Neurocircuitry of Reward and Addiction:

What Do We Know – What Do We Need to Learn?

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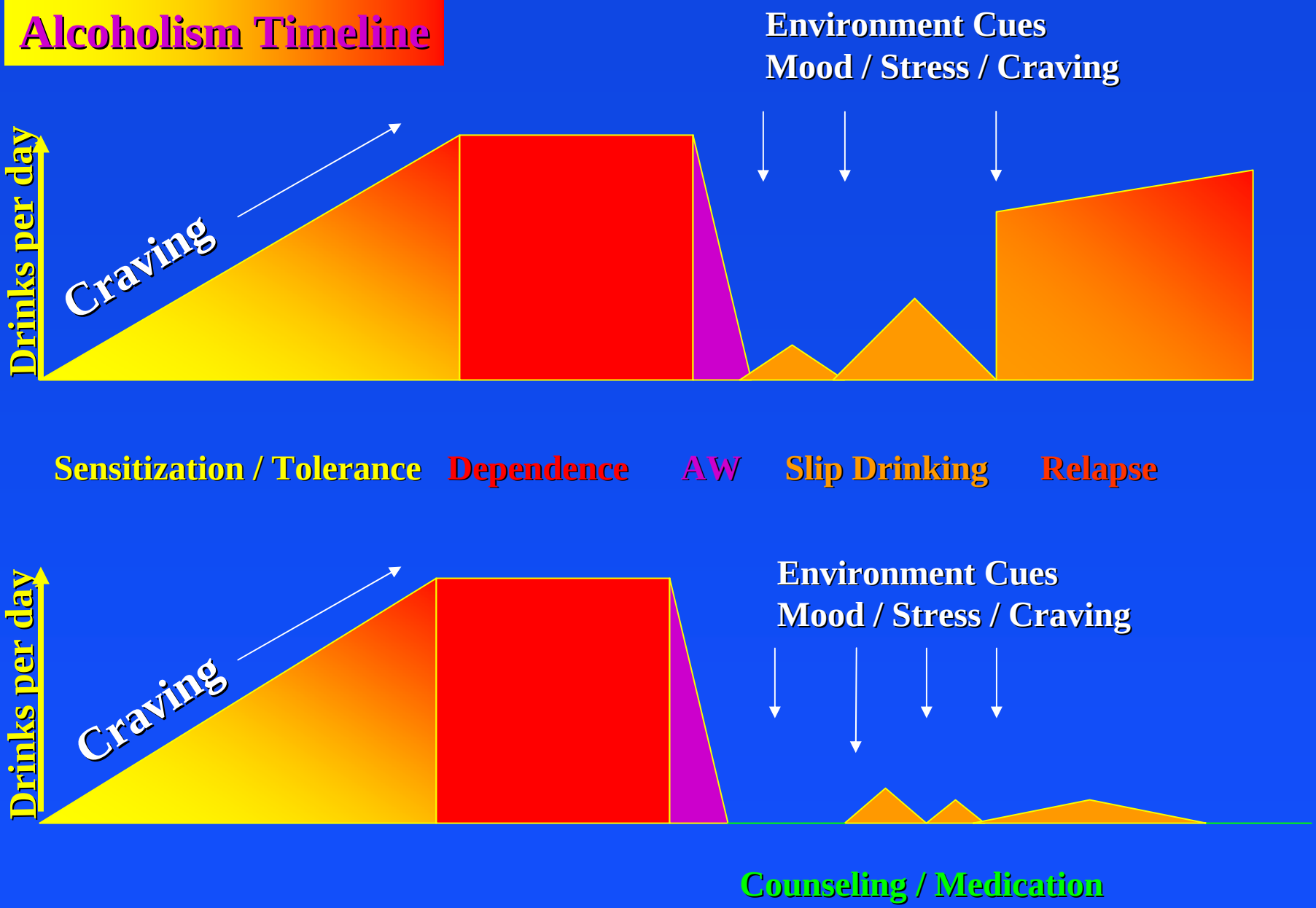
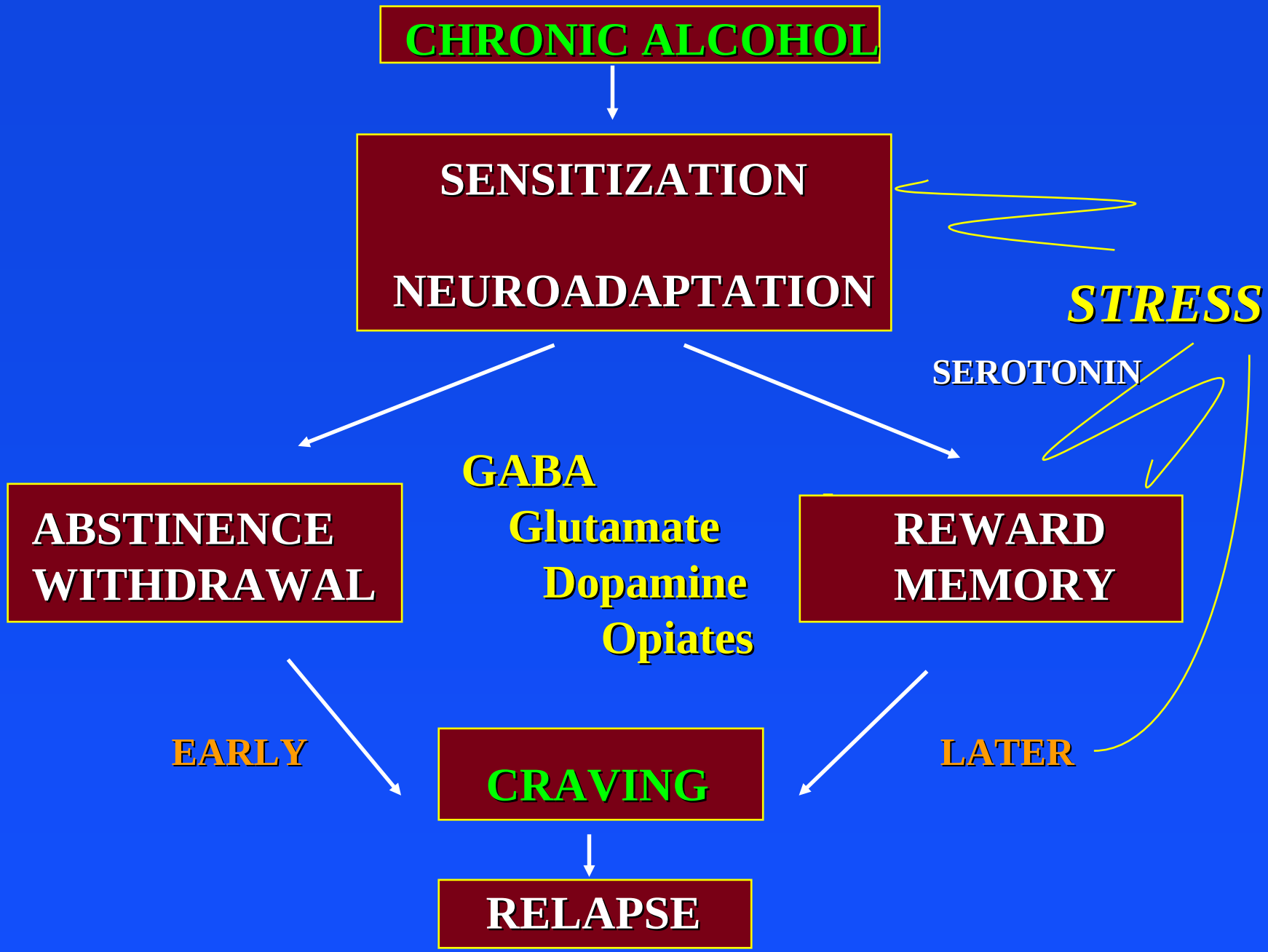
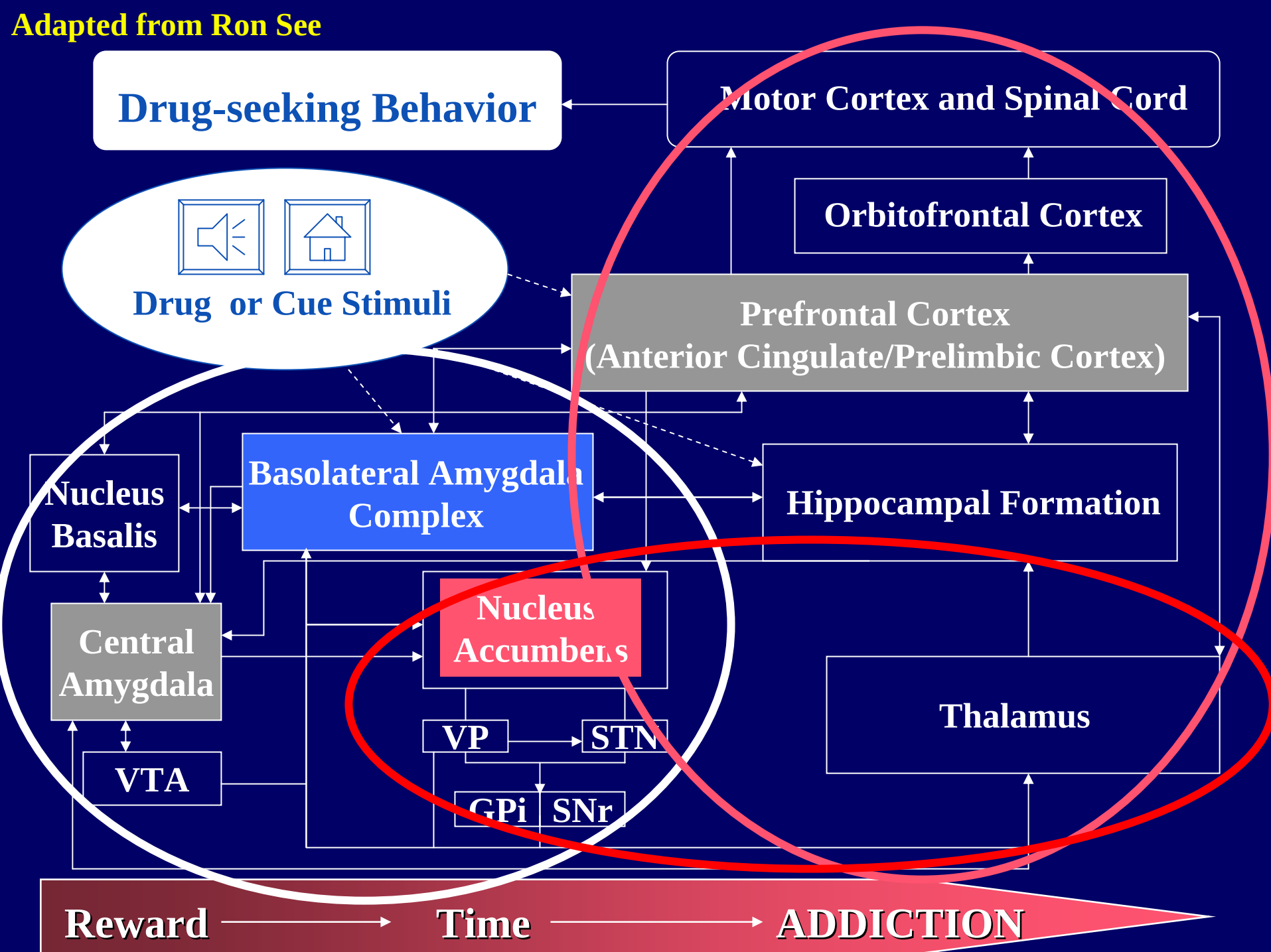
How has this conference helped me?

My ideas are Krystalized!

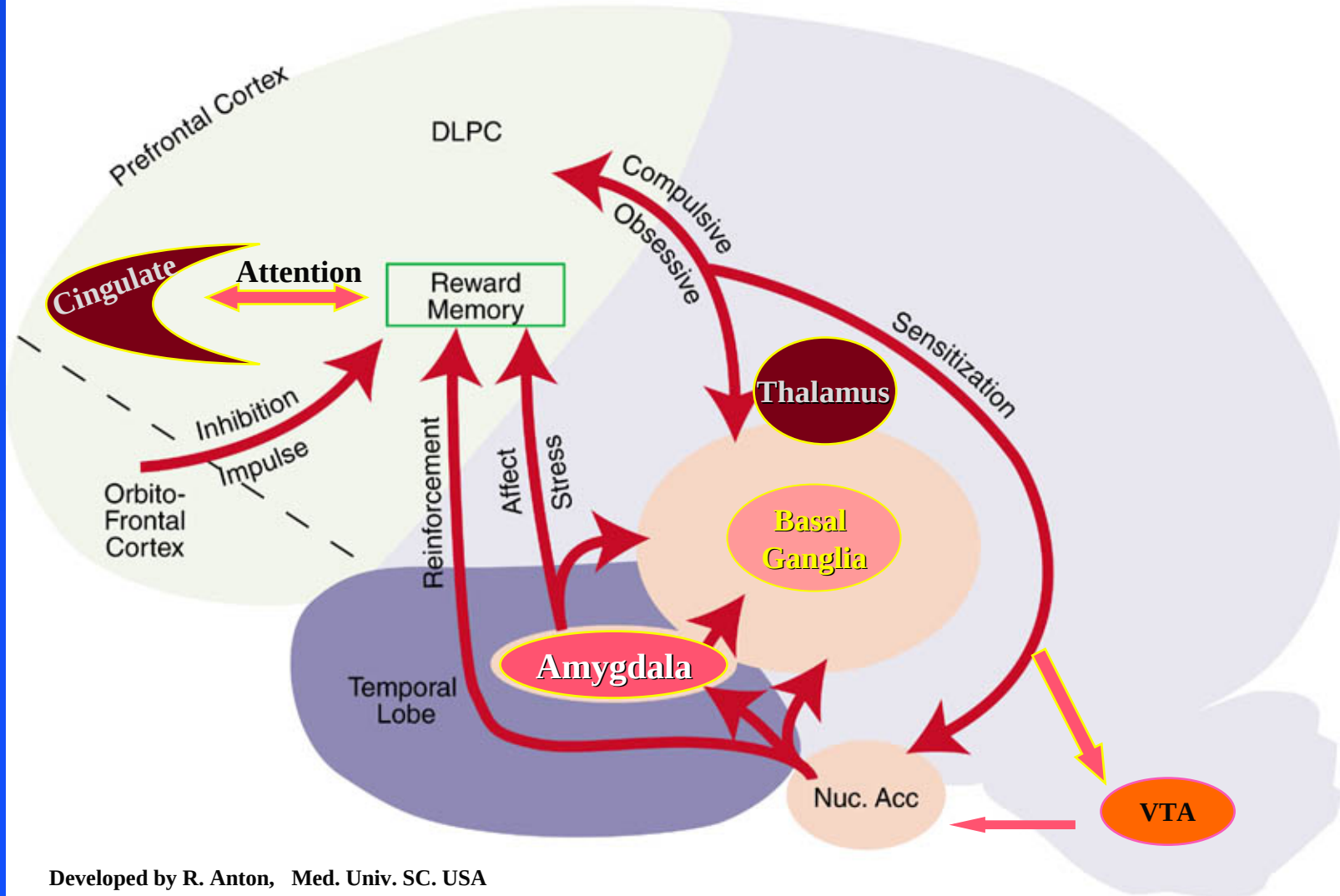
Alcoholism Timeline



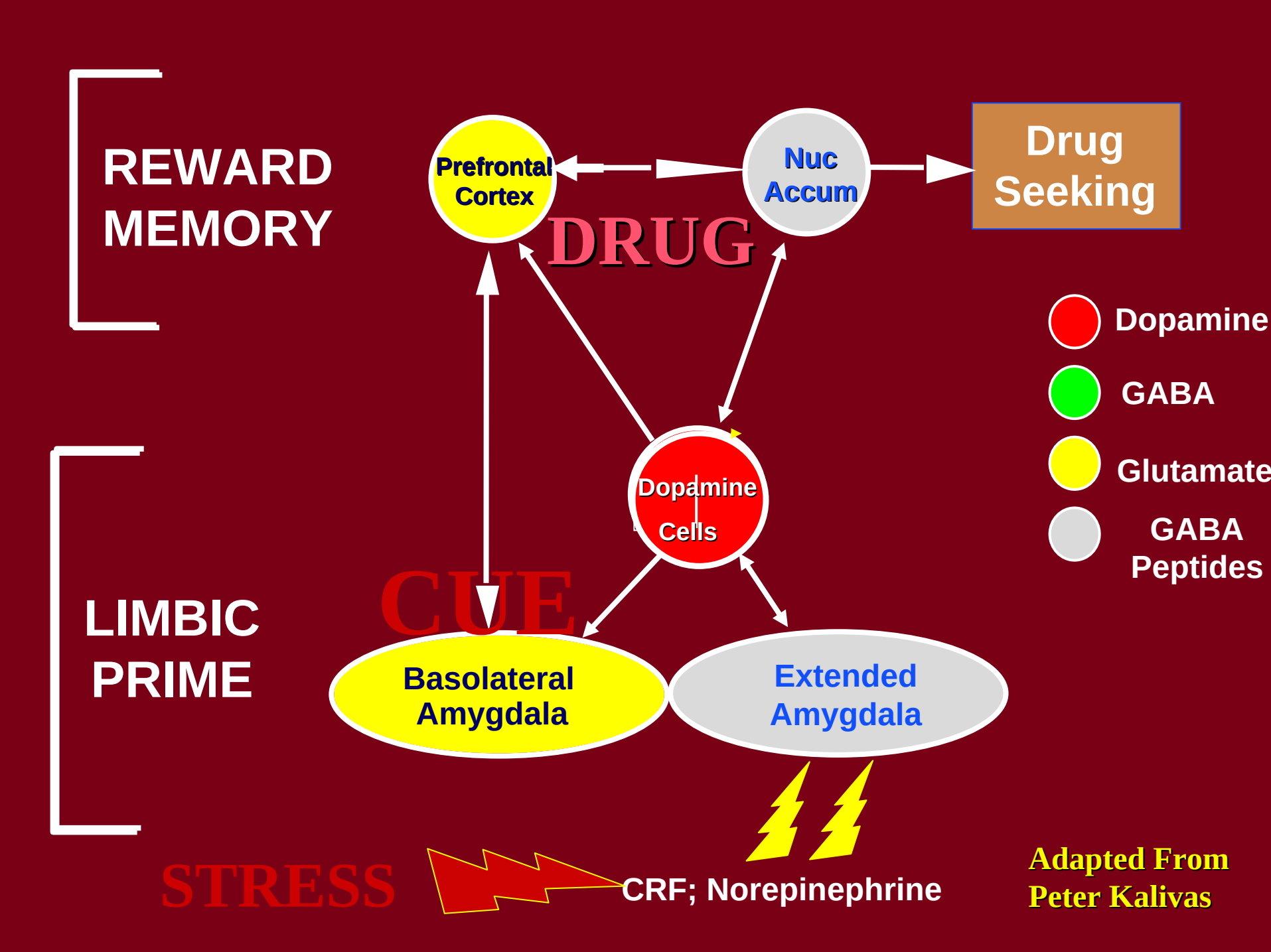

CHRONIC ALCOHOL
SENSITIZATION
NEUROADAPTATION
STRESS
SEROTONIN
GABA
Glutamate
Dopamine
Opiates
ABSTINENCE
WITHDRAWAL
REWARD
MEMORY
EARLY
LATER
CRAVING
RELAPSE


Adapted from Ron See
Drug-seeking Behavior
Motor Cortex and Spinal Cord
Orbitofrontal Cortex
Drug or Cue Stimuli
Prefrontal Cortex
(Anterior Cingulate/Prelimbic Cortex)
Nucleus Basalis
Basolateral Amygdala Complex
Hippocampal Formation
Central Amygdala
Nucleus Accumbens
VP
STN
VTA
GPi
SNr
Thalamus
Reward
Time
ADDICTION

Neuroanatomical Network of the Components of Craving



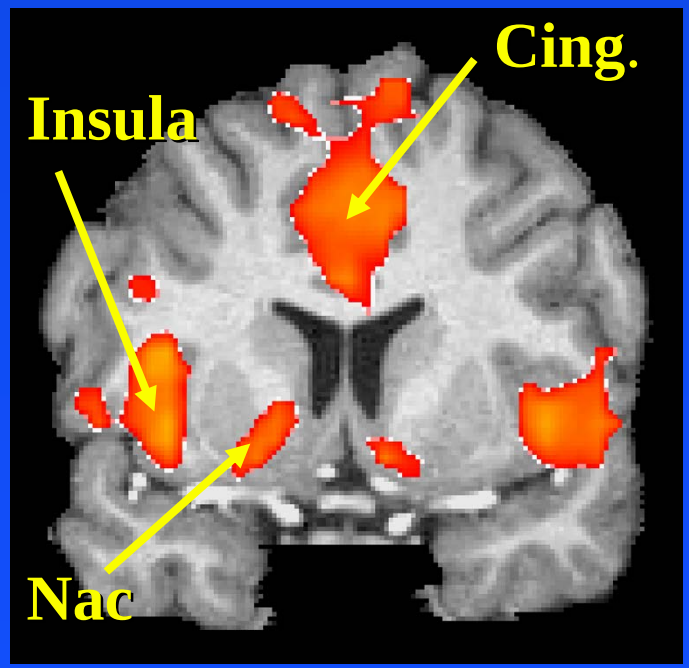
Developed by R. Anton, Med. Univ. SC. USA


REWARD
MEMORY
Prefrontal Cortex
Nuc Accum
Drug Seeking
DRUG
Dopamine
GABA
Glutamate
GABA Peptides
Dopamine Cells
LIMBIC PRIME
CUE
Basolateral Amygdala
Extended Amygdala
STRESS
CRF; Norepinephrine
Adapted From Peter Kalivas

Functional Activity in the Presence of Cues for Ethanol

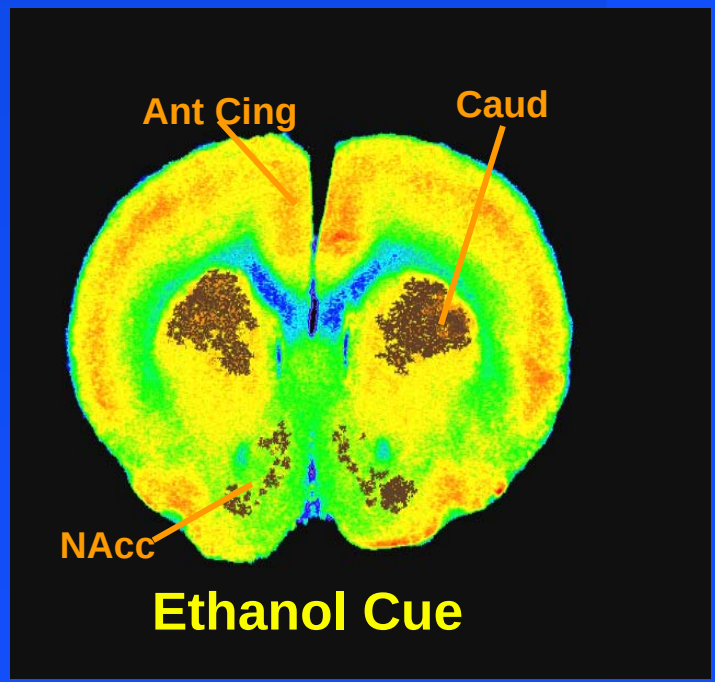
Myrick et. al. MUSC

MAN



Porrino et. al. WFU

RAT



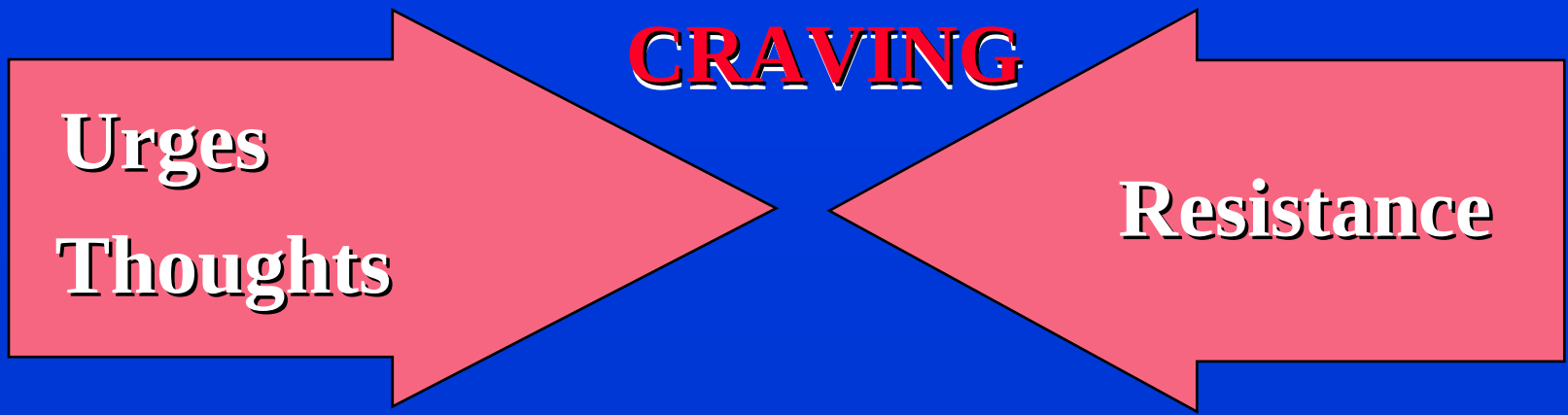
Other Study Findings…

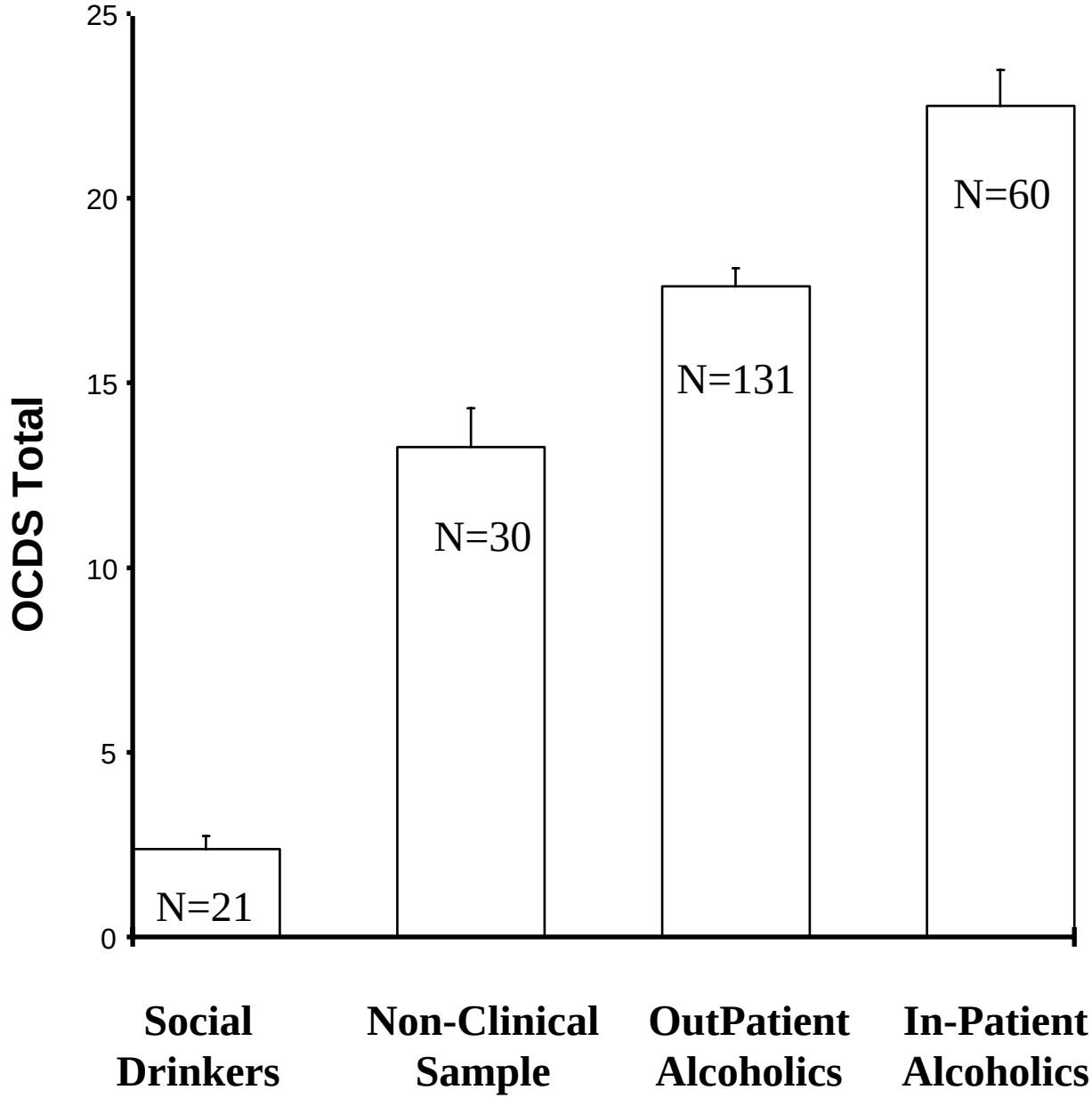
	INSULA	CINGULATE	NAC	OFC
COCAINE				
Grant, 1996		X		X
Breiter, 1997	X		X	
Mass, 1998		X		
Childress, 1999		X		
Wang, 1999	X			X
Garavan, 2000		X		
Kilts, 2001		X	X	
Wexler, 2001	X			
HEROIN				
Sell, 2000	X			X
NICOTINE				
Brody, 2002	X	X		X

Alcohol Cue Imaging Studies

	Insula	Cingulate	Vent. Striatum/ Nac	OFC	Basal Ganglia
Model 1995					X
Braus 2001					X
Wrase 2002		X	X	X	
Myrick In press	X	X	X		

Broader Concept of Craving




OCDS Total
25
20
15
10
5
0
N=21
N=30
N=131
N=60
Social Drinkers
Non-Clinical Sample
OutPatient Alcoholics
In-Patient Alcoholics

What Do We (Think) We Know!

- Alcoholics and other drug addicted individuals can be scanned and do experience craving (urge to use) within the scanner.
- This craving can be manipulated through cue induction.
- Paradigms testing reward and emotive circuits do work in the scanner environment.
- Limbic, paralimbic, as well as cortical brain regions are involved with incentive reward, attention, and possibly resistance mechanisms associated with alcohol and drug cues.
- Receptor systems and neurotransmitter levels can be measured in relationship to state of craving and alcohol/drug use.
- There is some homology between rodent and human brain regional activation to cues.

What Do We Need To Learn?

Mechanism Related

- Need to know the developmental course of brain regional activation changes. Do early stage alcoholics differ from chronic severe alcoholic?
- How does the circuit work.What gets activated first and how is the signal propagated?
- What is the underlying neurochemistry controlling activation in a specific region and its connections to other regions?
- Do all regional activations to cues represent incentive salience (reward)? Or do some represent motive resistance/inhibitory mechanisms or allostatic relief mechanisms?
- How does “stress” alter cue induced brain activation?

What Do We Need To Learn?

Treatment Related

- How does pharmacological pretreatment both acutely and chronically affect cue induced brain regional activation?
- Does specific behavioral interventions (ex. CBT) alter cue induced regional brain activation?
- Does cue induced regional brain activation predict treatment response to either pharmacological or psychosocial interventions?
- What does commonality of regional brain activation tell us about overlap with other disorders such as OCD, depression, ADHD and other impulse control disorders?

What Do We Need To Learn?

Genetic Relationships

- Does genetic variability predict cue induced activation or its developmental course? Family Hx positive versus negative for instance?
- Do genes controlling specific neuronal systems involved with the incentive reward pathway predict who will have regional brain activation from alcohol or alcohol/drug cues?
- Will specific functional allelic differences in certain neurotransmitter systems predict pharmacological variability in alteration of cue induced regional brain activation? Mu opiate receptor allelic differences predicting naltrexone suppression of limbic activation?

Alcohol Cue Imaging

	Technique	Cue	Findings
Modell, 1995	SPECT	taste	R Caudate
George, 2001	fMRI	taste/ visual	L DLPC, Anterior thalamus
Schneider, 2001	fMRI	odor	R Amg/hippo area, Sup Temp gyrus, cerebellum
Braus, 2001	fMRI	visual	Ventral putamen, basal ganglia
Wrase, 2002	fMRI	visual	Ventral striatum, Ant Cing, Orbitofrontal gyrus
Hommer, 1997	PET	mCPP	Blunted OFC and PFC, ↑cerebellum and post cing