Using Science to Improve Gambling Disorder Treatment

Jon E. Grant
University of Chicago

1

Disclosures

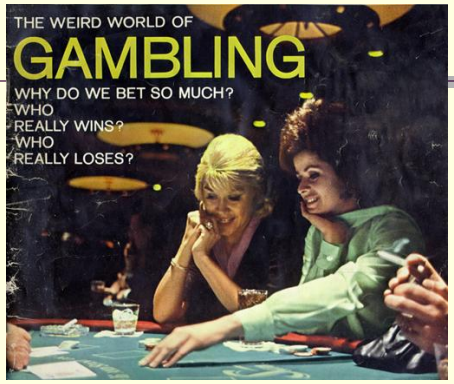
- **Research Grants from: NIDA, Biohaven and Janssen Pharmaceuticals**
- **Off-label use of medications**

2

Learning Objectives

- List the clinical features of gambling disorder and neurocognitive and biological underpinnings of the disorder
- Assess the evidence-based treatment approaches to gambling disorder
- Describe how understanding gambling from multiple perspectives may improve our treatments.

3



Source: Look Magazine, March, 1963

4

Gambling Disorder

Persistent and recurrent maladaptive gambling behavior:

Preoccupation	Lying
Tolerance	**Illegal acts**
Inability to control	Impairment
Withdrawal	Relying on others
Escape	Chasing losses

DSM-5, American Psychiatric Press, 2013

5

The Brain

6

Why should we care about the brain?

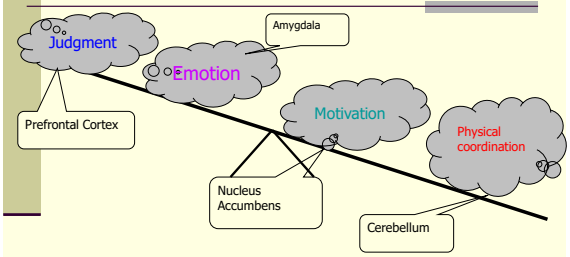
- Mental health practitioners have recognized the limitations of how psychopathology has been characterized over the past 40 years.
- Individuals with the same diagnosis may present with completely non-overlapping symptoms and respond differently to the same treatments.
- Neurobiology may allow us to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

7

Developmental Biology

- Gambling addiction generally start in young adulthood.
- Environmental and genetic influences - vulnerability to and expression of gambling addiction
- Changes in brain structure and function during adolescence might influence the motivation to engage in risk-taking behaviors.

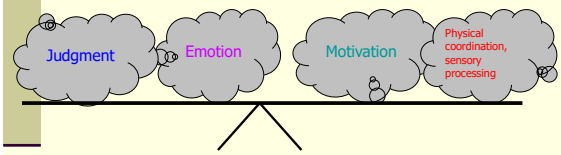
8



Notice: Judgment is last to develop!

9

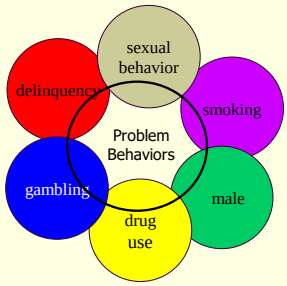
Age 24



Balance

10

Youth Problem Behaviors

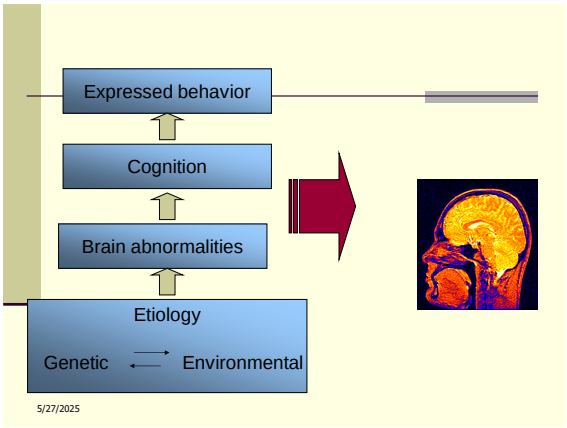


11

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.

12



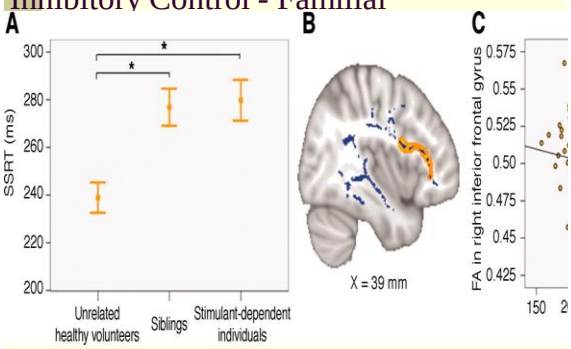
13

Neurocognition in Gambling

- Executive function deficits are greater in those with gambling than in control subjects, including:
  - Planning
  - Cognitive flexibility
  - Inhibition

14

Inhibitory Control - Familial



15

Impulsivity Across Psychiatric Groups

- **Substance use disorders**
- **Behavioral addictions**
- **ADHD**
- **Bipolar disorder**
- **Personality disorders**
- **Suicidality**

16

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.

17

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

18

Biochemistry – Opioid System

- The endogenous opioid system influences the experiencing of pleasure.
- Opioids modulate mesolimbic dopamine pathways via disinhibition of γ-aminobutyric acid input in the ventral tegmental area.
- Addictions have been associated with elevated blood levels of the endogenous opioid β-endorphin.

19

Glutamate

- Levels of glutamate within the nucleus accumbens mediate reward-seeking behavior
- Restoring extracellular glutamate concentration in the nucleus accumbens seems to decrease cravings.

20

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.

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

21

Treatment Implications

22

Duration of Untreated Illness

- Examined 250 people with gambling disorder
- Mean time to treatment was 9 years
- How does the behavior change the brain over those 9 years?
- Staging of illness

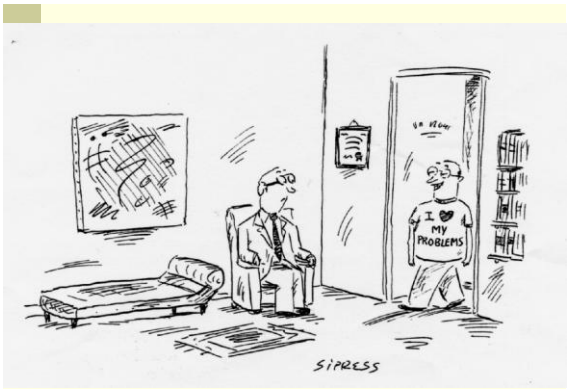
23

24

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.

25



26

Treatment

- Pharmacotherapy
  - No medication FDA-approved for GD
- Cognitive-Behavioral Therapy (CBT)
  - Length of treatment unknown; brief interventions have shown benefit;
  - Multiple versions of CBT have shown benefit

Yau YH, Potenza MN. Gambling disorder and other behavioral addictions: recognition and treatment. Harv Rev Psychiatry. 2015 Mar-Apr;23(2):134-46.

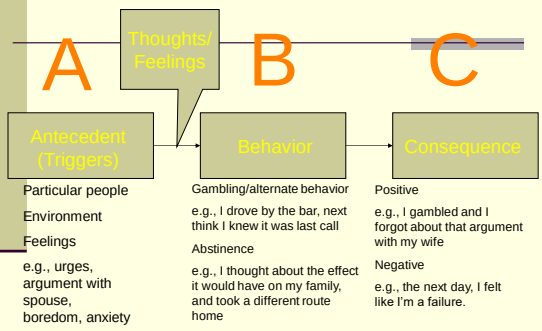
27

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.

28



29

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

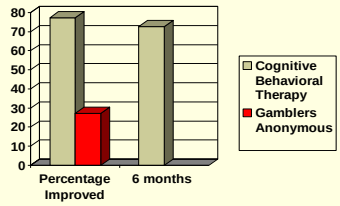
30

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.

31

Motivational Interviewing Plus Imaginal Desensitization



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

32

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?)

33

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.

34

Brief Interventions/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.

35

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.

36

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.

37

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.

38

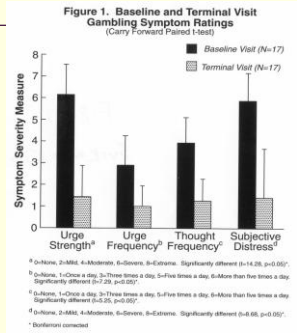
Naltrexone for Gambling Disorder

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.

39

N-acetylcysteine (NAC)

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

Open-Label study of NAC in Gambling Disorder

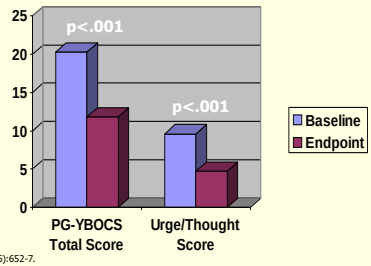
- n=27 subjects, mean age 50.8 years, 44.4% female
- Dose titration from 600mg/d-1800mg/d
- Required to have moderate cravings to gamble

40

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.

41

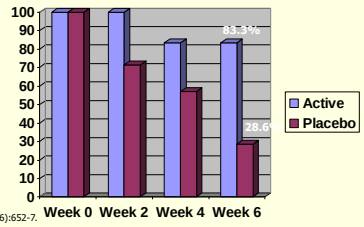
Open-Label Study of NAC in GD

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



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

42

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

43

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

44

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.

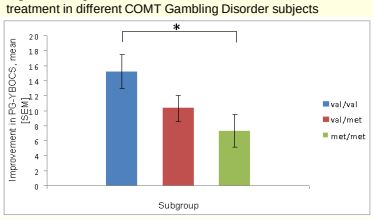
45

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.

46

What about other treatments?

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

47

Clinical Subtyping

Neurocognition?
Genetics?
Imaging?

48

QUESTIONS?

jongrant@uchicago.edu

49