Dopamine Imaging, Stress and Neuroendocrine Changes in Alcoholics and Subjects at Risk for Alcoholism

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Johns Hopkins University NIAAA Interactive Research Grants (IRPGs)

Sons/Daughters of Alcoholics

Alcoholics

Endocrine Core
AA10158
G. Wand- PI

Recruitment Core
AA12837
M. McCaul- PI

PET Core
AA12839
D. Wong- PI
Specific Aims

I. To examine PET derived measurements of dopamine release as a function of alcohol dependence status and risk of alcoholism (i.e., family history, trait anxiety, and novelty seeking).

II. To examine HPA axis activation by opioid blockade and by psychological stress as a function of alcohol dependence status and risk of alcoholism.

III. To examine the relationship between DArel and cortisol production.

IV. To examine the association between PET D2 receptor (D2R) and DA transporter (DAT) density and risk for alcoholism.

V. To examine the relationship between PET D2R/DAT density and alcohol sensitivity and liking.
Mesolimbic Reward Pathway

- PFC
- Postsynaptic
- DA
- nucleus accumbens
- Presynaptic
- OP
- VTA
- OPIOID NEURON
- Alcohol
What is the evidence that stress alters mesolimbic dopamine release and drug reward?
Effects of Stress in Animals

• Increases drug self-administration.

• Increases drug-induced DA release, in part through increasing expression of adenyl cyclase signal transduction.

• Self-admin attenuated by ↓ glucocorticoids levels.

• Glucocorticoids mimic stress effects on self-admin and DA release.

• Glucocorticoids are key stress hormones involved in mesolimbic dopaminergic sensitization.
Dopamine Release without Stress

Dopamine Release after Stress

Drug
Alcohol Choice and Amphetamine Effects in Social Drinkers

• Moderate drinkers reported significantly greater amphetamine effects than light drinkers

• Responses to alcohol predicted subsequent responses to amphetamine

Screening and Assessment: Alcohol Dependence and Risks of Alcoholism Studies

- NEO Personality Inventory
- Brief Symptom Inventory (BSI)
- Beck Depression Inventory (BDI)
- State-Trait Anxiety Inventory (STAI)
- Semi-Structure Assessment for the Genetics of Alcoholism (SSGA)
- Timeline Followback
- Life Expression Survey (LES)
- Perceived Hassles and Uplifts Scale
- History and Physical Exam
- Breathalyzer
- Urine Drug Screen
- Urine Pregnancy
- Blood for Genetic Testing
# PET Procedures

## Alcohol Dependence

<table>
<thead>
<tr>
<th>Min</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>-35</td>
<td>State-Trait Anxiety Inventory</td>
</tr>
<tr>
<td>-25</td>
<td>Blood Sample</td>
</tr>
<tr>
<td>-15</td>
<td>Analog Drug Effect Scales</td>
</tr>
<tr>
<td>-5</td>
<td>Blood sample</td>
</tr>
<tr>
<td>3</td>
<td>Analog</td>
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<tr>
<td>6</td>
<td>Analog</td>
</tr>
<tr>
<td>10</td>
<td>Analog</td>
</tr>
<tr>
<td>15</td>
<td>Analog and Blood Sample</td>
</tr>
<tr>
<td>25</td>
<td>Analog</td>
</tr>
<tr>
<td>35</td>
<td>Blood Sample</td>
</tr>
<tr>
<td>55</td>
<td>Analog and Blood Sample</td>
</tr>
<tr>
<td>75</td>
<td>Blood Sample</td>
</tr>
<tr>
<td>85</td>
<td>Analog and State-Trait Anxiety Inventory</td>
</tr>
</tbody>
</table>

## Risks of Alcoholism

<table>
<thead>
<tr>
<th>Min</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>-35</td>
<td>State-Trait Anxiety Inventory, Perceived Stress Scale, Combined Hassles and Uplifts Scale</td>
</tr>
<tr>
<td>-25</td>
<td>Blood Sample</td>
</tr>
<tr>
<td>-15</td>
<td>Analog Drug Effect Scales</td>
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<tr>
<td>15</td>
<td>Analog</td>
</tr>
<tr>
<td>25</td>
<td>Analog and State-Trait Anxiety Inventory and Blood Sample</td>
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<tr>
<td>45</td>
<td>Blood Sample</td>
</tr>
<tr>
<td>55</td>
<td>Analog and State-Trait Anxiety Inventory</td>
</tr>
<tr>
<td>65</td>
<td>Blood for GH</td>
</tr>
<tr>
<td>85</td>
<td>Analog and State-Trait Anxiety Inventory</td>
</tr>
</tbody>
</table>
Striatal Subdivisions

- Ventral striatum (VS): Ventral to a line tangent to IC bisector and lower corner of lateral ventricle (A)
- Caudate nucleus (CDN) and Putamen (PUT) are further divided by the anterior-commissure plane
  - Cognitive striatum: Anterior and posterior CDN + anterior PUT
  - Motor striatum: Posterior PUT

# Subject Population

## Risk for Alcoholism Study (N = 21)

- **Positive Family History:** N=5  
  - Age: 21± 1.92  
  - Race: 1 Black, 4 White  
  - Gender: 3 M, 2 F

- **Negative Family History:** N=16  
  - Age: 21± 2.86  
  - Race: 2 Black, 2 Asian, 11 White  
  - Gender: 8 M, 7 F

## Alcohol Dependence Study (N = 12)

- **Alcohol Dependent:** N=5  
  - Age: 45± 4.15  
  - Race: 1 Black, 4 White  
  - Gender: 5 M

- **Control Subjects:** N=7  
  - Age: 44± 6.31  
  - Race: 5 Black, 2 White  
  - Gender: 6 M, 1 F
Study Design: Alcohol Dependence and Risks of Alcoholism

PET Scan Day

PET 1
-5 min : IV saline
0 min : IV $[^{11}\text{C}]$raclopride high specific activity
0-90 min PET scan 1 (35 frames)

PET 2
-5 mins : IV amphetamine 0.3 mg/kg
0 min IV $[^{11}\text{C}]$raclopride high specific activity
0-90 min PET scan 2 (35 frames)
Risks of Alcoholism: Results

Drug Liking

Good Effect

Rush

Desire

Minutes

Placebo
Active
Risks of Alcoholism: Results

1. Peak Desire
   - AUC Cortisol
   - $r = 0.73$
   - $P = 0.003$
   - $N = 16$

2. AUC Rush
   - AUC Cortisol
   - $r = 0.63$
   - $P = 0.017$
   - $N = 16$

3. AUC Drug Liking
   - AUC Cortisol
   - $r = 0.60$
   - $P = 0.023$
   - $N = 16$
Intrasynaptic Dopamine Binding Potential Images Generated from $[^{11}\text{C}]$raclopride Dynamic PET Studies in a SOA subject with Saline and Amphetamine (0.3 mg/Kg) Challenge

Parametric mapping method Zhou et al NeuroImage 2003
Risk of Alcoholism: PET Results

- DA release correlated with Cortisol
- DA release correlated with liking, rush, good effect
- Peak Cortisol correlated with liking, desire, good effect
- Wide variance in cortisol responses

L. Oswald, et. al. 2004
Risk of Alcoholism Study

Dopamine Release

Parametric Image Modeling

Risk of Alcoholism Study

Dopamine Release vs. Drinks Per Episode

Drinks per Episode

Left Ventral Striatum

N = 16
r = 0.53
p < 0.04

L. Oswald, et. al. 2004
Risk of Alcoholism Study

Dopamine Release and NEO Excitement Seeking

L. Oswald, et. al. 2004
Risk of Alcoholism Study

Dopamine Release and Neo Agreeableness Factor

NEO Agreeableness factor and Ventral Striatum

n = 15
r = 0.657
p < 0.008

L. Oswald, et. al. 2004
Study Design Timeline: Alcohol Dependence Study

- Screening Visit
- 8 Day Inpatient GCRC Stay:
  - Day 1: Admission, repeat some screening measures
  - Day 2-4: Washout and MRI/mask
  - Day 5: 2 PET scans
  - Day 6: Naloxone Challenge
  - Day 7: Trier Stress Test
  - Day 8: Cognitive Testing and Discharge

*In addition, there are psychological measures administered throughout the stay.*
Alcohol Dependence Subjects
Baseline Binding Potential

Alcohol Dependent Mean (n=5)
Controls Mean (n=7)

*P = 0.0289
*P = 0.009
*P = 0.044
*P = 0.009

SEM
Amphetamine-induced Dopamine Release

Alcohol Dependent Subjects

(Lammertsma Tissue Reference Model)

Alcohol Dependent Subjects (n=5) Means, SEM
Controls (n=7) Means, SEM
Dopamine Release vs. Peak Distrust (AMP-PET)

Alcohol Dependent Subjects (N = 5)

Logan Tissue Reference Method

- Right Posterior Caudate; $r = 0.93$, $p = 0.036$
- Right Ventral Striatum, $r = 0.949$, $p = 0.014$
Dopamine Release vs. Peak Fidgety (AMP-PET)

Alcohol Dependent Subjects (N = 5), Logan Tissue Reference Method

Right Ventral Striatum; $r = 0.931$, $p = 0.021$
Dopamine Release vs. Peak Cortisol 
(Amphetamine PET)

Alcohol Dependent 
Right Ventral Striatum, Logan Tissue Reference Method

% DAR (Logan) RVS

Peak Cortisol
Dopamine Release vs. Peak Want for Alcohol

Alcohol Dependents, N=5, Lammerstma Tissue Reference Method, Left Ventral Striatum
Washout Day 1

\[ r = 0.976 \]
\[ p = 0.004 \]
\[ N = 5 \]
Dopamine Release vs. Peak Desire for Alcohol

Right Ventral Striatum Alcohol Dependents, N=5, Lammerstma Tissue Reference Method

Washout Day 3

\[ r = 0.973 \]
\[ p = 0.005 \]
\[ N = 5 \]
Study Design: Alcohol Dependence And Risks of Alcoholism Studies

- Trier Stress Test
  - Cortisol, B-endorphin, ACTH, Prolactin
- Naloxone Challenge
  - Cortisol, B-endorphin, ACTH
- PET
  - Cortisol, Growth Hormone
# Trier Stress Test: Alcohol Dependence and Risks of Alcoholism Studies

<table>
<thead>
<tr>
<th>Active Session</th>
<th>Placebo Session: Risks of Alcoholism Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noon:</td>
<td>Noon:</td>
</tr>
<tr>
<td>Arrival, urine toxicity, breathalyzer, and pregnancy test</td>
<td>Arrival, urine toxicity, breathalyzer, and pregnancy test</td>
</tr>
<tr>
<td>12:45:</td>
<td>12:45:</td>
</tr>
<tr>
<td>State-Trait Anxiety Inventory, Combined Hassles and Uplifts Scale, Perceived Stress Scale</td>
<td>State-Trait Anxiety Inventory, Combined Hassles and Uplifts Scale, Perceived Stress Scale</td>
</tr>
<tr>
<td>1:00:</td>
<td>1:00:</td>
</tr>
<tr>
<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>1:15:</td>
<td>1:15:</td>
</tr>
<tr>
<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>1:30:</td>
<td>1:30:</td>
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<tr>
<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>1:32:</td>
<td>1:32:</td>
</tr>
<tr>
<td>Taped instructions to subjects</td>
<td>Taped instructions to subjects</td>
</tr>
<tr>
<td>1:35:</td>
<td>1:35-1:50:</td>
</tr>
<tr>
<td>10 minute speech preparation time</td>
<td>Read Quietly</td>
</tr>
<tr>
<td>1:45:</td>
<td>1:45:</td>
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<tr>
<td>Speech</td>
<td>1:55:</td>
</tr>
<tr>
<td>1:50:</td>
<td>1:55:</td>
</tr>
<tr>
<td>Serial 13s</td>
<td>Hormone measures, BP, HR State-Trait Anxiety Inventory</td>
</tr>
<tr>
<td>1:55:</td>
<td>2:10:</td>
</tr>
<tr>
<td>Hormone measures, BP, HR, State- Trait Anxiety Inventory</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>2:10:</td>
<td>2:10:</td>
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<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>2:25:</td>
<td>2:25:</td>
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<td>Hormone measures, BP, HR</td>
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<td>2:40:</td>
<td>2:40:</td>
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<tr>
<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>2:55:</td>
<td>2:55:</td>
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<tr>
<td>Hormone measures, BP, HR</td>
<td>Hormone measures, BP, HR</td>
</tr>
<tr>
<td>3:00:</td>
<td>3:00:</td>
</tr>
<tr>
<td>Discharge</td>
<td>Discharge</td>
</tr>
</tbody>
</table>
Risks of Alcoholism Study
Trier Session (n = 10)
Dopamine Release vs. Peak $\beta$-endorphin

Left Posterior Caudate (Active Trier session)

$r = -0.882$

$p = 0.048$

$N = 5$
Dopamine Release vs. Peak ACTH

Right Anterior Putamen, Active Trier session

Dopamine Release vs. Peak ACTH (Active Trier)
Right Anterior Putamen: Alcohol Dependents (N=5)

r = -0.916
p = 0.029
N = 5
Future Directions

DA Receptor Density, DA Release, and DAT

Day 1
- $[^{11}C]RAC$, HSA baseline
- $[^{11}C]RAC$ HSA AMPH (0.3 mg/kg)

Day 2
- $[^{11}C]WIN$, HSA
- $[^{11}C]RAC$, LSA
Summary - Risks of Alcoholism

1. DA release correlates with cortisol release.
2. DA release correlates with drug liking and other positive effects.
3. Cortisol release correlates with drug liking and other positive effects.
4. Similar pattern to animal models.
5. Who has the endophenotype of cortisol lability and how did they get it? We examine associations between polymorphisms in the tyrosine hydroxylase gene and DArel.
Summary (con’t)
Risks of Alcoholism

6. The number of drinks consumed was positively associated with DAR in the left (r=0.45, p<0.05) but not the right ventral striatum.

7. DAR was positively associated with the NEO personality measure of excitement-seeking (r=0.50, p<0.06) and negatively associated with agreeableness (r=-0.66, p<0.008).

L. Oswald, et. al. 2004
Summary-Alcohol Dependence

1. Decreases in many regions occurred in basal D2 and amphetamine-induced dopamine release in caudate-putamen regions in alcohol dependent subjects versus controls.

2. The correlation of dopamine release vs. cortisol in response to amphetamine in alcohol dependent subjects is blunted, whereas a positive correlation emerged for the social drinking group.

3. Dopamine release correlates with hormonal measures taken during the active Trier session.

4. Amphetamine-induced dopamine release correlates with wanting of alcohol during washout within alcohol dependent subjects.
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Specific Hypotheses:

- Alcohol dependent subjects will have lower cortisol responses to naloxone or psychological stress compared to age-matched, social drinkers.
- The magnitude of cortisol responses will correlate inversely with measures of craving obtained acutely within test sessions and chronically over the CRC stay.
- Cortisol production is directly proportional to DArel.
- High risk alcohol dependent subjects will relapse before low risk dependent subjects.
- DArel will predict time to relapse.
- Cortisol production in response to naloxone or psychological stress will predict time to relapse.
- We predict impaired DArel and low D2-receptor density in alcoholics.
- We predict continuum in DArel and cortisol production as a function of risk and alcohol dependence status such that high risk alcohol dependent subjects < low risk alcohol dependent < low risk social drinkers < high risk social drinkers.
- We examine associations between polymorphisms in the tyrosine hydroxylase gene and DArel.
# Subject Population

## Risk for Alcoholism Study (N = 16)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Age (Mean ± SD)</th>
<th>Race</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Family History</td>
<td>4</td>
<td>22 ± 1.71</td>
<td>1 Black, 3 White</td>
<td>3 M, 1 F</td>
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<tr>
<td>Negative Family History</td>
<td>12</td>
<td>21 ± 3.12</td>
<td>1 Black, 2 Asian, 9 White</td>
<td>7 M, 5 F</td>
</tr>
</tbody>
</table>

## Alcohol Dependence Study (N = 12)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Age (Mean ± SD)</th>
<th>Race</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Dependent</td>
<td>5</td>
<td>45 ± 4.15</td>
<td>1 Black, 4 White</td>
<td>5 M</td>
</tr>
<tr>
<td>Control Subjects</td>
<td>7</td>
<td>44 ± 6.31</td>
<td>5 Black, 2 White</td>
<td>6 M, 1 F</td>
</tr>
</tbody>
</table>
Risk of Alcoholism Study

Dopamine Release

Aims for Wand Study

- To examine the association between DA release and risk for alcoholism. We hypothesize that high-risk subjects will be greater DA releasers compared to low-risk subjects.

- To examine the relationship between HPA axis dynamics and risk for alcoholism. We hypothesize that high-risk subjects will have a more labile cortisol response to psychological stress and opioid blockade compared to low-risk subjects.

- To examine the relationship between cortisol responses to activation of the HPA axis and DA release. We hypothesize that high cortisol producers in response to stress will also be high DA releasers.
Risk of Alcoholism Study

Dopamine Release

Pooled Data: N = 21, Mean ± SEM

Dopamine Release (percent change in BP)

Brain Regions

LAP, RAP, LPP, RPP, LACH, RACH, LPCH, RPCH, LVS, RVS

Parametric Image Modeling

Risk of Alcoholism Study

Dopamine Release

Amphetamine-induced Dopamine Release

Alcohol Dependent Subjects

(Logan Tissue Reference Model)

- Alcohol Dependent Subjects (n=5) Means, SEM
- Controls (n=7) Means, SEM

Brain Regions:
- Anterior Putamen
- Posterior Putamen
- Anterior Caudate
- Posterior Caudate
- Ventral Striatum
Right Anterior Caudate: Dopamine Release vs. Peak Cortisol
Logan Tissue Reference Method, Alcohol Dependent Subjects (N = 4)
Amphetamine-induced Dopamine Release

Alcohol Dependent Subjects

(Logan Tissue Reference Model)

Alcohol Dependent Subjects (n=5) Means, SEM
Controls (n=7) Means, SEM

Brain Regions

Dopamine Release (Mean Percent Change in BP)
Right Posterior Caudate: Dopamine Release vs. Peak Dizziness Score
Logan Tissue Reference Method

**Regression values based on pooled dataset, n = 12**
Left Ventral Striatum, Dopamine Release vs. Peak Want, Alcohol Dependents, N=5, Logan Tissue Reference Method

Washout Day 1

R = 0.969
P = 0.006
N = 5
To examine DArel and cortisol production in relation to time to alcohol relapse following CRC discharge stress as a function of risk status.

To examine DArel and cortisol production in relation to time to alcohol relapse following CRC discharge stress as a function of risk status.