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

Dieter J. Meyerhoff, Dr.rer.nat.
Professor of Radiology and Biomedical Imaging
UCSF
Center for Imaging of Neurodegenerative Diseases (CIND/VAMC)
SF Treatment Research Center (SFTRC/LPPI)
Acknowledgements

Timothy C. Durazzo, Neuropsychologist
Assistant Professor of Radiology and Biomedical Imaging, UCSF

No disclosures.

Support from NIH AA10788 (DJM), DA025202 (DJM), DA009253 (JG), DA10399 (TCD)

Clinical personnel at SFVAMC, Kaiser Permanente SF, UCSF Treatment Research Center
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)

![Graph showing the number of Medline citations from 1960 to 2020. The citation count increases significantly from 2000 onwards.](image-url)
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

sober alcohol dependent
1 year later after resuming drinking

Hommer et al., 2001

Rosenbloom and Pfefferbaum 2008
3D MRI: Tissue Loss (Atrophy)

57 year old alcoholic

~1100 mL
ca. 1866 kg
ca. 160,000 drinks

57 year old social drinker

~1300 mL
ca. 60 kg
ca. 5,000 drinks

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 \(\rightarrow\) tissue loss
    - Drug abstinence \(\rightarrow\) tissue regeneration

- 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

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., bupropion, 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-Acetyl-Aspartate: neuronal marker
myo-Inositol: 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

-10%
p < 0.05

-10%
p < 0.05
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

MRI signal difference

cognitive activity - rest - activity - rest - ......
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)

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

www.humanconnectomeproject.org
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

Days of Abstinence

0 50 250

Scale score

6 8 10 12

p = 0.0001

n.s.

average performance of healthy controls

1 week 1 month 8 months

n = 13

Impaired … recovery

Most cognitive domains improve, except visuospatial and fine motor skills.
Cognition in Abstinent Alcoholics: Effects of Smoking

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

recover 1% brain tissue within 1 month

0 ± 0 ml/mo; n = 10

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

Brain tissue gain [cc]

- Abstainers n = 5
- Relapsers n = 7

Days after enrollment into treatment

Gazdzinski et al. 2005
Metabolic Recovery in Abstinent Alcoholics

MRS of Hippocampus

NAA: Neuronal recovery in nsRA

Cho: Remyelination in nsRA

control $\bar{x} \pm SD$

All main effects and interactions $p < .05$

Gazdzinski et al. 2007
Metabolite and Cognitive Changes Related non-smoking alcoholics over 5 weeks of abstinence

\[ \triangle \text{Visuospatial Learning vs.} \triangle \text{Frontal WM Cho} \]

\[ r = 0.74, p = .005 \]

\[ \triangle \text{Visuospatial Learning vs.} \triangle \text{Thalamic Cho} \]

\[ r = 0.80, p = .005 \]

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

- **Neurobiological recovery possible!**

- Factors affecting recovery
  - age
  - drug use severity and duration
  - stress
  - comorbidities (medical, psych, other drug use …)
  - cognition

- Cigarette smoking common detriment to successful recovery
  - 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
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 neurobiiology contributes to higher risk for drinking after treatment
What have we learned?
Networks ... Circuits ... Networks ... Circuits

Brain Reward/Executive Oversight System (BREOS)

Nonaddicted Brain

Addicted Brain

abstainer  relapser

e.g., Volkow et al. 2003
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
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.