



Conceptual Framework of Harmful Gambling:

AN INTERNATIONAL COLLABORATION,
THIRD EDITION

BIOLOGICAL FACTORS

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Table of Contents

<u>1 Biological Factors</u>	3
<u>1.1 Genetic Inheritance</u>	3
<u>1.2 Neurobiology</u>	4



1 BIOLOGICAL FACTORS

Biological factors may help explain why some people and not others develop harmful gambling. These biological factors may have a genetic, heritable component, and/or be shaped by environmental factors such as childhood adversity. There is a large body of research that describes biological differences, for example in brain structure and chemistry, between people with gambling problems and healthy comparison groups. The evidence is very strong that neurobiological factors play a role in gambling and harmful gambling. As much

of this evidence is gathered at a single time point (also known as 'cross-sectional' data) it is less clear whether these differences reflect vulnerability to problem gambling, or a consequence of prolonged gambling. Genetic studies provide strong evidence that a genetic vulnerability to harmful gambling exists, but it is less clear what specific genes and neurotransmitters are involved, and how the mechanisms that affect those genes are expressed (epigenetics). In this section we discuss biological factors that contribute to harmful gambling, including genetic inheritance and neurobiology.

1.1 GENETIC INHERITANCE

Studies on families help to give some insight into the extent of genetic inheritance of harmful gambling. Indeed, harmful gambling is significantly more common in the relatives of problem gamblers. However, there is considerable variability in the extent to which this occurs, with rates ranging from 8% to 50%.¹⁻⁴ The variability among studies is partly a function of differences in how harmful gambling is defined or assessed, and whether first, second, or third degree relatives are being examined.

Regardless of the exact percentage, studies of families do not answer the more important question concerning whether the higher rate is due to genetic inheritance or environmental influences. Twin studies are the gold

standard design to disentangle these contributions, and rely on the comparison of 'concordance rates' for the illness between identical (monozygotic, or MZ) twin pairs and non-identical (dizygotic, or DZ) twin pairs. Twin studies indicate that genetic factors account for approximately 50% of the propensity to develop problem gambling^{3, 5, 6} (see Lobo⁷ for review).

Heritability estimates should be treated with caution: past studies of gambling are based mostly on male twin pairs (although heritability appears similar where female twins have been tested³), and include a substantial proportion of people that may not have a clinical problem gambling diagnosis.⁷ More generally, heritability estimates are population statistics that do not reveal the relative balance of factors within any individual, (i.e., a heritability of 50% does not

mean that in any person with a gambling problem, half their risk is genetic and half is environmental). Heritability estimates are also modified by changes to the environment (e.g., to gambling availability). Nevertheless, the estimates for problem gambling are consistent with corresponding heritability estimates for substance dependence (30 to 70%^{8, 9}) and most major psychiatric disorders.⁶ Indeed, the high degree of comorbidity among harmful gambling, substance use disorders, depression, and several other conditions is partly due to a common genetic vulnerability.^{3, 10, 11}

These estimates also leave a substantial role for environmental factors. Twin studies separating the contributions of shared environment (e.g., parental upbringing) from non-shared (i.e., unique friends or hobbies) typically reveal a strong role for non-shared environmental factors, comparable in strength to the genetic component, but only a minor role for shared environment.^{3, 5, 12} Recent work is beginning to consider how genetic and environmental factors combine to determine risk. For example, the genetic influence on gambling involvement and problem gambling was greater in people living in disadvantaged neighbourhoods.¹³

Research using molecular genetic techniques has tried to identify specific genes that are involved in developing gambling problems. Two genome-wide

association studies have been conducted to date.^{14, 15} Both were relatively small studies that did not identify any significant genes after taking into account the millions of genetic sites being tested, but exploratory associations with genes implicated in Parkinson's disease and alcohol dependence were observed.

Other studies have tested for specific gene variants that are implicated from research on the underlying neural systems, such as genes affecting dopamine transmission (see 3.4.2 Neurobiology). This 'candidate gene approach' has shown higher levels of a number of gene variants in groups with gambling problems, including dopamine D1, D2 and D3 receptors,^{7, 16-18} as well as genes involved in serotonin transmission,¹⁹ although like much of the field of candidate gene studies, failures to replicate the results have been high. In one of the first gambling studies to consider an epigenetic mechanism, levels of DNA methylation (a process in which gene expression is typically reduced, without changes to the actual DNA sequence) in the dopamine D2 receptor genes were associated with treatment seeking status and length of gambling abstinence in people with gambling problems.²⁰ Overall, it is likely that harmful gambling is affected by many genes and is also shaped in fundamental ways by the environment, and future epigenetic studies are needed.

1.2 NEUROBIOLOGY

Studies comparing groups of problem gamblers and healthy participants have investigated a range of neurocognitive and biological markers of harmful gambling. These studies indicate altered function in the brain system responsible for reward processing, risk-based decision making, and inhibitory control.²¹⁻²³

The evidence from neuropsychological studies is strong: a large number of studies have indicated behavioural markers of impulsivity and impaired decision making (see below). These studies are being conducted with increasingly large groups of pathological gamblers, where sources of diversity and relationships with clinical outcomes are beginning to be identified (e.g., Alvarez-Moya et al.;²⁴ Goudriaan et al.;²⁵ and, Kräplin et al.²⁶).

The evidence for corresponding biological markers is at an earlier stage, with some notable mixed findings (see below) and a reliance on small groups of problem gamblers that have not allowed investigation of sources of variability. Due to the types of research designs commonly used in neuropsychological research, it is unclear whether the neurobiological changes that have been described reflect pre-existing vulnerability or are the consequence of harmful gambling.

Neurocognitive studies make use of behavioural tasks that have established links to brain function, typically from research on patients with focal brain injury. People with gambling problems show risky decision making on a number of tasks linked to the ventromedial prefrontal cortex^{27, 28} (see Kovacs et al.²³ for a systematic review of the Iowa Gambling Task and gambling disorder).

Impulsivity, or the tendency towards rapid or unplanned behaviour, is a construct identified in personality research on harmful gambling (see Section 3.3.1 Personality and Temperament), which can also be examined with neurocognitive tests. People with gambling problems show clear signs of impulsive choice—for example, preferring immediate over delayed rewards on delay discounting tasks.²⁹⁻³¹ Impaired performance on response inhibition ('impulsive action') tasks like the Stop Signal Task is also observed (Chowdhury et al.,³² systematic review), along with broader deficits in executive function in more severe cases of pathological gambling.^{33, 34} Impulsivity during intense mood states ('urgency') is related to difficulties in emotional regulation, which can affect gambling behaviour. Further, people with gambling disorder showed excessive activity in the prefrontal cortex during a task that required emotional reappraisal of unpleasant images.³⁵

Functional neuroimaging techniques, primarily functional magnetic resonance imaging (fMRI), have been used to examine brain responses as people with gambling problems perform reward, decision making, and impulse control tasks in the brain scanner. These kinds of tasks activate a brain network in humans, commonly termed the 'brain reward system', which includes the ventral striatum/nucleus accumbens and medial prefrontal cortex, as well as extended circuitry like the dopaminergic midbrain, amygdala, and insula.

fMRI studies in problem gamblers have repeatedly shown changes in these regions compared to healthy control participants,³⁶⁻³⁹ although the direction of signal change (i.e., over-activity or under-activity) is not consistent.²² Similar discrepancies are observed in neuroimaging studies in substance use disorders.⁴⁰ Other studies using electroencephalography (EEG) in problem gamblers show a similar pattern of inconsistency between hyper-sensitivity and hypo-sensitivity to winning outcomes.^{41, 42}

Activity within this brain reward system may also be shaped by the structural characteristics of gambling games (see Section 2.3.1 Structural Characteristics). For example, near-misses trigger brain responses in the striatum and insula that overlap with those seen in actual wins,⁴³ and these brain responses are heightened in people with gambling problems.^{44, 45}

Neurological patients with focal brain injury to the insula failed to show a behavioural response to near-misses and showed weaker beliefs in the Gambler's Fallacy.⁴⁶ Neuroimaging studies have begun to depict how the brain reward system responds to other structural characteristics and cognitive distortions such as illusion of control and winning/losing streaks.^{47, 48}

Dopamine is a key neurotransmitter within the brain reward system. It is implicated in problem gambling by a syndrome in Parkinson's disease where problem gambling can arise as a rapid side effect of dopamine agonist medications.^{49, 50} Problem gamblers have altered levels of dopamine metabolites in plasma⁵¹ and elevated frequencies of some genetic polymorphisms that affect the dopamine system (Lobo et al.⁵²; see Section 3.4.1 Genetic Inheritance).

Positron emission tomography (PET) imaging can be used to measure dopamine transmission in the brain. In contrast to substance use disorders, in which lower levels of both dopamine receptors and dopamine release are described,⁵³ people with gambling problems appear to show no significant group difference in dopamine receptor levels,⁵⁴⁻⁵⁶ but do show increased dopamine release in response to either amphetamine challenge or a gambling task.⁵⁶⁻⁵⁹

Other neurotransmitters are also implicated. The most promising form of a pharmacotherapy for problem gambling is the opioid receptor antagonist naltrexone, a long-standing treatment for heroin and alcohol dependence. Naltrexone reduced urges to gamble relative to a placebo,⁶⁰ although some clinical trials have not replicated this effect (e.g., Kovanen et al.⁶¹ looking at the effects of 'as needed' naltrexone). A family history of alcohol use disorder was a predictor of

a beneficial response to naltrexone in clinical studies.⁶² In an animal model of risky decision making, the 'rat Gambling Task', naltrexone improved performance in a subset of animals that were deficient on the task at baseline.⁶³ However, in a PET study that imaged the opioid system in people with gambling disorder, the amount of opioid released in response to a low dose of amphetamine was found to be reduced,⁶⁴ and this is difficult to reconcile with the clinical effectiveness of naltrexone as an opioid antagonist. In summary, although some clinical trials have supported the benefits of opioid antagonists, the mechanism of action is not known.

Noradrenaline is another important neurotransmitter that plays a key role in regulating arousal. Abnormalities in noradrenergic transmission could, in principle, predispose some individuals to greater elevations in physiological arousal when gambling (e.g., heart rate, skin conductivity).⁶⁵ These peripheral forms of arousal may serve as markers for harmful gambling, but evidence of their reliability is mixed.⁶⁶⁻⁶⁸ Other work has begun to investigate the serotonin system,¹¹ which may be particularly relevant to the comorbidity with mood and anxiety disorders.⁶⁹ In addition to pharmacological treatments that are informed by these neurobiological findings, recent proof-of-principle studies have begun to examine forms of brain stimulation in gambling disorder, including transcranial magnetic stimulation⁷⁰ and direct current stimulation.⁷¹

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