THE NEUROSCIENCE OF GAMBLING: FROM RECREATIONAL USE TO GAMBLING DISORDER

T. Celeste Napier, Ph.D.

Department of Psychiatry and Behavioral Sciences
Rush University College of Medicine
Chicago, IL USA
For many people, gambling is harmless entertainment, but for some, it can become a problem.

Problem gambling is a progressive disorder.
Initial motivation:
  Rewarding
Repetitive engagement:
  Learning & Memory
Recreational Disorder

- Impaired control
- Persistence
- Unsuccessful attempts to quit
- Narrowing of interests
- Neglect of other areas of life
Recreational Disorder

The functional neuroscience of decision-making
Dopamine Pathways

- Frontal cortex
- Striatum
- Substantia nigra

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine-tuning)
- Compulsion
- Perseveration

VTA
Nucleus accumbens
Hippocampus
Raphe nucleus

Serotonin Pathways

- Functions
- Mood
- Memory processing
- Sleep
- Cognition

NIDA
Reward-Motivated Behaviors

Natural Rewards

- food
- water
- sex
- nurturing
Natural Rewards Elevate Dopamine Levels

**FOOD**

- % of Basal DA Output
- Time (min)
- Empty Box Feeding

**SEX**

- DA Concentration (% Baseline)
- Copulation Frequency

- Mounts
- Intromissions
- Ejaculations

*Di Chiara et al., Neuroscience, 1999.*

Drugs of Abuse Increase Dopamine

**NICOTINE**

% Basal Dopamine Release

0 1 2 3 4 5hr

Time After Nicotine

**MORPHINE**

% Basal Dopamine Release

0 1 2 3 4 5hr

Time After Morphine

**COCAINE**

% Basal Dopamine Release

0 1 2 3 4 5hr

Time After Cocaine

**AMPHETAMINE**

% Basal Dopamine Release

0 1 2 3 4 5hr

Time After Amphetamine

Di Chiara and Imperato. PNAS, 1988
Dopamine Increases During Gambling-Like Tasks in Laboratory Rats

St Onge, Ahn, Phillips and Floresco, J Neurosci 2012
Dopamine Increases During Gambling-Like Tasks in Humans

Joutsa et al., Neurolmage 2012
Psychology of Gambling

Risk-taking – it is human nature to feel excited when taking risks.

‘natural high’

adrenalin rush (PNS)

dopamine elevation (CNS)
Activation of the reward pathway by addictive drugs and risk-taking.
Recreational Disorder

The functional neuroscience of decision-making

Choosing to gamble reflects what brain processes?
Adapted from Volkow et al., Neuropharmacology, 2004
Inhibitory Control: Drug and Behavioral Addictions

Addictions Change Brain Circuits that Govern Decisions

Adapted from Volkow et al., Neuropharmacology, 2004
‘Psychology’ of Gambling

Risk-taking – it is human nature to feel excited when taking risks – ‘natural high’

Social – ‘game night’, sports, lottery, glamour

Escapism - the gambling environment can provide an escape from everyday life - glitzy casino, loud and exciting amusement arcade or online betting company - all of which stimulate and arouse our senses
‘Psychology’ of Gambling
Bio-Behavioral Factors

Biology/genes

Biology/Environment Interactions

Environment
Why Do People Choose to Gamble?

To feel good
To have new: feelings, sensations, experiences, and to share them

To feel better
Escapism anxiety, worries, fears, depression
Choosing to gamble

To feel good.
To have new feelings, sensations, experiences and to share them.

Genetic Predisposition

Developmental
- Risk-taking, sensation-seeking
- Interacting with, and approval from peers
“Rapidly changing wiring leads to mental agility – and risky behavior”

By Jay N. Giedd

Time of high sensitivity to rewards, and increased vulnerability to developing addictions. With potential for long-term consequences.
Miss match for development of brain regions that govern emotions and judgement.

Cortical development and decision making

"Adolescence is marked by peaks in sensation, novelty, and reward seeking ... stem from ... increases in responsiveness in limbic and paralimbic brain structures".

CF Geier. Hormones and Behavior 64:333-342, 2013. (Hwang et al., 2010)
Social Engagement

Adolescent Risk-Taking

- Creates new friendships
- Safety in association as they leave parents

Increased adolescent risk-taking linked to the influence of peers on valuation of rewards

Choosing to gamble

To feel better (less studied).

Escapism
- Co-morbidity w mental hlth disorders
  - esp substance use disorders
  - onset and persistence of GD predicted by prior diagnosis of mood disorders, anxiety, ICD, SUD (Kessler et al. Psychol Med, 2008)
- Environment
  - Life stresses
  - Brain trauma
Why Do People Choose to Gamble?

To feel good

To feel better
A person engages in gambling hoping to change his or her mood, or emotional state.

Translation –
...hoping to change their brain.

How does gambling change the brain?
Memories are a Critical Aspect of Addiction Processes

It’s about people, places, and things.
Remembering Causes Craving

Kober et al., NPP 2016
The Addiction Process:

Everitt
Eur Jr Neurosci
effects that maintain drug seeking and use

Reward
(positive reinforcement)

Relief
(negative reinforcement)

Progression of addictive process

Individual factors: Genetics, life stress

Heilig et al.,
Neuroscience and Biobehavioral Reviews
35: 334, 2010
Progression to Problem Gambling

Recreational Disorder

Reframe concepts of
- stigma
- treatment expectations
GAMBLING DISORDERS ARE A BEHAVIORAL ADDICTION

In DSM-V, gambling disorder joins substance-related addictions in a renamed group called “Addiction and Related Disorders.”

Addiction: A chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.
Is continued drug abuse a voluntary behavior?

“The initial decision to take drugs is mostly voluntary. However, when drug abuse takes over, a person’s ability to exert self control can become seriously impaired.”

“Brain imaging studies from drug-addicted individuals show physical changes in areas of the brain that are critical to judgment, decision making, learning and memory, and behavior control.”
addiction is a disease of the brain

“It is considered a brain disease because drugs change the brain — they change its structure and how it works. “

“Addiction is similar to other diseases, such as heart disease. Both disrupt the normal, healthy functioning of the underlying organ, have serious harmful consequences, are preventable, treatable, and if left untreated, can last a lifetime.”
Does relapse to drug abuse mean treatment has failed?

“No. The chronic nature of the disease means that relapsing to drug abuse is not only possible, but likely.

Treatment of chronic diseases involves changing deeply imbedded behaviors, and relapse does not mean treatment failure. For the addicted patient, lapses back to drug abuse indicate that treatment needs to be reinstated or adjusted, or that alternate treatment is needed.”
Addictions are chronic illnesses with relapse rates similar to those of other chronic illnesses.
Relapse Rates Are Similar for Drug Addiction and Other Chronic Illnesses

McLellan et al., JAMA, 2000.
Addiction is similar to other chronic illnesses also because recovery is often a long-term process requiring repeated treatments.
Measuring the Outcome of Treating Chronic Illnesses

Hypertension Tx

Addiction Tx

Stage of Tx

Stage of Tx

NIDA
Neuroscience Underpinnings of the Switch from Recreational to Problem Gambling

Initially hijacks normal reward pathways (especially in vulnerable individuals)

Reduces inhibitory control

Involves learning and memory – changes the brain

Reframe concepts of stigma and treatment outcomes.
There is no FDA-approved pharmacotherapy.

Using neuroscience to inform medication development for gambling disorders.

Development of effective preclinical models of particular aspects of the problem gambling process.
Addiction Changes Brain Circuits that Govern Decisions

- **Non-Addicted Brain**
  - Saliency
  - Drive
  - Memory
  - **Control**
  - NOT
  - GO

- **Addicted Brain**
  - Saliency
  - Drive
  - Memory
  - **Control**
  - GO
  - X
comparative functional neuroanatomy
Features of Gambling: Humans versus Rats

- Money: $1 (more likely) vs. $1000 (less likely)
- Reward: small reward (more likely) vs. large reward (less likely)
ICSS: Intra-Cranial Self-Stimulation
ICSS: Intra-Cranial Self-Stimulation
Determination of Small and Large Rewards Using ICSS

- ICSS
- 50-60Hz (small reward)
- 100Hz (LARGE reward)
- more likely “certain”
- less likely “risky”

Graph showing:
- # of Responses / 2min
- Frequency (Hz)
- n=9 rats

Frequency (Hz):
- 50-100-150
- 50Hz (small reward)
- 100Hz (LARGE reward)
Probability Discounting Task

Current Generator

“CERTAIN” LEVER

small reward (lower current)
Probability of reward delivery is always 100%

“RISKY” LEVER

LARGE reward (higher current)
“risky” lever
Probability of reward delivery =
100%
80%
70%
60%
50%
40%
30%
15%
5%
Risky Decision-Making

Large Reward Probability
- 80%
- 50%
- 20%
- 10%

% Selection

LARGE REWARD

SMALL REWARD

Rokosik and Napier, Journal of Neuroscience Methods, 2011
Activating Dopamine Receptors Increases Risk-Taking

Selection of Large Reward (% Total)

Probability of Delivery (Large Reward)

* baseline
* chronic pramipexole

Rokosik & Napier. Neuropsychopharmacology, 2012
Selection of Large Reward (% Total)

Probability of Delivery (Large Reward)

RECOVERY

baseline
pramipexole withdrawal

REINSTATEMENT
chronic pramipexole
pramipexole withdrawal
pramipexole reinstatement

Rokosik & Napier. Neuropsychopharmacology, 2012
Addictions are the Quintessential Bio-Behavioral Disorders
Pramipexole-Induced Risk-Taking: High and Low Responders

Selection of Large Reward (% Total) vs. Probability of Delivery (Large Reward)

“Risky” (n=22)

“Cautious” (n=12)

addiction changes brain circuits that govern decisions
# Neurotransmitters in Gambling

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Study Modality</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td>CSF, blood, urine, drug, fMRI</td>
<td>Arousal, excitement</td>
</tr>
<tr>
<td>Serotonin</td>
<td>CSF, blood, drug, PET, randomized clinical trial</td>
<td>Impulse control, cognition, memory</td>
</tr>
<tr>
<td>Dopamine</td>
<td>CSF, blood, urine, drug, PET</td>
<td>Reward processing, reward-based learning, reinforcement</td>
</tr>
<tr>
<td>Opioid</td>
<td>Randomized clinical trial</td>
<td>Pleasure, urges</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Blood</td>
<td>Stress</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Randomized clinical trial</td>
<td>Compulsiveness, cognitive inflexibility</td>
</tr>
</tbody>
</table>

Modified from Potenza MN. *Curr Opin Neurobiol.* 2013
Dopamine Pathways

- Functions
  - Reward (motivation)
  - Pleasure, euphoria
  - Motor function (fine-tuning)
  - Compulsion
  - Perseveration

Serotonin Pathways

- Functions
  - Mood
  - Memory processing
  - Sleep
  - Cognition

Frontal cortex

Striatum

Substantia nigra

Nucleus accumbens

VTA

Hippocampus

Raphe nucleus
MIRTAZAPINE (REMERON®)

Nullifying drug-induced sensitization: Behavioral and electrophysiological evaluations of dopaminergic and serotonergic ligands in methamphetamine-sensitized rats

Mirtazapine treatment after conditioning with methamphetamine alters subsequent expression of place preference
Amy A. Herrold, Fei Shen, Martin P. Graham, Laura K. Harpere, Sheila E. Specio, Clark E. Tedford, T. Celeste Napier

The atypical antidepressant mirtazapine attenuates expression of morphine-induced place preference and motor sensitization
Steven M. Graves, Amanda L. Persons, Jennifer L. Riddle, T. Celeste Napier

Repeated mirtazapine nullifies the maintenance of previously established methamphetamine-induced conditioned place preference in rats
Robin M. Voigt, Amanda L. Mickiewicz, T. Celeste Napier
KETANSERIN (SUFREXAL®)

Nullifying drug-induced sensitization: Behavioral and electrophysiological evaluations of dopaminergic and serotonergic ligands in methamphetamine-sensitized rats


Opposing effects of 5-HT₂A and 5-HT₂C receptor antagonists in the rat and mouse on premature responding in the five-choice serial reaction time test

Paul J. Fletcher, Maria Tampakeras, Judy Sinyard, Guy A. Higgins

A comparison of multiple 5-HT receptors in two tasks measuring impulsivity

John C. Talpos, Lawrence S. Wilkinson, Trevor W. Robbins

Serotonin 2A receptors contribute to the regulation of risk-averse decisions

Julian Macoveanu, James B Rowe, Bettina Hornboll, Rebecca Elliott, Olaf B Paulson, Gitte M Knudsen, Hartwig R Siebner
HYPOTHESIS

Treatment with mirtazapine or ketanserin will reduce aspects of gambling-like behavior in rodents.
Cost/Benefit Decision-Making

- money
- reward
- ICSS

$1 $1000

more likely less likely

small reward LARGE reward

low effort? high effort?
Cost/Benefit Decision-Making

**Fixed Ratio**
- small reward (50-60Hz) “low effort” lever
  - FR-3

**Variable Ratio**
- LARGE reward (100Hz) “high effort” lever
  - VR-6 = 1, 3, 6, 9, 11
  - VR-8 = 1, 3, 8, 13, 15
  - VR-10 = 1, 5, 10, 15, 19
  - VR-12 = 1, 6, 12, 18, 23
  - VR-15 = 1, 8, 15, 23, 30

Current Generator

[Image of a rat in an experimental setup]
Cost/Benefit Task

% Selection

VR LEVER

FR3 LEVER

VR6

VR8

VR10

VR12

VR15

VR18
Cost/Benefit Task: Effects of Ketanserin

Ketanserin (1mg/kg)

Ketanserin (5mg/kg)

Baseline
KET
No KET

VR Lever (LARGE Reward)
FR Lever (Small Reward)
VR Lever (LARGE Reward)
FR Lever (Small Reward)
Cost/Benefit Task: **Effects of Mirtazapine**

![Graph showing the effects of Mirtazapine on % Selection in the Cost/Benefit Task.](image)

- VR Lever (LARGE Reward): Baseline vs. MIRT (5mg/kg) vs. No MIRT
- FR Lever (Small Reward): Baseline vs. MIRT (5mg/kg) vs. No MIRT

**n=6**

**Significance Levels:**
- **:** Indicates a significant difference between groups at p < 0.05.
- **:** Indicates a highly significant difference between groups at p < 0.01.
Rats will expend considerable effort to obtain the LARGE reward (i.e., VR-15; up to 30 lever presses).

Pretreatment with ketanserin or mirtazapine reduced behavioral readouts of risk-taking.

Thus, ketanserin and mirtazapine may be useful in reducing gambling-like behavior in humans that suffer from problem gambling.
ACKNOWLEDGEMENTS

Amanda L. Persons, PhD
Nathan Holtz, PhD

The Napier Lab:
Brinda Bradaric, PhD
Lihua Chen, PhD
Sandie Rokosik, PhD
Steve Graves, PhD
Stephanie Tedford, PhD
Wesley Wayman, PhD
Salvatore Grasso, BS

Financial Support:

NATIONAL CENTER FOR RESPONSIBLE GAMING
Advancing Research, Education and Awareness

National Institute on Drug Abuse
The Science of Drug Abuse & Addiction
National Institute of Neurological Disorders and Stroke

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH
dopamine receptors are lower in addiction

Cocaine

Meth

Alcohol

Heroin

Control

Addicted
Developing brain
Vulnerable brain

Humans (yrs) 8 12 18 20 24 26
birth Childhood Adolescence Adulthood

- Synaptic Overproduction
- Synaptic Pruning
- Myelination
- Gonadal hormones rise in serum