Desire and Its Modulation:

Imaging the Brain Substrates of “GO!” and “STOP” in Addiction

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Understanding Vulnerability

To Relapse

To Addiction
Is Matthew Perry’s Brain To Blame?
Imaging the Substrates of “GO!” and “Stop”!

1. **Background**
   - Our interest in cue-induced “GO!” states
   - How we have studied them

2. **Brain Responses in the “GO!” state**
   - To Cocaine Cues
   - To Natural Rewards

3. **Can The “GO!” Response be Blunted or Blocked (Stopped!) by Medication?**

4. **Do Patients with Addictions have possible “Stop!” Deficits**
   - Functional Evidence
   - Structural Evidence
Addiction Cycle

Stop drug

Withdrawal

RELAPSE
Addiction Cycle

Craving → Withdrawal → Craving

Craving

Craving

Craving

Craving
<..my lover was cold and cruel and hardly faithful.... ...But I never fell out of love. Every time I see a movie in which people are doing coke, I want it. I can almost taste it in the back of my throat, and I still love that taste. You don’t get over the drugs; you don’t ever fall out of love.......

Patti Davis   TIME
May 7, 2001
Drug Desire

“Craving”

Desire for euphoria

Desire to avoid WDRWL or discomfort
How Do Drug Cues Come to Trigger Drug Craving?

Drug Cues ---- signal --- Cocaine

Drug Cues

Desire

“Craving”

“GO!”
How can we study this state, under controlled conditions?

Cue Reactivity Paradigms

- Polygraph Lab
- Brain Imaging Setting
What are the Neuroanatomical Substrates of Cue-Induced Craving?

Limbic Structures as Candidates
PET Session Timeline

- PET O-15
- Cocaine Patients
- Cocaine-naïve Controls

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Were we able to elicit the “GO!” state?

(under these hostile Laboratory Conditions)?
Subjective Response
During Cue-induced Cocaine Craving

- Cocaine high
- Cocaine craving
- Wish for rush
- Wish to get rid of bad feelings
- Cocaine withdrawal
- How relaxed?
- How good?

Detoxified cocaine patients (N=14)
Comparison subjects (N=6)
Did we find limbic activation?
Pt. 30023

Amygdala

Anterior Cingulate

Nature Video     Cocaine Video

Cocaine Pt. 30023
Brain Activation During Craving Triggered By Cocaine Cues

Three views of the brain’s activity* in cocaine patients viewing a cocaine video which triggered desire for cocaine.

*Statistical parametric map showing brain regions differentially activated by a cocaine video as compared to a non-drug (nature) video.

Childress, et al. 1999
Limbic Activation
During Cue-induced Cocaine Craving

Change in rCBF

Limbic Regions

- Amygdala b
- Anterior cingulate b
- Temporal pole c
- Hippocampus
- Orbitofrontal cortex

Detoxified cocaine patients (N=14)
Comparison subjects (N=6)
The Increased Blood Flow Response to Cocaine Cues Occurs from a Hypoactive (Limbic) Baseline

PET Session Events

- Baseline 1
- Non-Drug 1
- Non-Drug 2
- Baseline 2
- Cocaine 1
- Cocaine 2

Relative rCBF

L. Amygdala

Controls (N=6)

Cocaine Pts. (N=14)
Comparison Region Response During Cue-induced Cocaine Craving

Comparison Regions

- Detoxified cocaine patients (N=14)
- Comparison subjects (N=6)

Change in rCBF

- Caudate
- Lenticular
- Cerebellum
- Dorsolateral Prefrontal Cx
- Visual cortex
- Thalamus
Summary thusfar:

1. Drug cues can elicit a profound, affect-positive state of drug desire

2. This can be used to study brain substrates in the imaging setting

3. Limbic activation (amygdalar; anterior cingulate -- not hippocampal)
Activation of Amygdala and Anterior/Posterior Cingulate by Cocaine Cues

Cocaine Patients (n=3)

Bold fMRI
Differential Activation of L. Orbitofrontal, R. Ventral Striatum (NAc)/ Amyg/Basal Forebrain, Insula and Anterior Cingulate by Cocaine (vs. Non-Drug) Cues

ASL Perfusion fMRI

AFNI, p< .05, corrected.
Differential Activation of VTA and Amygdala by Heroin-Video Cues in Methadone Patients vs. Controls

ASL perfusion fMRI

(AFNI map; p<.05, corrected)
Brain Substrates of Cocaine Cue Reactivity

University of Pennsylvania (Childress, et al)
NIDA Addiction Research Center (Grant, et al)
Harvard (McLean; MGH) (Maas, et al)
Medical College of Wisconsin (Garavan, et al)
Emory University (Kilts, et al)
Yale (Wexler, et al)
Brookhaven National Laboratories (Wang, et al)

**Limbic activation:** Anterior cingulate, amygdala, insula, ventral striatum (NAc), orbitofrontal cortex

**Other:** DLPFC, cerebellum
Amygdala

Anterior Cingulate

Nature Video

Sexual Video

Pt. SX_4
Areas of Brain Activation in Males and Females During Viewing of Erotic Film Excerpts

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Abstract: Various lines of evidence indicate that men generally experience greater sexual arousal (SA) to erotic stimuli than women. Yet, little is known regarding the neurobiological processes underlying such gender differences. To investigate this issue, functional magnetic resonance imaging was used to compare the neural correlates of SA in 20 male and 20 female subjects. Brain activity was measured while male and female subjects were viewing erotic film excerpts. Results showed that the level of perceived SA was significantly higher in males than in females. When compared to viewing emotionally neutral film excerpts, viewing erotic film excerpts was associated with bilateral blood oxygen level-dependent (BOLD) signal increases in the anterior cingulate, medial prefrontal, orbitofrontal, insular, and occipitotemporal cortices. Only for the group of male subjects was there evidence of significant activation of the thalamus and hypothalamus, areas sexually dimorphic in the brain known to play a pivotal role in physiological arousal and sexual behavior. When directly compared between genders, hypothalamic activation was found to be significantly greater in males. Furthermore, in females only, the magnitude of hypothalamic activation was positively correlated with reported levels of SA. These findings reveal the existence of similarities and dissimilarities in the way the brain of both genders responds to erotic stimuli. They further suggest that greater SA generally experienced by men, when viewing erotic material, may be related to the functional gender difference found here with respect to the hypothalamus. Hum. Brain Mapping 16:1–13, 2002. ©2002 Wiley-Liss, Inc.

Keywords: erotica; sexual arousal; sexual behavior; gender differences; emotion; motivation; functional magnetic resonance imaging; limbics system; hypothalamus

DOI 10.1002/hbm.10014
What are the Neurochemical Substrates of Cue-Induced Craving?

*DA Activation as One Candidate*
What is the neurochemistry of cue-induced craving?

Using C-11 Raclopride to Index Endogenous Dopamine Release

Cue Induced Craving

DA concentration

Raclopride binding
What is the neurochemistry of cue-induced craving?

Using C-11 Raclopride to Index Endogenous Dopamine Release

PET Imaging Session

Video C-11 Raclopride injection

-5 0 20 40 60
C-11 Raclopride Uptake in Basal Ganglia

(Activity summed over scan series)
Evidence for increased endogenous DA (reduced binding potential) in cocaine video vs. neutral condition

Pt. RAC_001
Can a Medication Blunt the Subjective and Brain Responses during Cue-Induced Craving?

GABA B agonists as Candidates
Can we modulate the “GO!” with GABA B Agonists?

Hypothesis:

*If* limbic DA release is one substrate for cue-induced cocaine craving, *then* GABA B agonist medications might help blunt both subjective and brain responses to cocaine cues.
Absence of Limbic Activation During Cocaine Cue Exposure in Cocaine Patients (n=3) Taking the GABA B Agonist Baclofen

Limbic Activation During Cue-Induced Cocaine Craving in Unmedicated Cocaine Patients (n=14)
Absence of Limbic Activation During Cocaine Cue Exposure in Cocaine Patients (n=3) Taking the GABA B Agonist Baclofen

Absence of Limbic Activation During Cocaine Cues in a Paraplegic Cocaine Patient (BAC_07) Taking Baclofen for 3.5 years

Limbic Activation During Cue-Induced Cocaine Craving in Unmedicated Cocaine Patients Cohort (n=14)
“GO!” Summary:

1. Drug cues elicit a profound, affect-positive state of drug desire.

2. Limbic activation occurs (amygdalar; anterior cingulate -- not hippocampal).

3. Neuronaligand competition and GABAergic medication studies suggest DA may be one substrate.
But….“GO!” doesn’t go all the way in explaining Addiction

Observations:

1) Craving episodes are very common, but not every episode eventuates in drug use.

2) Patients vary in their ability to manage drug craving.
Things I Never Hear from My Cocaine Patients

“Yeah, the high was terrific, but it was waaay too good. I could see it was going to get out of hand if I kept it up…so I gave it up. I just stopped.”

“Sure, I loved the high, but I was beginning to spend too much on it. Had to stop. So I did.”
Treatment populations are a special subgroup of those who have used rewarding drugs.....

Lots of people like pleasurable drug effects

Some who continue to addiction can stop without intervention

But....Treatment Seekers: BIG “STOPPING” Problems !!

Most people who continue to regular use can stop easily

Lots of people like pleasurable drug effects
Lots of people enjoy sex, chocolate, and gambling. Some continue to addiction, but can stop without intervention. Many people engage in these activities very regularly, without problems. But Treatment Populations: BIG "STOPPING" Problems!!

Why it’s hard to say NO

• Ventromedial prefrontal (orbital) cortex has been implicated in “future sensitivity” and adaptive decision-making.

• Lesions in this region cause impairment in “gambling” (Bechara) and “decision-making” (Rogers) tasks.

• Stimulant abusers perform poorly on some of these tasks.
Why it’s hard to say NO........

“Bad Brakes?”
(Poor Frontal Endowment)
Hypothesis:

Our treatment-seeking cocaine patients may show hypoactivity in medial aspects of the ventral orbital cortex, relative to non-stimulant user controls.
We analyzed the medial (rectal gyrus) and lateral aspects of the ventral orbital cortex, separately.

Cocaine patients (n=14)

Controls (n=6)
Right rectal gyrus, left lateral orbitofrontal, and right lateral orbitofrontal regions do not consistently differ between cocaine pts. vs. controls.
Hypoactivity in L. Ventromedial Orbitofrontal Cortex of Cocaine Patients Using O-15 PET

![Graph showing relative rCBF for different conditions and groups.](image-url)
Resting Hypoactivity in L. Ventromedial Orbitofrontal Cortex (VMOFC) of Cocaine Patients (n=9) vs. Controls (n=7)

ASL Perfusion fMRI

(VoxBo software; p<.05, corrected)
Do cocaine patients’ brains show structural (gray matter) differences when compared to controls?
Eight 3-D Views of Differentially Reduced Gray Matter Densities in Cocaine Dependent Patients (n=13) as compared to Cntrl group (n=17) by the method of Voxel Based Morphometry.
Axial Slices showing the percentage of decreased gray matter density in Cocaine users versus Controls

Only regions of significant gray matter density reduction are shown

From lft to rt: Every second mm from -14 to +2 mm from the plane of the AC. Scale is from least difference (0%, black) to most (14%, white). Slices are shown in neurological convention.
“STOP!” Summary

1) By definition, treatment-seeking populations of substances users are not very good at STOPPING drug use on their own.

2) Treatment-seeking stimulant users may have deficits in “future sensitivity” which contribute to their “STOPPING” difficulties.

3) The ventromedial prefrontal (orbital) cortex may be critical to “future sensitivity”.

4) We found functional and structural defects in the medial OFC of our treatment-seeking cocaine users.
Too much “GO!”?    Too Little “STOP!”

**Double Trouble**

*Throbbing amygdalae?  Bad brakes?  Both?*

*(Withered Frontals)*
Opiates, Brownies, Sex, Cocaine...Gambling

From Desire...to Disorder

Throbbing amygdalas?  Bad brakes?  Both??
Cue-induced Craving
“GO!”

Craving Modulation
“STOP!”

Neuroanatomy?

PET O-15
fMRI

Neurochemistry?
C-11 raclopride

PET O-15
fMRI

Neuroanatomy?

GABA B agonists
Neuroimaging & Conditioned Factors

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