Unbridled passions: Imaging the brain substrates of relapse vulnerability

Brief Research Overview
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Brain-Behavioral Vulnerabilities (Neuroimaging) Group
Team and Collaborators

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Current Collaborations

Genetics
GABA B, D3, FKBP5
PET D3/D2
FNIRS (mobile imaging) of frontal regions
“Disrupted Reconsolidation” to reduce cocaine cue reactivity
“Unconscious” cocaine cue phenomena
Orbitofrontal morphology (cocaine pts.)

Food
Sexual Risk
Reward and inhibition probes

Michael Lowe (Drexel)
Addiction
Our research efforts…

*driven by our addicted patients’ struggles with*

**RELAPSE**

- **CUES**
- **PRIMES** (a “taste”)
- **STRESS**

(WITHDRAWAL / cognitive disruption)
..Let us consider......

Are YOU having a “GO!” moment?
We humans are exquisite reward detectors!
But hmmnnn….is there a disadvantage, a “dark side” to our reward sensitivity?
Yes -- a possible “dark side” to reward sensitivity....

A brain that responds very quickly to reward signals (even when “unseen” -- without our awareness) may have greatly helped our early species survival –

....BUT – ironically -- very rapid, almost automatic, brain responses may NOT help in the battle against relapse –> greater reward sensitivity may be a...relapse vulnerability!!
VULNERABILITY

“GO!”

“STOP!”

*** A delicate balance ***

For understanding the brain vulnerabilities in relapse.... and, potentially, in addiction, itself....
In a normal, adult brain....

...the brain’s frontal circuitry acts as a “brake” (STOP!) on downstream motivational (GO!) systems critical for survival – for pursuing rewards such as food and sex – for responding to danger (fear and aggression).

This enables good moment-to-moment decision-making...good evaluation of risk...good impulse control.
In a vulnerable brain….

..the brain’s frontal (STOP!) circuitry is not modulating downstream (GO!) systems – the “brain brakes” may be bad – or the connection between the brakes and the other regions may be “broken”.

Result: poor decision-making…poor impulse control…greater risk-taking…poor inhibition…an “over-reacting” brain
For understanding the brain vulnerabilities in relapse.... and, potentially, in addiction, itself....
Drug cues

Throbbing, pulsating desire

Relapse
Drug cues → “GO!” → Relapse
How Do Drug Cues Come to Trigger Drug Craving?

Drug Cues ---- signal --> Cocaine

Drug Cues ---- signal --> Cocaine

Desire

"Craving"

"GO!"
Outline

Context:

- Two brain systems implicated in relapse vulnerability: “GO!” and STOP! Circuits

Goal: If we can capture the brain’s “GO!” response to drug cues, we can use this response to predict individual relapse vulnerability, and to screen candidate medications for their ability to impact these brain targets.

- Can we image the brain response to drug cues?

- Is there individual variation in “cue-vulnerability”?
  (Genetics? Epigenetics / prior Trauma/Abuse?)

- Can we link the cue-triggered brain responses to RELAPSE?

- Is there hope? Can we impact the “cue-vulnerable” phenotype with a (DA-modulating) medication?

- What’s next on the horizon?
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Can we image the brain response to drug cues?

**YES --**

We showed that cocaine cues triggered motivational (limbic) circuitry – initially using radioactive water as a brain activity tracer (with PET).

And our lab replicated this in for other drug reward cues, using fMRI...

...and for other natural reward cues:
- For food cues
- And for sexual cues

What about cue-triggered desire for...

**FOOD?**

Highly palatable food cues trigger motivational circuitry in young women at-risk for weight gain.

**SEX?**

Will the brain to romantic/sexual cues predict risky sexual behavior in young urban women at high risk for STI/HIV?

And we showed that cocaine and sexual cues could trigger these same circuits even when "unseen", presented outside conscious awareness!

**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.

**Unseen**

Cue Paradigm

33 msec targets
467 msec "masks"

(An analysis of this measure of reward circuits, reflected by secondary responses of motoric, autonomic, attentional, and reward cues, with subjects medication, on a topographic continuity, identify distinct behavioral profiles, and may lead to sensory drive triggered...)

**Unseen** Reward Cues trigger

Limbic activation:
- amygdala
- v. striatum
- v. pallidum
- insula

OFC
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• Is there hope? Can we impact the “cue-vulnerable” phenotype with a (DA-modulating) medication?

• What’s next on the horizon?
Is there individual variation in “cue-vulnerability”? Genetics? Epigenetics / prior Trauma/Abuse?

Yes

Genetic

DAT 9 carriers $\uparrow$ cue response

Carriers of the “hypercortisol” allele of FKBP5 $\uparrow$ cue response

Epigenetic (e.g., prior adversity)

Prior trauma $\uparrow$ cue response

Prior abuse $\uparrow$ cue response

Prior trauma $\uparrow$ resting amygdala connectivity
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- **Can we image the brain response to drug cues?**

- **Is there individual variation in “cue-vulnerability”?**
  - (Genetics? Epigenetics / prior Trauma/Abuse?)

- **Can we link the cue-triggered brain responses to RELAPSE?**

- **Is there hope? Can we impact the “cue-vulnerable” phenotype with a (DA-modulating) medication?**

- **What’s next on the horizon?**
Can we link the cue-triggered brain responses to RELAPSE?

Yes

- Cocaine cue response = RAPID relapse
  - 33 msec cue task

- Cocaine cue response = MORE future cocaine use
  - 500 msec cue task

- Cocaine cue response = POOR outcome
  - 6 sec cue task

Cue-triggered brain responses to 6 sec cocaine cues predict relapse.

Yes - we can link the brain response to (visible) cocaine cues to relapse.

Individuals who will proceed to "POOR" urine outcomes (>90% cocaine-positive or missing) have a heightened brain response to cocaine cues whereas those proceeding to "GOOD" outcome have a low response.

ACNP, 2015
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- Is there hope? Can we impact the “cue-vulnerable” phenotype with a medication?

- What’s next on the horizon?
Is there hope? Can we impact the “cue-vulnerable” phenotype with a medication? What kind?

Yes

As drug cues trigger endogenous dopamine (DA) release…..

PET Evidence of striatal DA release to cocaine cues in humans

B. Brain maps obtained with SPM showing the difference in the distribution volume images of [123I]tetrodotoxin between the neutral and the cocaine cue condition (p < 0.05, uncorrected, threshold > 100 voxels). Note that there were no differences in the ventral striatum (-4 and -8 planes).


… we have tested medications that can blunt DA signaling:

GABA B agonists inhibit DA cell firing in VTA / DA release in striatum / cue effects in animals --

Dopamine D3 receptor antagonists / partial agonists can blunt drug reward cue effects in animals --

Cariprazine (Vraylar) is an atypical anti-psychotic with preferential D3:D2 activity at low doses
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• Can we image the brain response to drug cues? YES
• Is there individual variation in “cue-vulnerability”? YES (Genetics? Epigenetics / prior Trauma/Abuse)? YES
• Can we link the cue-triggered brain responses to RELAPSE? YES
• Is there hope? Can we impact the “cue-vulnerable” phenotype with (DA-modulating) medications? YES
• What’s next on the horizon?
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- Is there hope? Can we impact the “cue-vulnerable” phenotype with a (DA-modulating) medication?
- What’s next on the horizon?
NIDA P30 DA046345 *(PET Addiction Center of Excellence, Mach / Kranzler)*
Upcoming call for Pilot Project proposals (2-3 pages) – suited to our existing PET tracers -- with **strong translational** emphasis for Opioid Use Disorders

NIDA R01DA039215 *(Targeting Dopamine D3 Receptors in Cocaine)*

Continue ongoing imaging assessment of the D3(D2) partial agonist Cariprazine on our probes for reward and inhibition*, monitor brief relapse window

NIDA UG1DA050209 *(“CLIN” -> Clinical Laboratory with Integrated Neuroscience for assessing target engagement and early efficacy of medications for substance use disorders, pending)*

Candidate anti-relapse medications will be tested in opioid patients who are also taking long-acting depot naltrexone: commercially-available candidates include cariprazine (our D3/D2 partial agonist, Vraylar), the dual orexin-antagonist suvorexant (Bellsomra), and cannabidiol (Epidiolex) a non-euphorogenic phytocannabinoid recently approved for treatment-resistant childhood epilepsy – and with some demonstrated impact on cue-triggered responses and on opioid self-administration and opioid withdrawal (it has positive allosteric modulation at mu opioid and kappa opioid receptors). Other potential future agents include GABA B PAMS (Indivior), selective orexin 1 antagonists (Indivior), and D3 antagonists (Indivior).

• **What’s next on the horizon? Stay tuned:**
**Brain targets: Relapse Prevention**

"GO!"

"STOP!"

NEW: **PET** tools to complement our fMRI probes

* to infer endogenous DA
* to measure receptor occupancy
Relapse-relevant Brain Targets.....

...to accelerate the way forward in anti-relapse medication development for cocaine and other substance use disorders.
Thank You
Acknowledgements

NIDA U54  Cooperative Cocaine Medication Development Ctr.
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NIDA R01 DA 12162  (Coc Cue + Baclo)
NIDA R01 DA  15149 (Coc Cue – ASL fMRI)
NIDA R03 I-Start – J. Suh
NIDA K01 (Nic Cue, Franklin)
NIDA K23 (Opiate Cue, Langleben)
NIDA CSP #1021 (Baclofen Multi-site Clinical Trial)
NIDA R01 DA025906  ( “Unseen” Coc Cue Extinction )
NIDA R21/R33  DA026114 (Coc Cue + Real-time fMRI )
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