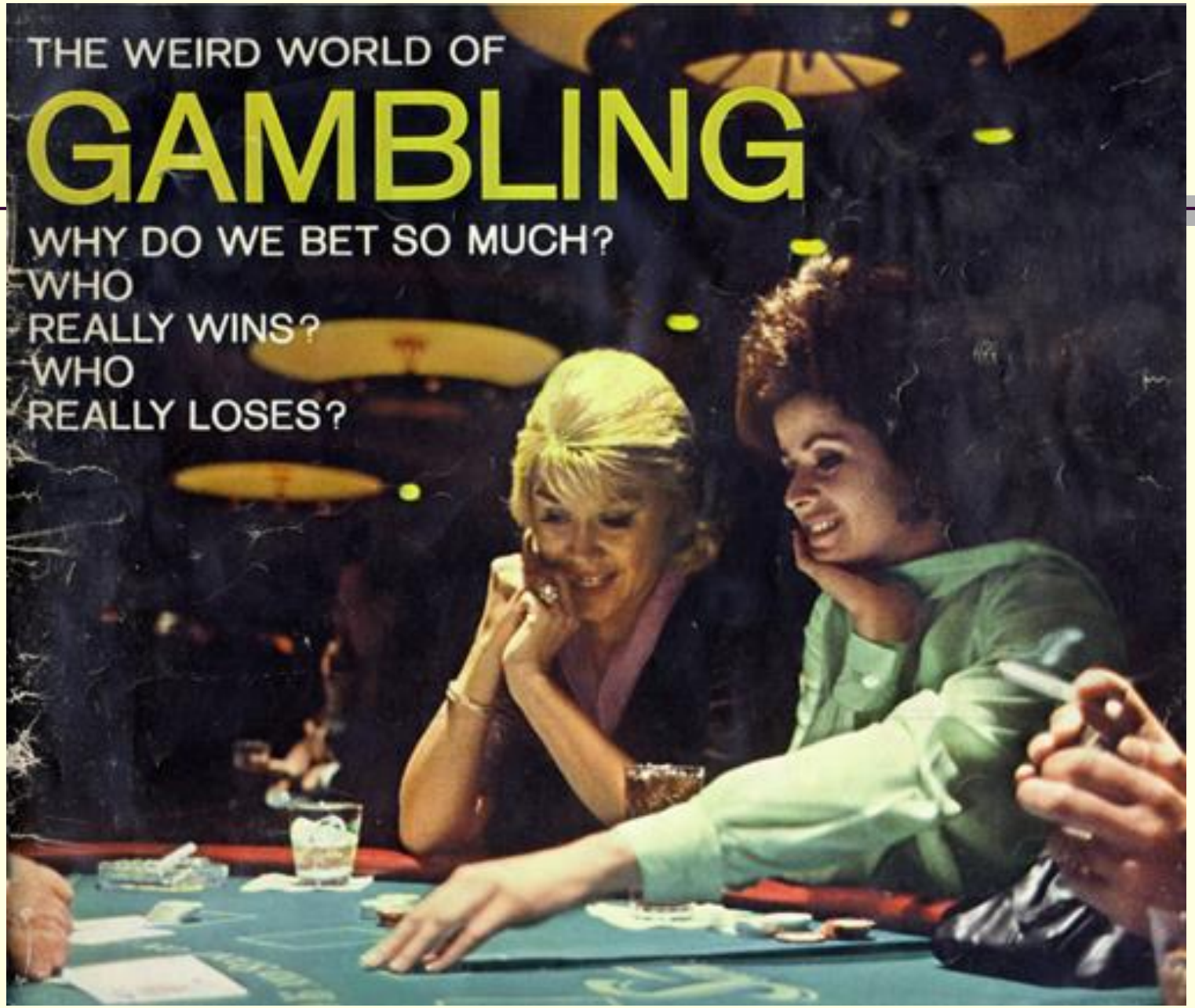
Understanding the Gambling Brain

Jon E. Grant

University of Chicago

Disclosures

- **Research Grants from: Biohaven and Janssen Pharmaceuticals**



Source: Look Magazine, March, 1963

Gambling Disorder

Persistent and recurrent maladaptive gambling behavior:

Preoccupation

Tolerance

Inability to control

Withdrawal

Escape

Lying

Illegal acts

Impairment

Relying on others

Chasing losses

DSM-5, American Psychiatric Press, 2013

The Brain

Why should we care about the brain?

- Mental health practitioners have recognized the limitations of how psychopathology has been characterized over the past 40 years.
- Individuals with the same diagnosis may present with completely non-overlapping symptoms and respond differently to the same treatments.
- Neurobiology may allow us to identify characteristics that will aid in developing novel circuit-based treatments, predicting response, and determining long-term prognosis

Genetics

- Few individuals who gamble develop gambling disorder - this suggests some individuals may have increased susceptibility to developing gambling disorder.
- Gambling disorder susceptibility, gambling and gambling-related problems are distributed along a continuum, with gambling disorder at one extreme end of this spectrum.
- Twin and birth-cohort studies - may provide insight into genetic factors associated with gambling disorder and gambling disorder vulnerability

Chamberlain SR et al. Addict Behav. 2017 Sep;72:79-85.

Genetics

- Twin studies - permit estimation of genetic and environmental contributions to a specific phenotype such as gambling disorder.
- Evidence from the Vietnam Twin Era Registry - suggests heritable factors explain about 35%–54% of the likelihood of developing gambling disorder
- Evidence from twin studies - indicates there exists significant genetic correlation between gambling disorder and SUDs (tobacco, cannabis, stimulants and alcohol), and depression, anxiety and OCD.

Molecular Genetics

- Genome-wide association studies (GWASs) may identify genetic variants that are significantly associated with specific phenotypes.

- Two GWASs of gambling disorder - neither study identified genomic regions reaching significance.

Potenza MN, et al. Nat Rev Dis Primers. 2019 Jul 25;5(1):51.

Neurocognition in Gambling

- Impulsivity - defined as a predisposition to rapid reactions to stimuli, either internal or external, often with limited previous forethought or regard for the impact of negative consequences.

- Specific neurocognitive tasks may be used to evaluate different domains of impulsivity.

  - Impulsive responses - assessed through go–no-go or stop-signal tasks.

  - Impulsive choices - evaluated through monetary tasks

  - Risk-reward decision-making evaluated through the Iowa Gambling Task.

Neurocognition in Gambling

- Compulsivity - defined as a tendency to perform repetitive overt or covert behaviors in a habitual manner that lead to functional impairment
- Compulsivity - 4 different cognitive domains:
  - Contingency-related cognitive flexibility (i.e., learning and unlearning behavior based on contingencies),
  - Set shifting (i.e., reorienting attention to different characteristics to achieve goals),
  - Attentional bias (i.e., attending to or avoiding relevant stimuli), and
  - Habit learning (i.e., repeating complex, familiar behaviors learned behaviors with limited forethought).

Ioannidis K, et al. Neuropsychopharmacology. 2019 Jul;44(8):1354-1361

Brain Circuits

- Impulsive and compulsive acts segregate, but intercommunicate.
- Compulsive behaviors may be driven by the caudate nucleus and inhibited by the orbitofrontal cortex (OFC)
- Impulsive behaviors may be driven by the ventral striatum or nucleus accumbens and inhibited by the ventromedial prefrontal cortex

Hodgins DC, et al. Lancet. 2011 Nov 26;378(9806):1874-84.

Brain Neurochemistry

- 4 main neurotransmitter systems contribute to the pathophysiology of gambling disorder:
- Serotonin with respect to impulse control
- Dopamine with respect to reward-related behaviors,
- Norepinephrine with respect to arousal and excitement, and
- Opioids with respect to motivations and urges.

Grant JE, et al.Prog Neuropsychopharmacol Biol Psychiatry. 2020 Apr 20;99:109852.

Dopamine

- Dopamine is a catecholamine neurotransmitter derived from the amino acid tyrosine.
- Dopamine brain pathways - traditionally implicated in rewarding and reinforcing behaviors.
- Elevated levels of dopamine have been found in the CSF of individuals with gambling disorder
- D3 receptor levels correlate with impulsivity and problem-gambling severity in gambling disorder

Grant and Potenza, Gambling Disorder, 2nd Edition. APPI, 2022

Opioid System

- Challenge studies with oral amphetamine showed a blunted opioid response in those with gambling disorder.
- Clinical trials implicate opioids in gambling disorder pathophysiology
- Specific subgroups (e.g., individuals with gambling disorder and a family history of addictions or strong gambling urges) may be inclined to respond favorably to opioid receptor antagonists

Grant and Potenza, Gambling Disorder, 2nd Edition. APPI, 2022

Neuroimaging

- Reward sensitivity dysfunction - central to the pathophysiology of gambling disorder.
- Studies indicate - blunted activation of frontostriatal circuits involving the striatum and ventromedial prefrontal cortex during the reward anticipation and outcome phases.
- Gamblers may gamble to compensate for a general insensitivity to natural rewards such as food and sexual activity.

Grant JE, et al. Prog Neuropsychopharmacol Biol Psychiatry. 2016 Feb 4;65:188-93

Neuroimaging

- Reward-learning dysfunctions may contribute to gambling disorder. Monetary task-based fMRI studies suggest increased activation of areas within a salience network (e.g., dorsal anterior cingulate cortex and the anterior insula).
- Salience network - implicated in the allocation of attention to salient events.
- Increased activation of the salience network could reflect recruitment of attentional resources to gambling-related cues in gambling disorder.

Potenza MN, et al. Gambling disorder. Nat Rev Dis Primers. 2019 Jul 25;5(1):51.

Neuroimaging

- Individuals with gambling disorder - diminished activation of the amygdala prior to ceasing loss-chasing behavior.
- Amygdala has been implicated in cost-benefit analyses with a goal to avoid losses
- Reduced activation of the amygdala - reflects impaired probabilistic learning (i.e., acquiring information that is based on the likelihood of prior events that have been paired with specific outcomes).

Potenza MN, et al. Gambling disorder. Nat Rev Dis Primers. 2019 Jul 25;5(1):51.

Brain: Convergence of gambling and gaming

- Since 1990s- interest in whether there might be a connection between video gaming and gambling.
- Two activities share much in common at structural level.
- Recent technological developments have led to some video games resembling, promoting, or intersecting with gambling products or facilitating continuous in-game purchasing to obtain random rewards.

Fineberg NA, et al. Eur Neuropsychopharmacol. 2018 Nov;28(11):1232-1246.

Convergence of gambling and gaming

- Examples of this convergence-video games that realistically simulate gambling without money being directly involved (aside from being used to purchase virtual currency)…
  - social casino games;
  - video games that include options to acquire monetized items (e.g., skins) that enable unregulated gambling on external platforms;
  - presence of gambling within competitive gaming events

Carragher N, et al. Addiction. 2021 Dec 9. doi: 10.1111/add.15780.

Convergence of gambling and gaming

- 54% of games on Facebook include gambling themes.
- 2018 review of 22 popular video games found that 5 retail games met the conventional criteria for gambling, including the option to cash out winnings.
- Is gaming a risk factor for gambling? A study of young adults reported 94% of gamblers played video games & 55% of video gamers gambled

Grant and Potenza, Gambling Disorder, 2nd Edition, APPI, 2022

Factors predicting who gambles after gaming

- Impulsivity
- Risk-taking propensity

King A, et al. Issues Ment Health Nurs. 2020 Dec;41(12):1063-1075.

COVID19 and Gambling

- 4% reported an overall gambling increase during the pandemic.
- Individuals reporting an increase - higher for online casinos, online horse betting, online lotteries, and lower for sports betting.
- Gambling increases -associated with increased alcohol use
- Stress increased in gamblers
- Treatment seeking did not increase

Price A, et al. Int J Ment Health Addict. 2022 Jan 20:1-15.

Treatment Implications


Snapshots at jasonlove.com
GAMBLERS ANONYMOUS
"Betcha I recover before you do."

Gamblers Anonymous

- 22.4% attended only 1 meeting,
- 15.5% attended only 2 meetings,
- 7.5% earned a 1-year abstinence pin.
- Those who stayed more likely to have initial realistic expectations of GA and a spouse in GamAnon.


I ♥ MY PROBLEMS
SIPRESS

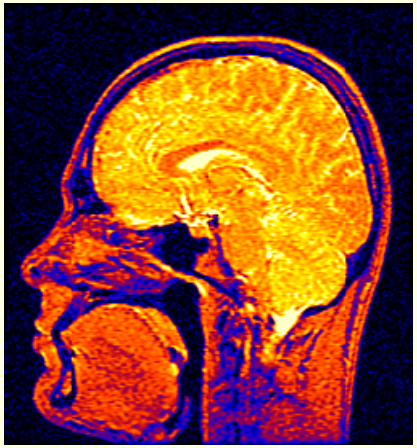
Expressed behavior

Cognition

Brain abnormalities

Etiology

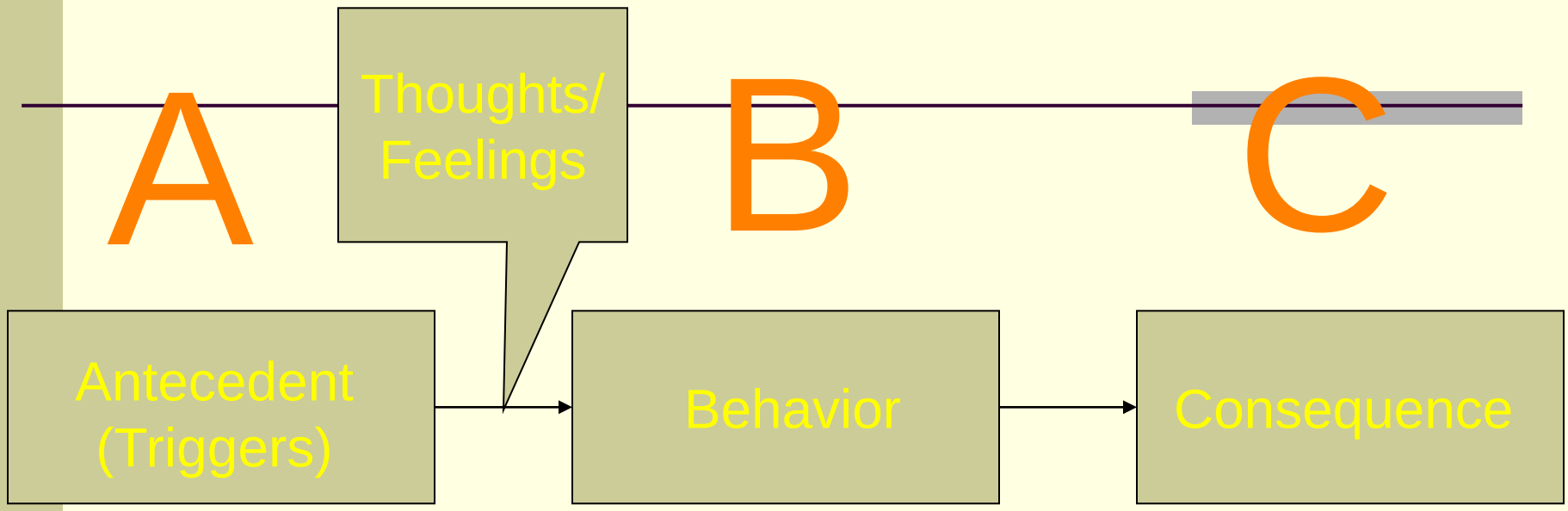
Genetic ⇄ Environmental



Cognitive Behavioral Therapy

- Psychoeducation
- Increased awareness of irrational cognitions, and cognitive restructuring.
- Identification of gambling triggers and the development of non-gambling sources to compete with the reinforcers associated with gambling.

Hodgins DC, et al. Lancet. 2011 Nov 26;378(9806):1874-84.



Particular people

Environment

Feelings

e.g., urges, argument with spouse, boredom, anxiety

Gambling/alternate behavior

e.g., I drove by the bar, next think I knew it was last call

Abstinence

e.g., I thought about the effect it would have on my family, and took a different route home

Positive

e.g., I gambled and I forgot about that argument with my wife

Negative

e.g., the next day, I felt like I'm a failure.

Imaginal Exposure

Client and Therapist develop an imaginal exposure script that includes all the relevant internal and external triggers that relate to gambling

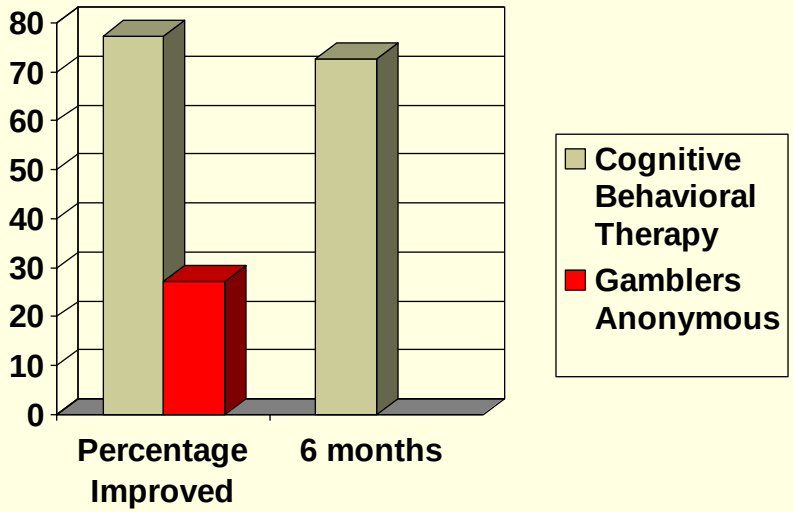
Urges or cravings can be activated using exposure to triggering events via imaginal exposure exercises.

Grant JE, et al. Br J Psychiatry. 2009 Sep;195(3):266-7

Imaginal Exposure

"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



Grant JE, et al. Br J Psychiatry. 2009 Sep;195(3):266-7

Motivation to Quit Gambling

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

Contingency Management

- Re-arranging the reinforcers in a person's environment

- Incentives or rewards to encourage specific behaviors

  Vouchers, group acknowledgements, family prizes

Christensen DR, et al. BMJ Open. 2018 Apr 3;8(4):e018804.

Self-Directed Interventions

- Use CBT principles and apply them to workbooks or online programs
- Workbooks: self-assessment, goal setting, goal implementation, and goal maintenance
- Significant reductions in gambling frequency and severity
- Drop-out rates are higher than for professional face-to-face interventions

Hodgins DC, et al. Lancet. 2011 Nov 26;378(9806):1874-84.

Groups

- Cognitive restructuring
- Coping skills/identification of high-risk situations.
- Imaginary exposure with response prevention.
- Financial limit setting and activity scheduling of leisure activities.
- Problem-solving training
- Relapse prevention

Hodgins DC, et al. Lancet. 2011 Nov 26;378(9806):1874-84.

Online Interventions

- Online training: education activities (games, quizzes, trivia) related to gambling issues (cognitive distortions, myths, facts) designed to increase engagement and awareness

- Self-guided online CBT

Sagoe D, et al. J Behav Addict. 2021 Sep 17;10(3):546-565.

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.

Grant JE, et al. Prog Neuropsychopharmacol Biol Psychiatry. 2016 Feb 4;65:188-93.

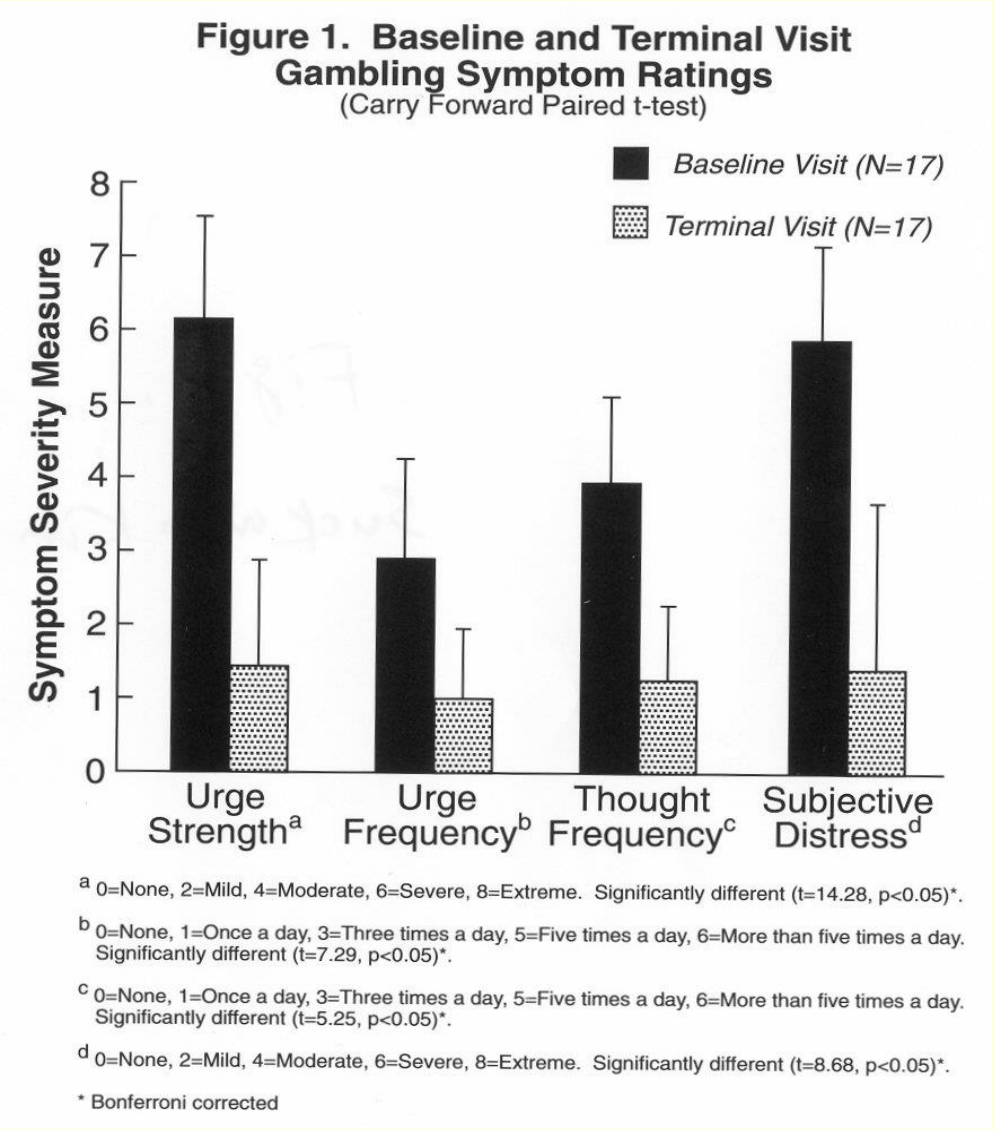
Naltrexone for Gambling Disorder

METHODS

- n=77 with GD
- Double-blind, placebo-controlled
- 11-weeks
- Dose titration: 25mg/d – 250mg/d

RESULTS

- Significant benefit in CGI-Improvement (both patient and clinician-rated) and Gambling Symptom Rating Scale



Kim SW, et al. Biol Psychiatry. 2001 Jun 1;49(11):914-21.

Kim et al. Biol Psychiatry 2001;49(11):914-21

N-acetylcysteine (NAC)

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

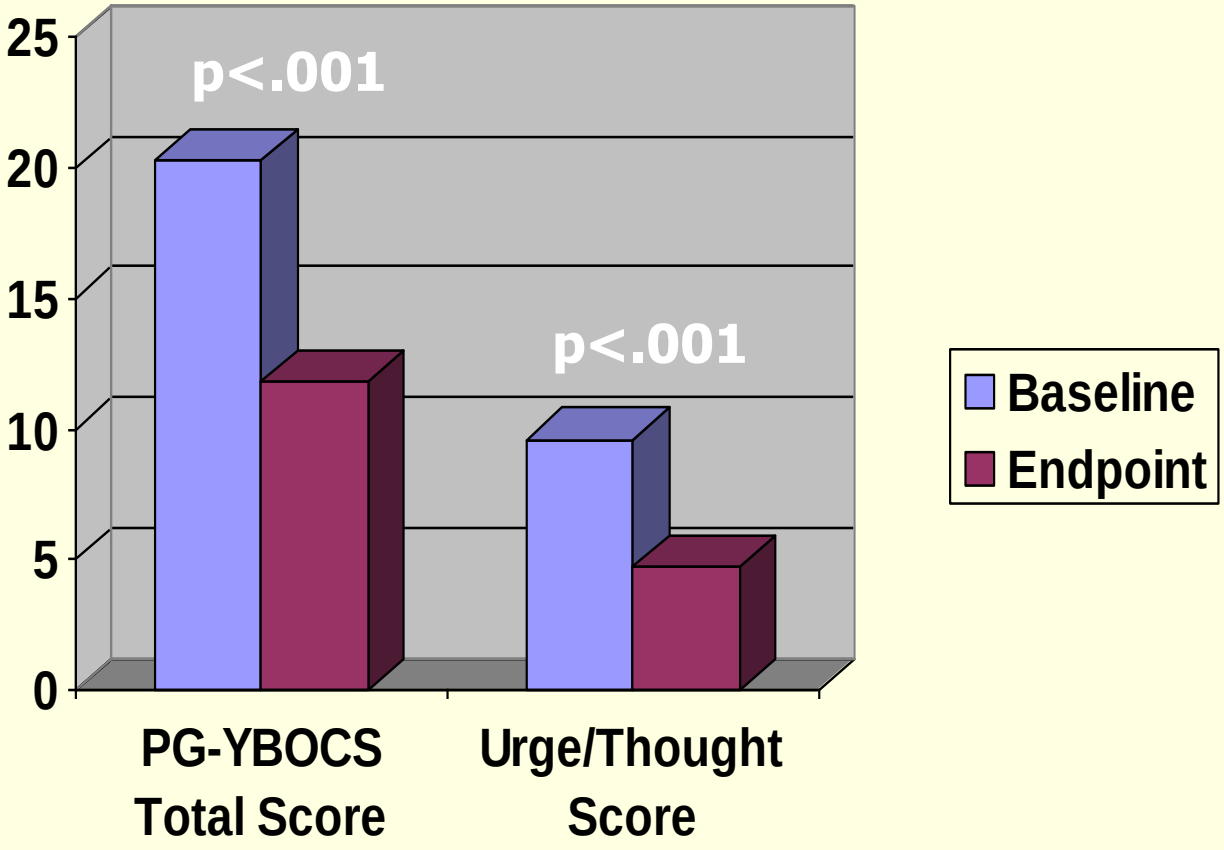
Open-Label study of NAC in Gambling Disorder

- n=27 subjects, mean age 50.8 years, 44.4% female
- Dose titration from 600mg/d-1800mg/d
- Required to have moderate cravings to gamble

Open-Label Study of NAC in GD

RESULTS

- YBOCS: Scores decreased 41.9% from baseline to endpoint



Grant JE, et al.
Biol Psychiatry. 2007 Sep 15;62(6):652-7.

Open-Label Study of NAC in GD

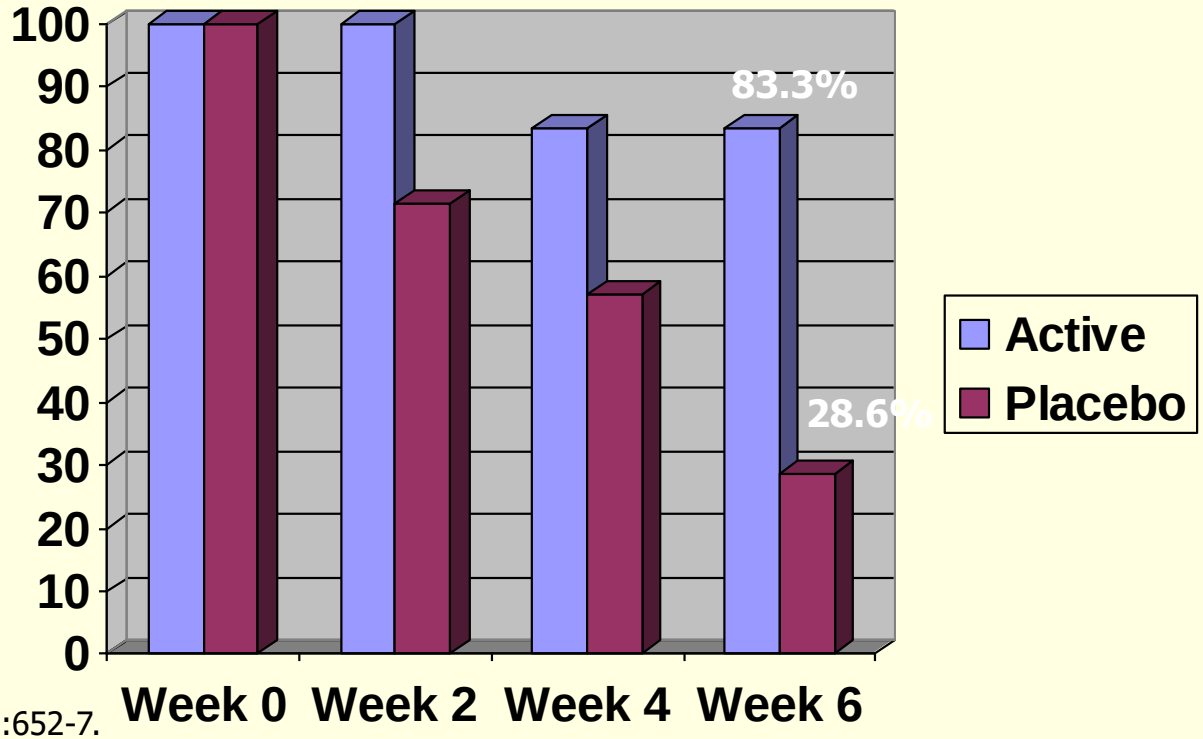
Responders (≥30% decrease in PG-YBOCS and "Much" or "Very much" improved on CGI-I scale) randomized to NAC or placebo for 6-weeks

RESULTS

- N=16 (59.3%) met responder criteria

- Mean effective dose: 1476.9 (±311.3) mg/d

Figure. Percentage of subjects meeting responder criteria each week of the double-blind discontinuation phase



Grant JE, et al.
Biol Psychiatry. 2007 Sep 15;62(6):652-7.

Memantine

Memantine antagonizes NMDA (N-methyl D-aspartate) receptors, a type of glutamate receptors.

Impulsive decision-making may be dependent on neural regions within the prefrontal cortex that are under probable glutamatergic control.

Grant JE, et al.
Psychopharmacology (Berl). 2010 Dec;212(4):603-12

Open-Label Study of Memantine in Gambling Disorder

RESULTS

- Cognitive flexibility improved from baseline to endpoint
- GD subjects were comparable to healthy controls at study endpoint

	Baseline v Endpoint		Baseline v Controls		Endpoint v Controls	
	T	P-value	T	P-value	T	P-value
IDE total errors	2.20	**0.037**	2.09	**0.041**	1.06	0.294

- Pharmacological modulation of the glutamate system may reduce gambling and may do so by improving neurocognitive function related to cognitive flexibility.

Grant et al. Psychopharmacology (Berl) 2010 Dec;212(4):603-12

COMT Inhibitors: Open-Label Study of Tolcapone in Gambling Disorder

- Lower dopamine levels in the prefrontal cortex are thought to contribute to deficits in cognitive processing
- Suboptimal prefrontal cortex dopamine levels may mean that irrelevant sensory information is not filtered out of processing and cannot focus more on salient features of the environment

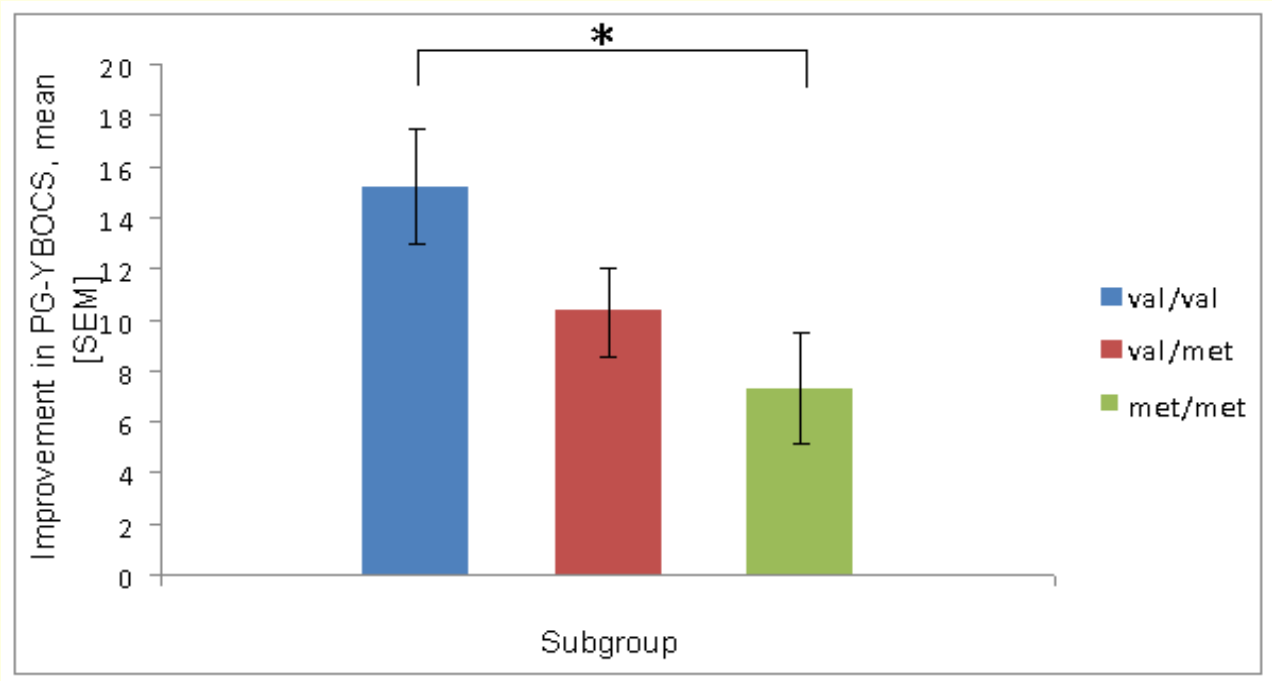
Grant JE, et al. Eur Neuropsychopharmacol. 2013 Nov;23(11):1587-96.

Open-Label Study of Tolcapone in Gambling: Genotyping

RESULTS

- **val/val** COMT polymorphism was associated with significantly greater improvement from tolcapone compared to **met/met**

Figure. Change in PG-YBOCS from baseline to end of treatment in different COMT Gambling Disorder subjects



Tolcapone and genotype appear to have interactive effects on dopamine-related executive functioning, with tolcapone enhancing Val-COMT subjects but either not improving or impairing Met-COMT subjects

Grant JE, et al. Eur Neuropsychopharmacol. 2013 Nov;23(11):1587-96.

What about other treatments?

- Psychodelics?
- Brain stimulation?
- New drugs or therapies on the horizon?

QUESTIONS?

jongrant@uchicago.edu