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

Dean F. Wong, MD, PhD
dfwong@jhmi.edu

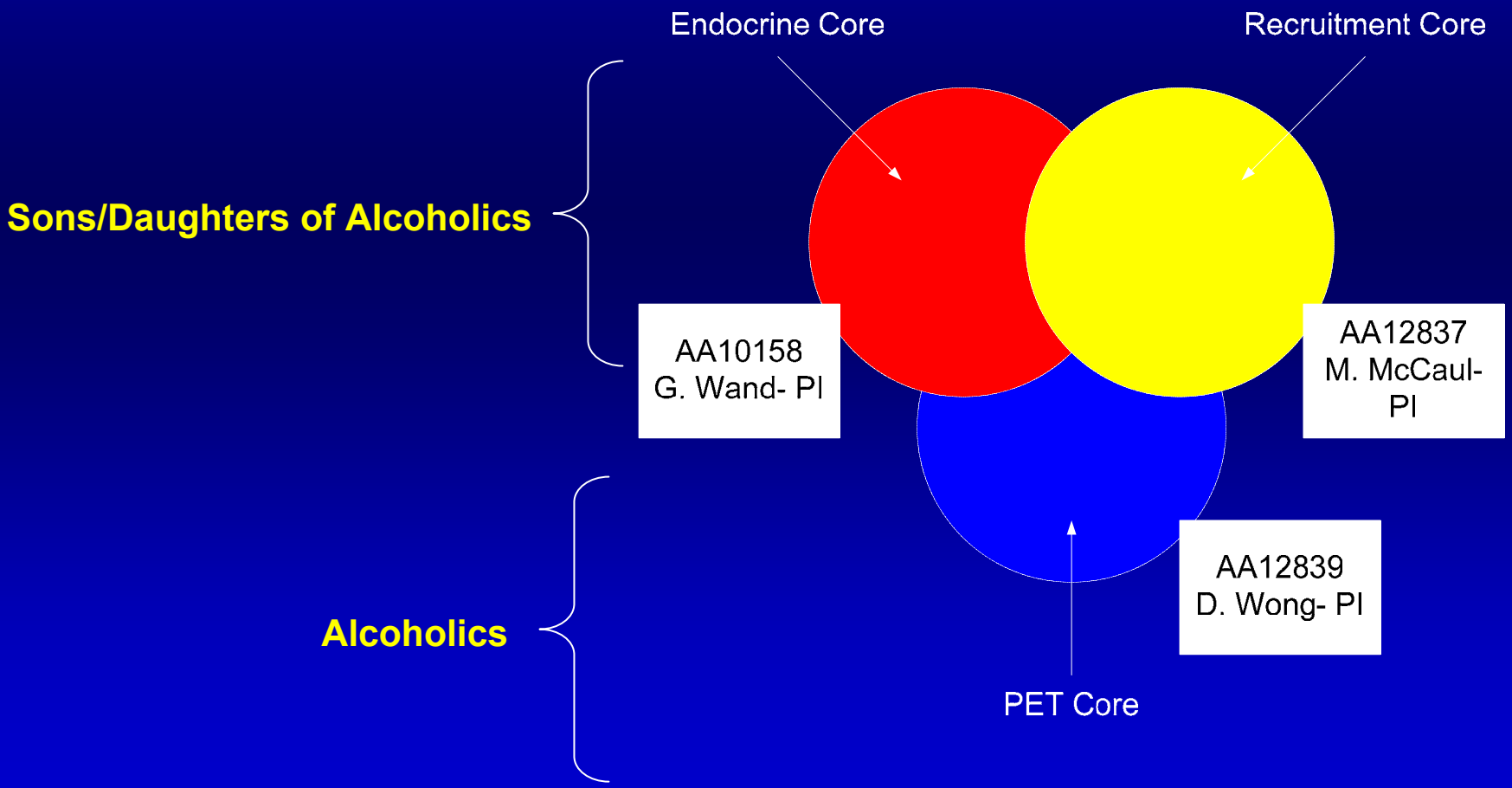
Radiology Vice Chair for Research Administration and Training
Professor of Radiology and Psychiatry, Johns Hopkins School of Medicine and Radiation Health Sciences, JHU School of Public Health, Baltimore, Maryland

Johns Hopkins Psychiatry and Radiology

Collaborators:

Lynn Oswald PhD; Betsy McCaul PhD; Gary Wand MD; Weiguo Ye MD; James Brasic MD, MPH; Mohab Alexander MD; Anil Kumar MD; Hiroto Kuwabara MD PhD; Yun Zhou PhD

Johns Hopkins University NIAAA Interactive Research Grants (IRPGs)



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).

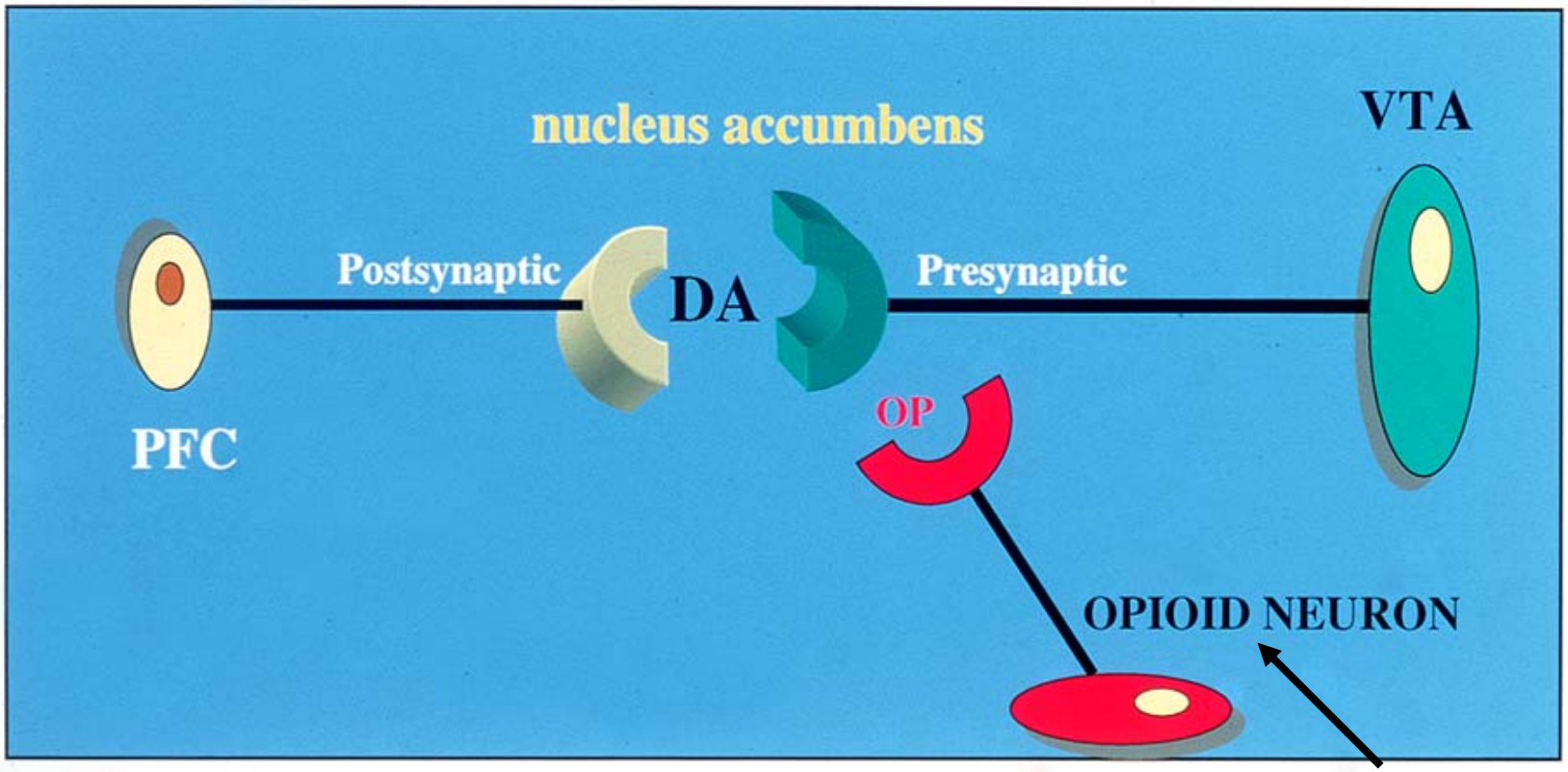
II. To examine HPA axis activation by opioid blockade and by psychological stress as a function of alcohol dependence status and risk of alcoholism.

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.

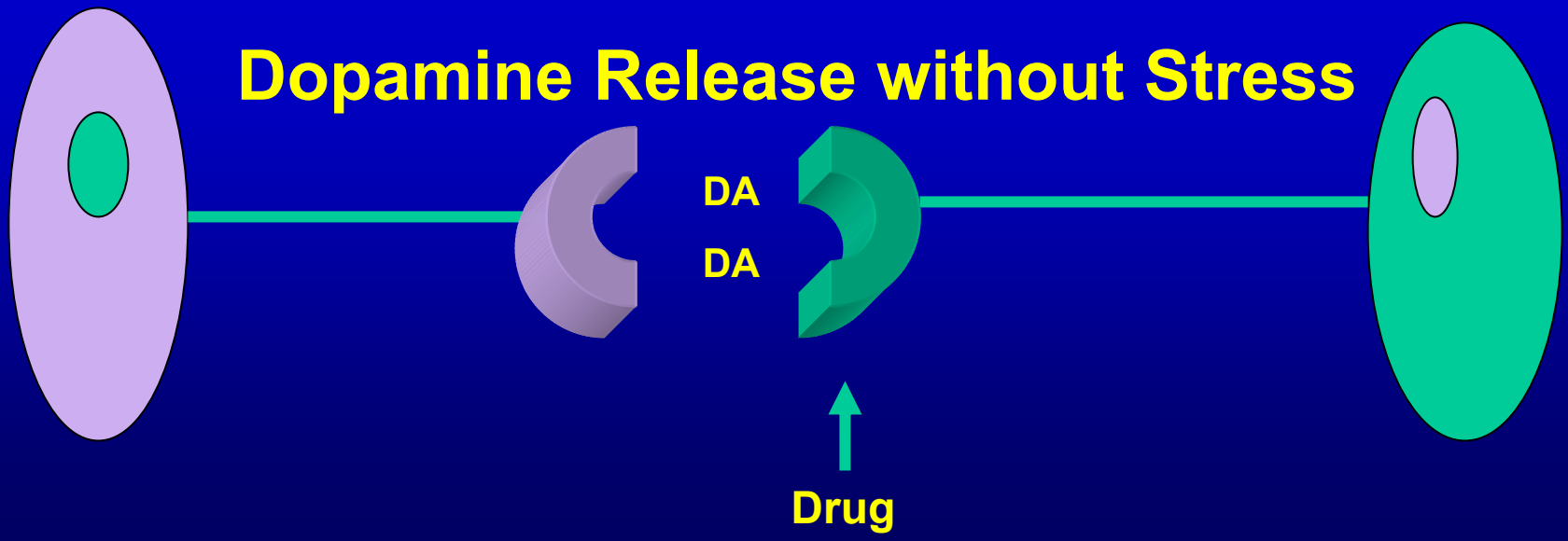
Mesolimbic Reward Pathway

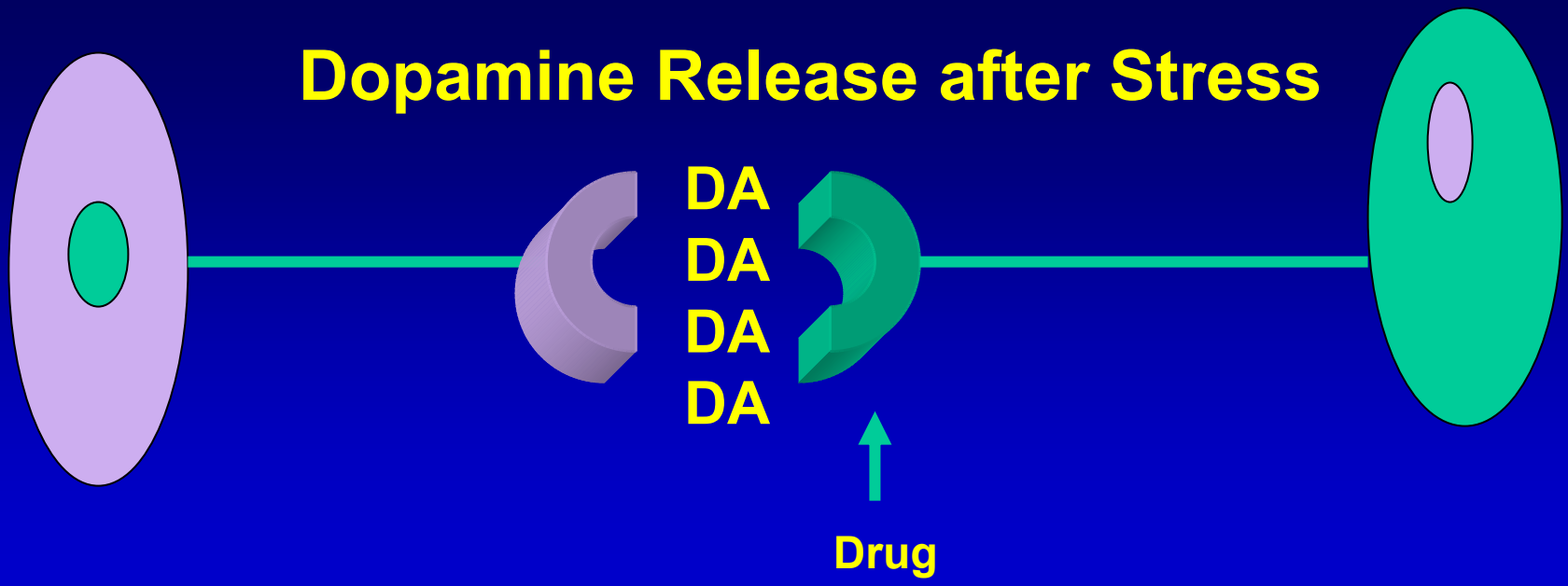


What is the evidence that stress alters mesolimbic dopamine release and drug reward?

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
DA
DA
Drug


Dopamine Release after Stress
DA
DA
DA
DA
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

Stoops et al. (2003) Alcoholism : Clinical and Experimental Research 27: 804-811

Holdstock and de Wit (2001) Alcoholism : Clinical and Experimental Research 25: 540-548.

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

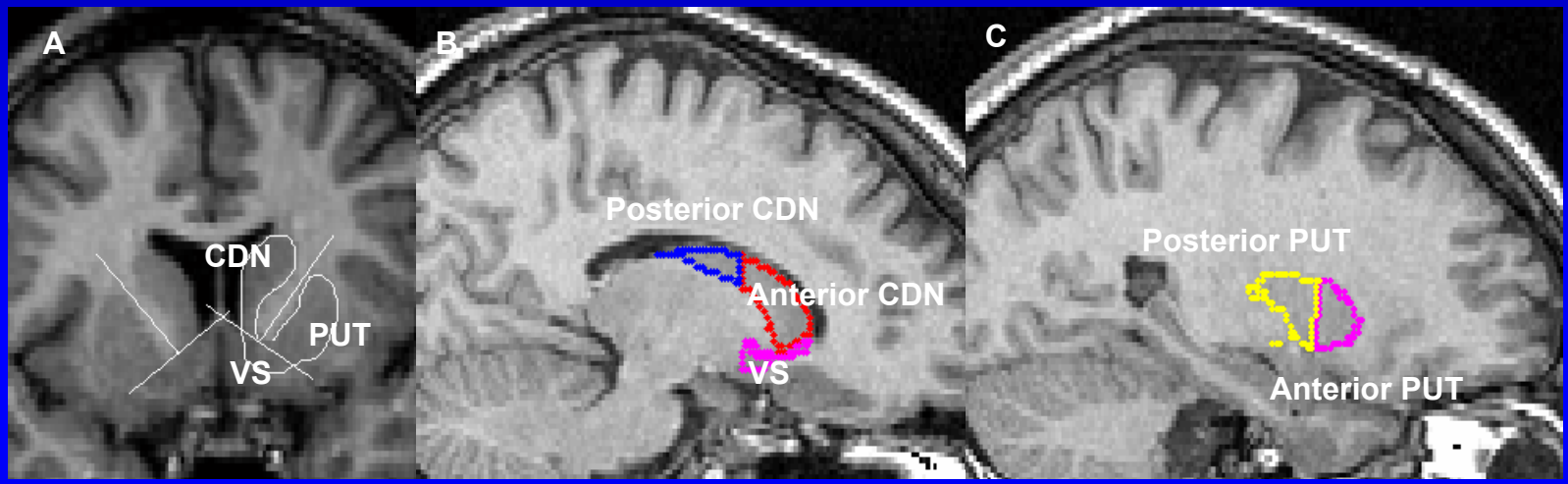
Alcohol Dependence

Min	
-35	State-Trait Anxiety Inventory
-25	Blood Sample
-15	Analog Drug Effect Scales
-5	Blood sample
3	Analog
6	Analog
10	Analog
15	Analog and Blood Sample
25	Analog
35	Blood Sample
55	Analog and Blood Sample
75	Blood Sample
85	Analog and State-Trait Anxiety Inventory

Risks of Alcoholism

Min	
-35	State-Trait Anxiety Inventory, *Perceived Stress Scale, Combined Hassles and Uplifts Scale*
-25	Blood Sample
-15	Analog Drug Effect Scales
0	*Blood sample*
3	Analog
6	Analog
10	Analog
15	Analog
25	Analog and *State-Trait Anxiety Inventory and Blood Sample*
45	Blood Sample
55	Analog and *State-Trait Anxiety Inventory*
65	*Blood for GH*
85	Analog and State-Trait Anxiety Inventory

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 CND + anterior PUT
  - Motor striatum: Posterior PUT

Kuwabara et al (2003) Soc of Nuc Med

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}C]raclopride high specific activity

0-90 min PET scan 1 (35 frames)

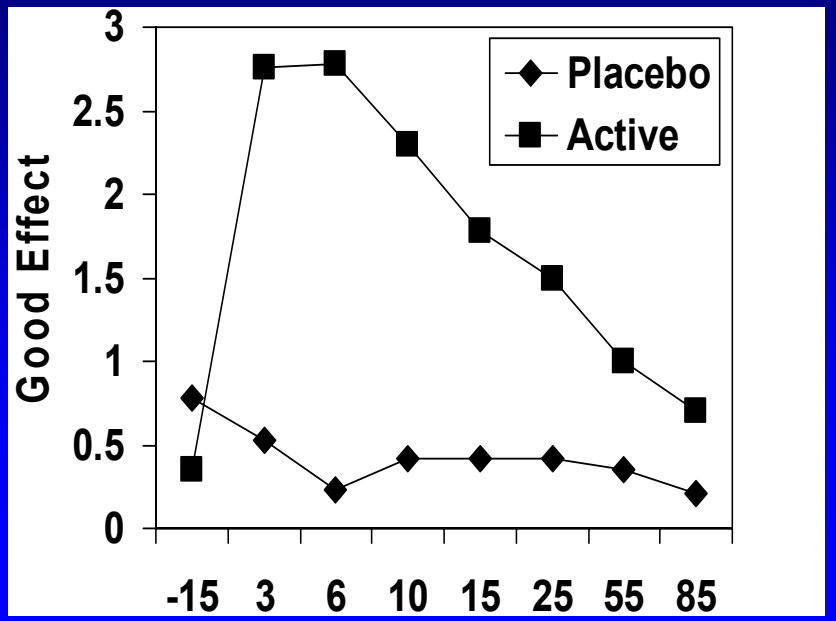
PET 2

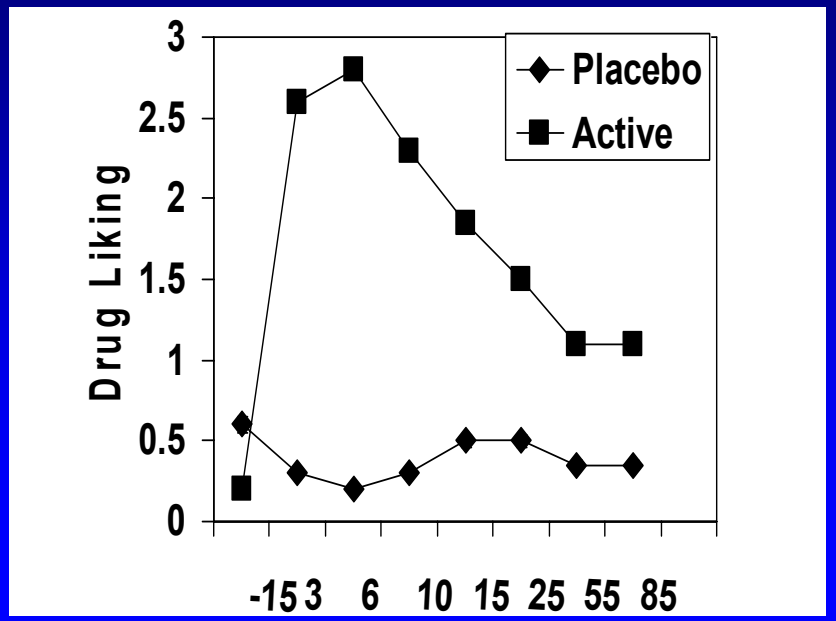
-5 mins : IV amphetamine 0.3 mg/kg

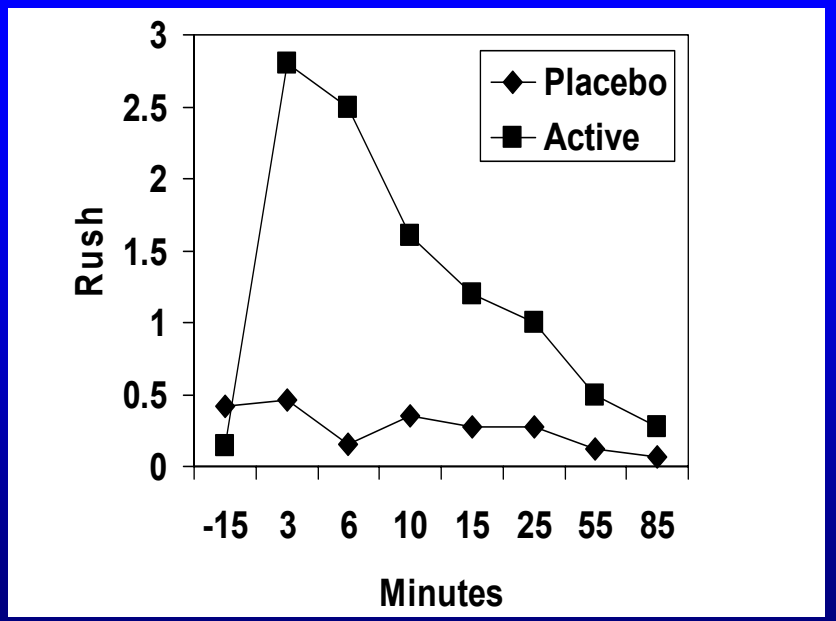
0 min IV [^{11}C]raclopride high specific activity

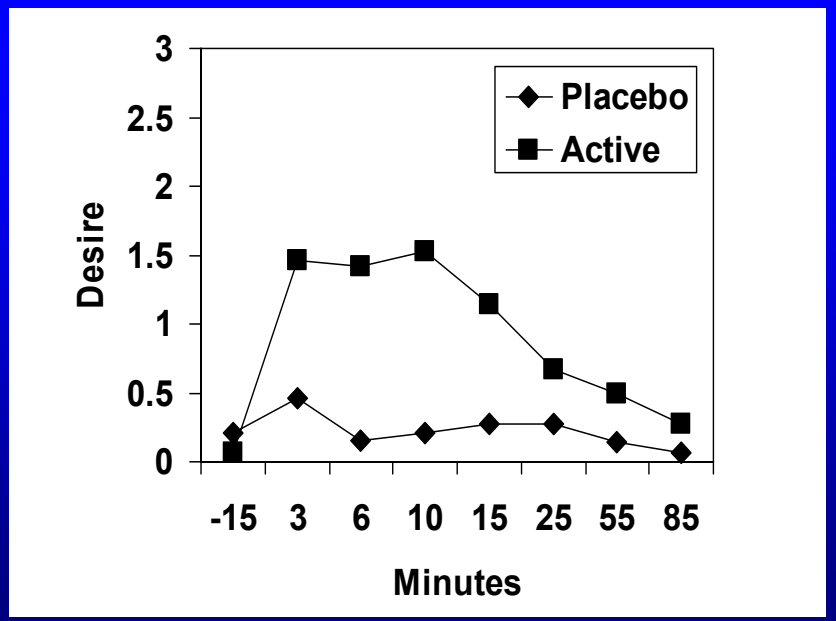
0-90 min PET scan 2 (35 frames)

Risks of Alcoholism: Results

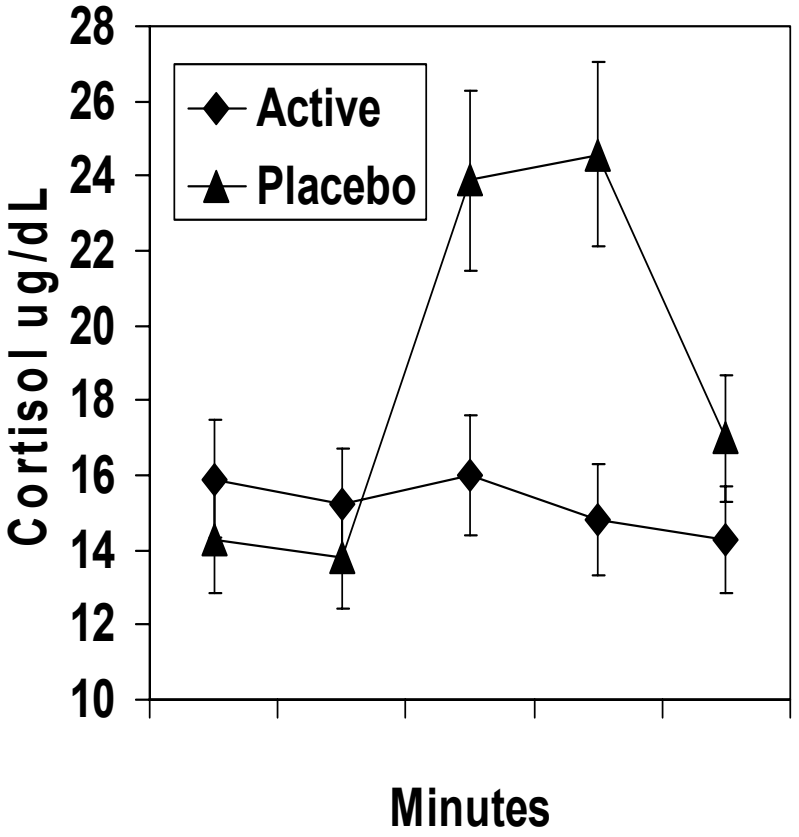


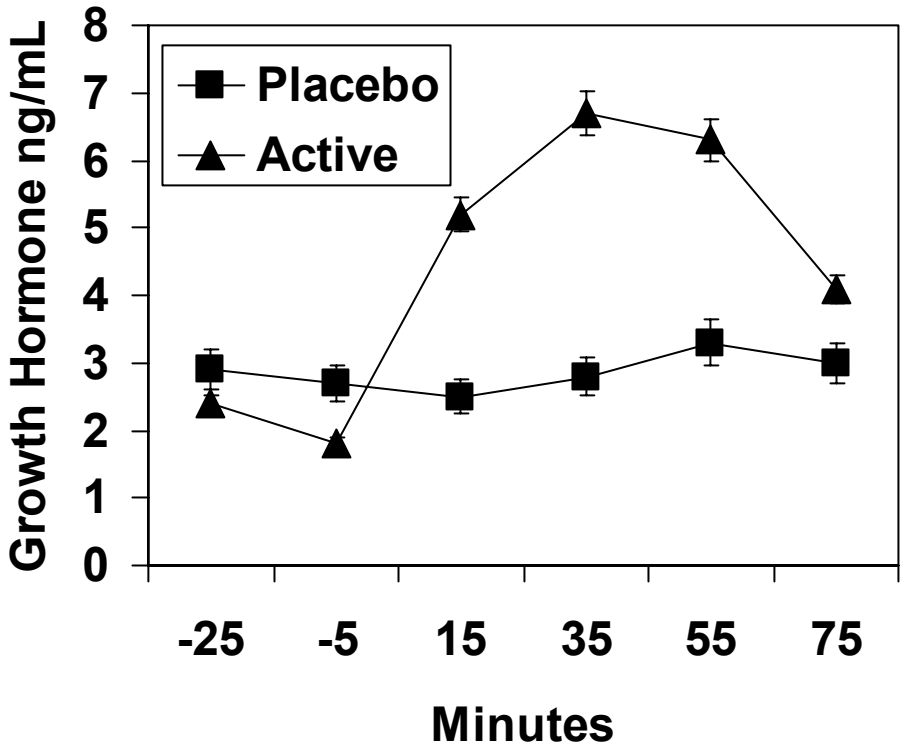




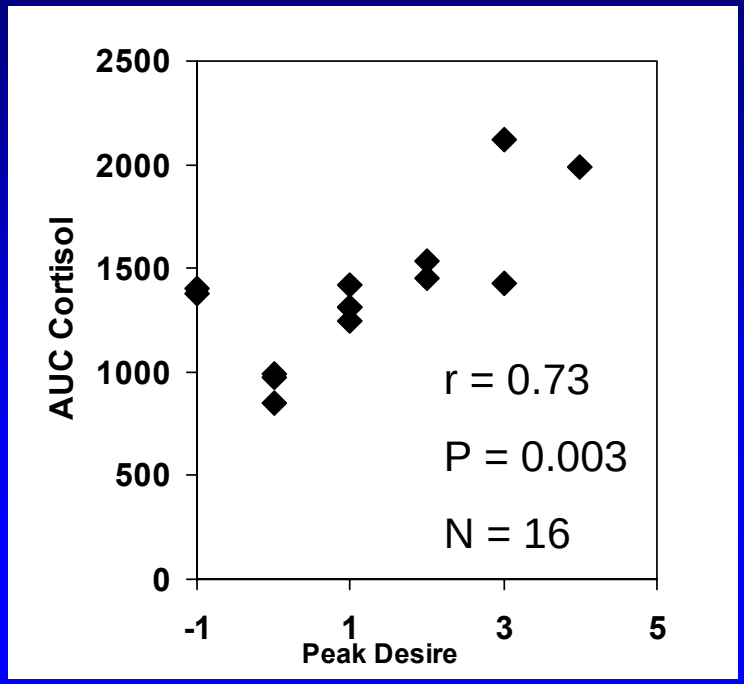


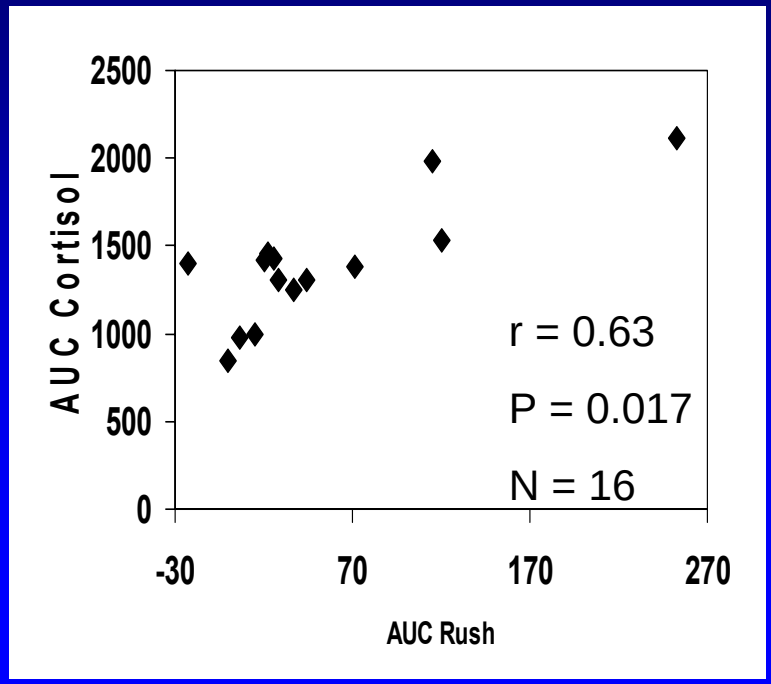
Risks of Alcoholism: Results

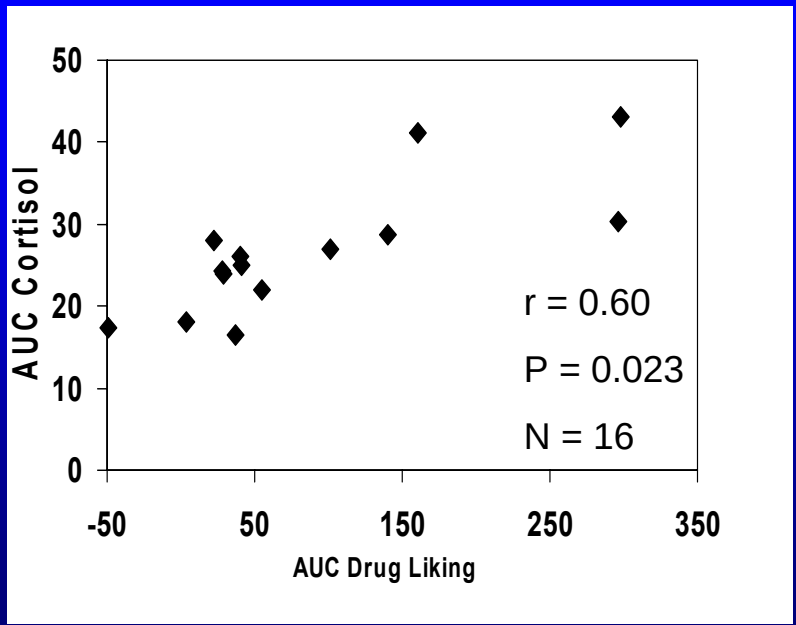




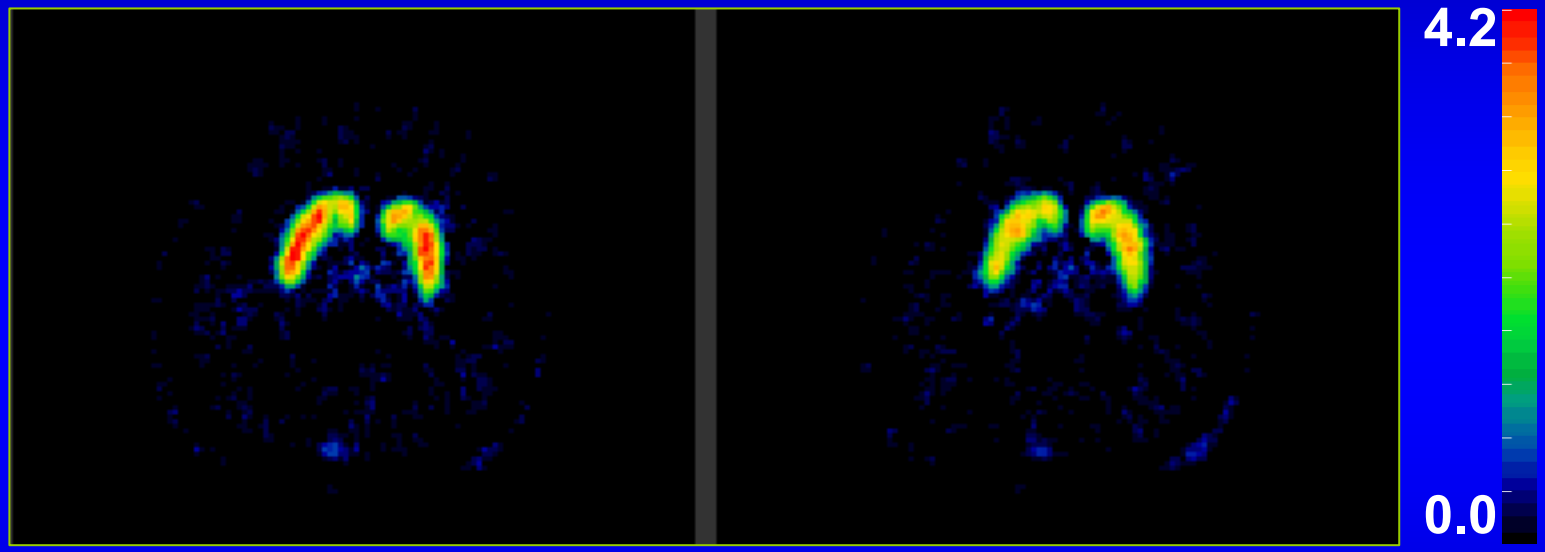
Risks of Alcoholism: Results



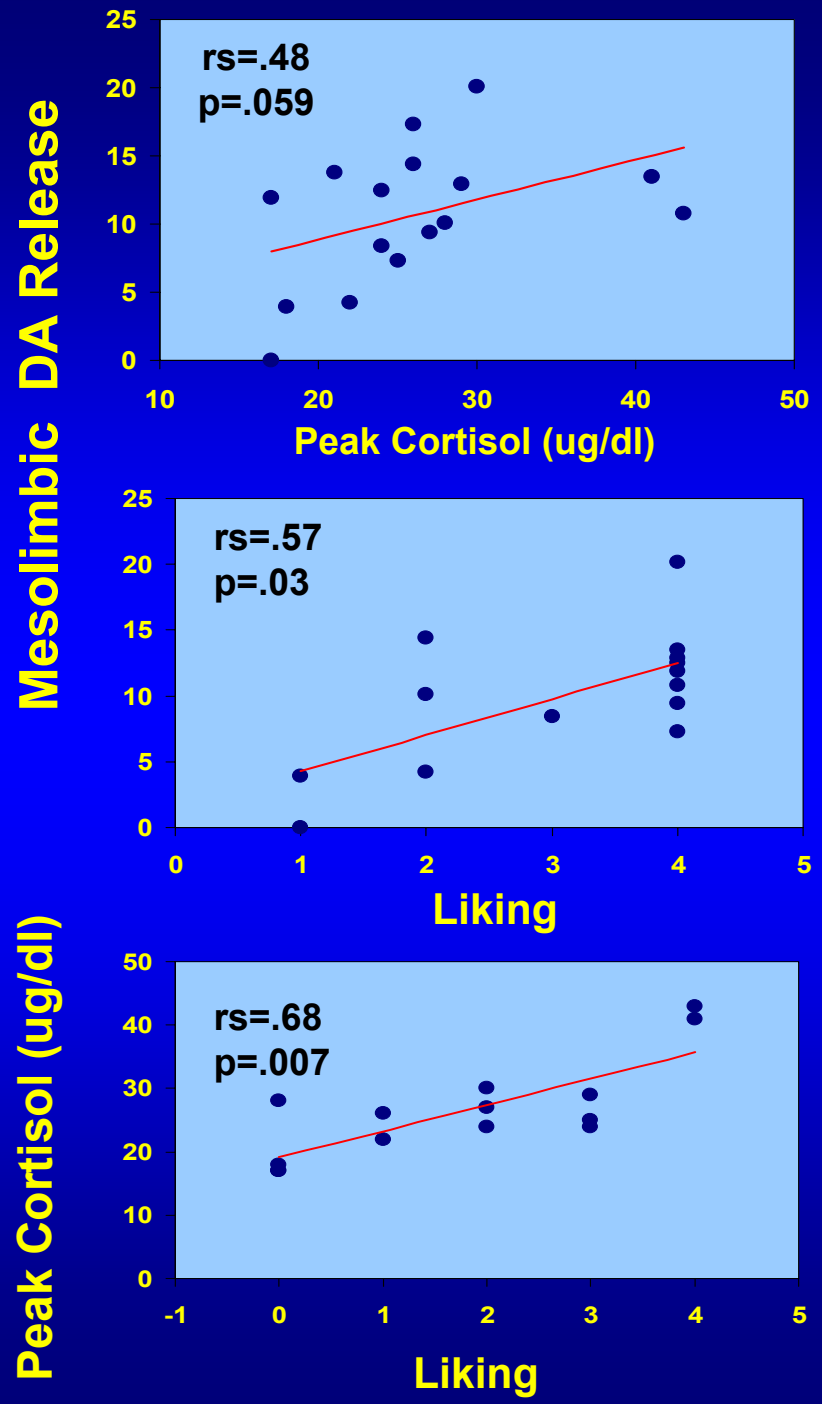




Intrasynaptic Dopamine
Binding Potential Images Generated from [^{11}C]raclopride Dynamic PET Studies in a SOA subject with Saline and Amphetamine (0.3 mg/Kg) Challenge



Parametric mapping method Zhou et al NeuroImage 2003



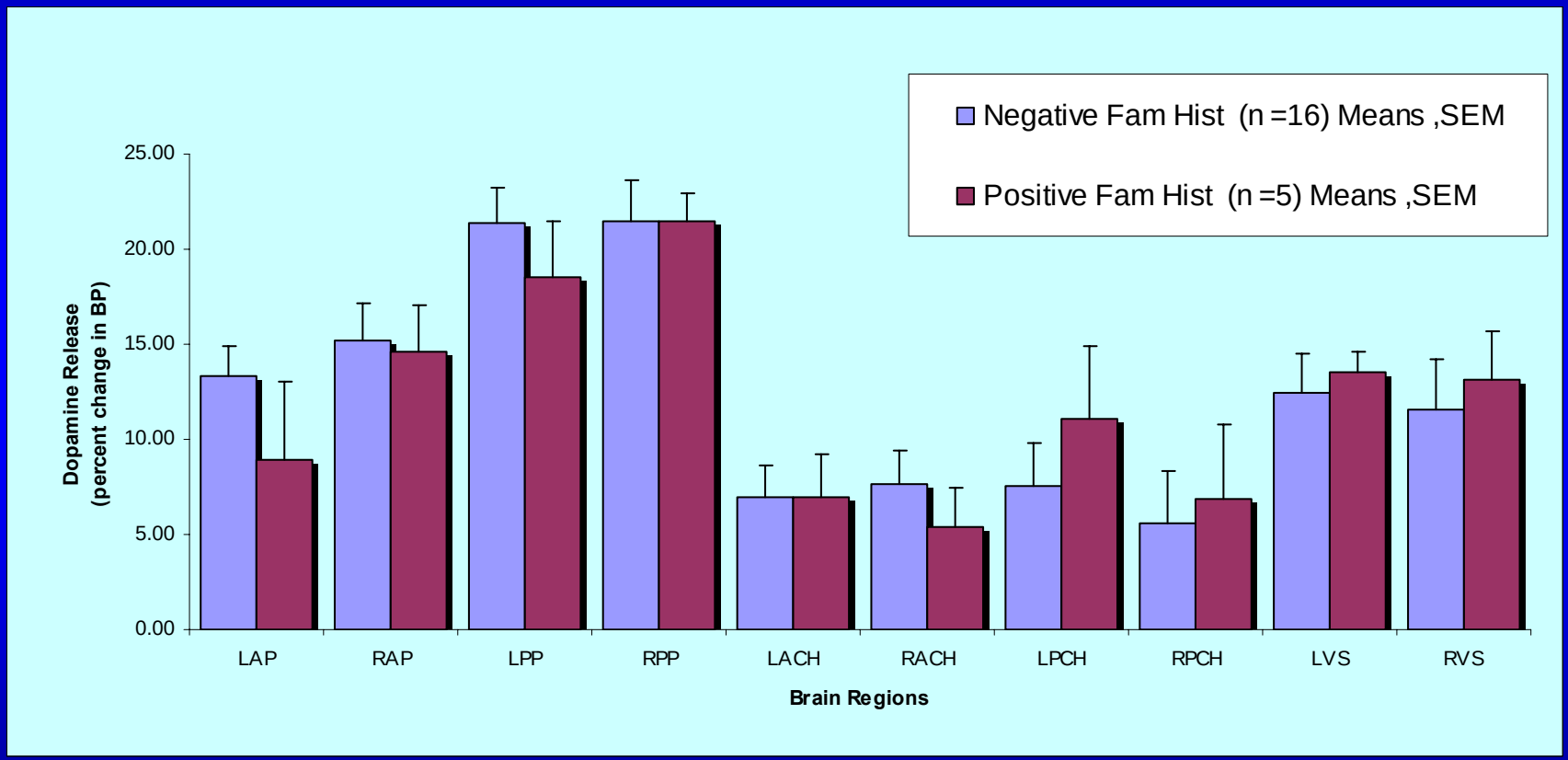
Risk of Alcoholism: PET Results

- 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

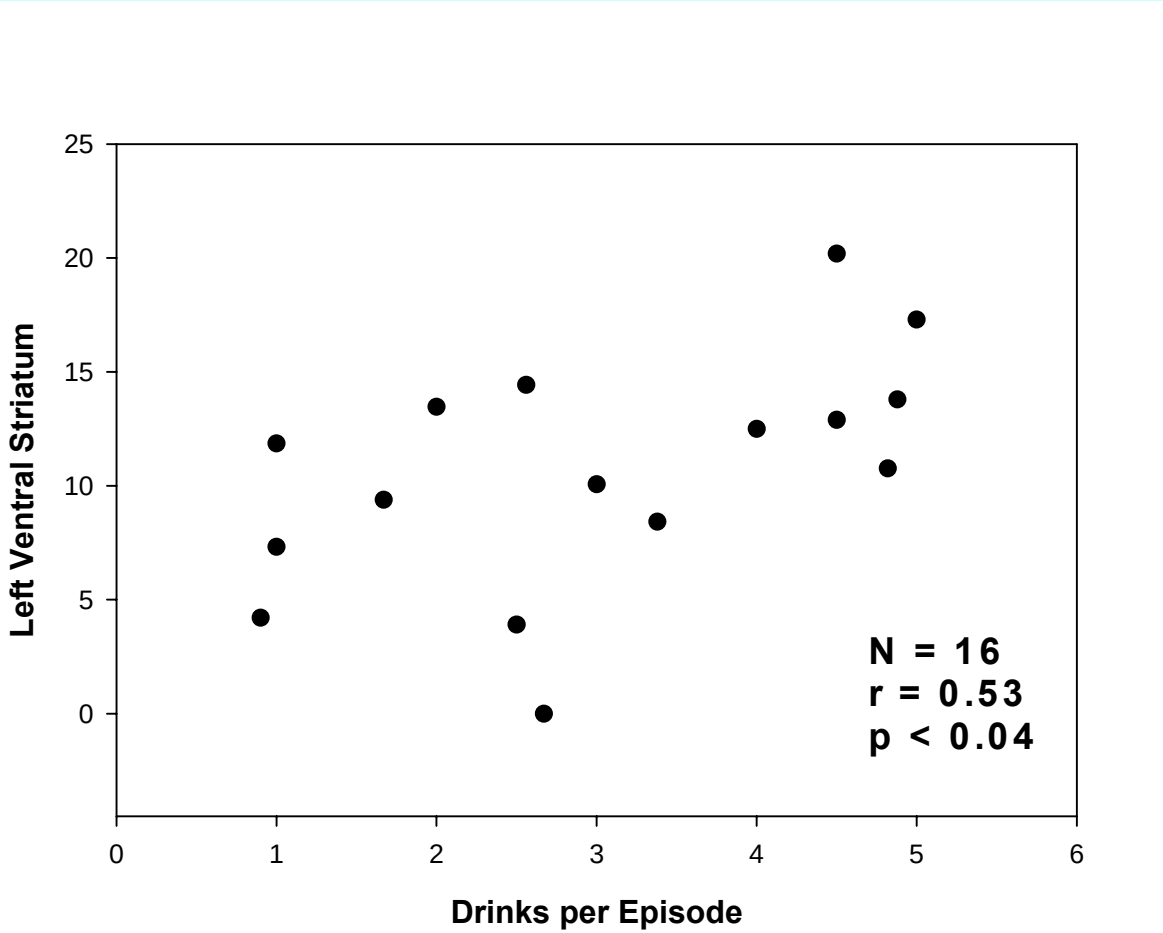


Parametric Image Modeling

Ref: Zhou et al Neuroimage (2003)

Risk of Alcoholism Study

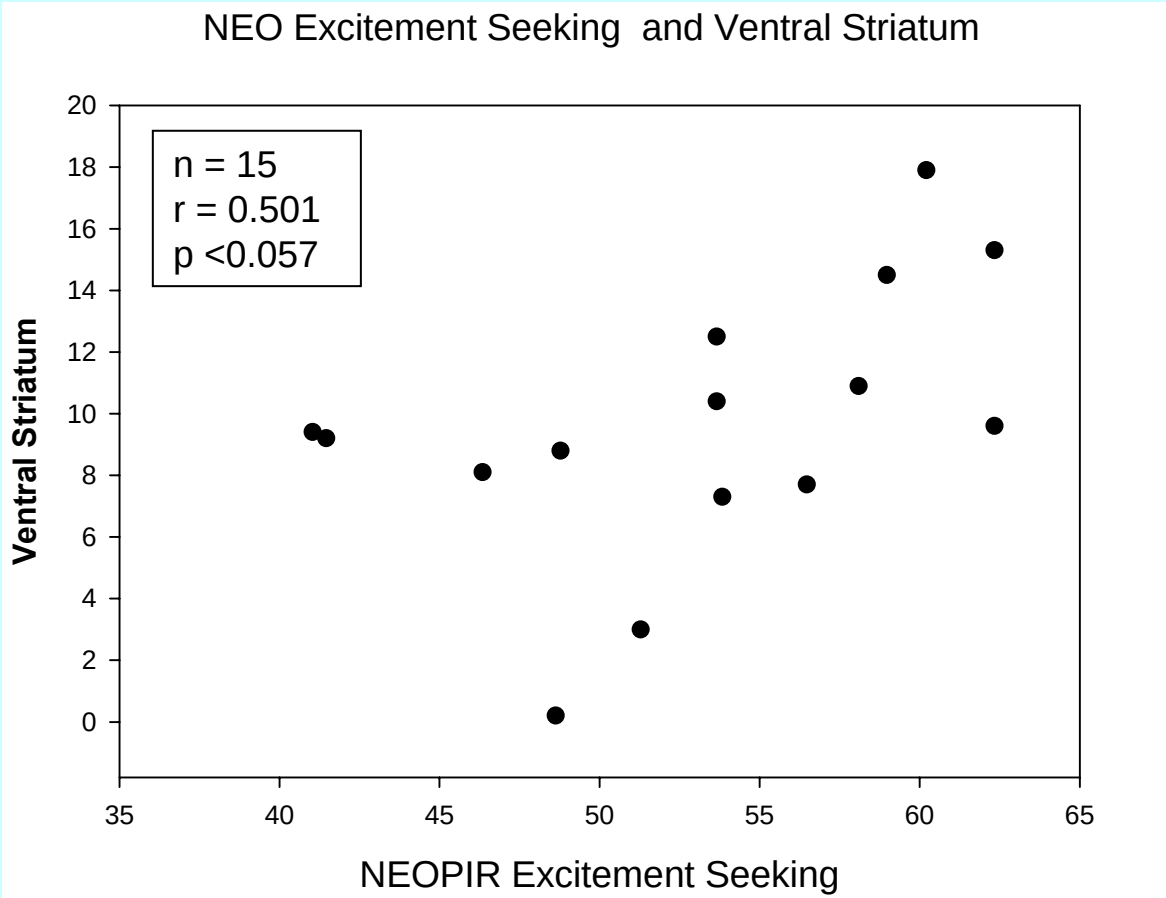
Dopamine Release vs. Drinks Per Episode



L. Oswald, et. al. 2004

Risk of Alcoholism Study

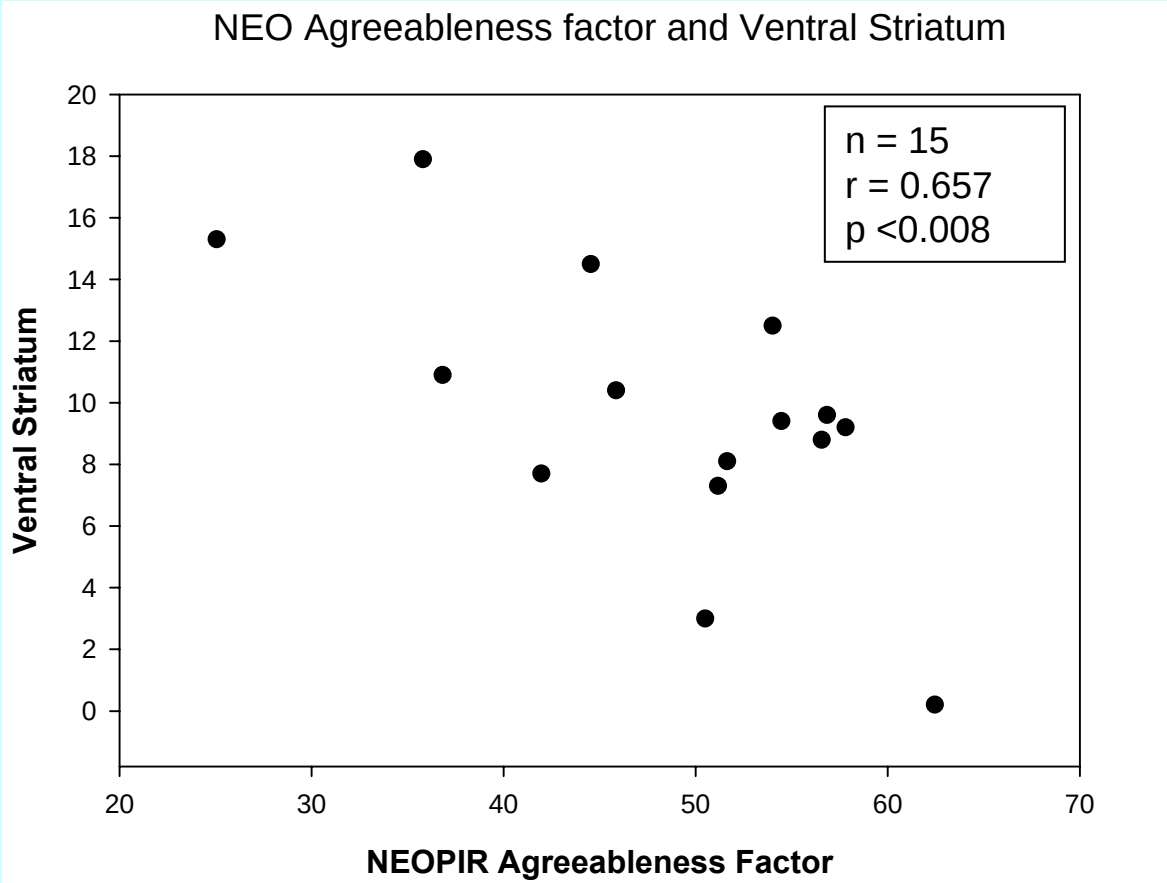
Dopamine Release and NEO Excitement Seeking



L. Oswald, et. al. 2004

Risk of Alcoholism Study

Dopamine Release and Neo Agreeableness Factor



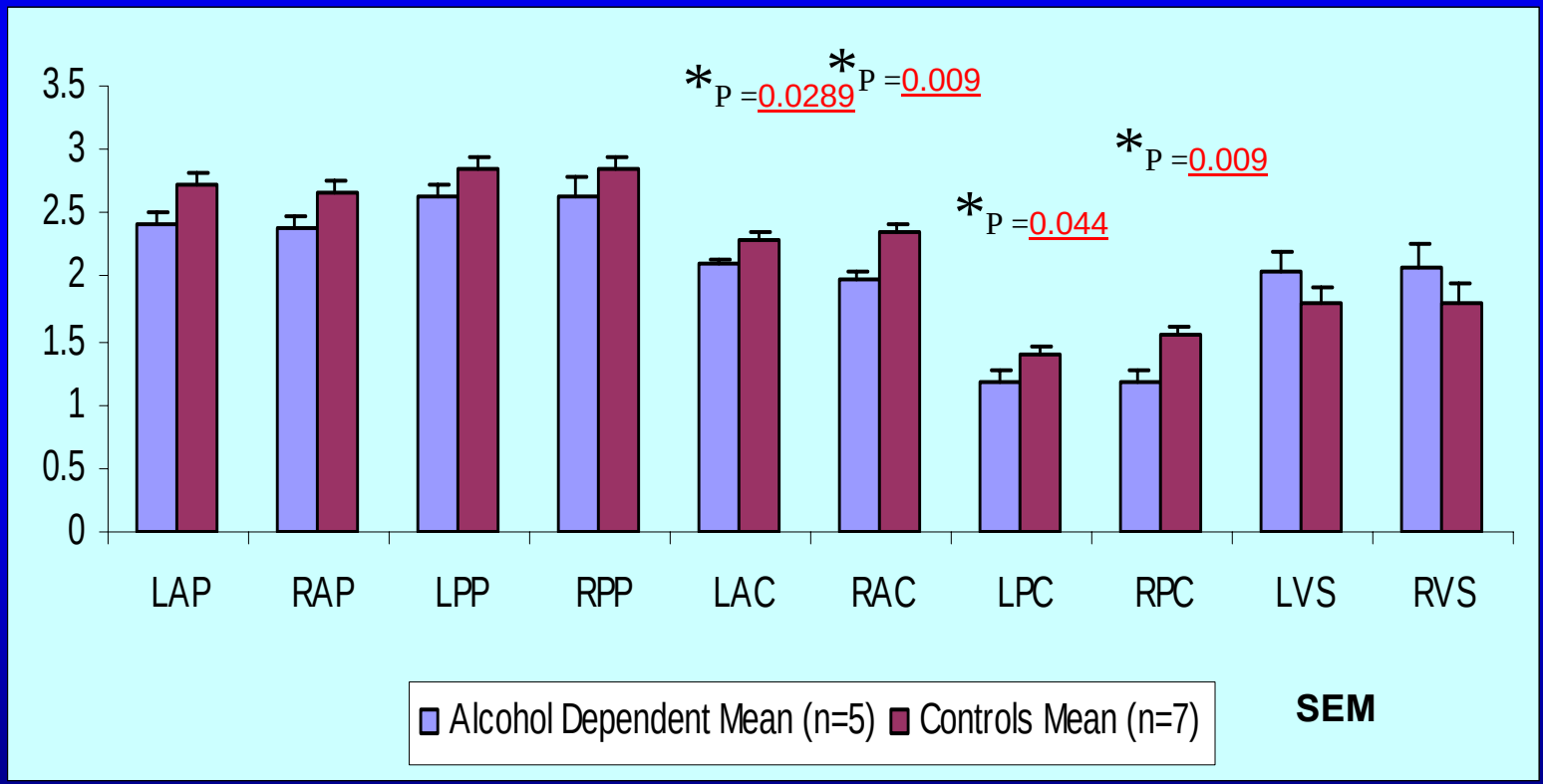
L. Oswald, et. al. 2004

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

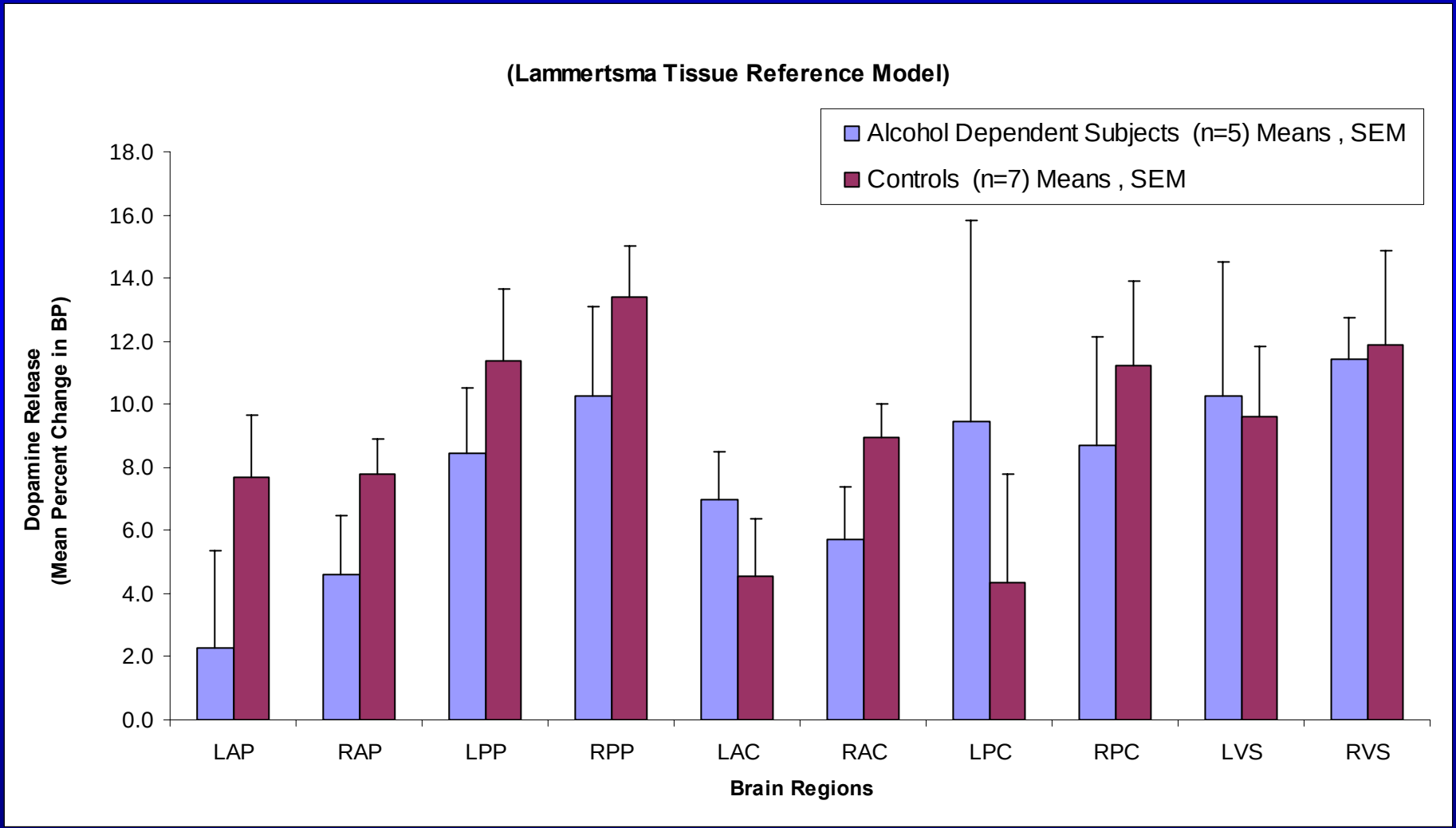
*In addition, there are psychological measures administered throughout the stay.

Alcohol Dependence Subjects
Baseline Binding Potential



Amphetamine-induced Dopamine Release

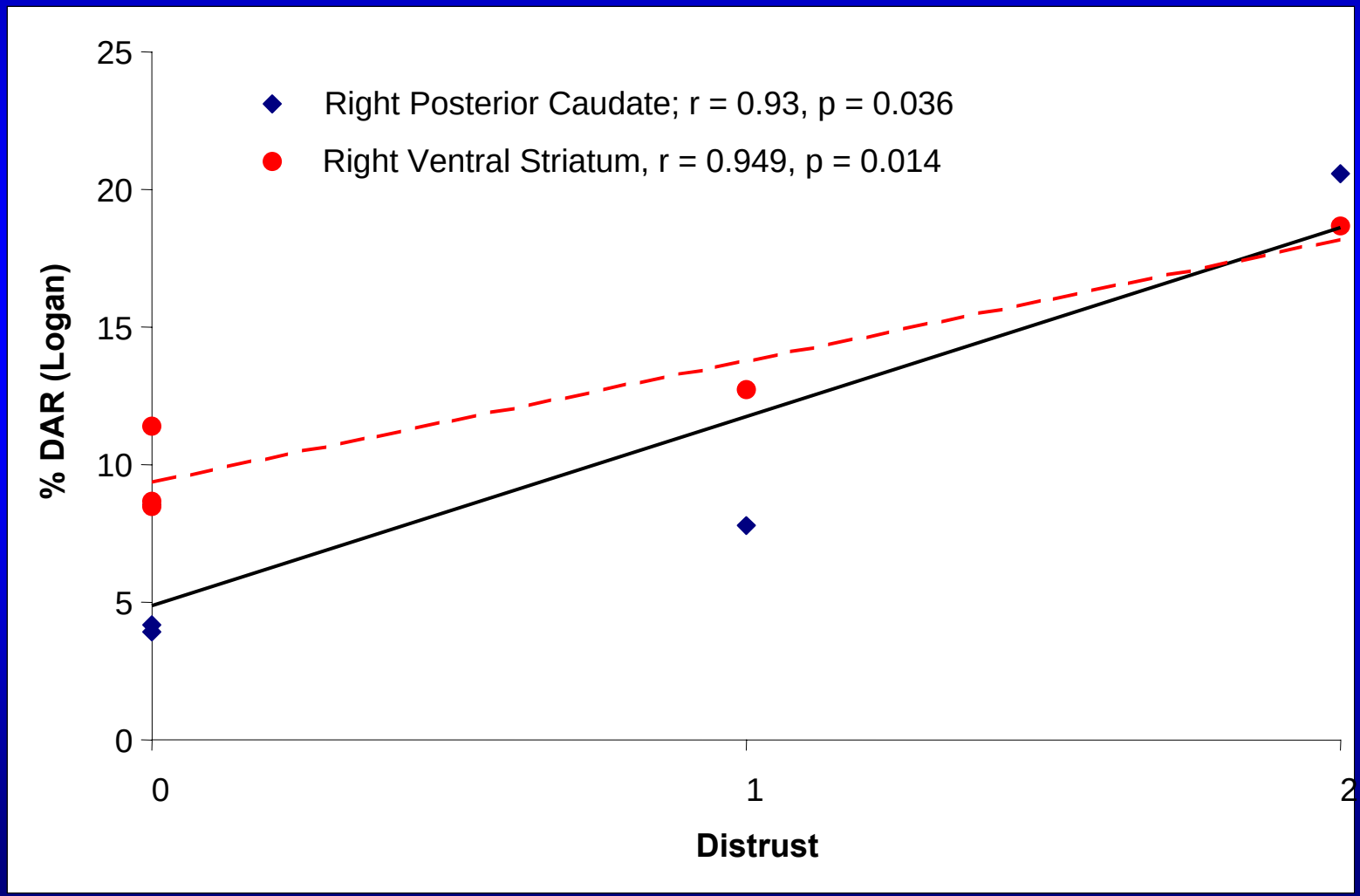
Alcohol Dependent Subjects



Dopamine Release vs. Peak Distrust (AMP-PET)

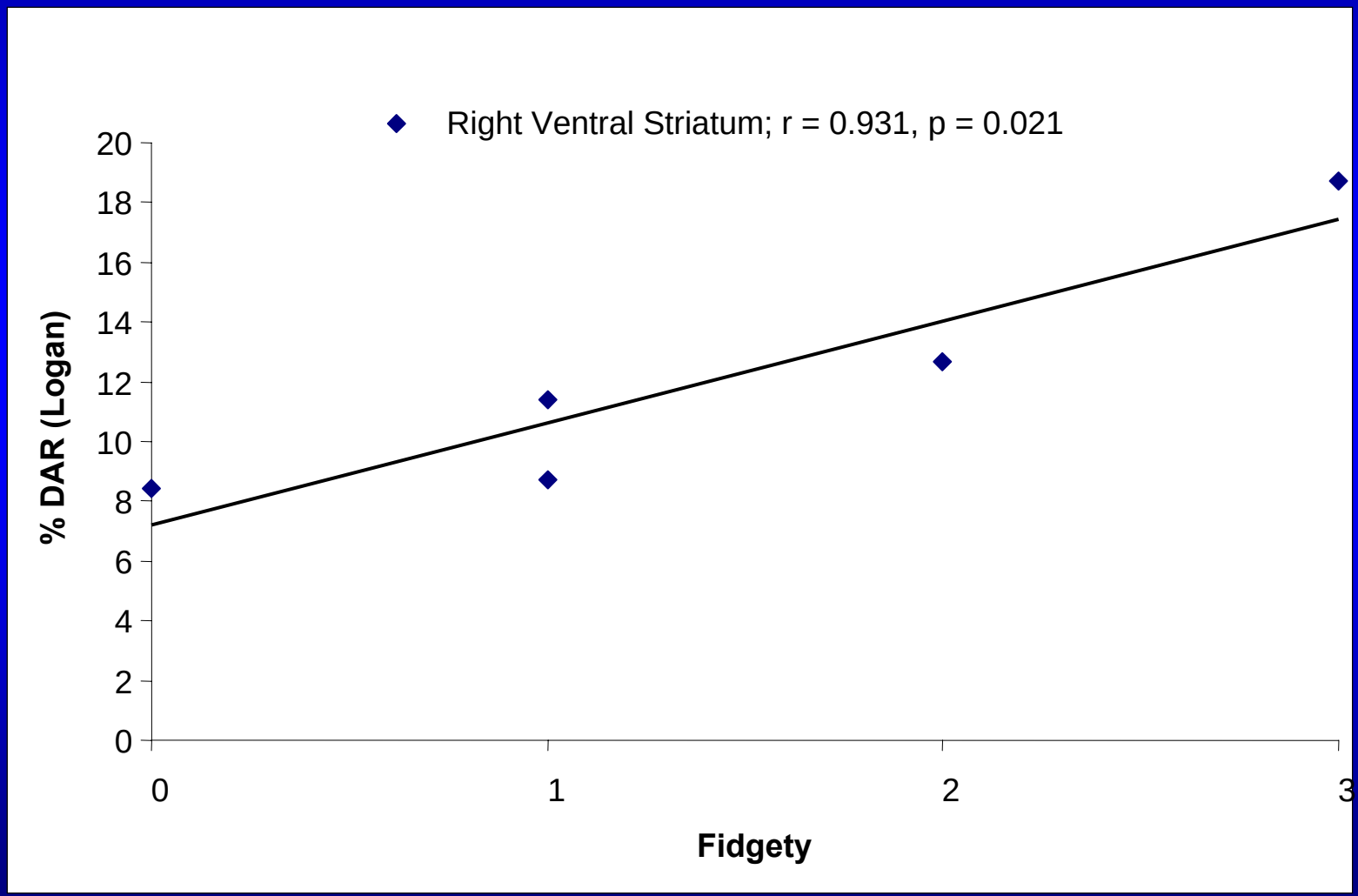
Alcohol Dependent Subjects (N = 5)

Logan Tissue Reference Method

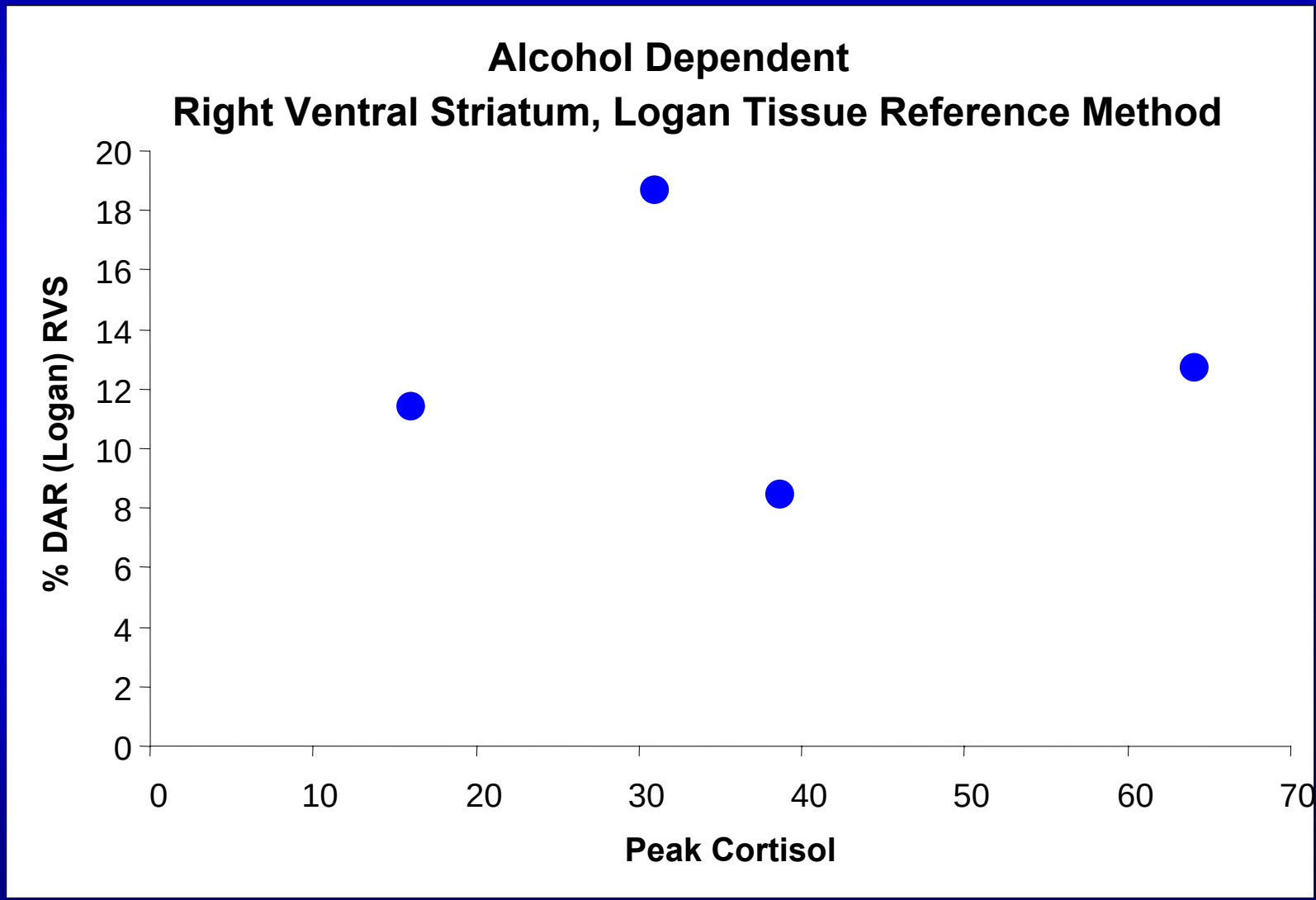


Dopamine Release vs. Peak Fidgety (AMP-PET)

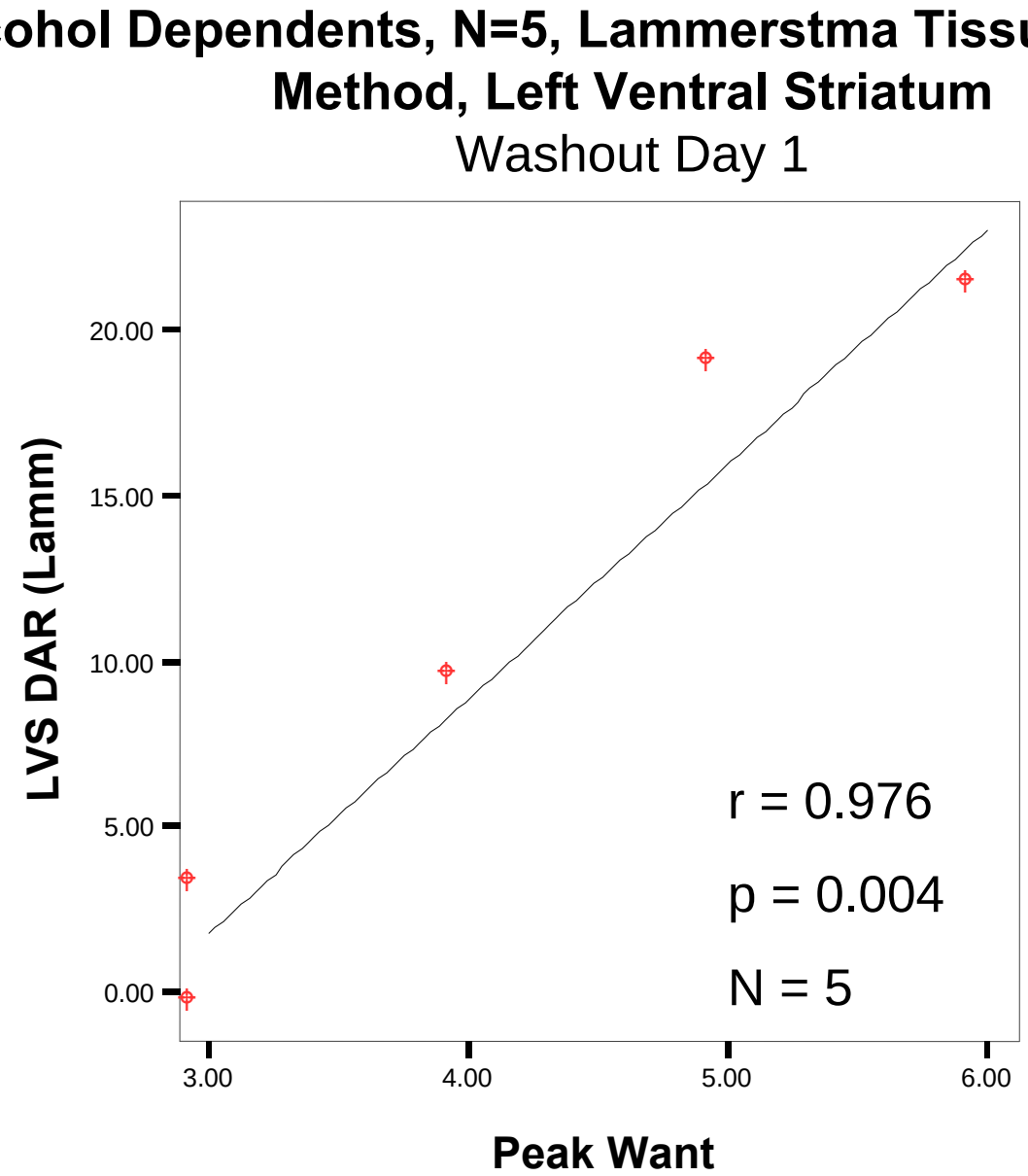
Alcohol Dependent Subjects (N = 5), Logan Tissue Reference Method



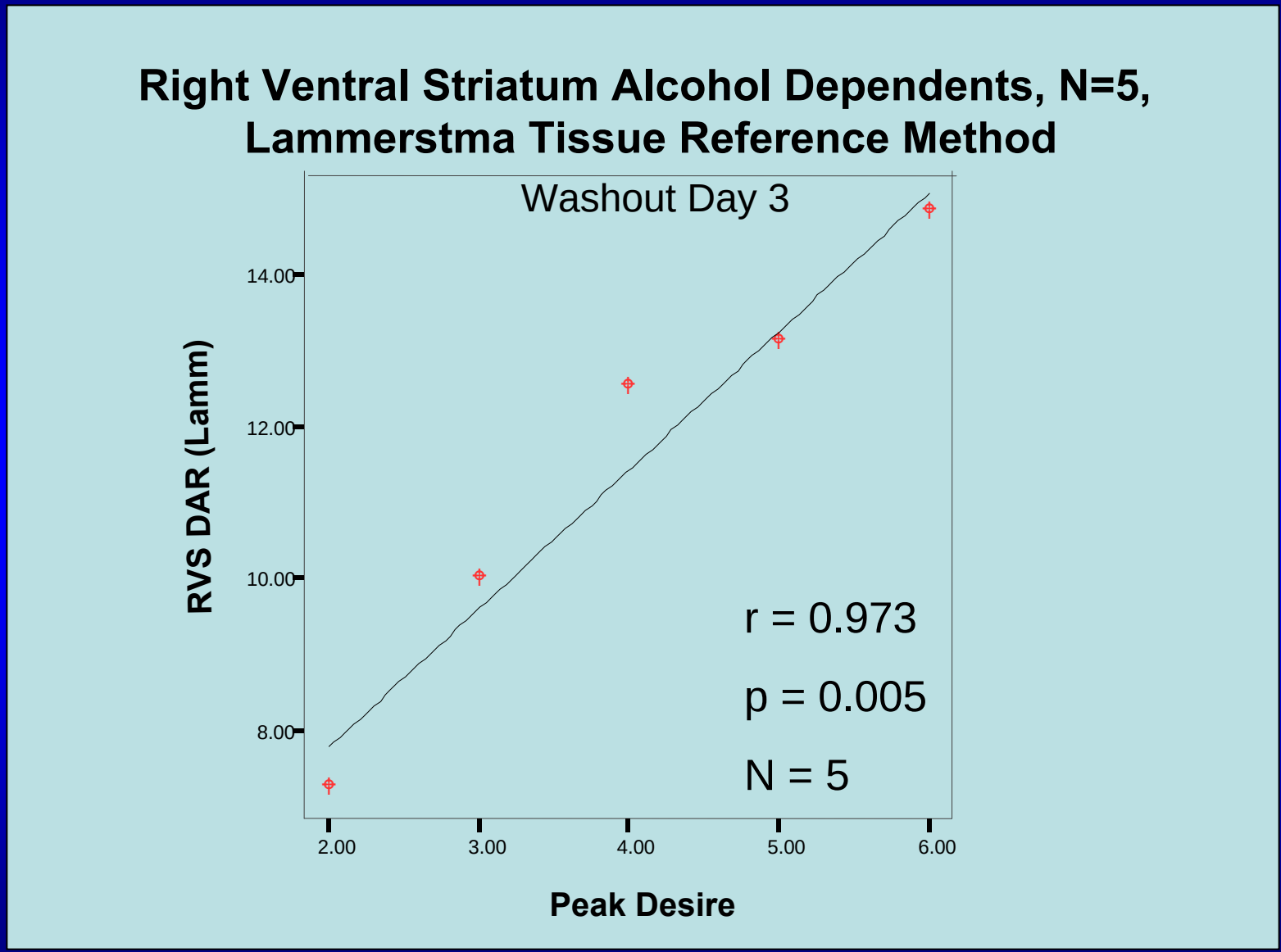
Dopamine Release vs. Peak Cortisol (Amphetamine PET)



Dopamine Release vs. Peak Want for Alcohol



Dopamine Release vs. Peak Desire for Alcohol



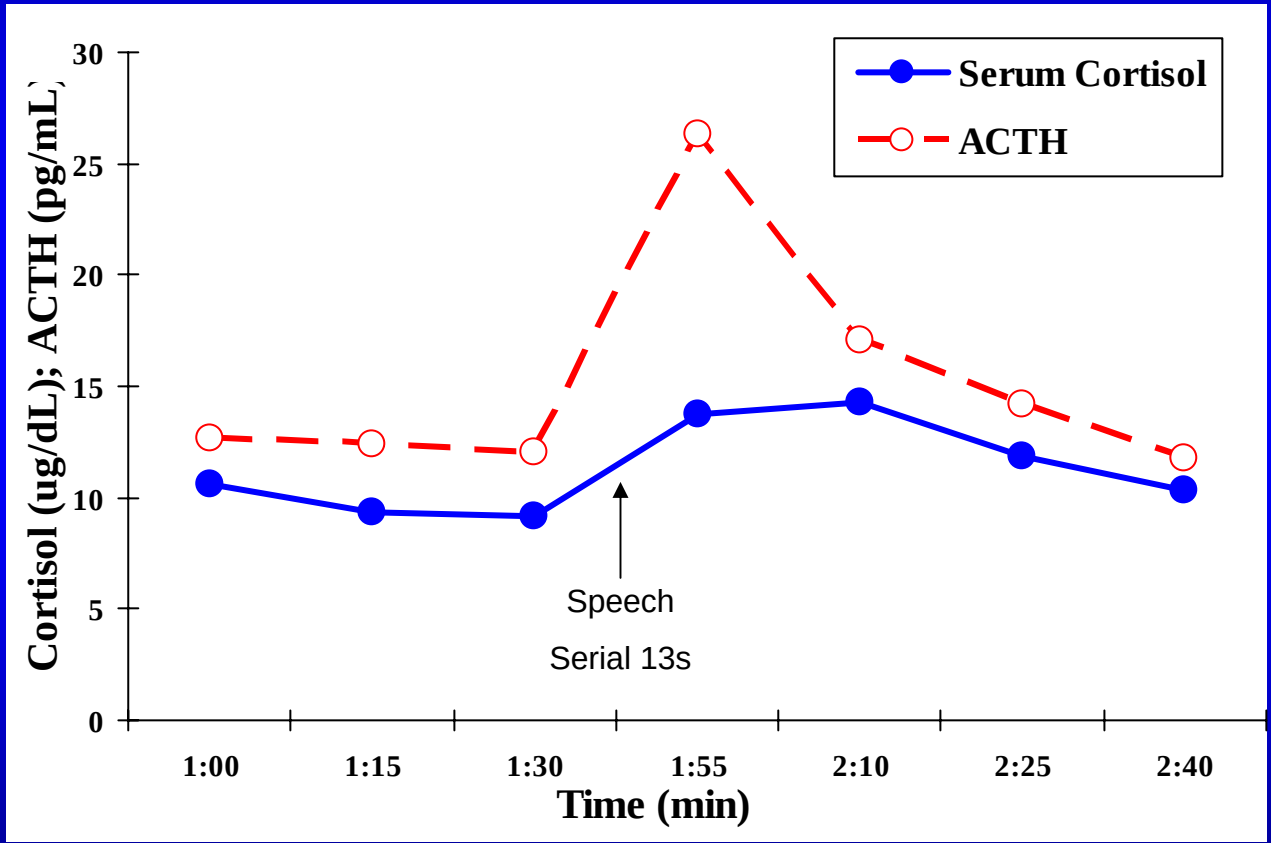
Study Design: Alcohol Dependence And Risks of Alcoholism Studies

- 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

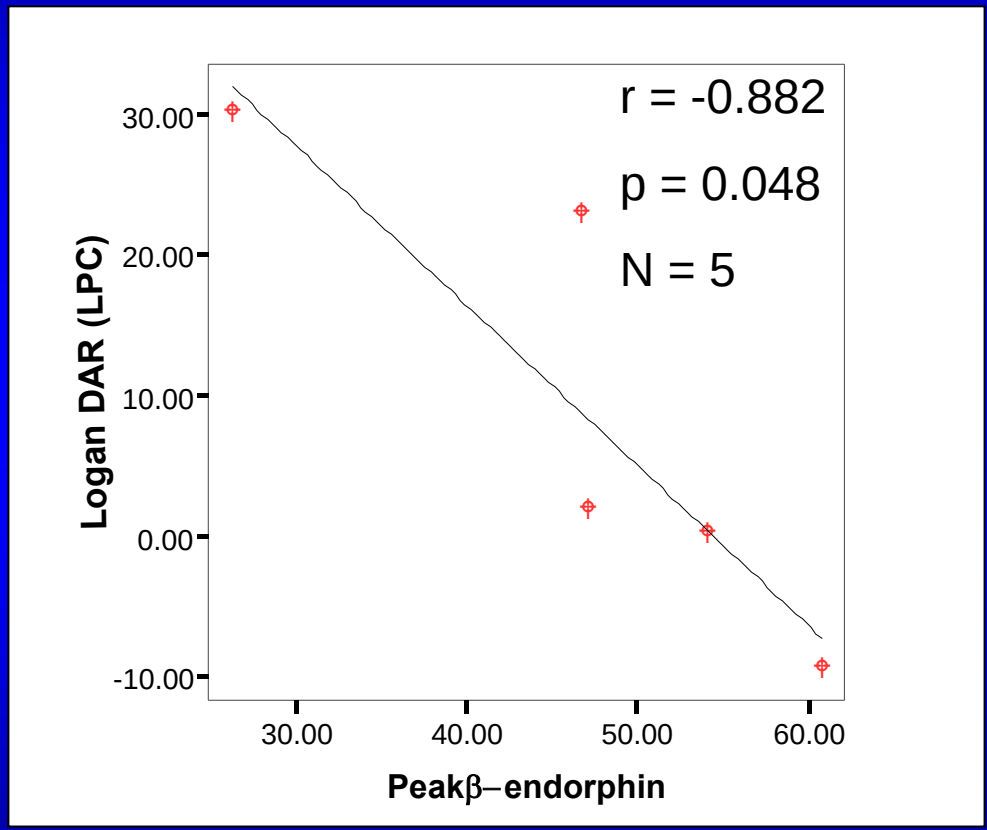
Active Session		*Placebo Session: Risks of Alcoholism Only*	
Noon:	Arrival, urine toxicity, breathalyzer, and pregnancy test	Noon:	Arrival, urine toxicity, breathalyzer, and pregnancy test
12:45:	State-Trait Anxiety Inventory, Combined Hassles and Uplifts Scale, Perceived Stress Scale	12:45:	State-Trait Anxiety Inventory, Combined Hassles and Uplifts Scale, Perceived Stress Scale
1:00:	Hormone measures, BP, HR	1:00:	Hormone measures, BP, HR
1:15:	Hormone measures, BP, HR	1:15:	Hormone measures, BP, HR
1:30:	Hormone measures, BP, HR	1:30:	Hormone measures, BP, HR
1:32:	Taped instructions to subjects	1:32:	Taped instructions to subjects
1:35:	*10 minute speech preparation time*	*1:35-1:50: Read Quietly*	
1:45:	*Speech*		
1:50:	*Serial 13s*		
1:55:	Hormone measures, BP, HR, State- Trait Anxiety Inventory	1:55:	Hormone measures, BP, HR State-Trait Anxiety Inventory
2:10:	Hormone measures, BP, HR	2:10:	Hormone measures, BP, HR
2:25:	Hormone measures, BP, HR	2:25:	Hormone measures, BP, HR
2:40:	Hormone measures, BP, HR	2:40:	Hormone measures, BP, HR
2:55:	Hormone measures, BP, HR	2:55:	Hormone measures, BP, HR
3:00:	Discharge	3:00:	Discharge

Risks of Alcoholism Study
Trier Session (n = 10)



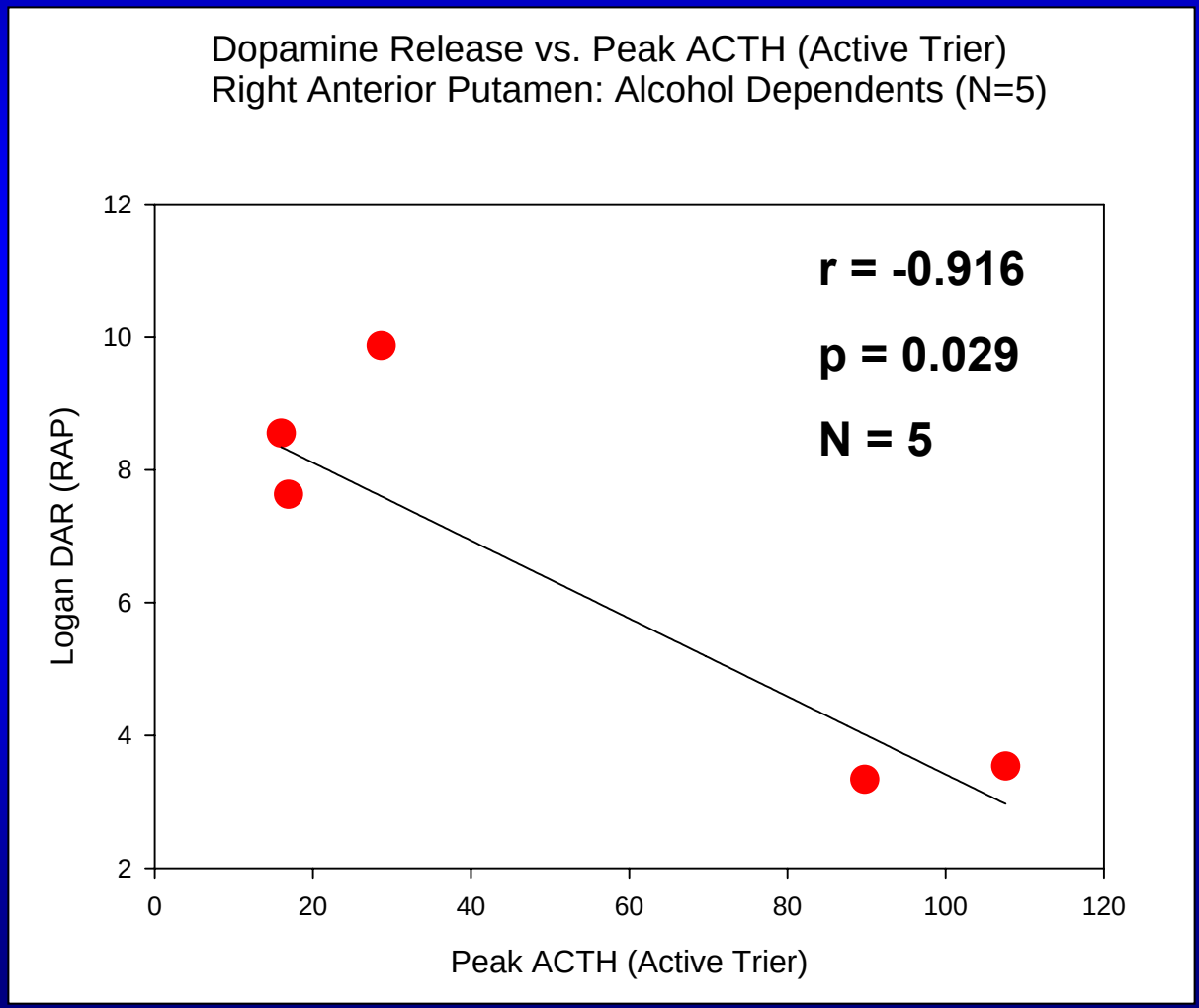
Dopamine Release vs. Peak β-endorphin

Left Posterior Caudate (Active Trier session)



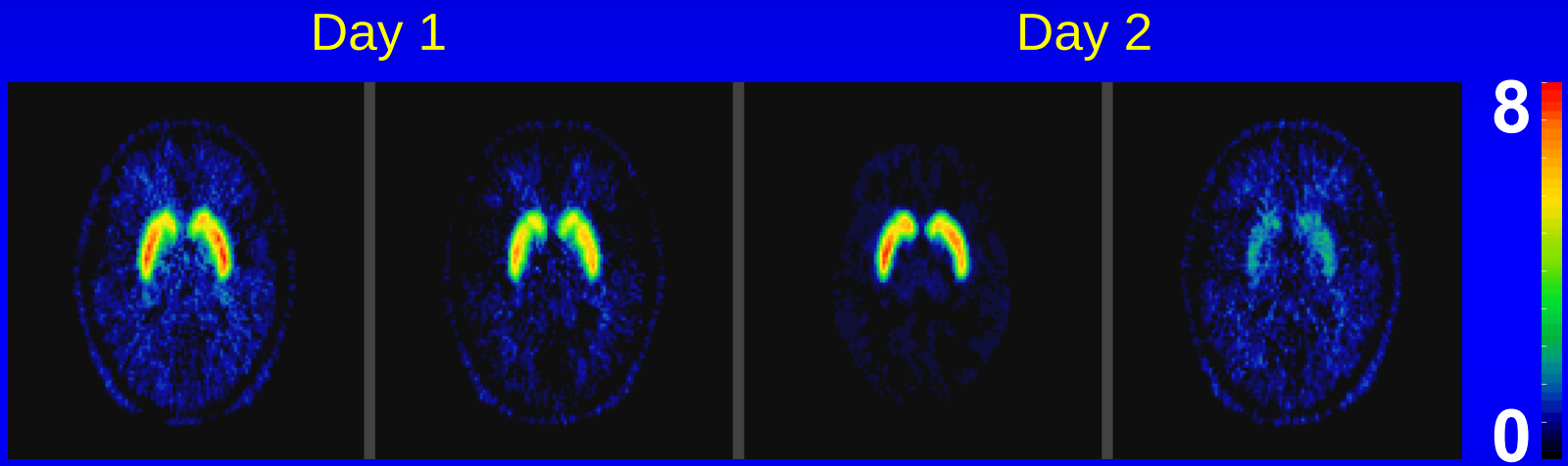
Dopamine Release vs. Peak ACTH

Right Anterior Putamen, Active Trier session



Future Directions

DA Receptor Density, DA Release, and DAT



[^{11}C]RAC, HSA baseline

[^{11}C]RAC HSA AMPH (0.3 mg/kg)

[^{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.

Acknowledgements

Special thanks to Lauren Sims, Ayon Nandi , Marika Maris, Maria Thomas

Grant Support:

RO1 AA12839

AA10158, AA12837

K24DA00412

Contact: dfwong@jhmi.edu

Acknowledgements

Wong Lab

Clinical Procedures/Coordination

M. Thomas, Ph.D., M. Maris, B.S., L Sims, B.S., J. Brasic, M.D., Ph.D., F. Ye, M.D., M. Alexander, M.D., A. Maini, M.D., J. Hilton, D.Sc., A. Nandi, B.S

Data Analysis

A. Kumar, M.D., Y Zhou., Ph.D., H. Kuwabawa, M.D., Ph.D., O. Rousset, Ph.D., A. Crabb, M.S., C. Endres, Ph.D., J.S. Lee, Ph.D., C. Rohde, Ph.D. (BioStats), D. Schretlen, Ph.D. (Psychiatry), M. Pomper, M.D., Ph.D. (JH Neuroradiology)

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)

Positive Family History: N=4

Age = 22± 1.71 Race: 1 Black, 3 White Gender: 3 M, 1 F

Negative Family History: N=12

Age = 21± 3.12 Race: 1 Black, 2 Asian, 9 White

Gender: 7 M, 5 F

Alcohol Dependence Study (N = 12)

Alcohol Dependent : N=5

Age = 45± 4.15 Race: 1 Black, 4 White Gender: 5 M

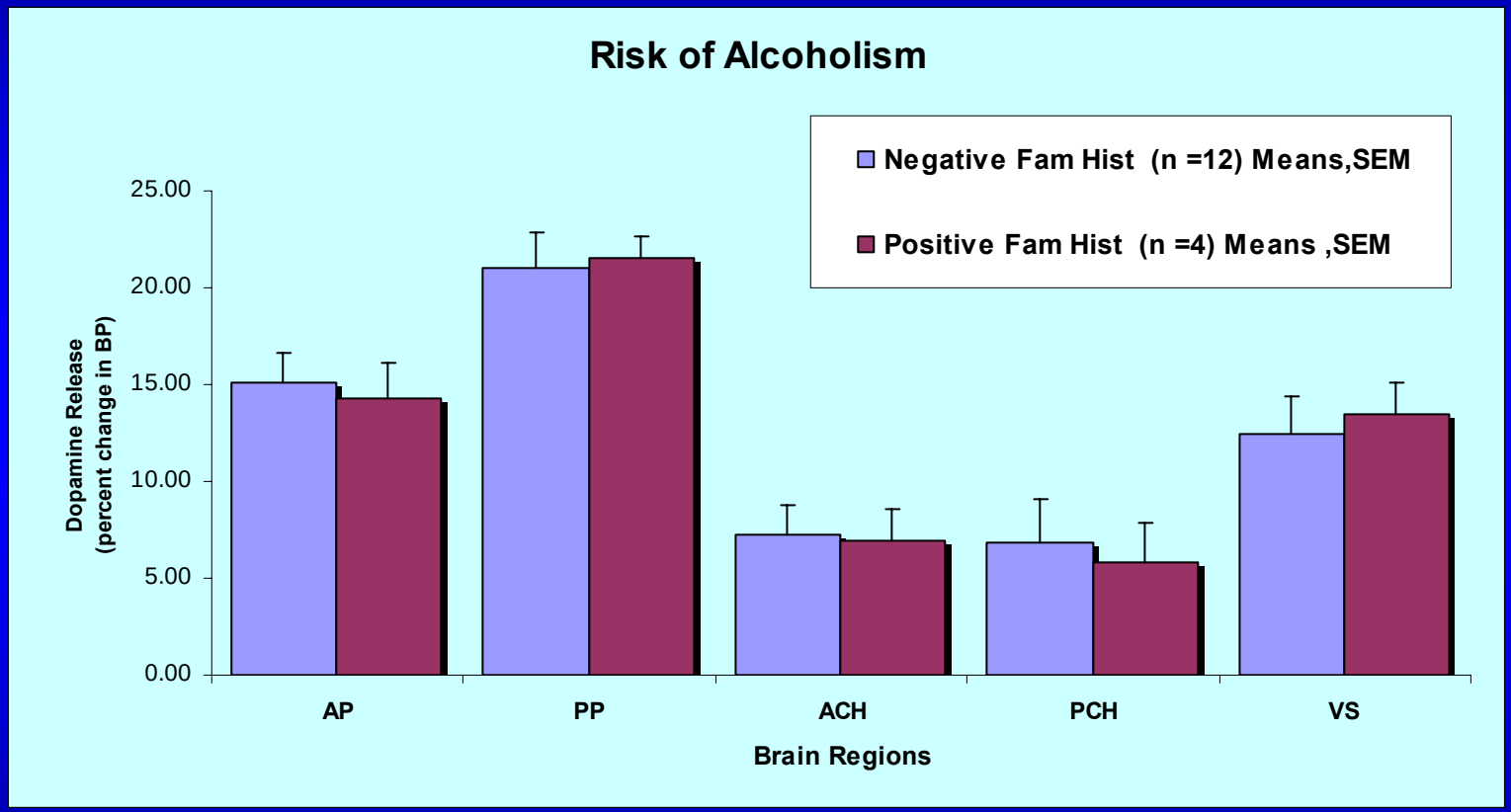
Control Subjects: N=7

Age = 44± 6.31 Race: 5 Black. 2 White

Gender: 6 M, 1 F

Risk of Alcoholism Study

Dopamine Release



Parametric Image Modeling

Ref: Zhou et al (2003)

Aims for Wand Study

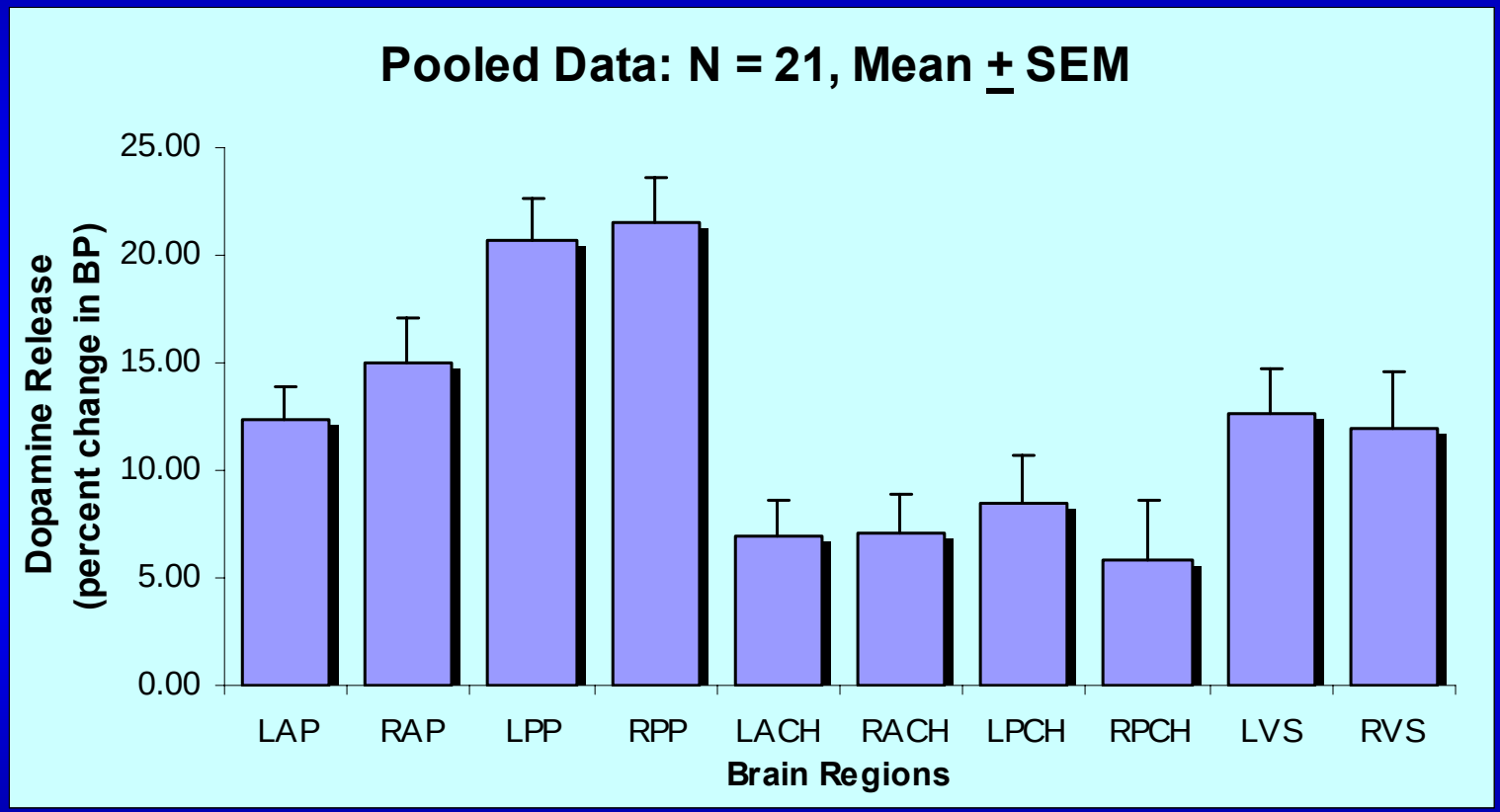
- To examine the association between DA release and risk for alcoholism. We hypothesize that high risk subjects will be greater DA releasers compared to low risk subjects.

- To examine the relationship between HPA axis dynanamics 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

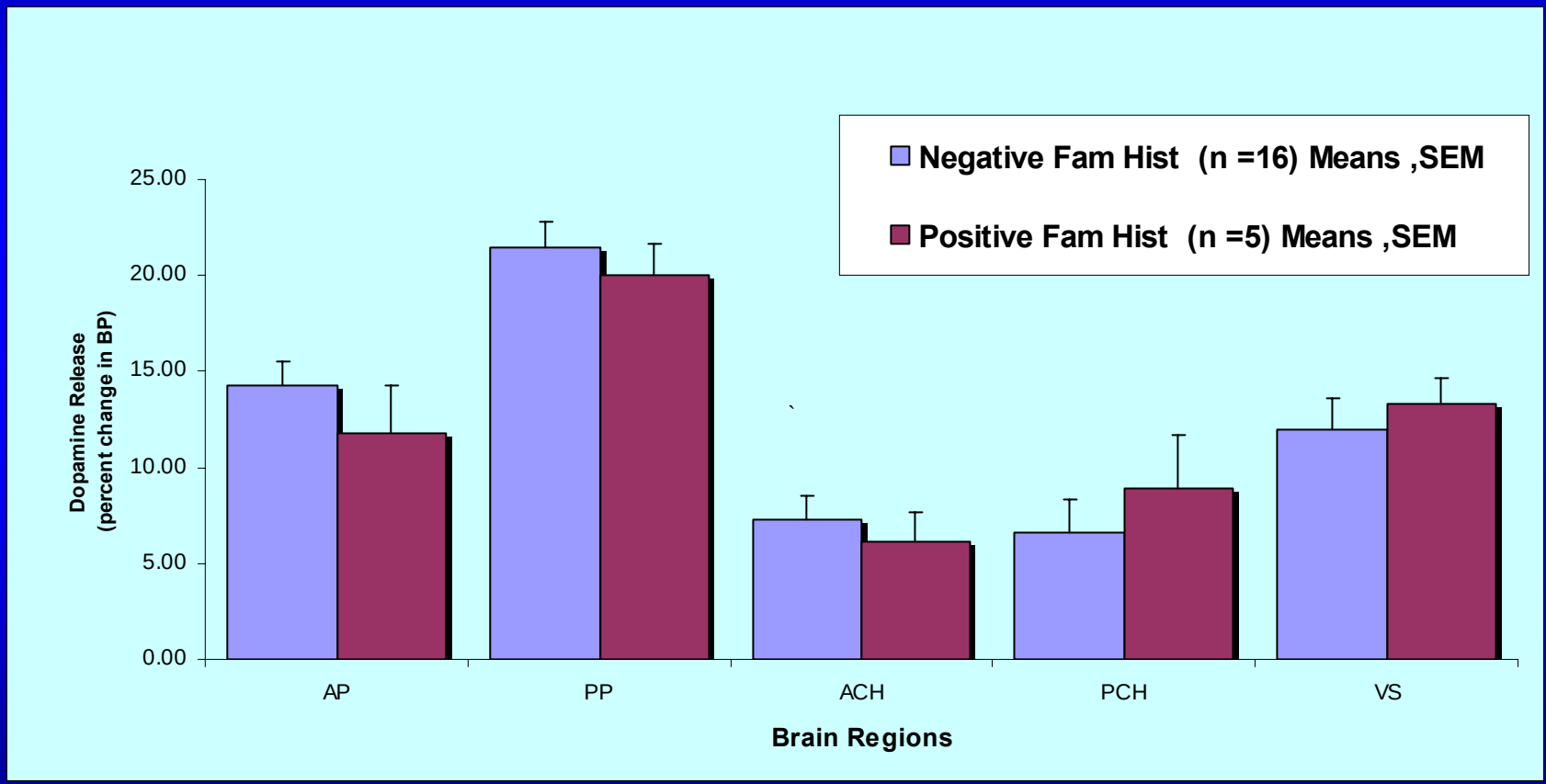


Parametric Image Modeling

Ref: Zhou et al (2003)

Risk of Alcoholism Study

Dopamine Release

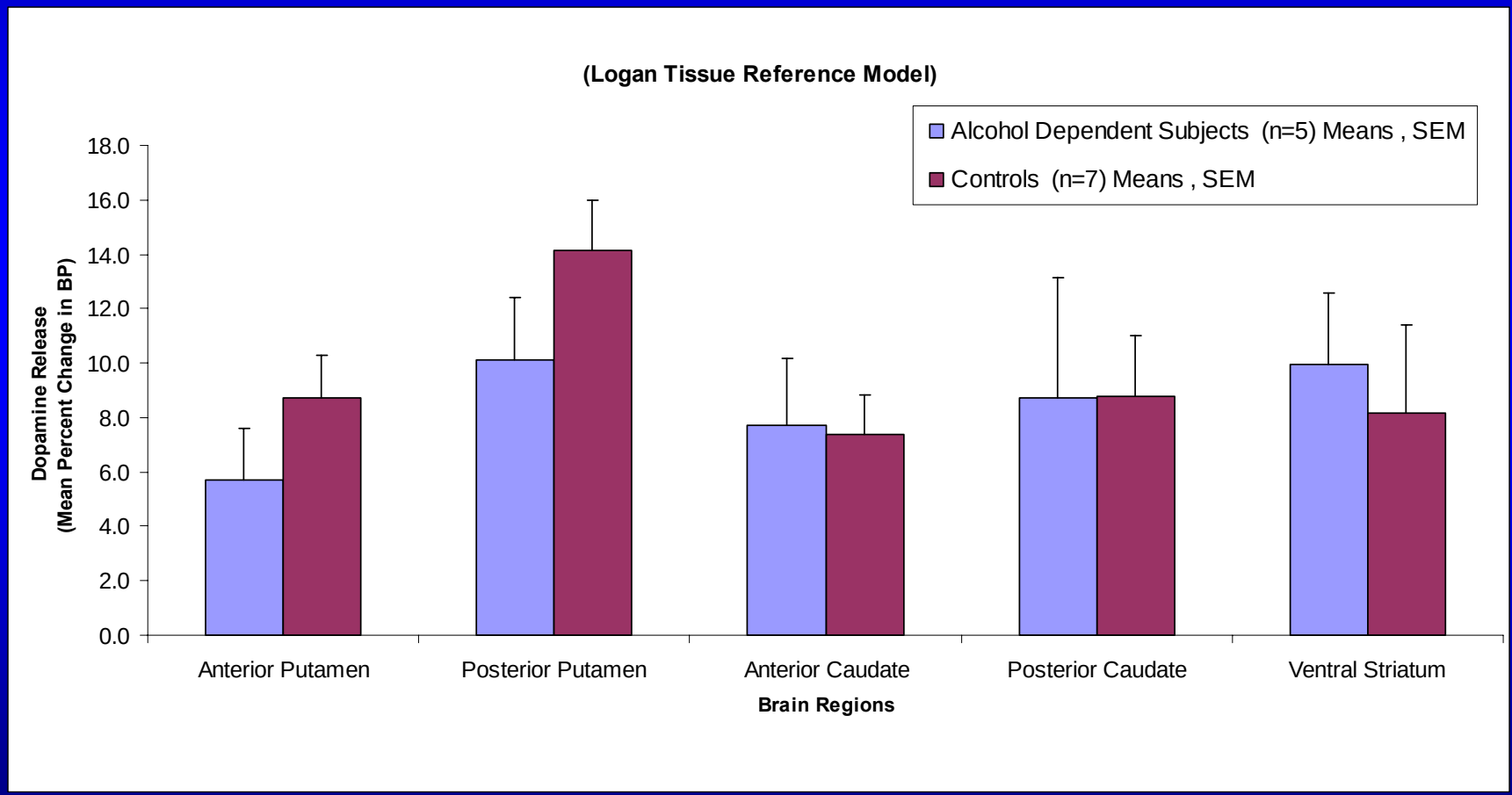


Parametric Image Modeling

Ref: Zhou et al (2003)

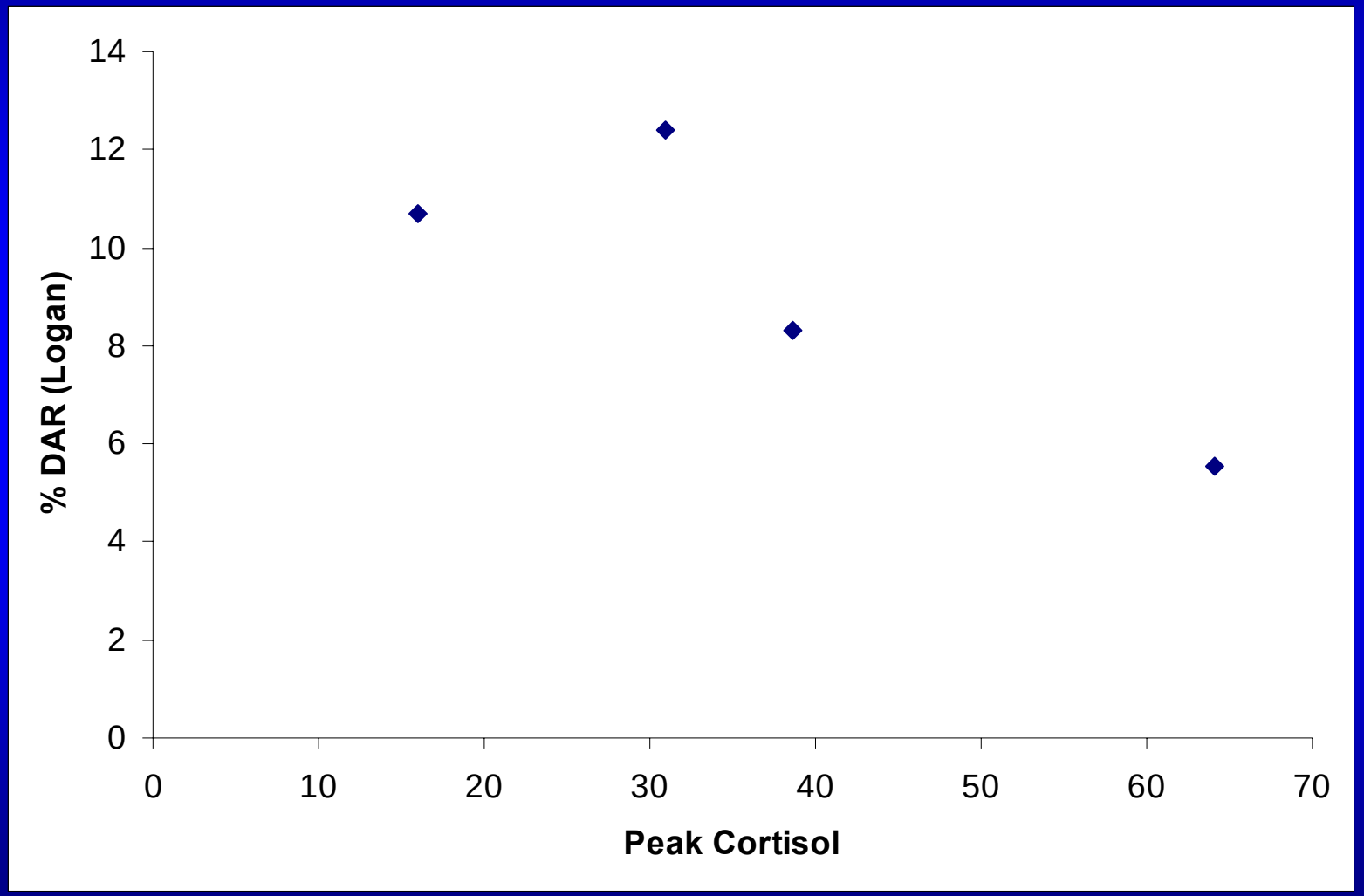
Amphetamine-induced Dopamine Release

Alcohol Dependent Subjects



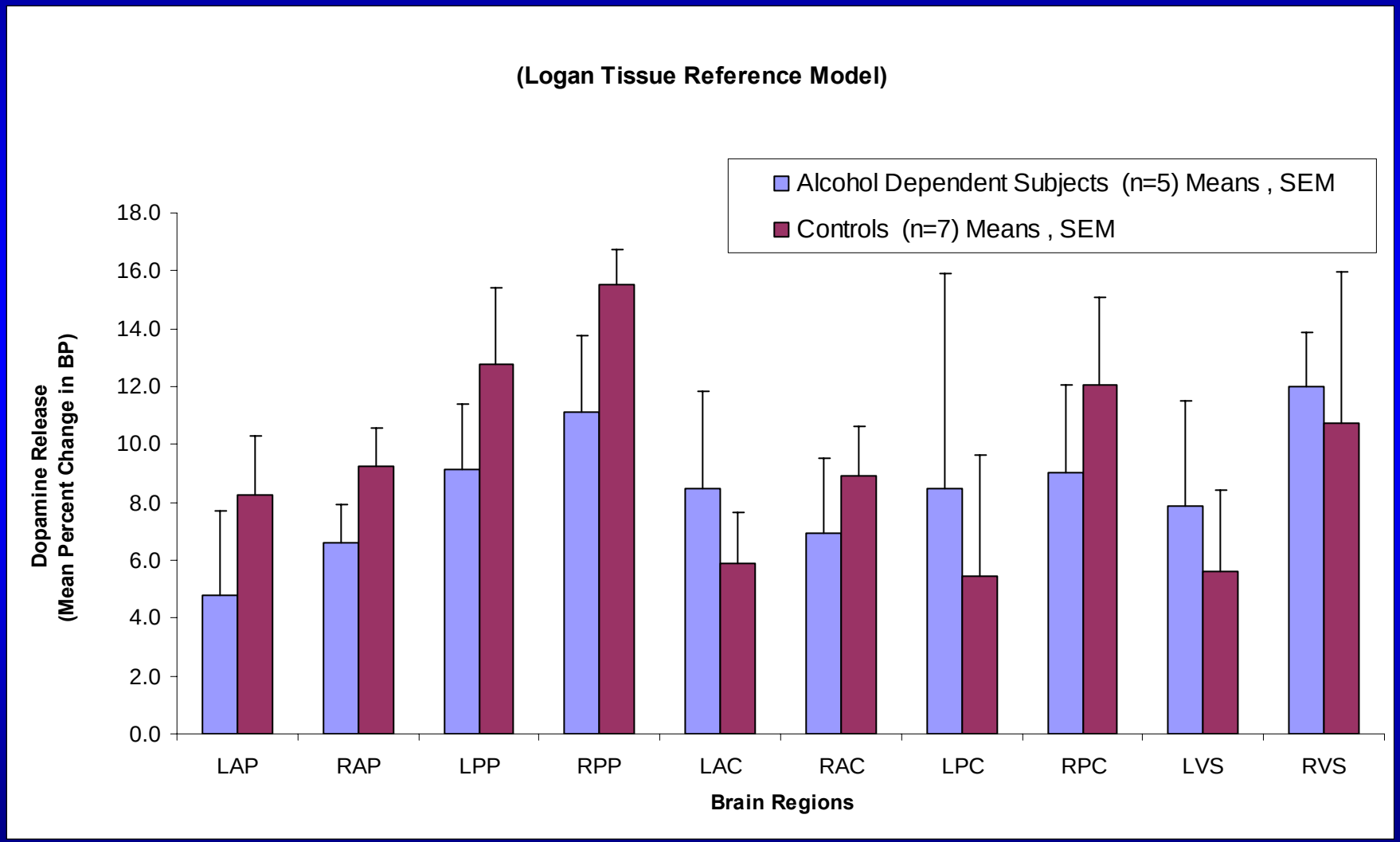
Right Anterior Caudate: Dopamine Release vs. Peak Cortisol

Logan Tissue Reference Method, Alcohol Dependent Subjects (N = 4)



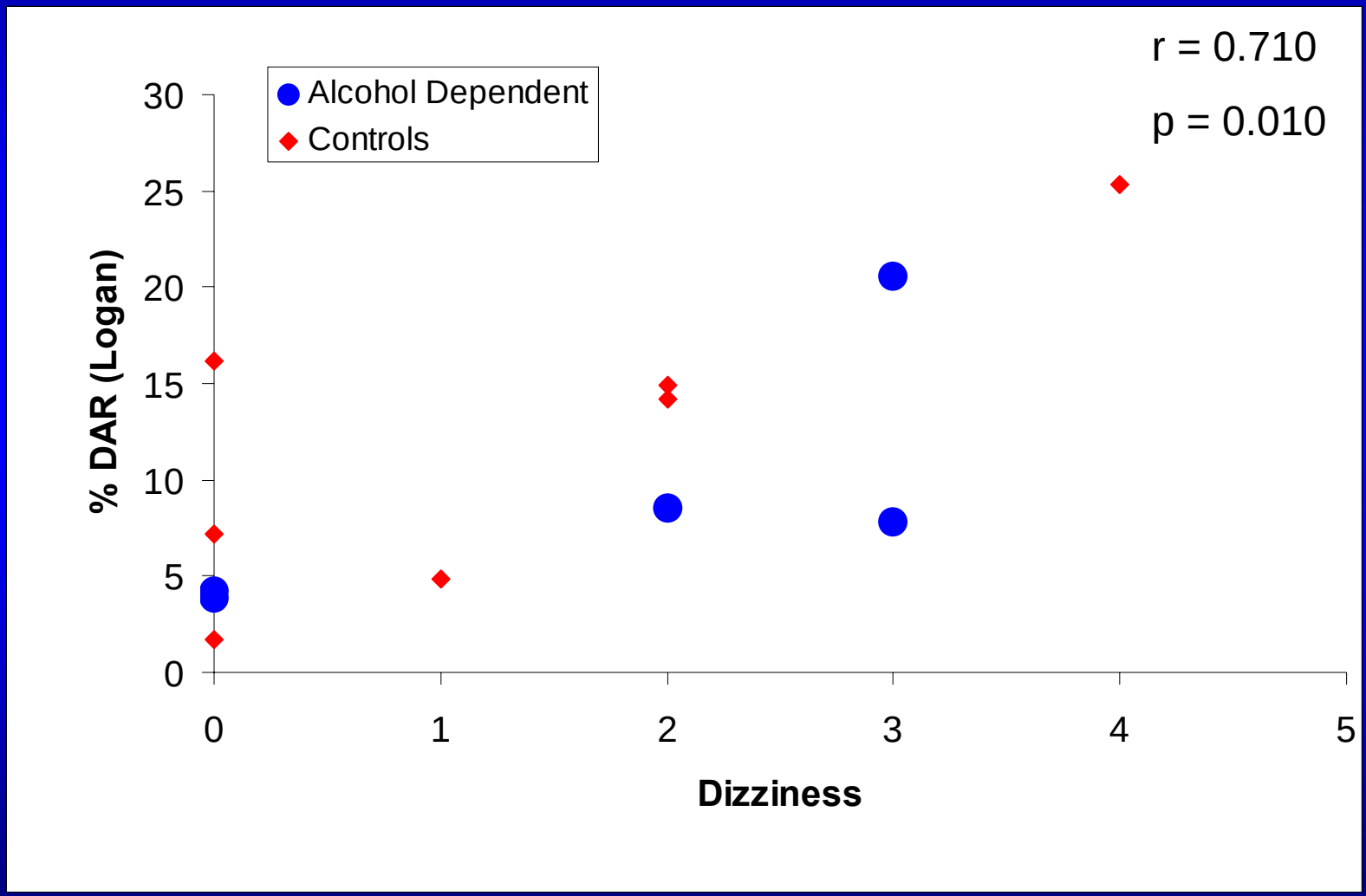
Amphetamine-induced Dopamine Release

Alcohol Dependent Subjects



Right Posterior Caudate: Dopamine Release vs. Peak Dizziness Score

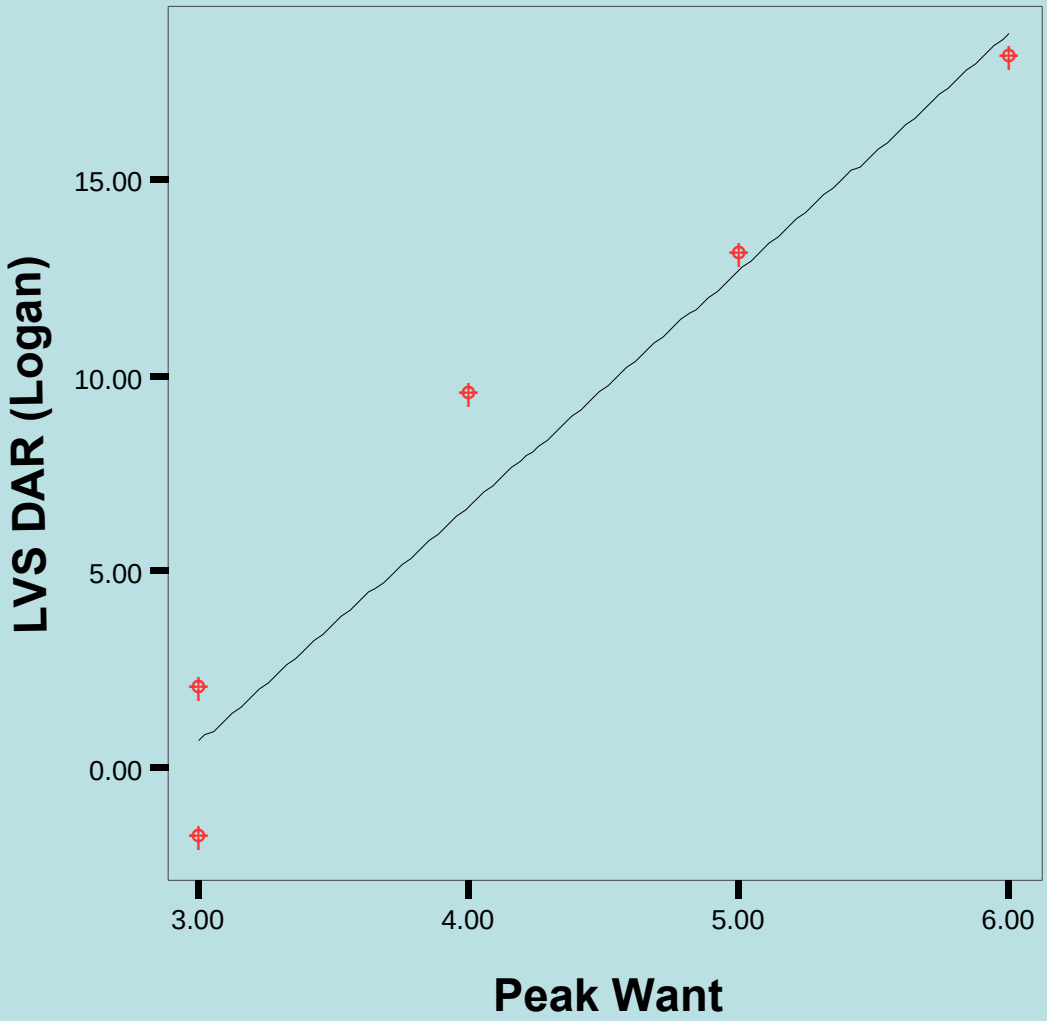
Logan Tissue Reference Method



**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