Brain Imaging studies in substance abuse

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Costs: Health, Crime, Productivity

Costs in billions of dollars (2002)

- Drug abuse: $181B
- Alzheimer: $145B
- Cancer: $228B
- Heart: $400B

ONDGP, CDC, Lewin group

www.nida.nih.gov/Infofacts
Amphetamine abuse

Buxton J Roy Soc Medi 2000
“Chasing the dragon”
Inhaled Heroin- Spongiform leukoencephalopathy

Complications of drug abuse

ETOH/atrophy  Stroke  endocarditis  HIV dementia
Brain Imaging in Addiction research

- **Structural**
  - Morphology

- **Physiological**
  - Functional MRI
  - Positron Emission Tomography
Do drugs of abuse alter morphology?

- Area and perimeter
  - Chronic morphine $\Rightarrow$ mesolimbic DA neurons

- Cell size, cytoskeletal proteins, dendritic complexity

![Image A: Morphine](image1.png)
![Image B: Morphine](image2.png)
![Image C: Saline](image3.png)
![Image D: Saline](image4.png)
Drugs of abuse alter cell morphology

- **Where?**
  - Affects dopamine regulated circuits

- **When?**
  - Short exposure
  - Changes are persistent

- **So what?**
  - Morphology ↔ Behavior
Chronic MA ⇒ a selective pattern of cerebral deterioration with prominent effects in the limbic system (and medial temporal lobe—not shown)

Thompson 2004 J Neurosci
Brain changes are persistent

Last drug use (2 yrs)

Persistence in playing disadvantageous cards

Larger volume correlated with better cognitive performance, suggesting a compensatory response to initial neurotoxicity.

Chang et al. 2005 Biol Psych
Cocaine and White Matter: Rodent

Saline vs. Cocaine treated rats

Decreased fractional anisotropy in rodent splenium

Cocaine $\Rightarrow$ ↓ myelin basic protein

Percent Expression of MBP

Saline | Cocaine
---|---
![Saline Graph](image1.png) | ![Cocaine Graph](image2.png)

$P = 0.031$
**Cocaine and White Matter: Humans**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cocaine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rostrum</td>
<td>338 ± 40</td>
<td>369 ± 63</td>
</tr>
<tr>
<td>Genu</td>
<td>533 ± 48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>580 ± 54</td>
</tr>
<tr>
<td>Rostral body</td>
<td>361 ± 39&lt;sup&gt;a&lt;/sup&gt;</td>
<td>415 ± 62</td>
</tr>
<tr>
<td>Anterior mid-body</td>
<td>360 ± 49</td>
<td>374 ± 57</td>
</tr>
<tr>
<td>Posterior mid-body</td>
<td>357 ± 47</td>
<td>376 ± 60</td>
</tr>
<tr>
<td>Isthmus</td>
<td>385 ± 76</td>
<td>361 ± 51</td>
</tr>
<tr>
<td>Splenium</td>
<td>560 ± 46</td>
<td>564 ± 57</td>
</tr>
</tbody>
</table>

<sup>a</sup>Areas of significant reduction in cocaine-dependent subjects.
Structural abnormalities

- Result of chronic exposure?
- Precede / predispose to addiction?
- Compensatory or neurotrophic?
- What confers vulnerability to some structures or tissues?
Structural

Physiological

- Blood Oxygen Level Dependent (BOLD) fMRI
- PET
Stages of addiction

From Koob and LeMoal. Neurobiology of Addiction 2006
Acute reinforcement

- Reward circuit
  - All drugs of abuse elevate ventral striatal dopamine
3 functional divisions of the Corpus striatum:

Motor, associative, limbic
Imaging mesocorticolimbic DA reward system

- Drug infusion
- Monetary reward
- Error prediction
- Decision-making
Cocaine blocks dopamine transporter (DAT) in humans

First demonstration in humans that cocaine, at doses used by addicts

- leads to significant blockade of DAT
- this blockade is associated with rewarding effects
Mesolimbic pathway is activated by cocaine in humans

Breiter et al. Neuron 1997
fMRI signal correlates with rush (VT) and craving (Nacc)

Multiple Correlation of Rush and Craving Ratings to Cocaine fMRI Data (N=10)

**Rush:**
- NAc/SCC
- BF/GP
- Amygdala (-)
- VT
- Parahip

**Craving:**
- NAc/SCC
- BF/GP
- Amygdala
- VT
- Parahip

Figure 5. Multiple Correlation Images
Correlation images associated with rush and with craving are displayed as coronal images, respectively, in the top row and the bottom row. Each correlation map is presented as a pseudocolor p value map superimposed on a gray scale structural image. Coronal images represent slices from +15 mm, 0 mm, −18 mm, and −24 mm with respect to the anterior commissure. Regions highlighted in this figure were more strongly correlated with one behavioral measure than another and include the NAc/SCC, BF/GP, Amygdala, VT, and parahippocampal gyrus.
Dopamine reward circuit ≠ Hedonic circuit

- **Motivation**
  - Liking vs. wanting

- **Anticipation**
  - “it’s the action”

- **Prediction errors**
  - A pleasant surprise
Striatum responds to anticipation of reward and punishment

Medial caudate: anticipation of large reward OR large punishment

Nucleus accumbens: anticipation of large reward NOT large punishments

Knutson et al. J Neurosci 2001
…..Prediction error?

Fioriello, Tobler, Schultz
Science 2003
Dopamine reward prediction model

Midbrain VT DA response = Reward occurred – Reward predicted

Schultz, Dayan, & Montague 1997

Unexpected Reward

Expected Reward

Unexpected No-Reward

Schultz, Dayan, & Montague 1997
No prediction
Unexpected reward

Predict reward
Unexpected no-reward

Conditioned Stimulus
Reward

Expectation of reward

<table>
<thead>
<tr>
<th>Reward</th>
<th>No reward</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cond. Stimulus</td>
<td>Expectation of reward</td>
</tr>
</tbody>
</table>
Receiving SU Unexpected – AN greater than CW (XNO+RecSU)-(XNO+RecNO)

No prediction
Reward occurs

SVC p<0.02, FEW, FDR, Cluster

p=0.005
5vox uncorr.

Courtesy Guido Frank, MD
Reward circuitry responds to drug /sexual cues outside of awareness

- Male treatment seeking cocaine users
- Response to “backward masked” 33 ms cues

Figure 1. “Unseen” cue paradigm. 24 randomly-presented 33 msec targets in each of four categories (cocaine, sexual, aversive and neutral, interspersed with grey-screen nulls) were immediately followed by a 467 msec neutral “masking” stimulus. Under these conditions, the 33 msec stimuli can escape conscious detection (see Methods for additional task details).

doi:10.1371/journal.pone.0001506.g001

Limbic activation by unseen cues (33 ms) correlate with affectivity

“…by the time the motivational state is experienced, the limbic reward circuitry has a running start”
Stages of addiction

- Acute Reinforcement/Social Drinking
  - Escalating/Compulsive Use
    - Binge Drinking
  - Dependence
  - Withdrawal
  - Protracted Withdrawal
  - Recovery?

Genetic variables
- Environmental factors
- Stress
- Conditioning effects

From Koob and LeMoal. Neurobiology of Addiction 2006
What are neural substrates mediating withdrawal?

Tanabe, Neuropsychopharm. 2007
Thalamic CBF correlates with subjective withdrawal
Stages of addiction

From Koob and LeMoal. Neurobiology of Addiction 2006
Iowa Gambling Task

- A laboratory test measuring decision-making under conditions of uncertainty as encountered in real-life
- Ventral medial frontal (vMPFC) lesions

“Bad” decks:
- large reward, large losses
- negative long term

“Good” decks:
- Small rewards, small losses
- Positive long term
Iowa Gambling Task

Bechara 2001
Brain activity during decision-making on modified IGT

- **Anterior Cingulate**
  - Attention
  - Conflict

- **Ventral striatum**
  - Reward, expectation, reinforcement

- **Medial PFC**
  - Emotion

- **OFC/DLPFC**
  - Top down cognitive bias
Reduced activity in VMPFC and OFC in drug abusers
Modified GT performance

Net score (good - bad)

Time block

Control
SDPG
SD
Prefrontal cortex in drug addiction
Dopamine D2 receptor correlates with OFC and cingulate gyrus metabolism

Volkow

- Compulsive behavior
- Impaired Decision making
- Impaired inhibitory control
What have we learned from imaging?

- Substance dependence is associated with altered brain structure and physiology
- Observed alterations *in vivo* are generally consistent with animal models
  - Some inconsistencies: rat splenium vs. human genu
- Insights that cannot be gleaned from animals (drug cues engage limbic system outside of awareness)
What have we learned from imaging?

- Imaging studies reveal disruption to brain regions that are important for motivation, reward, executive function.
  - Support view of addiction as disease of brain and abnormal behavior as result of dysfunction of neural substrate.
Limitations

- No standardization
  - Imaging
  - Paradigms
  - Cognitive metrics
- Cross-sectional
- Brain development
  - age onset, age at time of study
- Environment
- Characterizing of drug abuse
  - severity, duration, polysubstance (non specific vs. specific)
Future studies

- Chicken or egg?
  - Study at-risk individuals who have not had drug exposure
    - At-risk youth who have not had years of drug abuse
    - Sensation or risk seeking individuals
    - Behavioral addictions
  - Study effect of acute drug

- Developmental
  - Longitudinal studies

- Multi-variate approaches
  - age, environment, stress, genes: effects on cellular adaptations