What can human brain imaging tell us about addiction and recovery from substance abuse?

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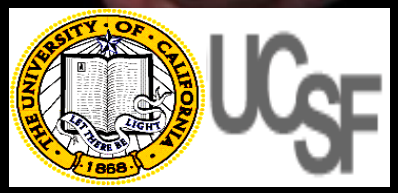

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Chronic Drug Use Damages the Brain

- A Century of Studies
  - Histology, histopathology (microscopic anatomy)
  - Pathophysiology
  - Histochemistry
  - Molecular biology
  - Single cell recordings
  - Neurocognition
- Animal models extremely helpful
  - dependence, tolerance, withdrawal
  - isolate specific factor
  - forced drug administration
  - …. but limited

Why study the human brain?

- System is in its native state/natural environment
- Humans self-administer drugs
  - Voluntarily and continued, despite awareness of being on path of destruction
  - Loss of control over drug taking
  - Complex drug interactions: >1 drug to achieve different effect/desired result
- Human brain biology
  - Structure, physiology, chemistry, function, behavior
  - Basis for change

What can neuroimaging tell us about human addiction?

- Critical elements of addiction
  - "Consistent pattern of repeated self-administration of a substance in doses that reliably produce rewarding psychoactive effects and/or avoid or terminate withdrawal symptoms"
  - "Continued use despite significant impairment of psychological, social, occupational, physical functioning"
  - Great difficulty achieving sustained abstinence, even when strongly motivated to stop

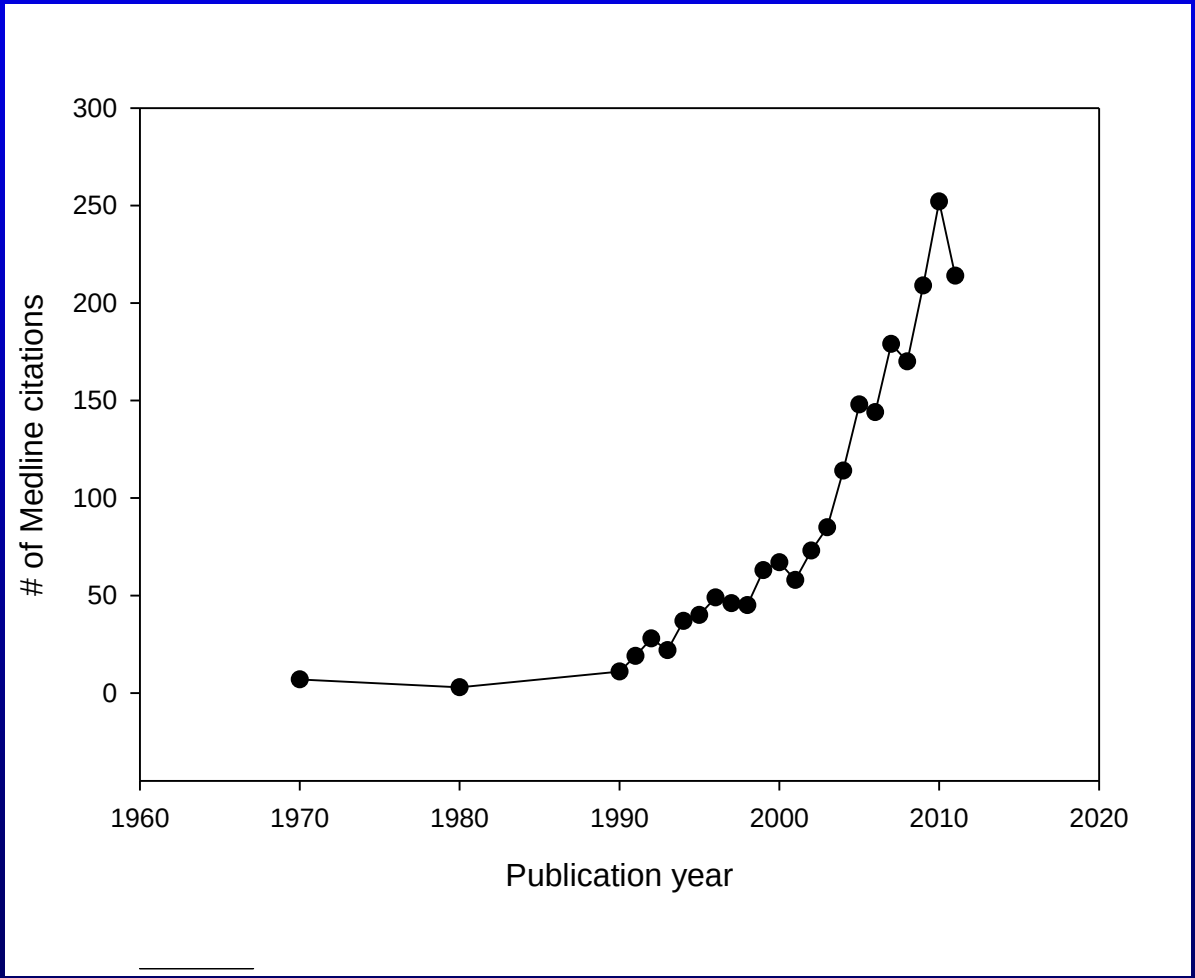
    ⇒ chronic relapse/remit cycle

Outline

- Neuroimaging of addiction
  - Structural MRI
  - Nuclear imaging
  - MR Spectroscopy (MRS)
  - MR Perfusion, blood flow
  - Functional MRI (fMRI)
  - MR Diffusion
- Relevance to cognition, behavior
- Neuroimaging of recovery with abstinence
- Neuroimaging for prediction of relapse
- Implications for treatment

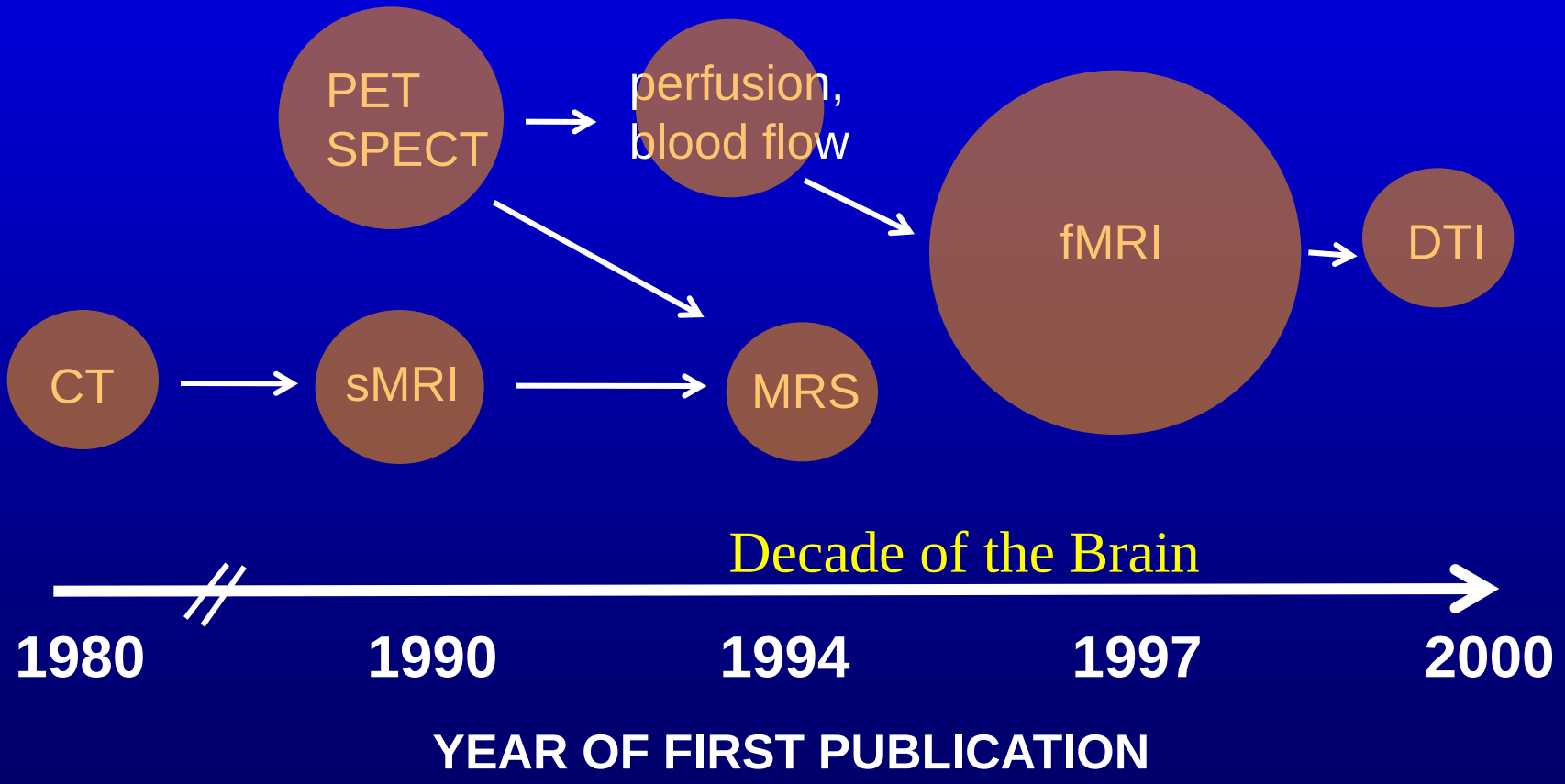
Human Neuroimaging, Drug Use Disorders

Medline Citations 1964-2011 (~2200)



Human Neuroimaging, Drug Use Disorders

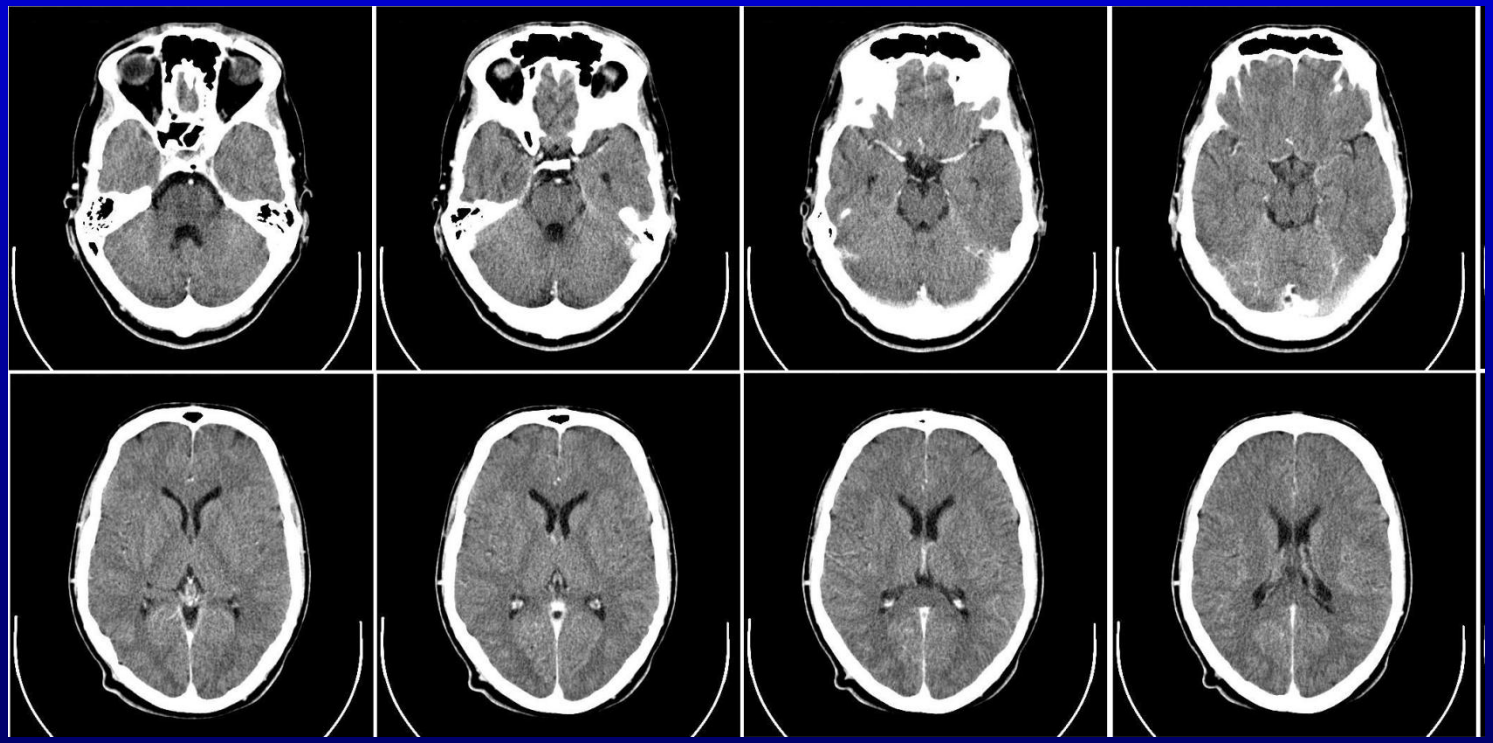
Medline search, Modalities



What have we learned?

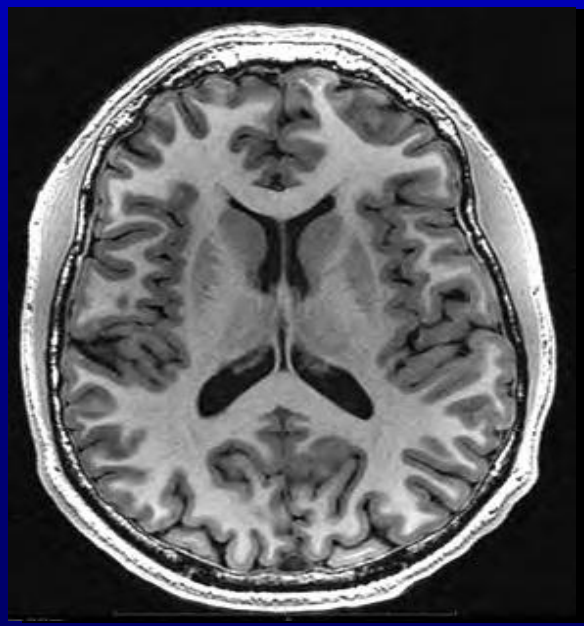
- CT ~1980 - 2000

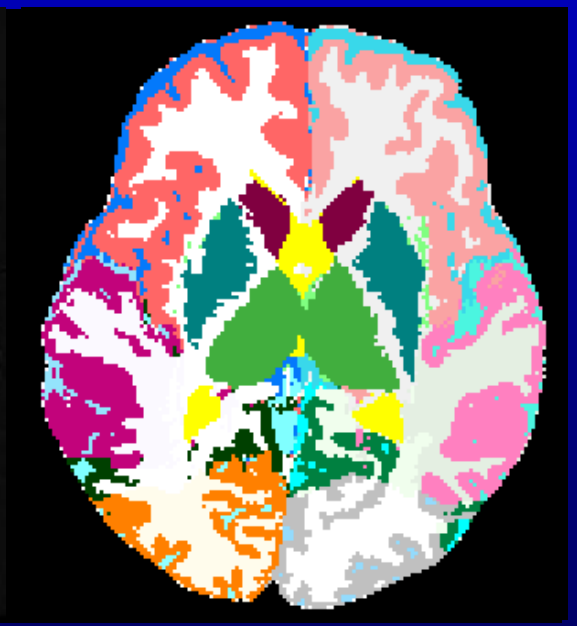
  less brain tissue, more cerebral spinal fluid



What have we learned?

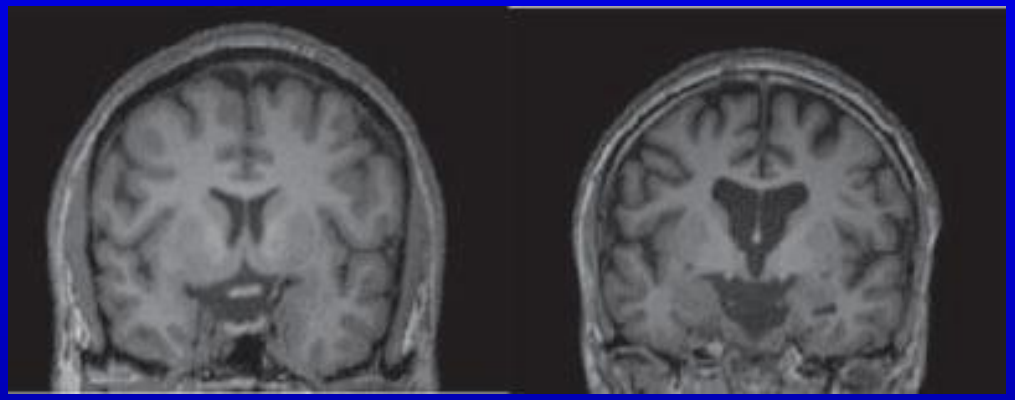
- Magnetic Resonance Imaging (MRI) since ~1990
  - Brain structure, lesion detection
  - Differentiation of tissue types (gray and white matter)
  - Voluming of brain structures, quantitative comparisons



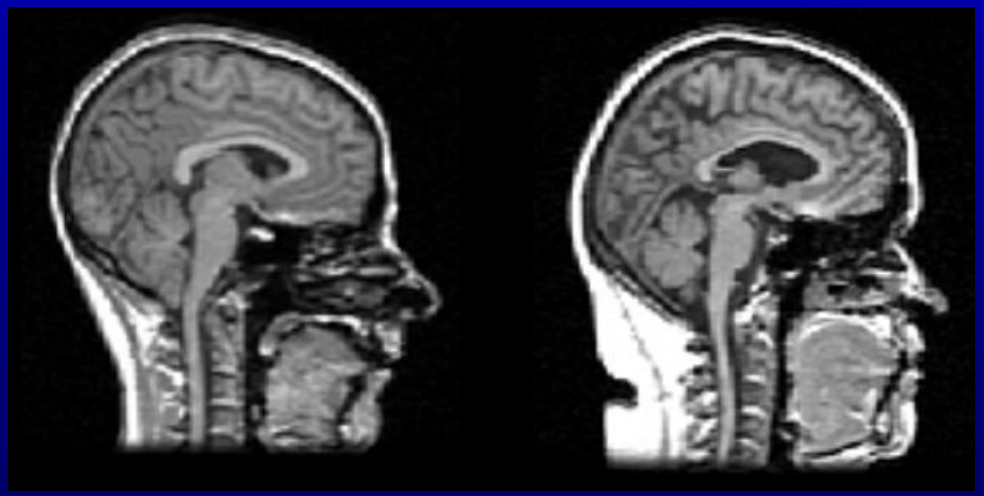


MRI of Alcohol Dependence: Atrophy

Healthy control Alcohol dependent



Mann et al. 2009

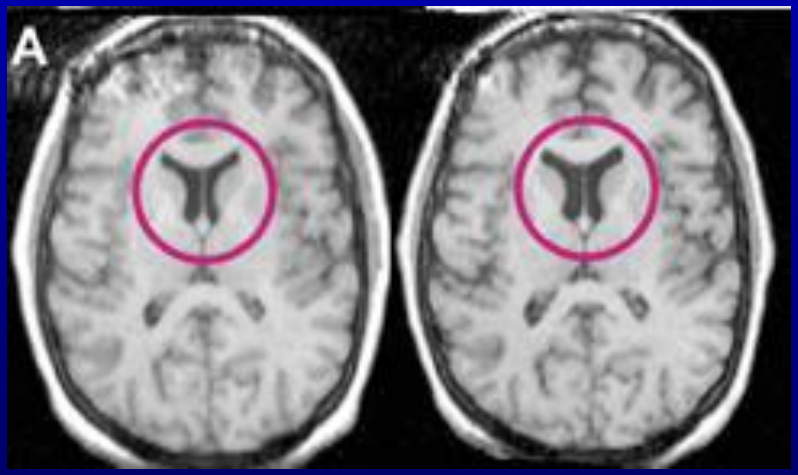


Hommer et al., 2001

sober alcohol dependent

↓

1 year later after resuming drinking

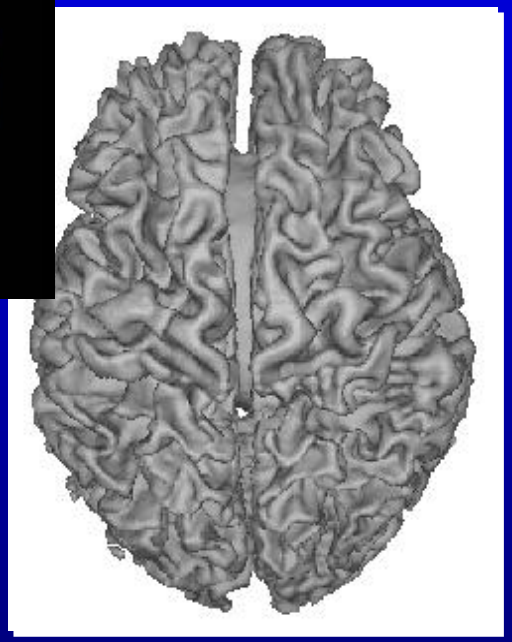


Rosenbloom and Pfefferbaum 2008

3D MRI: Tissue Loss (Atrophy)

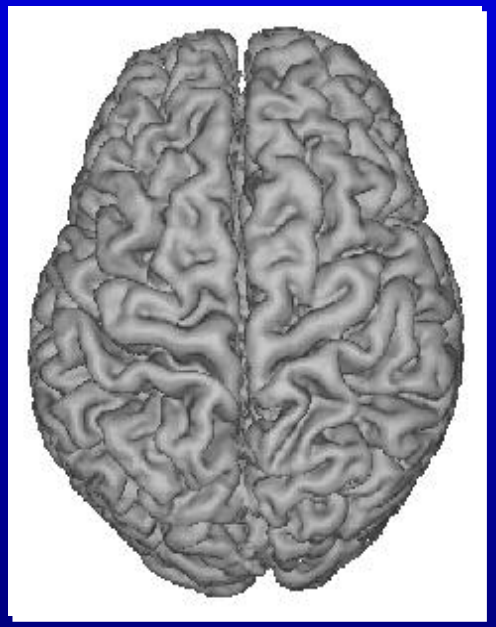
~1100 mL

57 year old
alcoholic



ca. 1866 kg
ca. 160,000 drinks

57 year old
social drinker



ca. 60 kg
ca. 5,000 drinks

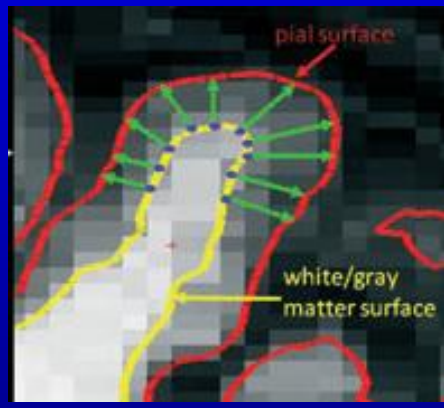
~1300 mL

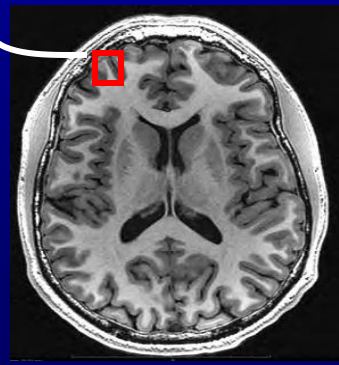
Lifetime alcohol consumption

Sullivan, NIAAA Monograph 2000

What have we learned?

- Structural MRI since ~1990
  - Structural voluming allows quantitative comparisons
    - Tissue loss frontal lobe > subcortical brain > cerebellum
    - Tissue loss influenced by age and sex
  - Thinner cortex relates to function/behavior
  - Repeat MRI can monitor structural changes
    - Non-destructive to tissue
    - Chronic drug use ⇒ tissue loss
    - Drug abstinence ⇒ tissue regeneration





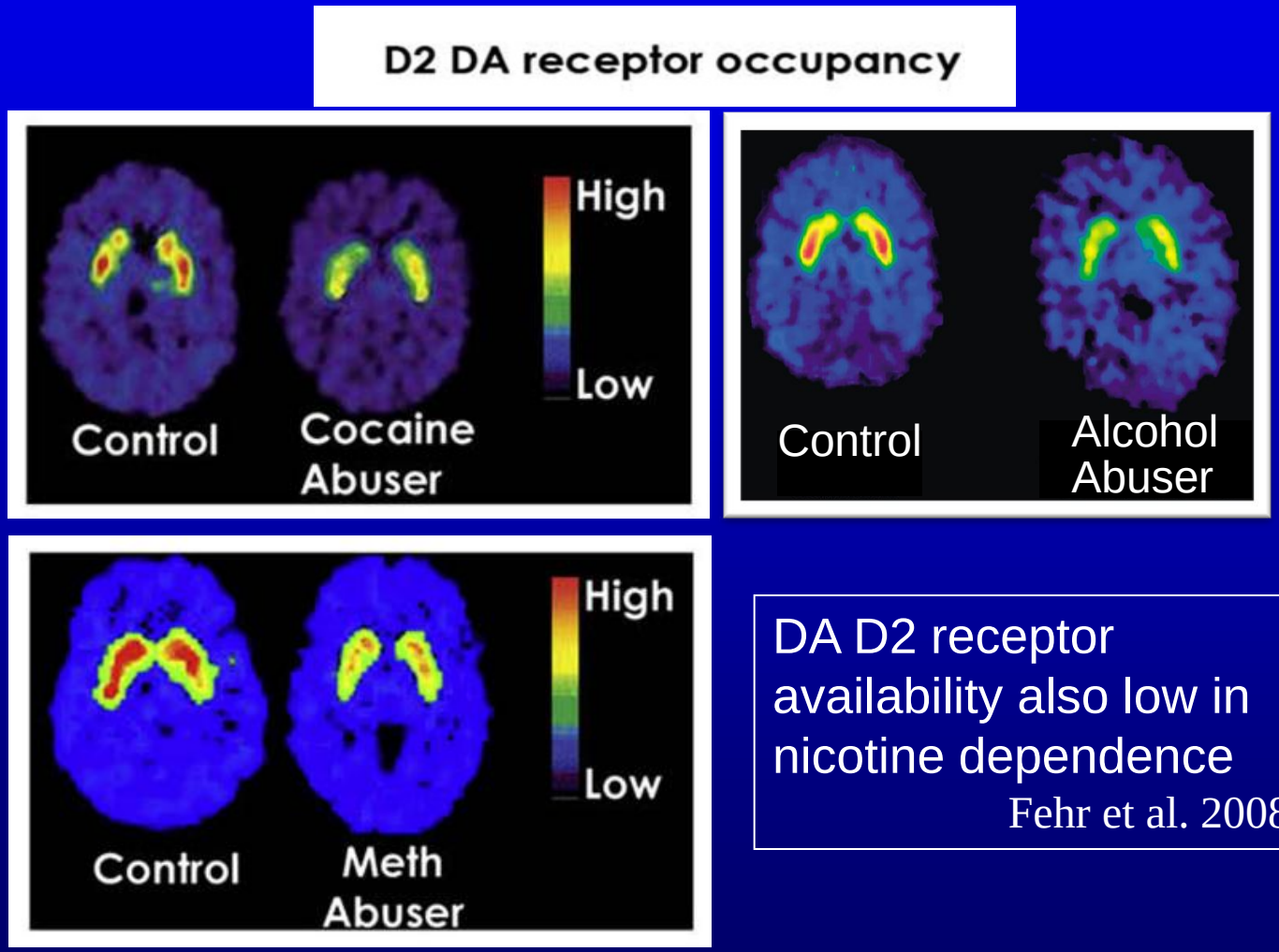
What have we learned?

Nuclear imaging (PET & SPECT) since ~1990

- Short-lived radionuclides built into biologically active molecules (tracers), injected into blood stream
- Tracers allow imaging
  - **Blood flow**: down or up in different brain regions
  - **Glucose metabolism**: low in frontal lobe of drug users, less energy production ⇒ impaired function (e.g., cognitive control)
  - **Receptor density, availability**
    - Dopamine (DA), serotonin release, transport
    - Striatal dopamine (DA) receptors low across different drug dependencies (marker of addiction)
      - Premorbid risk factor ? Consequence of drug use ?

Positron Emission Tomography (PET)

Imaging of Dopamine Receptors



DA D2 receptor availability also low in nicotine dependence

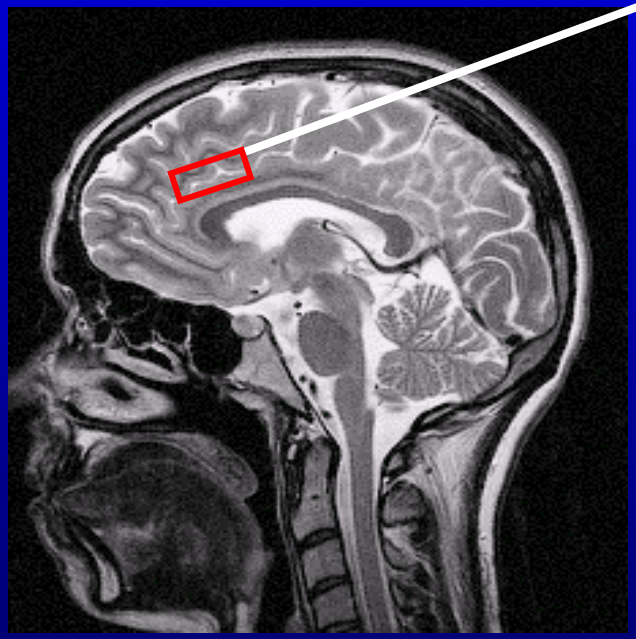
Fehr et al. 2008

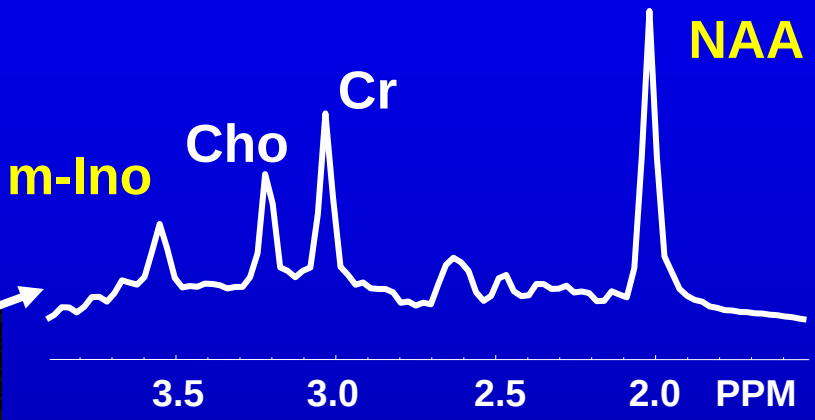
Volkow, Wang et al. 2002, 2009

What have we learned?

- PET and SPECT since ~1990
  - Dopamine (DA) release
    - Strong when drug-naive, weak in chronic users
    - Associated with craving, drug-seeking, relapse
  - Faster DA release more reinforcing (addictive)
  - Treatment strategies suggested
    - Reduce reward from high DA by blocking DA release, increase DAT
      e.g., NRT, varenicline, methadone, naltrexone
    - Enhance tonic DA to increase inhibitory control (executive function)
      e.g., burpropione, modafinil
    - Enhance GABA to weaken motivational drive to take drugs
      e.g., topiramate, baclofen
    - Increase Glutamate to reduce response to conditioned stimuli
      e.g., acamprosate, NAC

MR Spectroscopy (MRS)
non-invasive measurement of brain chemicals





N-**A**cetyl-**A**spartate: neuronal marker

myo-**Ino**sitol: astrocyte marker

Peak areas proportional to metabolite concentrations

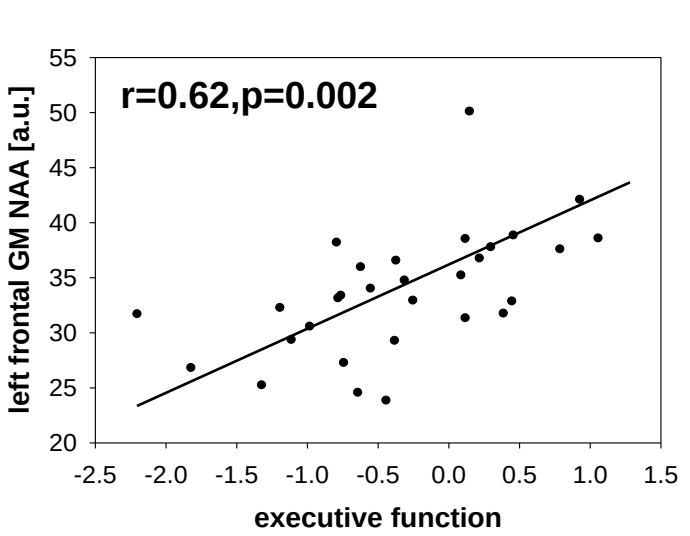
"concentrations" of neurons, glial cells

What have we learned?

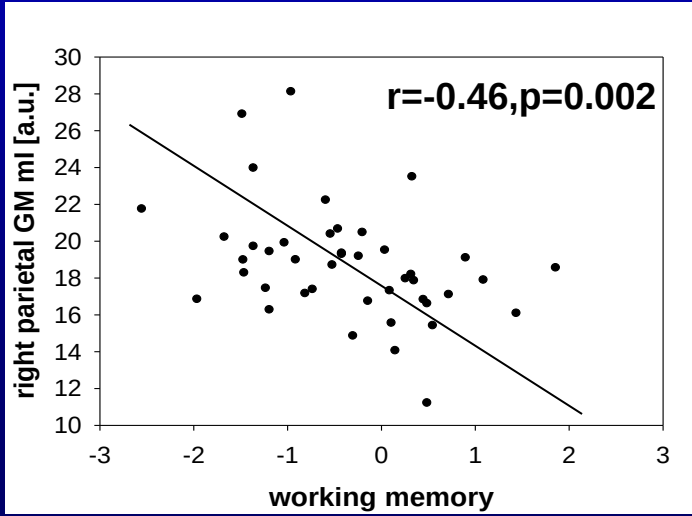
- MR Spectroscopy (MRS), metabolic imaging since ~1994
  - Measures naturally occurring chemicals (metabolites) that represent neurons, glial cells, myelin, may underlie tissue loss
  - Widespread injury to neurons from chronic use of illicit drugs, alcohol, and/or smoking
  - Injury mostly in frontal brain (also atrophy, low glucose metabolism (PET)); region regulates actions, emotions
  - Metabolic abnormalities exacerbated by chronic smoking
  - Metabolite concentrations relate to cognition/behavior (biomarker)

Metabolite Levels Correlate with Cognition

here: Alcohol Dependence



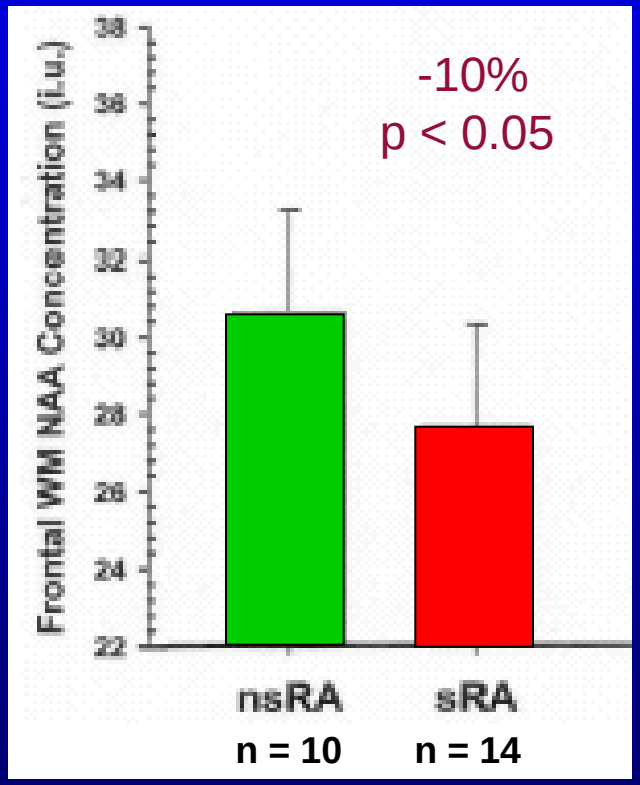
neuronal marker **NAA**
in frontal lobe
vs.
processing speed,
executive function



astrocyte marker **m-Ino**
in parietal lobe
vs.
working memory

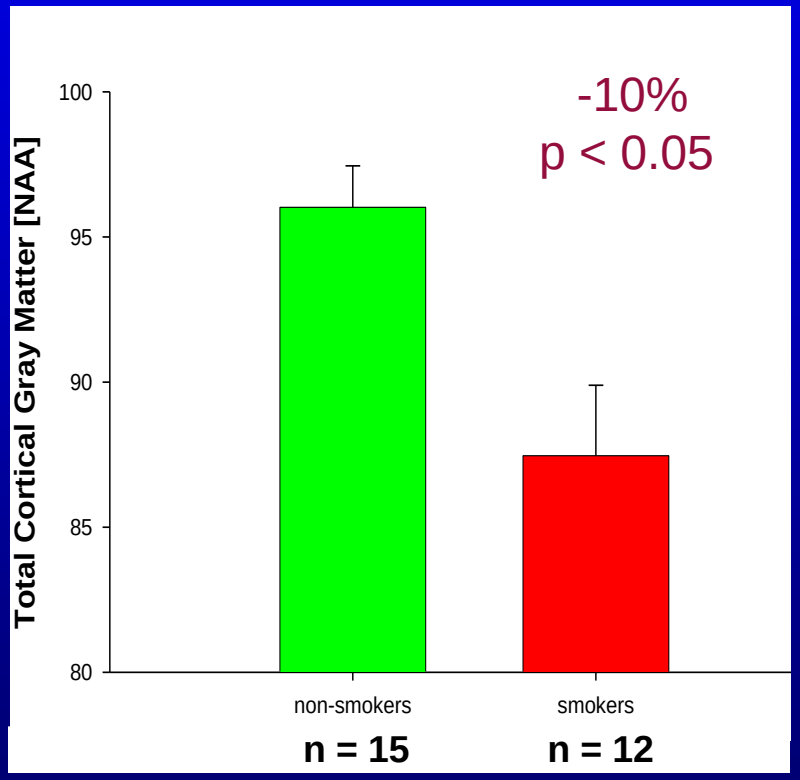
Neuronal Injury in Chronic Smokers

alcohol dependent



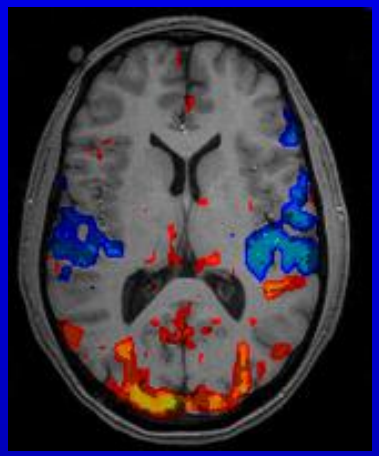
Durazzo et al. 2004

non-alcoholic controls



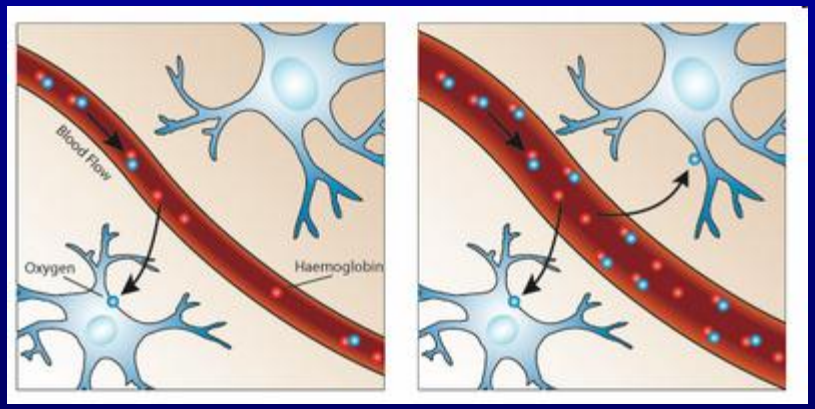
Durazzo et al. 2009

Functional MR Imaging (fMRI)



- Images neural activity at rest or during a cognitive task
- Activity depends on blood flow to brain region in use
  - Fresh, oxygen-carrying blood changes MRI signal intensity at location of oxygen use by neurons
  - Neuronal “activity” can be measured from MRI signal changes

resting

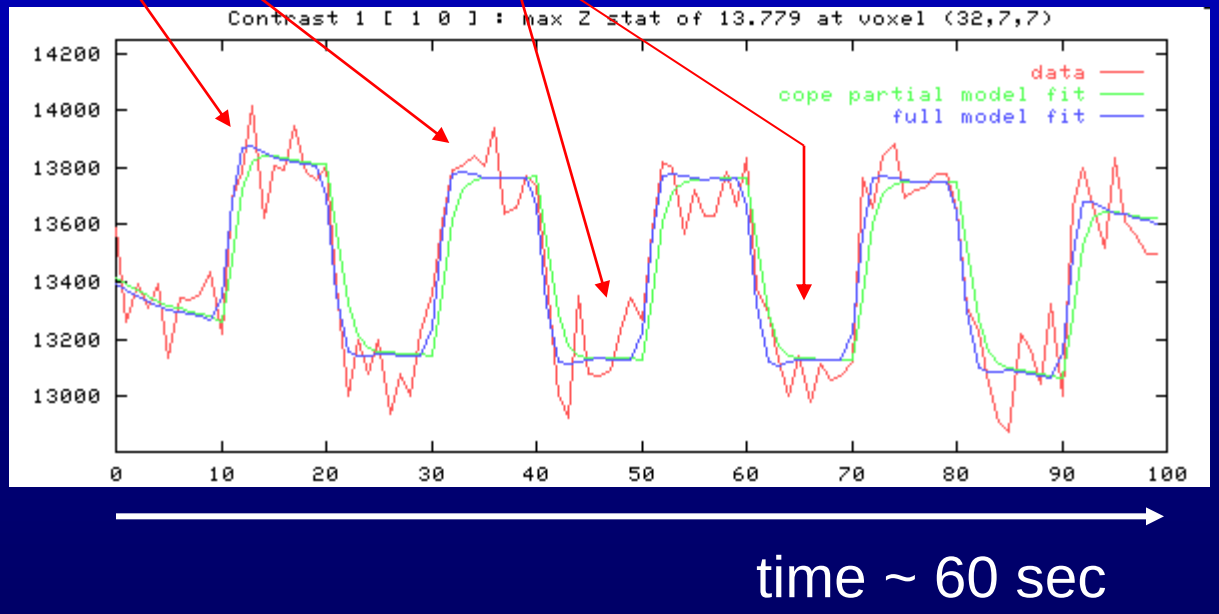


activated

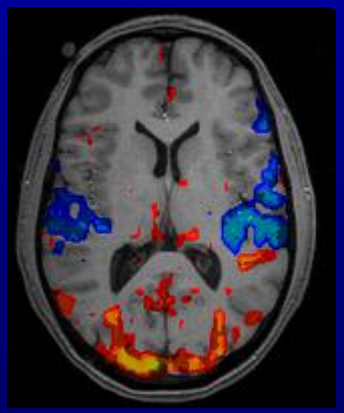
Functional MR Imaging (fMRI)

- MR signal difference related
  - temporally to cognitive task
  - spatially to area of cognitive processing
  - to subjective feelings, perceptions

cognitive activity - rest - activity - rest - ……



signal difference



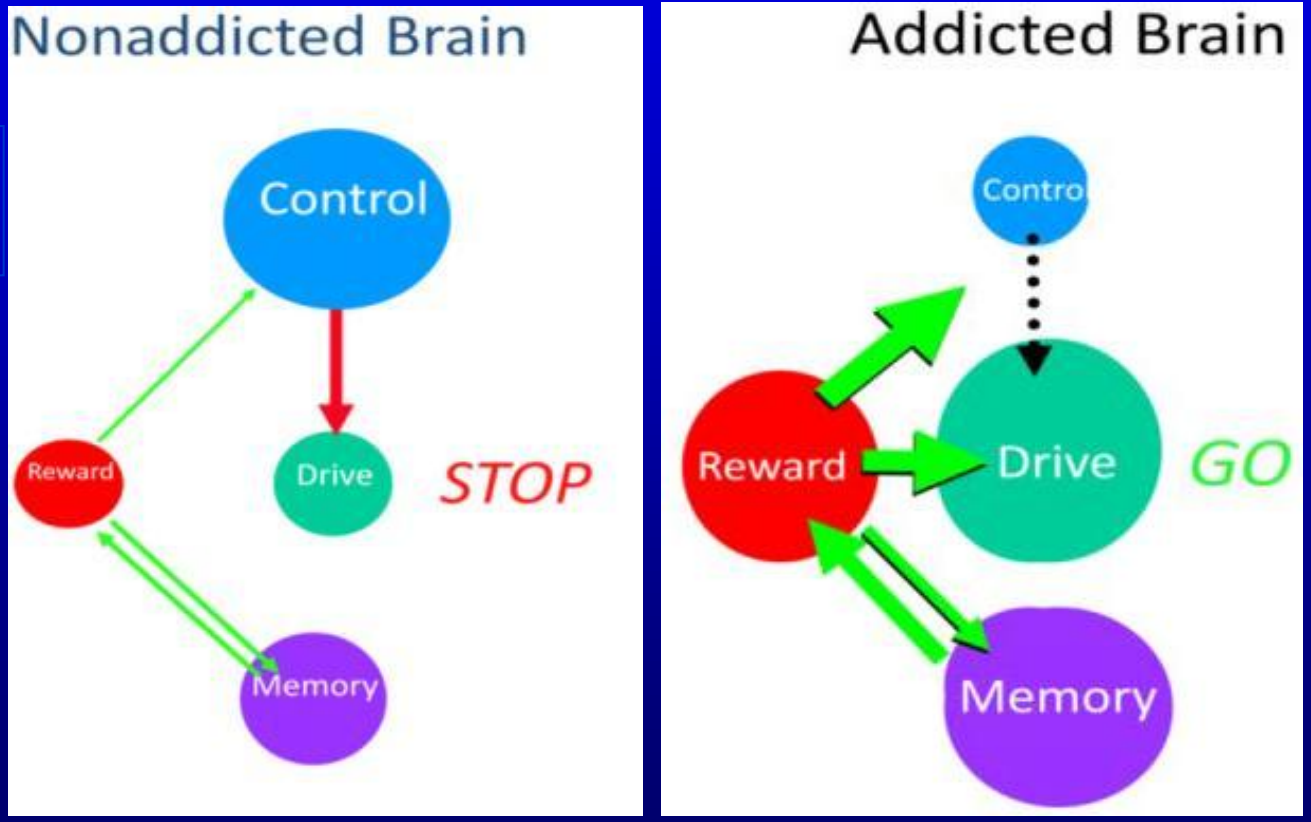
What have we learned?

- fMRI since ~1997
  - Generally **increased** brain activity in
    - "pleasure centers": to **drug stimuli** in addicts
    - anterior brain, brainstem: "feeling high", "craving"
    - memory and retrieval centers: "craving"
  - Generally **decreased** brain activity in
    - "pleasure centers": to **non-drug stimuli** in addicts
    - frontal brain: impaired control of impulsive behavior, reward
  - Treatment interventions must strengthen and remediate these brain regions/circuits
  - Brain = complex network of overlapping **functional** circuits (functional connectivity)

What have we learned?
Functional Circuits

Brain Reward/Executive Oversight System (BREOS)

top-down control

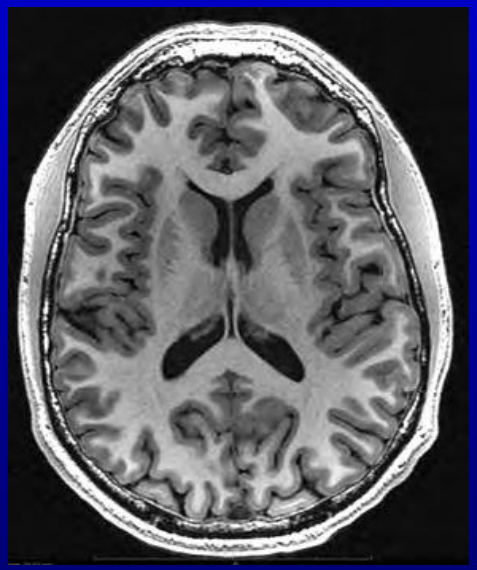


bottom-up action

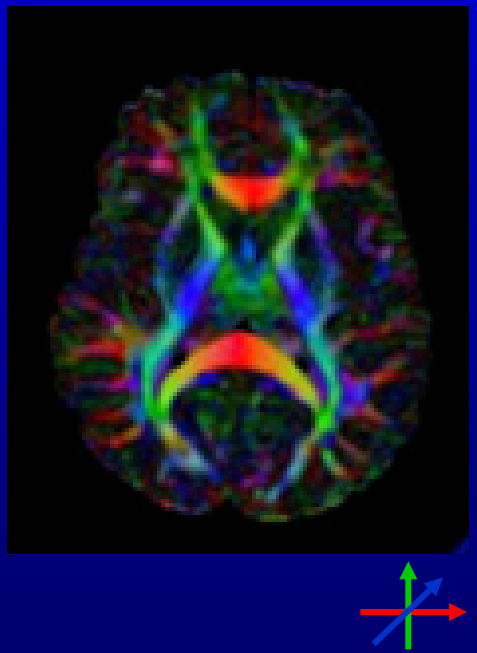
e.g., Volkow et al. 2003

MR Diffusion Tensor Imaging (DTI)
Water Diffusion in Neuronal Fiber Bundles
Structural Connectivity

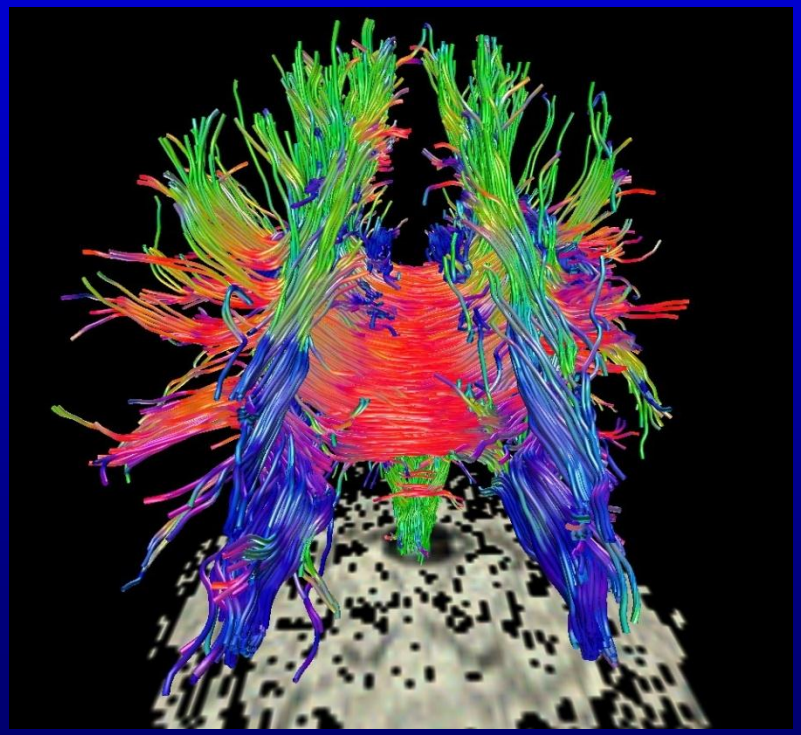
structural MRI



DTI
fiber bundles

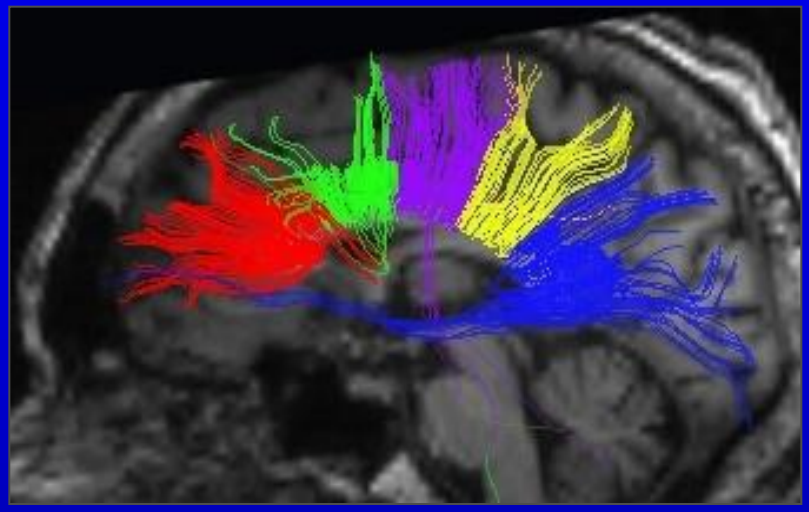


DTI 3D View

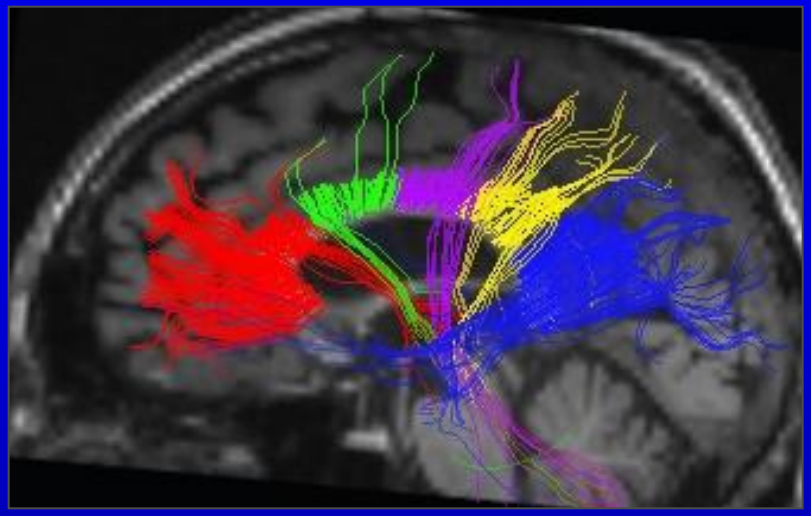


Diffusion directions color-coded

Callosal Fibers in Alcohol Dependence



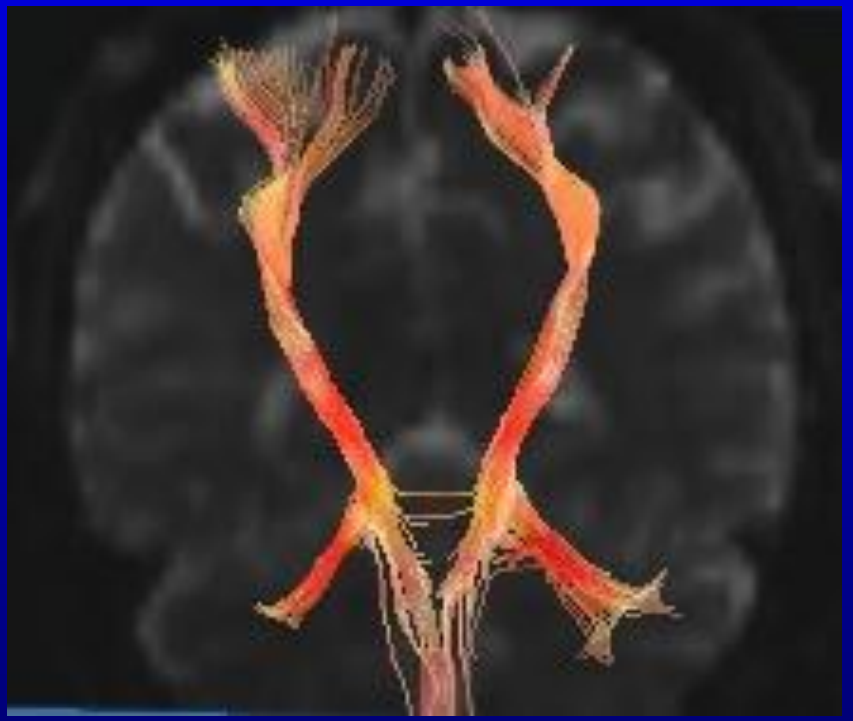
control
M, 51 years



alcoholic
M, 51 years

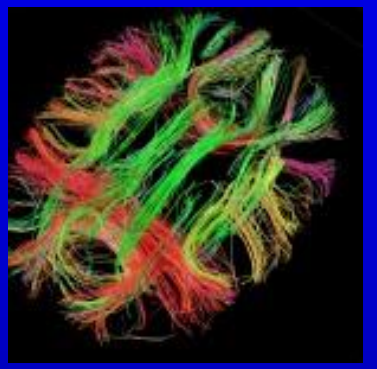
Fiber Tracking with Diffusion Tensor Imaging (DTI)

healthy cingulum

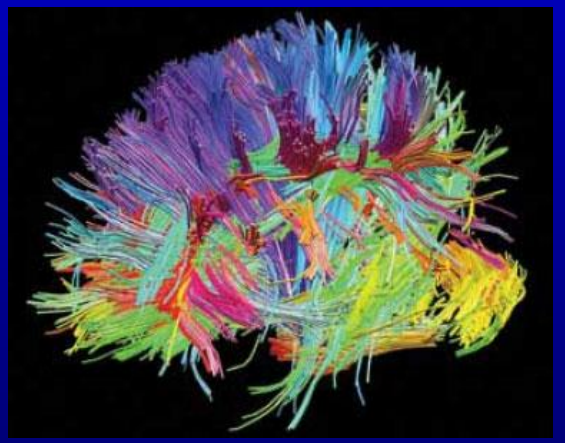


healthy corticospinal tract

What have we learned?
Structural Connectivity



- DTI since ~2000
  - "Wiring" of the brain
  - Visualization of distinct fiber bundles between brain regions (micro-structure)
  - Brain = complex network of overlapping **anatomical** circuits



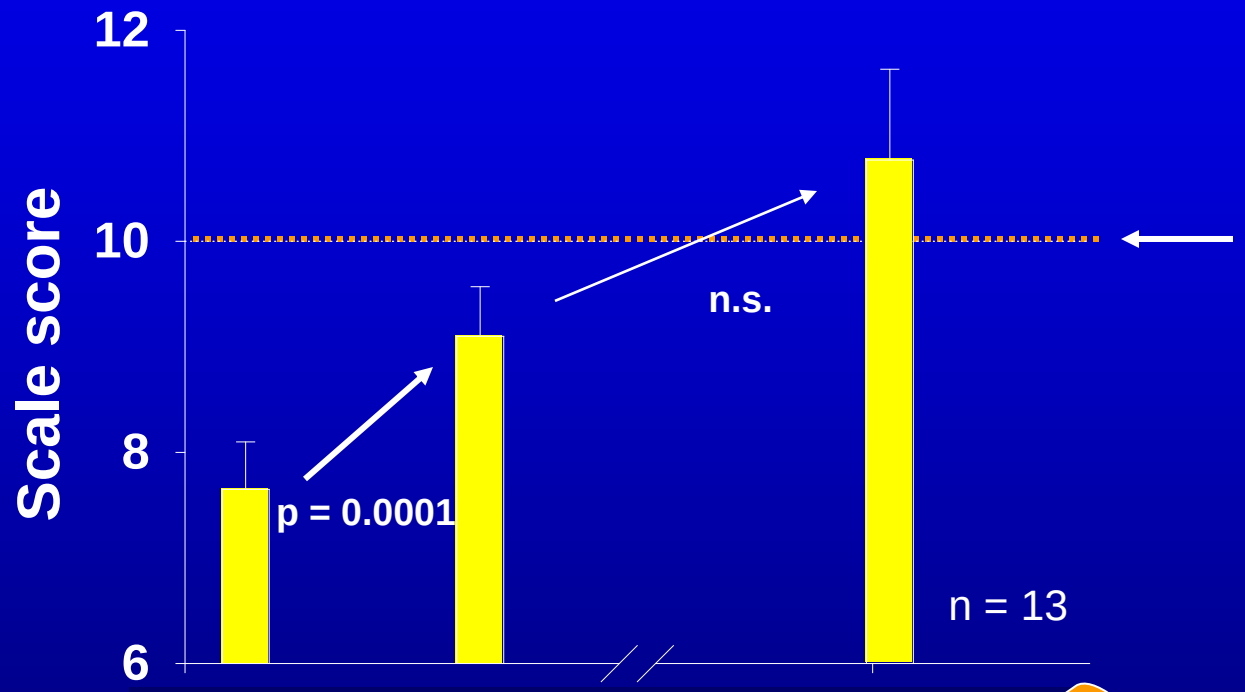
  - Viability of specific fiber pathways related to specific cognitive deficits
  - Can be used to monitor specific/targeted treatment

Neuroimaging During Abstinence

- Remove an insult ⇒ intrinsic brain repair (neuroplasticity)
- Improvements of brain biology and function

Cognition During Abstinence from Alcohol

visuomotor scanning speed and incidental learning



average performance of healthy controls

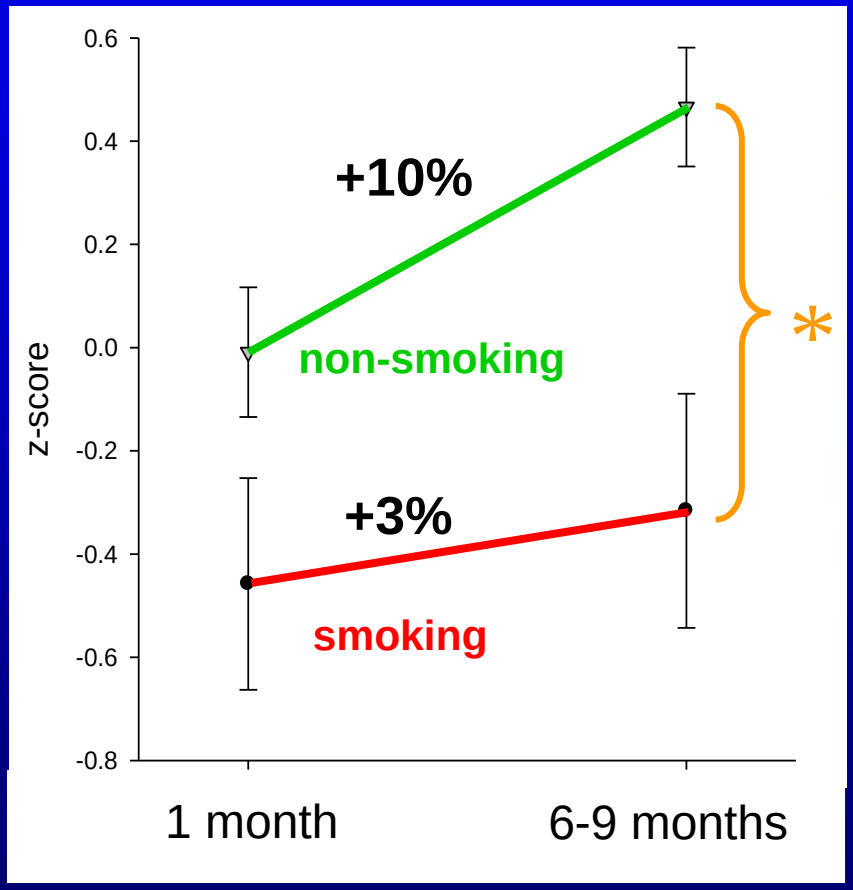
Impaired …

… recovery

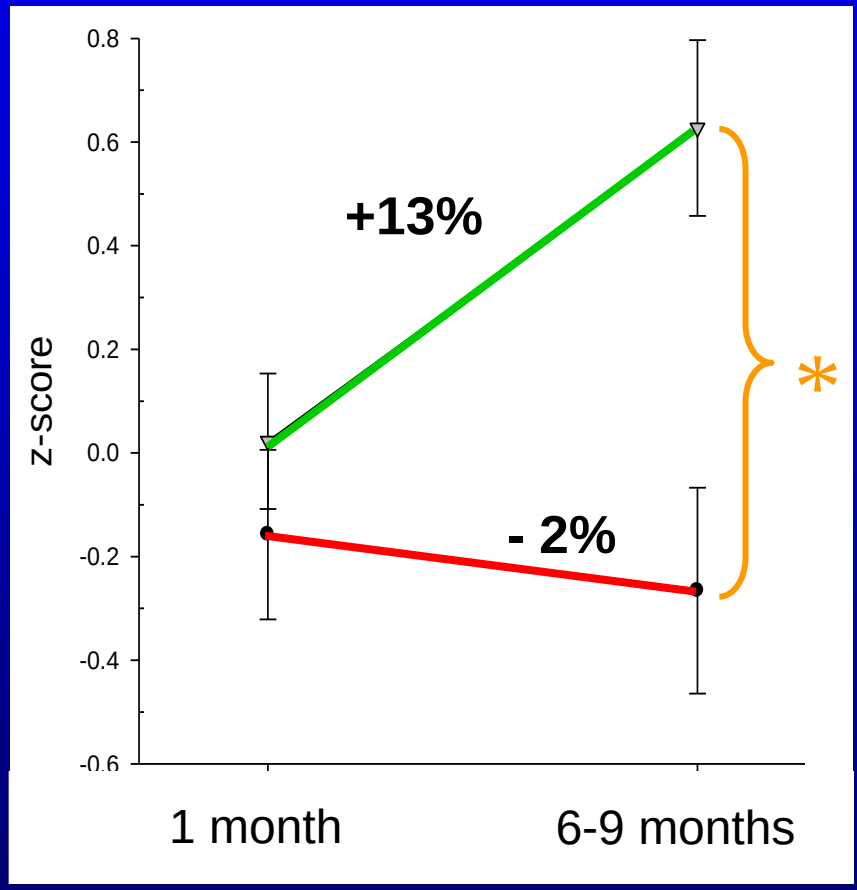
Most cognitive domains improve, except visuospatial and fine motor skills.

Cognition in Abstinent Alcoholics: Effects of Smoking

cognitive efficiency



executive skills



All interactions and simple effects $p < .05$.

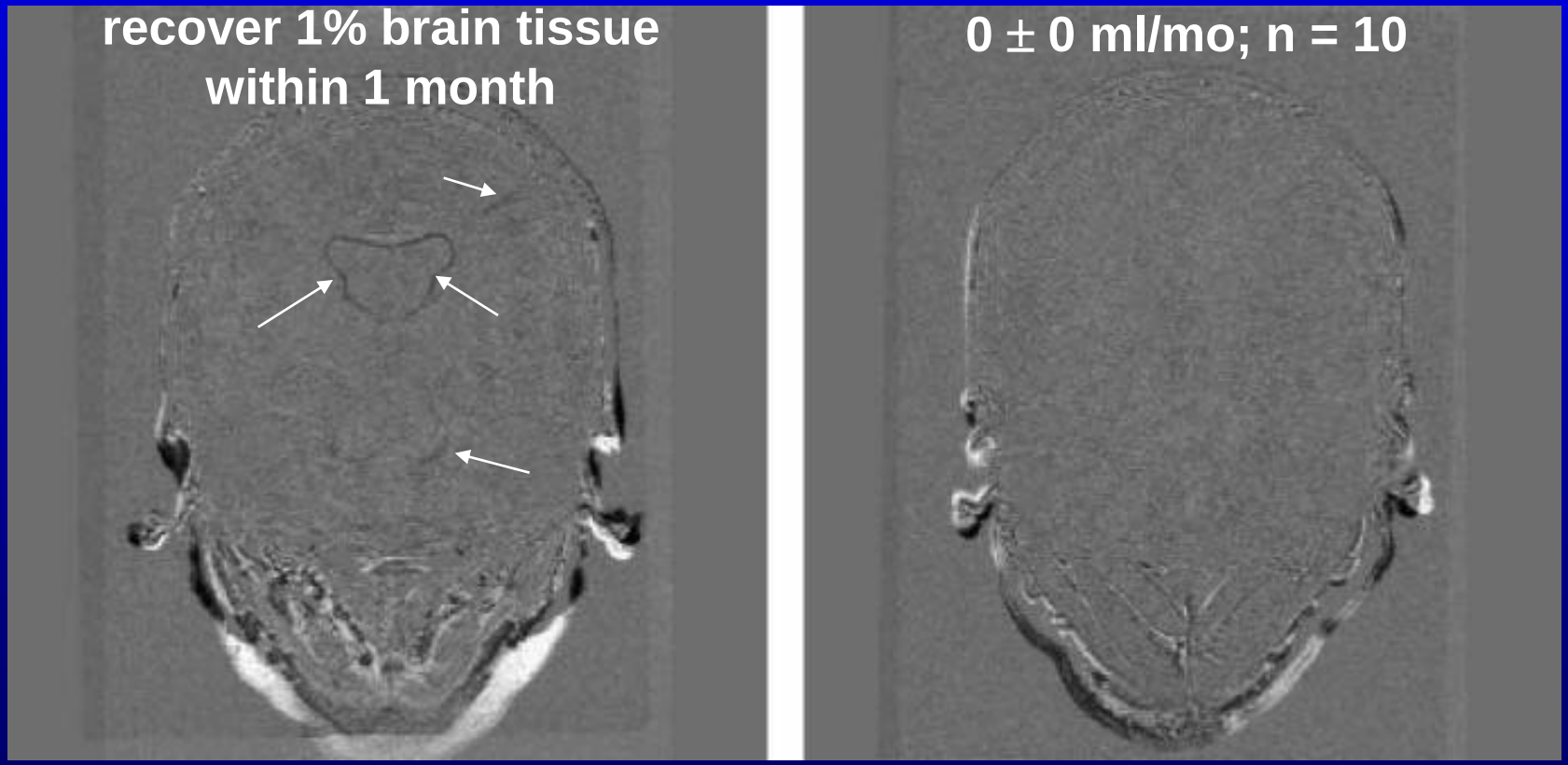
Cognitive improvements, performance at 6-9 months ~ Smoking severity in sRA

Durazzo et al., Alcohol 2007

Structural Recovery over 3 Weeks
Subtraction MRI

abstinent alcoholic, 3 weeks
ventricular volume decrease

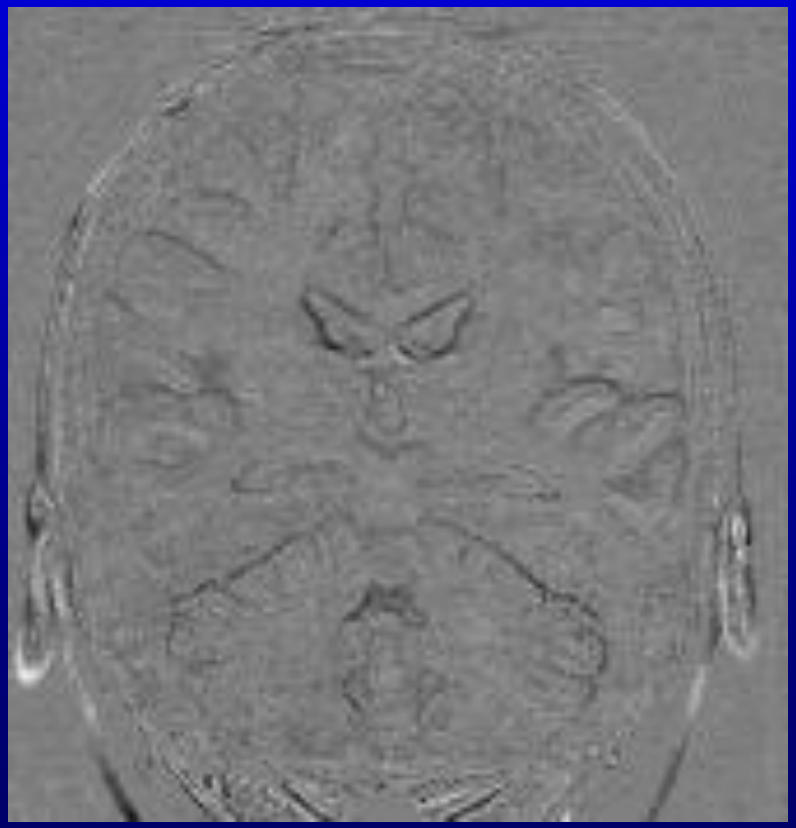
light social drinker, 2 years
no change



BSI method: Freeborough and Fox 1997

Structural Recovery over 8 Months
Subtraction MRI

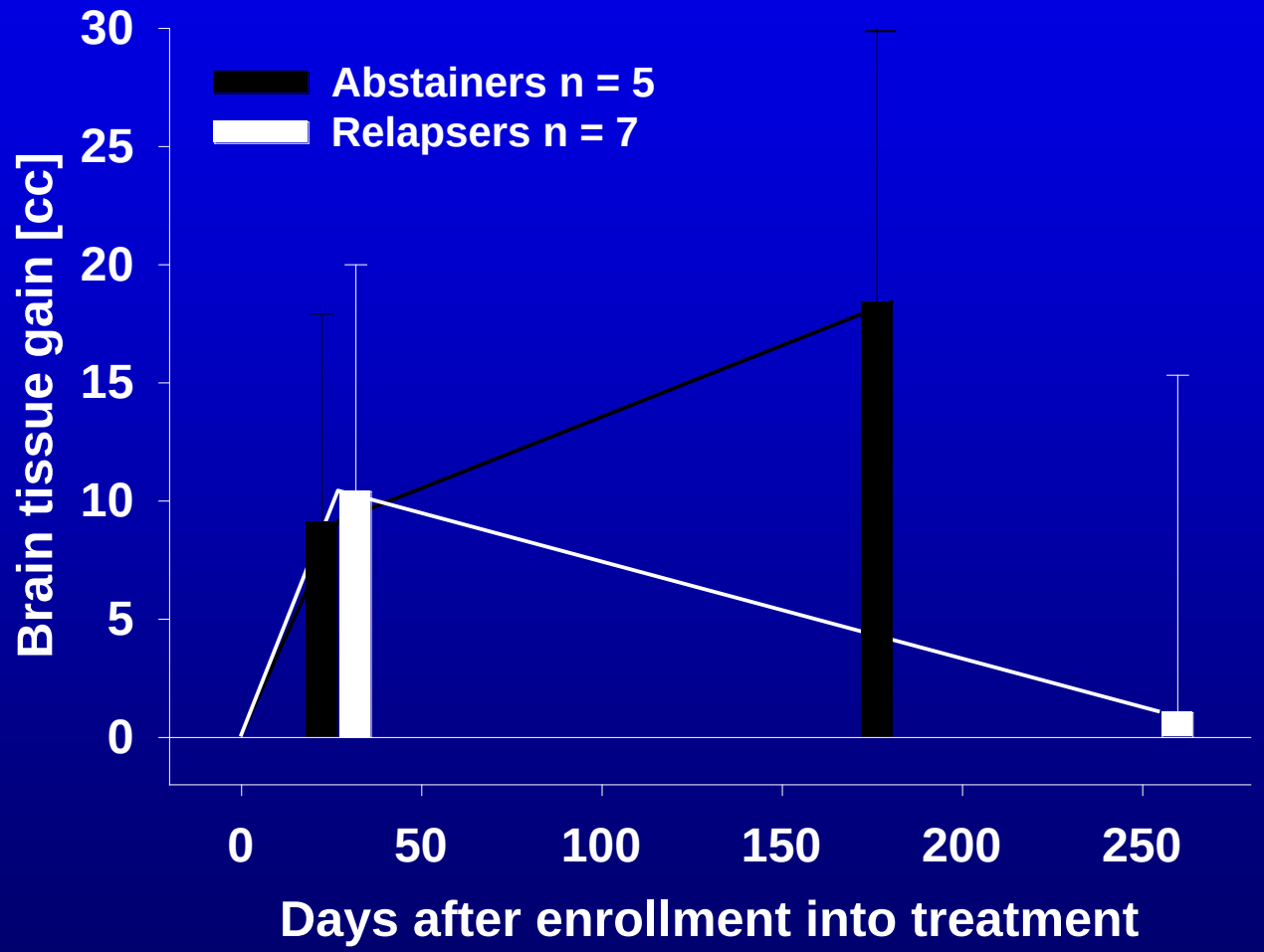
abstinent alcoholic, 8 months
ventricular and sulcal volume decreases



light social drinker, 2 years
no change

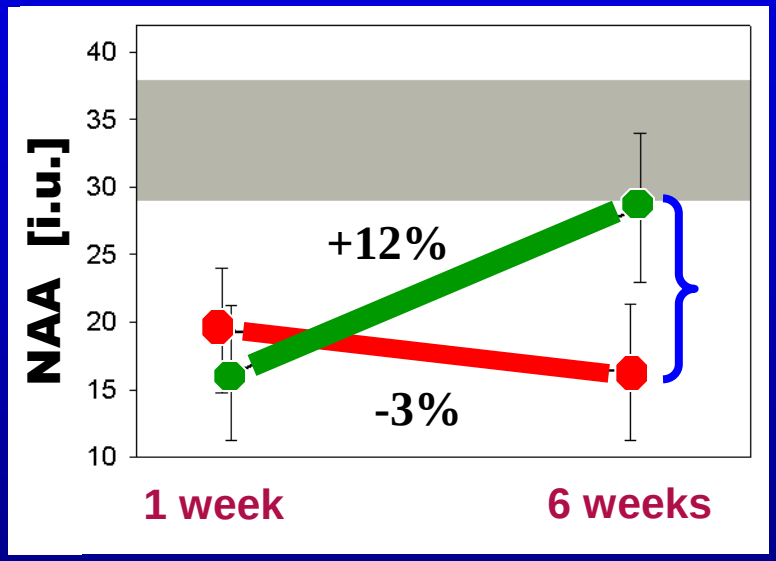
Gazdzinski et al. 2005

Structural Change in Recovering Alcoholics
entire brain tissue volume

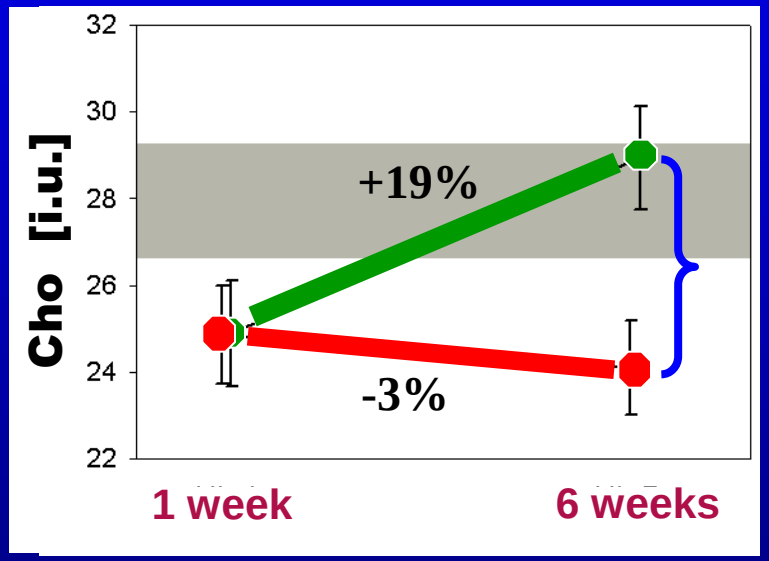


Gazdzinski et al. 2005

Metabolic Recovery in Abstinent Alcoholics
MRS of Hippocampus



control
$\bar{X} \pm SD$



NAA: Neuronal recovery in nsRA

Cho: Remyelination in nsRA

All main effects and interactions $p < .05$

nsRA n = 23

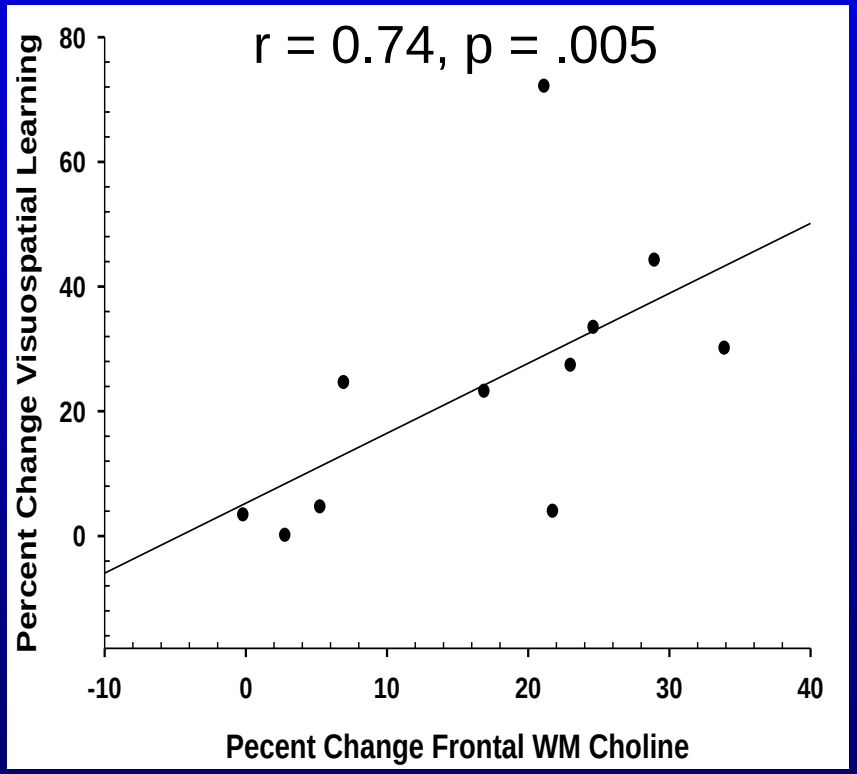
sRA n = 28

Gazdzinski et al. 2007

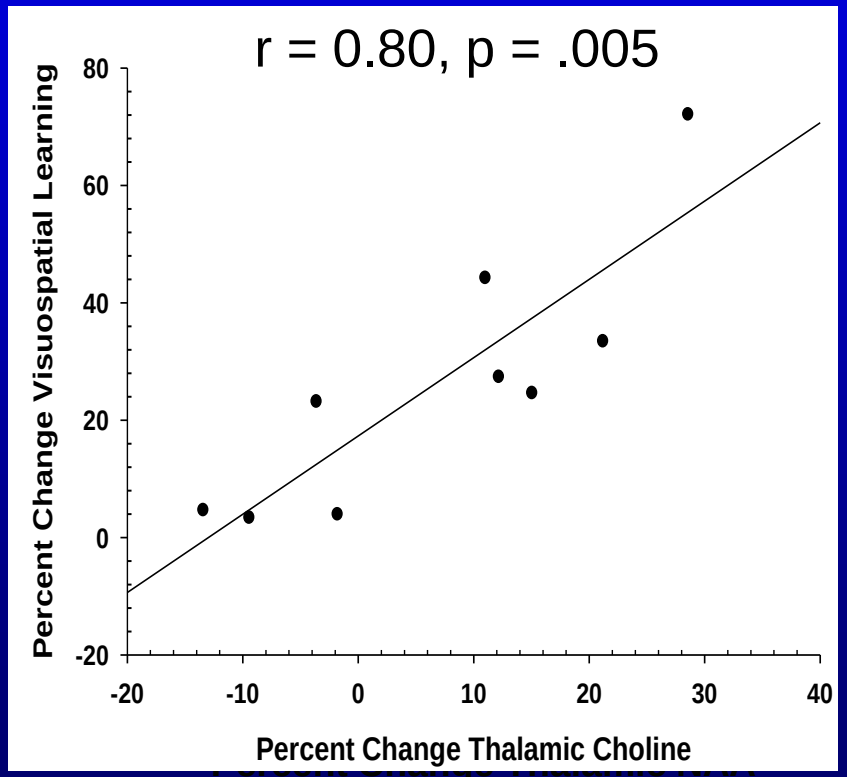
Metabolite and Cognitive **Changes** Related

non-smoking alcoholics over 5 weeks of abstinence

∆ Visuospatial Learning vs. ∆ Frontal WM Cho



∆ Visuospatial Learning vs. ∆ Thalamic Cho



Durazzo et al. Alcohol 2006, ACER 2007

What have we learned?
Brain Changes during Drug Abstinence

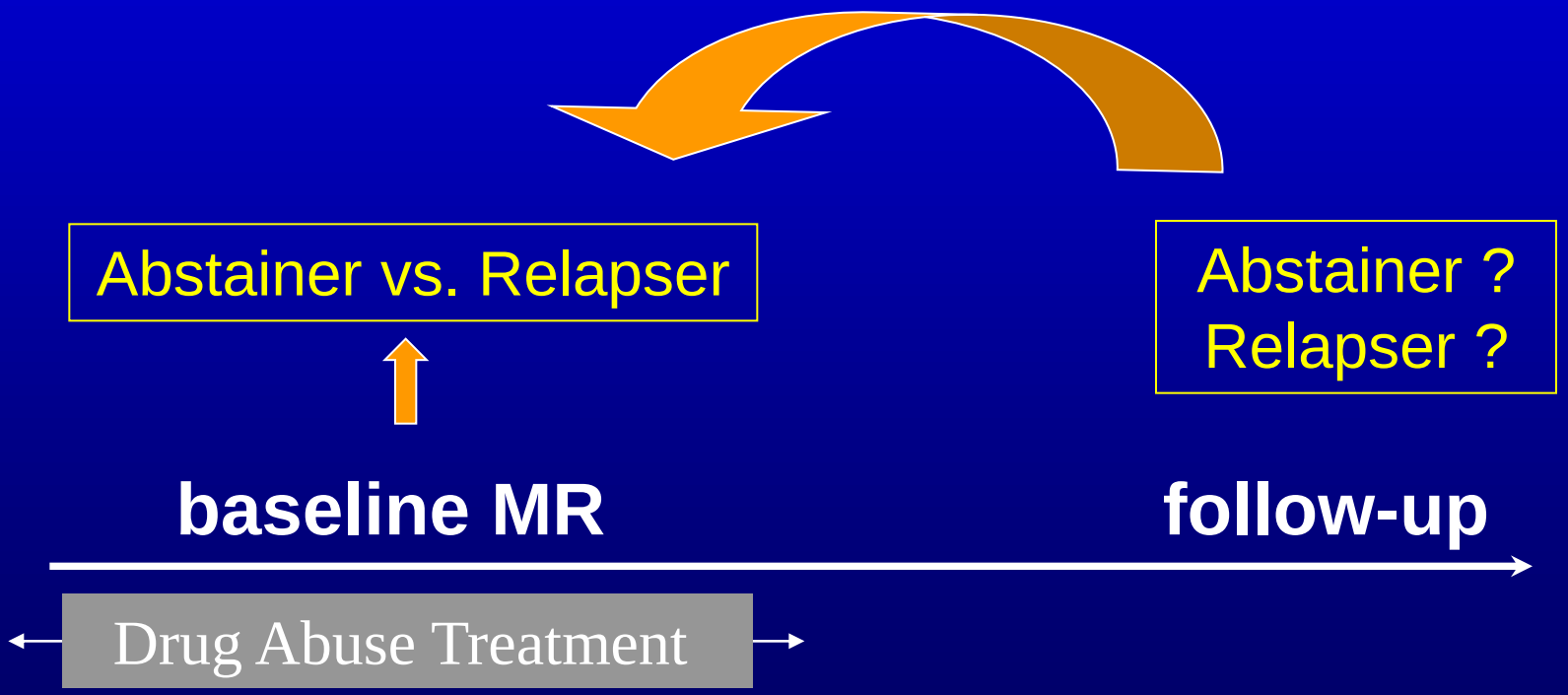
- Cognition: improvements - rapid and slow;
  ⇒ treatment outcome, quality of life;
  linked to specific neural systems/networks
- <u>Neurobiological recovery possible !</u>
- Factors affecting recovery
  - age
  - drug use severity and duration
  - stress
  - comorbidities (medical, psych, other drug use …)
  - cognition
- <u>Cigarette smoking common detriment to successful recovery</u>
  - **suppresses neuroplasticity !**

What have we learned?

- Imaging of neuroplasticity during abstinence
  - **MRI**: Brain tissue gains – rapid and slow
  - **MRS**: Neuronal recovery – slow
    Re-myelination – rapid
    Neurotransmitter rebalancing – rapid
  - **Perfusion MRI**: Improved blood flow to cortex - rapid
  - **DTI**: Repair of fiber pathways - rapid
  - **PET/SPECT**: Dopamine D2 receptor availability – very slow ⇒ lifelong relapse risk?
  - **fMRI**: Functional processing altered, amenable to change – slow

Neuroimaging and Relapse Prediction I

- Defining aspect of human addiction: Relapse
- Within 1 year, 40 - 80% of drug/alcohol abusers relapse, ~90% of cigarette smokers

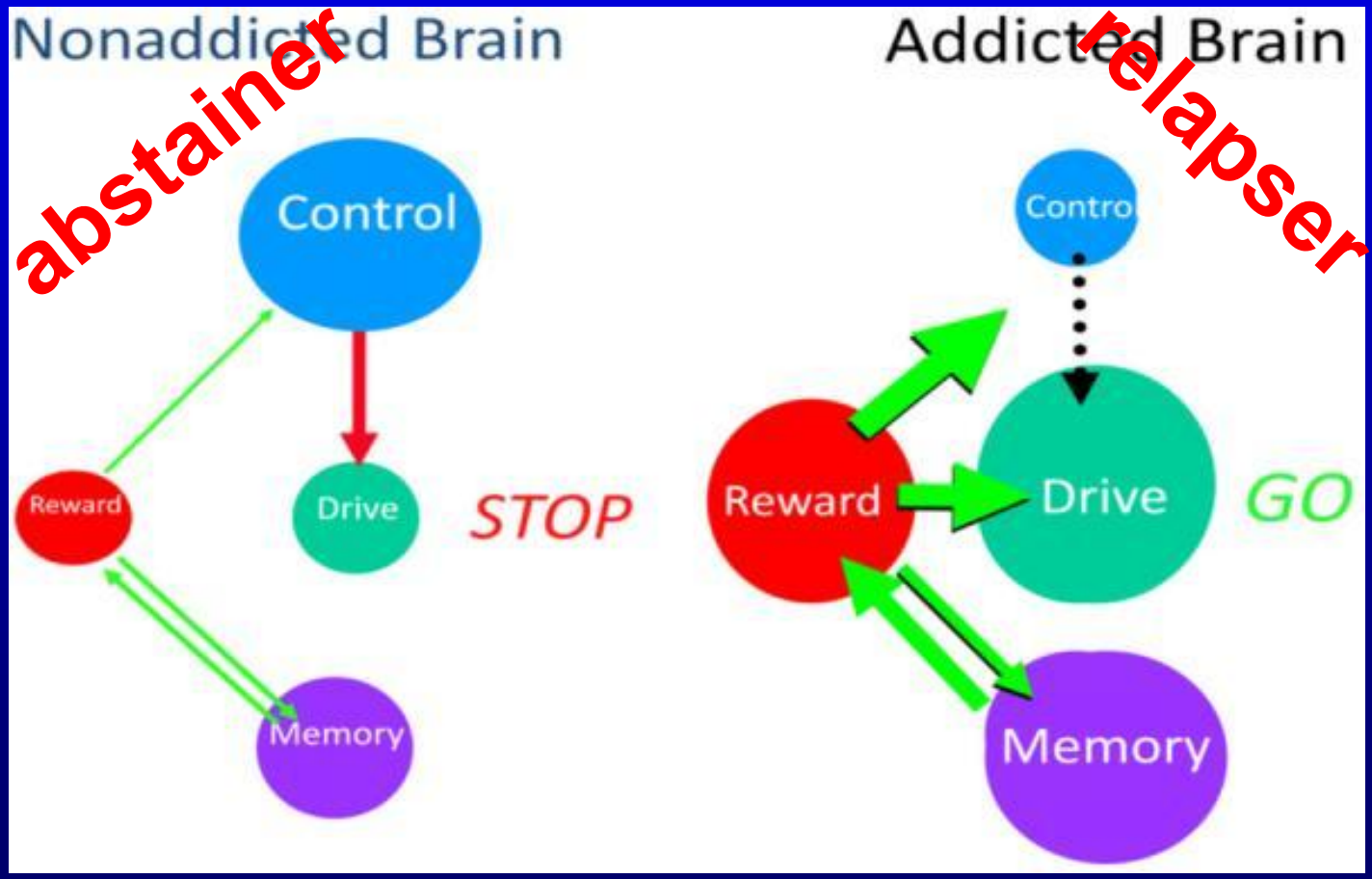


Neuroimaging and Relapse Prediction II

- Subsequent relapsers have biological abnormalities in BREOS when coming into treatment
  - **MRI:** smaller prefrontal cortex (cognitive control)
    smaller insula (salience, drive)
    smaller amygdala (learning, decision-making)
  - **MRS:** neuronal injury in prefrontal cortex, insula
  - **fMRI:** less activation in prefrontal cortex, more activation in limbic regions; greater response to drug-stimuli
  - **Perfusion MRI:** less blood flow (= function) in frontal cortex
- **Abnormal neurobiology contributes to higher risk for drinking after treatment**

What have we learned?
Networks … Circuits … Networks … Circuits

Brain Reward/Executive Oversight System (BREOS)



e.g., Volkow et al. 2003

A Fascinating Journey.

Neuroimaging and Addiction I

1. Addiction = disease with well established neural abnormalities and related cognitive deficits
2. Non-invasive, unique information; linked to cognition, behavior, clinical, genetic, environmental variables ...

   ⇒ biomarkers of addiction, recovery, relapse;
3. Organization of the brain into networks/circuits
4. Research tool that complements animal studies
5. Longitudinal neuroimaging: predisposition vs. consequence of drug use

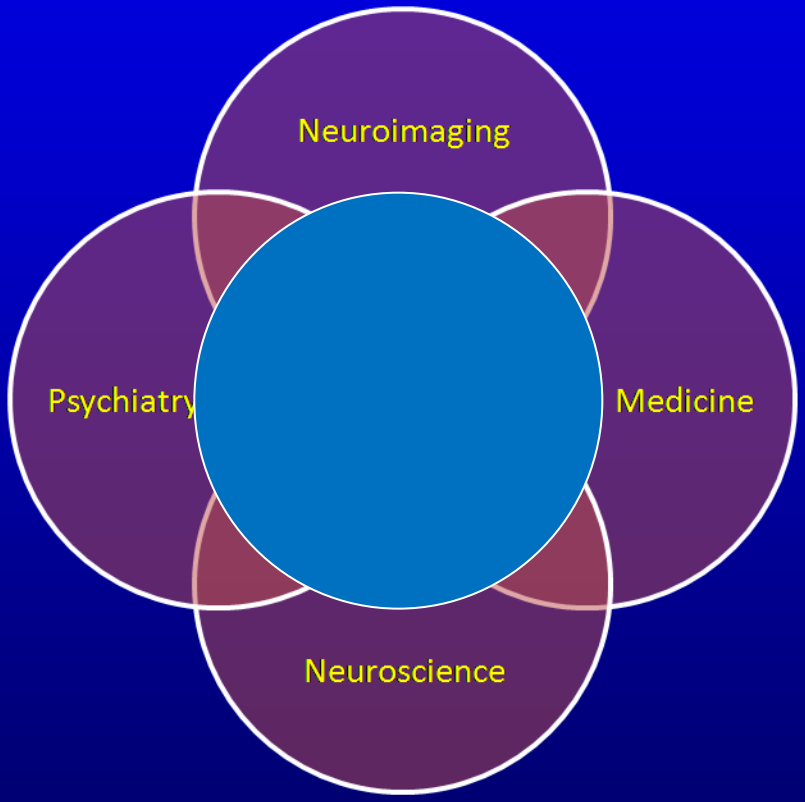
A Fascinating Journey.
Neuroimaging and Addiction II

6. Brain recovers with abstinence (plasticity), but vulnerability to relapse persists
7. Identifies those at greatest relapse risk
   ⇒ can help focus treatment resources!
8. Informs new drug treatment approaches (pharmacological and behavioral)
9. Helps identify children and adolescents, who would benefit most from prevention efforts

Where are we going?
Neuroimaging and Addiction

- Refine methods
  - acquisition, multimodal MR, network analyses, statistics
- Further neuroimaging work in relation to
  - gender
  - co-morbid disorders (depression, anxiety etc.)
  - comorbid drug use (polysubstance use !)
  - different drug use patterns
  - treatment outcome
  - development of addiction and resilience
- Translation to more effective treatment interventions and early prevention

Where are we going?



Neuroimaging and cognitive neuroscience have revolutionized psychiatry!

Together with medicine, they will advance addiction research and become clinically useful.

Thanks for listening!

Research is good medicine.