MRI Studies of Addiction: Implications for Treatment Development

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What is Addiction?

- Addict (verb) - “to devote or give (oneself) habitually or compulsively”; from Latin *addicere* - bound to or enslaved
- Historical Shifts in Usage of Term
- Core Components of Addiction (Shaffer, 1999)
  - Continued Behavior Despite Adverse Consequences
  - Diminished or Lost Control / Compulsive Engagement
  - Craving or Urge State Component

Changing Perspectives on Addiction

2001

Aided by brain imaging advances, scientists are looking for evidence that compulsive nondrug behaviors lead to long-term changes in reward circuitry

'Behavioral' Addictions: Do They Exist?

ADDICTION

The concept of addiction is changing, as this special news package describes: There's more emphasis on how drugs and even behaviors may wreak long-term damage to the brain.

COMPULSIVE BEHAVIORS
LONG-TERM CHANGES

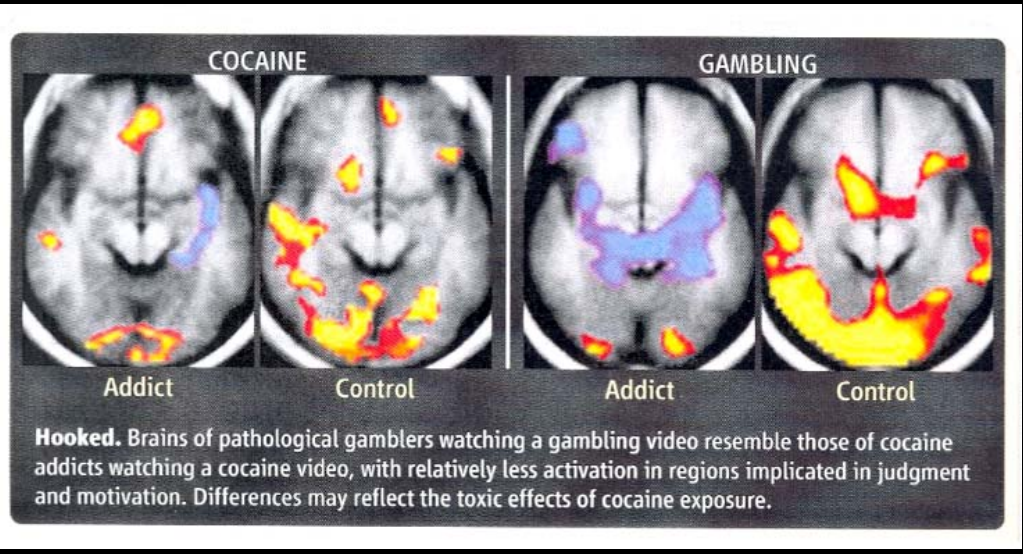
Verona Addiction Conference, June 8, 2010

2010

Shared brain vulnerabilities open the way for nonsubstance addictions: Carving addiction at a new joint?

Joseph Frascella,[1] Marc N. Potenza,[2] Lucy L. Brown,[3] and Anna Rose Childress[4,5]

Behavioral Addictions Debut in Proposed *DSM-V*



Hooked. Brains of pathological gamblers watching a gambling video resemble those of cocaine addicts watching a cocaine video, with relatively less activation in regions implicated in judgment and motivation. Differences may reflect the toxic effects of cocaine exposure.

Holden, Science, 2001, 2010; Frascella et al, Ann NY Acad Sci, 2010

Relationship Between PG and SUDs

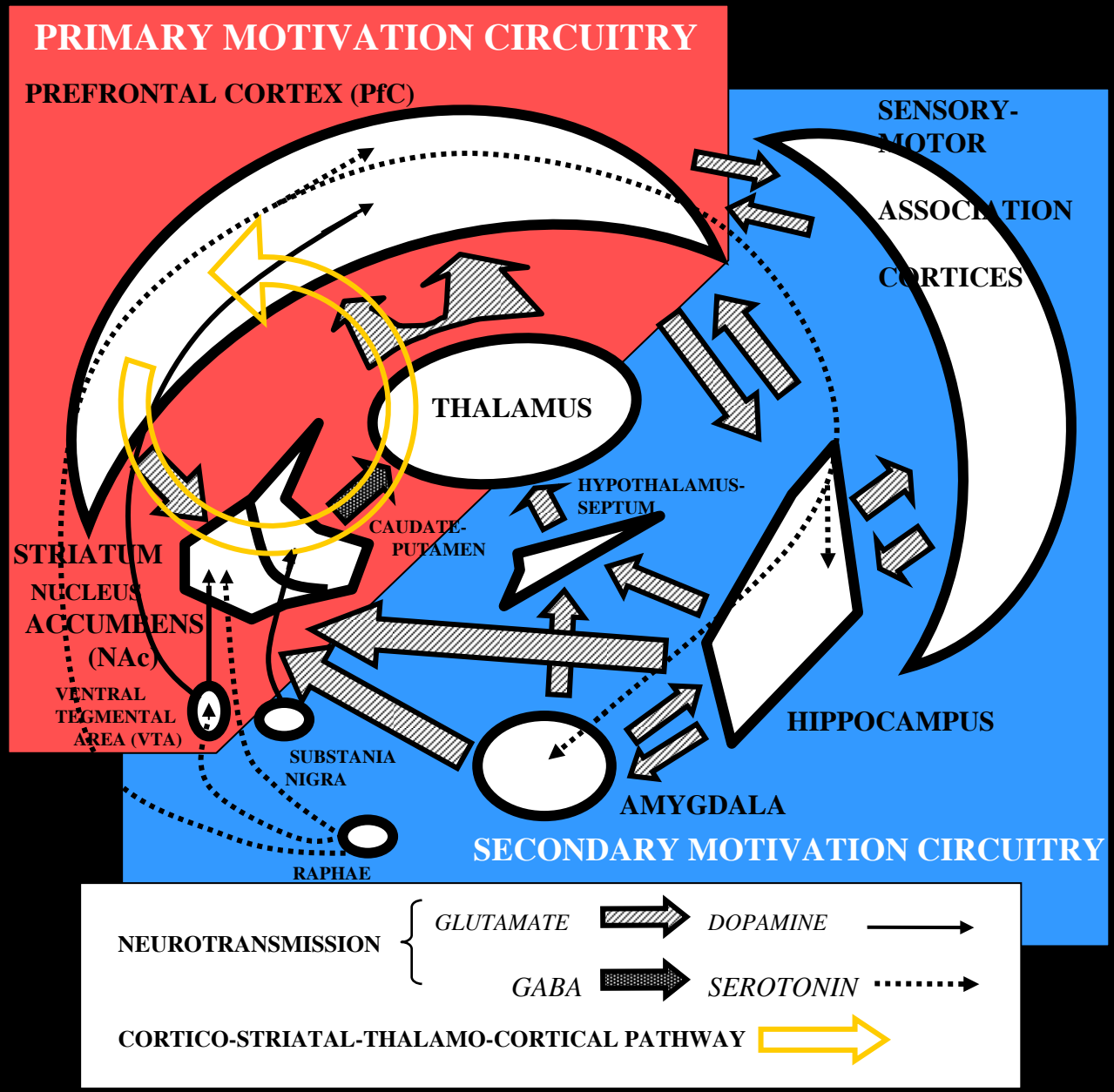
- **High Rates of Co-Occurrence**
  - Population and Clinical Samples
- **Similar Clinical Courses**
  - High Rates in Adolescence, Lower Rates in Older Adults
  - "Telescoping" Pattern in Women
- **Similar Clinical Characteristics**
  - Tolerance, Withdrawal, Repeated Attempts to Cut Back or Quit
  - Appetitive Urge or Craving States
- **Similar Biologies**
  - Genetic Contributions, Neural Circuits
- **Similar Treatments**
  - Self-Help, CBT, MI, Naltrexone and Nalmefene, N-AC

Impulsivity as an Endophenotype

- Defining Impulsivity (Moeller et al, 2001)
  - "A Predisposition Toward Rapid, Unplanned Reactions to Internal or External Stimuli [With Diminished] Regard to the Negative Consequences of These Reactions to the Impulsive Individual or to Others"
- Impulsivity Across Psychiatric Groups
  - ICDs, SUDs, Bipolar D/O, ADHD, ASPD, BPD, Suicidality, SIB
- Behavioral Measures of Impulsivity
  - Choice Impulsivity - Risk/Reward Assessment & Decision-Making Paradigms (Monetary Reward/Punishment, Discounting, Gambling Tasks)
  - Response Impulsivity - Disinhibition/Attentional Paradigms (Go/No-Go, Stroop)

Motivational Neural Systems and Addiction

- Mesolimbic System
  - DA in Ventral Tegmental Area, Nucleus Accumbens
- Frontal Cortical Systems
  - 5-HT, DA
- Important Roles for Other Neurotransmitter Systems
  - GABA, Glutamate, Opioids, …



Chambers, Taylor & Potenza, Am J Psychiatry, 2003

Roles for Neurotransmitters

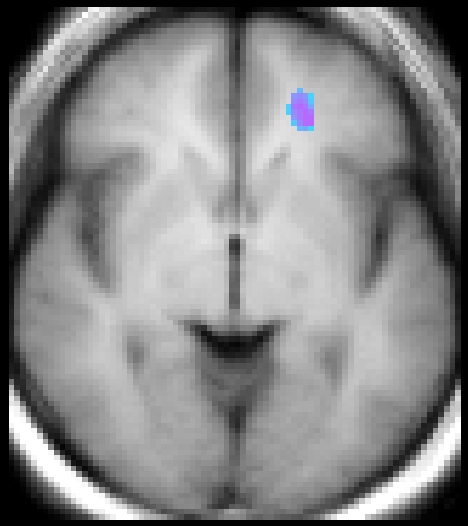
Neurotransmitter	Role in Impulse Control
Norepinephrine (NE)	Arousal, Excitement
Serotonin (5HT)	Behavior Initiation/Cessation
Dopamine (DA)	Reward, Reinforcement
Opioids	Pleasure, Urges

Potenza and Hollander, 2002

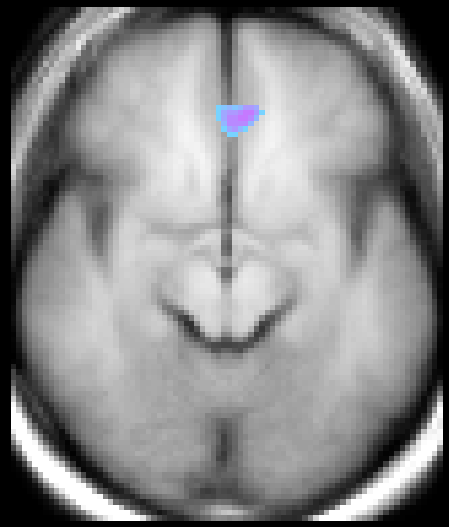
5-HT & Impulse Control

- Low CSF 5-HIAA Associated w/ Impaired Impulse Control (Potenza and Hollander, 2002)
- Altered Biochemical and Behavioral Responses to m-CPP (5HT1R and 5HT2R Partial Agonist) (DeCaria et al, 1998)
- Blunted 5HT Response in vmPFC in Impulsive Aggression (Siever et al, 1999; New et al, 2002)

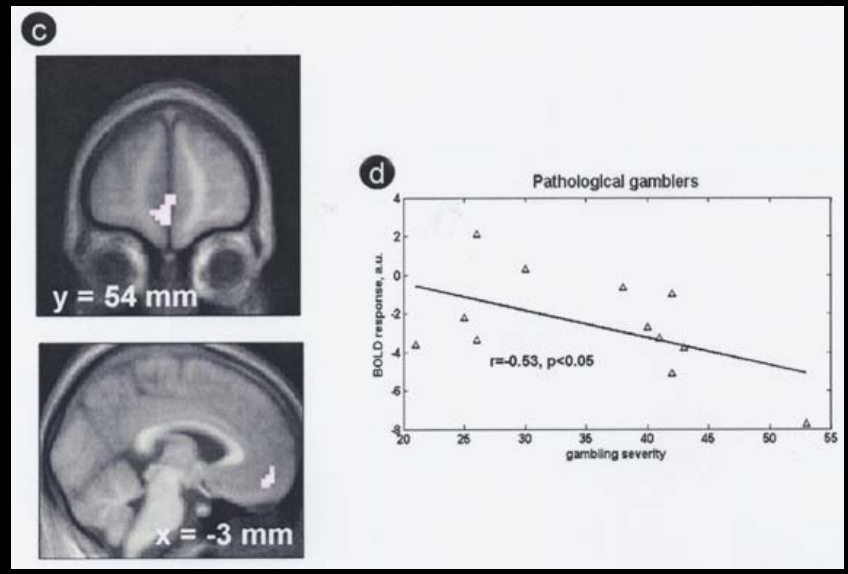
vmPFC, PG and SUDs



Stroop
PG - Control
(Potenza et al, 2003, *Am J Psychiatry*)



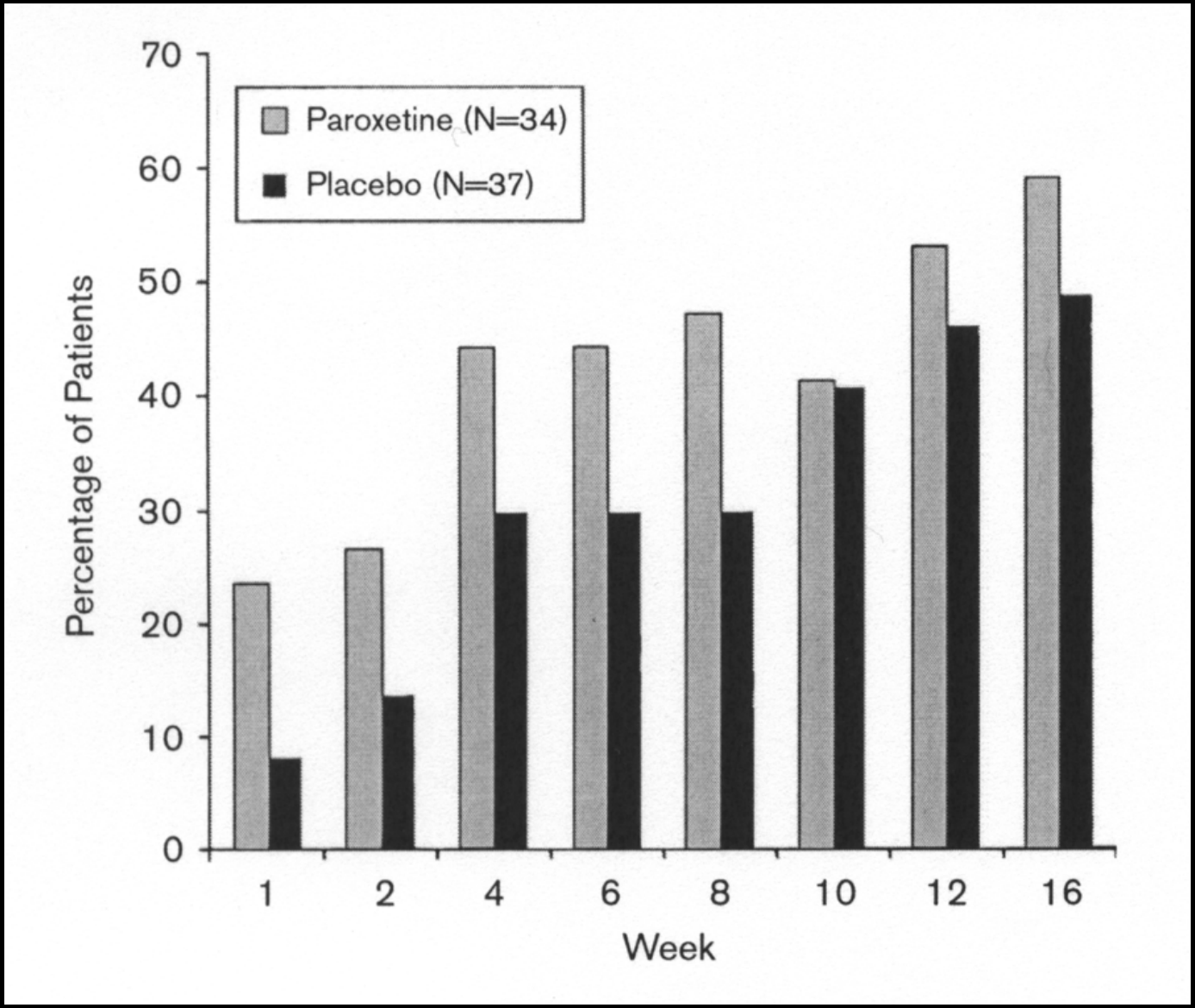
Gambling Tape
PG-Control
(Potenza et al, 2003, *Arch Gen Psychiatry)*



Simulated Gambling
Reuter et al, 2005, *Nat Neurosci*

Controls > SUD/PG in vmPFC on IGT
Tanabe et al, 2007, *Hum Brain Mapp*

Paroxetine



Grant et al, 2003

Escitalopram, PG and Anxiety

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Grant and Potenza, 2006

Impulsivity During Treatment

- Self-Reported Impulsivity Decreased During Treatment in a Placebo-Controlled Trial of Paroxetine in the Treatment of PG (Blanco et al., 2009)
- PG-YBOCS Scores and Measures of Impulsivity Were Correlated at Treatment Onset (r=0.51; p=0.001)
- Changes in Impulsivity Correlated with Changes in PG-YBOCS Scores (r=0.49; p=0.002)

Risk/Reward Decision-Making, Reward Processing & Addiction

- Subjects with PG or SUDs Perform Disadvantageously on Gambling Tasks (Petry et al, 2001; Bechara, 2003)
- Rapid Discounting of Rewards (Bickel et al, 1999; Petry et al, 2001)
- Behavioral Measures of Reward Discounting Associated with SUD Tx Outcome (Krishnan-Sarin et al, 2007)

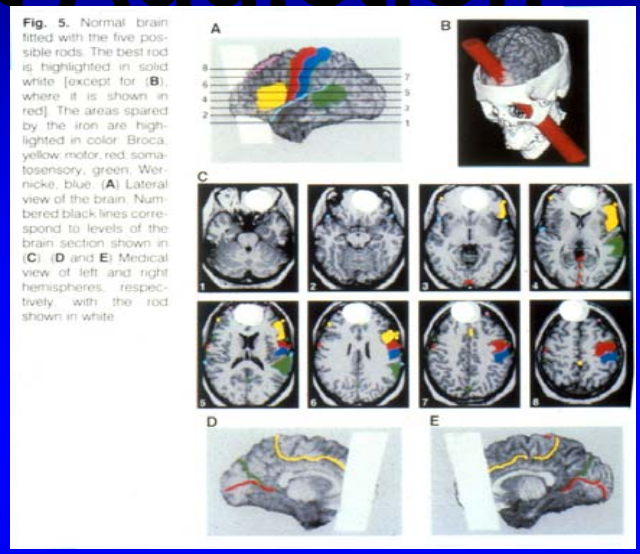
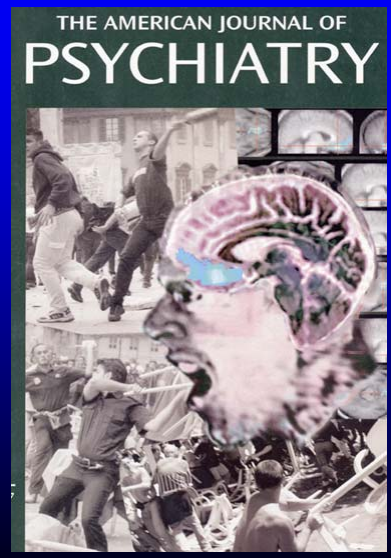


Fig. 5. Normal brain fitted with the five possible rods. The best rod is highlighted in solid white [except for (B), where it is shown in red]. The areas spared by the iron are highlighted in color: Broca, yellow; motor, red; somatosensory, green; Wernicke, blue. (A) Lateral view of the brain. Numbered black lines correspond to levels of the brain section shown in (C). (D and E) Medical view of left and right hemispheres, respectively, with the rod shown in white.



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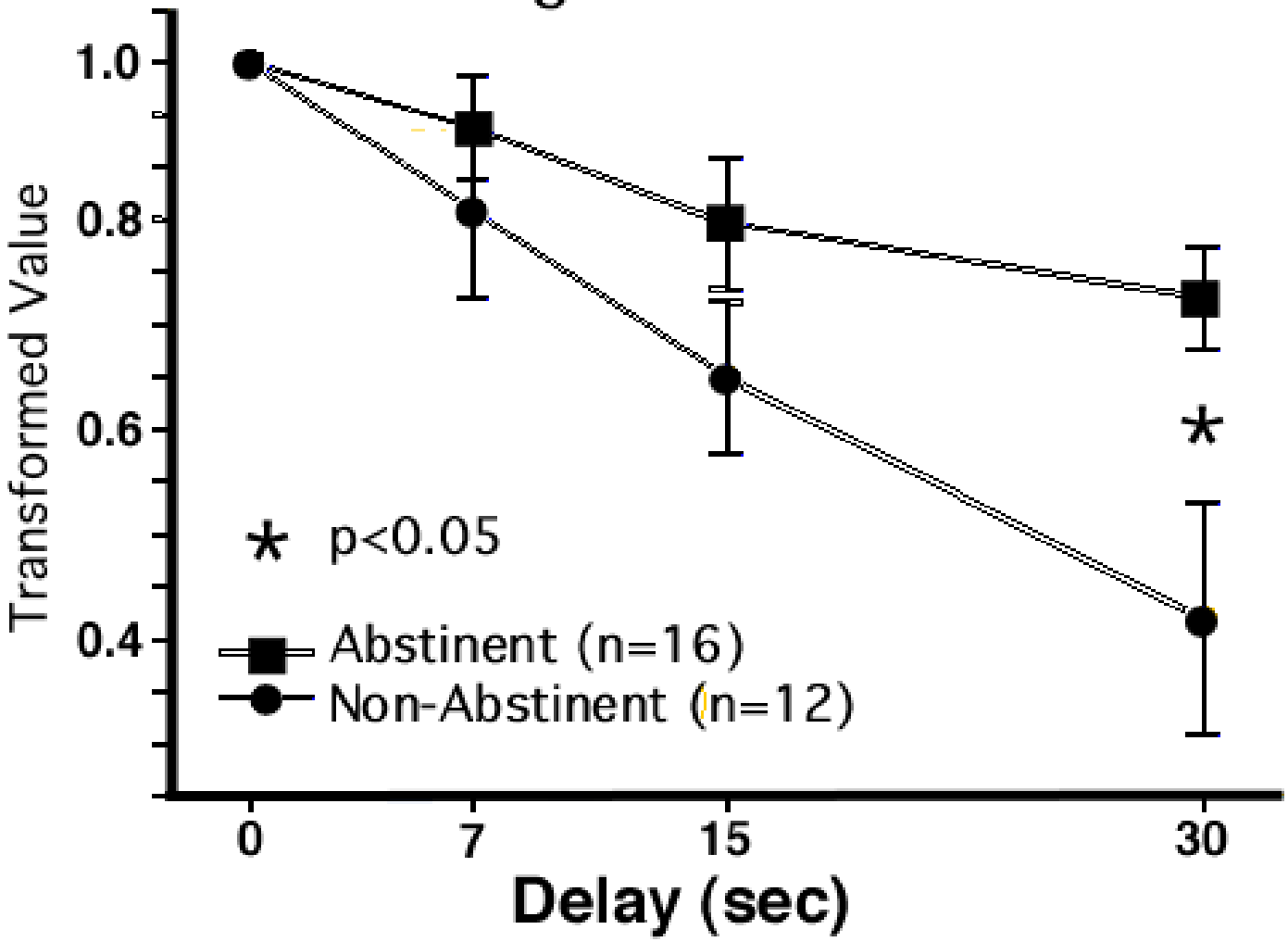
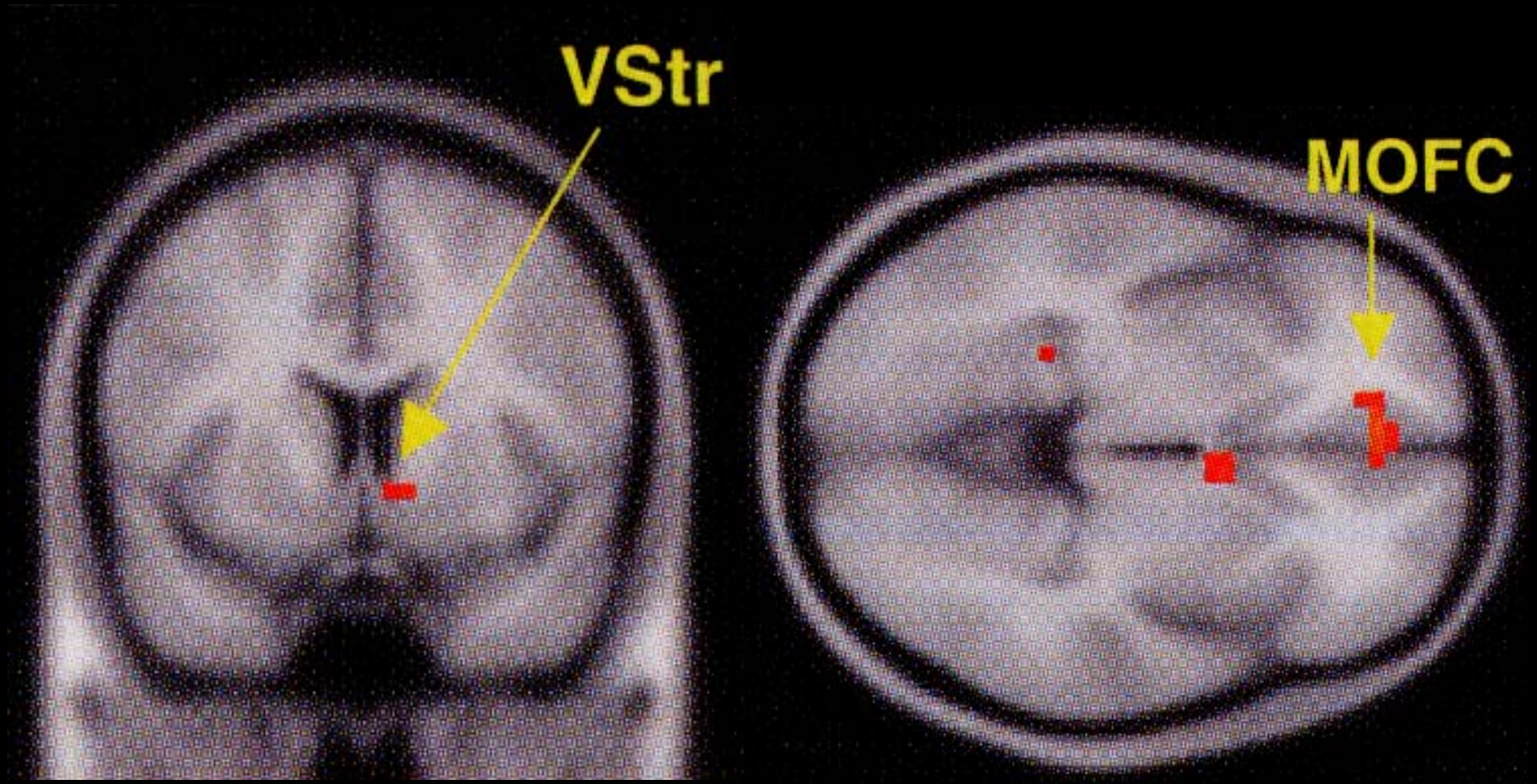
Delay Discounting Impulsivity and Smoking Treatment Outcome



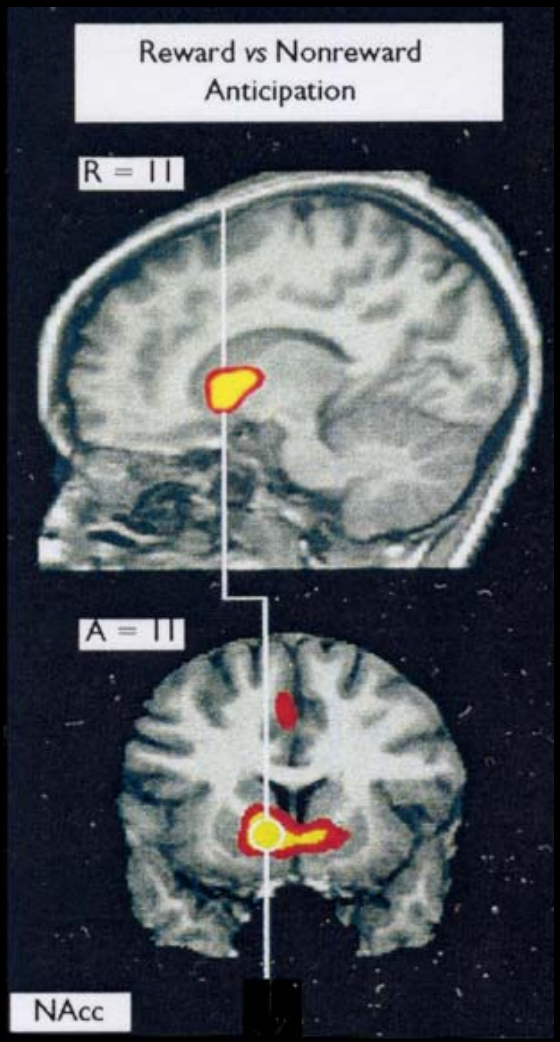
Krishnan-Sarin et al, Drug Alc Depend, 2007

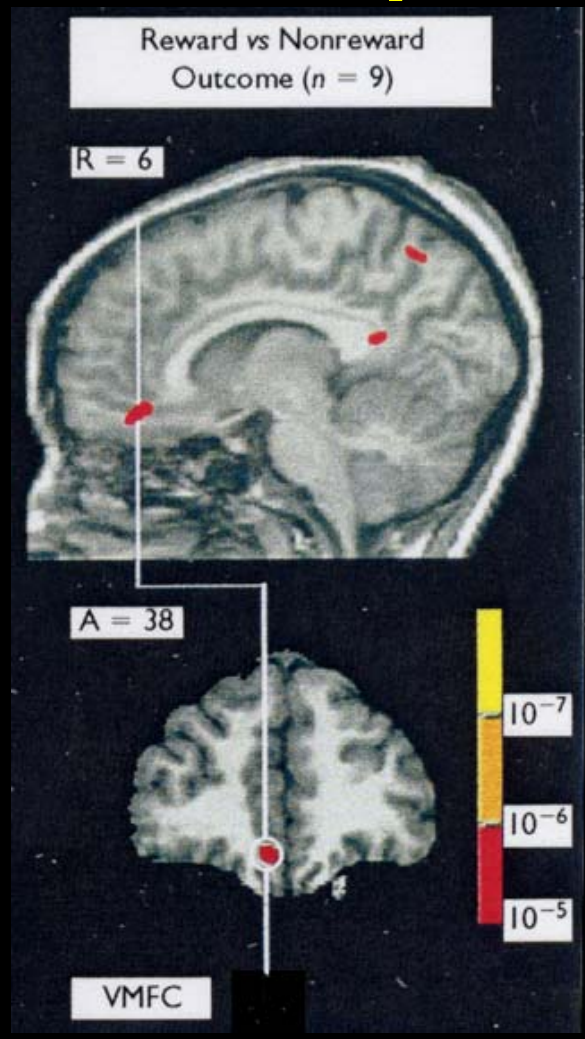
Small, Immediate Rewards Preferentially Activate Ventral Striatum and vmPFC



McClure et al, 2004

Reward Anticipation and Outcome Activate VS and vmPFC, Respectively





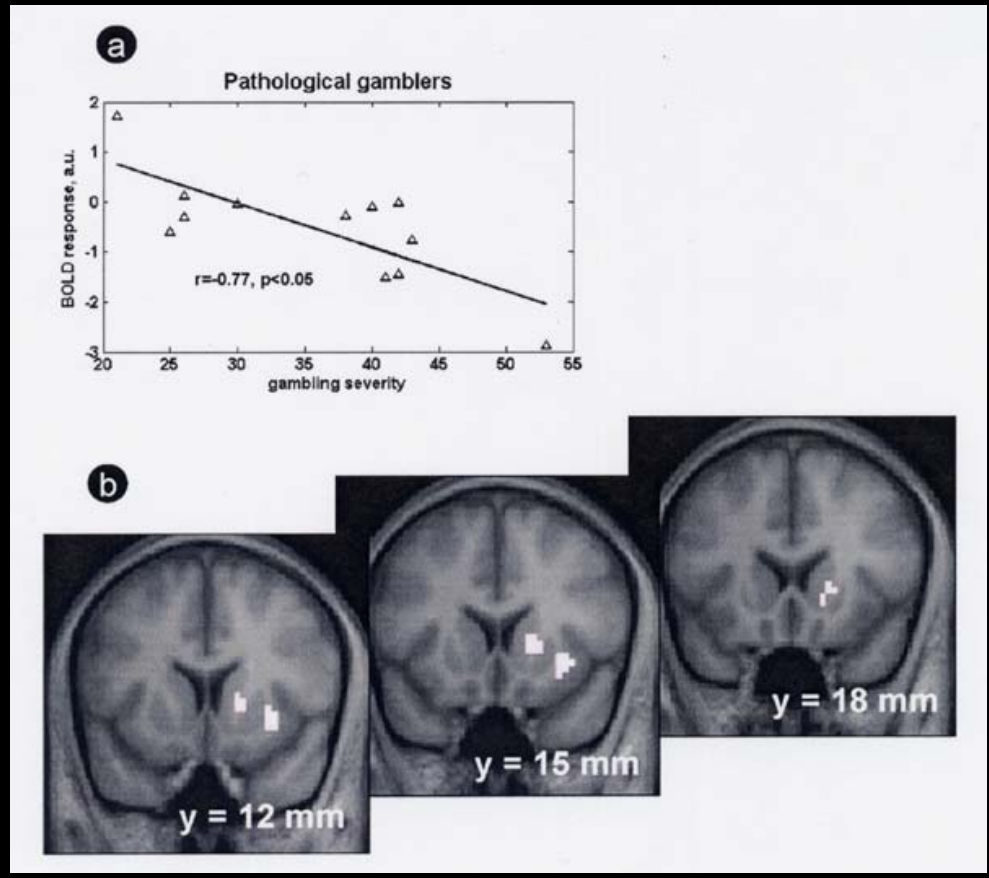
Knutson et al, 2001

Reward Processing in Addiction

- Adults w/ AD vs Those w/o AD Show Less Activation of NAc in Anticipation of Working for Monetary Reward (Hommer et al, 2004; Wrase et al, 2007)
- Similar Findings in Adolescents and Adults FH+ Vs. FH- for AD (Hommer et al, 2004)
- VS Activation in Adults w/AD Correlates Inversely with Self-Reported Impulsivity (Beck et al, 2009)
- Extends Across Addictions - Less Activation of NAc in PG vs. Control During Monetary Wins vs. Losses (Reuter et al, 2005)

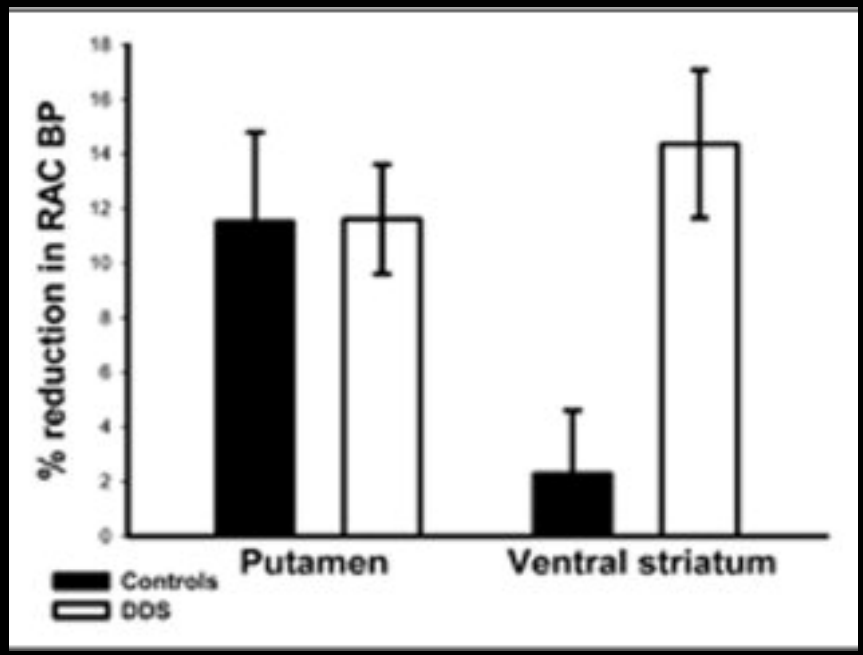
Less Ventral Striatal Activation in PG

Addiction Tapes
$(PG\text{-}C_{PG})+(CD\text{-}C_{CD})$
Potenza, 2008

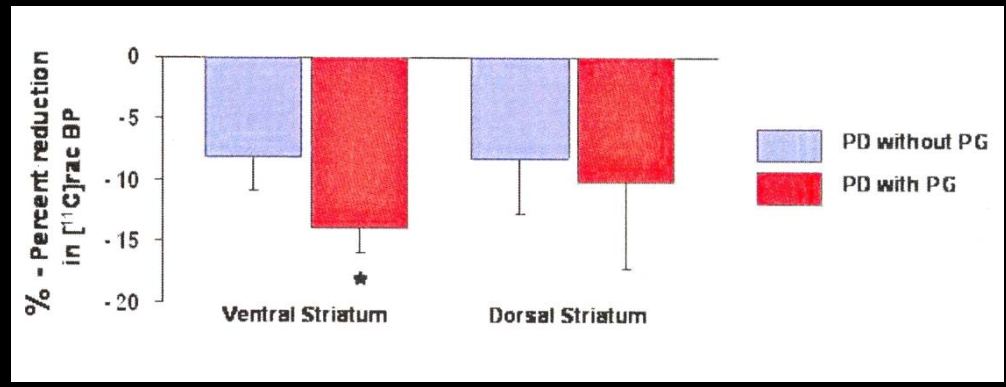


Reuter et al, Nature Neurosci, 2005

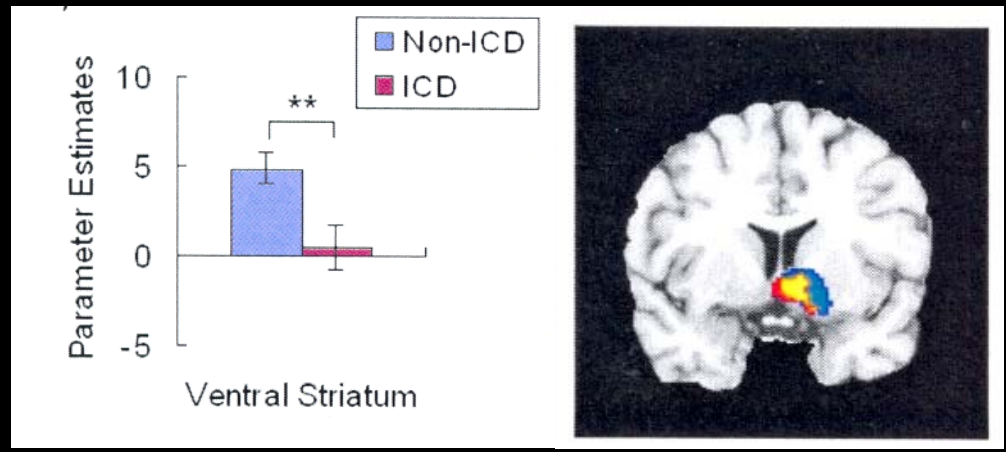
Ventral Striatal Dysfunction Implicated in DDS and ICDs in PD



DDS in PD
Evans et al, 2006



PG in PD, Steeves et al, 2009



ICDs in PD, Rao et al, in press

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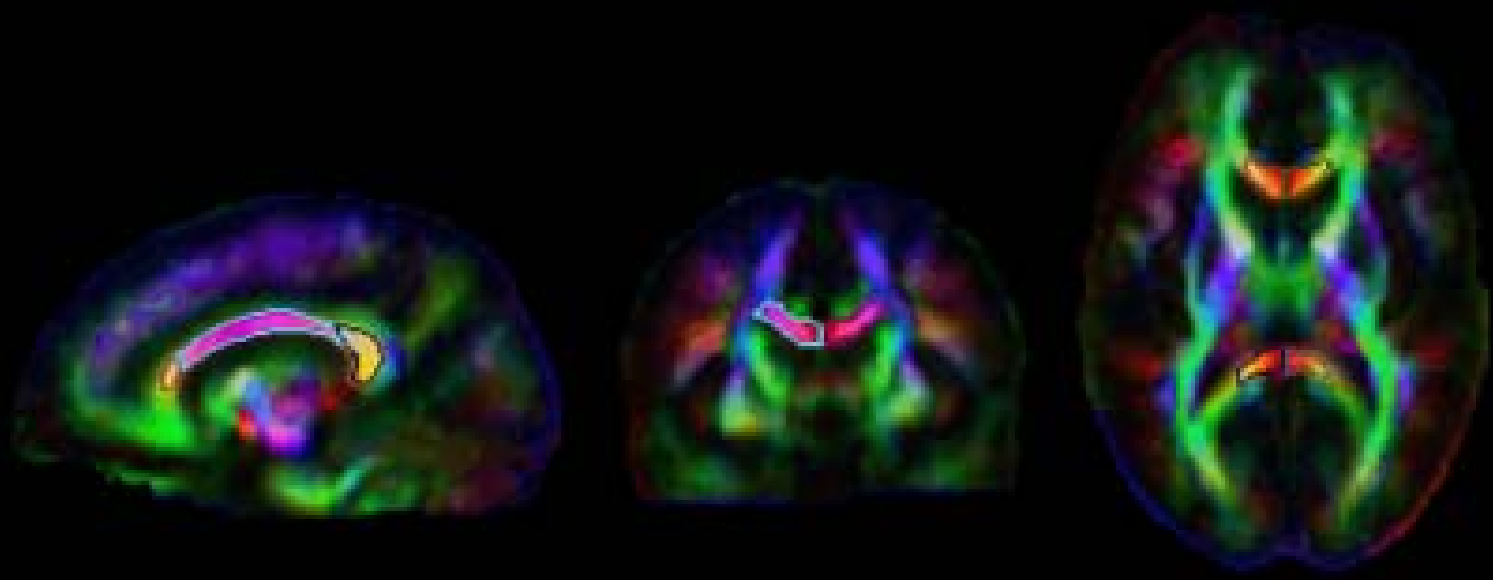
PG Subjects Show Diminished WM Integrity (Lower FA) in Genu of CC



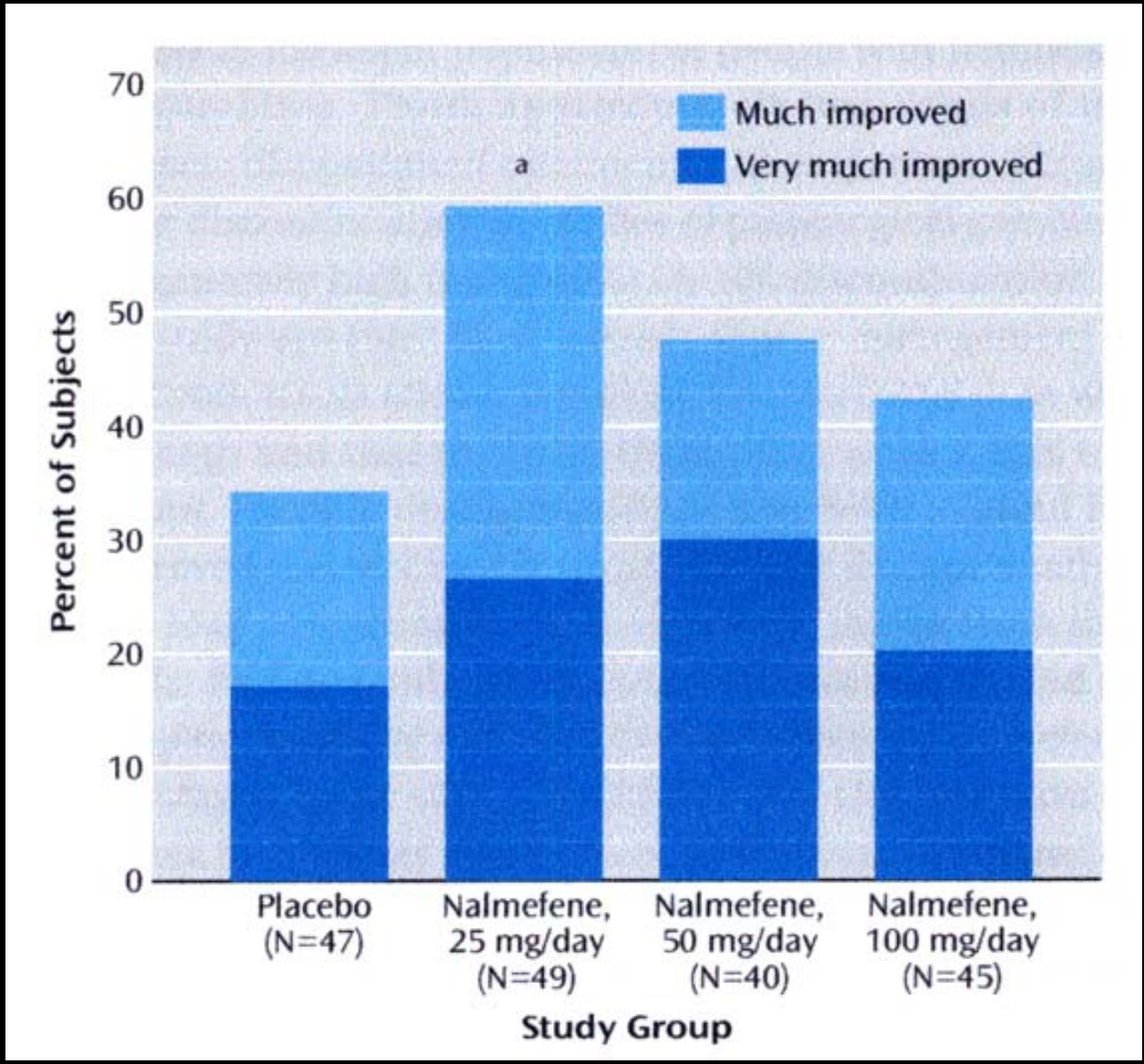
	Mean(SD) FA Values			
	PG	HC	F	p
L Genu	0.47(0.07)	0.53(0.05)	9.33	0.004
R Genu	0.47(0.07)	0.53(0.06)	8.17	0.007

Yip et al, submitted

Pharmacological Treatment of AD

- Shared Genetic Contributions to PG and EtOH Dependence (Slutske et al, 2000)
- FDA-Approved Drugs for AD (None for PG/ICDs)
  - Disulfiram, Naltrexone, Acamprosate
- Naltrexone and Other Opioid Antagonists Indirectly Modulate Dopamine Neurotransmission in VTA-NAc Pathway
- Might Naltrexone or Other (Mu-)Opioid Receptor Antagonists Be Effective in Treating PG?

Nalmefene: CGI



Grant et al, Am J Psychiatry, 2006

Predicting Outcome

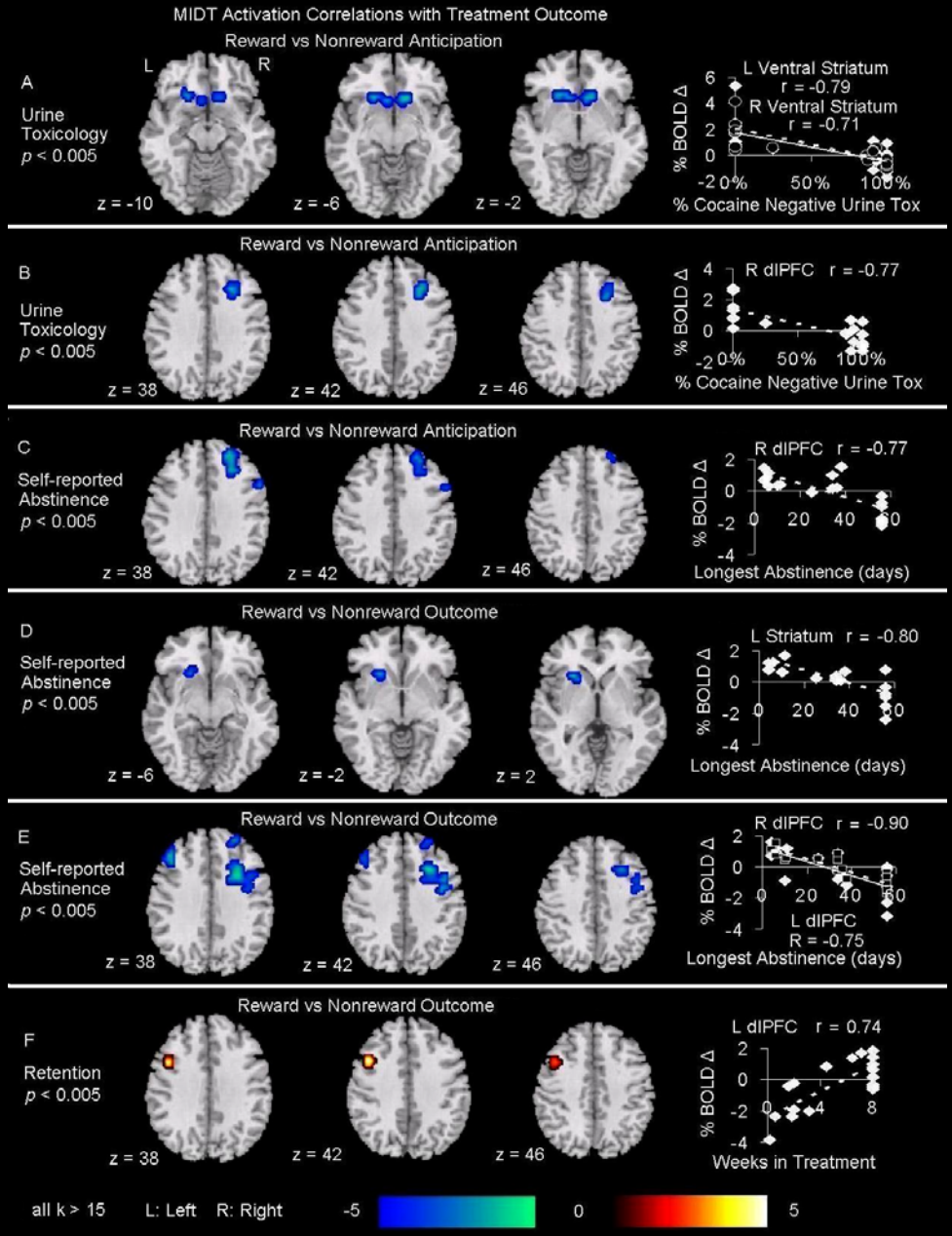
- Among Subjects Receiving Active Drug (n=214) in Two Placebo-Controlled Trials of Naltrexone and Nalmefene, The Factor Most Strongly Associated with Outcome was a Family History of Alcoholism (OR=1.74; p=0.006)
- Among Subjects Receiving Higher Doses of Active Drug, Gambling Urges Were Associated with Treatment Outcome (OR=5.86; p<0.05)
- Among Those Receiving Placebo (n=70), Response Was Most Strongly Associated with Younger Age (OR=0.70; p=0.01)

Source: Grant et al, 2008

Behavioral Therapies in Addiction

- Behavioral Therapies for Drug Addiction Are Efficacious and Widely Used (Carroll et al, 2008)
- Despite Their Widespread Use, Little is Known Regarding Brain Changes Associated with Treatment Outcomes in Behavioral Treatments for Addictions
- Specific Treatments May Demonstrate Efficacy Through Changes in Different Brain Circuits
- Specific Aspects of Outcome (Retention vs. Abstinence) May Differentially Relate to Specific Aspects of Brain Function

Reward Processing & Tx Outcome in CD



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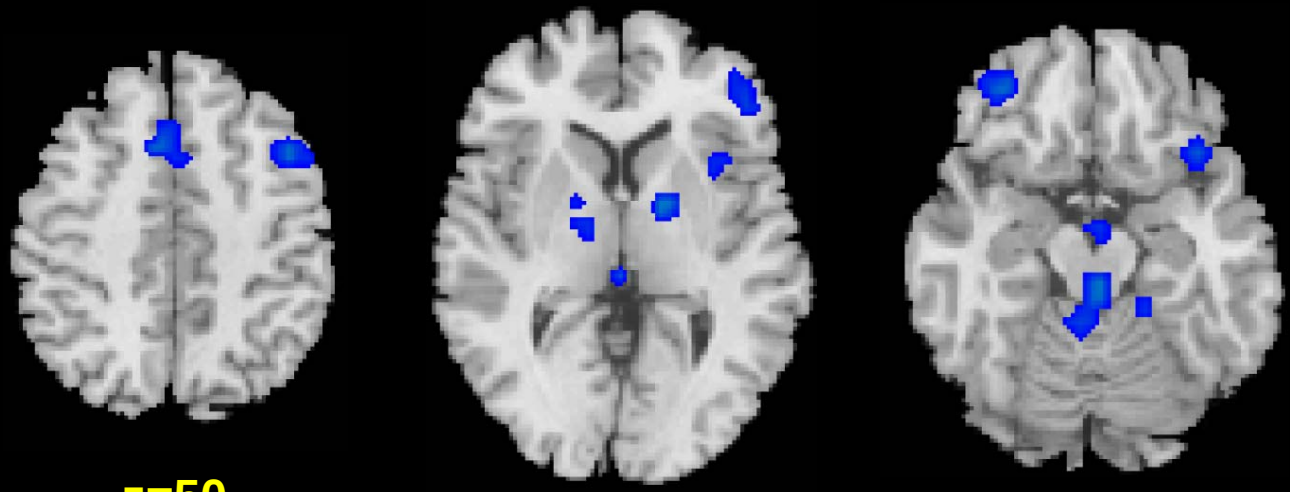
Zia et al, under review

Pre-Treatment fMRI Stroop Measures Associated with Tx Outcomes

Brewer et al, 2008

fMRI Stroop Measures Change After Behavioral Tx (CBT and TAU)



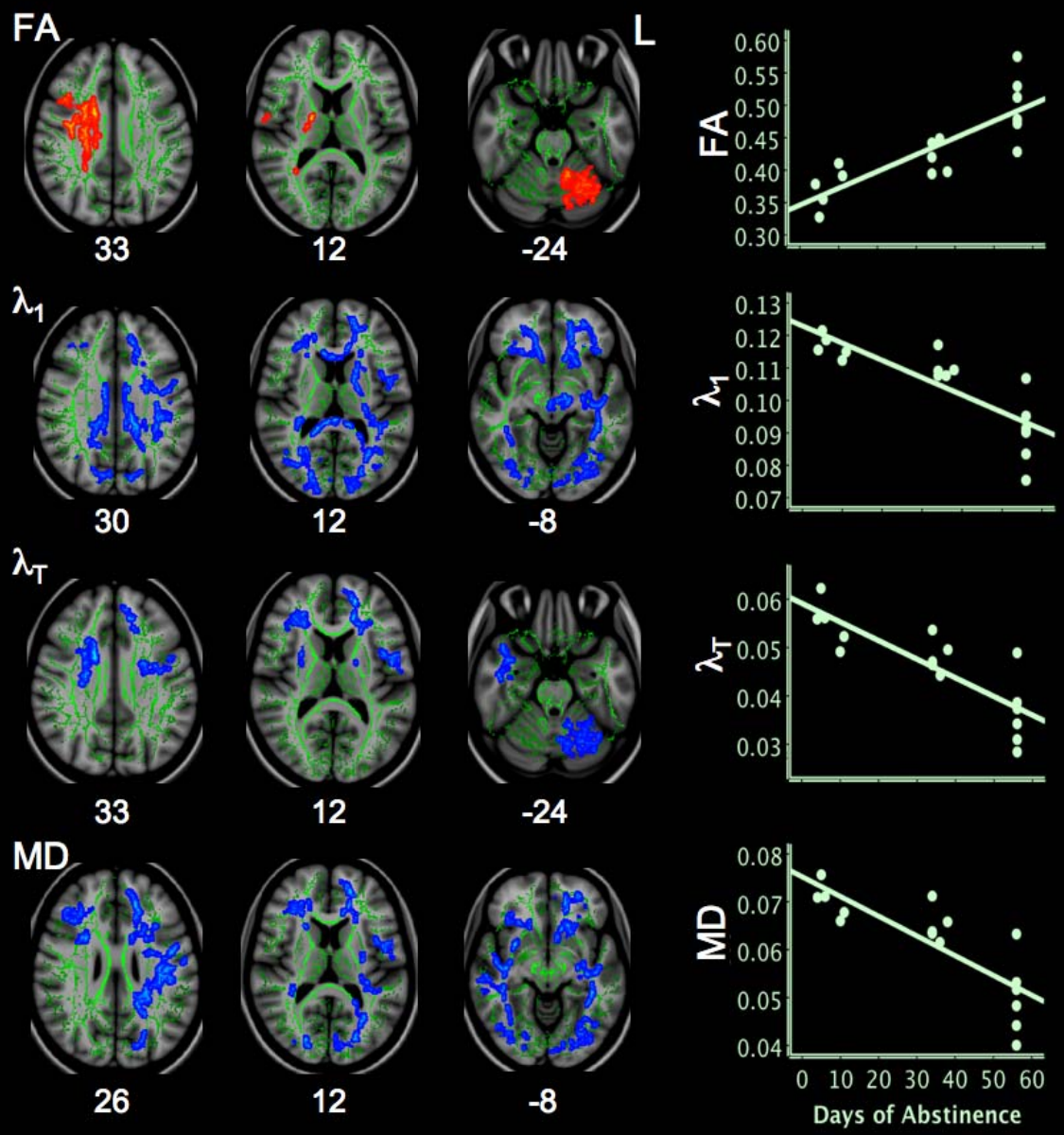
z=50 z=6 z=-14

Post-Tx Vs. Pre-Tx Contrast of Incongruent Vs. Congruent Stroop Stimuli

n=12 subjects, p<0.005; k>20

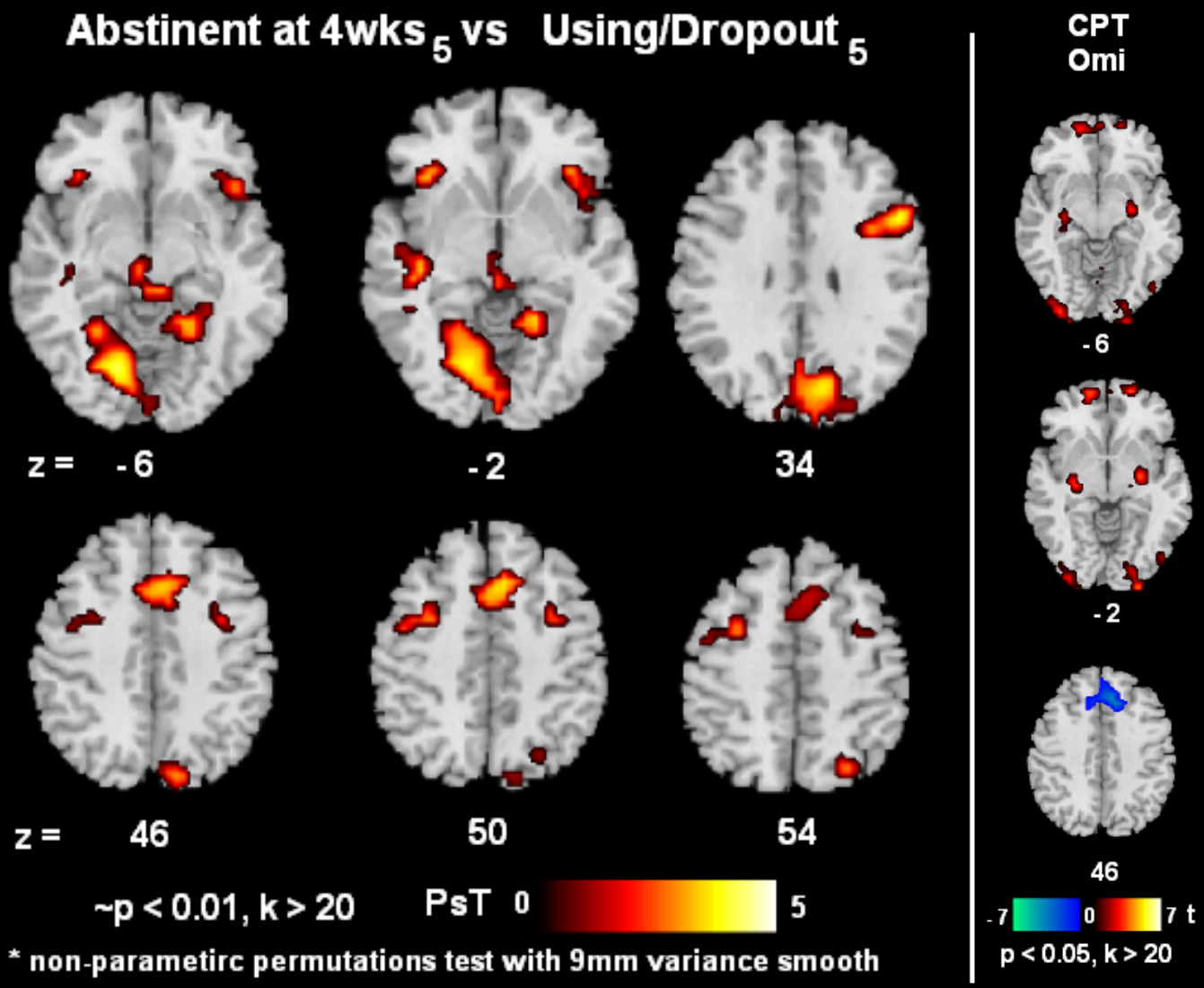
DeVito et al, revise and resubmit

Poorer WM Integrity Associated with Shorter Duration of Cocaine Abstinence in CD Subjects



Xu et al, 2010

fMRI Stroop in Adolescent Smokers: Relationship with Tx Outcome, Attention



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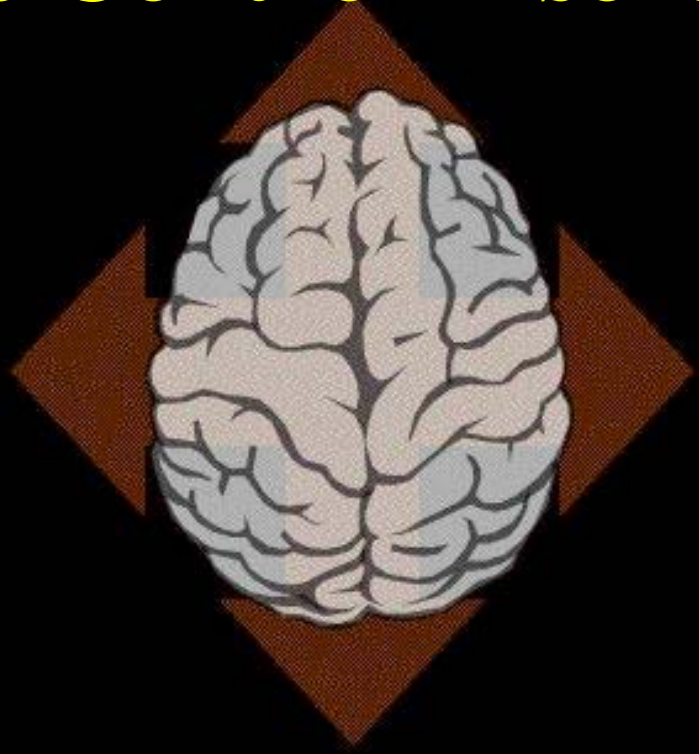
Krishnan-Sarin, Potenza et al, in progress

Conclusions & Future Directions

- There Exist Multiple Shared Features Between PG and SUDs and and These Have Implications for Treatment Development
- MRI Assessments Integrated into RCTs Investigating Therapies for Addiction Can Provide Important Information Relating to Neural Mechanisms of Action
- Specific Aspects of Outcome Appear Differentially Related to Brain Function
- Future Research Should Investigate Specific Therapies and Employ Information Gained to Develop Improved (Complementary) Treatments

The International Society for Research on Impulsivity and Impulse Control Disorders (ISRI)



www.impulsivity.org
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