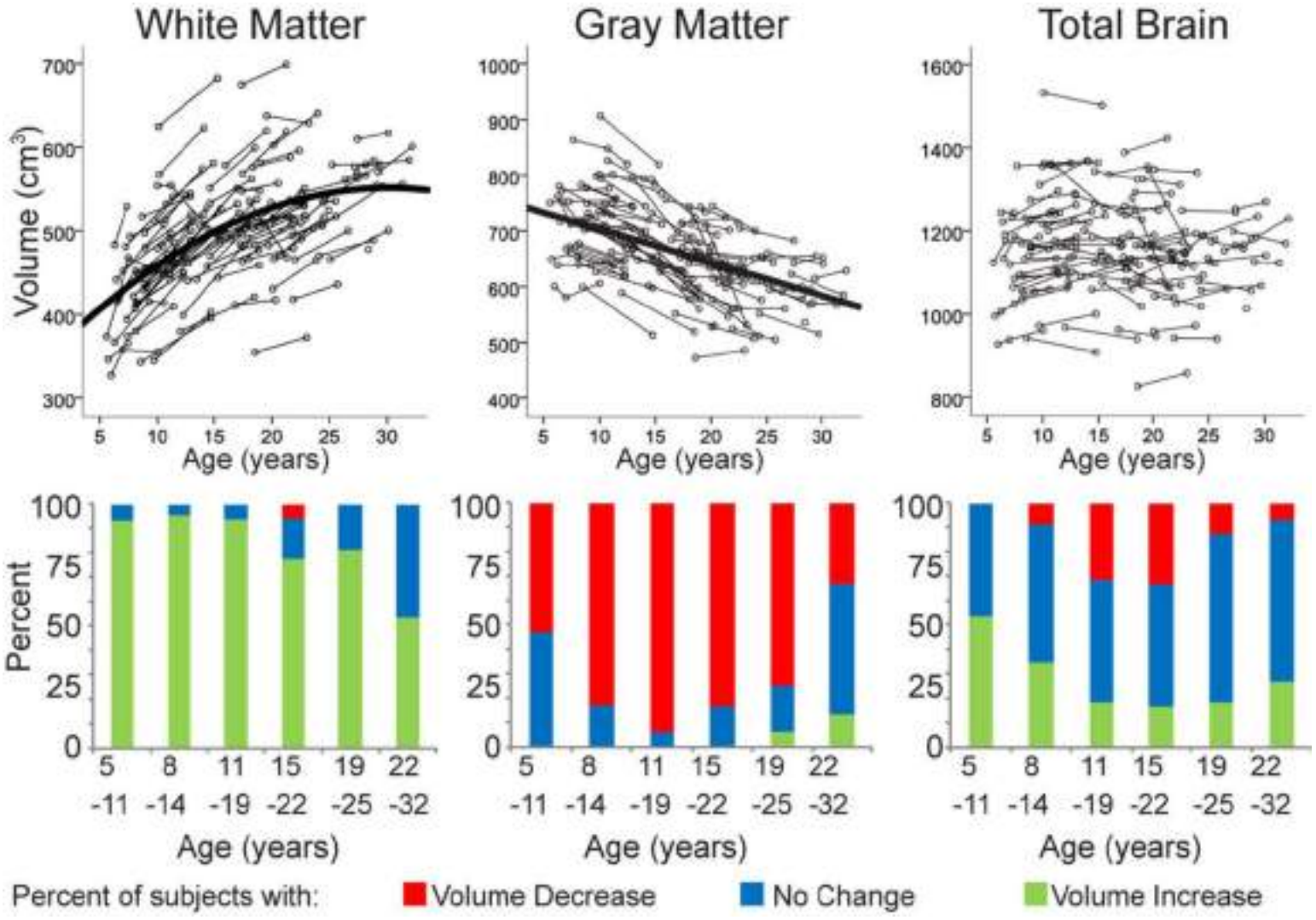


SPECT

Alcohol abuse effects

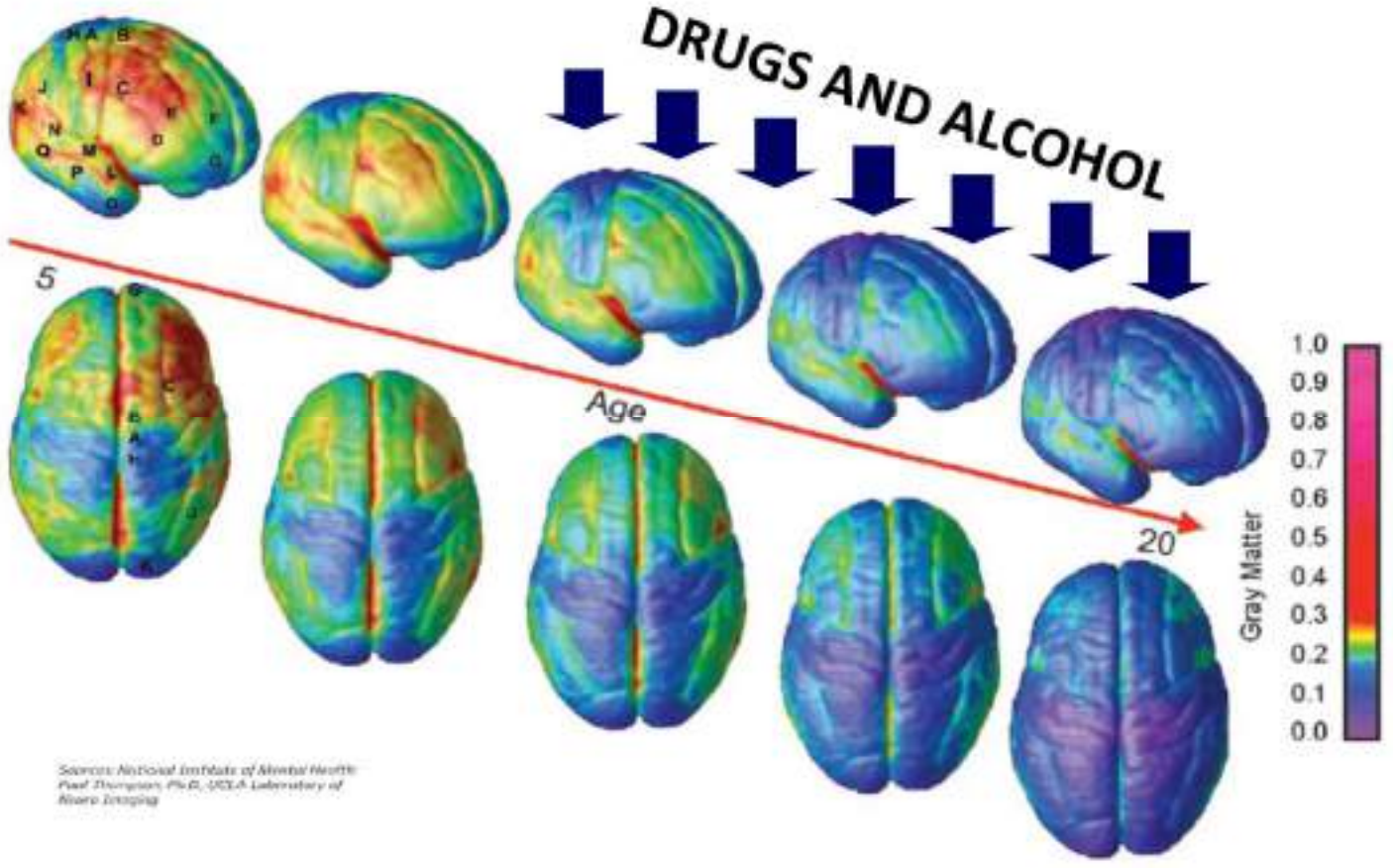


Brain development



Lebel C, Beaulieu C.. The Journal of Neuroscience, July 27, 2011

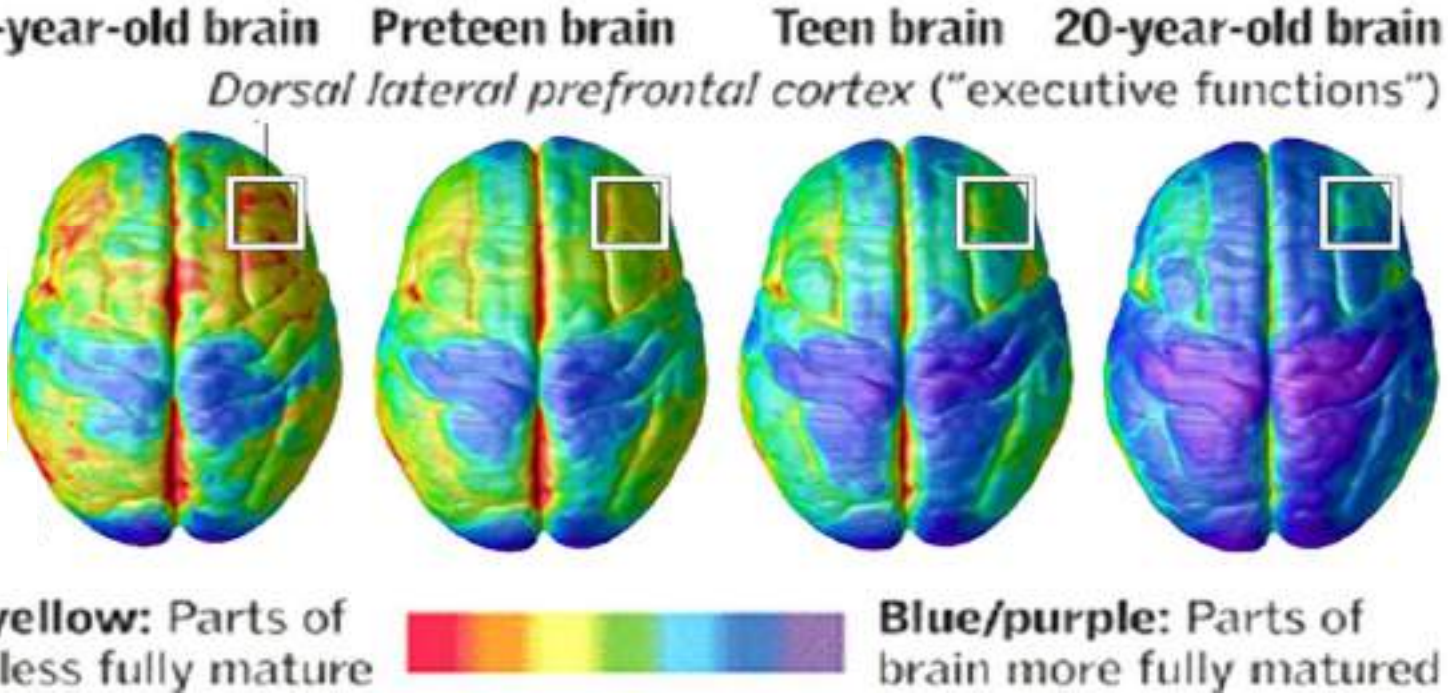
Deviation of Brain development: drug use can generate a bias of this ”Work in Progress” with permanent impairment



Judgment last to develop

Source: National Institute of Mental Health
Paul Thompson, Ph.D., UCLA Laboratory of Neuro Imaging

The area of the brain that controls "executive functions" — including weighing long-term consequences and controlling impulses — is among the last to fully mature. Brain development from childhood to adulthood:



Nora Volkow et all..

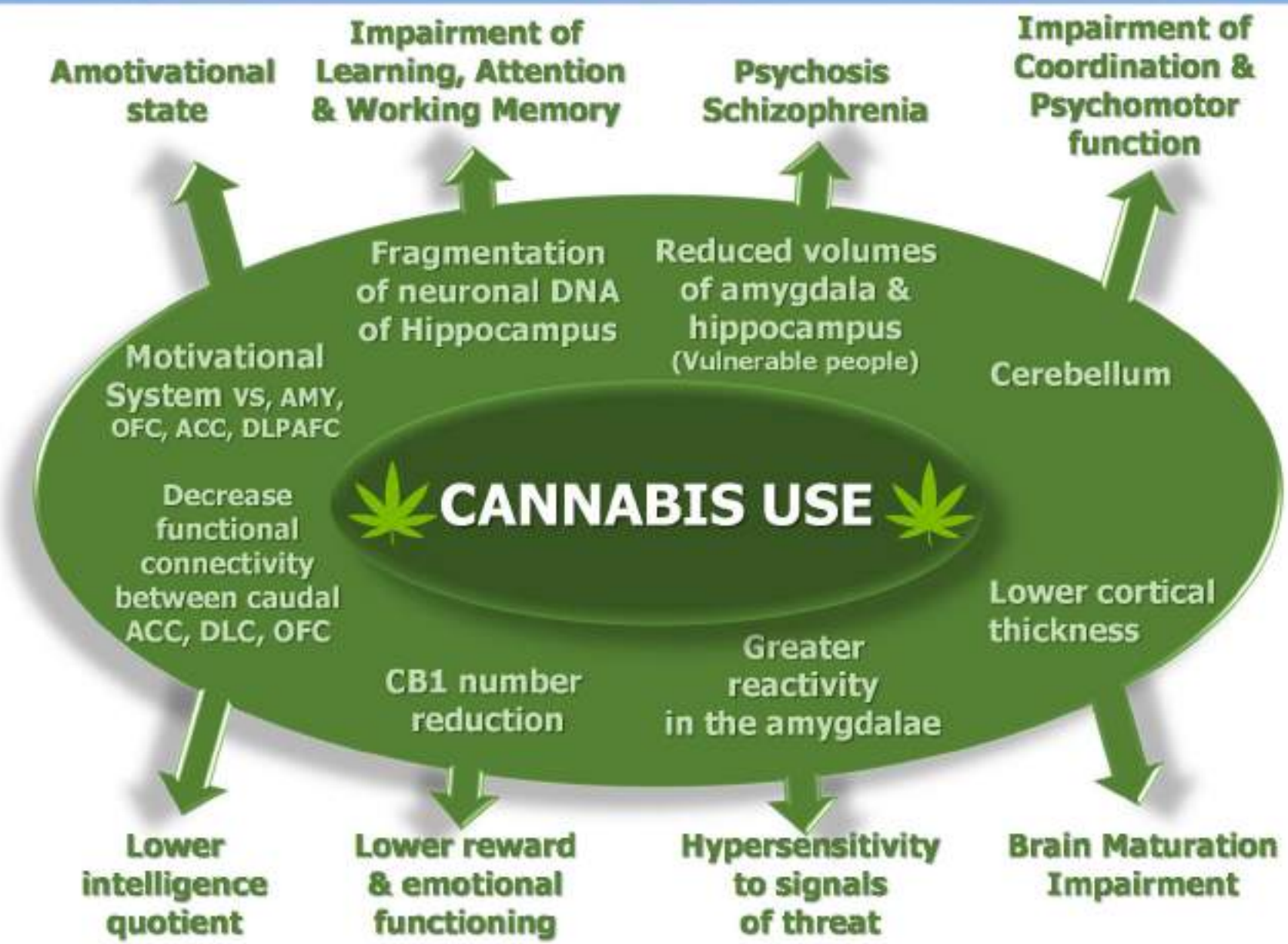
Director of the National Institute on Drug Abuse (NIDA) at the NIH

NIH National Institute on Drug Abuse
The Science of Drug Abuse & Addiction

JAMA Psychiatry. **2016**

Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review.

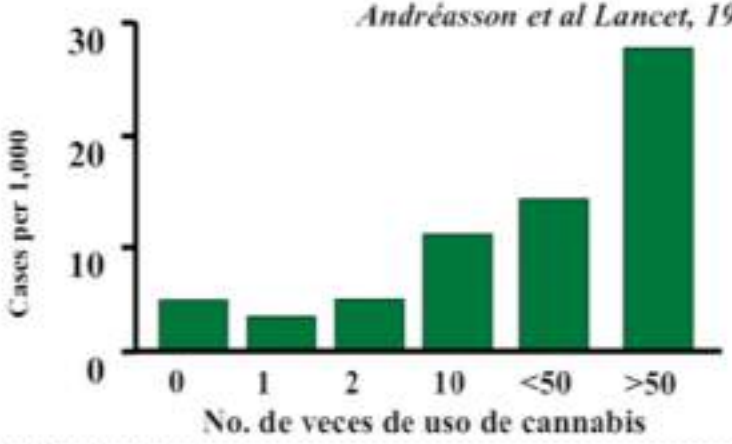
- **Current efforts to normalize cannabis use are being driven largely by a combination of grassroots activism, pharmacological ingenuity, and private profiteering, with a worrisome disregard for scientific evidence, gaps in our knowledge, or the possibility of unintended consequences.**
- *Gli attuali sforzi per normalizzare l'uso di cannabis sono guidati in gran parte da una combinazione di attivismo di base, l'ingegno farmacologico, e affarismo privato, con un disinteresse preoccupante per prove scientifiche, lacune nella nostra conoscenza, o la possibilità di conseguenze impreviste.*


Amotivational state
Impairment of Learning, Attention & Working Memory
Psychosis Schizophrenia
Impairment of Coordination & Psychomotor function
Fragmentation of neuronal DNA of Hippocampus
Reduced volumes of amygdala & hippocampus (Vulnerable people)
Motivational System vs, AMY, OFC, ACC, DLPAFC
Cerebellum
CANNABIS USE
Decrease functional connectivity between caudal ACC, DLC, OFC
Lower cortical thickness
CB1 number reduction
Greater reactivity in the amygdalae
Lower intelligence quotient
Lower reward & emotional functioning
Hypersensitivity to signals of threat
Brain Maturation Impairment

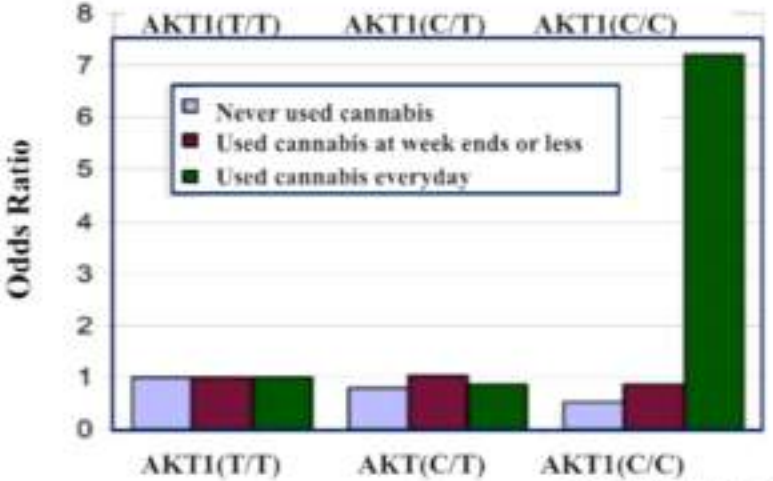
Psicosis asociada a Cannabis

Estudio de Conscriptos Suecos (n=45570)

Andréasson et al Lancet, 1987.



El uso Regular de Cannabis aumenta el riesgo de Esquizofrenia en aquellos genotipos AKT1 rs2494732

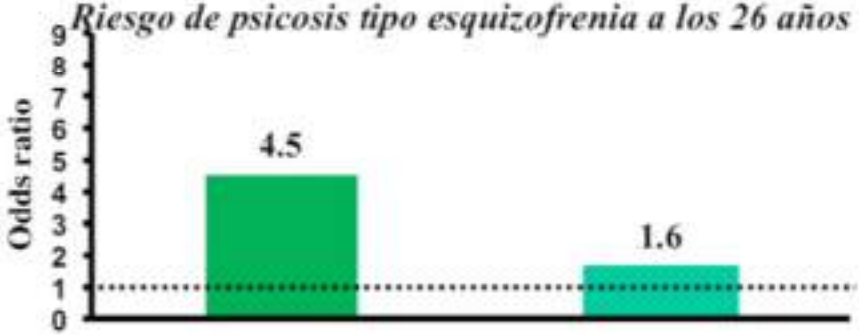


GXE model: p*=0.014

Di Forti et al., Biological Psychiatry, 2012.

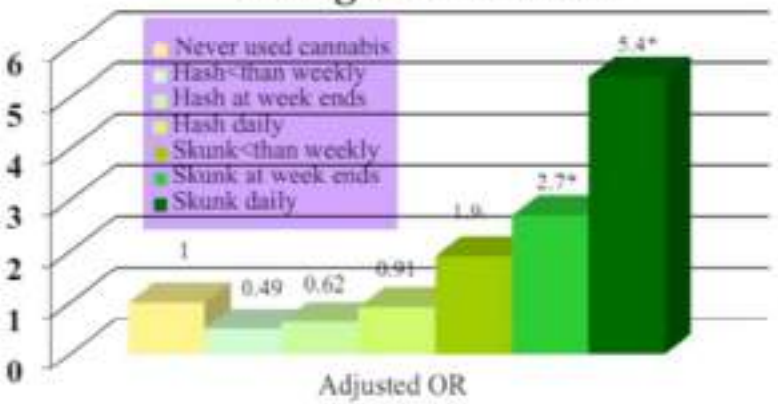
Estudio Prospectivo de Dunedin (n=1037)

Riesgo de psicosis tipo esquizofrenia a los 26 años



Arseneault et al BMJ 2002

Efecto de Cannabis de Alta Potencia en el Riesgo de Psicosis



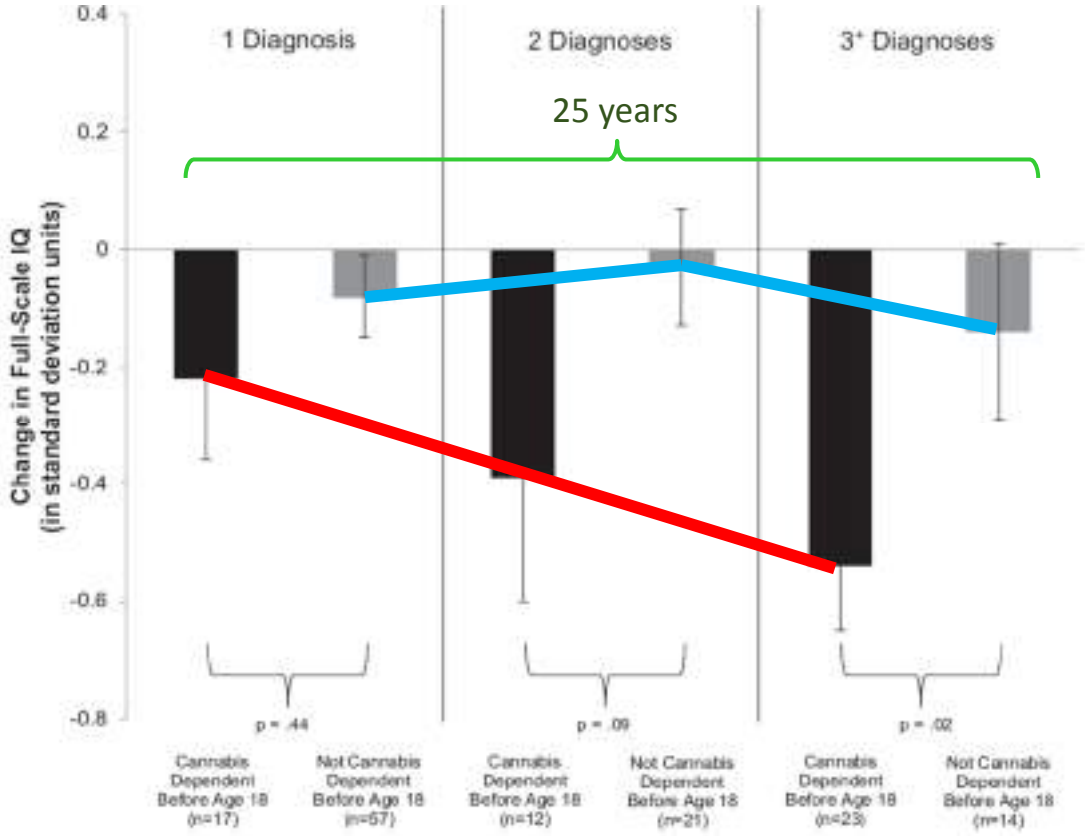
Di Forti M et al., The Lancet published online February 18, 2015.

Cannabis use in adolescence and loss I.Q.

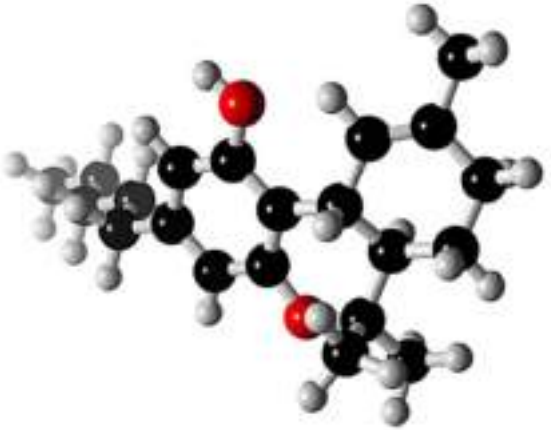
Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[g], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)



1037 individuals followed from birth (1972/1973) to age 38 yo



Dunedin prospective study of 1037 subjects born in 1972-73
Subjects were tested for IQ at age 13 and 38 years of age. They were also tested for THC use ages 18, 21, 26, 32 and 38 years of age.

Amygdala main functions

- Is in the limbic system (subcortical)
- Generates Fear **– is "the Panic Button"**
- Actevates Aggression
- Starts emotional response to sensory information
- Regulates emotion process
- Stimolates Sexual impulse & Arousal

Under the influence of drugs

Am. is implicated in:

- **Craving generation and the transition & maintenance of addiction**
- **Aggressivity increase**
- **Anxiety increase → Panic Attack**

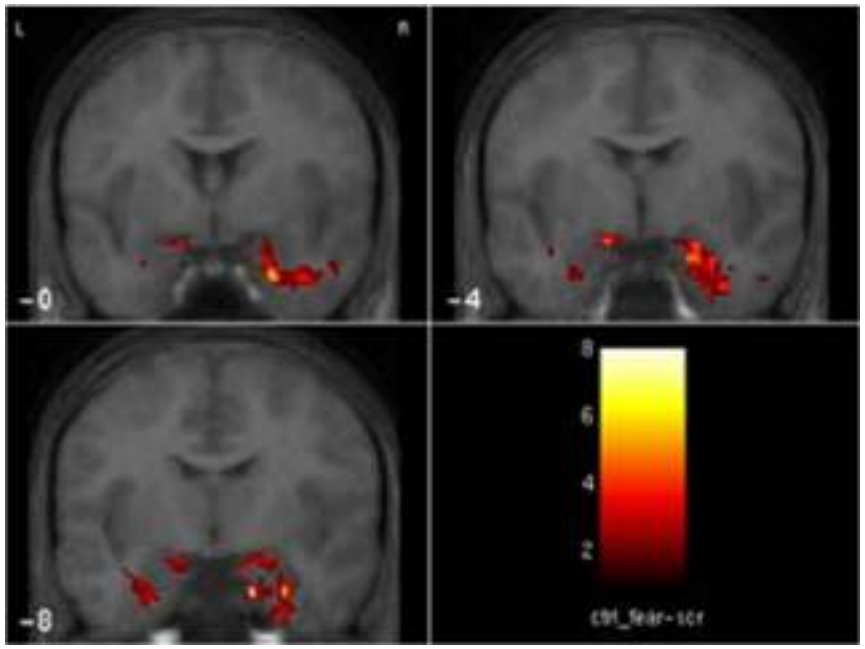

nature
nature
The look of fear
Amygdala
The Panic
Button

Amygdala activity & fear

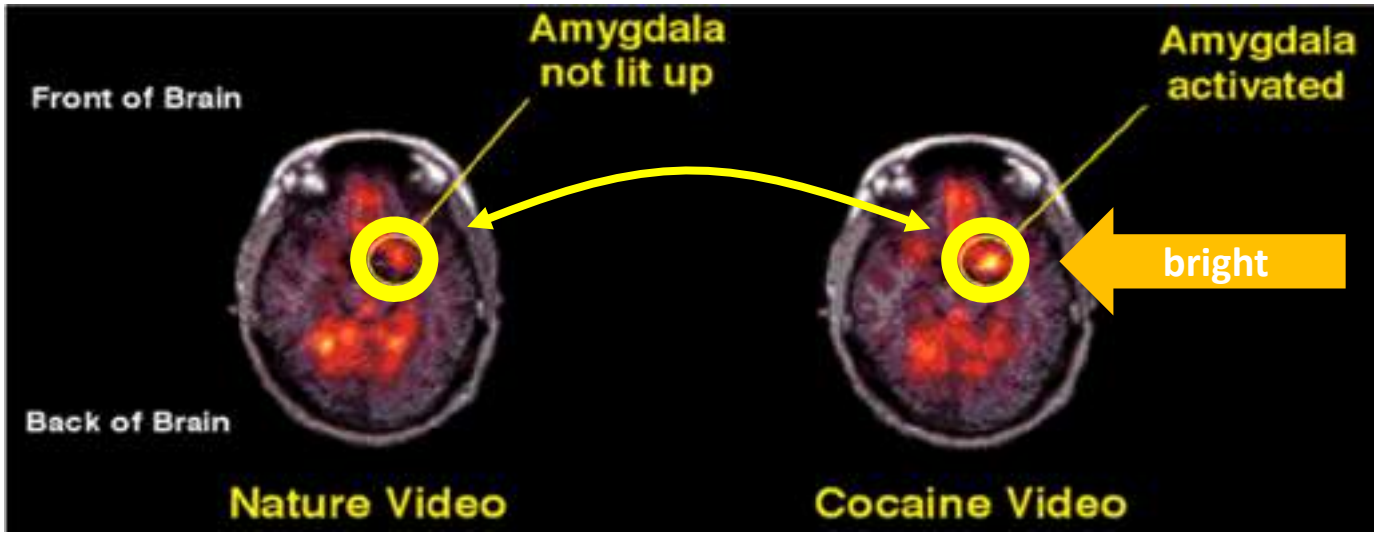
FEAR

FEAR

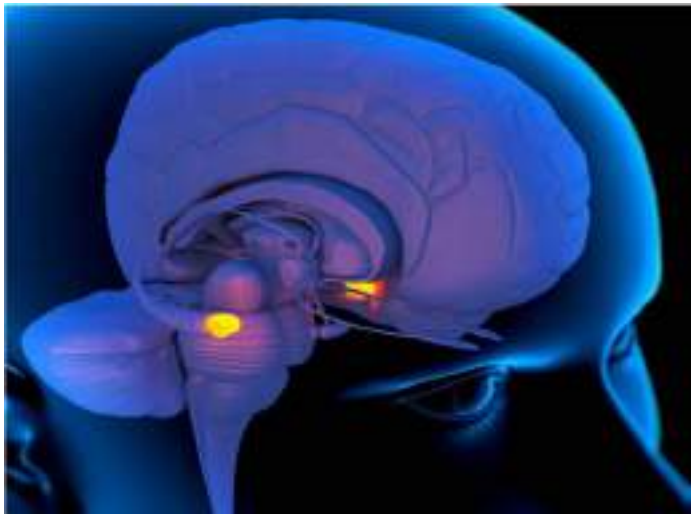
FEAR

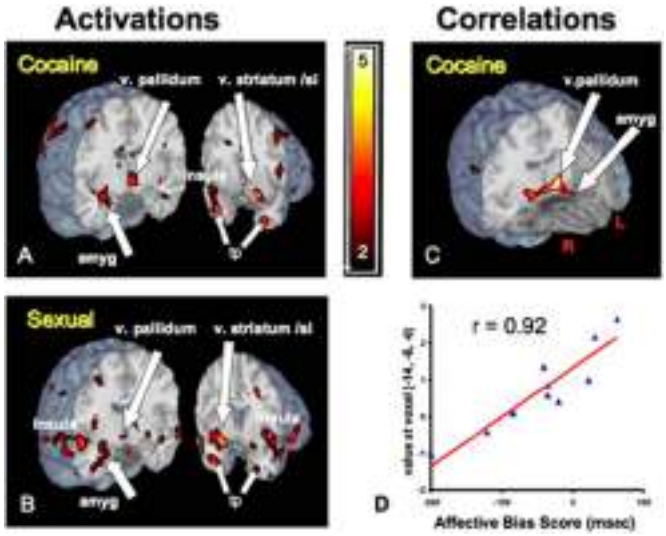


Increase of Amygdala activity and Craving



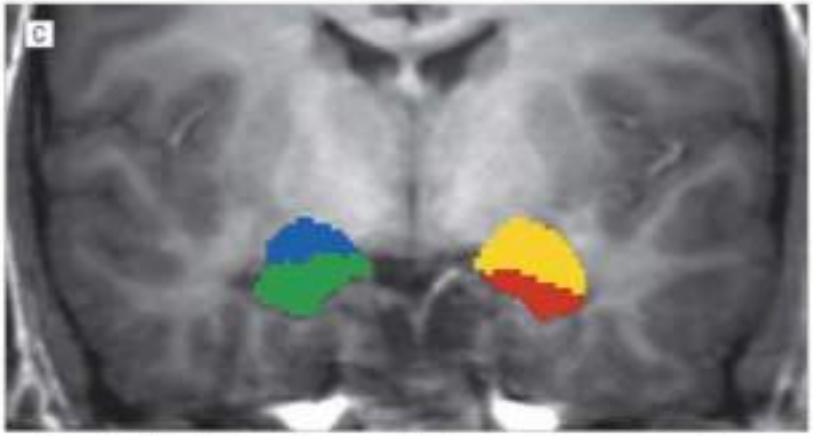
Kilts CD. Psychopharmacology Bull. 2001 Winter;35(1):84-94.
Imaging the roles of the amygdala in drug addiction.





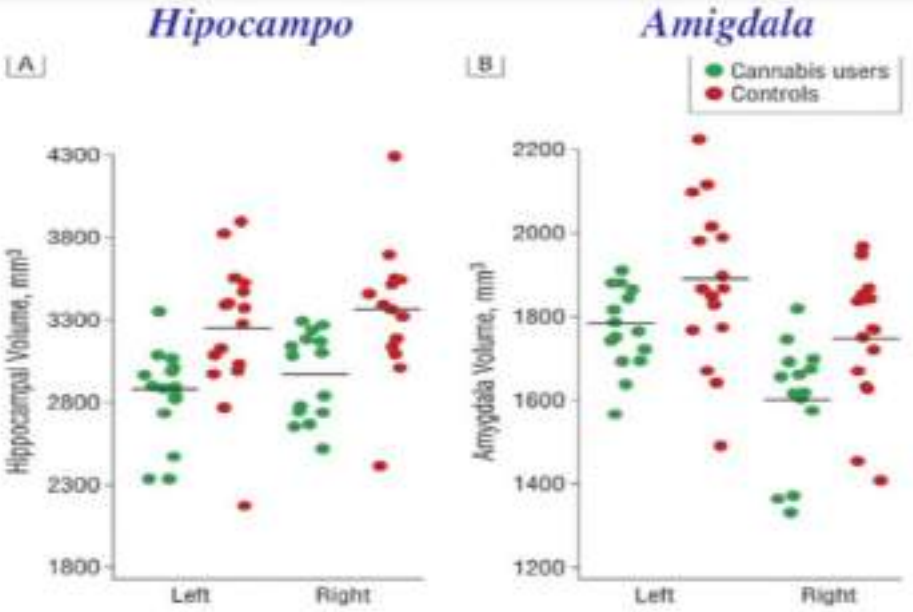
Anna Rose Childress and Dr. Charles O'Brien,

Brain abnormalities associated with intense and prolonged use of cannabis

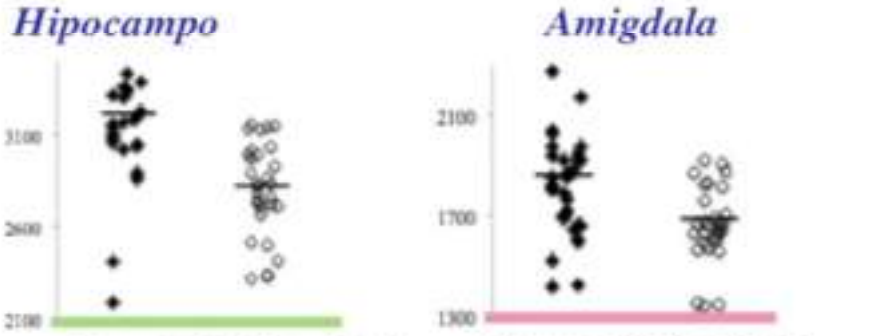


Amígdala Izq (amarilla) y der (azul)
Hipocampo Izq (roja) y der (verde)

The hippocampus and amygdala volumes are smaller in cannabis users than in control subjects, and that is related with an altered functioning of memory



Yucel et al., Arch Gen Psychiatry. 2008



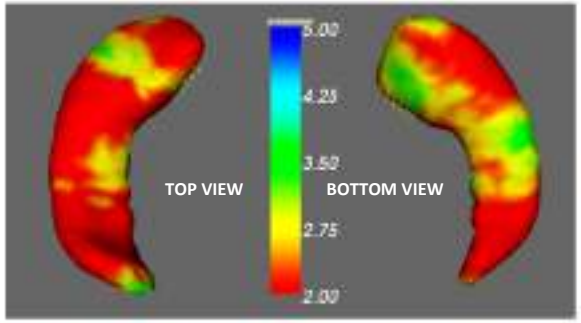
Lorenzeti et al., Biological Psychiatry 2015

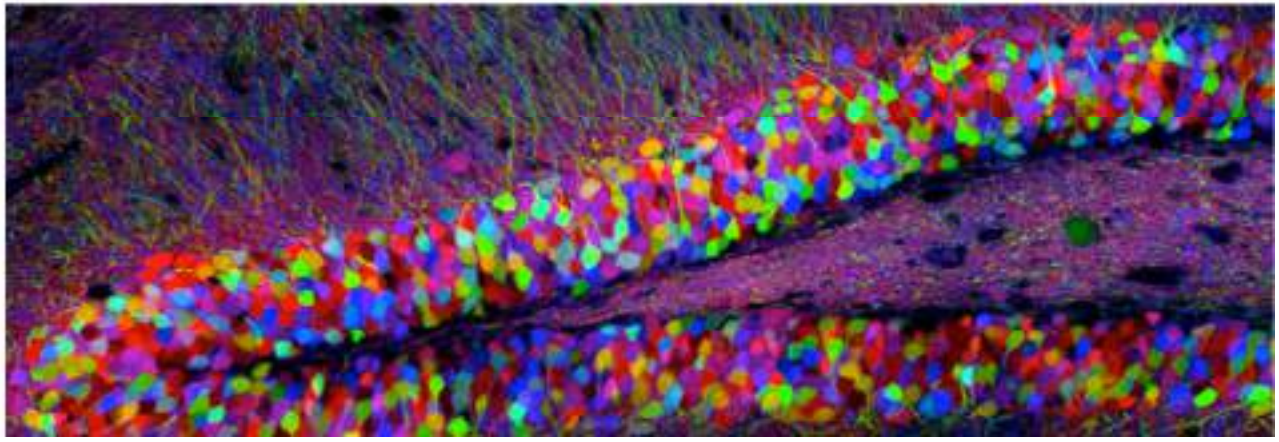
Hippocampus and temporal lobe:

«the Locus of Memories»

The Limbic System

Segmentation





Hippocampus and temporal lobe:

Main Functions

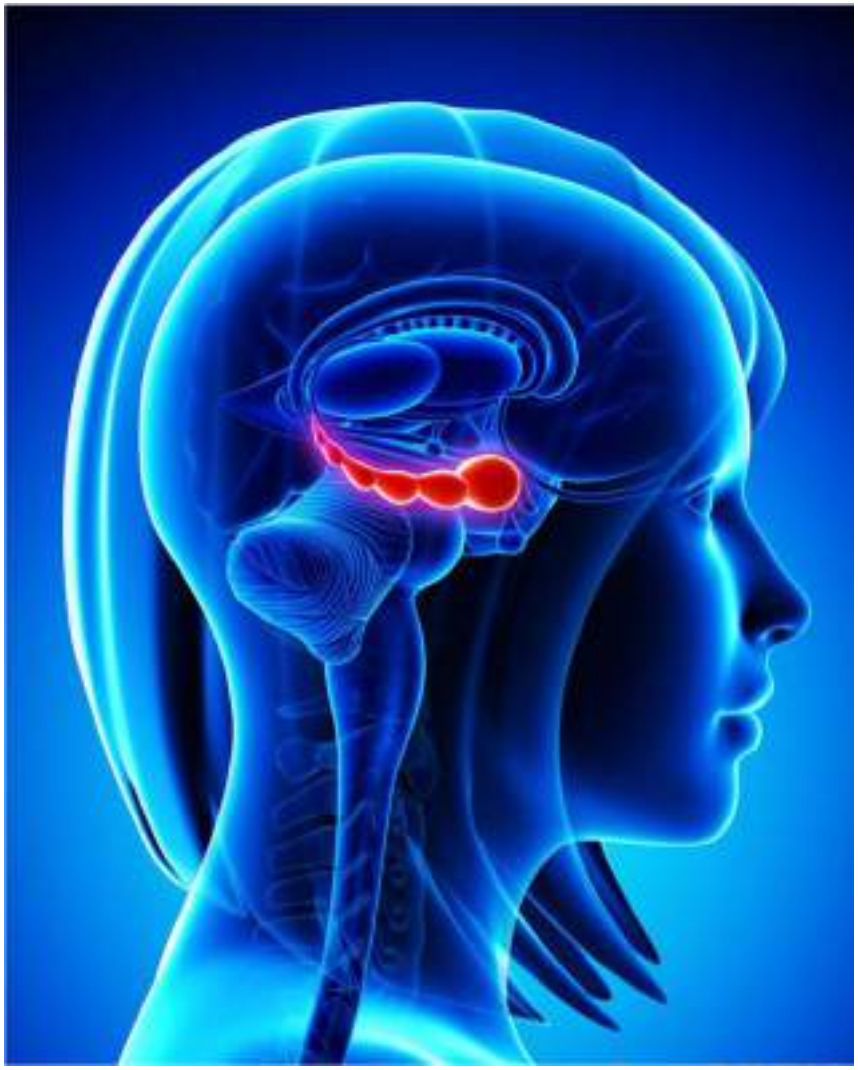
- Storing of new information
- Comparing sensory information with the brain's expectations of the external word
- Generates form spatial memories to navigate in the environment

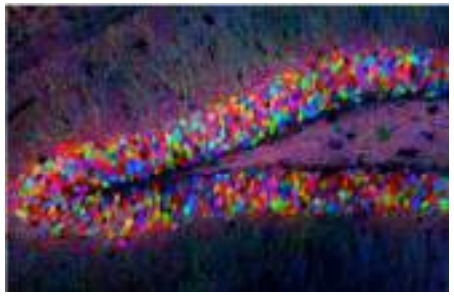
Under the influence of drugs

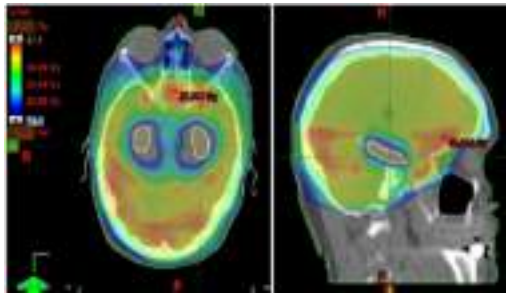
we stored in the hippocampus distorted memories in particular:

- a distorted perception and wrong interpretation of the reality and of the feeling, that can generate a distorted cognitive analysis and bad condition for correct interpretation of new events, reality analysis and decision making in the future

CANNABIS, HIPPOCAMPUS AND MEMORY EMPAIRMENT



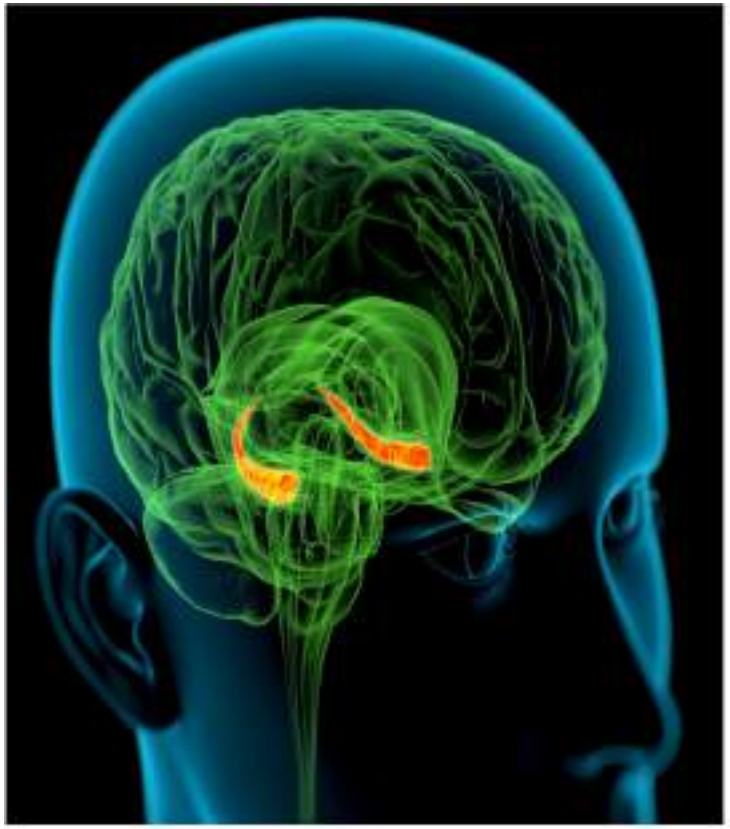




Cannabis and brain empairment

Narrowing of the neurons and DNA fragmentation

A. Ameri , 1999



For a long time the toxicity of marijuana has been underestimated.

The Δ9-THC induces:

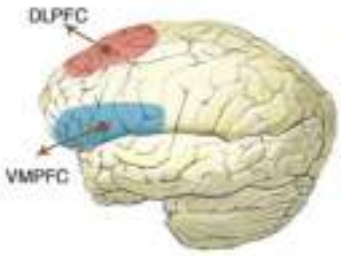
- **shrinkage of the hippocampus neurons**
- **DNA fragmentation**
- **cell death**

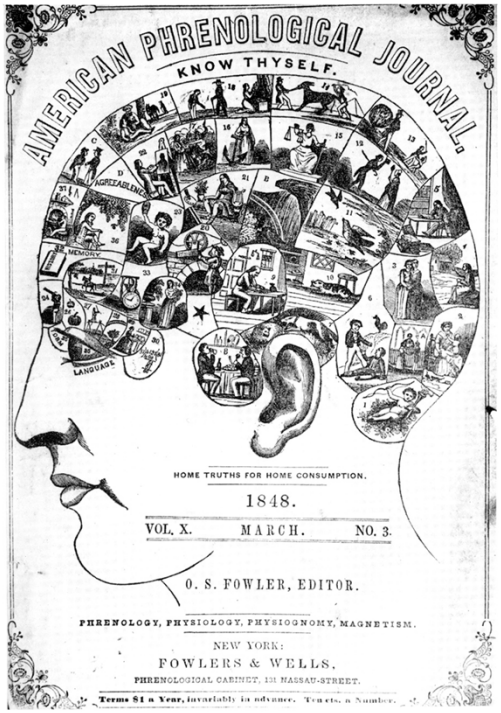
Acute Cannabinoids Impair Working Memory through Astroglial CB1 Receptor Modulation of Hippocampal LTD

Jing Han, Philip Kesner, Mathilde Metna-Laurent, Tingting Duan, Lin Xu, Francois Georges, Muriel Koehl, Djoher Nora Abrous, Juan Mendizabal-Zubiaga, Pedro Grandes, Qingsong Liu, Guang Bai, Wei Wang, Lize Xiong, Wei Ren, Giovanni Marsicano, Xia Zhang

Volume 148, Issue 5, Pages 1039-1050 (**March 2012**)
DOI: 10.1016/j.cell.2012.01.037

Prefrontal Cortex: «the controller»





Franz Joseph Gall
(1758-1828)

Prefrontal cortex: drugs & inhibition of functions

COGNITION

Under the influence of drugs

- **Low Control of Impulsivity**
- **Low Behavior control:**
  - Low Inhibition inappropriate Beh.
  - Low Promotion appropriate Beh.
- **Low Understanding of the consequences of own behaviors**
- Low Focusing capacity and Attention
- Alteration of Problem analysis and solving

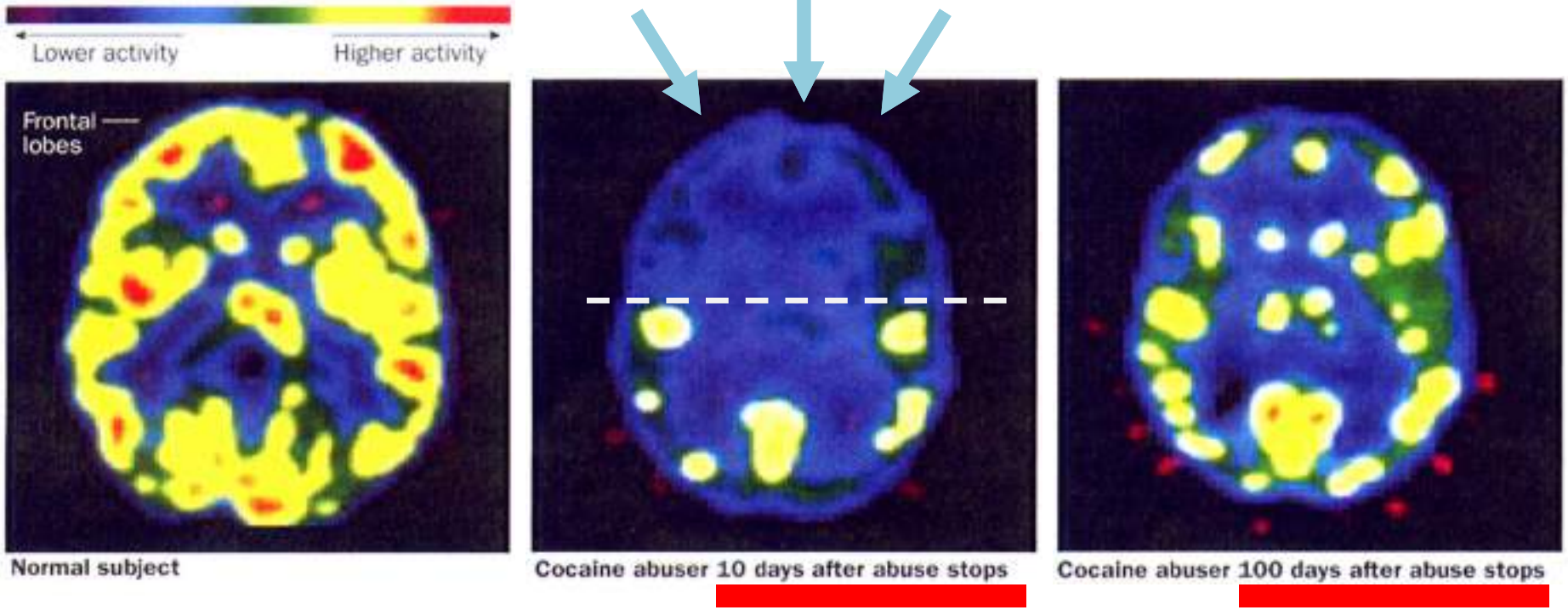
COCAINE and Glucose Methabolism in PFC

Nora Volkow

The brain of an addict

Cocaine use causes a decrease in glucose metabolism in the brain, especially in the frontal lobes, where planning, abstract thinking and regulation of impulse behavior are governed.

PET image shows a **low** glucose metabolism and **low activity of the PFC (inhibition)**,that is responsible for behaviour control, corr**e**ct reality perception, aw**a**reness, judgment, etc.



How long is the real toxicological effect on the brain?

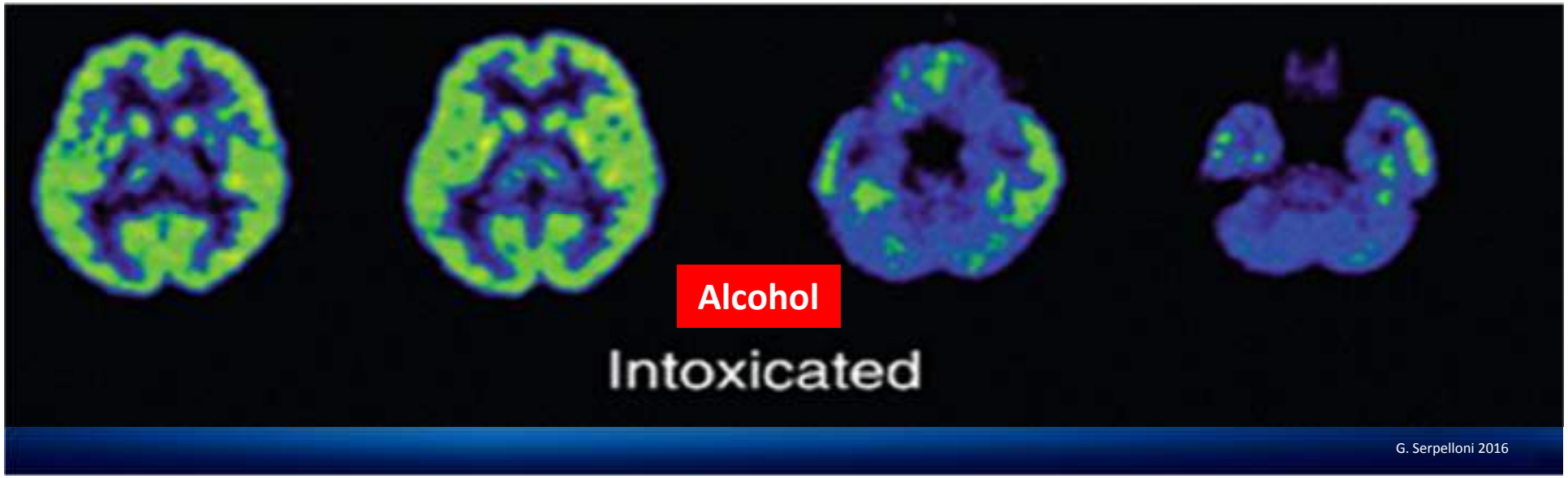
Glucose metabolism:

the energy source of the brain

To work properly the brain needs a good glocuse metabolism

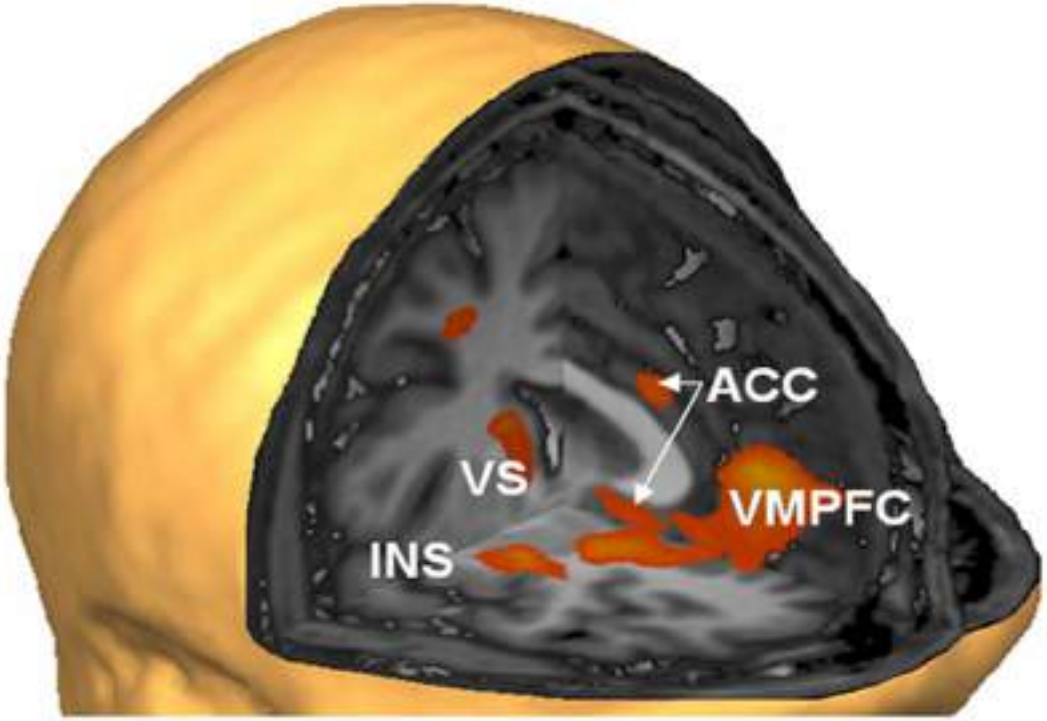
Cindee Madison and Susan Landau, UC Berkeley

PET scans can detect the low level of glucose metabolism associated with decreased cognitive functions, also in alcohol intoxicated individuals



PFC - Where is the “Moral brain”?

- A neuro-moral network was described consisting of right VM-PFC and its connections to ACC and in particular INSULA.



Mario F. Mendez, MD, PhD. The Neurobiology of Moral Behavior: Review and Neuropsychiatric Implications. CNS Spectr. 2009 November; 14(11): 608–620.
PMCID: PMC3163302 NIHMSID: NIHMS296407

PFC Connections impairment and Phineas Gage

An 1848 explosion forced a steel tamping rod through his head

Others said he was "no longer Gage"

a steel bar interrupted his PFC connections and he changed his personality, he became aggressive and inpolite, rude.

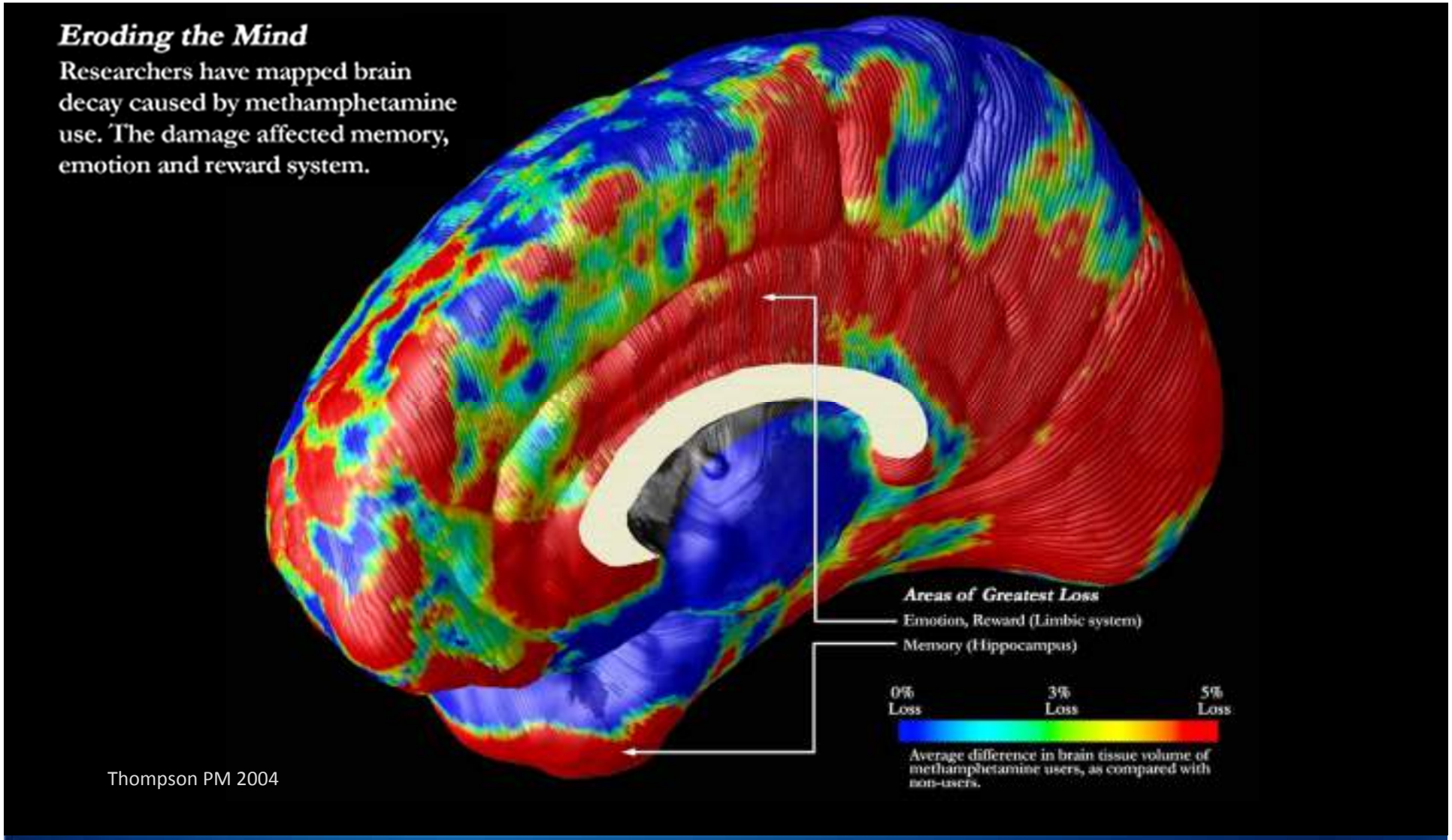
Gray matter

Contains neurons

Directs and controls the brain's higher cognitive and emotional functions.

It is one of the main targets of drugs

Methamphetamine Erode the Mind



MDMA effects ⟺ Alzheimer damage

Eroding the Mind: Researchers have mapped brain decay caused by methamphetamine use (left). The damage affected memory, emotion, and the reward system. Notice the similarities to the brain decay caused by Alzheimer's Disease (right).