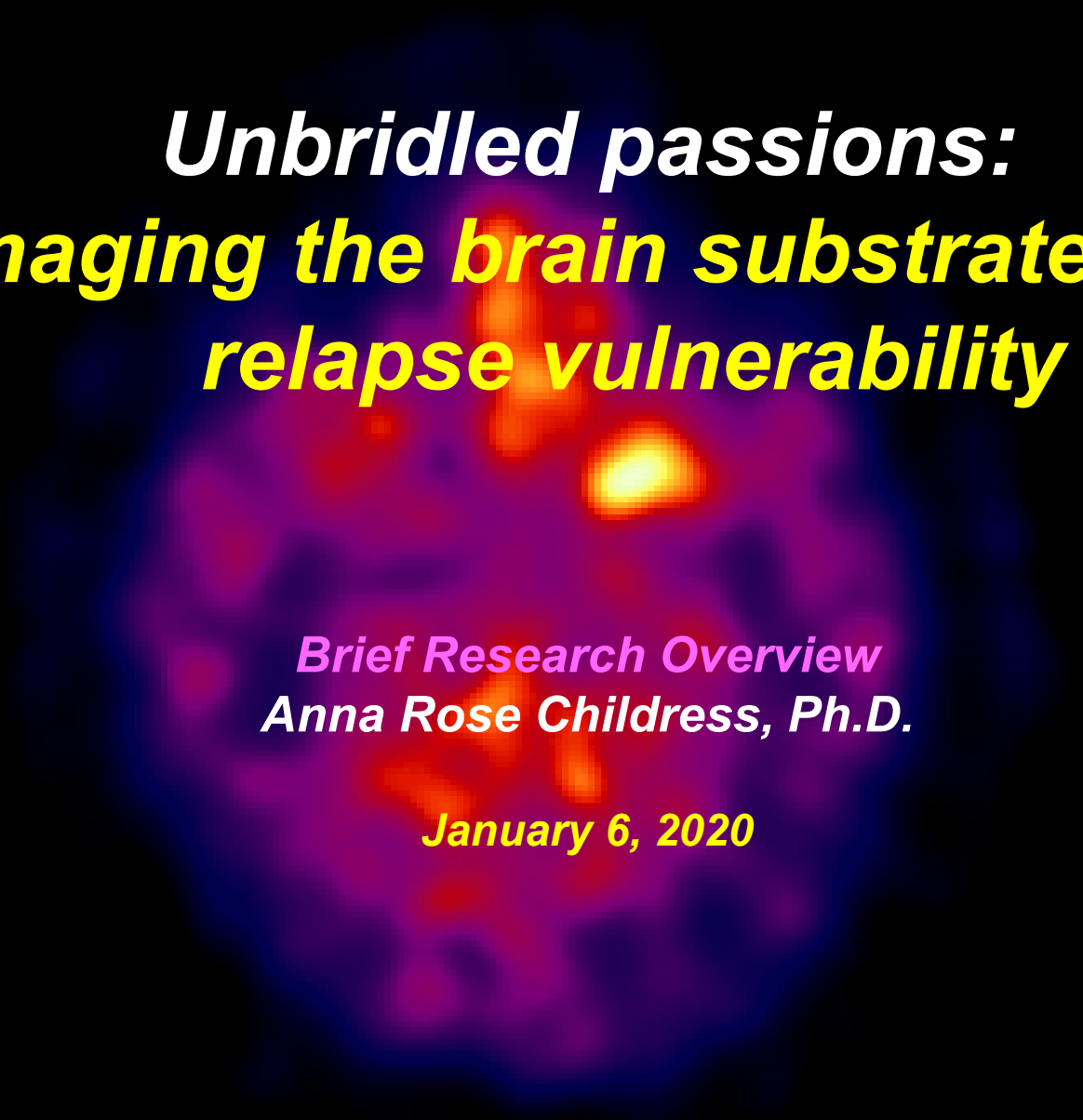
Unbridled passions: Imaging the brain substrates of relapse vulnerability



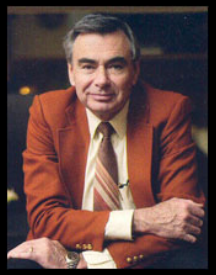
Brief Research Overview

Anna Rose Childress, Ph.D.

January 6, 2020

Brain-Behavioral Vulnerabilities (Neuroimaging) Group
Team and Collaborators


Childress


O'Brien


Franklin


Langleben


Wetherill


Kampman


Ehrman


Jagannathan


Young


Regier


Shi


Ely


Darnley

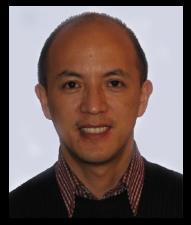

Taylor


Benson


Gawrysiak


Gonen

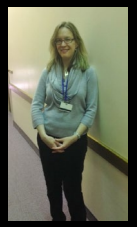

Hole


Z. Wang


Magland


Goldman


Marquez


Szucs-Reed


Suh


Fan


Downing


Kaempf


Maron


Spilka

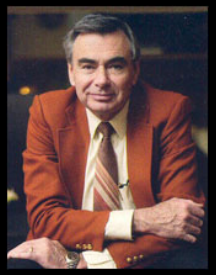

Padley


Keyser


Monge

Brain-Behavioral Vulnerabilities (Neuroimaging) Group
Team and Collaborators


Childress


O'Brien


Franklin


Langleben


Wetherill


Kampman


Ehrman


Jagannathan


Young


Regier


Shi


Ely


Darnley


Taylor


Benson


Gawrysiak

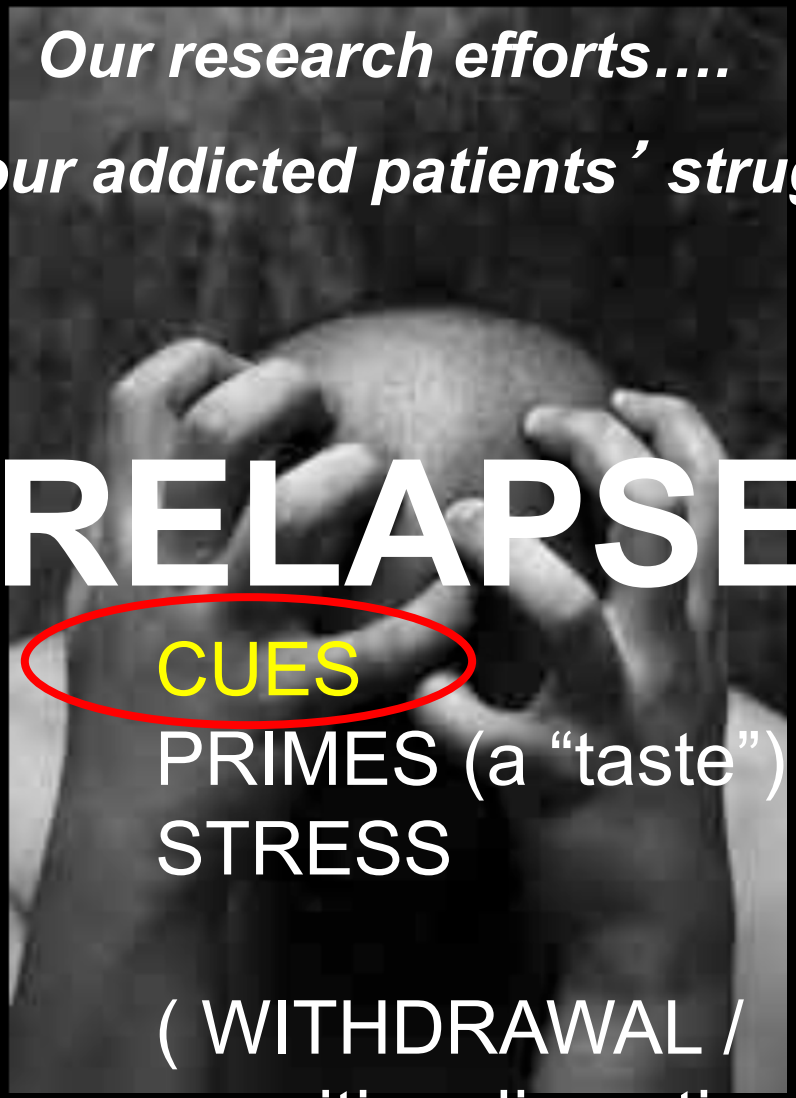
Current Collaborations

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	
Rick Crist (Psychiatry)	Bob Mach Jake Dubroff Rob Doot (Radiology)	Hasan Ayaz (Drexel)	Mike Saladin (MUSC)	Corinde Wiers (NIDA)	Vanessa Troiani (Geisinger)	Michael Lowe (Drexel)	Anne Teitelman (Penn SON)

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?

Reward

Reward

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

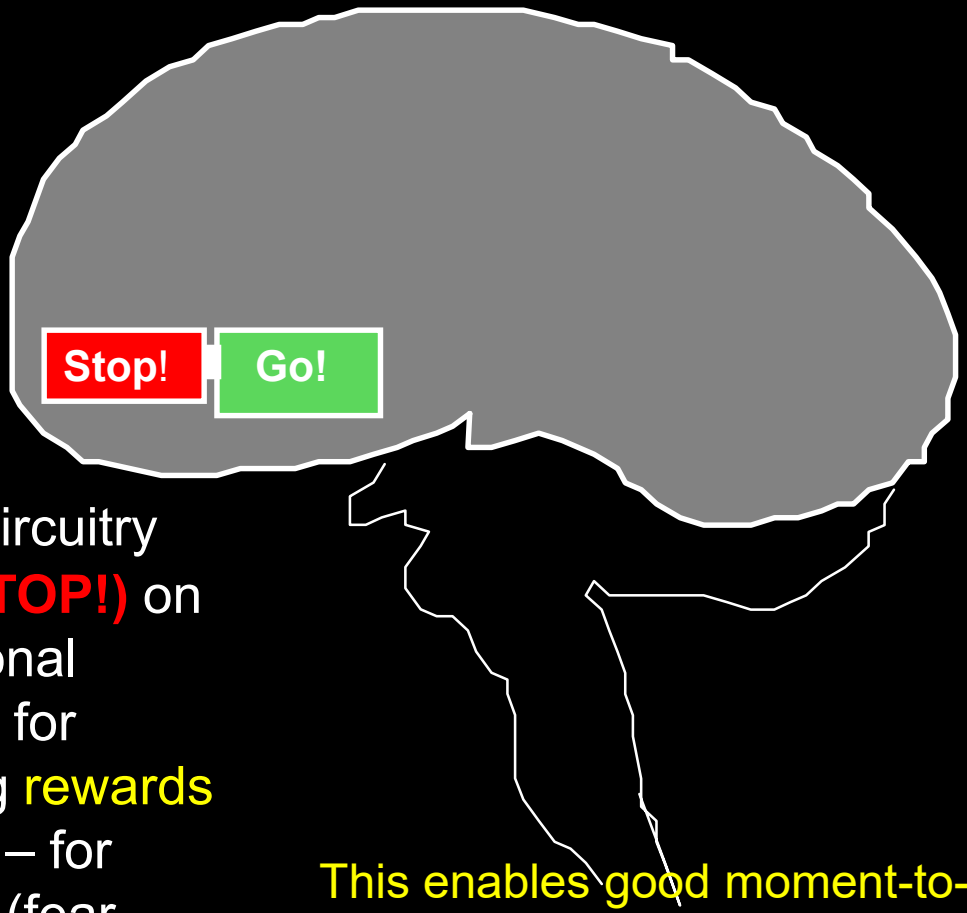
“ GO!”

“STOP!”

*** A delicate balance ***

For understanding the brain vulnerabilities in relapse…. and, potentially, in addiction, itself….

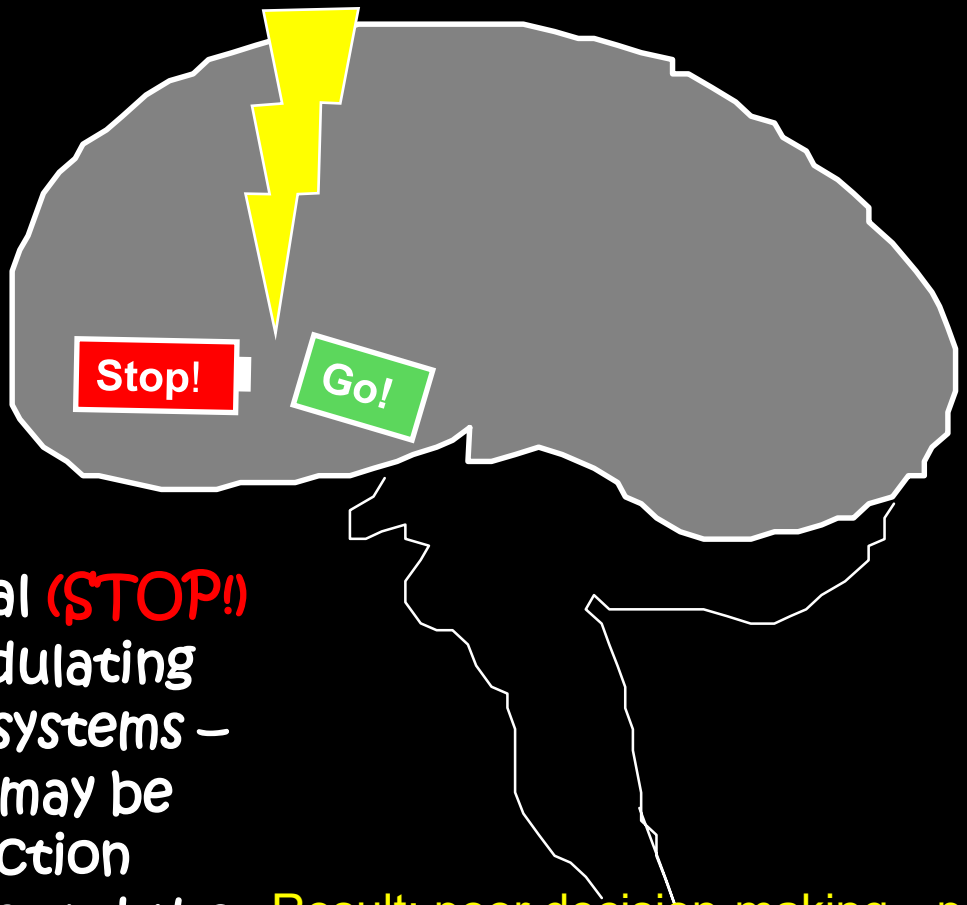
In a normal, adult brain….



…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

VULNERABILITY

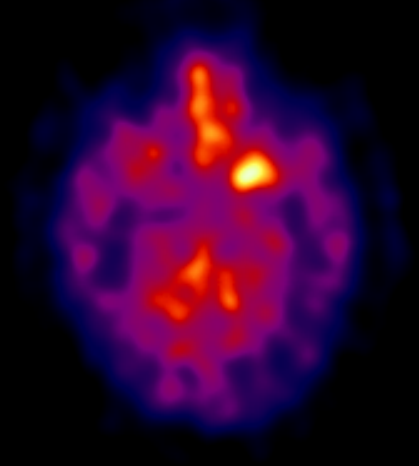
" GO!"

Brain substrates of cue-induced drug motivation……

"STOP!"

….and its regulation (or lack thereof : deficits in frontal modulatory circuits)

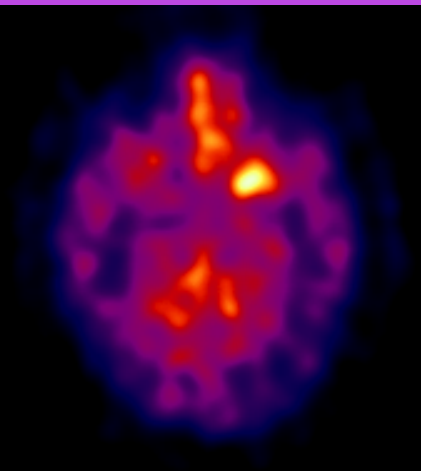
For understanding the brain vulnerabilities in relapse…. and, potentially, in addiction, itself….



Drug cues

Throbbing, pulsating desire

Relapse



Drug cues

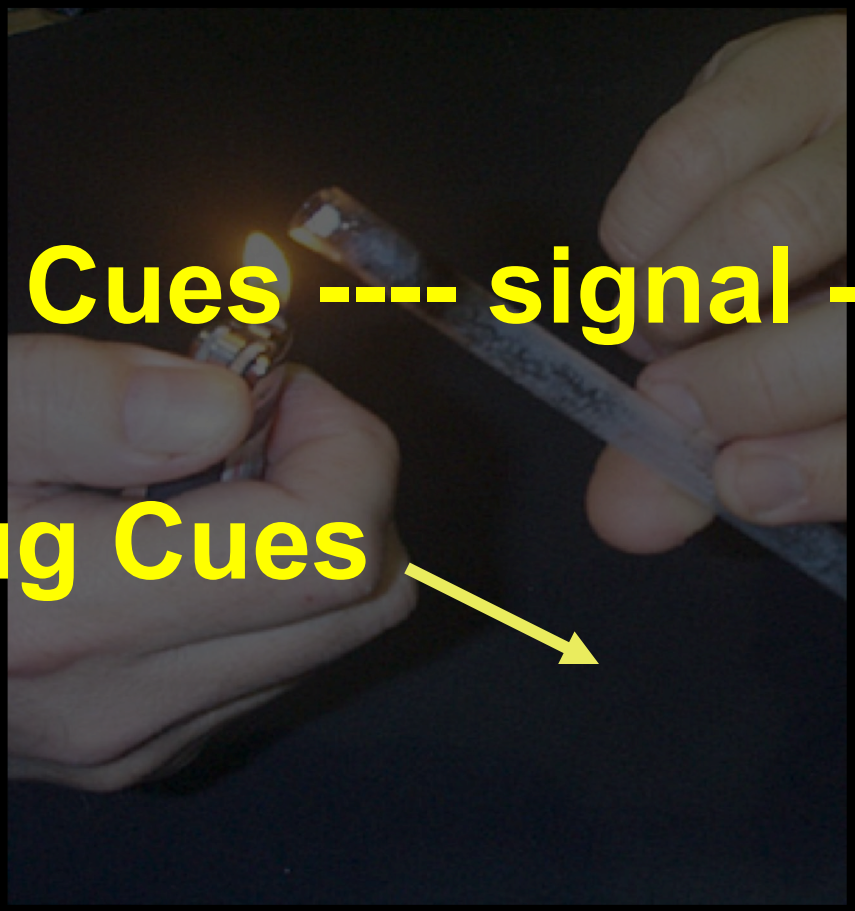
↓

"GO!"

↓

Relapse

How Do Drug Cues Come to Trigger Drug Craving?



Drug Cues ---- signal --> Cocaine

Drug Cues

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?***

Outline

Context :

- *Two brain systems implicated in relapse vulnerability: "GO!" and STOP! Circuits*

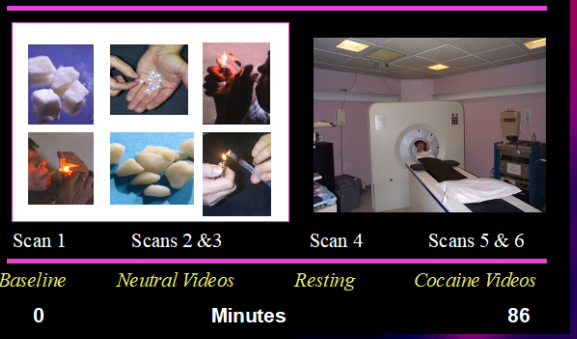
Goal: If we can capture the brain's "GO!" response to drug cues, we can use this response to predict individual relapse vulnerability, and to screen candidate medications for their ability to impact these brain targets.

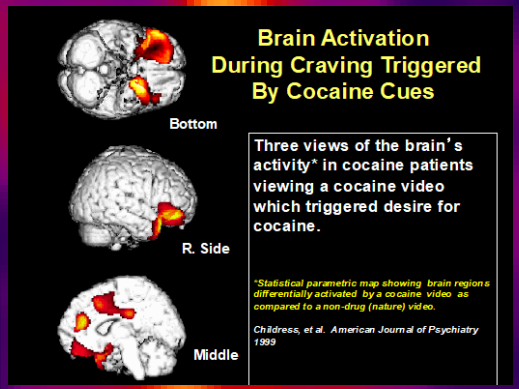
- ***Can we image the brain response to drug cues ?***
- *Is there individual variation in "cue-vulnerability" ?*
  (Genetics? Epigenetics / prior Trauma/Abuse) ?
- *Can we link the cue-triggered brain responses to RELAPSE ?*
- *Is there hope? Can we impact the "cue-vulnerable" phenotype with a (DA-modulating) medication?*
- *What's next on the horizon?*

- ***Can we image the brain response to drug cues ?***

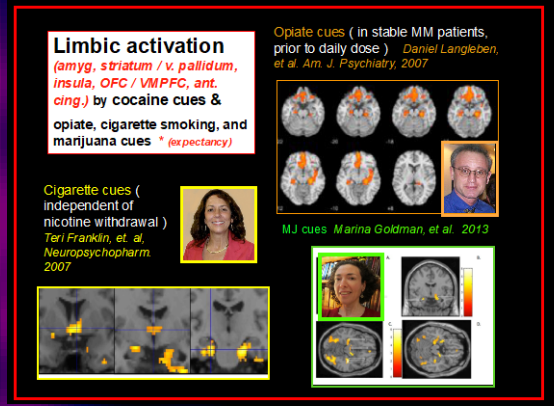
YES --

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



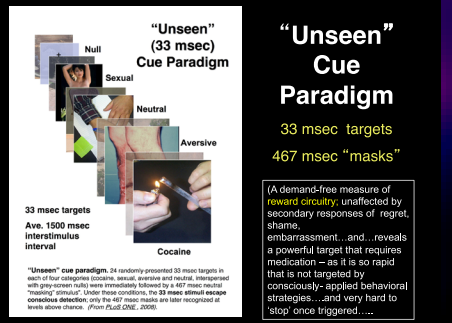


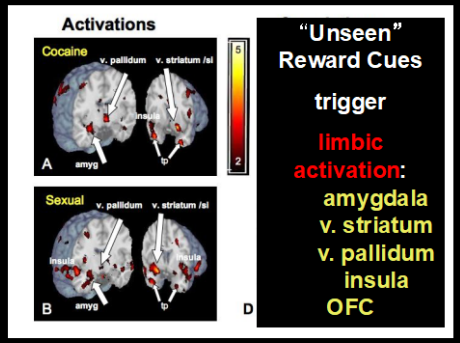
And our lab replicated this in for other drug reward cues , using fMRI…



…and for other natural reward cues: for food cues……and for sexual cues

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





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.

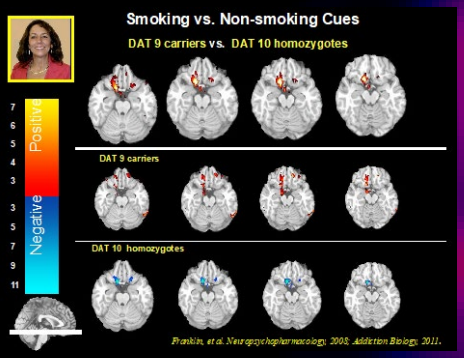
- *Can we image the brain response to drug cues ?*
- ***Is there individual variation in "cue-vulnerability" ?***
  (Genetics? Epigenetics / prior Trauma/Abuse) ?
- *Can we link the cue-triggered brain responses to RELAPSE ?*
- *Is there hope? Can we impact the "cue-vulnerable" phenotype with a (DA-modulating) medication?*
- *What's next on the horizon?*

- ***Is there individual variation in "cue-vulnerability" ?***
  Genetics? Epigenetics / prior Trauma/Abuse?

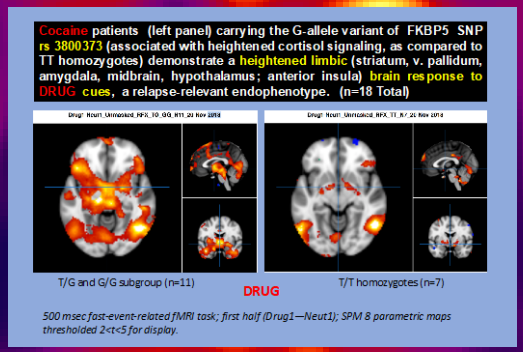
Yes *(Sex / hormonal – Franklin ; Wetherill)*

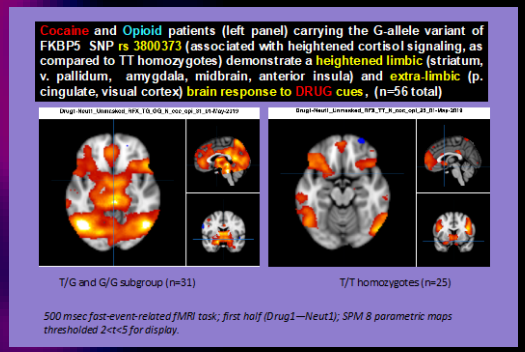
Genetic

DAT 9 carriers ↑ cue response



Carriers of the "hypercortisol" allele of FKBP5 ↑ cue response

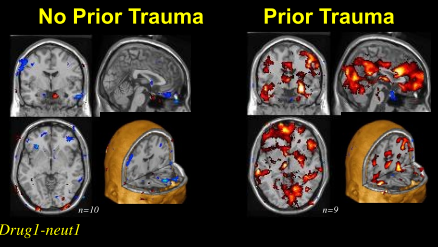




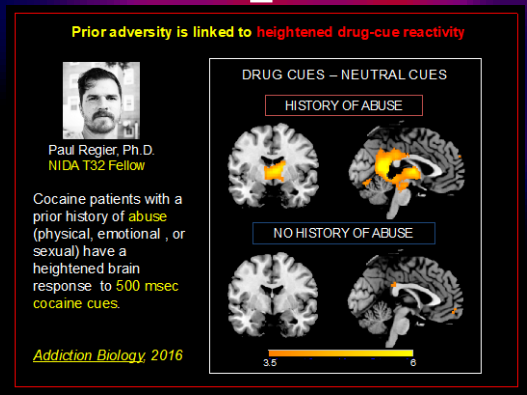
Epigenetic (e.g., prior adversity)

Prior trauma ↑ cue response

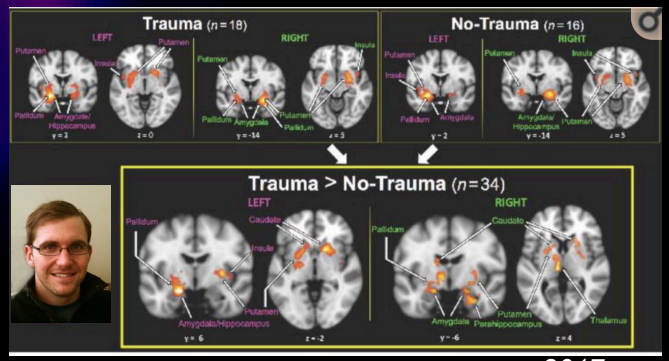
Enhanced Limbic Reactivity to 33 msec "Unseen" COCAINE Cues In CocainePatients with Prior Trauma



Prior abuse ↑ cue response



Prior trauma ↑ resting amyg connectivity



Drug and Alcohol Dependence , 2017

Outline

Context :

- *Two brain systems implicated in relapse vulnerability: "GO!" and STOP! Circuits*

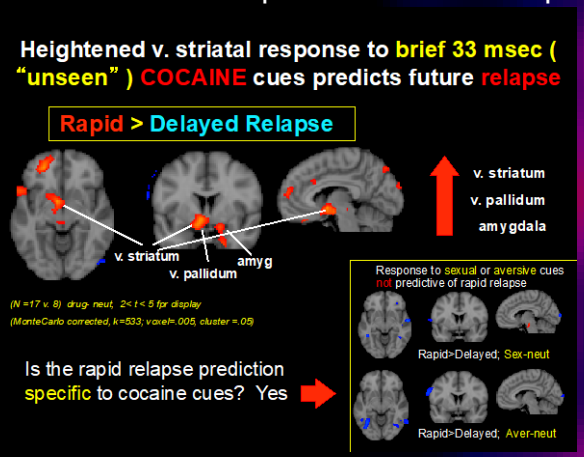
Goal: If we can capture the brain's "GO!" response to drug cues, we can use this response to predict individual relapse vulnerability, and to screen candidate medications for their ability to impact these brain targets.

- *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?*

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

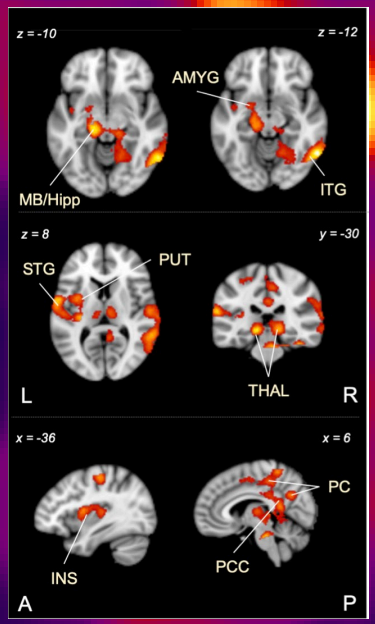
Yes

> Cocaine cue response = RAPID relapse



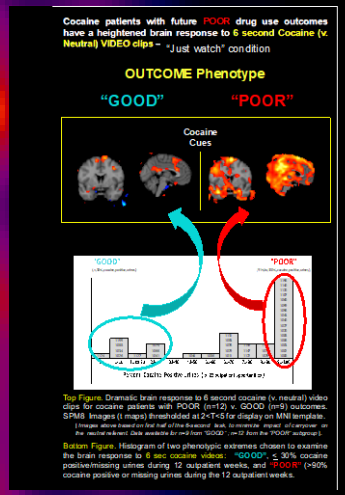
33 msec cue task

> Cocaine cue response = MORE future cocaine use



500 msec cue task

> Cocaine cue response = POOR outcome



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

6 sec cue task

Outline

Context :

- *Two brain systems implicated in relapse vulnerability: "GO!" and STOP! Circuits*

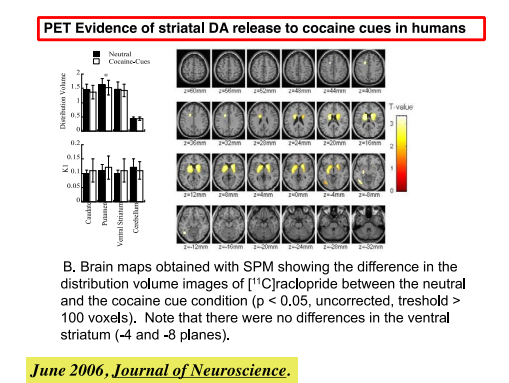
Goal: If we can capture the brain's "GO!" response to drug cues, we can use this response to predict individual relapse vulnerability, and to screen candidate medications for their ability to impact these brain targets.

- *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 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…..

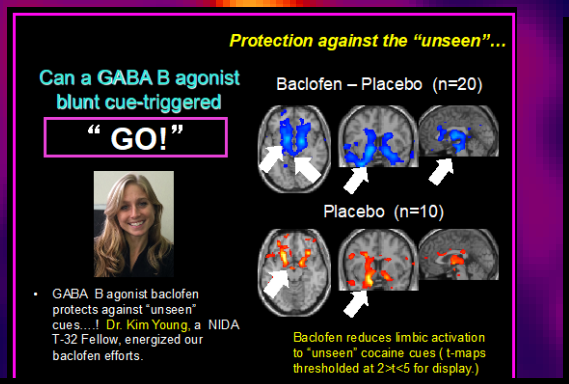


B. Brain maps obtained with SPM showing the difference in the distribution volume images of [^{11}C]raclopride between the neutral and the cocaine cue condition ($p < 0.05$, uncorrected, treshold > 100 voxels). Note that there were no differences in the ventral striatum (-4 and -8 planes).

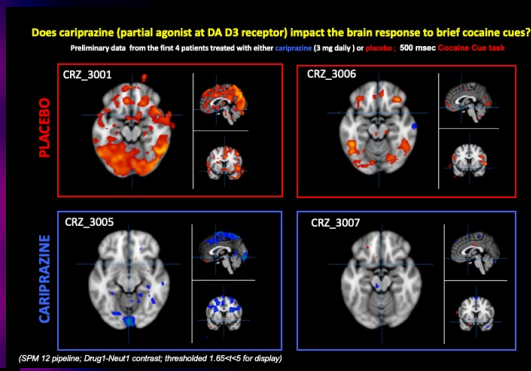
June 2006, Journal of Neuroscience.

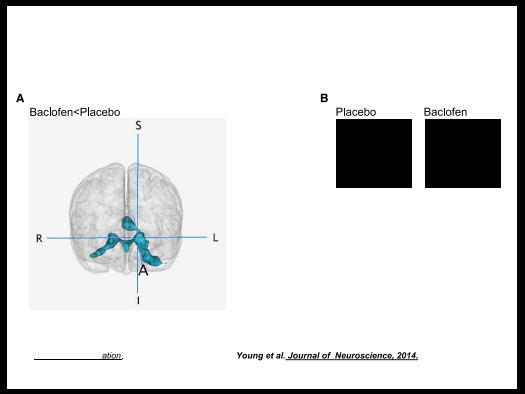
… we have tested medications that can blunt DA signaling:

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

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 ? 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?***

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?***

- ***What's next on the horizon?*** ***Stay tuned:***

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 cariprazaine (our D3/D2 partial agonist, Vraylar), the dual orexin-antagonist suvorexant (Bellsomra), and cannabidiol (Epidiolex) a non-euphorigenic phytocannibinoid 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).

Brain targets: Relapse Prevention

" GO!"

"STOP!"

fMRI

Scan Day 1

Scan	Anatomical Localizer	ASL Resting Scan	BOLD Resting Scan	Brief Cue I (33 msec)	Go-NoGO	Brief Cue II (500 msec)	High Res. Structural	De-Brief
Minutes	30 sec	5	5	8.25	5.5	8.25	3	

Scan Day 2

Scan	Anatomical Localizer	ASL Resting Scan	BOLD Resting Scan	Craving-Inhibition	High Res. Structural	Affect Regulation	De-Brief	Task Day: Behavioral Tasks (60 min)	De-Brief
Minutes	30 sec	5	5	7.5	3	7.5			

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

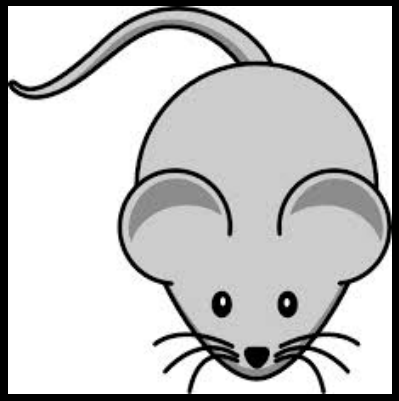
Dr. Robert H. Mach

* to infer endogenous DA

* to measure receptor occupancy

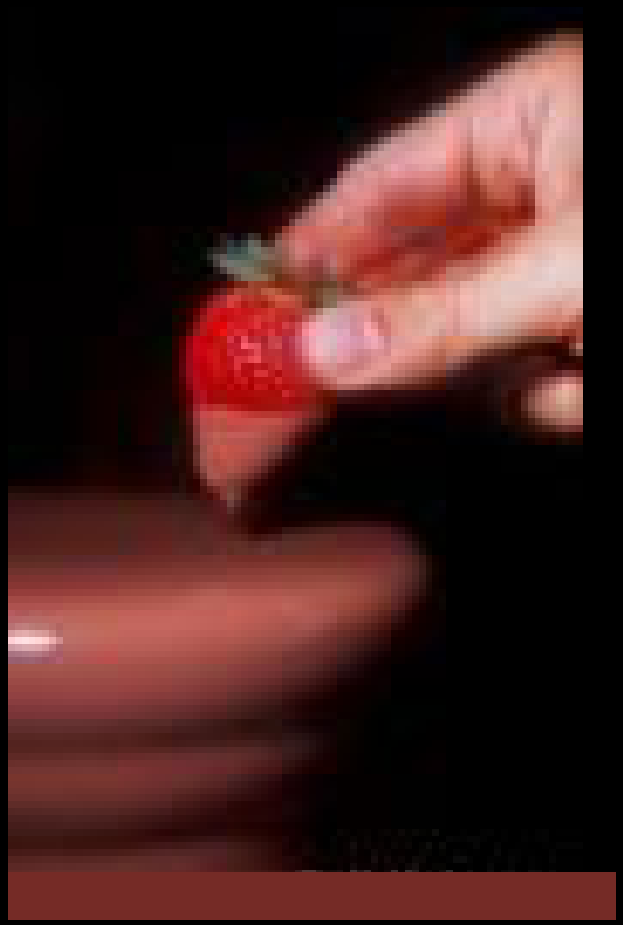
Relapse-relevant Brain Targets…..

Animal Models → NEURO targets / NEURO tools → Clinical Trials



….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.
NIDA P50 DA12756 (Cocaine Medication Development Ctr.)
NIDA P60 DA 005186 (Improving Treatment of Drug Abuse)
NIDA R01 DA 10241 (Coc Cue + Inhibition)
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)
NIDA T32 Translational Addiction Research (Childress/Pierce)
CURE Addiction Center of Excellence (Childress)
VA Medical Research Division / MIRECC
DANA Foundation