Knowing How Gamblers Think: Improving Treatment Outcomes

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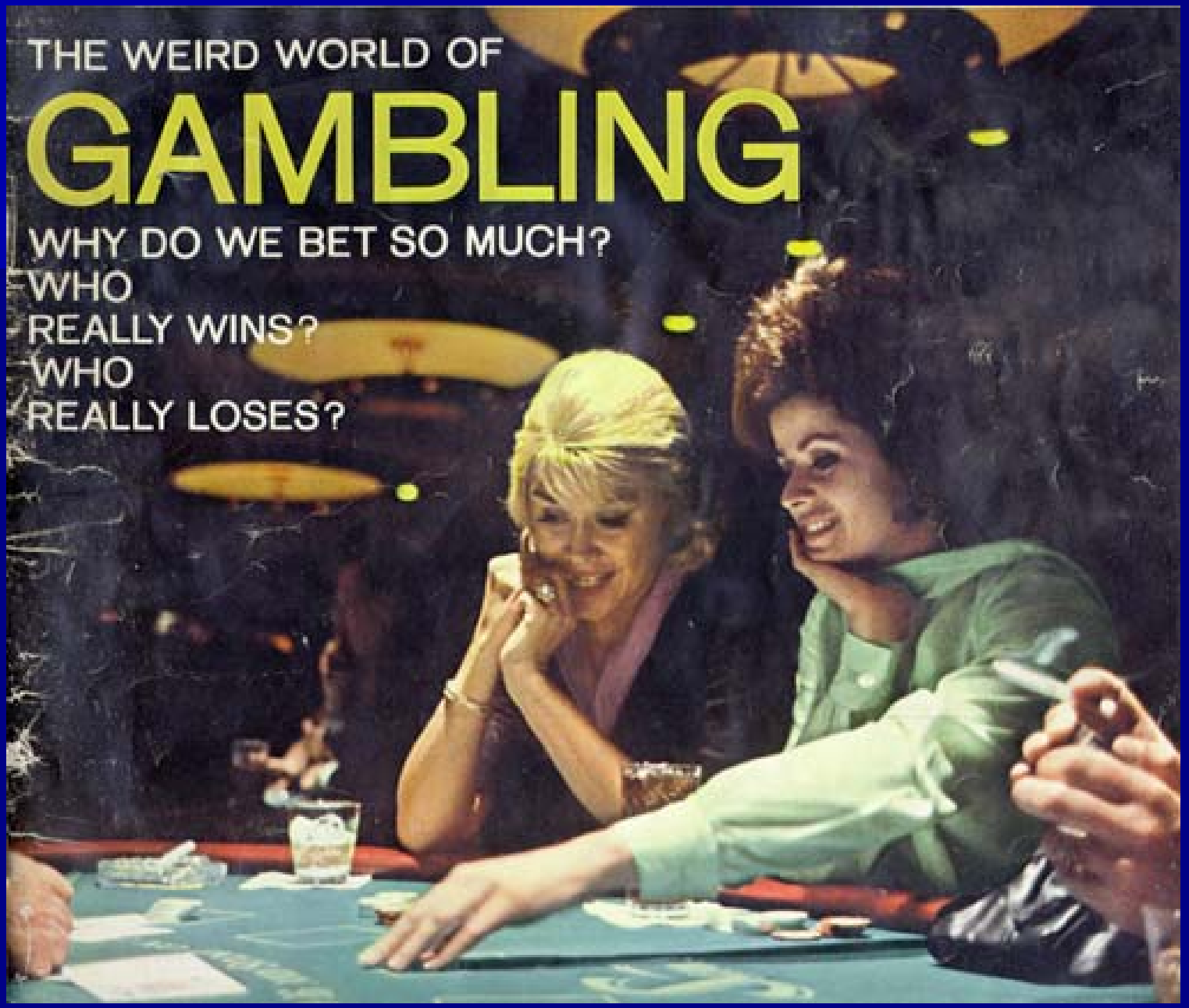


Source: Look Magazine, March, 1963

Costs

- **Problem and Pathological Gambling Are Associated with High Rates of:**
  - **-Divorce**
  - **-Poor General Health, Mental Health Problems**
  - **-Job Loss and Lost Wages**
  - **-Bankruptcy, Arrest and Incarceration**
- **Problem & Pathological Gambling Associated w/ Estimated Annual Societal Cost of $5 Billion**

Core Features of Pathological Gambling

- Repetitive or compulsive engagement in a behavior despite adverse consequences
- Diminished control over the problematic behavior
- An appetitive urge or craving state prior to engagement in the problematic behavior
- A hedonic quality during the performance of the problematic behavior.

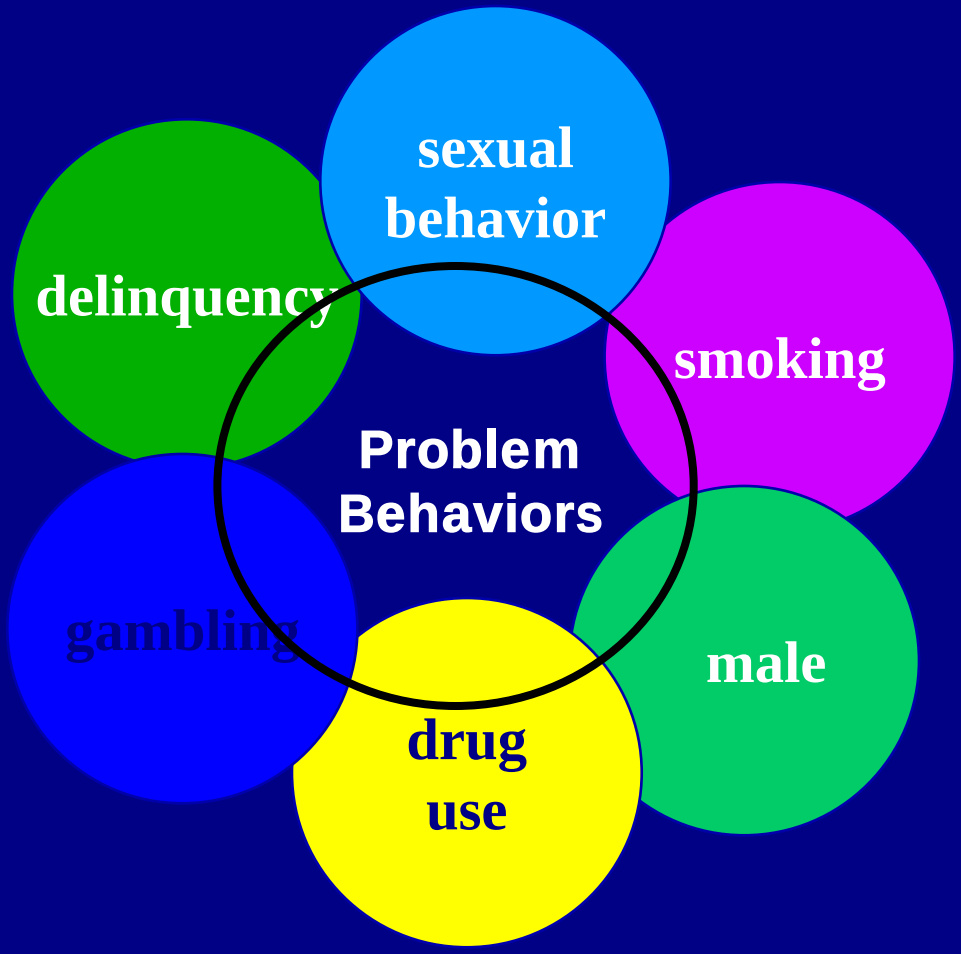
Common Core Qualities of Pathological Gambling

- Tolerance
- Withdrawal
- Repeated unsuccessful attempts to cut back or stop
- Impairment in major areas of life functioning

Developmental Biology

- High rates of problem gambling, substance problems, and other impulse behaviors start in young adulthood.
- Environmental and genetic influences
- Brain structure and function during adolescence might influence the motivation for risk-taking behaviors.

Youth Problem Gambling as a Component of Problem Behaviors



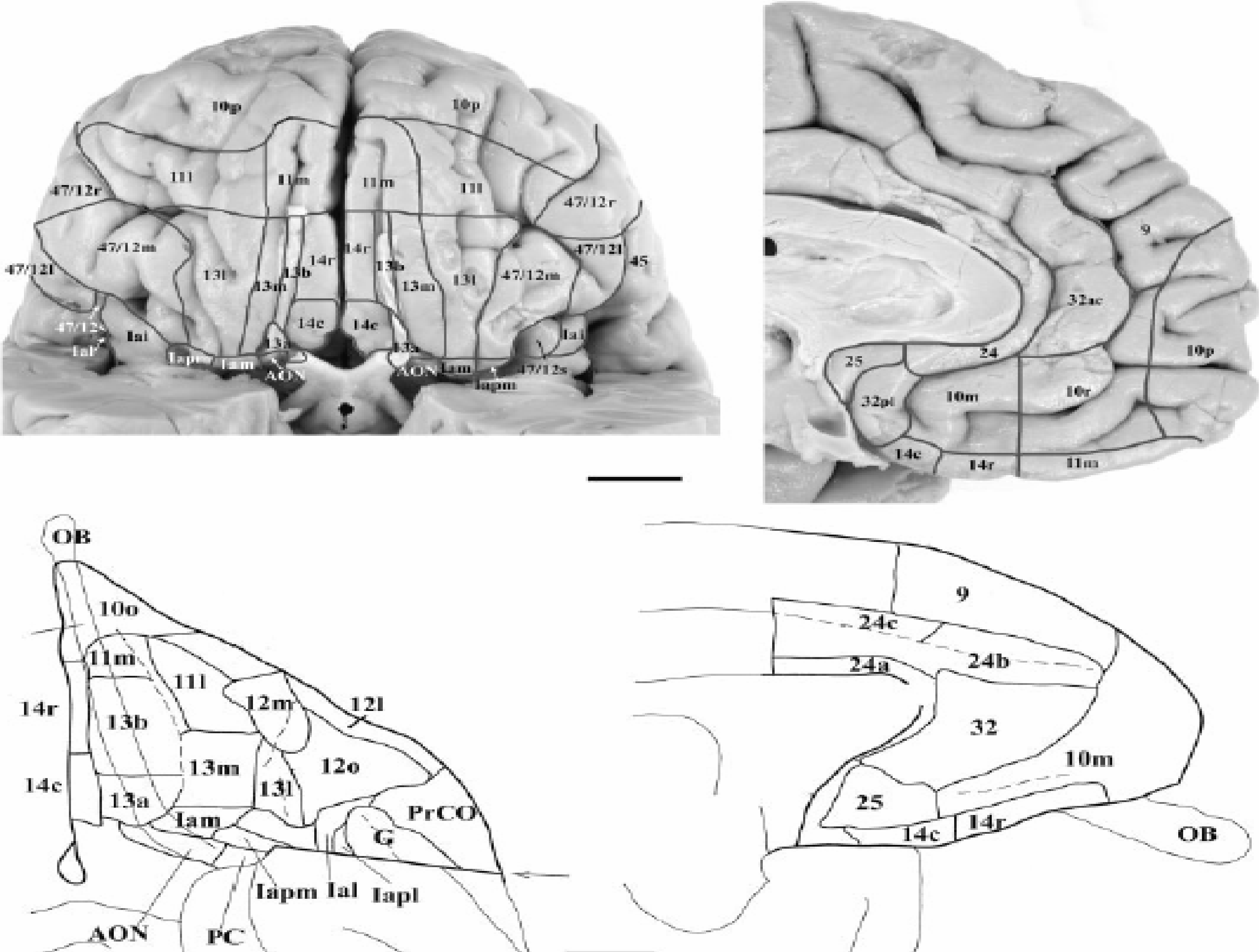
Source: Postcard, early 1900s

Biology

Motivational Neural Circuits

- Multiple brain structures underlying motivated behaviors.

- Motivated behavior involves integrating information regarding internal state (e.g., hunger, sexual desire, pain), environmental factors (e.g., resource or reproductive opportunities, the presence of danger), and personal experiences (e.g., recollections of events deemed similar in nature).


10p
10p
11l
11m
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11l
47/12r
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Ial
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AON
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9
24c
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32
10m
25
14c
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OB

- 10p is connected to the ventral striatum and ventral caudate nucleus.
- Ventral striatum is a critical area where the strength of motivation is regulated, that is, how strongly should one pursues the goal.
- This, in turn, is directly linked to the size of reward.

Roles for Neurotransmitters

Neurotransmitter	Role in Addictions
Norepinephrine	Arousal, Excitement
Serotonin	Behavior Initiation/Cessation
Dopamine/Glutamate	Reward, Reinforcement
Opioids	Pleasure, Urges

Role of Serotonin

- Decreased CSF serotonin associated with adult risk-taking behaviors - alcoholism and pathological gambling.
- Blunted serotonergic responses in the ventromedial prefrontal cortex - in individuals with impulsive aggression
- Implicated in disadvantageous decision-making - adults with gambling or drug addictions

Biochemistry – Opioid System

- The opioid system influences the experiencing of pleasure.
- Opioids system interacts with dopamine.
- Gambling has been associated with elevated blood levels of β-endorphin.

Glutamate

- Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior
- Increases in extracellular levels of glutamate, stimulates inhibitory metabotropic glutamate receptors, and reduces synaptic release of glutamate.
- Restoring extracellular glutamate concentration in the nucleus accumbens seems to decrease cravings.

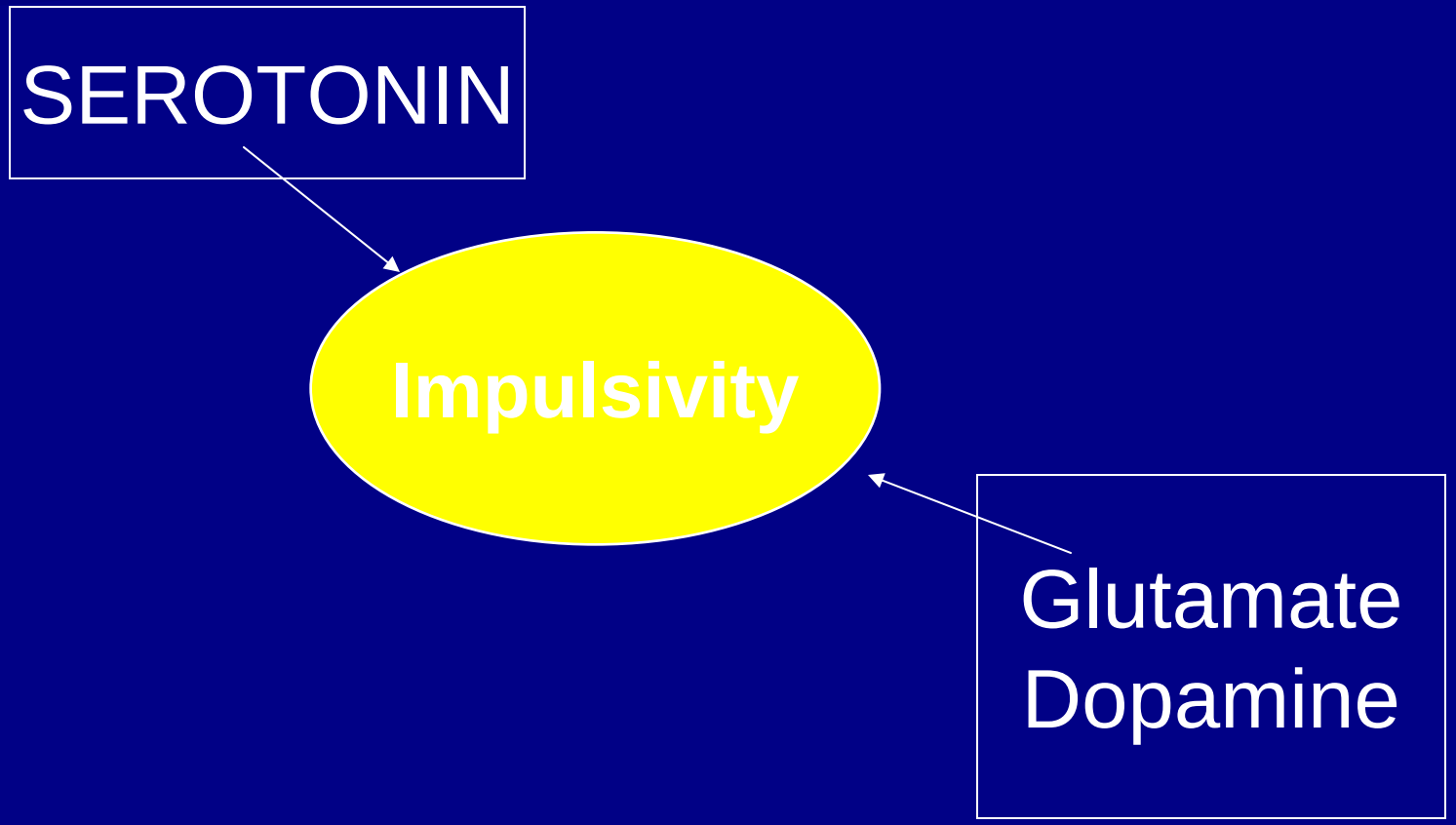
Role of Dopamine

- Dopamine release into the nucleus accumbens - translates motivated drive into action - a "go" signal
- Dopamine release associated with rewards and reinforcing
- Dopamine release - maximal when reward is most uncertain, suggesting it plays a central role in guiding behavior during risk-taking situations.

Dopamine, ICDs and Parkinson's

- **ICDs Reported in Association with Parkinson's Disease**
- **Association Linked to Dopamine Agonist Treatment**
- **Prior ICD and Family history of alcoholism Associated with ICD Presence in PD**

Neurochemistry of Impulsivity



Family/Genetic Factors

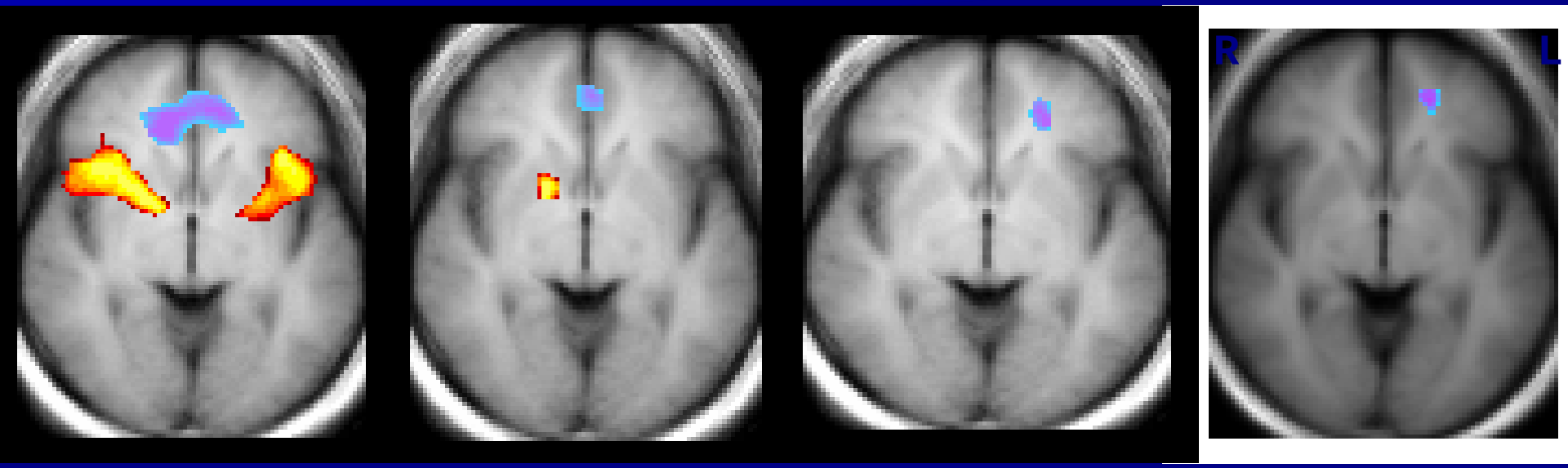
- Male twin study - 12 to 20% of the genetic variation in risk for gambling, and 3 – 8% of the nonshared environmental variation in the risk for gambling, was accounted for by risk for alcoholism.

- Additionally, 64% of the co-occurrence between gambling and alcoholism appears to be attributable to genes that simultaneously influence both disorders.

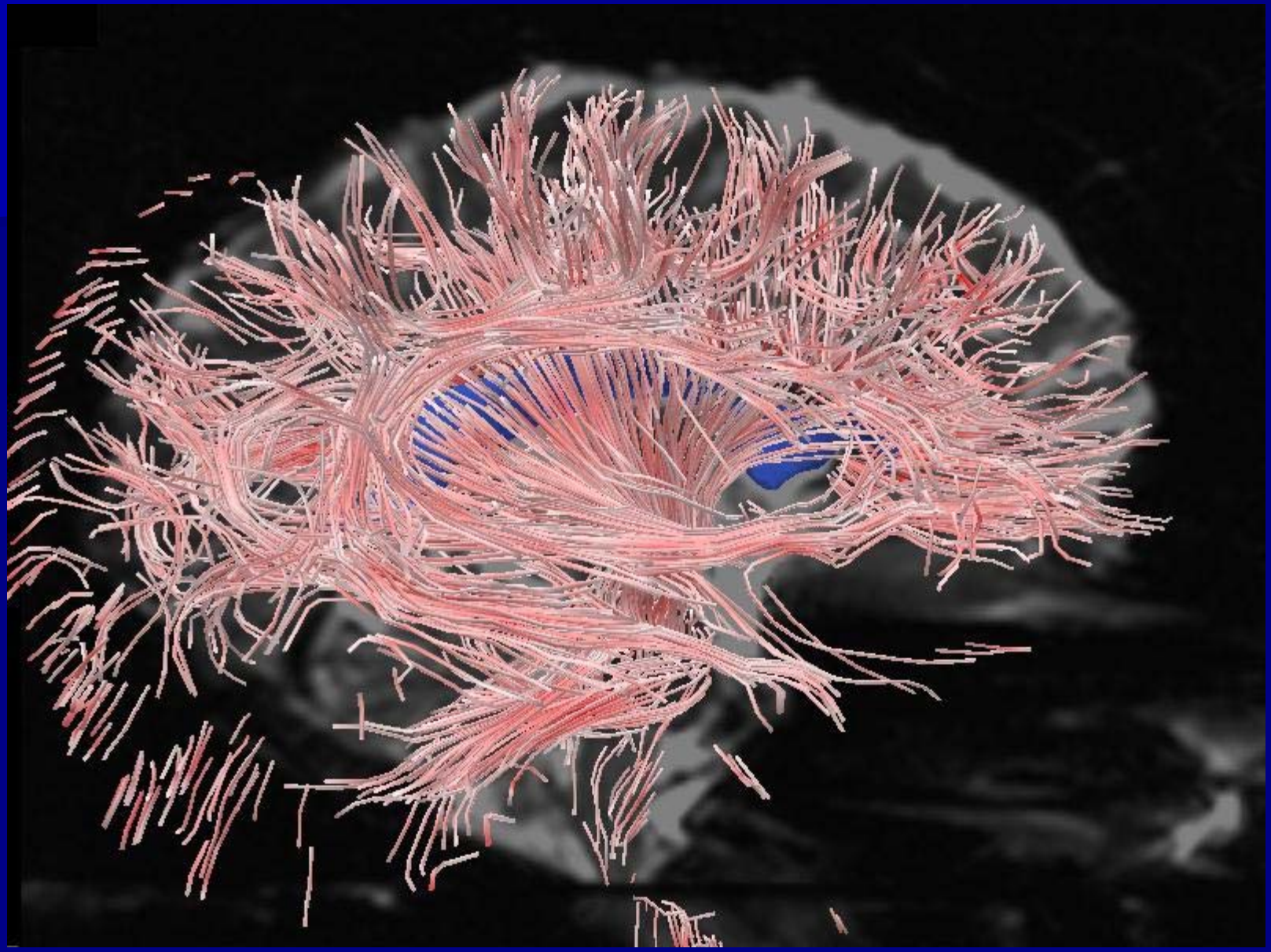
Neuroimaging

- Ventromedial prefrontal cortex (vmPFC) - implicated in decision-making circuitry in risk-reward assessment
- Decreased activation in vmPFC in PG subjects during gambling cues
- Responsiveness of the vmPFC to serotonergic drug challenges (m-CPP, fenfluramine) - blunted in impulsive people

Left vmPFC Implicated During Stroop Performance In ICDs□



PG Control PG - Control Bipolar - Cont



Neurocognition in Gamblers

- Executive function deficits, including planning, cognitive flexibility, and inhibition, greater in pathological gamblers compared to controls.

- Common adaptation to chronic addictive behaviors is hypofrontality – reduced baseline activity of prefrontal cortex, orbitofrontal cortex, anterior cingulate

Affects of Drugs on Cognition

- Alcohol
- Stimulants
- Nicotine

Smoking and Gambling

- Cigarette Smoking Associated with Increased Gambling Severity in Treatment-Seeking Problem Gamblers

- Among Help-Seeking Problem Gamblers, Current Daily Smoking Associated with More Psychiatric Problems

- Among Gambling Subjects, Former and Current Daily Smokers Report Stronger Gambling Urges

Is Game of Choice Associated with Cognition?

- Strategic vs. Non-Strategic
  - Sensation-seeking
  - Impulsive

Near Misses

- Near-misses were associated with significantly greater signal in the ventral striatum and anterior insula
- recruitment of win-related regions during near-miss outcomes underlies their ability to promote gambling behavior

Impulsivity

- A predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others

Impulsivity as an Endophenotype

- **Impulsivity Across Psychiatric Groups**
  - **Substance use disorders, impulse disorders, ADHD, bipolar disorder, personality disorders, suiciddality, SIB**

- **Behavioral Measures of Impulsivity**
  - **Risk/Reward Assessment & Decision-Making Paradigms (Monetary Reward/Punishment, Discounting, Gambling Tasks)**
  - **Response Disinhibition/Attentional Paradigms (Go/No-Go, Stroop)**


I ♥ MY PROBLEMS
SIPRESS

How Biology Informs Treatment

Pathological Gambling Subtypes

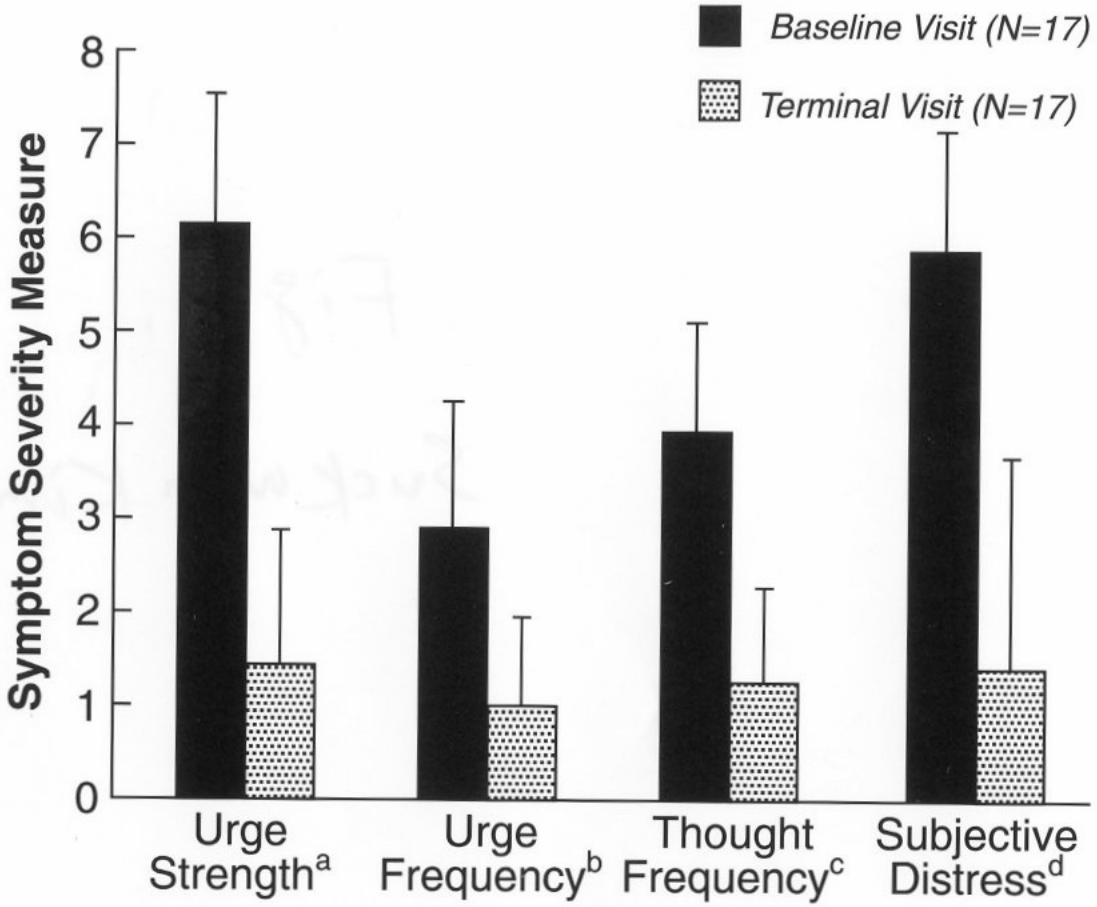
- Craving/Urge-driven
  - CBT
  - Opiate Antagonists
  - Glutamatergic Agents
- Problems with hypofrontality
  - CBT
  - Serotonergic agents
  - NMDA antagonists/glutamate

Opioid Antagonists

- The mu-opioid system:
  - underlies urge regulation through the processing of reward, pleasure and pain, at least in part via modulation of dopamine neurons in mesolimbic pathway through GABA interneurons.
  - linked to physiological responses during Pachinko.

Figure 1. Baseline and Terminal Visit Gambling Symptom Ratings

(Carry Forward Paired t-test)



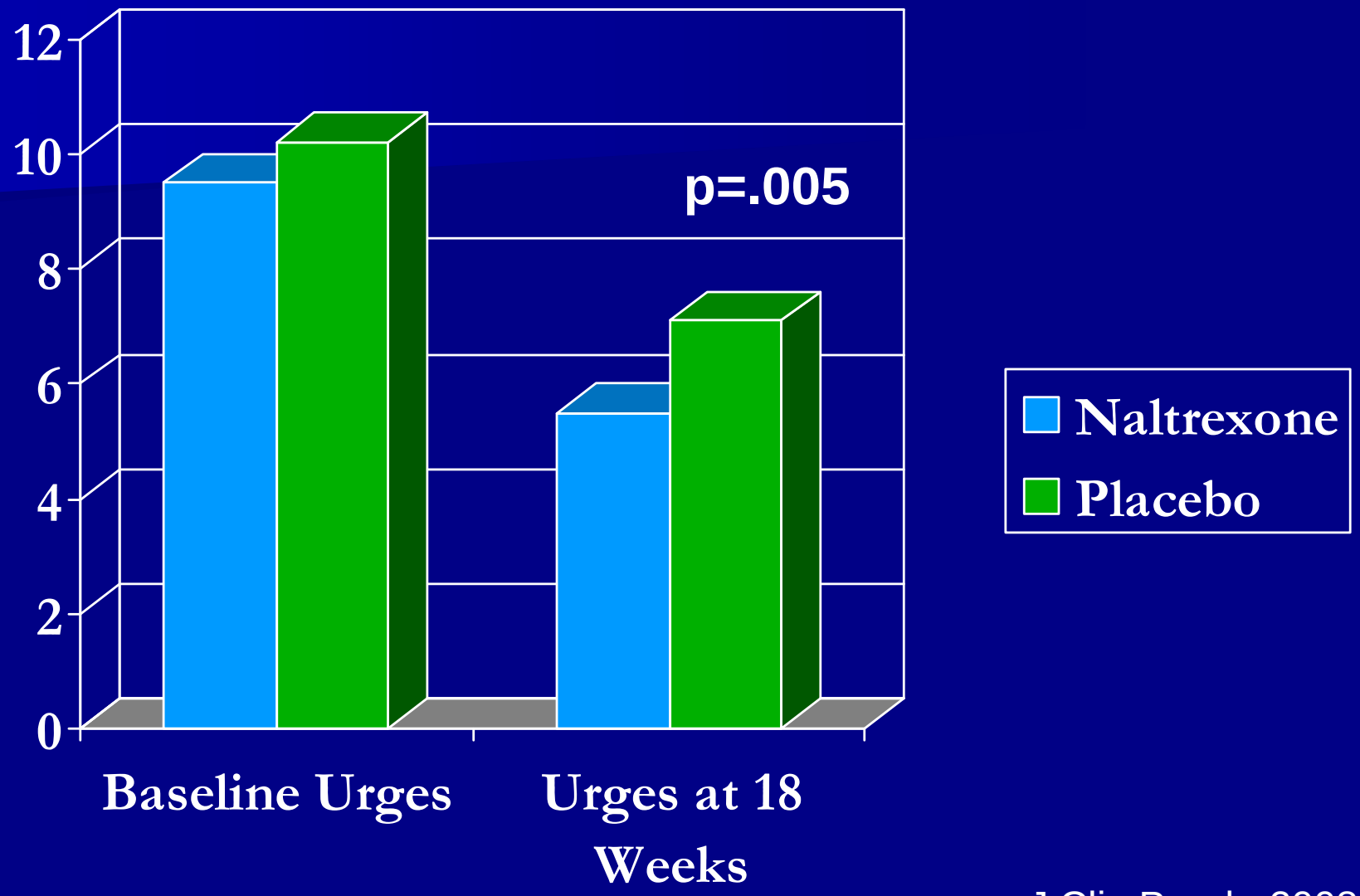
[a] 0=None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different ($t=14.28$, $p<0.05$)*.

[b] 0=None, 1=Once a day, 3=Three times a day, 5=Five times a day, 6=More than five times a day. Significantly different ($t=7.29$, $p<0.05$)*.

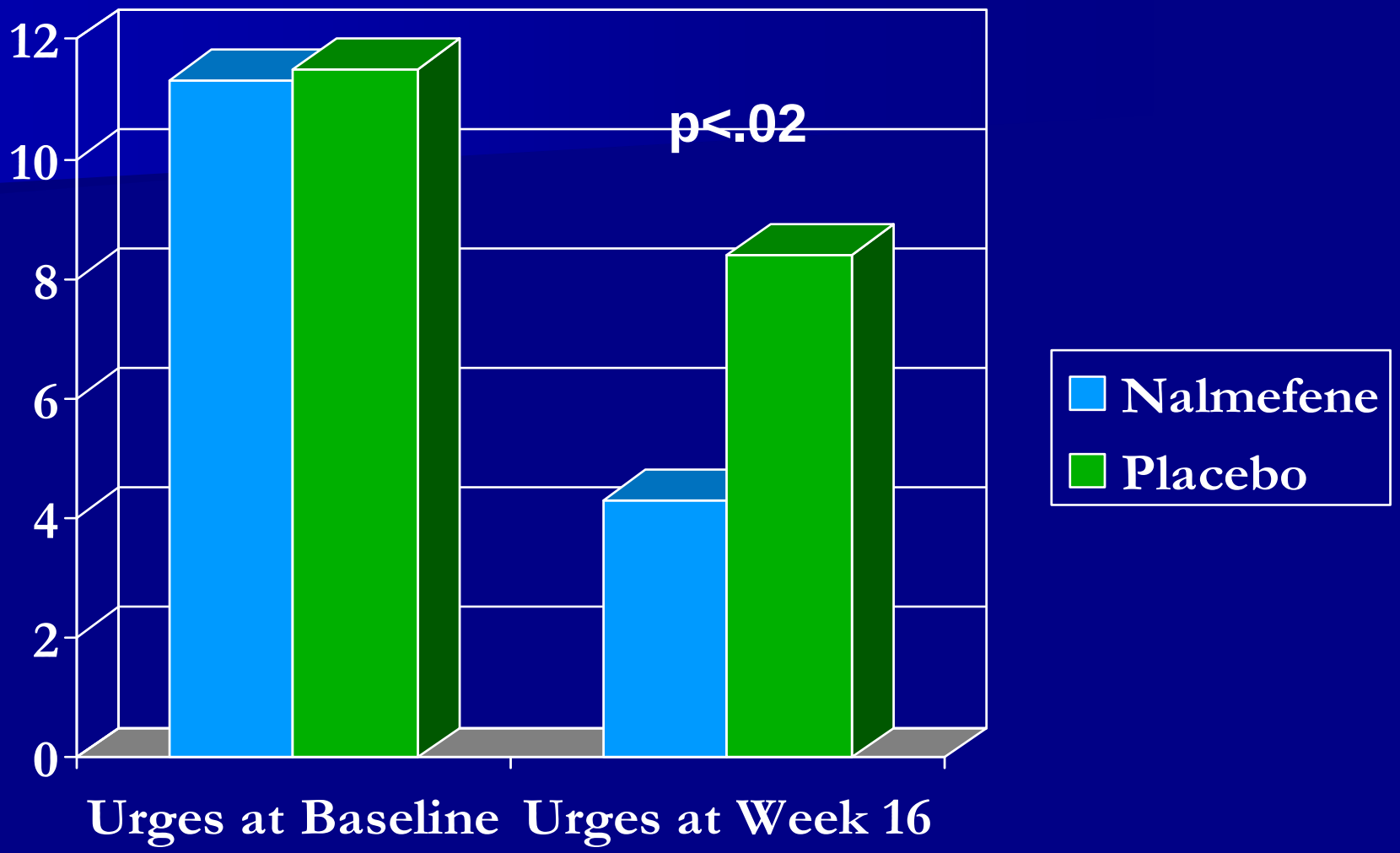
[c] 0=None, 1=Once a day, 3=Three times a day, 5=Five times a day, 6=More than five times a day. Significantly different ($t=5.25$, $p<0.05$)*.

[d] 0=None, 2=Mild, 4=Moderate, 6=Severe, 8=Extreme. Significantly different ($t=8.68$, $p<0.05$)*.

* Bonferroni corrected

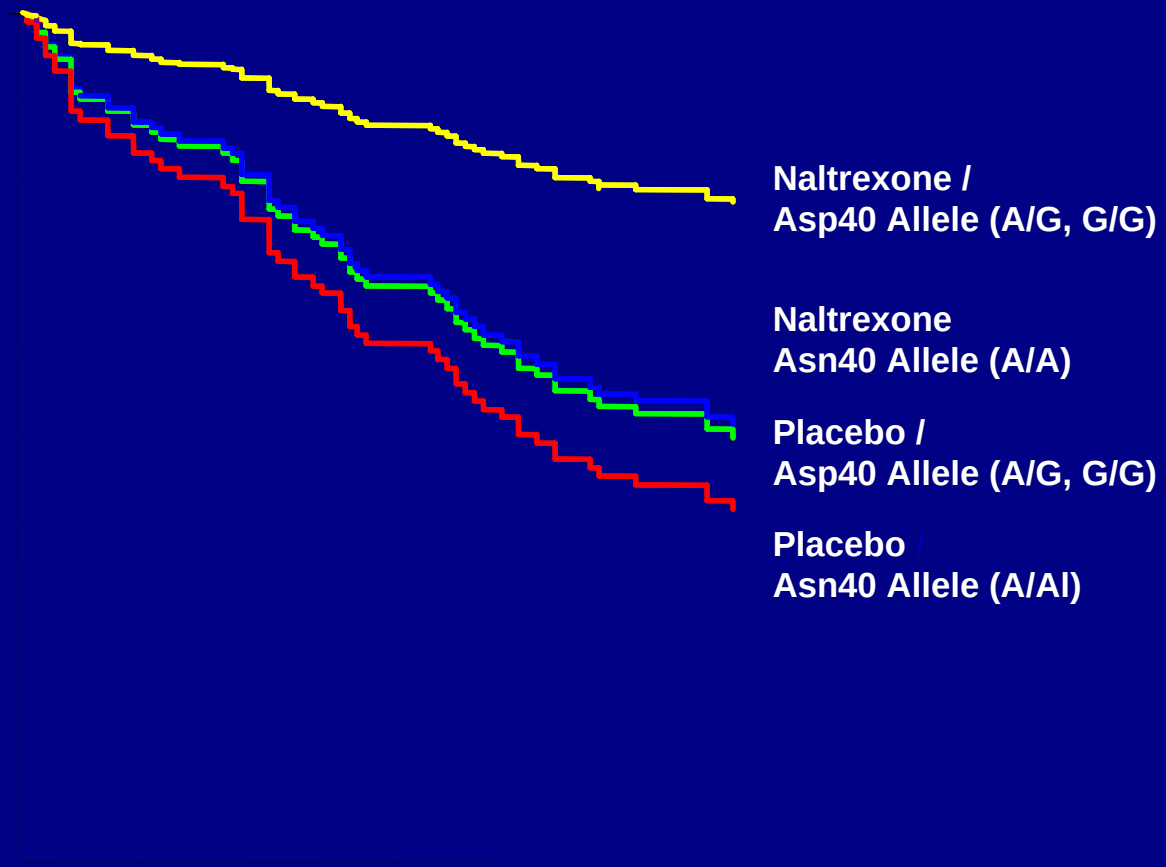


J Clin Psych, 2008



Am J Psychiatry, 2006

Relapse Rate by Genotype



Analysis of Maximum Likelihood Estimates **(N=282)**

Variable	Parameter Estimate	Standard Error	Chi-Square	Pr>ChiSq	Hazard Ratio
FH-AUD	0.55	0.24	7.53	**0.006**	1.74

Baseline urges were significantly associated with response to higher doses of opiate antagonists (i.e. nalmefene 50mg or 100mg or naltrexone 100mg or 150mg) (parameter estimate = 1.77; SE= 0.84; Wald $\chi 2$ =4.41; p= .036; HR= 5.86; HR 95% CI=1.12-30.6

N-Acetyl Cysteine

- Amino acid and antioxidant
- Lack of significant side effects
- Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior
- NAC potentially modulates brain glutamate transmission

TABLE 1. Data for the Cue-Reactivity Procedure: Motivational and General Measures[a]

	N-Acetylcysteine				Placebo			
	Cocaine		Neutral		Cocaine		Neutral	
Motivational Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD
N-Acetylcysteine								
Craving	5.81	4.29	1.32	2.41	7.25	5.27	1.09	2.34
Desire to use	6.19[b]	4.41	1.01	1.66	8.32	5.13	1.79	3.09
Interest	7.85[b]	5.28	2.81	2.61	9.65	6.03	3.30	3.49
Time viewed (seconds)	3.92[b]	1.70	2.86	1.40	4.86	2.27	2.58	1.33

[a] Means represent raw unadjusted means (i.e., not estimated marginal means) and standard deviations collected during the procedure.

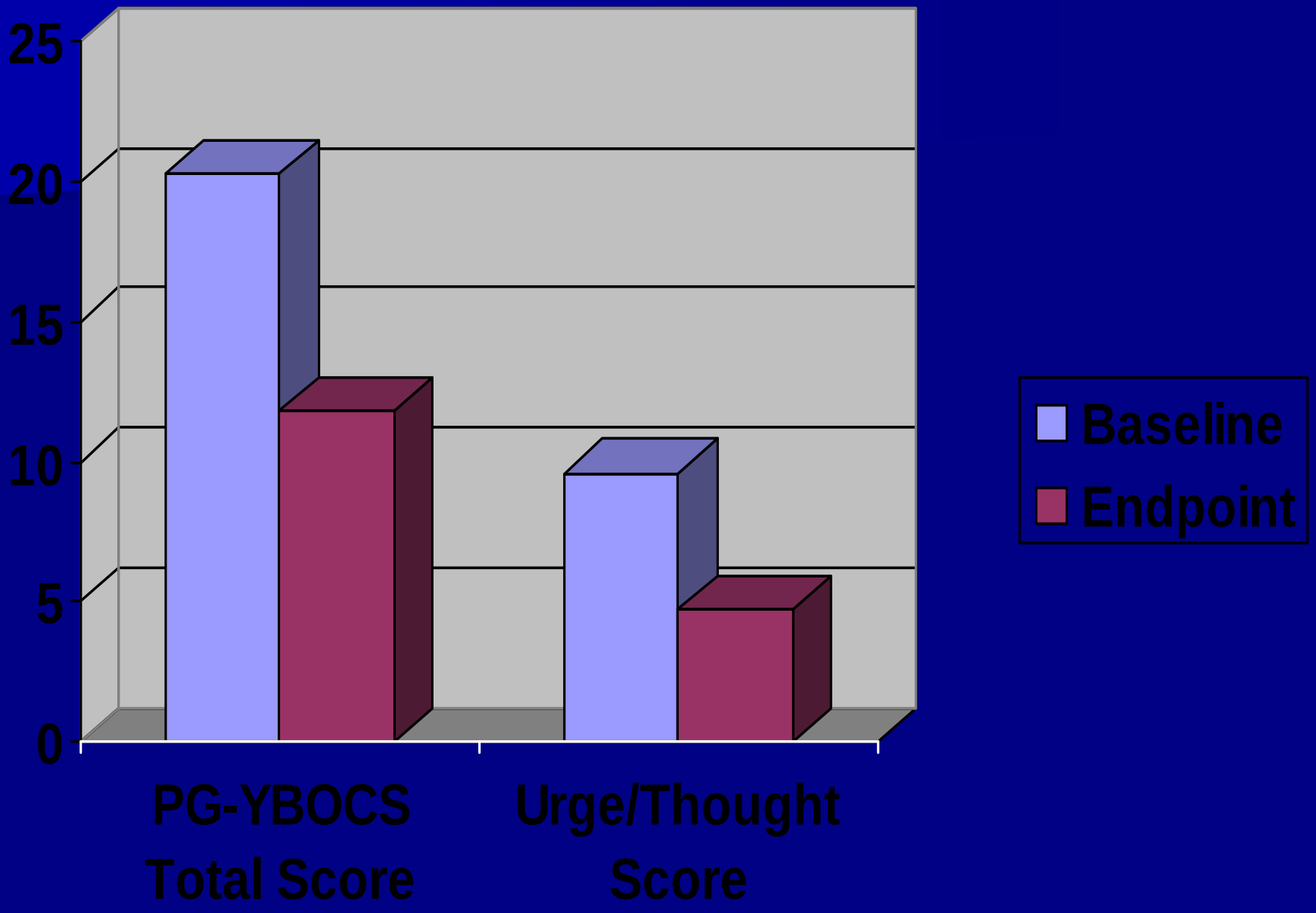
[b] Data for cocaine slides within *N*-acetylcysteine condition significantly less than cocaine slides within placebo condition ($p<0.05$).

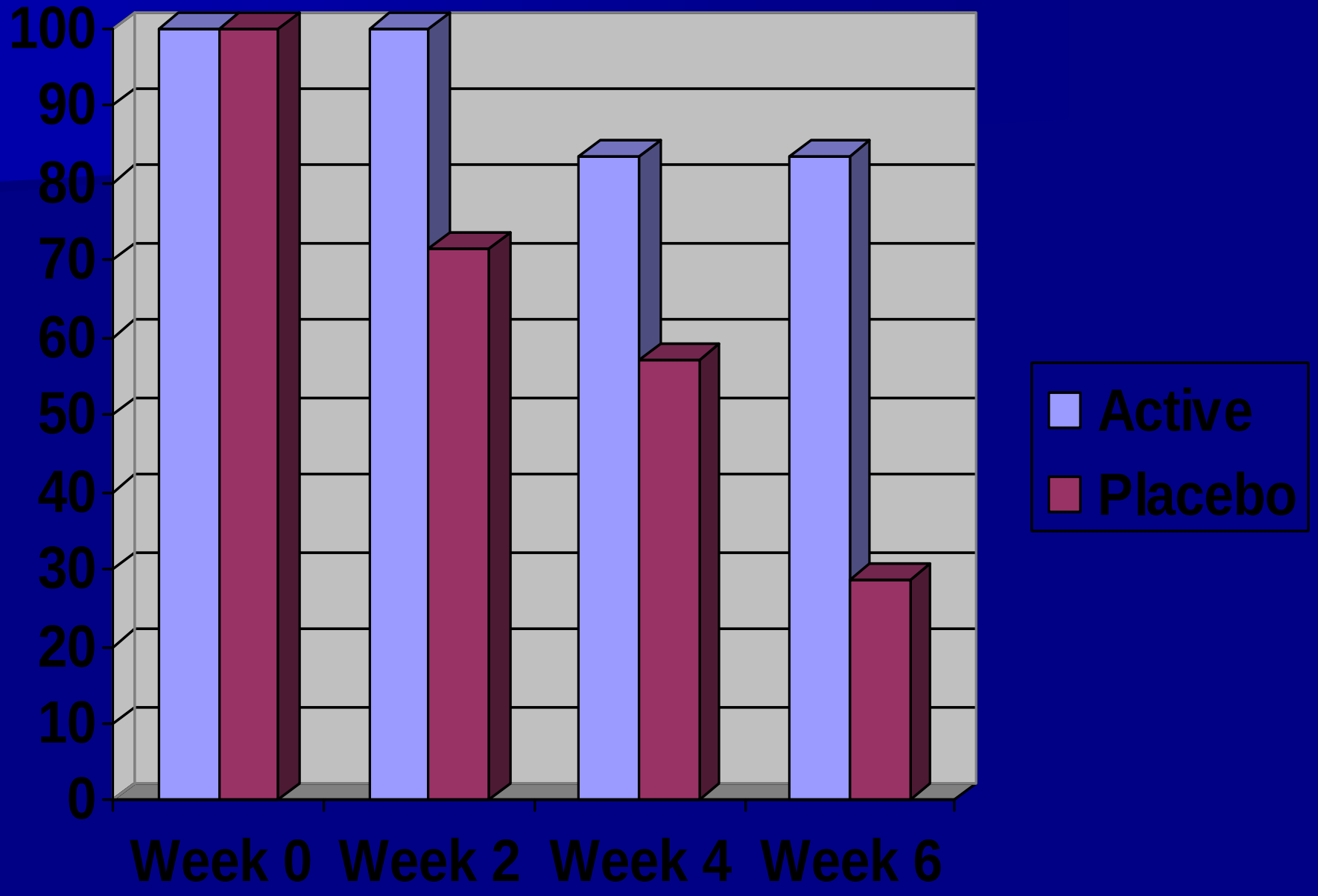
Open-Label Study

- 27 men and women aged 18 to 75 with a primary diagnosis of pathological gambling
- Required to have a score of 16 or greater on the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS)
- Stable dose of other psychotropics
- 8 weeks

- Dosing schedule:
  - 600mg/day x 2 weeks
  - 1200mg/day x 2 weeks
  - 1800mg/day x 2 weeks

- Those who responded were randomized for 6 additional weeks to double-blind medication


25
20
15
10
5
0
PG-YBOCS Total Score
Urge/Thought Score
Baseline
Endpoint


100
90
80
70
60
50
40
30
20
10
0
Week 0
Week 2
Week 4
Week 6
Active
Placebo

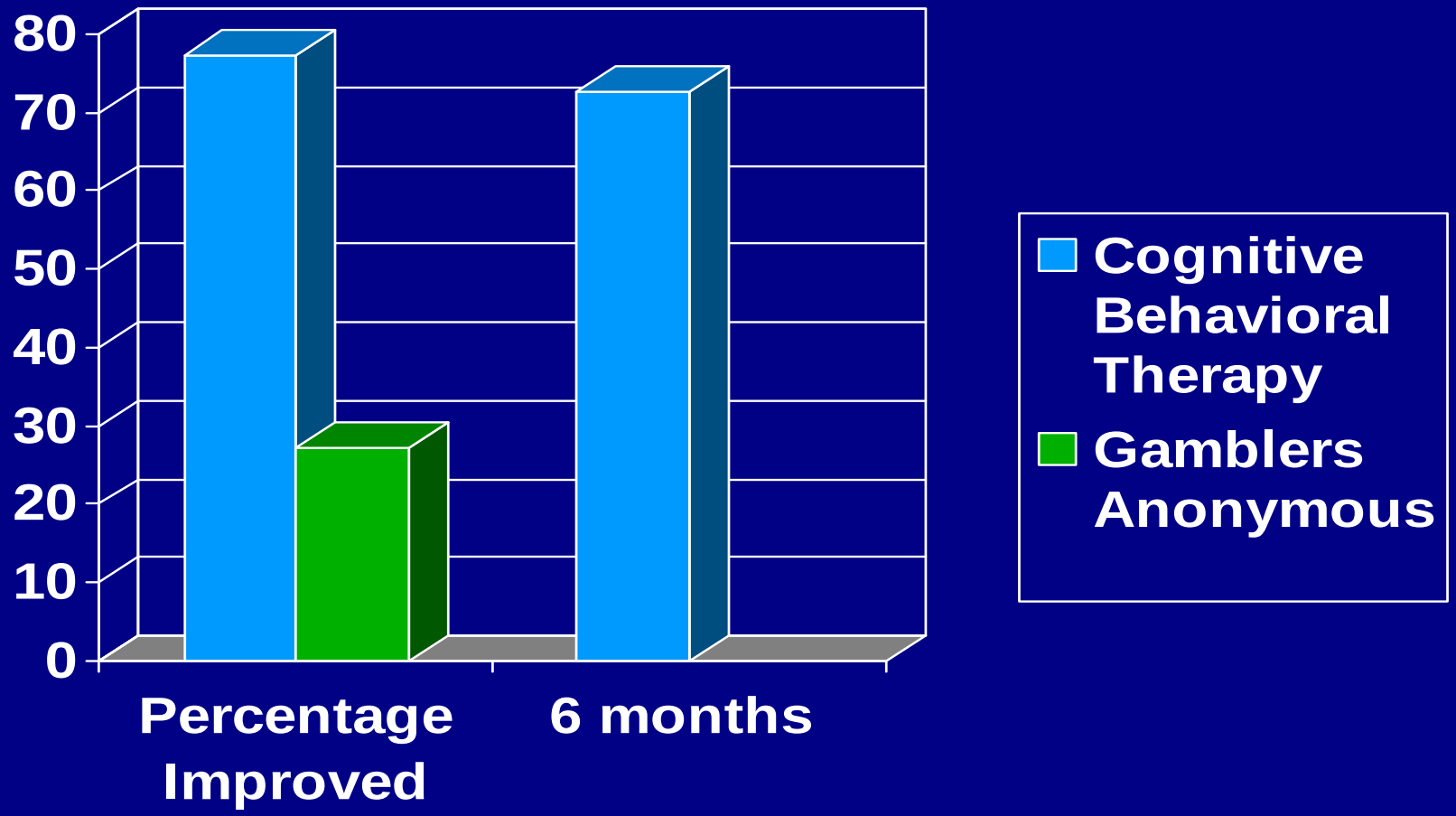
Imaginal Exposure

- Client and Therapist will develop an imaginal exposure script that includes all the relevant internal and external triggers that relate to your gambling
- Urges or cravings can be activated using exposure to triggering events via imaginal exposure exercises.

Script for PG:

- *"It's Friday and I have been looking forward to gambling all week. As I am thinking about gambling right now, my urge = 75. Work has been quite stressful and it will feel good to escape for a while and have some fun at the casino. I am bringing $200 and I have to leave the casino when that is gone, maybe 2-3 hours. I hope the money can last a little while so I don't have to leave so soon. I notice my heart flutter slightly, have butterflies in my stomach, and I can hardly wait to get there. I am hoping my favorite machine is available and the traffic on the way to the casino is not too bad.*

Motivational Interviewing Plus Imaginal Desensitization

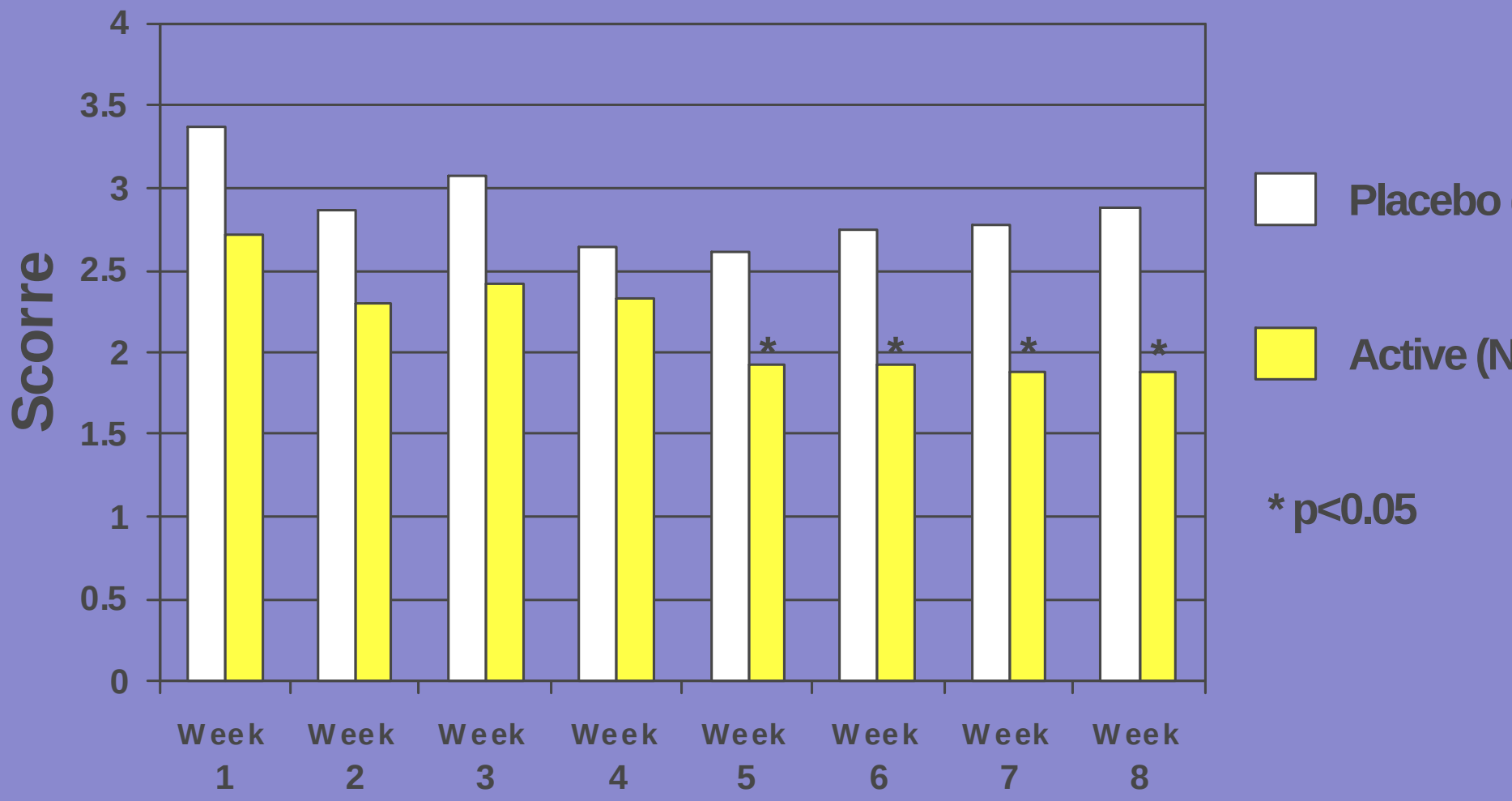


Hypofrontality

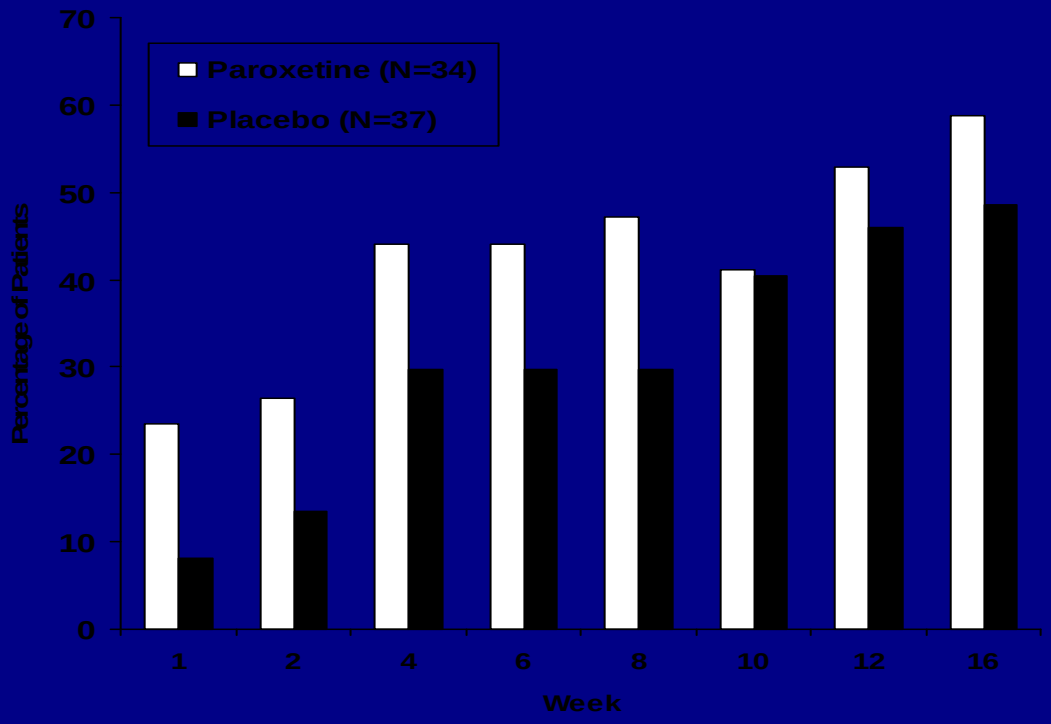
- Common adaptation to chronic addictive behaviors is hypofrontality – reduced baseline activity of prefrontal cortex, orbitofrontal cortex, anterior cingulate

- Results in individuals reporting "being driven by irresistible inner forces to gamble" and having "no ability to stop" themselves

Change in CGI-MD Score Following Paroxetine Treatmen t



Percentage of Patients Achieving Response (PG-CGI-I Score of 1 or 2) During Treatment with Paroxetine or Placebo



59% response rate in the paroxetine group
49% rate in the placebo group
45 completers (Grant et al. 2003)

Memantine

- Memantine antagonizes NMDA (N-methyl D-aspartate) receptors.
- Impulsive decision-making - neural regions under probable glutamatergic control within the prefrontal cortex.

	Visit 1	Visit 6	p-value
Abstinence, *n* (%)	n/a	18 (62.1)	<.001
Dollars lost per week	743	309	<.001
Hours gambled per week	10.4	4.0	<.001

Motivation to Quit Gambling

1) Positive aspects of gambling (what are the positive things gambling gives me?)	2) Negative aspects of quitting (what do I lose if I stop gambling?)
3) What are the negative consequences of gambling (current and future?)	4) What are the advantages of quitting gambling (what do I have to gain?)

The ABC's of Gambling

A = Activating event (Trigger)

B = Impulsive Beliefs

C = Consequence (urge and behavior)

D = Dispute Impulsive beliefs

E = Effect change

ABC Log

Date/ Time	A Activating Event (ICD Trigger)	B (Belief) (Rate certainty 0-100)	C (Con-sequence) (Rate intensity 0-100)	D (Dispute) Rate certainty 0-100	E (Effect Change) (Re-rate B certainty and C emotion 0-100)
			Urge (_____) Outcome I did __ Or did not__ engage in impulsive behavior		

Conclusions

- Pathological gambling is common and disabling
- Social and personal consequences are large and far-reaching
- Subtyping of individuals based on cognitive, neuroimaging, or genetic data may improve treatment outcomes