Neurocircuitry of Reward and Addiction:
What Do We Know – What Do We Need to Learn?

Raymond F. Anton, MD

Distinguished University Professor of Psychiatry
Director of the Center for Drug and Alcohol Programs
Scientific Director - Alcohol Research Center
Medical University of South Carolina

Supported by NIAAA – P50:Alcohol Research Center Grant
How has this conference helped me?
My ideas are Krystalized!
CHRONIC ALCOHOL

SENSITIZATION

NEUROADAPTATION

STRESS

SEROTONIN

GABA

Glutamate

Dopamine

Opiates

ABSTINENCE

WITHDRAWAL

REWARD

MEMORY

EARLY

CRAVING

LATER

RELAPSE
Drug-seeking Behavior

Motor Cortex and Spinal Cord

Orbitofrontal Cortex

Prefrontal Cortex
(Anterior Cingulate/Prelimbic Cortex)

Thalamus

STN

GPi

SNr

VP

VTA

Nucleus Basalis

Central Amygdala

Basolateral Amygdala Complex

Nucleus Accumbens

Reward

Time

ADDICTION

Adapted from Ron See
Dopamine
GABA
Glutamate
Peptides

Prefrontal Cortex
Nuc Accum

Drug Seeking

Prefrontal Cortex
Dopamine Cells

Basolateral Amygdala
Extended Amygdala

Drug
CUE

STRESS

LIMBIC PRIME

REWARD MEMORY

Adapted From Peter Kalivas
Functional Activity in the Presence of Cues for Ethanol

Myrick et. al. MUSC
MAN

Porrino et. al. WFU
RAT

- Insula
- Cing.
- Nac

Ethanol Cue
Other Study Findings…

<table>
<thead>
<tr>
<th></th>
<th>INSULA</th>
<th>CINGULATE</th>
<th>NAC</th>
<th>OFC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COCAINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grant, 1996</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Breiter, 1997</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass, 1998</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Childress, 1999</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Wang, 1999</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garavan, 2000</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Kilts, 2001</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wexler, 2001</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HEROIN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sell, 2000</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>NICOTINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brody, 2002</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Alcohol Cue Imaging Studies

<table>
<thead>
<tr>
<th></th>
<th>Insula</th>
<th>Cingulate</th>
<th>Vent. Striatum/Nac</th>
<th>OFC</th>
<th>Basal Ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Braus 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Wrase 2002</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Myrick In press</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Broader Concept of Craving

Urges
Thoughts

CRAVING

Resistance
Social Drinkers  Non-Clinical Sample  OutPatient Alcoholics  In-Patient Alcoholics

N=21  N=30  N=131  N=60

OCDS Total
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

<table>
<thead>
<tr>
<th>Technique</th>
<th>Cue</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>taste</td>
<td>R Caudate</td>
</tr>
<tr>
<td>fMRI</td>
<td>taste/visual</td>
<td>L DLPC, Anterior thalamus</td>
</tr>
<tr>
<td>fMRI</td>
<td>odor</td>
<td>R Amg/hippo area, Sup Temp gyrus, cerebellum</td>
</tr>
<tr>
<td>fMRI</td>
<td>visual</td>
<td>Ventral putamen, basal ganglia</td>
</tr>
<tr>
<td>fMRI</td>
<td>visual</td>
<td>Ventral striatum, Ant Cing, Orbitofrontal gyrus</td>
</tr>
<tr>
<td>PET</td>
<td>mCPP</td>
<td>Blunted OFC and PFC, ↑cerebellum and post cing</td>
</tr>
</tbody>
</table>