Desire and Its Modulation:

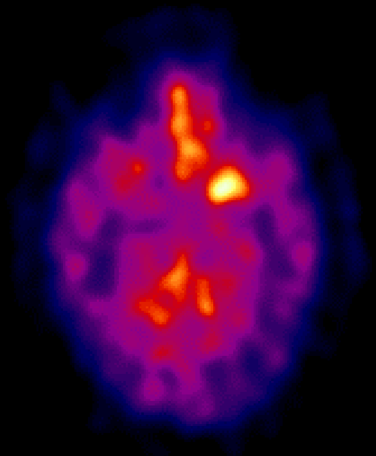
Imaging the Brain Substrates of "GO!" and "STOP" in Addiction

Anna Rose Childress, Ph.D.

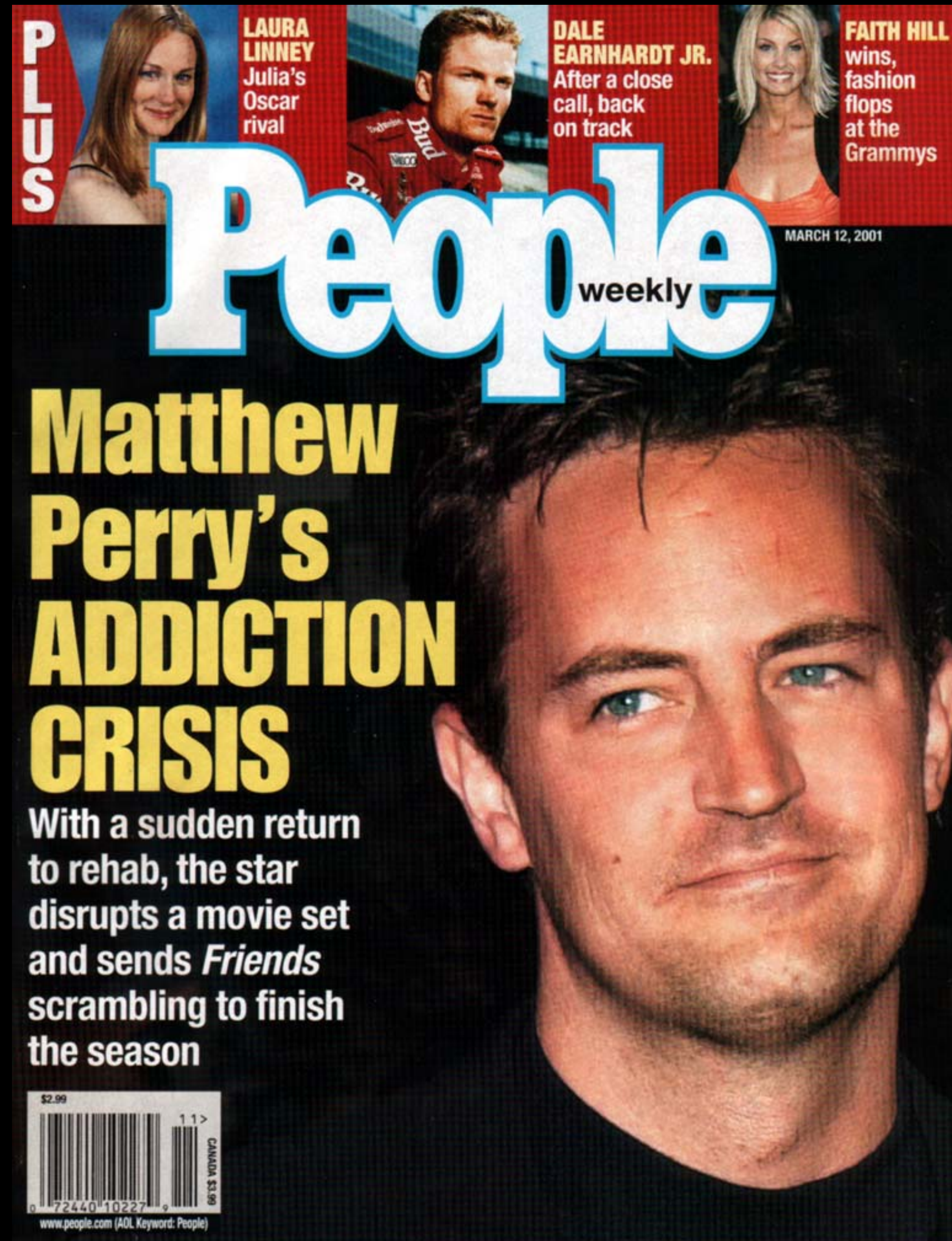
Brookhaven National Laboratories

March 5, 2002

Understanding Vulnerability



Is Matthew Perry's Brain To Blame?



Imaging the Substrates of “GO!” and “Stop” !

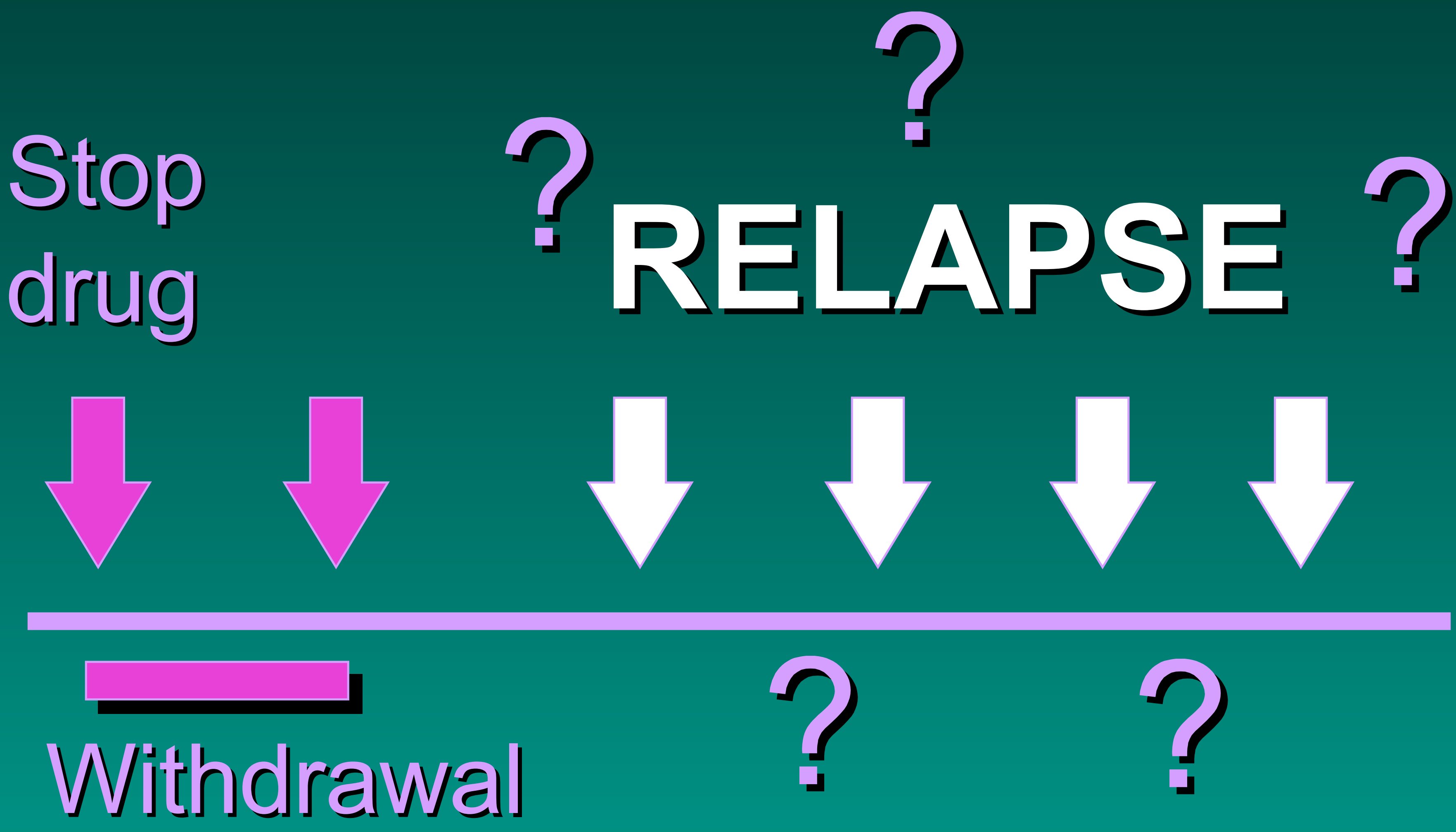
1. Background
   Our interest in cue-induced “GO!” states
   How we have studied them

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

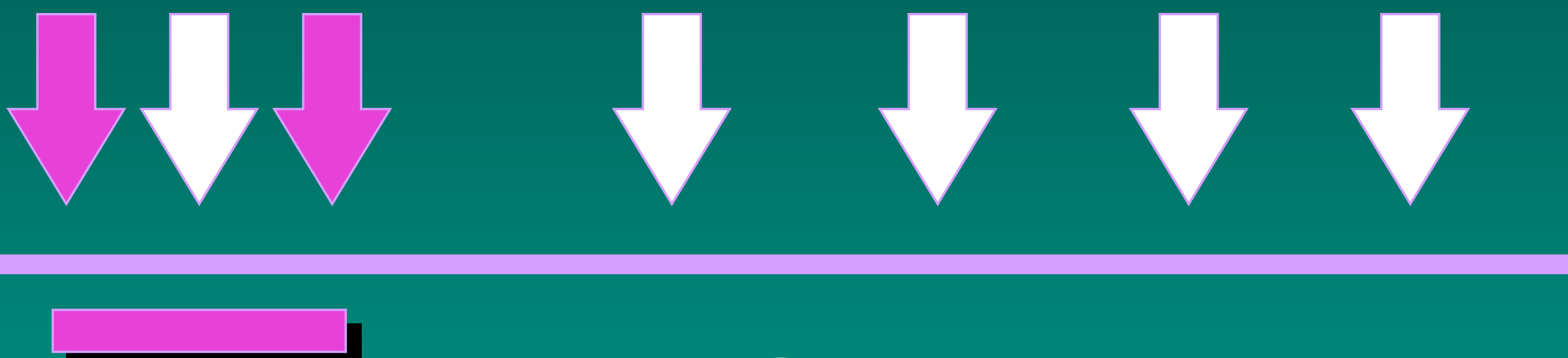


Addiction Cycle

Craving

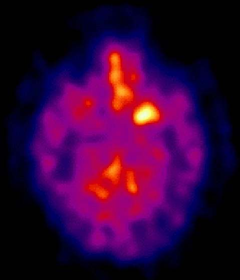
Craving

Craving



Withdrawal

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"

"Craving"

Desire to avoid WDRWL or discomfort

Desire for euphoria

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

Scan 1	Scans 2 &3	Scan 4	Scans 5 & 6
Baseline	*Neutral Videos*	*Resting*	*Cocaine Videos*

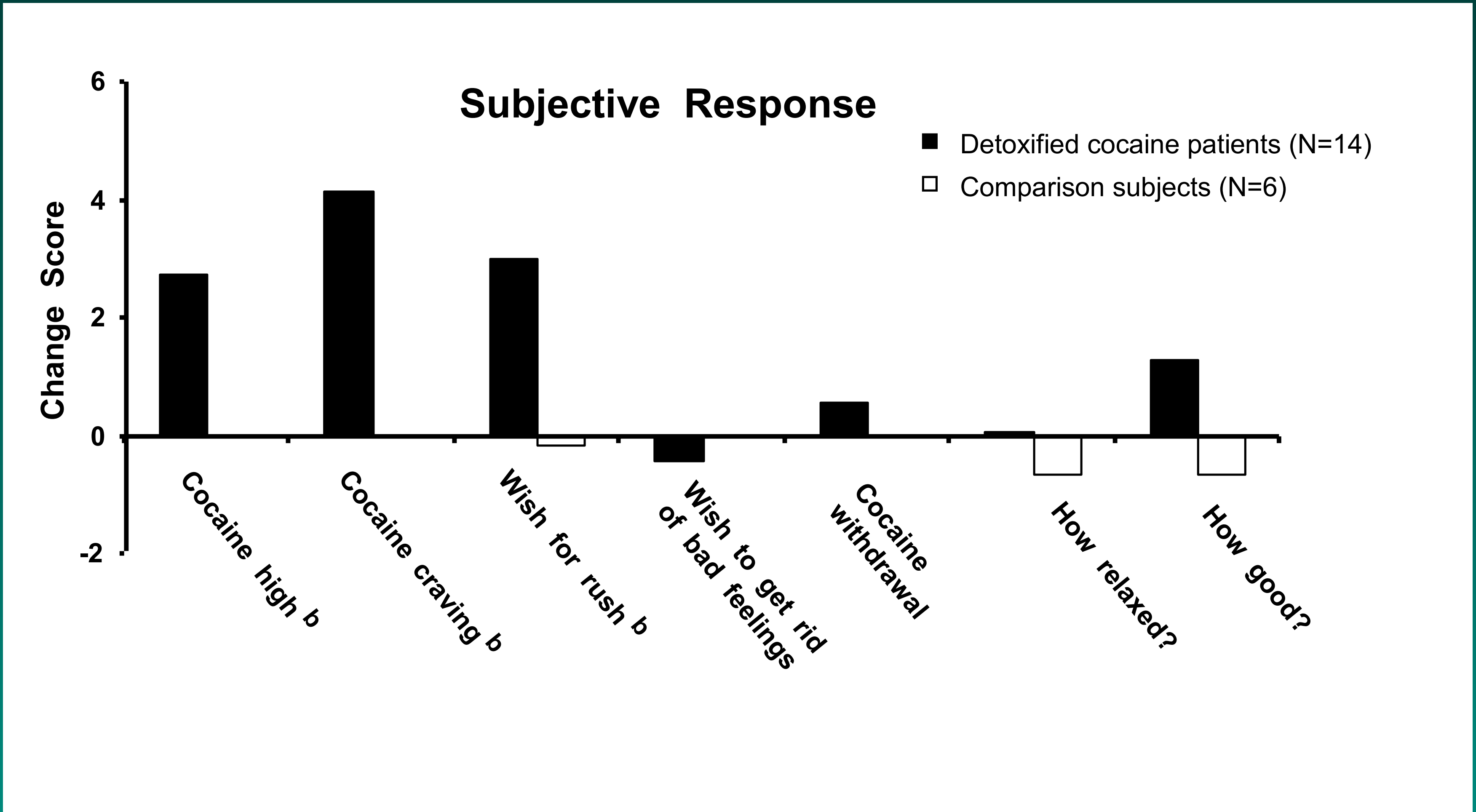
0 Minutes 86

Were we able to elicit the "GO!" state?

(under these hostile Laboratory Conditions)?

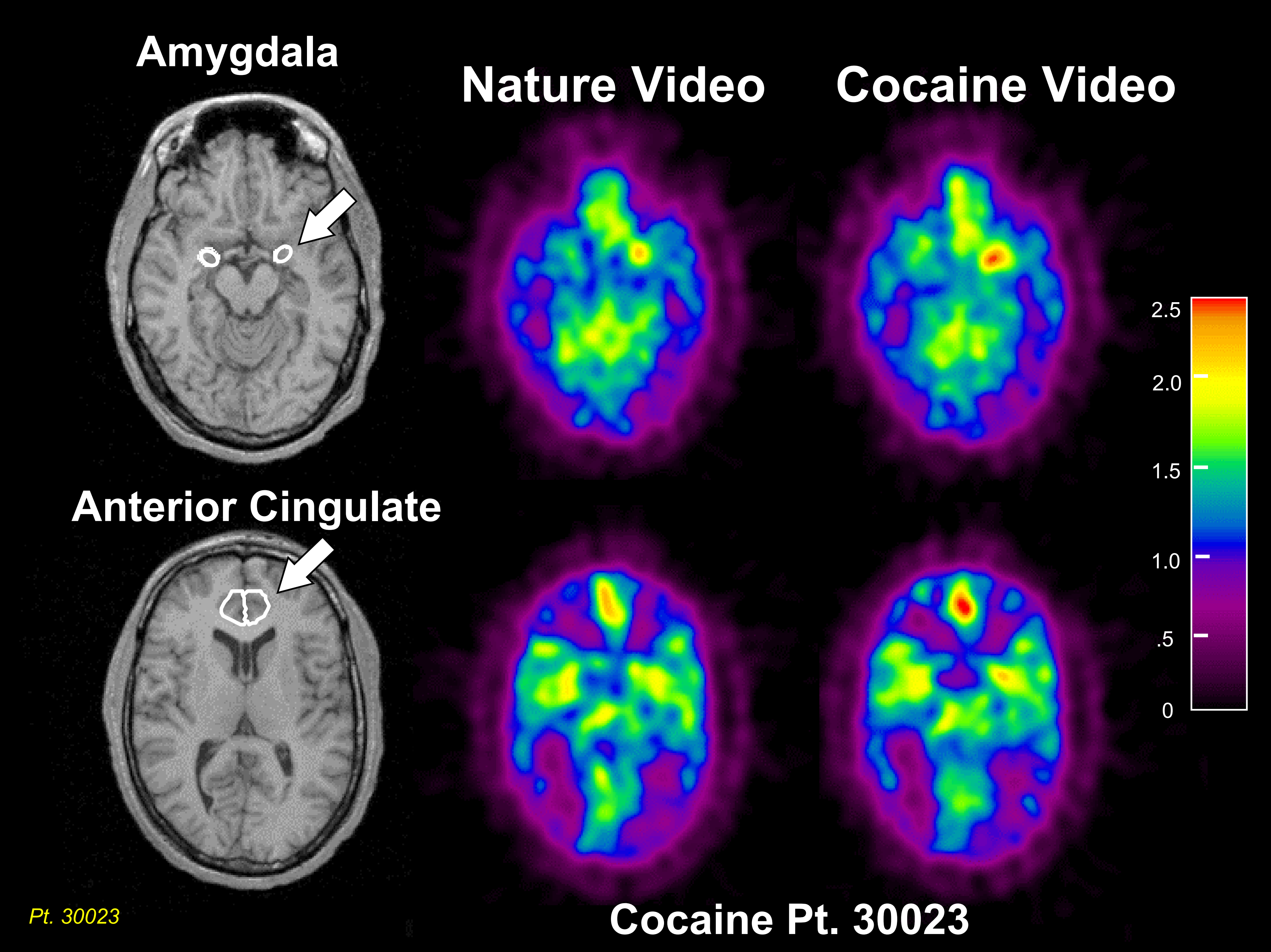
Subjective Response

During Cue-induced Cocaine Craving

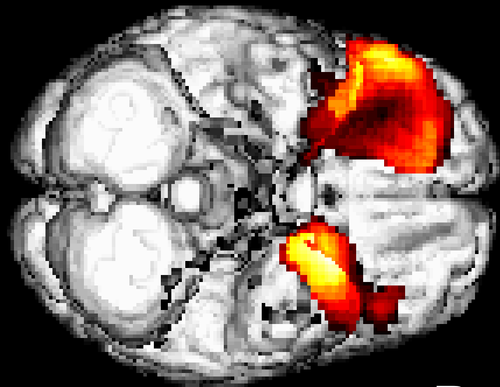


Did we find

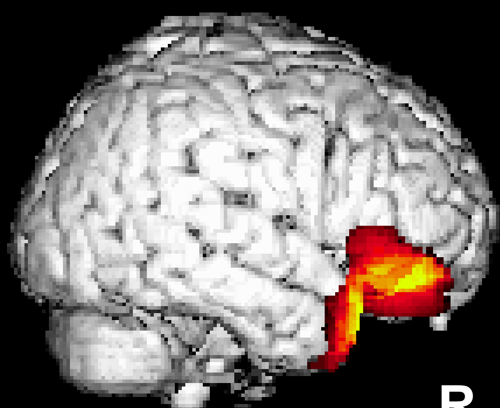
limbic activation?


Amygdala
Nature Video
Cocaine Video
Anterior Cingulate
2.5
2.0
1.5
1.0
.5
0
Pt. 30023
Cocaine Pt. 30023

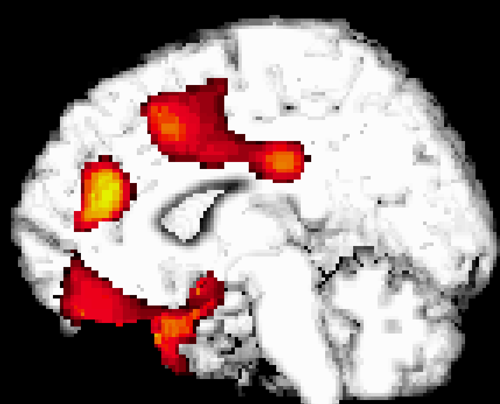
Brain Activation During Craving Triggered By Cocaine Cues



Bottom



R. Side



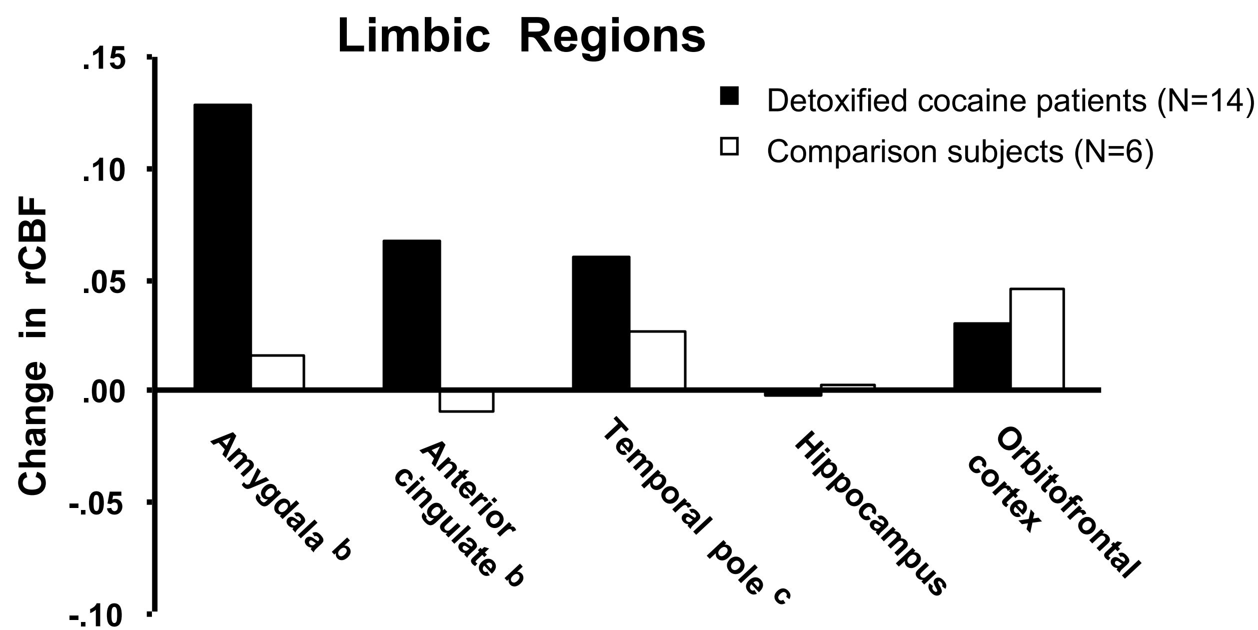
Middle

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

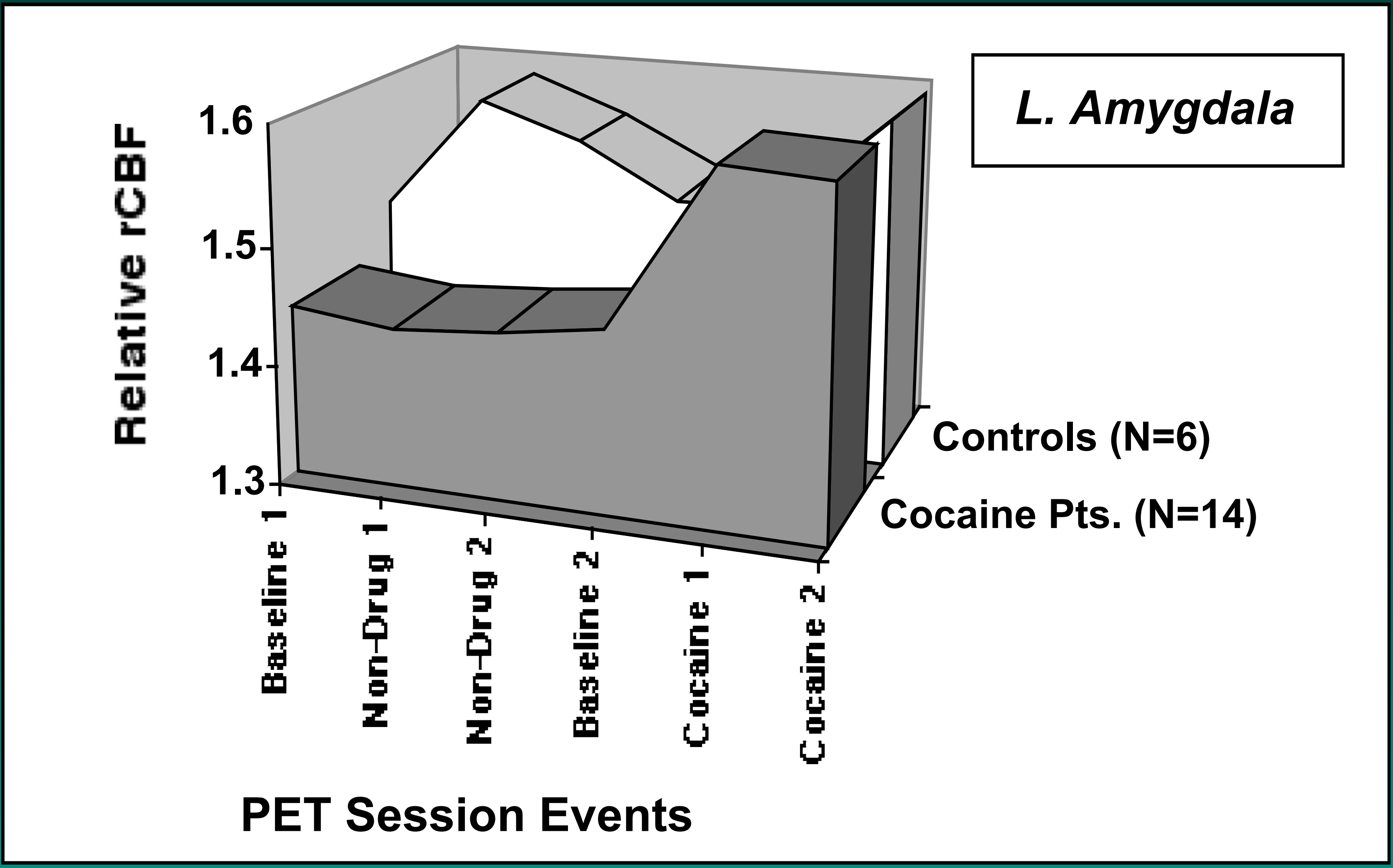
**Statistical parametric map showing brain regions differentially activated by a cocaine video as compared to a non-drug (nature) video.*

Childress, et al. 1999

Limbic Activation
During Cue-induced Cocaine Craving

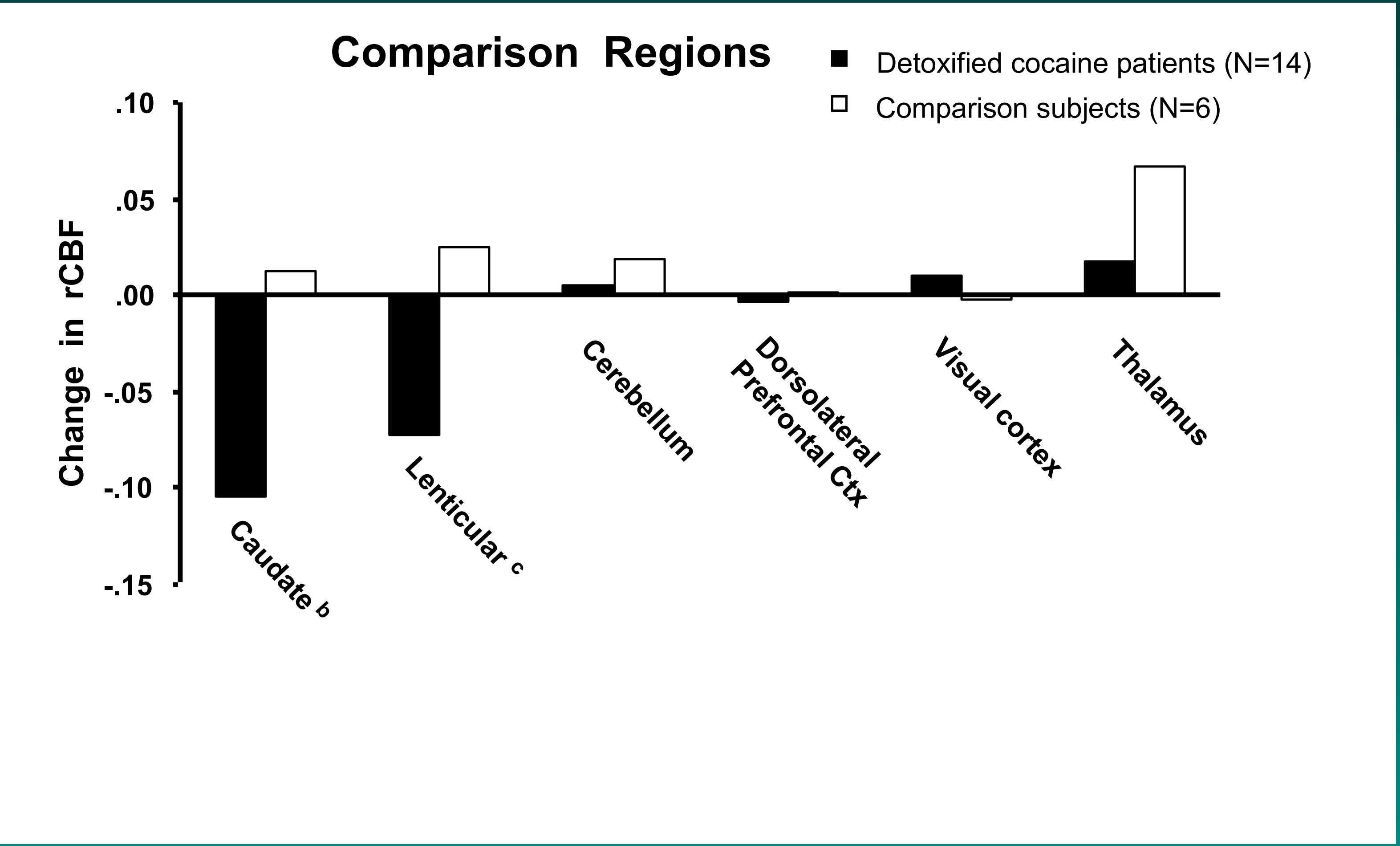


The Increased Blood Flow Response to Cocaine Cues Occurs from a Hypoactive (Limbic) Baseline



Comparison Region Response

During Cue-induced Cocaine Craving



Summary thusfar:

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

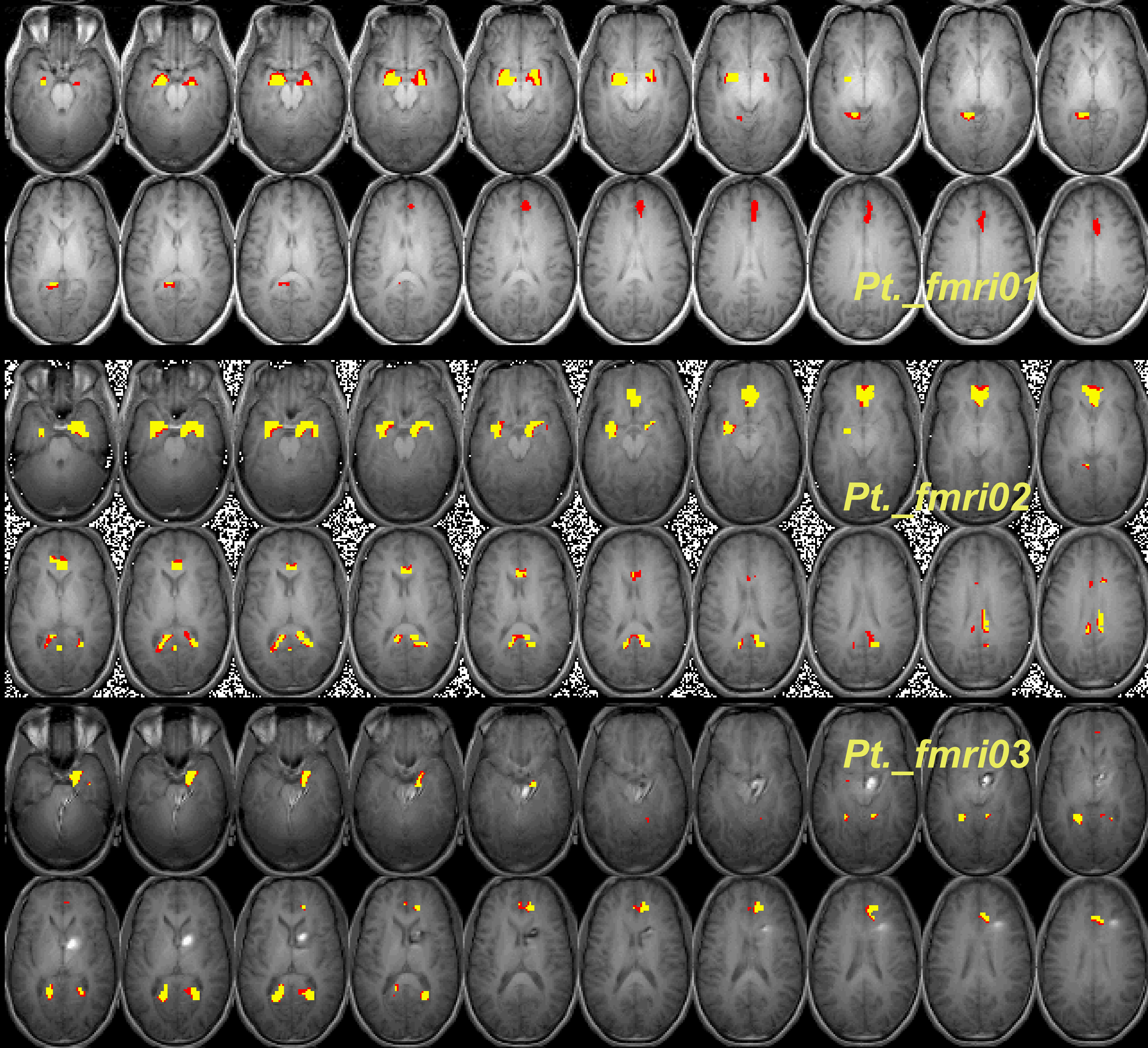
2. This can be used to study brain substrates in the imaging setting

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

Activation of Amygdala and Anterior/ Posterior Cingulate by Cocaine Cues

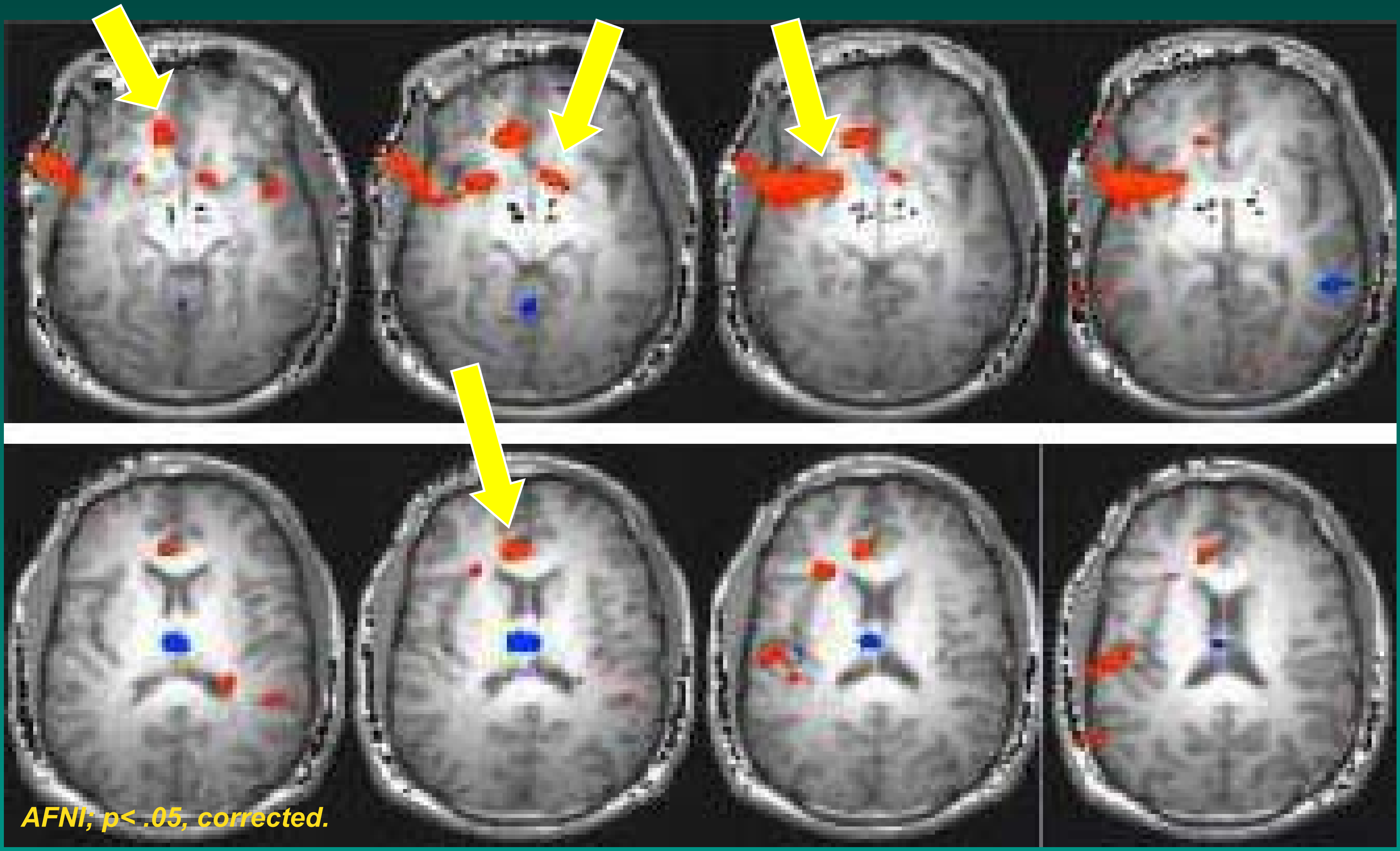
Cocaine Patients (n=3)

Bold fMRI



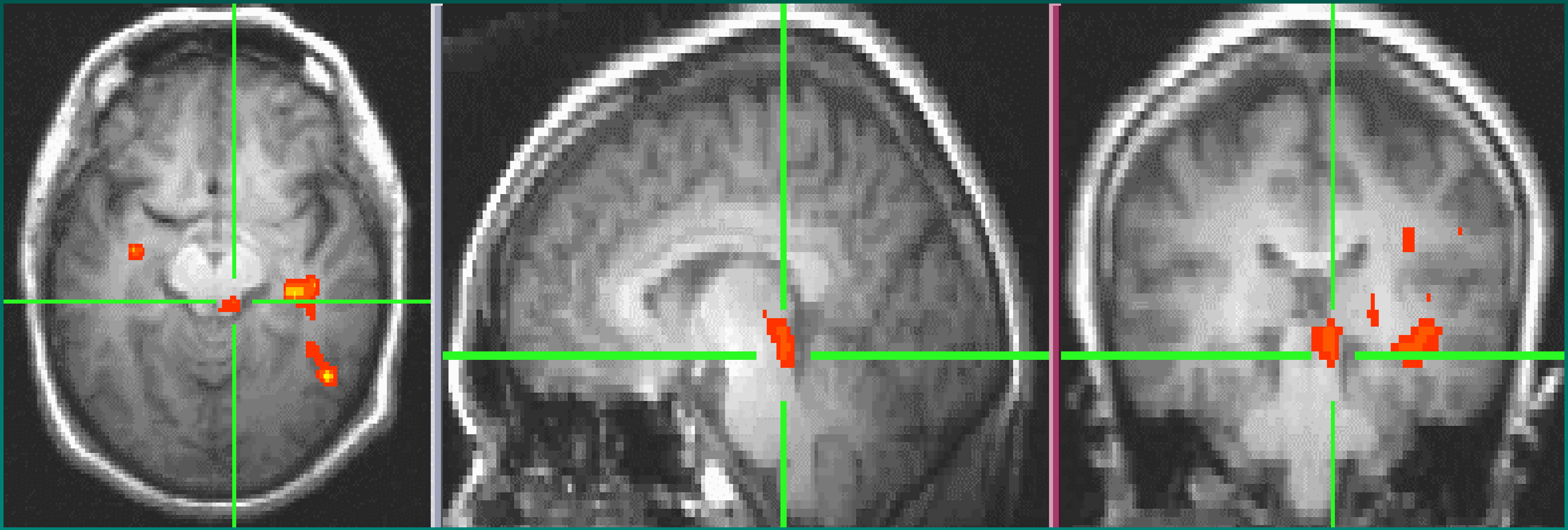
Differential Activation of L. Orbitofrontal, R. Ventral Striatum(NAc)/ Amyg/Basal Forebrain, Insula and Anterior Cingulate by Cocaine (vs. Non-Drug) Cues

ASL Perfusion fMRI



Differential Activation of VTA and Amygdala by Heroin-Video Cues in Methadone Patients vs. Controls

ASL perfusion fMRI



(AFNI map; p<.05, corrected)

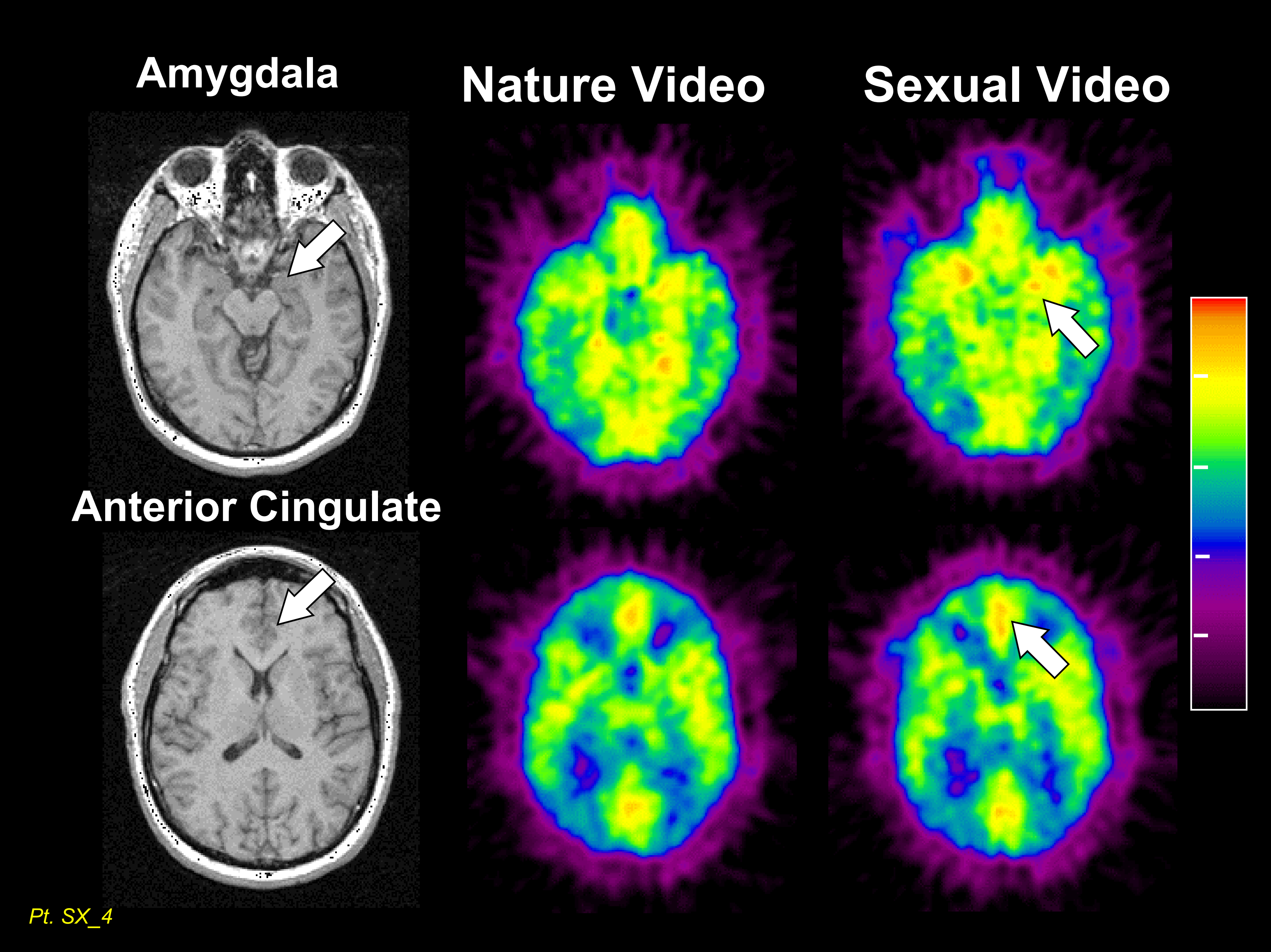
Brain Substrates of

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
Nature Video
Sexual Video
Anterior Cingulate
Pt. SX_4

AreasofBrainActivationinMalesandFemales DuringViewingofEroticFilmExcerpts

SherifKarama,[1,3] * Andre´RochLecours,[1,2,3] Jean-MaximeLeroux,[4]
PierreBourgou in,[2,3,4] GillesBeaudo in,[4,5] SvenJoub ert,[3]
andMarioBeauregard [1,3,4,5]
[1] Universite ´deMontre
´al,Centrederechercheen sciencesneurologiques,Montreal,Quebec,Canada
[2] MontrealNeurologicalInstitute,McGillUniversity,Montreal,Quebec ,Canad a
[3] Centrederecherche,Institutuniversitairedege ´riatriedeMon tre
´al,Montreal,Queb ec,Canada
[4] Centrehospitalierdel'Universite ´deMontre ´al(CHUM),Ho^pitalNotre-Dame,De
´partementde
radiologie,Montreal,Quebe c,Canada
[5] De ´partementderadiologie,Faculte ´deme ´decine,Universite
´deMon treal,Montreal,Quebec ,Canad a

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Abstract:Variouslinesofevidenceindicatethatmengenerallyexperiencegreatersexualarousal(SA)toerotic stimulithanwomen.Yet,littleisknownregardingtheneurobiologicalprocessesunderlyingsuchagender difference.Toinvestigatethisissue,functionalmagneticresonanceimagingwasusedtocomparetheneural correlatesofSAin20maleand20femalesubjects.Brainactivitywasmeasuredwhilemaleandfemalesubjects wereviewingeroticfilmexcerpts.ResultsshowedthatthelevelofperceivedSAwassignificantlyhigherin malethaninfemalesubjects.Whencomparedtoviewingemotionallyneutralfilmexcerpts,viewingeroticfilm excerptswasassociated,forbothgenders,withbilateralbloodoxygenleveldependant(BOLD)signal increasesintheanteriorcingulate,medialprefrontal,orbitofrontal,insular,andoccipitotemporalcortices,as wellasintheamygdalaandtheventralstriatum.Onlyforthegroupofmalesubjectswasthereevidenceof asignificantactivationofthethalamusandhypothalamus,asexuallydimorphicareaofthebrainknownto playapivotalroleinphysiologicalarousalandsexualbehavior.Whendirectlycomparedbetweengenders, hypothalamicactivationwasfoundtobesignificantlygreaterinmalesubjects.Furthermore,formalesubjects only,themagnitudeofhypothalamicactivationwaspositivelycorrelatedwithreportedlevelsofSA.These findingsrevealtheexistenceofsimilaritiesanddissimilaritiesinthewaythebrainofbothgendersresponds toeroticstimuli.TheyfurthersuggestthatthegreaterSAgenerallyexperiencedbymen,whenviewingerotica, mayberelatedtothefunctionalgenderdifferencefoundherewithrespecttothehypothalamus.Hum.Brain Mapping16:1–13,2002.

Keywords:erotica;sexualarousal;sexualbehavior;genderdifferences;genderdifferences;emotion; motivation;functionalmagneticresonanceimaging;limbicsystem;hypothalamus
HumanBrainMapping16:1–13(2002)_
DOI10.1002/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

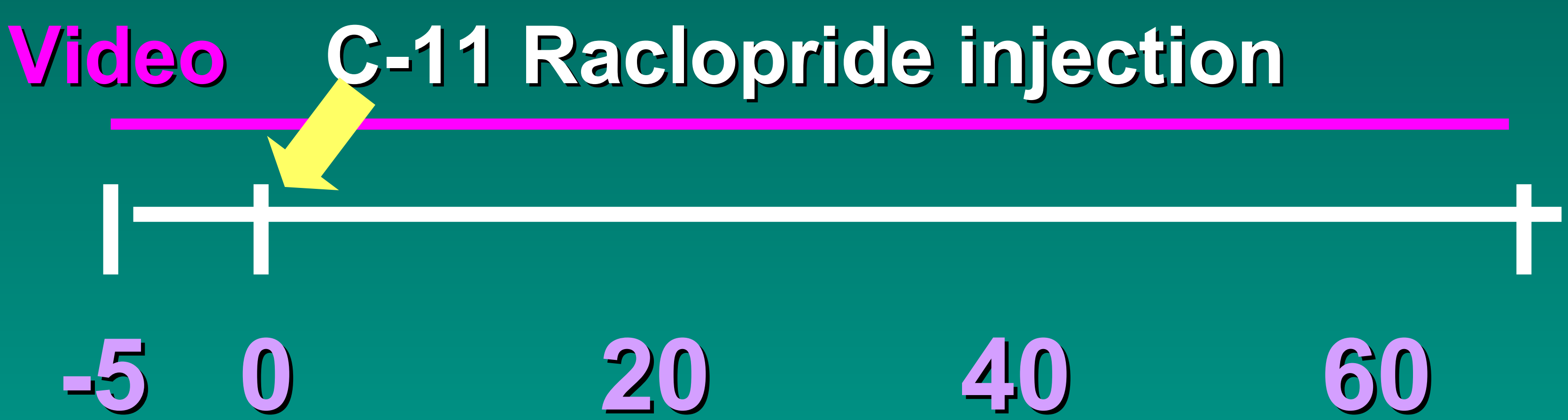
DA concentration ↑

Raclopride binding ↓

What is the neurochemistry of cue-induced craving?

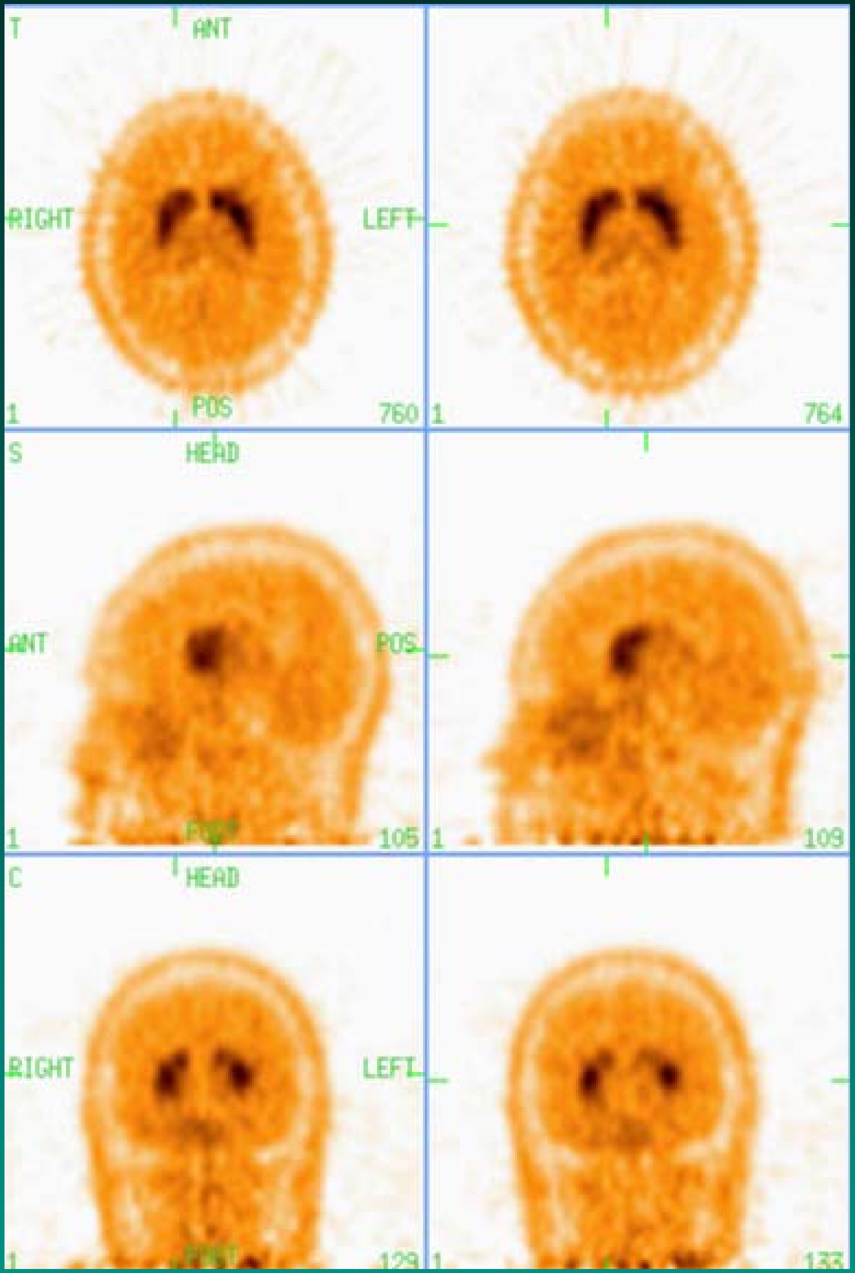
Using C-11 Raclopride to Index Endogenous Dopamine Release

PET Imaging Session

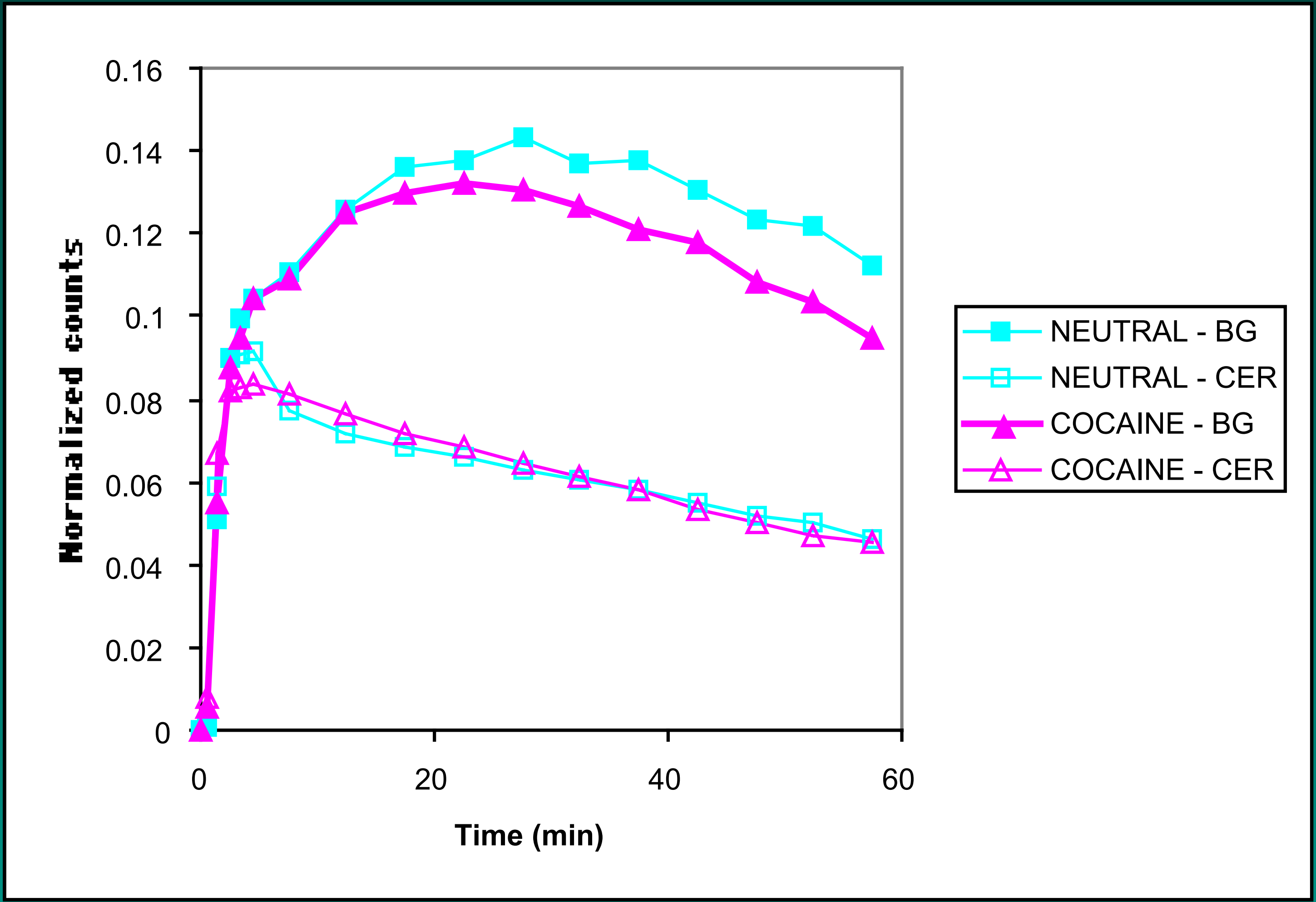


C-11 Raclopride Uptake in Basal Ganglia

(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?

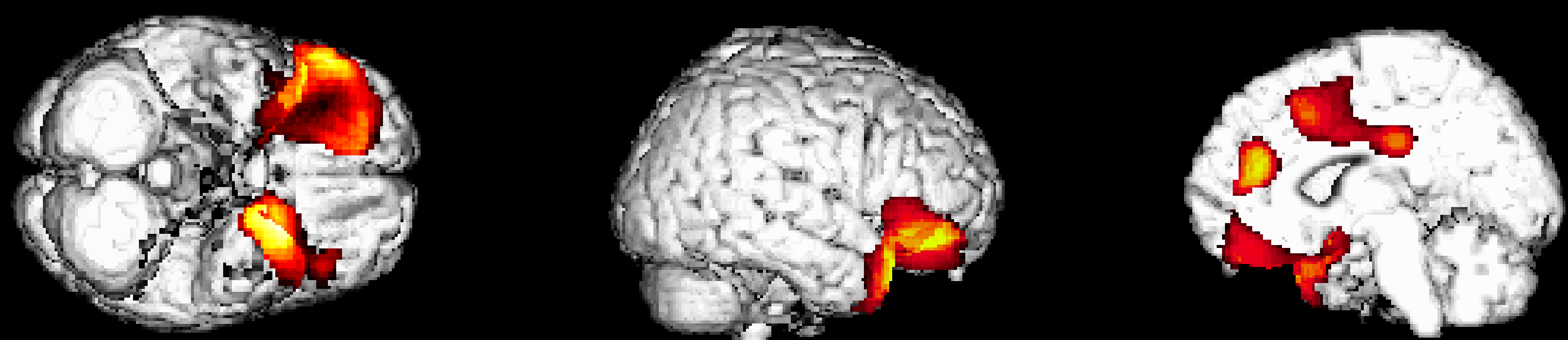
GABA B agonists as Candidates

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

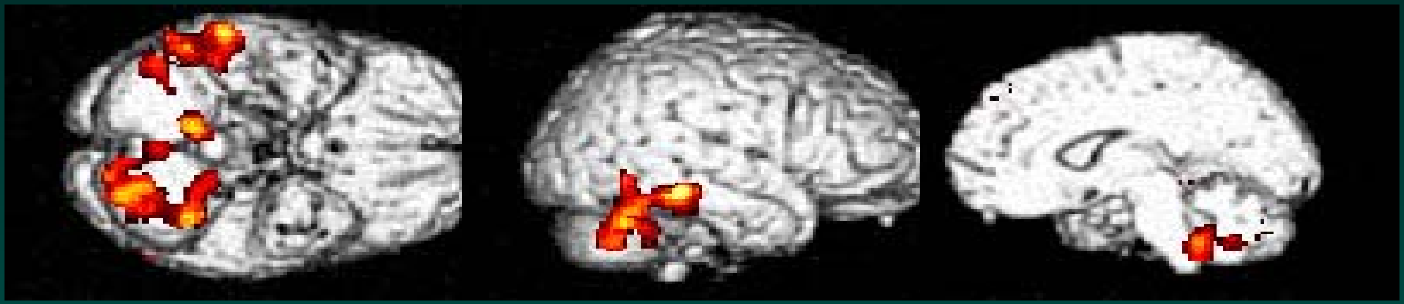
Hypothesis:

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.*

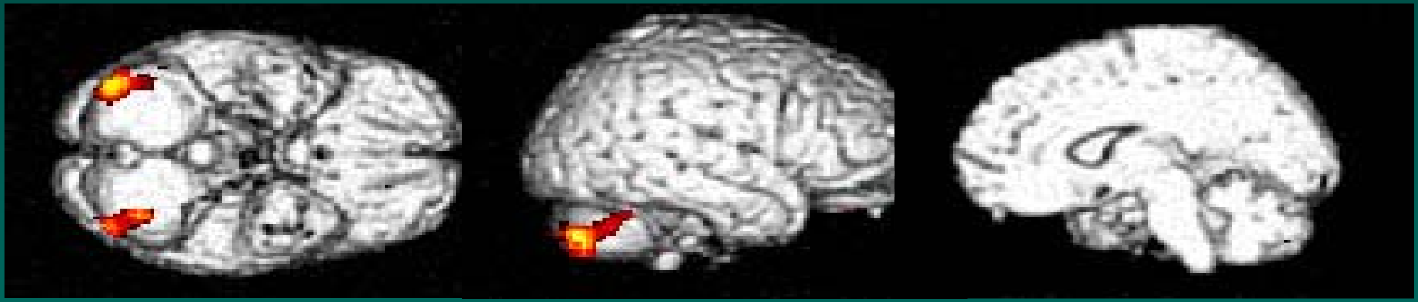
Absence of Limbic Activation During Cocaine Cue Exposure in Cocaine Patients (n=3) Taking the GABA B Agonist Baclofen



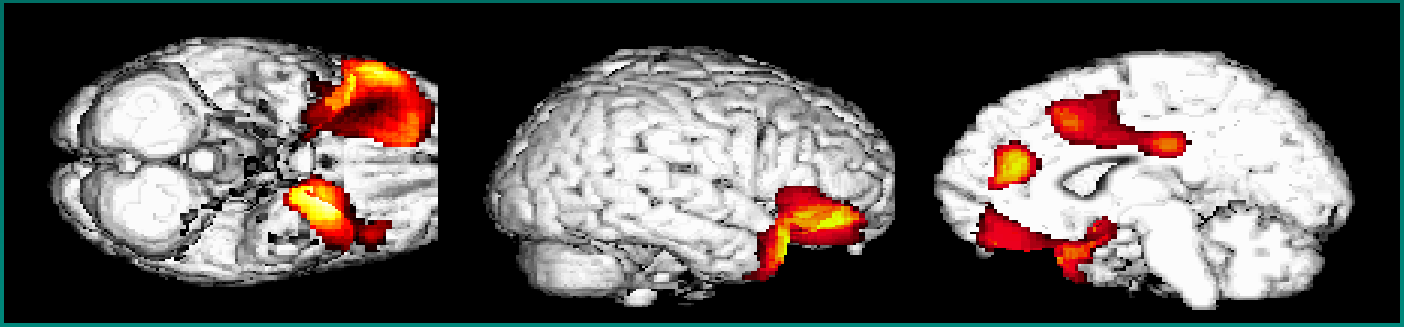
Limbic Activation During Cue-Induced Cocaine Craving in Unmedicated Cocaine Patients (n=14)



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. Neuroligand 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.

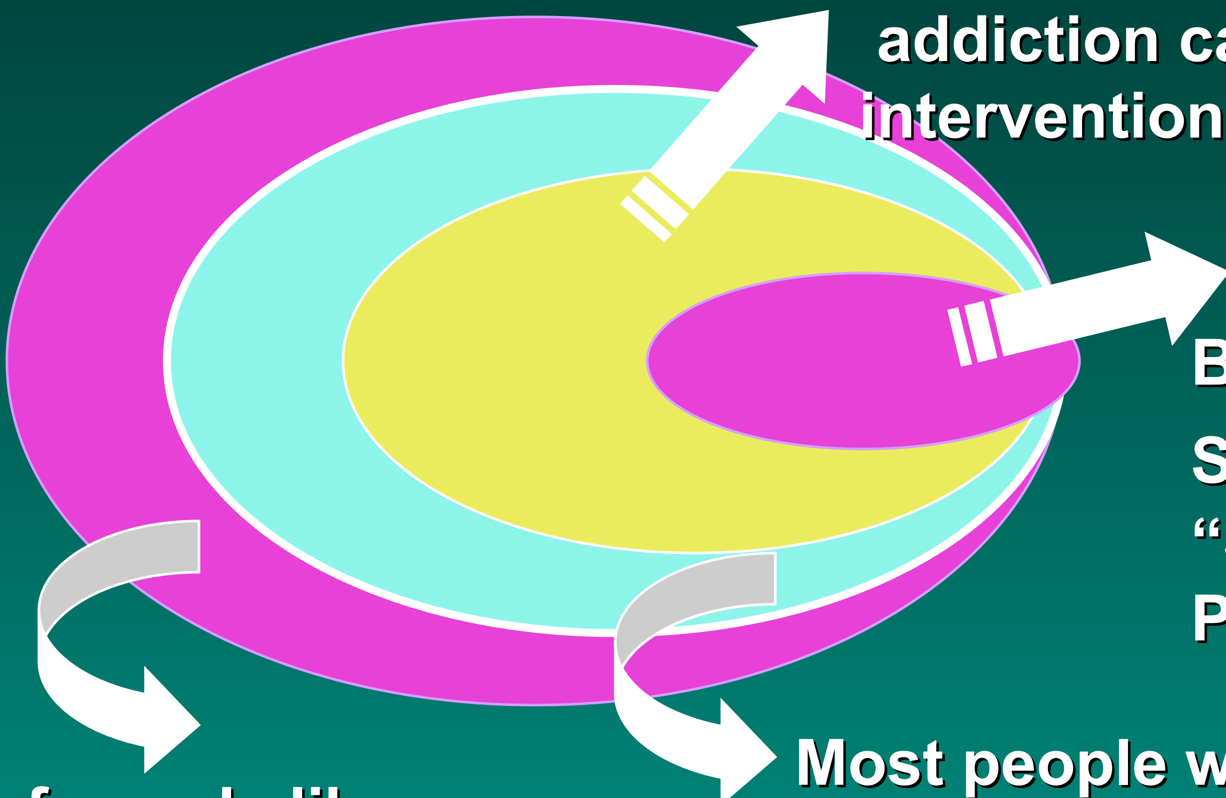
2) Patients vary in their ability to manage drug craving.

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…..



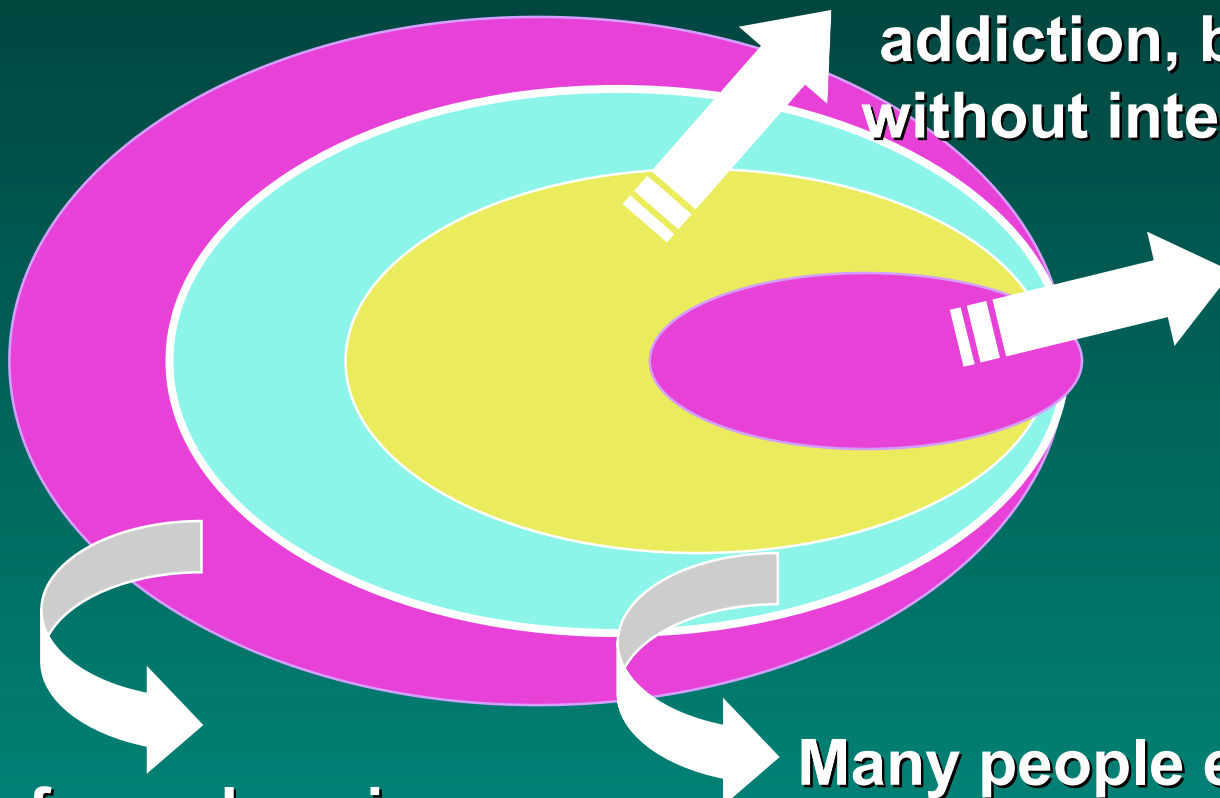
Some who continue to addiction can stop without intervention

But….Treatment Seekers: **BIG** "STOPPING" Problems !!

Lots of people like pleasurable drug effects

Most people who continue to regular use can stop easily

Understanding Vulnerability



Some continue to addiction, but can stop without intervention

But **Treatment Populations:**

BIG

"STOPPING"

Problems !!

Lots of people enjoy sex, chocolate, and gambling

Many people engage in these activities very regularly, without problems

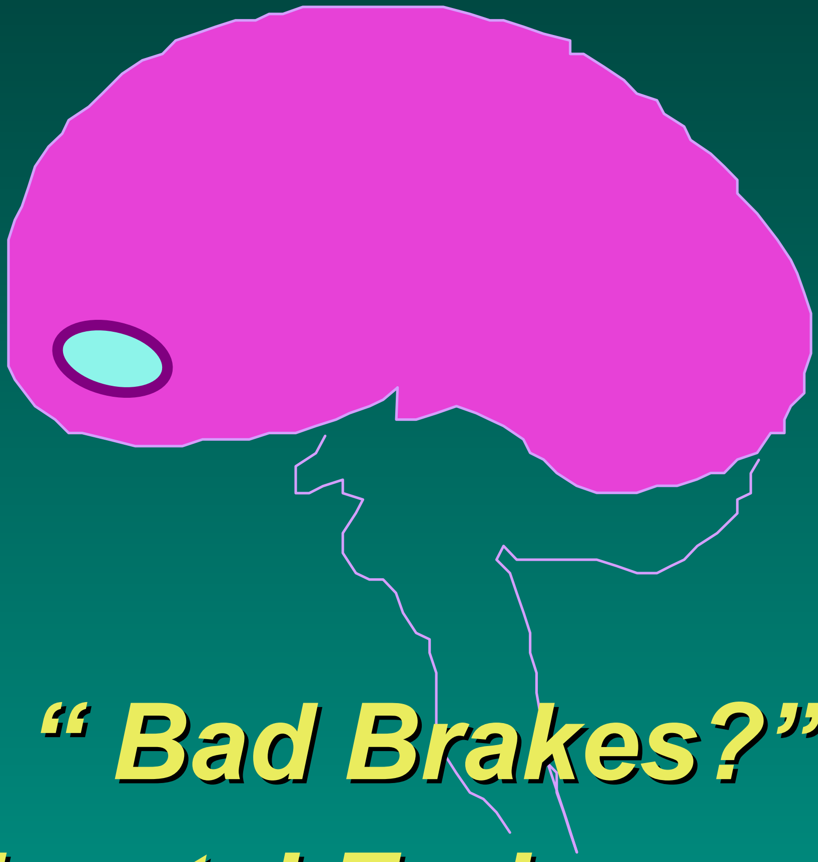
Why it's hard to say NO………

- 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?"

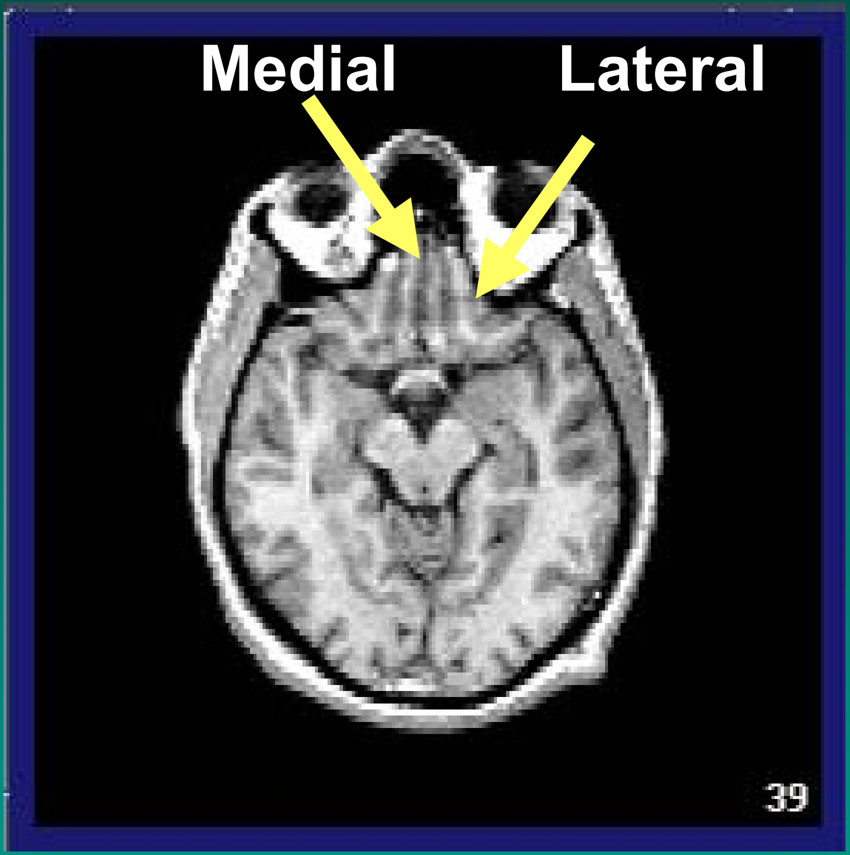
(Poor Frontal Endowment)

Why it’s hard to say NO………

Hypothesis:

Our treatment-seeking cocaine patients may show hypoactivity in medial aspects of the ventral orbital cortex, relative to non-stimulant user controls.

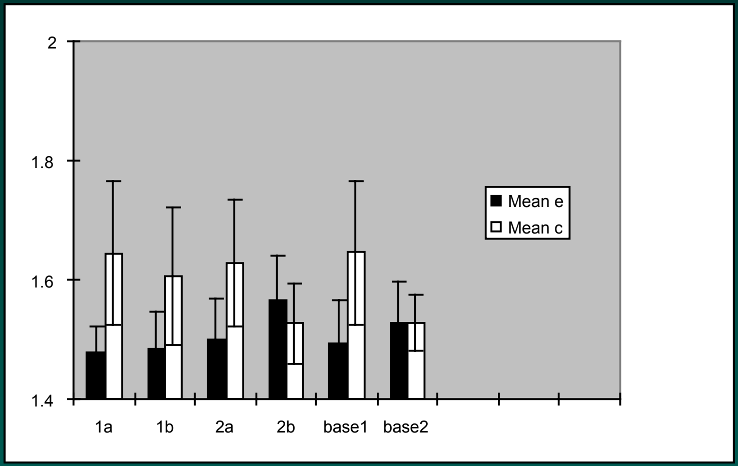
We analyzed the medial (rectal gyrus) and lateral aspects of the ventral orbital cortex, separately.



Cocaine patients (n=14)

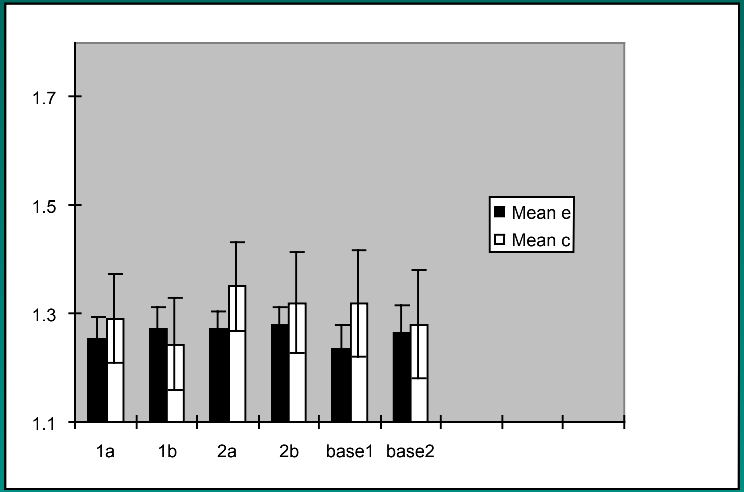
Controls (n=6)

Right Rectal Gyrus

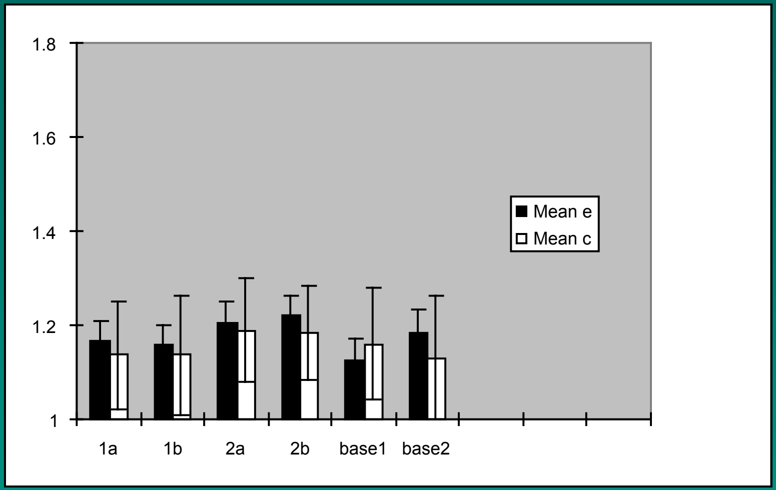


Right rectal gyrus, left lateral orbitofrontal, and right lateral orbitofrontal regions do not consistently differ between cocaine pts. vs. controls.

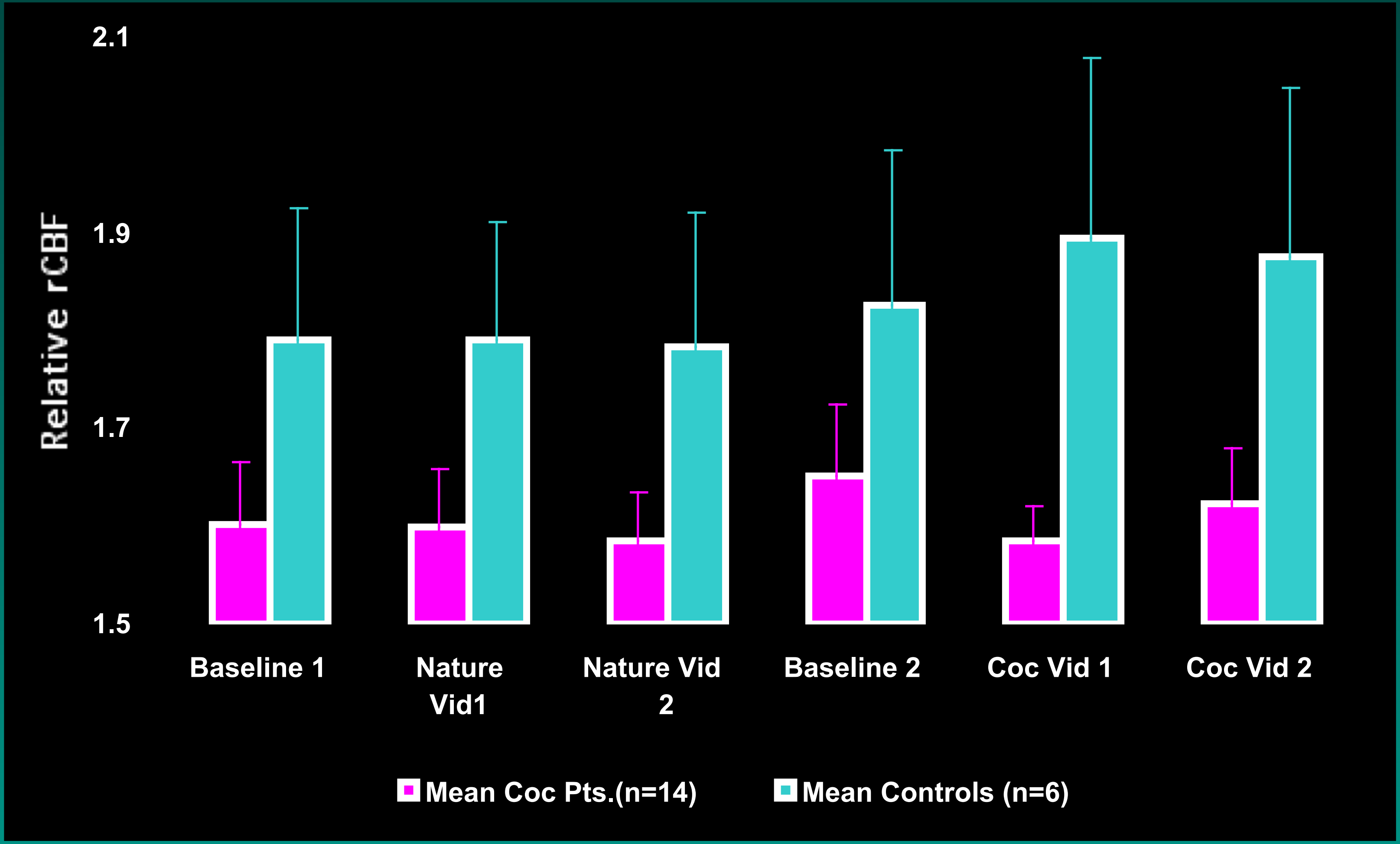
Left Lateral Orbitofrontal



Right Lateral Orbitofrontal

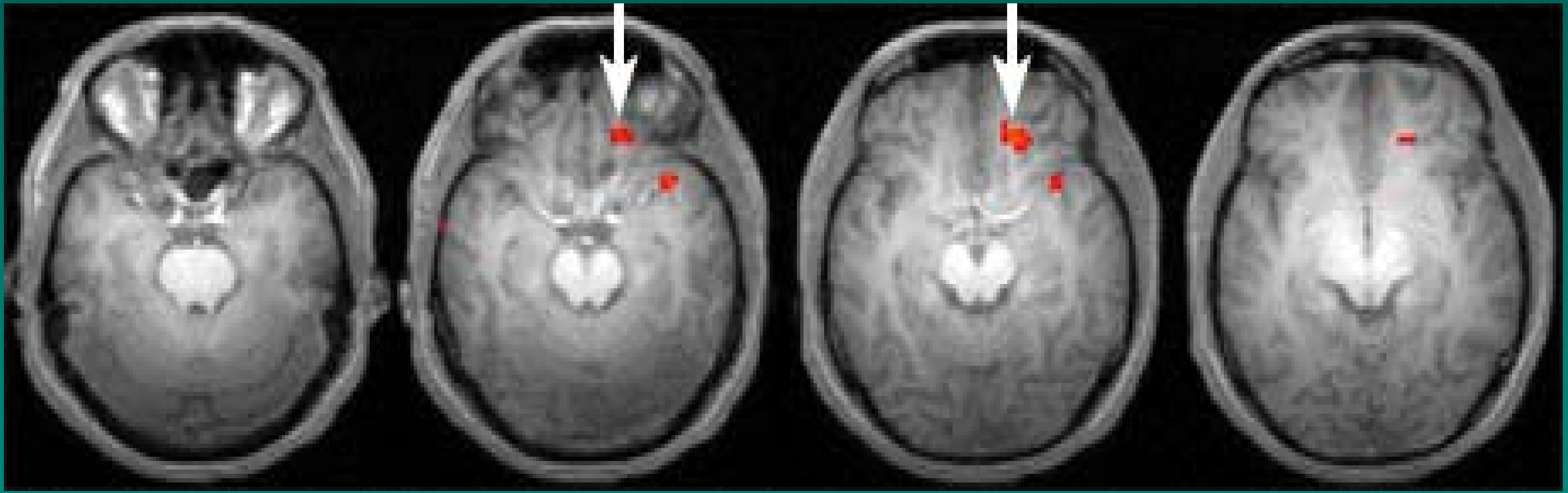


Hypoactivity in L. Ventromedial Orbitofrontal Cortex of Cocaine Patients Using O-15 PET



Resting Hypoactivity in L. Ventromedial Orbitofrontal Cortex (VMOFC) of Cocaine Patients (n=9) vs. Controls (n=7)

ASL Perfusion fMRI



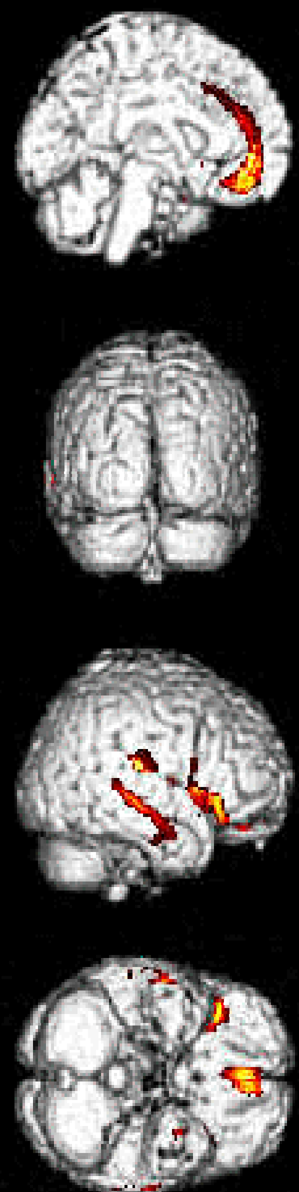
(VoxBo software; p<.05, corrected)

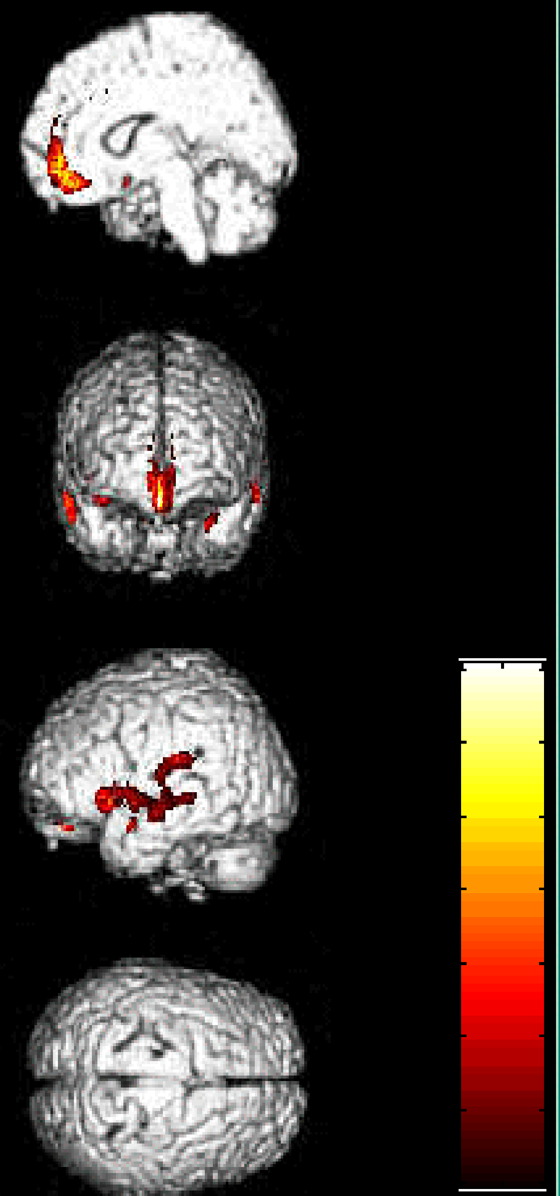
Relapse

Understanding Vulnerability

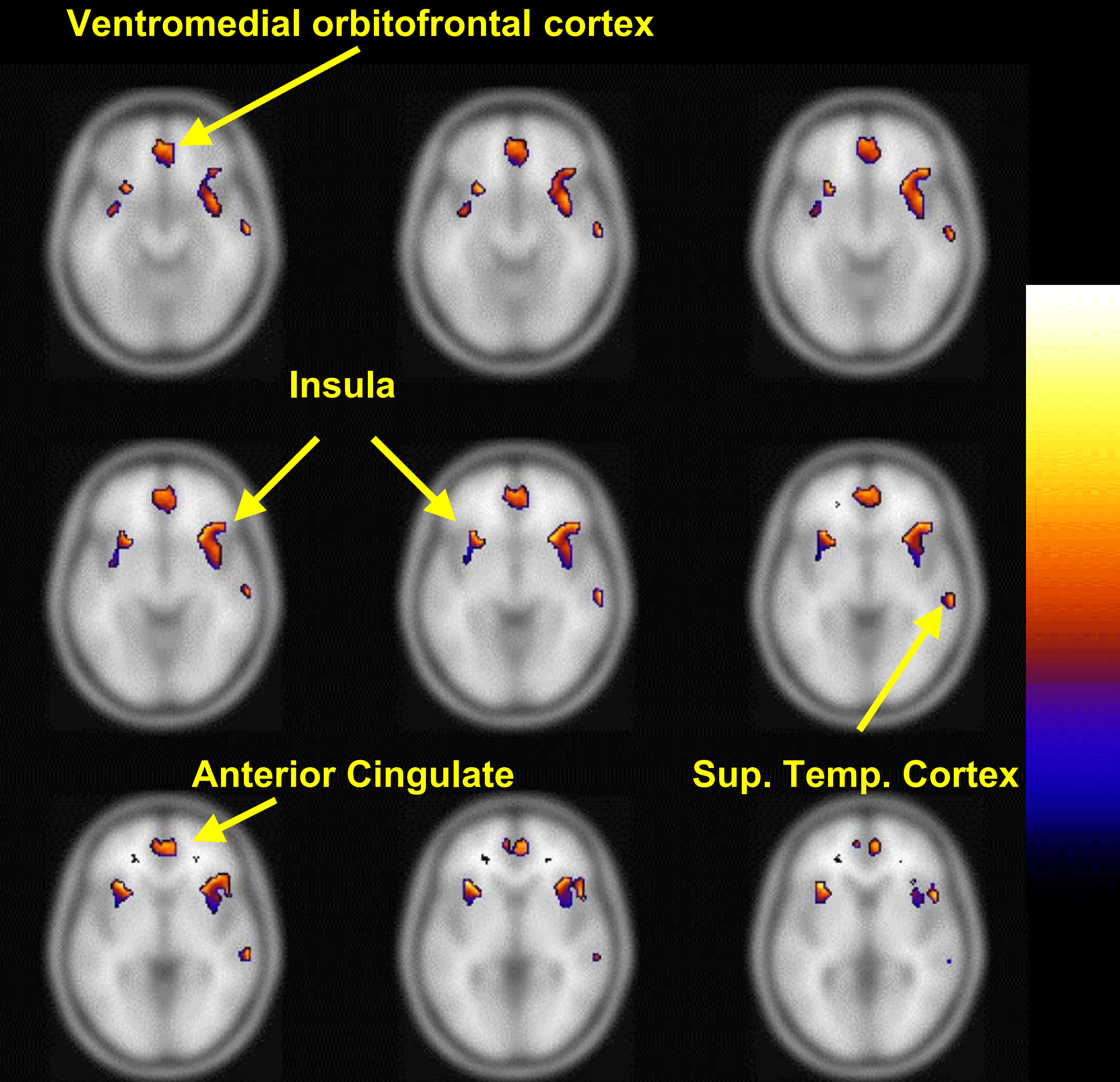
Do cocaine patients' brains show structural (gray matter) differences when compared to controls?

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!”

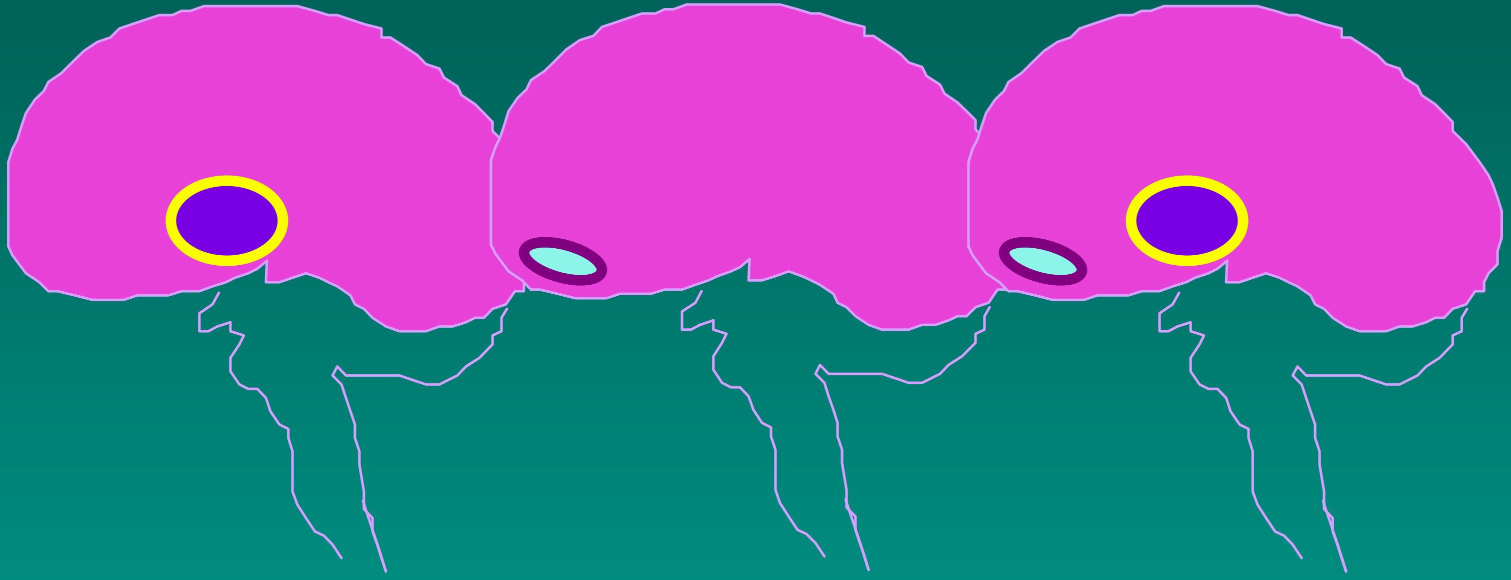
Double Trouble

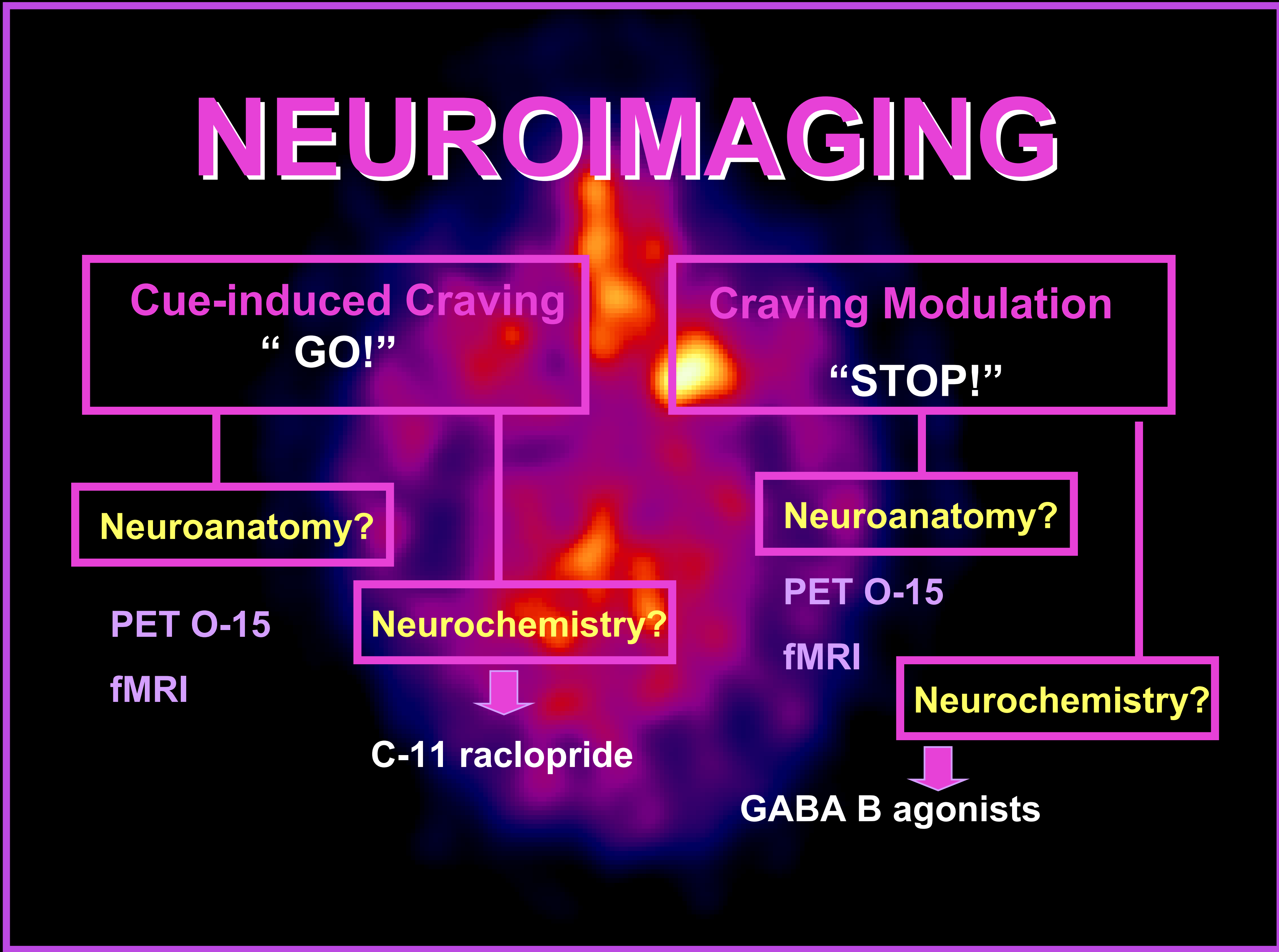
Throbbing amygdalae? *Bad brakes?* **Both ?**

(Withered Frontals)

Opiates, Brownies, Sex, Cocaine…Gambling

From Desire...to Disorder




NEUROIMAGING
Cue-induced Craving
“ GO!”
Craving Modulation
“STOP!”
Neuroanatomy?
PET O-15
fMRI
Neurochemistry?
C-11 raclopride
Neuroanatomy?
PET O-15
fMRI
Neurochemistry?
GABA B agonists

Neuroimaging & Conditioned Factors

Anna Rose Childress
Division Director

Research Assistants
Anna Fornash, Supevisor

Jason D. Gray
Kim Napier

Jillian Poston

Clinical Staff
Anita V. Hole
Frank Mulvaney
Gloria Carpenter

Ron Ehrman
Dir., Psychophysio. Lab

Substance Abuse Fellows
John Monterosso
Teri Franklin

Investigator
Steve Robbins
Nuclear Medicine Physician
Daniel Langleben
fMRI Physicist & Physician
John Listerud

Consultants/Collaborators: Nora Volkow, Paul Acton, John Detre, Dave Roberts, Wade Berretini, Antoine Bechara