Structural and Functional Correlates of Smoking Cues and Tobacco Craving

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Disclosure Information

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Despite Health Risks Many Smokers Cannot Maintain Abstinence

Most smokers would like to quit and try to quit

(Tingen et al., 1999)

Only 7% of Smokers Using Nicotine Replacement Therapy (NRT) Maintain Abstinence for Greater Than Six Months

(Hughes et al., 2003)

At one year, cessation rates are ~20% for those treated with Varenicline

(Oncken et al., 2006)
Nicotine dependence and the brain.

- Brain regions involved in subjective craving
- Brain reactivity to smoking cues
- Individual differences
When thinking about craving...

“It is tempting to speculate that activation of cortical regions with sensory and limbic functions, along with activation of the OFC, reflects an interplay of related networks.”

(London et al., 2000)

Functional Connectivity

Brain regions with fMRI signal fluctuations that are highly temporally correlated make up a functionally connected network.

Orbital and Medial Prefrontal (OMPFC) Network
Study Timeline

- Smoking
- Craving Assessment/Resting-State Scan
- Craving Assessment/Resting-State Scan
- Resting State fMRI 1 Hour Scan Session
- As craving changes does brain connectivity?
Change in Craving

Duration: One Hour
OMPFC Network

An Increase and Craving Corresponds with An Increase in Connectivity

Graph showing the relationship between change in craving and connectivity.
Cessation Treatment and the OMPFC Network

Pre-Treatment: Brain Reactivity to Smoking Cues

Post-Treatment

Individual Differences

- How does individual variability impact craving and drug use?
Hedonic response to cigarette smoking is related to dorsal striatal dopamine release.

-Dorsal Striatum is important in maintaining habitual drug use. (See et al., 2007)


Dorsal Striatal Anatomy and Drug Use

Compared to healthy controls: Stimulant-dependent individuals AND their siblings have enlarged dorsal striatum.

Ersche et al., 2012

Striatal Volume and Stimulant Use

- Increased Striatal Volume Associated with:
  - Stimulant Dependence (Ersche et al., 2012)
  - Methamphetamine Use (Churchwell et al., 2012)
  - Lifetime Nicotine Use (Das et al., 2011)

Craving and Striatal Volume

Brief Questionnaire of Smoking Urges

Subjective Craving

- Subjective craving involves a network of brain regions.

- Current smoking cessation aids impact craving-related brain regions.

- Individual variability within this network impacts the level of craving and drug use severity.
fMRI: Brain Reactivity to Smoking Cues

Gilbert DG, Rabinovich NE (1999): International smoking image series (with neutral counterparts), version 1.2. Carbondale, IL: Integrative Neuroscience Laboratory, Department of Psychology, Southern Illinois University.
Cue Reactivity

Meta Analysis

11 Studies

The Insula and Dorsal Anterior Cingulate Cortex

- Commonly react to smoking cues
- Are part of the “salience network”
- Insula is implicated in awareness of internal states
- Dorsal Anterior Cingulate cortex (dACC) plays a role in cognitive control
The Insula and Smoking Behavior

Brain Damage Involving the Insula Disrupts Smoking Addiction

- Forget et al., 2010
- Naqvi et al, 2007

Insula inactivation reduces nicotine self-administration in rodents.

Increased Insula Reactivity to Smoking Cues Predicts Relapse Vulnerability

- Janes et al, 2010


Dorsal Anterior Cingulate Cortex (dACC) Chemistry and Cue Reactivity

Magnetic Resonance Spectroscopy
dACC GABA and Cue Reactivity

Craving, Smoking Cues, & Brain

Subjective craving involves the integration of information across brain regions.

A consistent pattern of brain activation to smoking cues is emerging, which includes activation of cortical midline structures and the insula.

Individual variability in brain structure, chemistry, and function plays a role in the development and maintenance of nicotine dependence.
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Functional MRI and Drug Addiction: Current Status and Future Promise

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Why Do People Take Drugs?

- **Withdrawal avoidance**: (Wikler) Conditioned withdrawal-avoidance
- **Hedonic theory**: (Wise and Bozarth) MCL DA system mechanisms
- **Hedonic set point**: Reward system dysregulation (Koob et al), require more drug to produce same high and less likely natural rewards experienced as rewarding; can explain tolerance and anhedonia, but not compulsivity.
- **Learning theories**: (Robinson and Berridge)- Incentive sensitization: ‘wanting’ & ‘liking’ distinct neural systems;
  - ‘wanting’ is both paired with drug cues and sensitized to them in addiction and plays dominant role in drug-taking behavior (after sensitization). ‘Wanting’ is able, if not required, to act in automatic manner (may explain compulsive use without significant enjoyment)
  - **DA as a learning signal**: While NAc DA repeatedly released following drug intake (providing for over-learning), NAc DA no longer released (DiChiara) or DA neuronal activity reduced (Schultz) with loss of novelty supporting, after over-learning, automatic, unconscious drug seeking. Thus, ‘craving’ is an addicts attempt to explain otherwise unexplainable addictive behavior (Tiffany)
A Dopamine Synapse

DA

DA Transporter

DA Receptor
Effects of Drugs on DA Levels

**AMPHETAMINE**

- Accumbens
- Time After Nicotine: 0, 1, 2, 3 hr
- % of Basal Release

**COCAINE**

- Accumbens
- Time After Cocaine: 0, 1, 2, 3, 4, 5 hr
- % of Basal Release

**MORPHINE**

- Accumbens
- Dose (mg/kg): 2.5, 5, 10
- Time After Morphine: 0, 1, 2, 3, 4, 5 hr
- % of Basal Release

**ETHANOL**

- Accumbens
- Dose (g/kg ip): 0.2, 0.5, 1, 2.5
- Time After Ethanol: 0, 1, 2, 3, 4 hr
- % of Basal Release
Natural Rewards Also Elevate DA Levels

Di Chiara et al.

Fiorino and Phillips

FOOD

% of Basal DA Output

Empty Box Feeding

NAc shell

Time (min)

100 150 200

100 150 200

SEX

DA Concentration (% Baseline)

Samples

Female 1 Present

Female 2 Present

Mounts

Intromissions

Ejaculations

Copulation Frequency

Sample Number

Scr Scr

Scr

Scr

SEX

Sex

Female 1 Present

Female 2 Present

Di Chiara et al.

Fiorino and Phillips

Natural Rewards Also Elevate DA Levels
Drug Addiction Neurocircuitry

Volkow, Koob and Baler. ACS Chem Neuro 2015
How do you study these systems in humans?
Part 2

Functional Neuroimaging (PET and MRI)
Positron Emission Tomography (PET)

- Detects the distribution of positrons (a positively charged particle with the same mass as an electron) emitting tracers in tissue.

- PET is a “true” functional imaging technique that provides metabolic, receptor or endogenous ligand information.

- PET tracers have relatively short half lives (76 sec to 110 min), and thus typically require an on-site cyclotron.

- PET is best used today to measure changes in brain chemistry

- Poor spatial and temporal resolution
- Requires administration of isotopes
- Dosimetry limits: within sessions and life
- Major advantage: neurochemistry
  - Receptor localization
  - Neurotransmitter release
Reduced DRD2 Receptors in Addiction

Volkow, N.D. et al.,
DA DR2 Level Correlates with Pleasantness to IV MP in Controls

Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant

Volkow et al
What can MRI show us about brain structure & function

**Structure**
- White matter architecture
- And integrity

**Function**
- Task-induced brain activation

**Connectivity**
- Functional connectivity between brain regions

**Biochemistry**
- Metabolite and neurotransmitter concentrations
Magnetic Resonance Imaging
Magnetic Resonance Imaging

Magnet
Magnetic Resonance Imaging
What can we see in MRI?

$T_1$ weighted images: brain structure for reconstructions of the cortical surface or as overlay images for functional activity.
CSF=dark; Brain ‘white matter=bright; gray matter=gray.

$T_2$ weighted images: used in most medical scans.
CSF= bright; gray matter is brighter than white matter

Inversion recovery scans allow for suppressing tissue with certain properties and for optimal control of the contrast.

Echo planar images: poor spatial resolution but excellent temporal resolution (1 sec or so), used for functional imaging.
What is fMRI?

- fMRI is a noninvasive imaging technology that can be used to identify regions in the brain that get activated when individuals perform certain tasks.
- In contrast to conventional MRI scans showing brain structure, fMRI provides information about brain function.
  - **Advantages**: excellent temporal (sec) and spatial (mm) resolution; no ionizing radiation; within Ss design; direct alignment of functional and anatomical data
  - **Disadvantages**: no neurochemistry (receptors/transmitters- but MRS); not ‘quantifiable’- but ASL
How does fMRI Work?

- The brain receives and processes information through electrical impulses.
- The brain does not store the energy required for processing to occur.
- Instead, the brain receives this energy in the form of $O_2$ and glucose delivered by blood flow.
- When a brain region increases its function, blood flow to that region increases to deliver the needed energy substrates.
Neuronal activity-metabolic coupling

↑ Neuronal activity (psp, ap)
↑ Ion diffusion/ion imbalance
↑ Ion pumping
↑ Energy substrate demand (glucose, O2)
↑ Vasoactive release (NO, adenosine, K+)
↑ Vasodilation
↑ rCBF, rCBV (>oxygen extraction)
↑ Hboxy/Hbdeoxy
fMRI BOLD Transduction

(Blood Oxygenation Level Dependence)

Overall ↓ deoxy Hb

dehoxy Hb- paramagnetic

Oxy-Hb diamagnetic

Increased spin coherence

Local signal using T2 or T2* weighted sequences

[Like magic—contrast without administering a contrast agent (e.g. radiation)]
Where do the fancy colors come from?
fMRI Presentation Methods

2D Slice Array

Cortical Surface Model
Some Things That Are Hard in fMRI

- Measuring neural effects that take a long time to occur (ten minutes or more)
  - Learning, adaptation; Effects of some drugs
- Measuring neural effects associated with tasks that require big subject movements
  - Continuous speech; swallowing; head movement
- Distinguishing neural events closer than ~500 ms in time
- Measuring activation in brainstem nuclei
- Measuring differences in timing or strength of neural activity between brain regions
- Characterizing individual subject phenotypes

End of Part 2
Hypothesis: Functional connectivity between MCL circuitry components and their cortical projections are both altered in dependent individuals and will predict treatment outcomes (either individual elements or in combination)
Circuits Involved In Addiction

INHIBITORY CONTROL

REWARD

MOTIVATION/DRIVE

MEMORY/LEARNING
Drug Craving

- “an irresistible urge that compels drug-seeking behavior” (Halikas et al ‘91)
- conditioned drug-like state (Childress et al)
- cognitive systems involved in cue-induced craving, such as working memory, episodic retrieval (Grant et al)
- craving as a post hoc explanation for unexplainable behavior (Tiffany et al)
- Multiple triggers: cue-induced craving (internal vs. external); drug-induced; stress-induced
People, Places and Things

CS

Environmental Cues

CR

CRAVING

Drug "High"
Cocaine Cue Craving

Users Cocaine vs. Controls Cocaine → Users Nature (population specificity)

Cocaine Craving

Cocaine Cue Craving: Summary

- Distributed pattern of activation, primarily prefrontal and limbic—presumably reflecting the cognitive and emotional processes that participate in cue-induced craving state.

- Cocaine activates normal reward/emotional circuitry
  - Cocaine use may depress normal rewards—“hijacks circuitry”—implications for addict decision making

- Majority of regions (10/13) exhibited similar responses to sexual material, implicating common circuits in drug and non-drug reactivity

- Consistent with hypothesis that craving not unique phenomenon/circuitry, but rests upon normal reward/memory/emotional circuitry
Circuits Involved In Addiction

INHIBITORY CONTROL

PFC
ACC
OFC
SCC
Hipp
NAc
VP
Amyg

REWARD

MOTIVATION/DRIVE

MEMORY/LEARNING
Significance of Inhibitory Control

- Suppression of irrelevant/interfering stimuli or impulses: fundamental executive function essential for normal thinking and is characteristic of frontal lobe development
- Failure to develop and/or loss of IC can profoundly impact ability to gate prepotent, yet inappropriate and dangerous behaviors, e.g. cocaine use
- IC deficits (disinhibited behavior and loss of self-control) implicated in pathological gambling, ADHD, Tourette’s syndrome, OCD, some traumatic brain injuries
- Pharmacological effects of cocaine on MCL DA system insufficient to explain cognitive deficits often seen in chronic drug abusers (e.g. impaired attention, memory and IC reported; Goldstein et al)
- Cocaine users show decreased frontal, cingulate, insula and superior temporal gray matter and decreases in cingulate and OFC metabolism

Functional Implications and Involvement in drug abuse ??
Inhibitory Control Task

1000 msec ISI (600-900 msec variable on-time)

Respond (GO)

Inhibit Response (NOGO)

Inhibitory Control

Successful Inhibitions


Errors: U<C: R. MFG/preSMA, ACC, L. insula, L. IFG

Stops: U<C: ACC, Rt. insula
Inhibitory Control

Cocaine and Response Inhibition

- ACC, area critical for cognitive control esp. in urgent inhibitions, less responsive in USERS for STOPS and ERRORS

- STOP related hypoactivity in R insula and rostral ACC, emotional processing areas, not in other IC areas, suggests hypoactivity not ubiquitous but specific

- ACC also hypoactive in Scz (failure to monitor and integrate) and hyperactive in OCD (overactive monitoring) -consistent with problems in error monitoring system
Clinical Implications

- Hypoactivity in USERS: reduced IC, diminished action monitoring, reduced responsivity to self errors—may serve to prolong drug abuse.

- Suggests USERS may be compromised in endogenous control of behavior; thus behavior disproportionately determined by environmental contingencies, cues (drug craving cues) and automatic behaviors leading to reduced capacity to inhibit external influences.

- May inform therapeutic interventions and help identify casual users most at risk for becoming dependent.
Why Is Addiction So Resistant to Treatment?

- A poor understanding of the ‘addicted’ human brain and the complex actions of a drug on, and neuroplastic consequences to, various circuits and neurobiological mechanisms, underlie the failure to develop efficacious treatments (mostly still rely on a symptoms check list).

- How to study neuroplasticity in humans??
  - **Identify state/trait phenotypic alterations within core neurobehavioral systems** such as attention, inhibitory control and reward processes that can be used as potential ‘indirect’ biomarker targets in drug discovery and smoking interventions

  - **Identify key brain circuits/networks that underlie addiction**, with the working hypothesis that such circuits will provide concrete **biomarkers** for new therapeutic developments

How to measure circuits in humans?
Resting-State Functional Connectivity

- Synchronized, low-frequency fMRI fluctuations obtained during the ‘resting-state’
- Used to assess functional connectivity between brain areas
- May be useful to follow chronic drug-induced plasticity
Why should RSN reflect ‘interesting’ brain activity?

- Task induced brain activity assumes all neural function directed towards immediate behavior.
- Much of brain activity may be functional, adaptive, processing information BUT not directed towards immediate behavior.
  - Functional processes may have evolved to occur over longer time scales, rather than immediate goals.
- While clearly need to solve immediate tasks, most time spent consolidating past, stabilize brain ensembles and prepare organism for the future, which may be the majority of brain function?
- If true, then studying I/O functions of brain may miss an (the) most important function of brain, which may be revealed in distant behaviors or processing modifications that accumulate gradually over time.

Buckner and Vincent, 2007
Nicotine Addiction vs. Nicotine Action

- In addition to its addictive properties, nicotine improves performance on a wide variety of cognitive tasks, requiring different brain circuits, including attention, visual information processing, computational abilities, prepulse inhibition, vigilance, and working memory.
- Due to its synaptic localization, nicotine may exert a modulatory influence on multiple brain networks independent of any specific task.
- Cingulate has been implicated as a common target for nicotine (and other abused drugs) and may be a convergent region pivotal for nicotine’s diverse effects:
  - High concentrations of nicotinic binding sites in the cingulate (Nyback et al. 1989)
  - Nicotine dose dependently increased activity in cingulate (Stein et al. 1998)
  - Nicotine improves sustained attention by increasing activation in posterior cingulate (Lawrence et al. 2002)
  - Nicotine improves working memory by either enhancing (Ernst et al. 2001) or reducing (Kumari et al. 2003) cingulate activation.

Hypothesis: nicotine as both a trait and state will alter cingulate circuitry independent of any particular behavioral condition.
Functional Connectivity Maps for each Lt Cingulate ROI

Hong et al. Arch Gen Psych, 2009
Correlations Between FTND and dACC- Striatal Connectivity

Negative correlation between FTND and:

a/b) Lt dACC to bilateral striatum

c) Rt dACC to Rt striatum

Not affected by [nicotine], smoking duration or amount (pack-years), gender or age
Cocaine Dependence & Functional Connectivity

- Alterations in DRD2, OFC metabolism, NAA, glu, OFC/ACC gray matter, functional activity (e.g. IC)
- Loss of drug taking control, behavioral rigidity (esp learned reward associations, ie reversal learning), reward disturbances, mood disturbances-- all emphasize elements within the MCL
- Preclinical data also point to MCL dysfunction (e.g. NAcc, OFC), perhaps leading to changes in hedonic ‘set point’ (Koob)
- Connectivity strength at rest related to subsequent task behavioral performance and BOLD activation.

Hypothesis: resting-state brain connectivity between components of the MCL reward circuitry is altered in people who chronically abuse cocaine
Cocaine Dependence & Functional Connectivity

Gu et al. 2010

No changes from NAcc seed

Results in HC generally consistent with known anatomical pathways
Decreased rsFC in Cocaine Users

Functional connectivity DECREASED in MCL circuits (but not motor or auditory): dysfunctions might underlie behavioral alterations seen in cocaine dependent individuals?:

- Amygdala to mPFC: necessary for reversal learning
- VTA to thalamus/MD thalamus to Striatum: thal lesions dec cocaine SA; hypoactive in CU during visual attention task; serve as an important center of integration of networks that underlie the ability to modulate behaviors) (Haber and Calzavara, 2009)
- rACC to amygdala/hippocampus: related to response rigidity to drug related stimuli and the difficulty in unlearning current drug association?
- rACC to insula: reversal learning (Jocham et al, 2009); reward circuit recruitment (Clark et al 2009)

Data suggest possible difficulty in appropriately activating reward, learning & emotional circuitry in cocaine dependent individuals & invite new hypotheses for cocaine dependence & treatment

Gu et al. NeuroImage
Circuits Involved In Addiction

- **INHIBITORY CONTROL**
  - PFC
  - ACC
  - OFC
  - SCC
  - Hipp

- **MOTIVATION/DRIVE**
  - NAc
  - VP
  - Amyg

- **MEMORY/LEARNING**
Impulsivity & Compulsivity: Key Addiction Traits

Hypothesis

♦ Cocaine users (CUs) will have altered striatal-cortical rsFC, compared to HC

♦ Based on phenotypic similarities with OCD and nicotine dependence, CUs will have increased rsFC in striatal-iPFC (“go”) circuit as well as reduced rsFC in striatal-dACC (“stop”) circuit

♦ Balance between “go” and “stop” circuits will predict drug use compulsive behaviors
Striatal rsFC patterns

Hu et al JAMA Psych 2015
Striatal rsFC in Cocaine Dependence

Hu et al JAMA Psych 2015
Striatal Connectivity and IMPULSIVITY

**Correlation Results**

- **Current Use vs. rDC-IDLPFC**
  - Correlation coefficient: 0.272
  - p-value: 0.046

- **BIS vs. rDC-IDLPFC**
  - Correlation coefficient: 0.586
  - p-value: 0.007

- **Current Use vs. rDC-rDLPFC**
  - Correlation coefficient: 0.339
  - p-value: 0.012

- **BIS vs. rDC-rDLPFC**
  - Correlation coefficient: 0.485
  - p-value: 0.022
Striatal Connectivity and COMPULSIVITY: a dual process perspective

Hu et al JAMA Psych 2015
Significance

- Compulsive cocaine use, a defining characteristic of dependence, is associated with a imbalance of *increased* striatal-inferior PFC ("GO") and *decreased* striatal-dorsal ACC ("STOP") connectivity

- Impulsivity, both a risk factor for and a consequence of cocaine use, is associated with *increased* dorsal striatal-dlPFC connectivity uniquely in CU
The folks in the lab who REALLY did the work

Supported by NIDA-IRP
Can Striatal rsFC serve as a biomarker of cocaine treatment outcome?

- In humans, cocaine associated cues engage ventral and dorsal striatum plus a distributed network of cortical structures – dIPFC, OFC, ACC, PCC and insula
- Altered striatal function and hypo-frontality considered key neurobiological substrates of compulsive cocaine use
- Altered cortico-striatal functioning are also implicated in high trait impulsivity, characteristic of cocaine-addicted individuals
- No previous data on these circuits and treatment outcome prediction
- Striatal circuit seeds: NAc, Caudate, Putamen

Hypotheses:
Differences in cortico-striatal connectivity strength will:
1. emerge as a function of cocaine-addiction status
2. be most pronounced in individuals at greatest risk of relapse
3. contribute to higher impulsivity in cocaine-addicted individuals
Design

Pre-discharge assessment
6-min resting scan in final week of treatment
Neurocognitive/clinical assessment within a week of scan:

- Iowa Gambling Task
- Wisconsin Card Sorting Task
- Trail Making task
- NEO-PI
- Temperament and Character Inventory
- Cocaine Craving Questionnaire
- Obsessive Compulsive Cocaine Use Scale

Post-discharge assessment
Followed for 24 weeks post-treatment
Weekly interview and urine drug screen

Two groups – Status at day 30 post-treatment (DSM-IV for early remission)
Relapse – relapsed during first 30 days (n=24)
Non-Relapse – still abstinent at day 30 (n=21)
Putamen-Insula rsFC Predicts Relapse

No relationship between striatal connectivity and:

- Years of education;
- Years of smoking;
- cpd; Days of cocaine use;
- Amount spent on cocaine in last 90 days;
- Lifetime days cocaine use.

McHgh et al 2013
The putamen-pl circuit is related to trait impulsivity
CANNABIS ABSTINENCE - RELATIONSHIP TO NEURAL ACTIVITY

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Cannabis-Use Disorder (CUD)

- Cannabis is abused worldwide\(^1\)
  - psychiatric comorbidities, cognitive decline\(^2,3\)

- Significant public health problem
  - 6.3% lifetime prevalence of CUD\(^4\)

- Rates of use in the USA doubled from 2001-2002 and 2012-2013\(^5\)
  - Perception of cannabis as harmless increasing\(^4\)

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Treatments for Cannabis-Use Disorder

- No approved pharmacotherapy

- Behavioral treatments moderately effective
  - Cognitive behavioral therapy, contingency management, motivational enhancement therapy

- Efficacies are highly variable across individuals
  - Neurobiology of abstinence not well understood

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Question:

Are individual differences in pre-treatment neural function* and structure related to differences in treatment outcomes?
Neural Processing of Reward

- Altered in drug and behavioral addictions\(^1\)
- Caudate and putamen central hubs of reward-processing
  - Craving for marijuana\(^2,3\)
  - Reward learning, habit formation\(^4,5\)
- May contribute to acquisition of skills during treatment

Approach

- RCT of behavioral tx for cannabis-use disorder
  - CBT alone and in conjunction with contingency management

- 20 individuals scanned before treatment
  - Structure: high-resolution T1-weighted imaging
  - Function: monetary incentive delay task

- Compare abstinent versus non-abstinent individuals
Monetary Incentive Delay Task


## Demographics

<table>
<thead>
<tr>
<th></th>
<th>MJ (n = 20)</th>
<th>HC (n = 20)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean 26.65, St. Error 2.19</td>
<td>Mean 29.2, St. Error 2.25</td>
<td>0.66</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Shipley IQ</strong></td>
<td>Mean 93.1, St. Error 2.86</td>
<td>Mean 108.42, St. Error 2.36</td>
<td>16.85</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>20 (100.00%)</td>
<td>20 (100.00%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
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</tr>
<tr>
<td>African American</td>
<td>12 (60.00%)</td>
<td>7 (35.00%)</td>
<td>7.87</td>
<td>0.05</td>
</tr>
<tr>
<td>Caucasian</td>
<td>5 (25.00%)</td>
<td>13 (65.00%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (5.00%)</td>
<td>0 (0.00%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biracial</td>
<td>2 (10.00%)</td>
<td>0 (0.00%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Married/Serious</strong></td>
<td>1 (5.00%)</td>
<td>1 (5.00%)</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Employed</strong></td>
<td>10 (50.00%)</td>
<td>7 (63.16%)</td>
<td>0.69</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Tobacco user</strong></td>
<td>15 (75.00%)</td>
<td>2 (10.00%)</td>
<td>17.29</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Defining Abstinence

- Treatment responders: 21 or more days of consecutive abstinence
  - Predictive of longer-term abstinence following treatment\(^1,2\)
- 13 achieved abstinence (65%)
  - More days in treatment, more cannabis-negative urines, lower post-treatment ASI scores
  - More total days of abstinence at 1-year FU (Abstinent: 70% days abstinent; Non-abstinent: 33% days abstinent)

### Pre-Treatment Substance-Use

<table>
<thead>
<tr>
<th></th>
<th>Abstinent (n = 13)</th>
<th>Not Abstinent (n = 7)</th>
<th>F</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>St. Error</td>
<td>Mean</td>
<td>St. Error</td>
</tr>
<tr>
<td>Years of cannabis use</td>
<td>14.38</td>
<td>3.33</td>
<td>8.72</td>
<td>1.89</td>
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<tr>
<td>Age of 1st cannabis use</td>
<td>13.38</td>
<td>0.46</td>
<td>12.12</td>
<td>0.59</td>
</tr>
<tr>
<td>Pre-tx cannabis use (days)</td>
<td>16.15</td>
<td>2.69</td>
<td>20.14</td>
<td>4.05</td>
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<tr>
<td>Pre-tx alcohol use (days)</td>
<td>4.15</td>
<td>1.49</td>
<td>3.43</td>
<td>1.38</td>
</tr>
<tr>
<td>ASI cannabis</td>
<td>0.24</td>
<td>0.04</td>
<td>0.33</td>
<td>0.13</td>
</tr>
<tr>
<td>ASI alcohol</td>
<td>0.04</td>
<td>0.01</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>ASI other drug</td>
<td>0.02</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
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</tbody>
</table>

*No differences in co-occurring disorders (depression, anxiety)

**No differences in type of behavioral therapy received
Cannabis-Use Disorder vs Healthy Controls

Whole-brain, cluster-level corrected (pFWE<.01)
Relationship to Abstinence

HC Healthy Control, MJ Cannabis-Use

MJ- Abstinent, MJ+ Not Abstinent

[Graph showing the relationship between abstinence and caudate activity for HC, MJ, and MJ+ groups.]
FSL-FIRST: Automated Segmentation

Anatomical caudate and putamen ROIs
Caudate and Putamen Volume

HC Healthy Control, MJ Cannabis-Use

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HC Healthy Control, MJ Cannabis-Use

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Relationship to Abstinence

MJ- Abstinent, MJ+ Not Abstinent

MJ- Abstinent, MJ+ Not Abstinent
Summary

- No differences in striatal function or structure between HCs and individuals who later achieved abstinence.
- Individuals who did not later achieve abstinence:
  - Increased caudate activity
  - Decreased putamen volumes
- Abstinent and non-abstinent patients did not differ in pretreatment cannabis-use, demographic/psychiatric variables, type of treatment.
Conclusions

- Ability to achieve abstinence may partially depend on pretreatment striatal characteristics:
  - Craving, reward learning, habit formation\textsuperscript{1-4}
- Heightened functional engagement accompanied by decreased structural volume
  - Influence the acquisition of new adaptive skills – CBT
  - Reward-related (contingency) learning - CM

\textsuperscript{1}Cousijn et al. (2013) Addict Biol 18, 570-580;
\textsuperscript{2}Goldman et al. (2013) J Addict Med 7, 8-16;
\textsuperscript{3}Yin et al. (2004) Eur J Neurosci 19, 181-189;
\textsuperscript{4}Schönberg et al. (2007) 27, 12860-12867;
Can fMRI predict cannabis abstinence?

Treatment expectations

Ongoing alcohol and drug-use

Changes in reward processing

Treatment

Abstinence

Baseline cognitive functioning

Skill acquisition

Not yet...
Acknowledgments and Funding

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**Co-Authors:** EE Devito, H Kober, PD Worhunsky, KM Carroll, MN Potenza.
Functional MRI and Drug Addiction: Current Status and Future Promise

Elliot A. Stein, Ph.D.
NIDA-IRP
ASAM State of the Art Course
October 8, 2016
Disclosure Information

Elliot Stein, Ph.D.
No Disclosures
Why Do People Take Drugs?

- **Withdrawal avoidance**: (Wikler) Conditioned withdrawal-avoidance

- **Hedonic theory**: (Wise and Bozarth) MCL DA system mechanisms

- **Hedonic set point**: Reward system dysregulation (Koob et al), require more drug to produce same high and less likely natural rewards experienced as rewarding; can explain tolerance and anhedonia, but not compulsivity.

- **Learning theories**: (Robinson and Berridge)- Incentive sensitization: ‘wanting’ & ‘liking’ distinct neural systems;
  - ‘wanting’ is both paired with drug cues and sensitized to them in addiction and plays dominant role in drug-taking behavior (after sensitization). ‘Wanting’ is able, if not required, to act in automatic manner (may explain compulsive use without significant enjoyment)
  - **DA as a learning signal**: While NAc DA repeatedly released following drug intake (providing for over-learning), NAc DA no longer released (DiChiara) or DA neuronal activity reduced (Schultz) with loss of novelty supporting, after over-learning, automatic, unconscious drug seeking. Thus, ‘craving’ is an addicts attempt to explain otherwise unexplainable addictive behavior (Tiffany)
A Dopamine Synapse
Effects of Drugs on DA Levels

Di Chiara and Imperato

Course in Addiction Medicine
Natural Rewards Also Elevate DA Levels

**FOOD**

- NAc shell
- Empty Box
- Feeding

**SEX**

- DA Concentration (% Baseline)
- Copulation Frequency

Di Chiara et al.

Fiorino and Phillips
Drug Addiction Neurocircuitry

Volkow, Koob and Baler. ACS Chem Neuro 2015
How do you study these systems in humans?
Part the second

Functional Neuroimaging

(PET and MRI)
Detects the distribution of positrons (a positively charged particle with the same mass as an electron) emitting tracers in tissue. PET is a “true” functional imaging technique that provides metabolic, receptor or endogenous ligand information. PET tracers have relatively short half lives (76 sec to 110 min), and thus typically require an on-site cyclotron. PET is best used today to measure changes in brain chemistry.

- Poor spatial and temporal resolution
- Requires administration of isotopes
- Dosimetry limits: within sessions and life
- Major advantage: neurochemistry
  - Receptor localization
  - Neurotransmitter release
Reduced DRD2 Receptors in Addiction

Cocaine
Obesity
Methamphetamine
Alcohol

Volkow, N.D. et al., *Addict*. 2014

DARPA: State of the Art

Course in Addiction Medicine
DA DR$_2$ Level Correlates with Pleasantness to IV MP in Controls

Subjects with low receptors report MP as pleasant and those with high receptors as unpleasant

Volkow et al
What can MRI show us about brain structure and function

Structure
- White matter architecture
- And integrity

Function
- Task-induced brain activation

Connectivity
- Functional connectivity between brain regions

Biochemistry
- Metabolite and neurotransmitter concentrations
Magnetic Resonance Imaging
Magnetic Resonance Imaging
Magnetic Resonance Imaging
What can we see in MRI?

T₁ weighted images: brain structure for reconstructions of the cortical surface or as overlay images for functional activity.
CSF=dark; Brain ‘white matter=bright; gray matter=gray.

T₂ weighted images: used in most medical scans.
CSF= bright; gray matter is brighter than white matter

Inversion recovery scans allow for suppressing tissue with certain properties and for optimal control of the contrast.

Echo planar images: poor spatial resolution but excellent temporal resolution (1 sec or so), used for functional imaging.
What is fMRI?

- fMRI is a noninvasive imaging technology that can be used to identify regions in the brain that get activated when individuals perform certain tasks.
- In contrast to conventional MRI scans showing brain structure, fMRI provides information about brain function.

- **Advantages**: excellent temporal (sec) and spatial (mm) resolution; no ionizing radiation; within Ss design; direct alignment of functional and anatomical data
- **Disadvantages**: no neurochemistry (receptors/transmitters- but MRS); not ‘quantifiable’- but ASL
How does fMRI Work?

- The brain receives and processes information through electrical impulses.
- The brain does not store the energy required for processing to occur.
- Instead, the brain receives this energy in the form of $O_2$ and glucose delivered by blood flow.
- When a brain region increases its function, blood flow to that region increases to deliver the needed energy substrates.
Neuronal activity-metabolic coupling

↑Neuronal activity (ypsum, ap)
↑Ion diffusion/ion imbalance
↑ion pumping
↑energy substrate demand (glucose, O₂)
↑vasoactive release (NO, adenosine, K+)
↑vasodilation
↑rCBF, rCBV (>oxygen extraction)
↑Hb_{oxy}/Hb_{deoxy}
fMRI BOLD Transduction

(Blood Oxygenation Level Dependence)

Overall ↓ deoxy Hb

deoxy Hb - paramagnetic

Oxy-Hb diamagnetic

Increased spin coherence

Local signal using T2 or T2* weighted sequences

[Like magic—contrast without administering a contrast agent (e.g. radiation)]
Where do the fancy colors come from?
fMRI Presentation Methods

2D Slice Array

Cortical Surface Model
Some Things That Are Hard in fMRI

- Measuring neural effects that take a long time to occur (ten minutes or more)
  - Learning, adaptation; Effects of some drugs
- Measuring neural effects associated with tasks that require big subject movements
  - Continuous speech; swallowing; head movement
- Distinguishing neural events closer than ~500 ms in time
- Measuring activation in brainstem nuclei
- Measuring differences in timing or strength of neural activity between brain regions
- Characterizing individual subject phenotypes

End of Part 2
**Cortico-Striatal Circuitry and Drug Addiction**

Hypothesis:

Functional connectivity between MCL circuitry components and their cortical projections are both altered in dependent individuals and will predict treatment outcomes (either individual elements or in combination).
Circuits Involved In Addiction

- PFC
- ACC
- OFC
- SCC
- Hipp
- NAc
- VP
- Amyg

INHIBITORY CONTROL

REWARD

MOTIVATION/DRIVE

MEMORY/LEARNING

VTA
Drug Craving

- “an irresistible urge that compels drug-seeking behavior” (Halikas et al ‘91)
- conditioned drug-like state (Childress et al)
- cognitive systems involved in cue-induced craving, such as working memory, episodic retrieval (Grant et al)
- craving as a post hoc explanation for unexplainable behavior (Tiffany et al)
- Multiple triggers: cue-induced craving (internal vs. external); drug-induced; stress-induced
People, Places and Things

CS  Environmental Cues  CR

Drug "High"

CRAVING
Cocaine Cue Craving

Figure 2

A

Parietal cx

B

Ant/post cingulate

 USERS COCAINE > CONTROLS COCAINE =/> USERS NATURE (population specificity)

Garavan et al Am. J. Psych 2000
Cocaine Craving
Population (Controls, Cocaine Users) x Film (Cocaine, Erotic)

Cocaine Cue Craving: Summary

- Distributed pattern of activation, primarily prefrontal and limbic—presumably reflecting the cognitive and emotional processes that participate in cue-induced craving state.

- Cocaine activates normal reward/emotional circuitry
  - Cocaine use may depress normal rewards—“hijacks circuitry”—implications for addict decision making

- Majority of regions (10/13) exhibited similar responses to sexual material, implicating common circuits in drug and non-drug reactivity

- Consistent with hypothesis that craving not unique phenomenon/circuitry, but rests upon normal reward/memory/emotional circuitry
Circuits Involved In Addiction

INHIBITORY CONTROL

PFC
ACC
OFC
SCC
Hipp
NAc
VP
Amyg

REWARD

MOTIVATION/DRIVE

MEMORY/LEARNING

Course in Addiction Medicine
Significance of Inhibitory Control

- Suppression of irrelevant/interfering stimuli or impulses: fundamental executive function essential for normal thinking and is characteristic of frontal lobe development
- Failure to develop and/or loss of IC can profoundly impact ability to gate prepotent, yet inappropriate and dangerous behaviors, e.g. cocaine use
- IC deficits (disinhibited behavior and loss of self-control) implicated in pathological gambling, ADHD, Tourette’s syndrome, OCD, some traumatic brain injuries
- Pharmacological effects of cocaine on MCL DA system insufficient to explain cognitive deficits often seen in chronic drug abusers (e.g. impaired attention, memory and IC reported; Goldstein et al)
- Cocaine users show decreased frontal, cingulate, insula and superior temporal gray matter and decreases in cingulate and OFC metabolism

Functional Implications and Involvement in drug abuse ??
Inhibitory Control Task

Inhibitory Control

Successful Inhibitions

Failed Inhibitions

Inhibitory Control

Cocaine and Response Inhibition

- **ACC**, area critical for cognitive control esp. in urgent inhibitions, less responsive in USERS for STOPS and ERRORS

- STOP related hypoactivity in R insula and rostral ACC, emotional processing areas, not in other IC areas, suggests hypoactivity not ubiquitous but specific

- ACC also hypoactive in Scz (failure to monitor and integrate) and hyperactive in OCD (overactive monitoring) - consistent with problems in error monitoring system
Clinical Implications

- Hypoactivity in USERS: reduced IC, diminished action monitoring, reduced responsivity to self errors, serve to prolong drug abuse

- Suggests USERS may be compromised in endogenous and volitional control of behavior; behavior disproportionately determined by environmental contingencies, cues (drug craving cues) and automatized or habitual behaviors leading to reduced capacity to inhibit external influences.

- May inform optimal therapeutic interventions and help identify casual users most at risk for becoming dependent.
Why Is Addiction So Resistant to Treatment?

- A poor understanding of the ‘addicted’ human brain and the complex actions of a drug on, and neuroplastic consequences to, various circuits and neurobiological mechanisms, underlie the failure to develop efficacious treatments (mostly still rely on a symptoms check list).

- How to study neuroplasticity in humans??
  - Identify state/trait phenotypic alterations within core neurobehavioral systems such as attention, inhibitory control and reward processes that can be used as potential ‘indirect’ biomarker targets in drug discovery and smoking interventions
  - Identify key brain circuits/networks that underlie addiction, with the working hypothesis that such circuits will provide concrete biomarkers for new therapeutic developments

How to measure circuits in humans?
RESTING-STATE FUNCTIONAL CONNECTIVITY

- Synchronized, low-frequency fMRI fluctuations obtained during the ‘resting-state’
- Used to assess functional connectivity between brain areas
- May be useful to follow chronic drug-induced plasticity
Why should RSN reflect ‘interesting’ brain activity?

- Task induced brain activity assumes all neural function directed towards immediate behavior.

- Much of brain activity may be functional, adaptive, processing information BUT not directed towards immediate behavior.
  - Functional processes may have evolved to occur over longer time scales, rather than immediate goals.

- While clearly need to solve immediate tasks, most time spent consolidating past, stabilize brain ensembles and prepare organism for the future, which may be the majority of brain function?

- If true, then studying I/O functions of brain may miss an (the) most important function of brain, which may be revealed in distant behaviors or processing modifications that accumulate gradually over time.

Buckner and Vincent, 2007
Nicotine Addiction vs. Nicotine Action

- In addition to its addictive properties, nicotine improves performance on wide variety of cognitive tasks, requiring different brain circuits, including attention, visual information processing, computational abilities, prepulse inhibition, vigilance and working memory.
- Due to its synaptic localization, nicotine may exert a modulatory influence on multiple brain networks independent of any specific task.

- Cingulate has been implicated as a common target for nicotine (and other abused drugs) and may be a convergent region pivotal for nicotine’s diverse effects:
  - High concentrations of nicotinic binding sites in the cingulate (Nyback et al 1989).
  - Nicotine dose dependently increased activity in cingulate (Stein et al 1998).
  - Nicotine improves sustained attention by increasing activation in posterior cingulate (Lawrence et al 2002).
  - Nicotine improves attention by deactivating anterior and posterior cingulate (Hahn et al 2007).
  - Nicotine behavioral effects predicted by activation in posterior cingulate (Giessing et al 2007).

Hypothesis: nicotine as both a trait and state will alter cingulate circuitry independent of any particular behavioral condition.
Functional Connectivity Maps for each Lt Cingulate ROI

Nicotine  
Placebo  
Overlap
Correlations Between FTND and dACC- Striatal Connectivity

Negative correlation between FTND and:

a/b) Lt dACC to bilateral striatum
c) Rt dACC to Rt striatum

Not affected by [nicotine], smoking duration or amount (pack-years), gender or age
Cocaine Dependence and Functional Connectivity

- Alterations in DRD₂, OFC metabolism, NAA, glu, OFC/ACC gray matter, functional activity (e.g. IC)
- Loss of drug taking control, behavioral rigidity (esp learned reward associations, i.e. reversal learning), reward disturbances, mood disturbances-- all emphasize elements within the MCL
- Preclinical data also point to MCL dysfunction (e.g. NAcc, OFC), perhaps leading to changes in hedonic ‘set point’ (Koob)
- Connectivity strength at rest related to subsequent task behavioral performance and BOLD activation.

**Hypothesis:** resting-state brain connectivity between components of the MCL reward circuitry is altered in people who chronically abuse cocaine
Cocaine Dependence and Functional Connectivity

Gu et al. NeuroImage 2010

No changes from NAcc seed

Results in HC generally consistent with known anatomical pathways
Decreased rsFC in Cocaine Users

Data suggest possible difficulty in appropriately activating reward, learning and emotional circuitry in cocaine dependent individuals and invite new hypotheses for cocaine dependence and treatment.

Gu et al. NeuroImage 2010
Circuits Involved In Addiction

INHIBITORY CONTROL

MOTIVATION/DRIVE

REWARD

MEMORY/LEARNING

INHIBITORY CONTROL

MOTIVATION/DRIVE

REWARD

MEMORY/LEARNING
Impulsivity & Compulsivity: Key Addiction Traits

- Cocaine users (CUs) will have altered striatal-cortical rsFC, compared to HC.
- Based on phenotypic similarities with OCD and nicotine dependence, CUs will have increased rsFC in striatal-iPFC ("go") circuit as well as reduced rsFC in striatal-dACC ("stop") circuit.
- Balance between "go" and "stop" circuits will predict drug use compulsive behaviors.
Striatal rsFC patterns

Hu et al. JAMA Psych 2015
Striatal rsFC in Cocaine Dependence

Hu et al. JAMA Psych 2015
Striatal Connectivity and IMPULSIVITY
Striatal Connectivity and COMPULSIVITY: a dual process perspective
Significance

- **Compulsive cocaine use**, a defining characteristic of dependence, is associated with an imbalance of *increased* striatal-inferior PFC (“GO”) and *decreased* striatal-dorsal ACC (“STOP”) connectivity.

- **Impulsivity**, both a risk factor for and a consequence of cocaine use, is associated with *increased* dorsal striatal-dIPFC connectivity uniquely in CU.
The folks in the lab who REALLY did the work

Supported by NIDA-IRP
Can Striatal rsFC serve as a biomarker of cocaine treatment outcome?

- In humans, cocaine associated *cues* engage ventral and dorsal striatum plus a distributed network of cortical structures – dIPFC, OFC, ACC, PCC and insula

- Altered striatal function and hypo-frontality considered key neurobiological substrates of *compulsive* cocaine use

- Altered cortico-striatal functioning are also implicated in high trait *impulsivity*, characteristic of cocaine-addicted individuals

- No previous data on these circuits and treatment outcome prediction

Hypotheses:

Differences in *cortico-striatal* connectivity strength will:

1. emerge as a function of cocaine-addiction status
2. be most pronounced in individuals at *greatest* risk of relapse
3. contribute to *higher impulsivity* in cocaine-addicted individuals
Design

Pre-discharge assessment
6-min resting scan in final week of treatment
Neurocognitive/clinical assessment within a week of scan:
Iowa Gambling Task, Wisconsin Card Sorting Task, Trail Making task, NEO-PI, Temperament and Character Inventory, Cocaine Craving Questionnaire, Obsessive Compulsive Cocaine Use Scale.

Post-discharge assessment
Followed for 24 weeks post-treatment
Weekly interview and urine drug screen

Two groups – Status at day 30 post-treatment
(DSM-IV for early remission)
Relapse — relapsed during first 30 days (n=24)
Non-Relapse – still abstinent at day 30 (n=21)
Putamen-Insula rsFC Predicts Relapse

No relationship between striatal connectivity and:

- Years of education
- Years of smoking
- cpd: Days of cocaine use
- Amount spent on cocaine in last 90 days
- Lifetime days cocaine use

McHgh et al 2013
The putamen-pl circuit is related to trait impulsivity

McHgh et al 2013