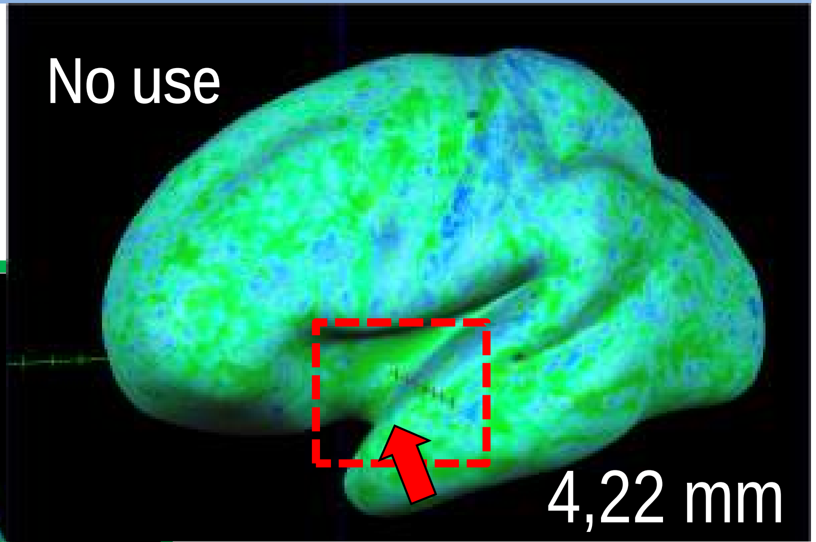
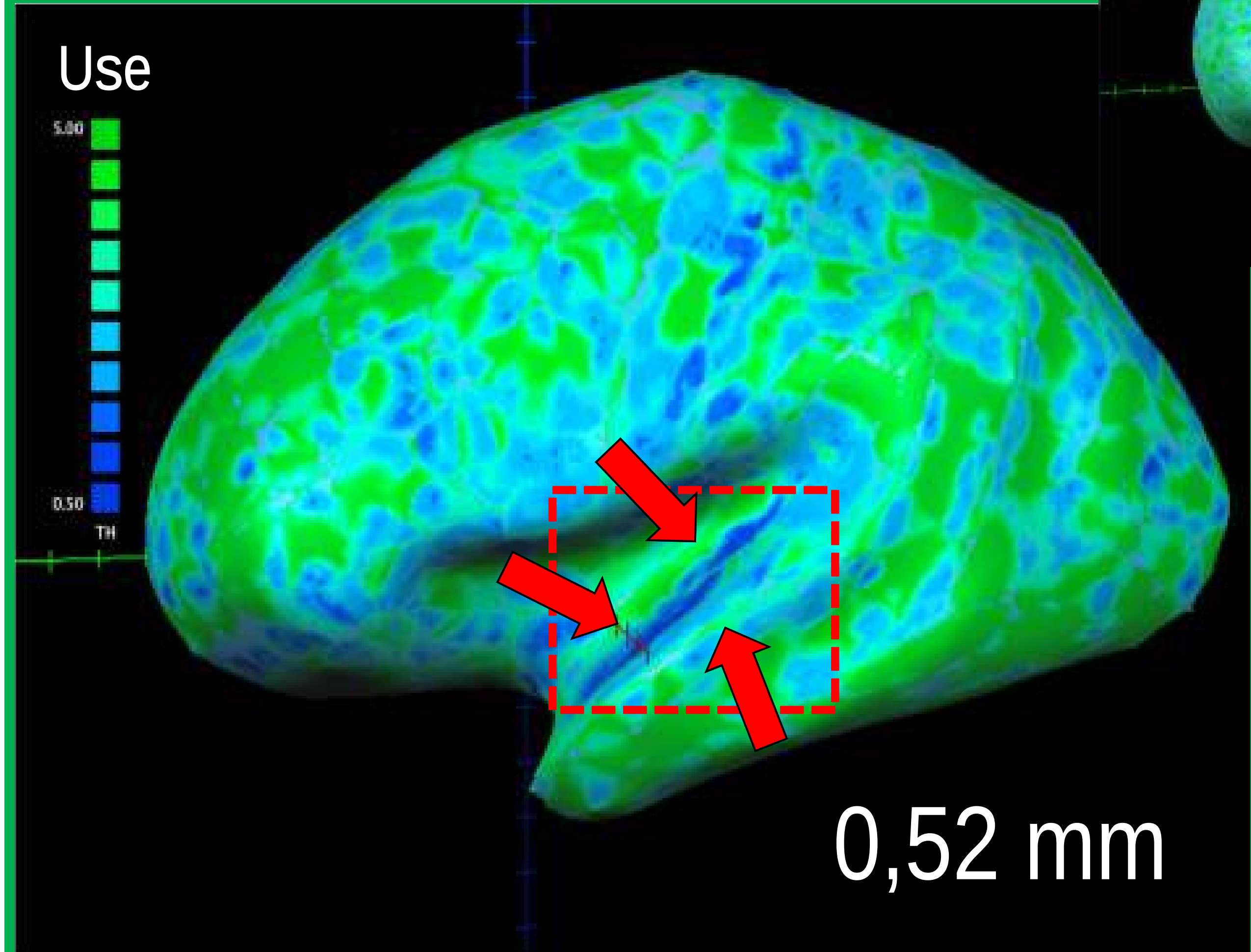
CANNABIS users and decrease of cortical thickness



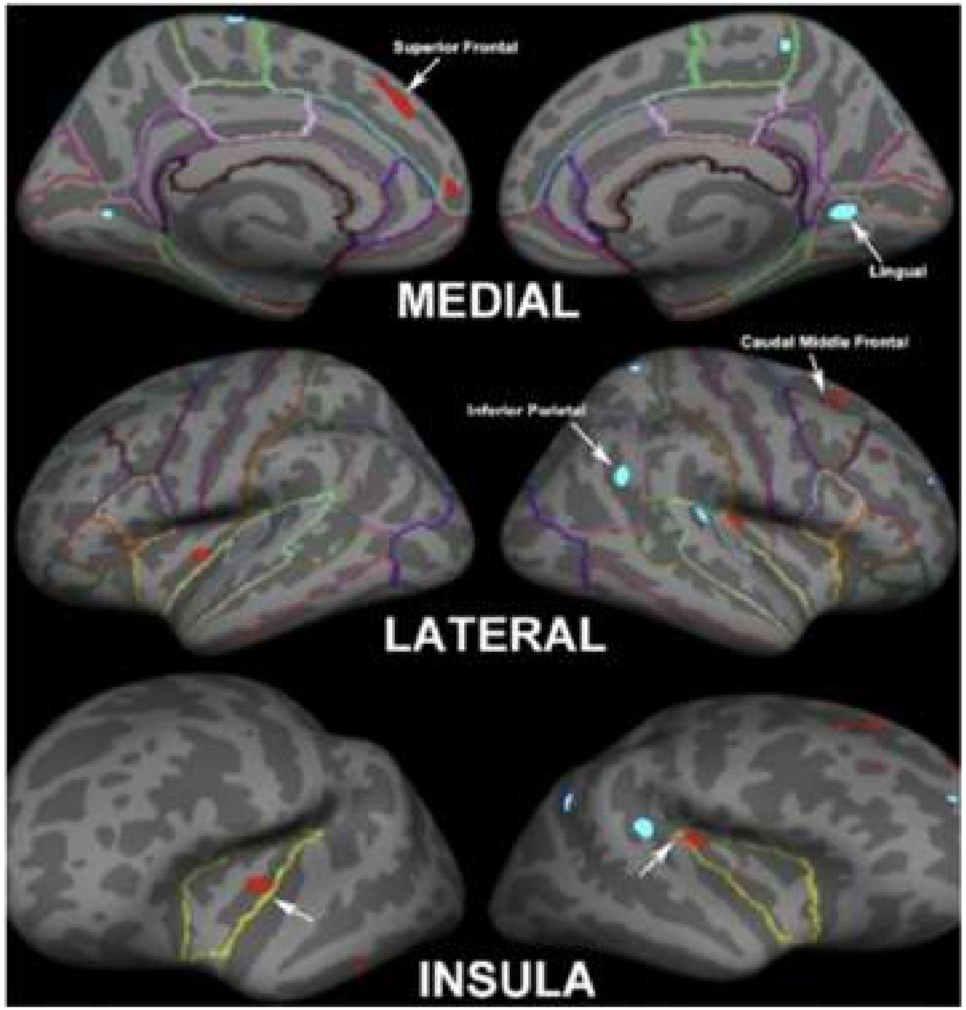


Temporal-mesial area

NEUROSCIENCE
VERONA GROUP
G.Serpelloni 2011

Cannabis use

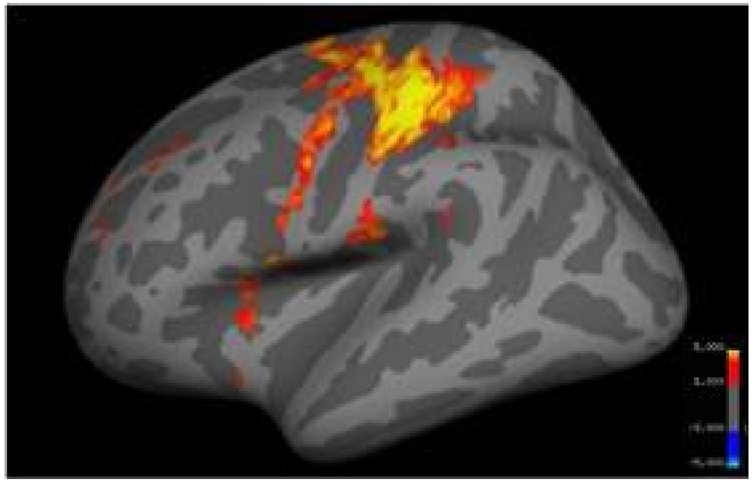
Decrease of cortical thickness




DEBORAH YURGELUN-TODD

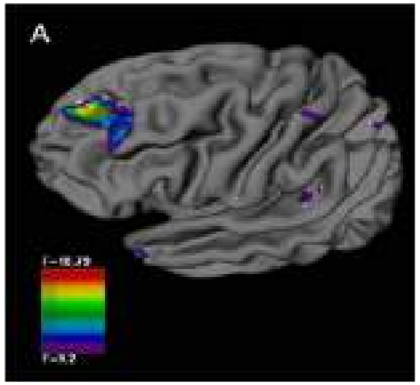
Professor of Psychiatry

B.A. 1974 Mount Holyoke College, MA; M.A. 1979 Psychology, Boston College; M.A. 1986 Psychology, Harvard University; Ph.D. 1988 Neuropsychology, Harvard University; Postdoctoral Fellow 1988-1990 Boston Neurobehavioral Institute



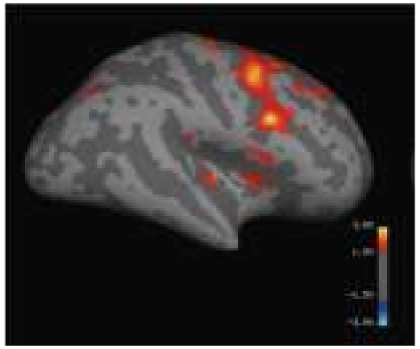
A morphometric analysis of adolescent marijuana smokers during completion of magnetic resonance imaging (MRI) in conjunction with a functional MRI (fMRI) paradigm

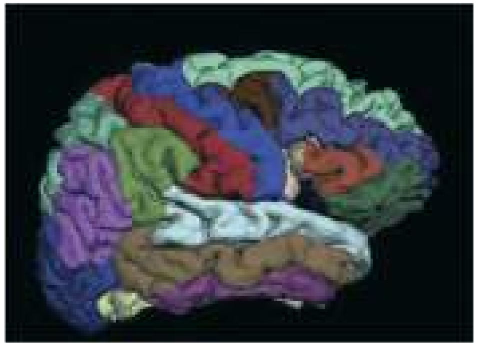
Cannabis use and progressive Cortical Thickness loss in areas rich in CB1 receptors during the first five years of schizophrenia (Eur. Neuropsychopharmacol., 2010)



Reduced Cortical Thickness of Medial Orbitofrontal Cortex in Smokers
(Biol Psychiatry, 2011)

Cortical Thickness Abnormalities in Cocaine Addiction—A Reflection of Both Drug Use and a Pre-existing Disposition to Drug Abuse? (Neuron, 2008)





Cortical Thickness, Surface Area, and Volume of the Brain Reward System in Alcohol Dependence: Relationships to Relapse and Extended Abstinence.
(Alcohol. Clin. Exp. Res., 2011)

Brain Connections

Tractography

LOOKING AT BRAIN INTERCONNECTION

Courtesy of V.J. Wedeen and L.L. Wald, Martinos Center for Biomedical Imaging at MGH

Under the influence of drugs

Brain Advance Access published June 4, 2012

doi:10.1093/brain/aws136 Brain 2012: Page 1 of 11 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Effect of long-term cannabis use on axonal fibre connectivity

Andrew Zalesky,[1] Nadia Solowij,[2] Murat Yücel,[1] Dan I. Lubman,[3] Michael Takagi,[1] Ian H. Harding,[1] Valentina Lorenzetti,[1] Ruopeng Wang,[4] Karissa Searle,[1] Christos Pantelis[1] and Marc Seal[5]

1 Melbourne Neuropsychiatry Centre, The University of Melbourne and Melbourne Health, Melbourne, 3053, Australia
2 School of Psychology, University of Wollongong, Wollongong, 2522, Australia
3 Turning Point Alcohol and Drug Centre, Eastern Health and Monash University, Melbourne, 3065, Australia
4 Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA 02129, USA
5 Murdoch Childrens Research Institute, Royal Children's Hospital Melbourne, 3052, Australia

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Wollongong,
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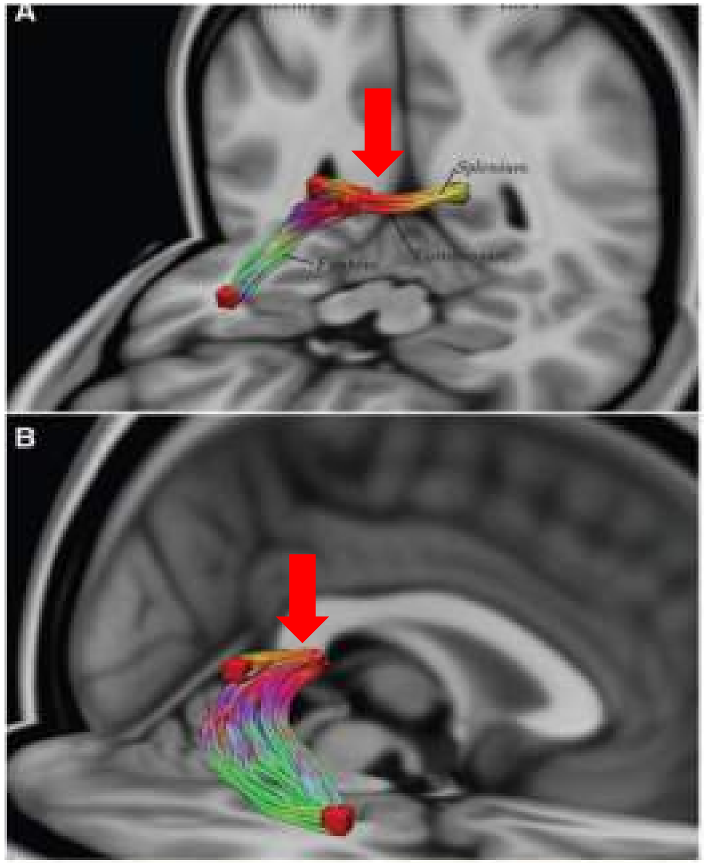
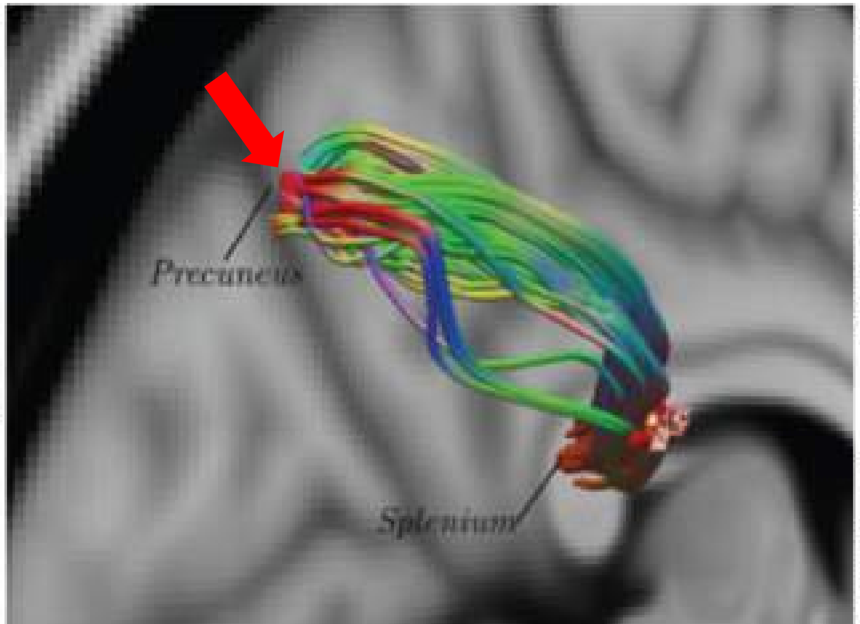
E-mail: nadia@uow.edu.au

Cannabis use (<18y) can produce interconnections decrease (red colour)

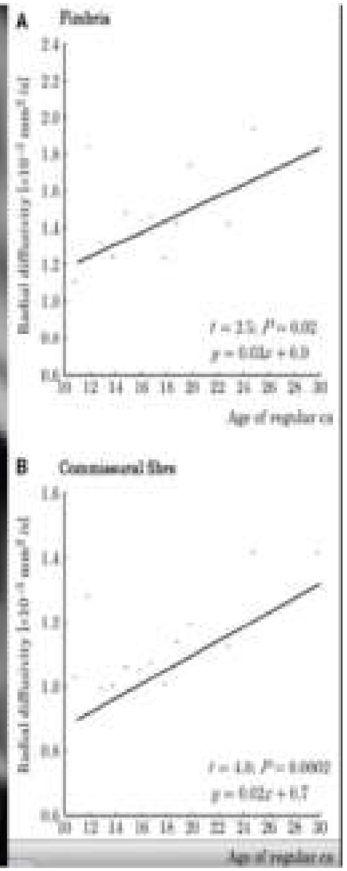
PONS of the Brain

Fewer streamlines interconnected the right precuneus with the splenium in cannabis users compared to non-users

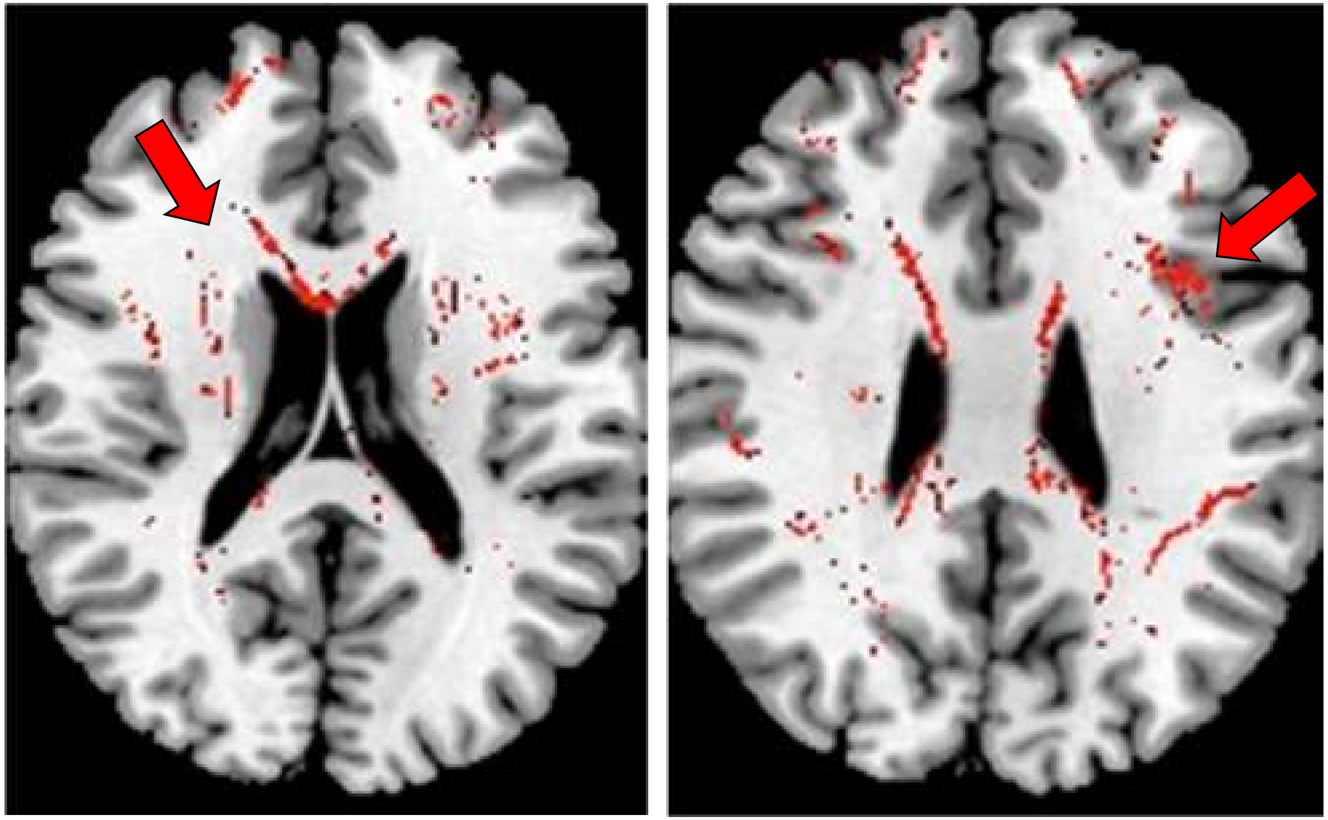




Among cannabis users (N = 59), there are axonal connections with reduced connectivity (measured by MRI in weighted distribution) in comparison with control subjects (N = 33). Zalesky, BRAIN 2012



Cannabis users also have a degeneration of white matter

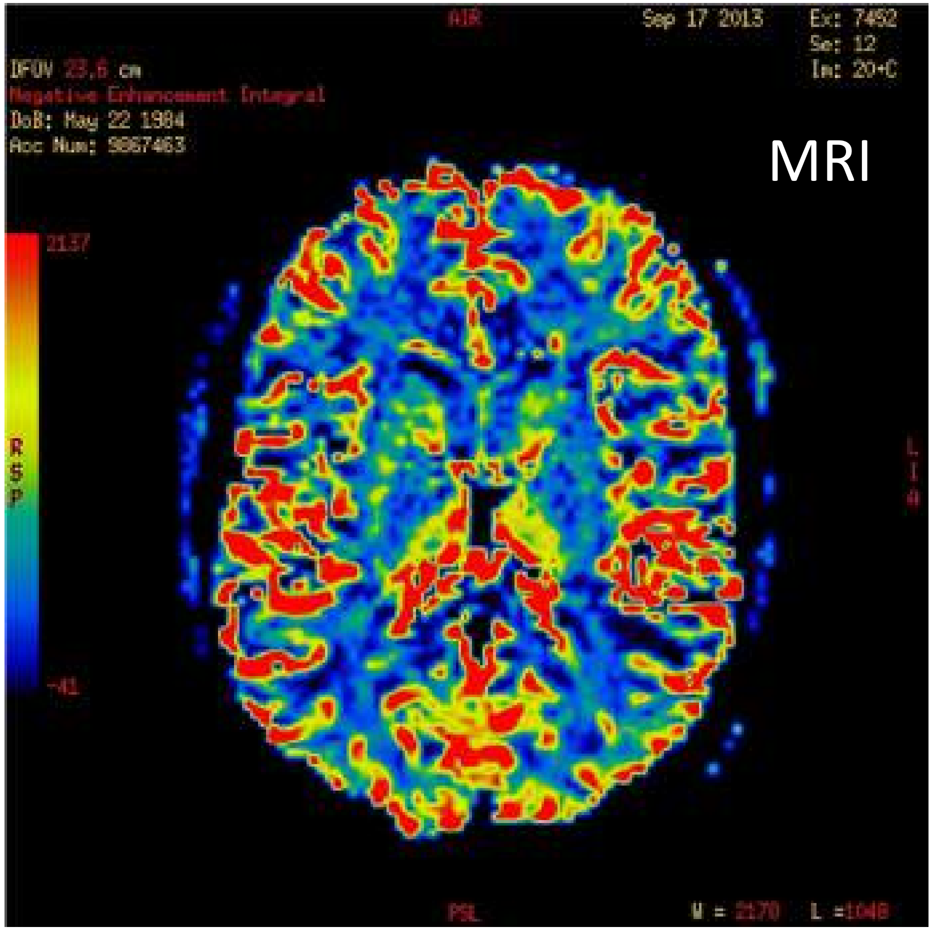


degeneration of white matter

TBSS (Tract Based Spatial Statistic)

NEUROSCIENCE
VERONA GROUP
G.Serpelloni 2011

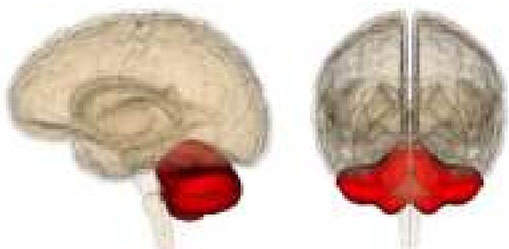
Marijuana Addiction Associated with White Matter Loss and Brain Changes in Healthy People and Those with Schizophrenia (2013 Matthew J. Smith et al. *Schizophrenia Bulletin)*



Healthy people who were marijuana users showed deficits in white matter (axons of neurons that are wrapped in myelin) compared to healthy people who did not use the drug. Similarly, patients with schizophrenia who used marijuana regularly had less white matter than those patients with schizophrenia who did not use the drug. There were also differences in the shapes of brain structures, including the striatum, the globus pallidus, and the thalamus, between cannabis users and non-users.

Image from MRI. The blue color depicts low blood volume, indicating areas of white matter.

Cerebellum



Under the influence of drugs:

- **Alteration of involuntary coordination of body movements**
- **Alteration of sensory-motor coordination (controls posture, maintains equilibrium, skilled movements)**
- **Alteration of cognitive, emotional, and even personality domains.**

- *Novelty Seeking scores are associated with different cerebellar GM volumes*

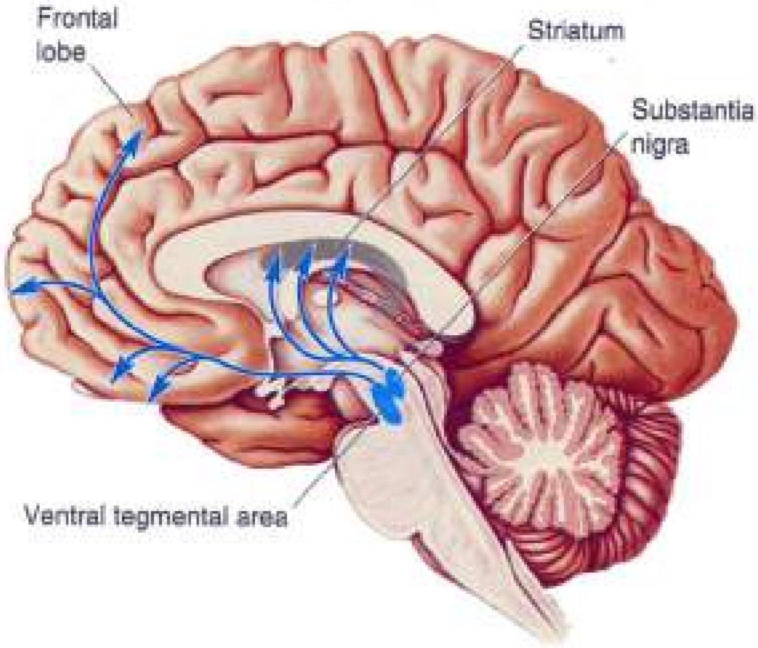
(Picerni 2013 FBN)

Important impairment of functions for:

- **Preventing car crashes**
- **Preventing Workplace accidents**

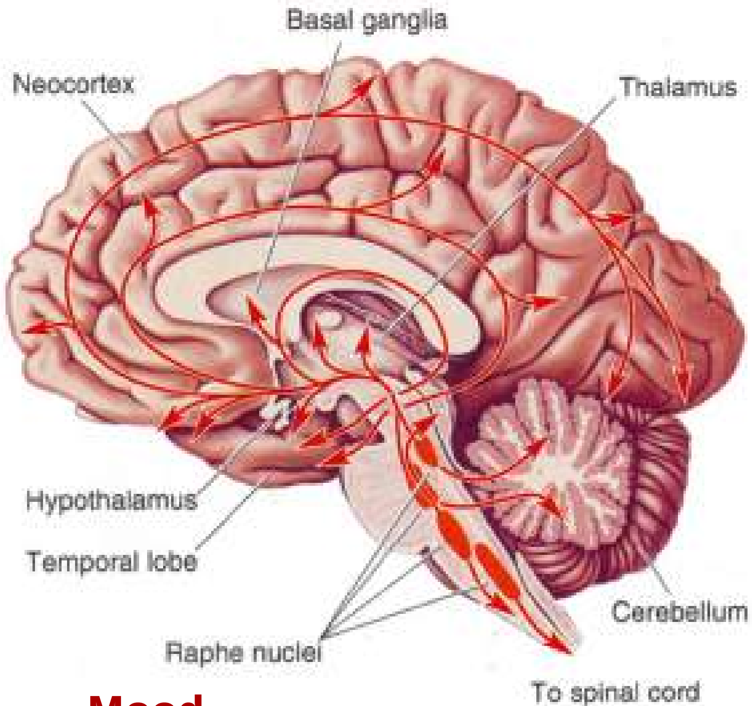
The most important Neural systems and Receptors

Dopamine system

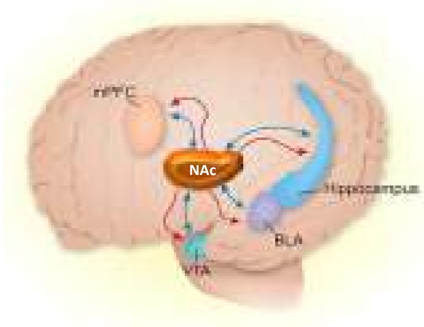


- Reward (motivation)
- Pleasure, euphoria
- Motor functions (fine tuning)
- Compulsion
- Preservation

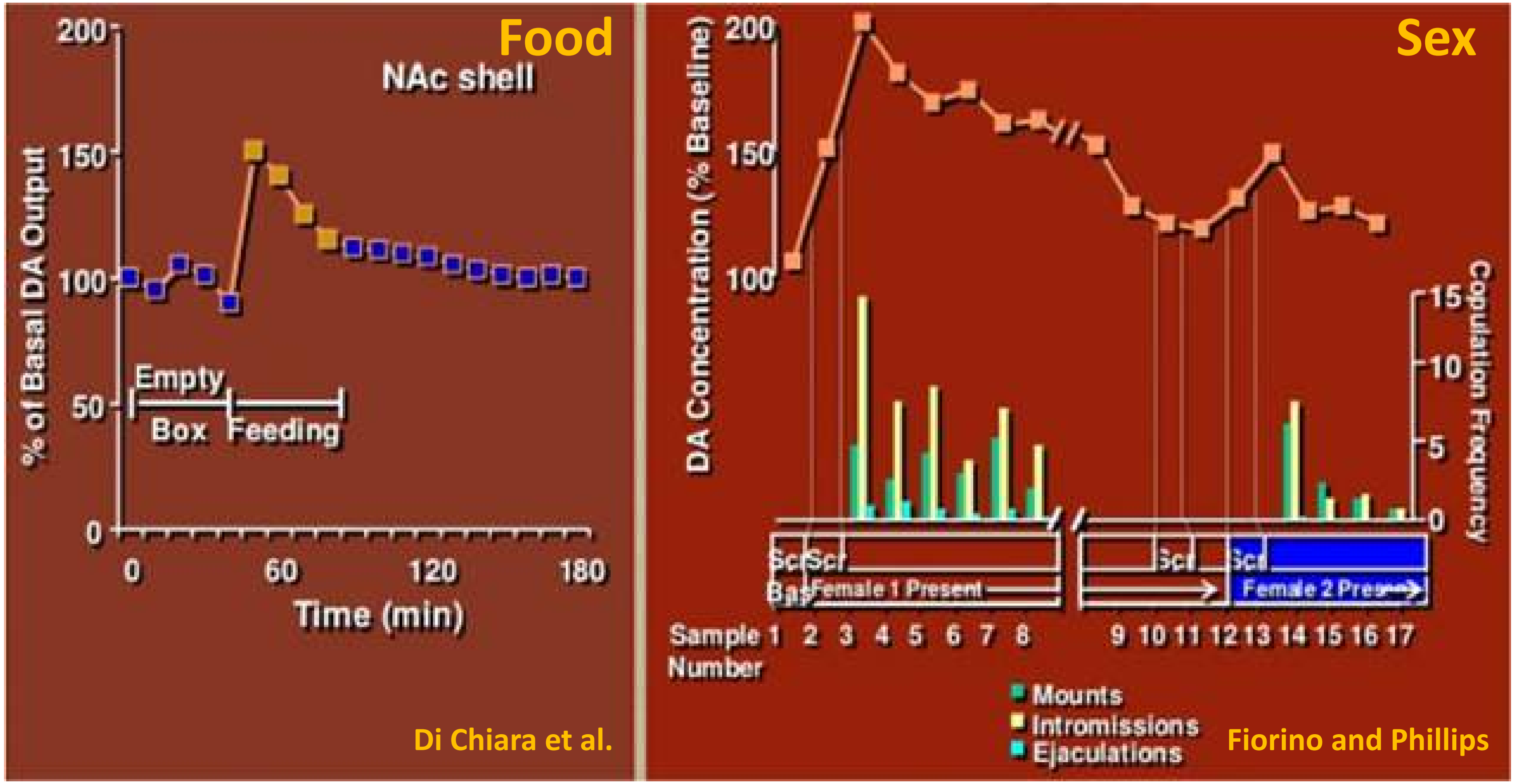
Serotonine system



- Mood
- Memory processing
- Sleep
- Cognition

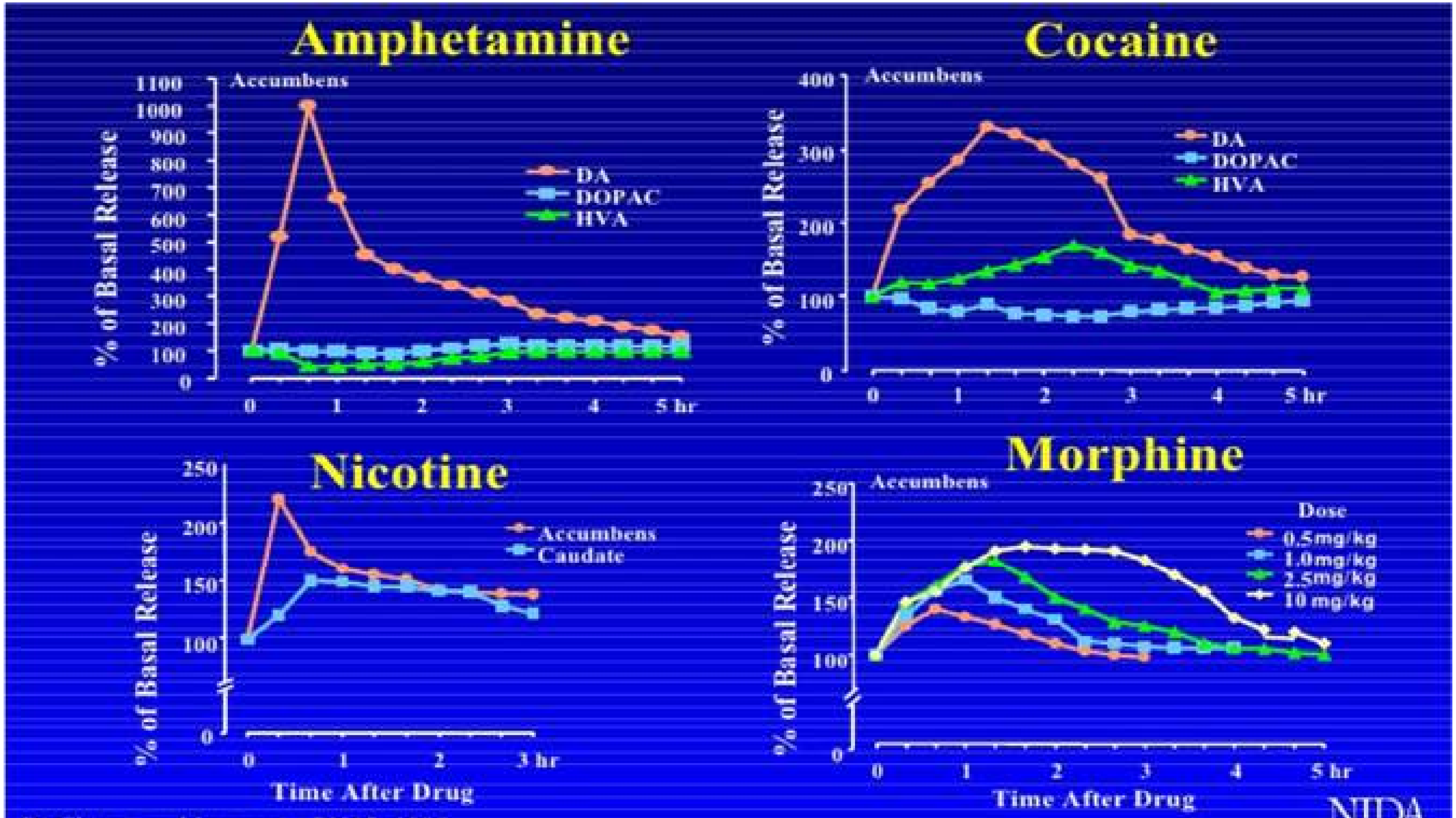


Nucleus accumbens and dopamine: food & sex reward



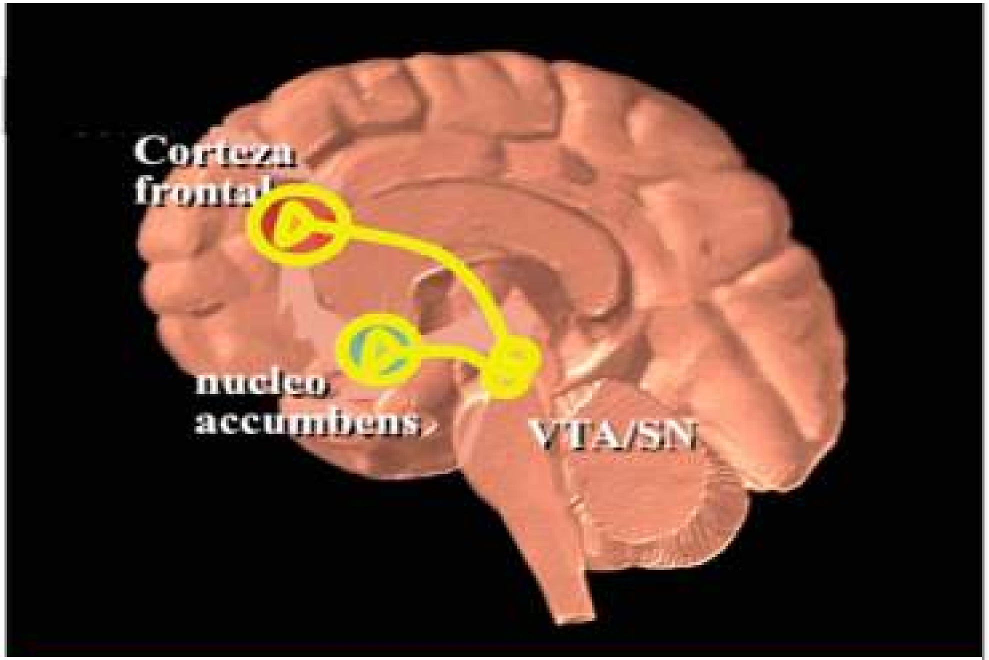
Nucleus accumbens

drugs generate a very high dopamine release

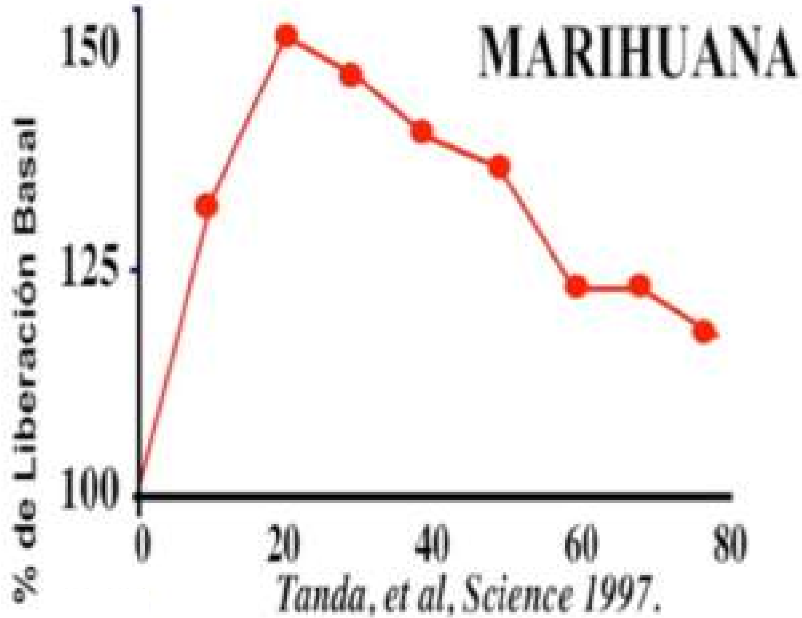


Di Chiara and Imperato, PNAS, 1988

The natural (food, sex, etc.) and synthetic (drugs) reinforcements increase dopamine in the Nac



Drug abuse increases dopamine in the nucleus accumbens from which neuro-adapters leading to addiction are triggered



N. Volkow courtesy

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

Low Dopamine Receptor Availability May Promote Cocaine Addiction

Reduced availability heightens reinforcing effects of cocaine in monkeys, and the drug drives this measure even lower.

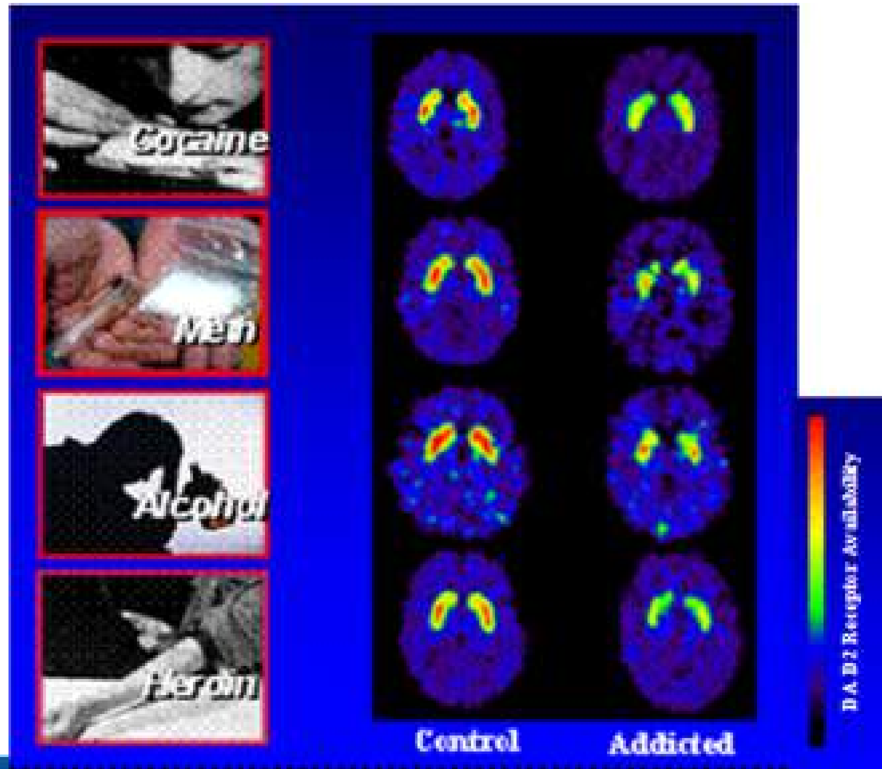
April 01, 2009, *Lori Whitten, NIDA Notes Staff*

In a study with rhesus monkeys, Dr. Michael Nader and colleagues at Wake Forest University recently showed that cocaine lowers availability of the dopamine D_2 receptors in the basal ganglia—the brain region that includes key components of the reward system. The consequences may include addiction-promoting alterations in cognitive functioning and decisionmaking.

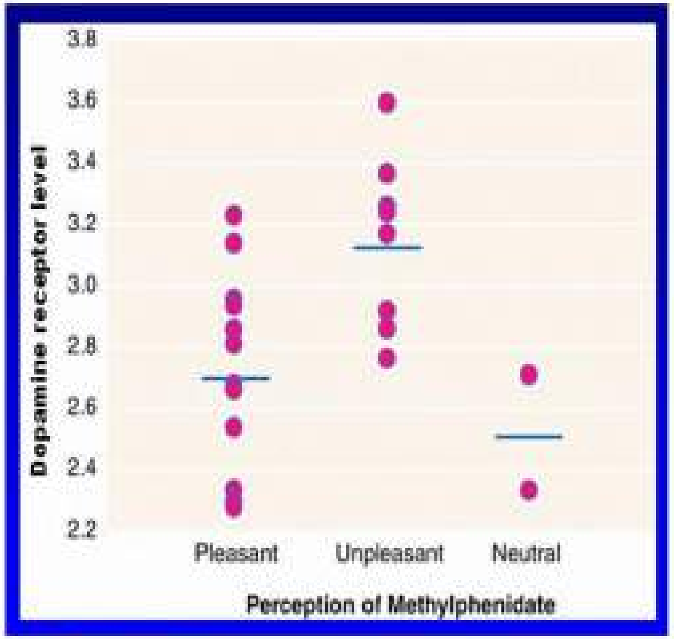
Dr. Nader's study also confirms previous findings that individual animals with lower D_2 receptor availability are especially responsive to cocaine's reinforcing effects.

In a promising finding for people trying to recover from cocaine addiction, receptor availability levels in some of the monkeys recovered after less than a year of abstaining from drug use.

Dopamine D2 Receptors are lower in Addiction

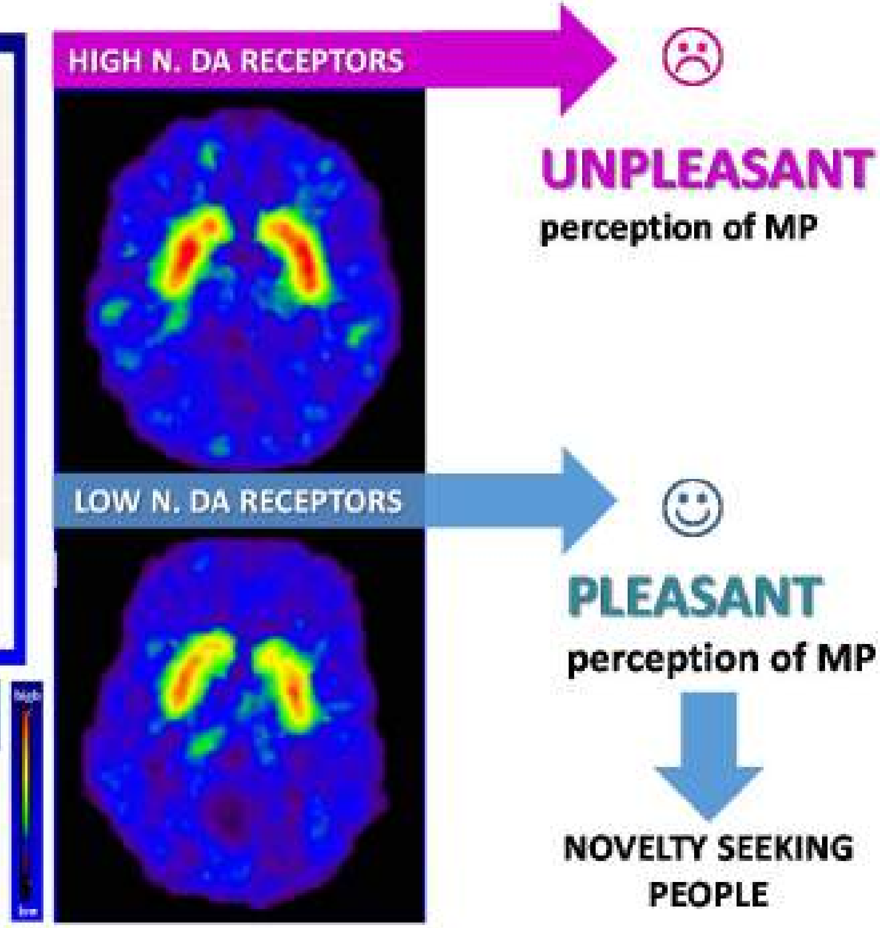


There are <u>Individual Differences in Response</u> to Drugs: number of Dopamine receptors influence drug <u>liking</u> and perception



Toxicogenitics &Toxicogenomics

Adapted from Volkow et al., Am. J. Psychiatry, 1999.



Effects of Drugs on neurobiological systems: there are personal differences

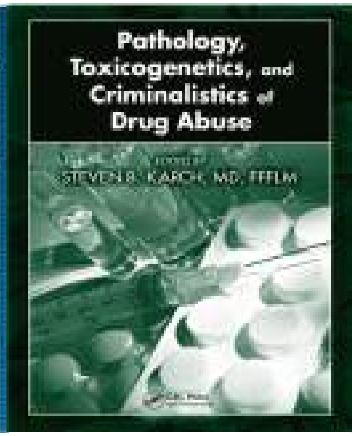
During the assessment of the neuro-psychological effects of the drugs, we must consider that these effects are different from person to person (with the same dose) in relation to the different neurobiological system and to the number of receptors.

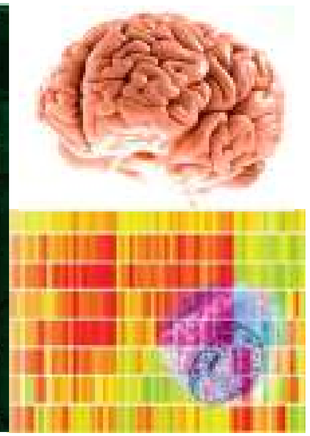
(this is a Toxicogenetic interest)

Toxicogenetics &Toxicogenomics

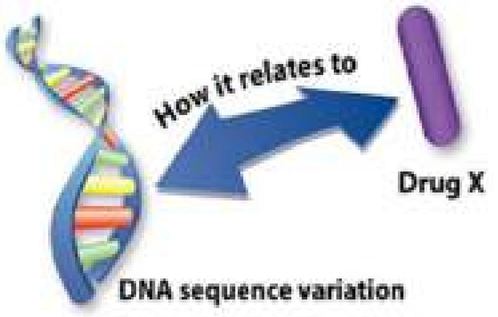
National Human Genome Research Institute

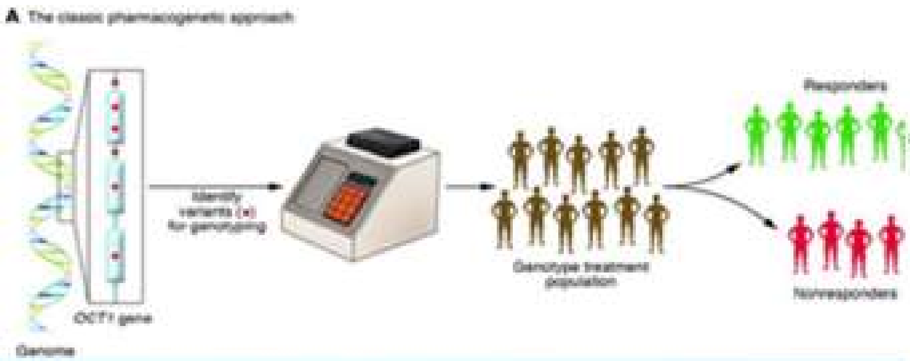
These disciplines can help to evaluate how an individual's genetic makeup, conditions the personal response to a particular toxic substance and interact with a range of genes.



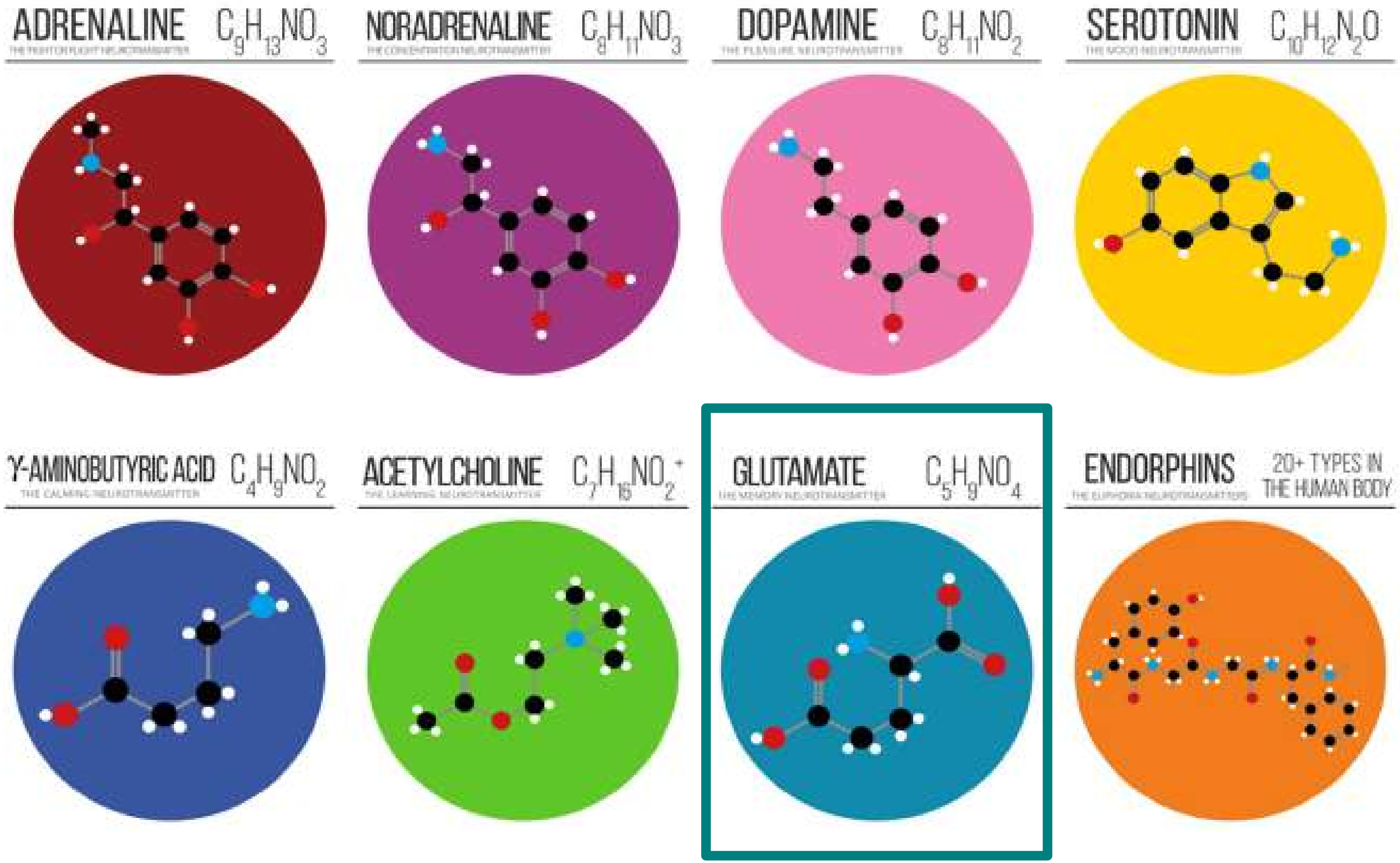


PERSONAL VARIABILITY



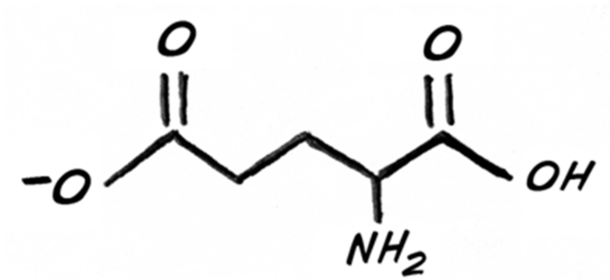


Brain Neurotransmitters



Glutamate:
Important in memory process and learning

- It is the most abundant **excitatory** metabolite in the brain and a precursor of gamma-aminobutyric acid (GABA)
- Alterations in the levels of **Glu** (increase & decrease) can generate neurocognitive deficits as learning and memory



William J. McEntee, Thomas H. Crook - Glutamate: its role in learning, memory, and the aging brain -

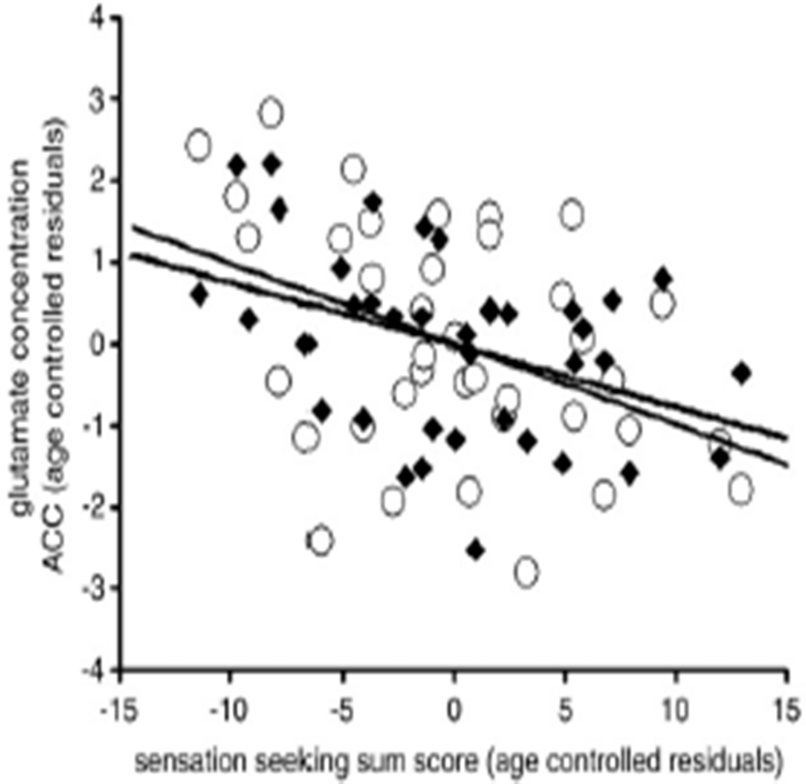
Low level of Glutamate
in anterior cingulate cortex, is related with Novelty Seeking personality trait & high risk behaviour expression

ELSEVIER

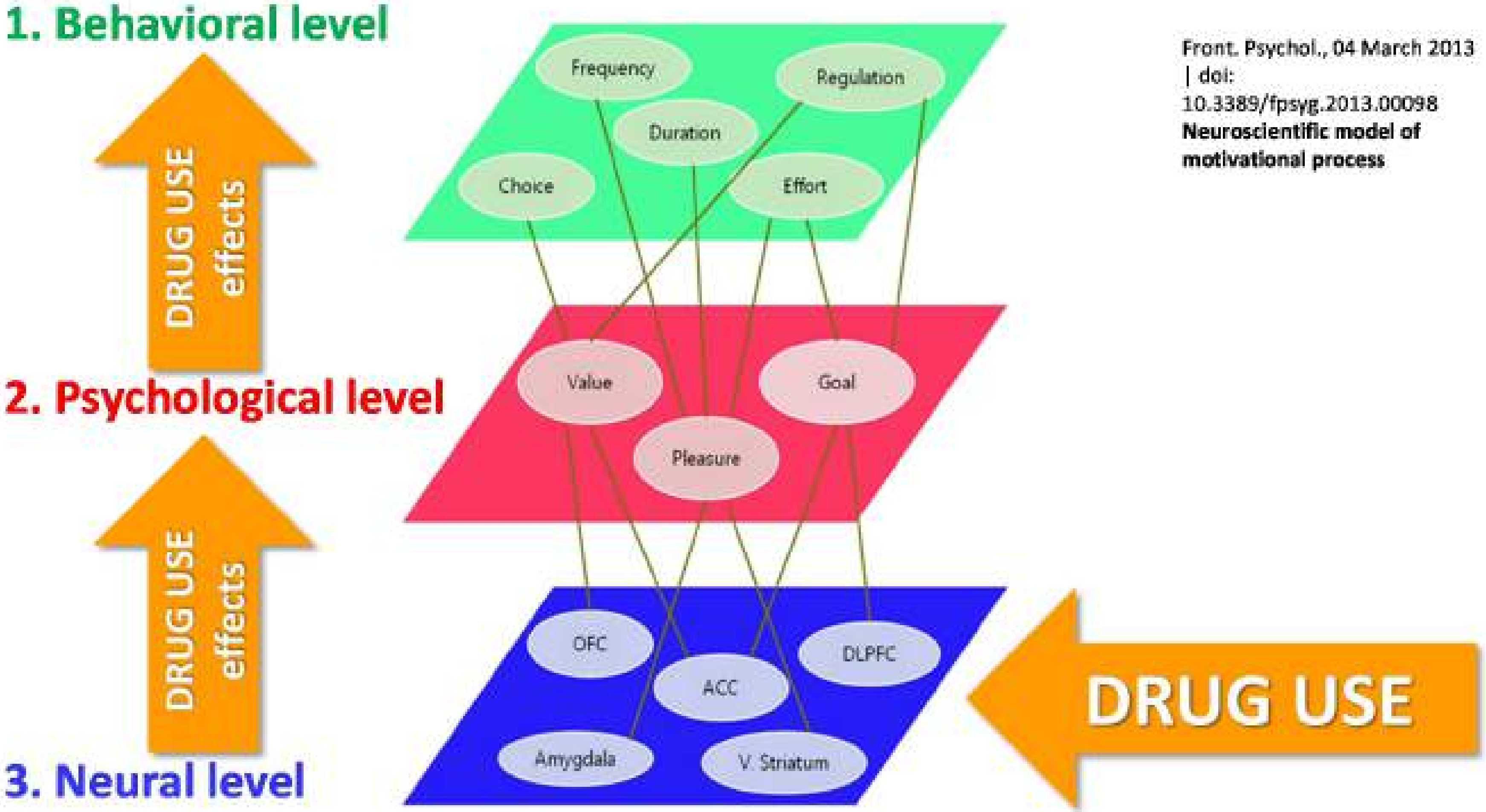
NeuroImage

Association between cerebral glutamate and human behaviour: The sensation seeking personality trait

J. Gallinat, D. Kunz, U.E. Lang, P. Neu, N. Kassim, T. Kienast, F. Seifert, F. Schubert, and M. Bajbouj

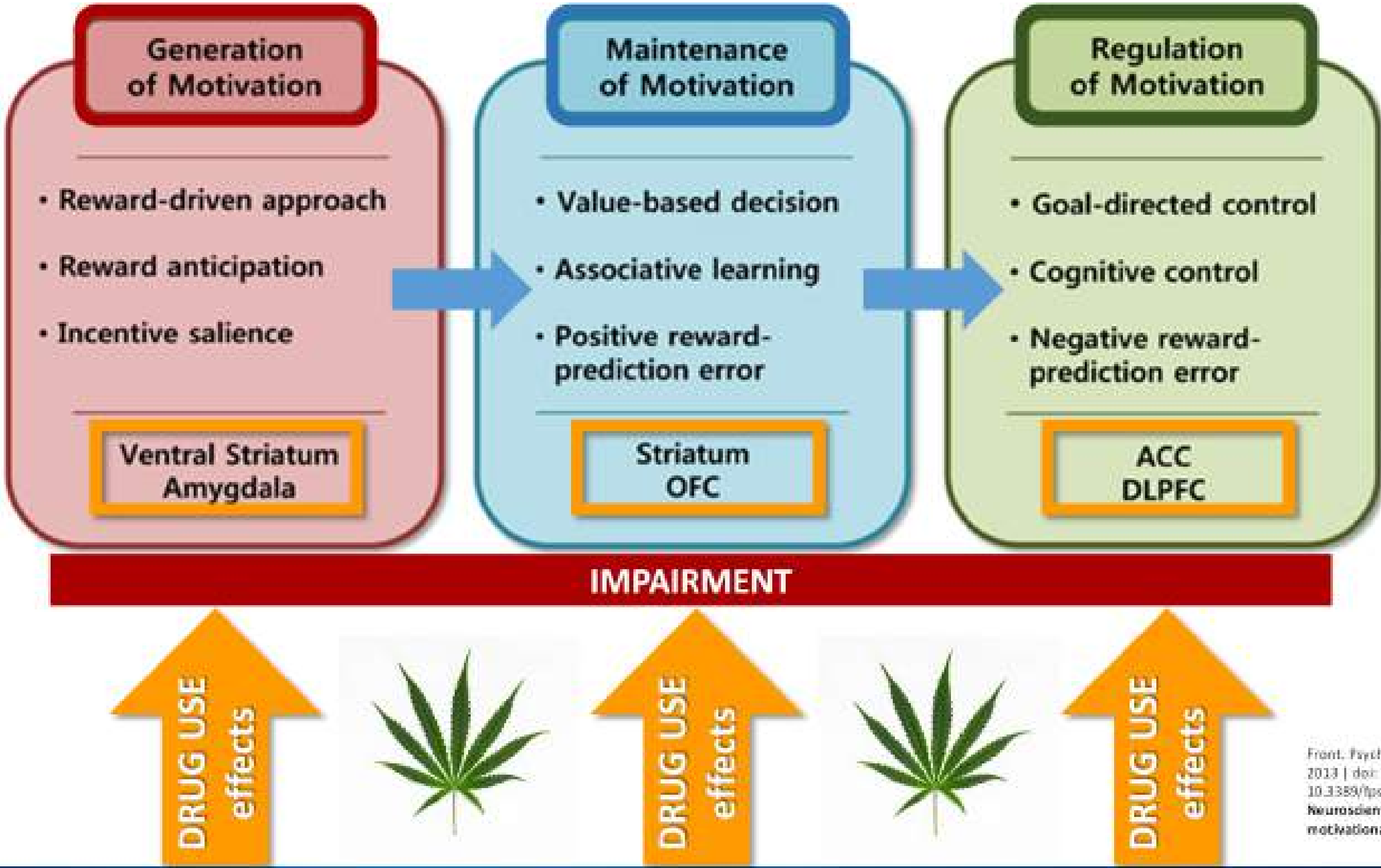


Motivational system: Levels of action of the drugs and consequences



Front. Psychol., 04 March 2013 | doi: 10.3389/fpsyg.2013.00098
Neuroscientific model of motivational process

Effects of drug use on the 3 subprocesses of the motivational process



Front. Psychol., 04 March 2013 | doi: 10.3389/fpsyg.2013.00098
Neuroscientific model of motivational process

1 Brain Structures and Systems

2 Cognitive function and behaviours, coordination funtions

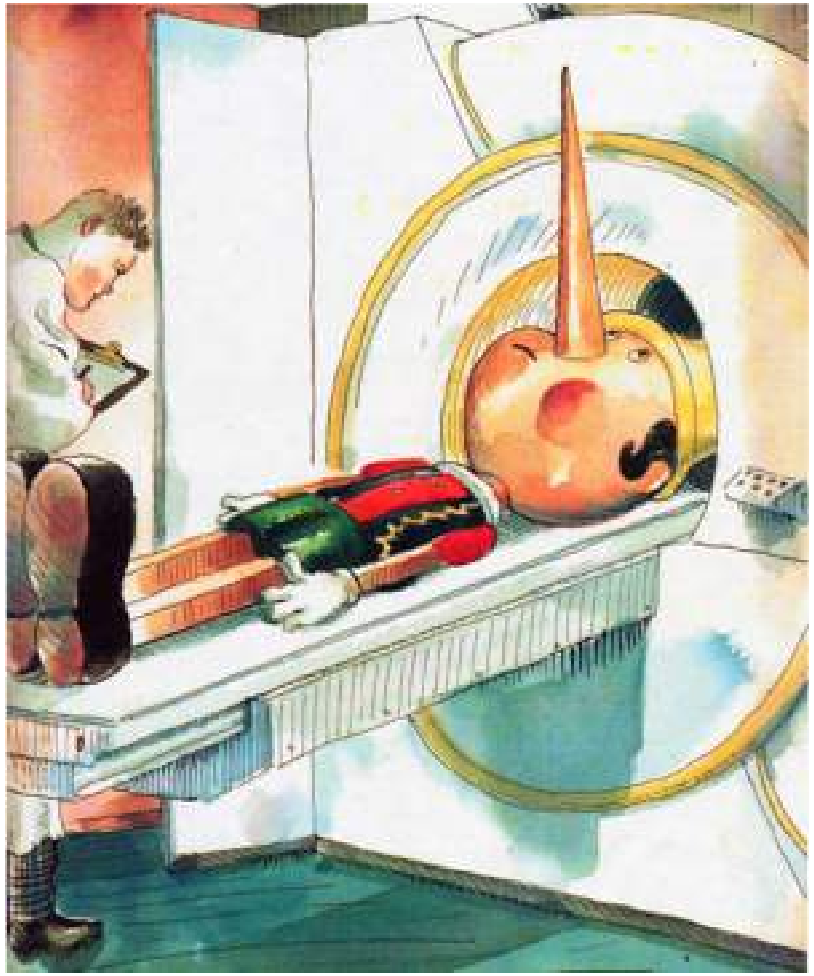
Impairment caused by primary conditions (genes) , clinical conditions or disease, drug use ....

3 **Forensic consequences and interest**

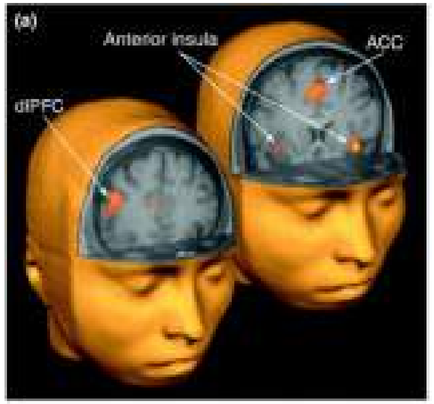
1. Most relevant brain structures and systems for Forensic Toxicology	2. Cognitive function and behaviours, Coordination functions	3. DRUGS USE and Forensic consequences and interest
Genotype: DRD4 7R, CN1R (dopamine receptors system), MAOA-L and brain development	Novelty seeking temperament → more risk of drug use and addiction (vulnerability condition).	• Different Responsibility & Imputability (?)
Limbic system: - Amygdala - Insula - Nucleus accumbens - Hippocampus, temporal lobe - Thalamus – ventral striatus	Aggressive behavior, Fear, Impulsivity, Hyperactivity, Emotion Reward Memory process (working memory) Motivation , Awarness	• Violent, antisocial or criminal behavior expression, • False memories/cognitive distortion, validity of Testimony • Intentionality and premeditation of the criminal behaviours
Prefrontal Cortex	Voluntary behavior control, Attention and concentration, mental flexibility	• Primary conditions that compromise a correct self control expression • Awareness level of self behaviours, rules & social norms • Capacity to understand ethics and moral principles, distinction between good and evil

1. Most relevant brain structures and systems for Forensic Toxicology	2. Cognitive function and behaviours, Coordination functions	3. DRUGS USE and Forensic consequences and interest
Cerebellum	Coordination	Ability to perform dangerous work or to drive
Gray Matter - Neurons - White Matter - dendritic arborization, intralobe connections ….)	General function and brain efficiency	Low I.Q., low mental flexibility, FITNESS TO PLEAD
Visual Motor Cortex	Visual function	Less efficiency of visual motor function in cannabis user and increased risk of car accident
Broca's & Wernicke's Areas	Speaking (expressive lenguage) and ability to understand	Validity of witness and statements in criminal proceedings
Glucose metabolism in the brain	Regular brain function in time	Real duration of the neuropsychological abnormalities and the loss of brain performance after taking substances (ex. Cocaine → glucose metabolism and PET)

Neuroimaging in LIE detection process

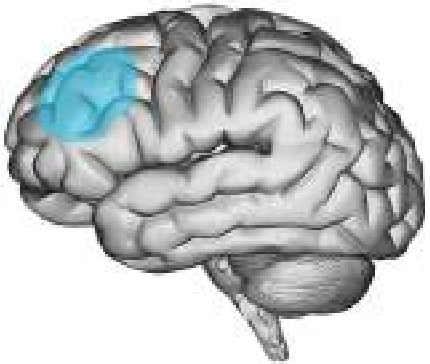


During the lie there is a simultaneous activation of 2 brain areas.

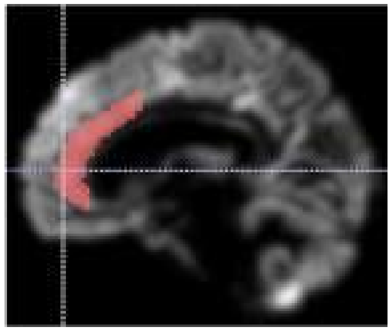


- **DLPFC - dorso lateral prefrontal Cortex**
- **ACC – Anterior Cingulate**
- **Cortex**

- Processing response **untrue** but credible



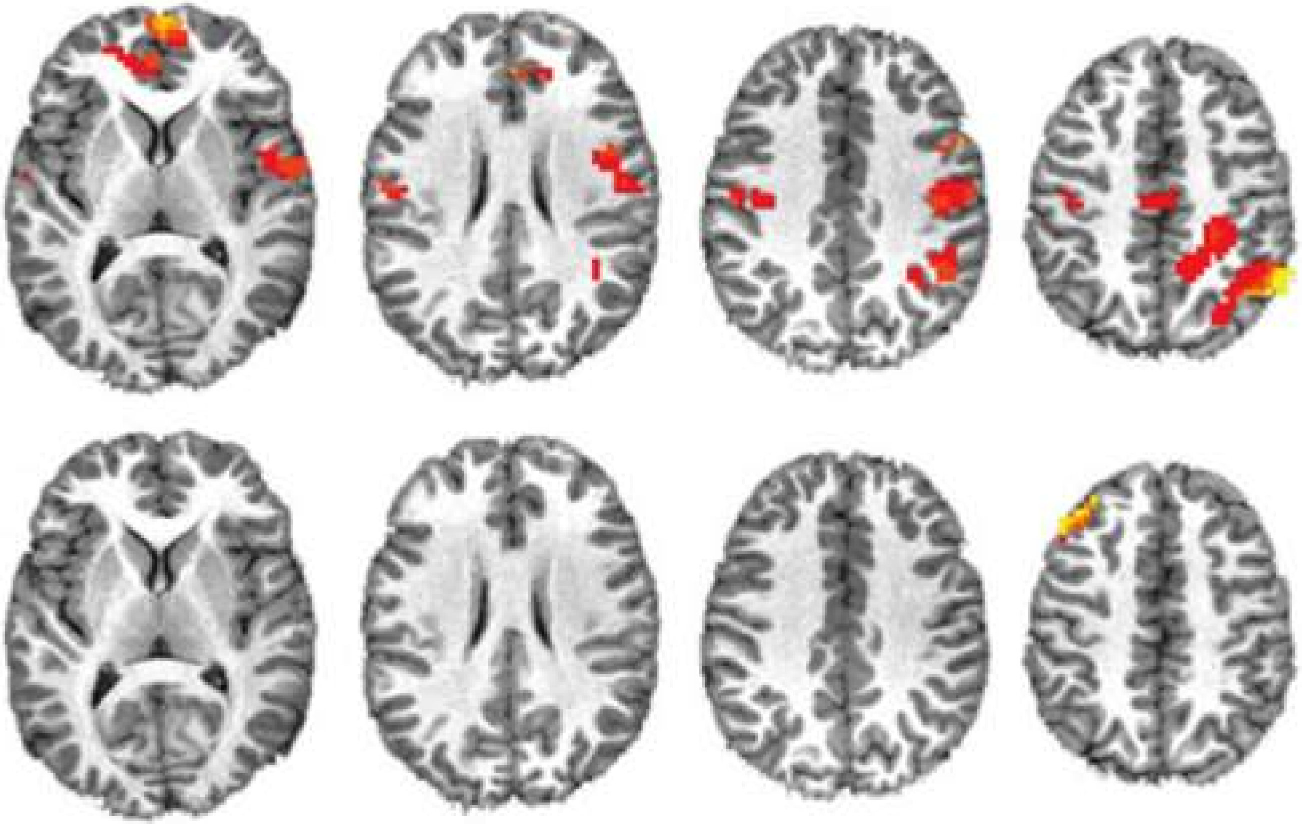
- Blocking the **truthful** answer replacing it with **false**



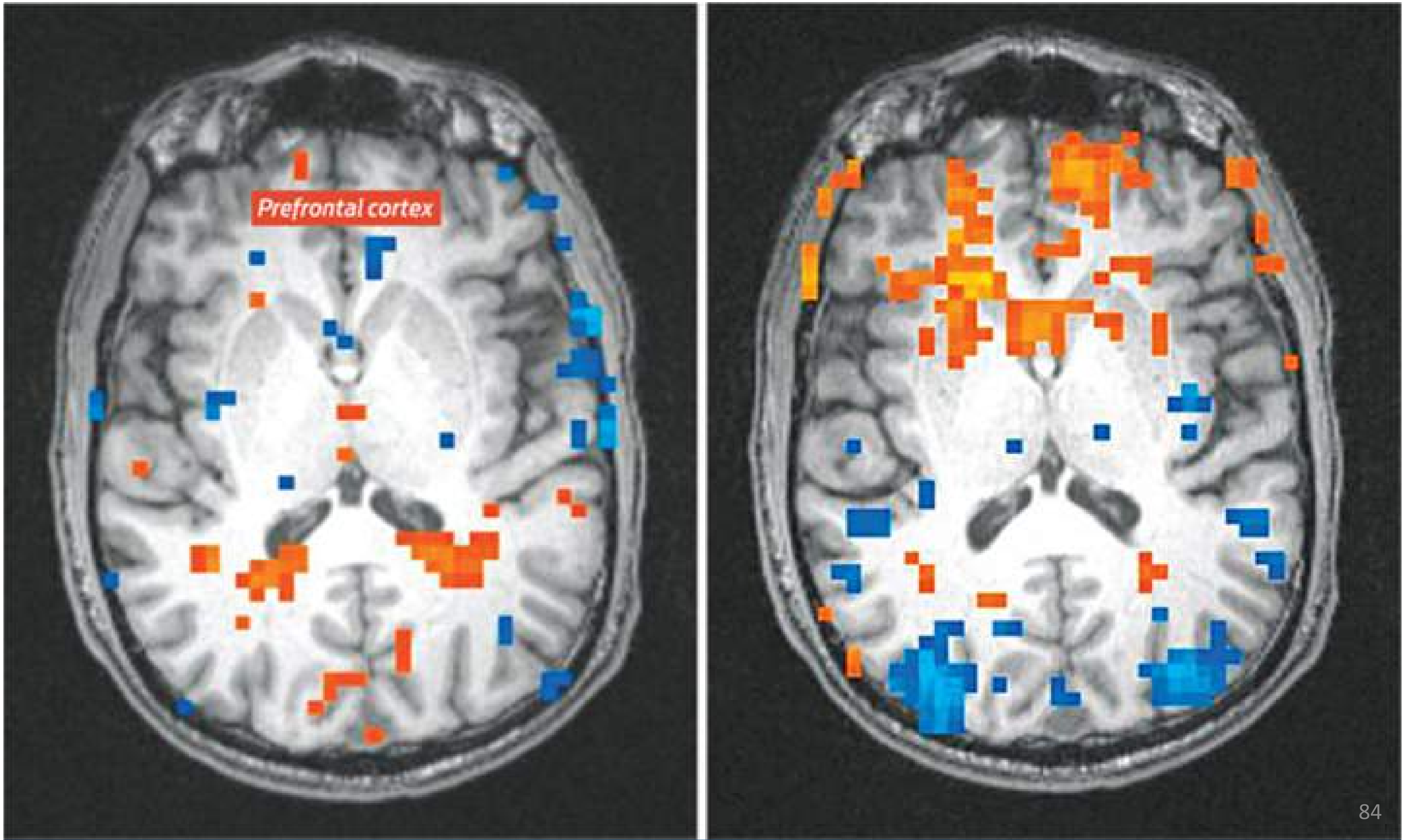
fMR and LIE

Answering with a Lie

Answering with the Truth



Truth Lie



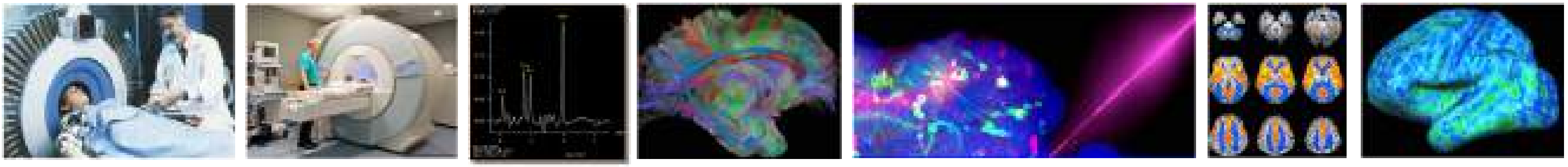
nature REVIEWS NEUROSCIENCE

But Detecting Lies with fMRI:
is a long way to go ………………….
Further research is necessary.

Functional MRI-based lie detection: scientific and societal challenges

Farah, M., Hutchinson, J., Phelps, E., & Wagner, A. (2014).
Neuroscience DOI: 10.1038/nrn3589

Assessing structures and functions of the brain



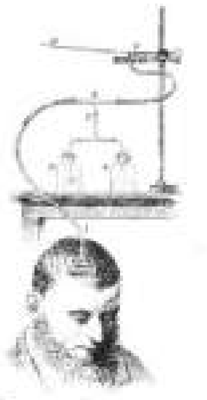
Main methods:

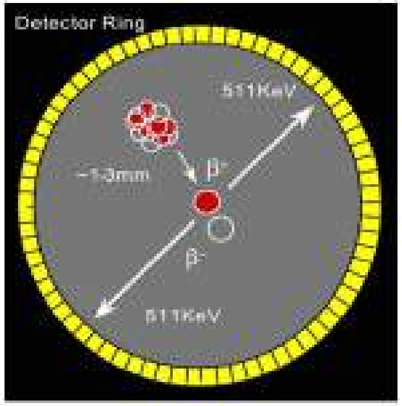
- » **PET** Positron Emission tomografy
- » **SPECT** Single Photon Emission Computed Tomography
- » **F -MRI** Functional Magnetic Resonance Imaging
- » **MRS** Spectrometry

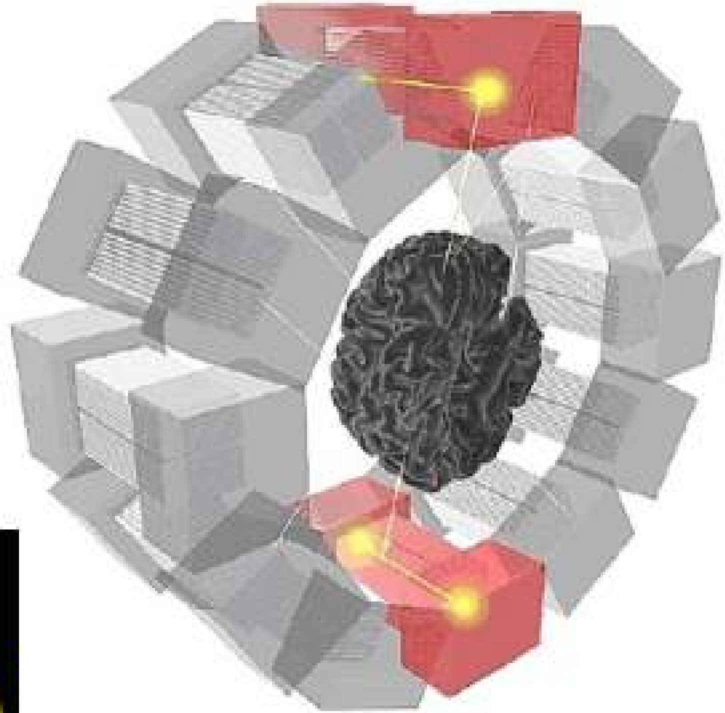
Positron Emission Tomography - PET

Is important for the study of glucose metabolism

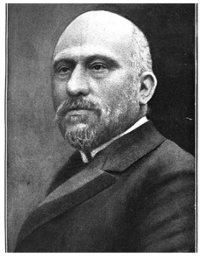
Cerebral blood flow (Mosso)





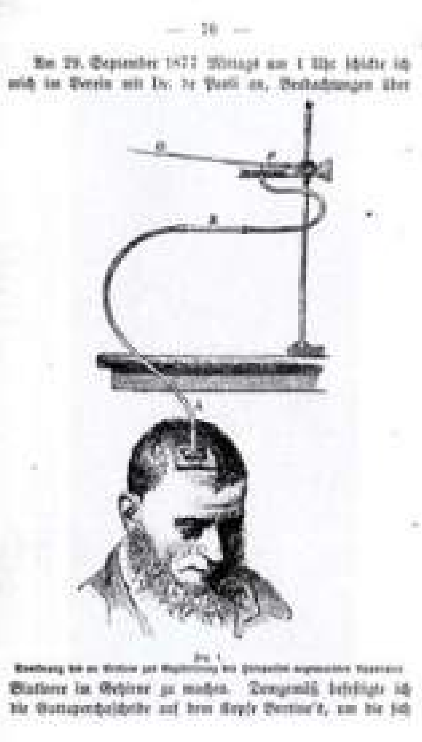


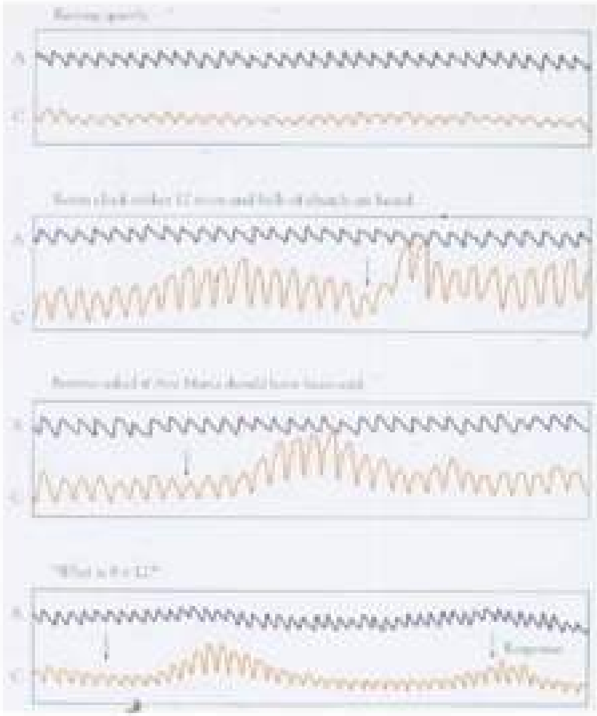
Cerebral Blood Flow

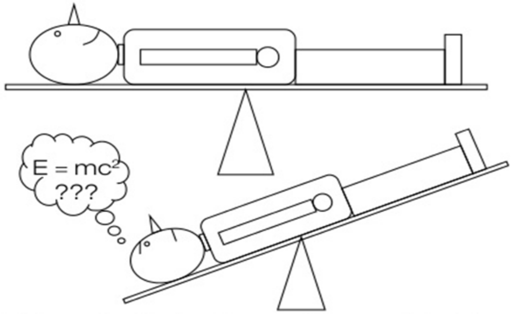


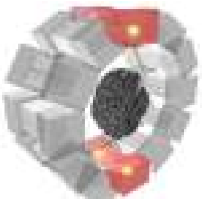
Angelo Mosso,

He worked with patients who had suffered head injuries that left them with permanent defects in the skull over the frontal lobes of the brain. **<u>He noticed that pulsations increased in magnitude during periods of mental activity</u>.** Mosso's recordings taken of the forearm (dark curves labeled A in each panel) and the head (light curves labeled C) show stronger brain pulsations after the events marked by the arrows have stimulated brain activity. Top panel, "resting quietly". Second panel, "clock strikes noon and bells of a church are heard". Third panel, "asked if Ave Maria should have been said". Bottom panel, "what is 8x12?"





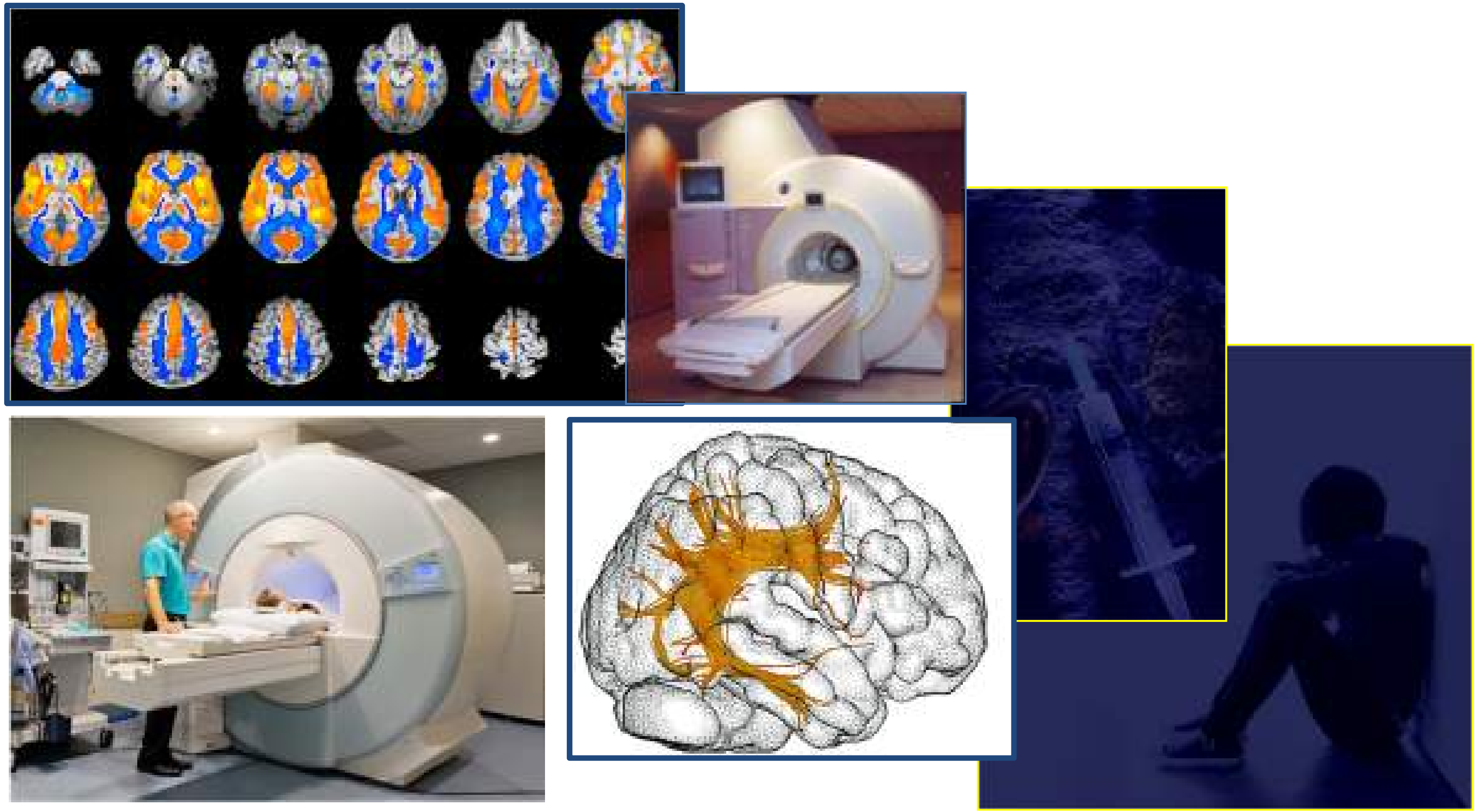




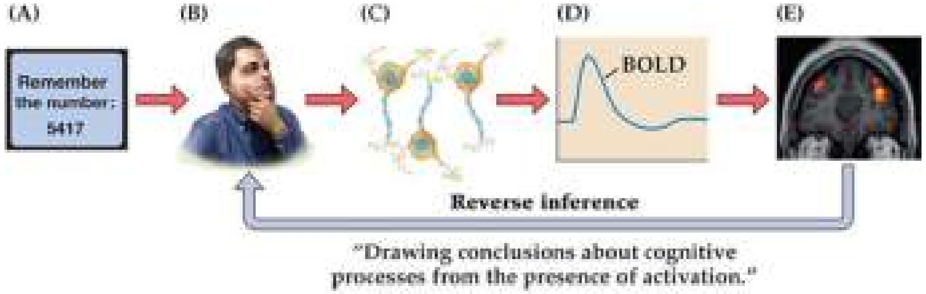
Angelo Mosso (30 May 1846 – 24 November 1910) is the 19th century Italian physiologist who invented the first neuroimaging technique ever, known as 'human circulation balance'

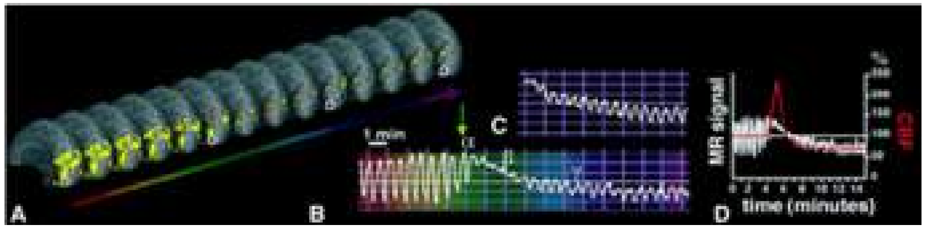
f-MRI: High field MR Imaging

To study of **<u>Functional and Structural</u>** brain abnormalities in drug users



BOLD technique



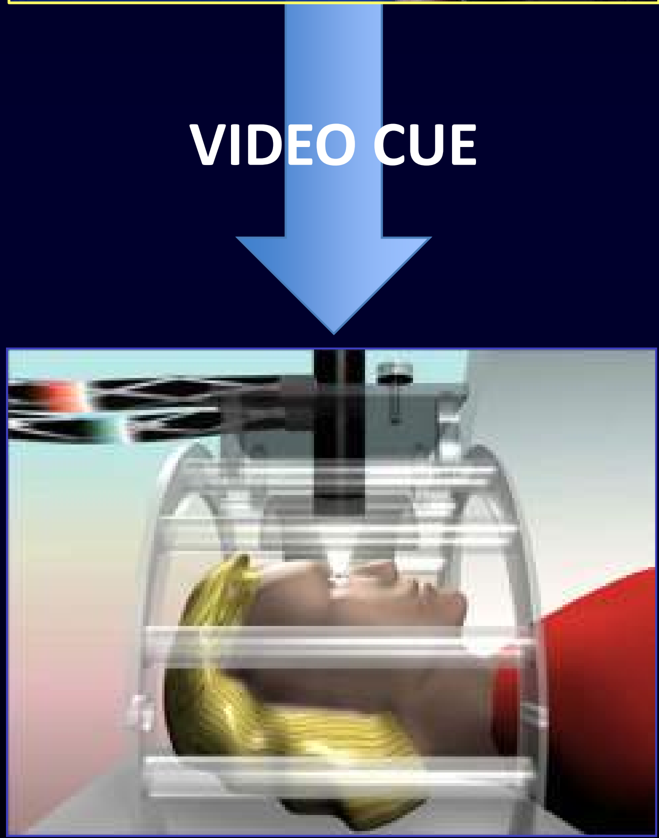


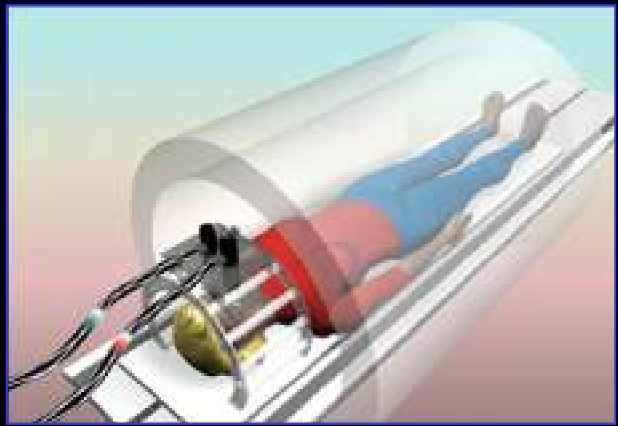
When neurons become active, their use of oxygen increases. This is followed within seconds by and increase in blood flow and volume, which results in a net decrease in the amount of deoxygenated hemoglobin present. This is detected with the BOLD technique. It is the basis for the most studies using fMRI to generate activation maps

f-MRI

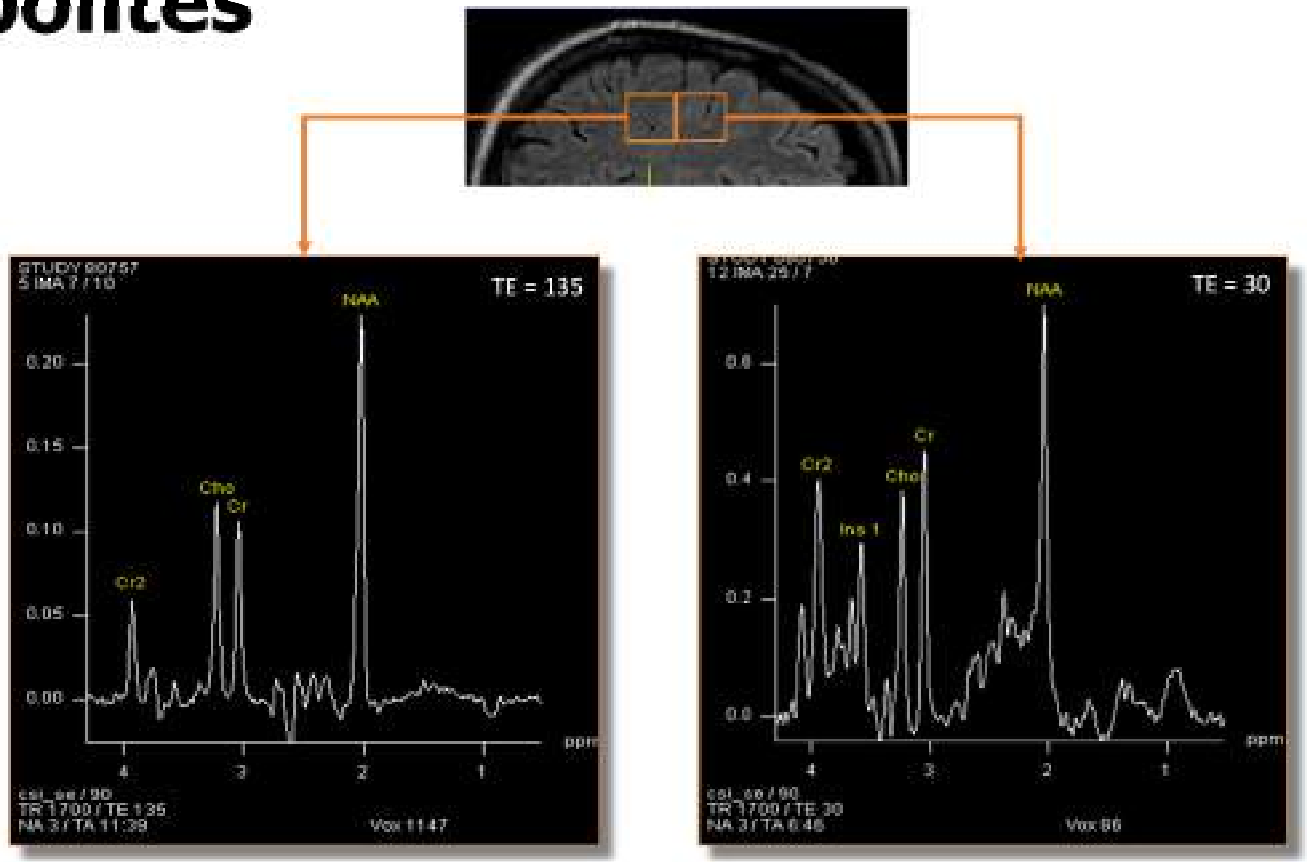
Is possible to see magnitudo of the amigdala activation to generate the craving and magnitudo of the responses of PFC (to control the craving)

There are different reactions in people with different structures and different capacity to control the impulses (different probability of relapse). → different therapies





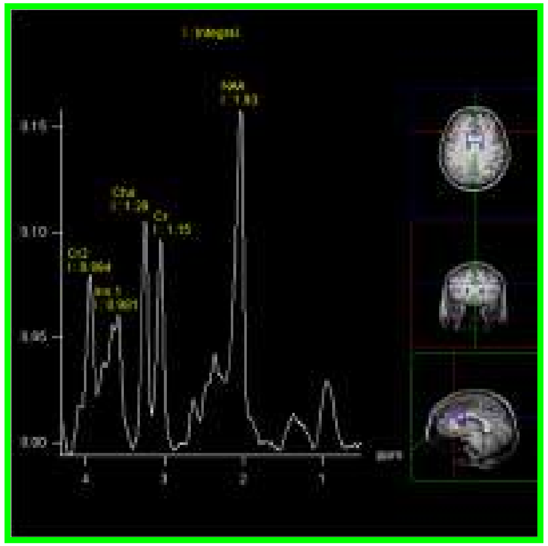
MR-SPECTROSCOPY: to determine brain metabolites



NAA: N-Acetil-Aspartate
Cho: Coline
Cr: Creatine

Ins: Mio-Inositolo
Glu: Glutamate
Gln: Glutamina

MR Spectroscopy



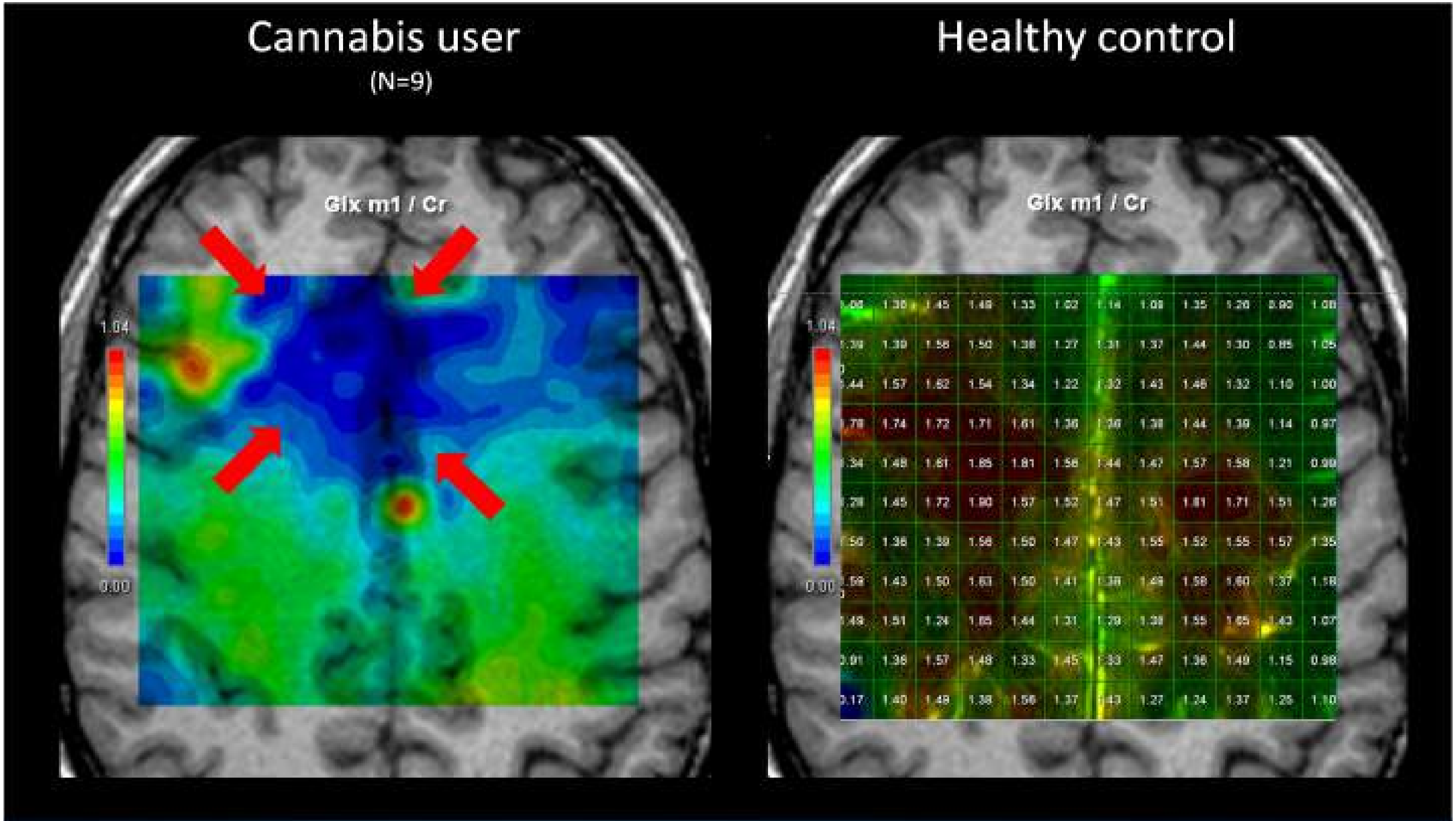
Ex. **Cannabis users**

- Reduced levels of Glu
- Altered neuropsycological tests

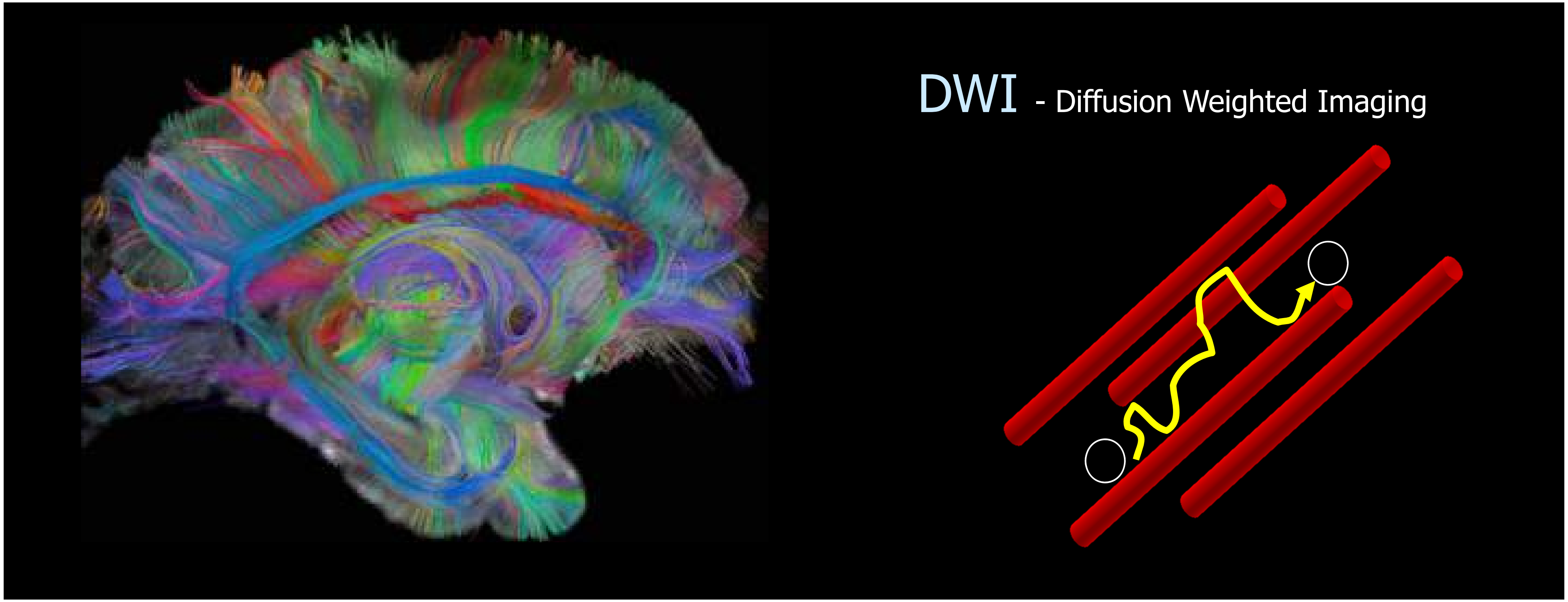
Similar results in schizophrenic patients

Low Glutamate level in cannabis use

Neuroscience Verona Group 2013

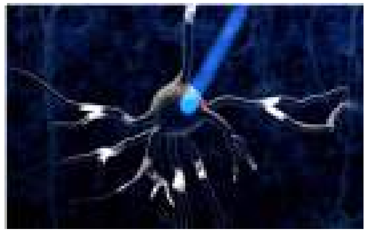


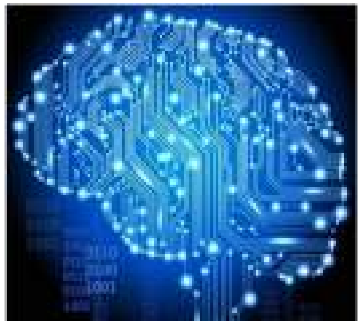
Diffusion Tensor (DTI)

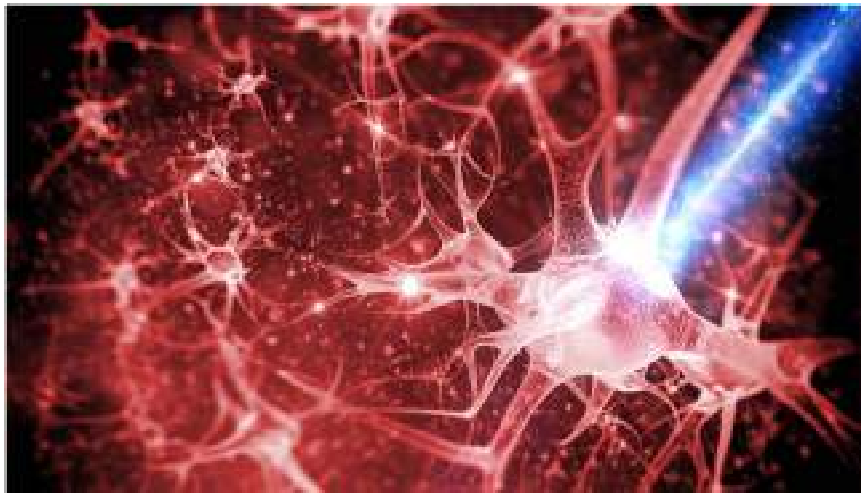


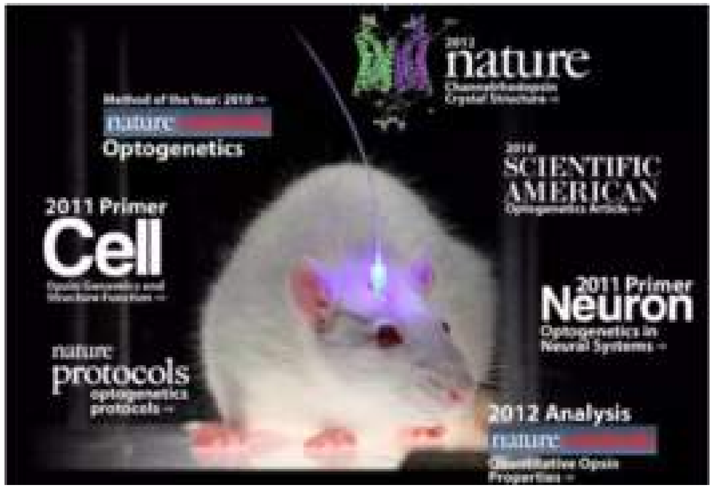
- Based on DWI principles
- Identify **White Matter Tracts**
- 3D Rendering
- *Calculate **White Matter integrity&density** index*

Optogenetic and brain: the future









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Thank you for attention

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