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Autonomic responses and decision-making during gambling

Gene-environment interactions and translational perspectives

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Abstract
Hultman, C. 2025. Autonomic responses and decision-making during gambling. Gene-environment interactions and translational perspectives. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2140. 101 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2445-6.

This thesis investigated autonomic responses and decision-making during two gambling tasks in a population of young adults. The included papers specifically addressed: 1) autonomic responses and subjective perceptions of slot machine outcomes, with a focus on the effects of near-misses; 2) decision-making strategies in human and animal gambling tasks; and 3) differential autonomic responsivity during gambling and decision-making as a function of polymorphic variants of the dopamine D2 receptor (Taq1A and C957T), including potential influences of prior gambling exposure and sex.

The four papers were based on data from an experimental study conducted at Västmanland Hospital in Västerås, Sweden. Participants (n = 270) completed two gambling tasks—a slot machine gambling task and the Iowa Gambling Task (IGT)—while their heart rate (HR) and skin conductance responses (SCR) were simultaneously recorded. Saliva samples were collected for DNA extraction. Additionally, Paper II included comparisons with adult outbred male Lister Hooded rats (N = 72) performing the rat Gambling Task (rGT).

Findings from Paper I contribute to the existing literature on the near-miss effect in gambling, demonstrating heightened autonomic responses to these structural features, along with distinct subjective perceptions of affect, motivation, and perceived chances of winning across different near-miss subtypes. Furthermore, females exhibited stronger responses to winning outcomes compared to males.

Comparisons of decision-making strategies in the IGT and rGT in Paper II revealed that human performance was characterized by exploration and learning over time, whereas rats displayed relatively stable preferences for advantageous choices throughout the task. Procedural differences in task protocols suggest that these models are suited to examining distinct aspects of decision-making.

Papers III and IV provide preliminary evidence that polymorphic variants of the D2 dopamine receptor are associated with differential autonomic sensitivity to slot machine gambling cues and rewards, as well as anticipatory responses linked to implicit guidance during decision-making under uncertainty. These relationships were further influenced by prior gambling exposure and sex, suggesting potential differential susceptibility to gambling stimuli.

In conclusion, near-misses should be considered in gambling regulation policies aimed at harm prevention. Translational inferences from both human and animal studies require careful methodological considerations and to what degree they capture similar psychological constructs that are relevant to real-world gambling behaviors. Furthermore, potential gene-environment interactions between genetic predispositions and gambling exposure in shaping emotional responses and decision-making warrant further investigation in well-powered studies.

Keywords: Gambling, autonomic nervous system, heart rate, skin conductance, near-miss, deci-sion-making, DRD2, ANKK1

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To Louie and Erik

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Hultman, C., Vadlin, S., Rehn, M., Sescousse, G., Nilsson, K.W., Åslund, C. (2023) Autonomic responses during Gambling: the Effect of Outcome Type and Sex in a large community sample of young adults. *Journal of Gambling Studies*, *39(1):159–82.*

II. Hultman, C., Tjernström, N., Vadlin, S., Rehn, M., Nilsson, K.W., Roman, E., Åslund, C. (2022) Exploring decision-making strategies in the Iowa gambling task and rat gambling task. *Frontiers in Behavioral Neuroscience, 16: 964348.*

III. Hultman, C., Rehn, M., Sescousse, G., Nilsson, K.W., Vadlin, S., Åslund, C. Associations between *Taq1A/C957T* Polymorphic Variants and Autonomic Responsivity in a Slot Machine Task: Influences of Previous Gambling Experiences and Sex. *Submitted.*

IV. Hultman, C., Rehn, M., Nilsson, K.W., Vadlin, S., Åslund, C. Effects of *Taq1A/C957T* polymorphic variants and somatic markers on decision-making performance in the Iowa gambling task. *Submitted.*

Contents

Abbreviations

A	Adenine
ADHD	Attention-Deficit/Hyperactivity Disorder
ANKK1	Ankyrin repeat and kinase domain containing 1
ANOVA	Analysis of variance
ANS	Autonomic nervous system
aSCR	Anticipatory Skin conductance response
BPM	Beats per minute
C	Cytosine
cG×E	Candidate gene-environment interaction
CI	Confidence interval
DNA	Deoxyribonucleic acid
DRD2	Dopamine receptor D2
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	Electrocardiograms
EDA	Electrodermal activity
EGM	Electronic gambling machine
G	Guanine
GLM	General Linear Model
GWAS	Genome-wide association study
HR	Heart rate
IGT	Iowa gambling task
mRNA	Messenger ribonucleid acid
PCR	Polymerase chain reaction
PGSI	Problem Gambling Severity Index
PNS	Parasympathetic nervous system
rGT	Rat Gambling Task
RNA	Ribonucleic acid
rRNA	Ribosomal ribonucleic acid
SALVe	Survey of Adolescent Life in Västmanland
SCR	Skin conductance response
SD	Standard deviation
SMH	Somatic marker hypothesis
SNP	Single nucleotide polymorphism
SNS	Sympathetic nervous system

T	Thymine
tRNA	Transfer ribonucleic acid
VMPFC	Ventromedial prefrontal cortex
µS	Microsiemens
ηp^2	Partial Eta Squared

Introduction

In 2013, gambling disorder was classified as the first formal 'behavioral addiction' alongside substance-related and addictive disorders in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* (American Psychiatric Association, 2013). This landmark reclassification has had significant implications for research and clinical practice and has led to extensive research aimed at disentangling the complexities of individual vulnerabilities to gambling problems (Rash et al., 2016). Neuroscientific research on gambling has gained increasing attention in recent years, with studies exploring the underlying processes influencing gambling decisions.

There are many similarities in the clinical, epidemiological, and neurobiological profile of gambling disorder and substance-use disorders (Balodis & Potenza, 2020; Clark, 2014; Grant & Chamberlain, 2020). As the first recognized non-substance-based behavioral addiction, neuroscience research of problem gambling provides insights into addictive behaviors without the confounding neurotoxic effects of drug-use (Balodis & Potenza, 2020). Despite rigorous work in this field, knowledge of the mechanisms underlying problematic gambling behavior remains incomplete. While increased involvement in gambling may lead to loss of control through reinforcement learning and conditioning effects, this does not fully explain why some individuals develop clinically significant gambling problems while, for most, it is a harmless pastime. It is therefore crucial to uncover what makes certain individuals more susceptible to problem gambling than others (Griffiths & Delfabbro, 2001).

Gambling takes many forms, including lotteries, wagering, sports betting, electronic gambling machines (EGMs), online casino gambling, roulette, poker, and dice. The recent *Lancet Public Health Commission* on gambling emphasized the risks associated with the increased digitalization and availability of online gambling products, particularly casino games and slot machines, which are known to pose a high risk of harm (Wardle et al., 2024). Since the boundaries between gaming and gambling are also becoming increasingly blurred as gambling features are incorporated into online games, children and adolescents are exposed to gambling-like activities to a greater extent (Wardle, 2021). Additionally, there is a rising prevalence of gambling and problem gambling among younger populations (particularly males) in Sweden (Selling, 2024). Exposure to addictive commodities often begins in

adolescence and, in some susceptible individuals, may evolve into addictions during emerging adulthood. Identifying underlying mechanisms for this progression is therefore vital to understanding addiction trajectories. A public health approach to gambling should consider the complex interplay between individual vulnerabilities and certain characteristics of gambling products to better understand and minimize gambling-related harm (Murch & Clark, 2016; Myles et al., 2019).

How can we understand the mechanisms that drive excessive gambling engagement and potential risk of developing problematic gambling behavior? Certainly, this is a challenging question that has led to the development of theoretical models accounting for multiple biopsychosocial, physiological, personality, learning, and environmental factors contributing to gambling disorder (Blaszczynski & Nower, 2002; Nower et al., 2022; Sharpe, 2002). Experimental research approaches provide a means to study these issues using objective measures of neurophysiological and behavioral responses under carefully controlled conditions. Neuroscience research of gambling is characterized by a vast heterogeneity of methods and approaches, including tasks measuring various cognitive constructs and behavioral outcomes, neural and psychophysiological activity measures, and studies involving both clinical and control samples. As with other psychiatric disorders, translational research—including animal studies—has provided valuable insights into the neurobiological underpinnings of gambling disorder (P. J. Cocker & C. A. Winstanley, 2015; Paul J. Cocker & Catharine A. Winstanley, 2015; Nautiyal et al., 2017; Potenza, 2009; Winstanley et al., 2016).

A few key findings from decades of gambling research asserts that:

1. Episodes of gambling are associated with changes in the activation of the autonomic nervous system (ANS) (Blaszczynski & Nower, 2002; Nower et al., 2022; Sharpe, 2002).
2. Individuals with gambling disorders exhibit impairments in inhibitory control, working memory, and decision-making (Grant et al., 2016; Hodgins et al., 2011).
3. Neural circuits involved in signaling and predicting rewards play a central role in the neurobiology of reinforcement learning during gambling (Clark et al., 2019).
4. From a public health perspective, the interplay between individual differences and the structural features of gambling products is crucial to understanding gambling-related harm (Murch & Clark, 2016; Myles et al., 2019; Wardle et al., 2024).

Moreover, genetic and family history findings suggest shared genetic factors between substance and behavioral addictions (King et al., 2017; Leeman & Potenza, 2013). The heritability in pathological gambling is estimated to 50-60 % (Lobo & Kennedy, 2009; Slutske et al., 2012), and genetic contributions increasing with problem gambling severity (Shah et al., 2005). Slutske et al. (2012) also found overlapping genetic risk factors for gambling disorder and alcohol-abuse disorders in both men and women. Research has also shown that 20% of the relatives of individuals with gambling disorder also suffer from the condition (Hodgins et al., 2011).

How might variations in certain genetic markers interact with certain gambling features in evoking differential emotional responses and guiding gambling decision-making? This thesis will focus on aspects related to both individual sensitivities to gambling stimuli and decision-making, as well as the influence of certain structural gambling characteristics, among young adults with moderate to no gambling experience. It will also shed light on translational aspects and contributions of animal models in gambling research.

Hopefully this thesis will contribute with increased understanding of the psychobiological aspects and individual susceptibility characteristics during gambling.

Problem gambling – definitions and prevalence

Gambling can be defined as wagering money or something of material value on an event with an uncertain outcome, in the hope of winning additional money and/or material goods (Williams, 2017). For most individuals, gambling is an enjoyable and harmless activity. However, for some, it can become compulsive and maladaptive, leading to severe negative consequences. The clinical diagnosis for such cases is gambling disorder, as described in the DSM-5 (American Psychiatric Association, 2013) and the 11th edition of the International Statistical Classification of Diseases and Related Health Problems (World Health Organization, 2022). However, gambling involvement exists on a continuum, and individuals may experience negative consequences without meeting the clinical criteria for Gambling Disorder. Therefore, subclinical criteria are often used in population estimates of problematic gambling, commonly referred to as Problem Gambling. Problem gambling causes considerable harm to individuals and imposes substantial costs for society, making it a public health concern. A recent review and meta-analysis estimated that, globally, 46.2 % of adults and 17.9 % of adolescents had engaged in gambling within the past year (Tran et al., 2024). Among adults, 8.7 % were classified as at-risk gamblers, while 1.41 % met the criteria for problematic

gambling. In adolescents, rates of problematic gambling were highest among those who participated in online or slot gambling (26.4 %) (Tran et al., 2024). In Sweden, the societal costs of problem gambling—including direct, indirect, and intangible costs—have been estimated at 1.42 billion euros (Hofmarcher et al., 2020). Recent estimates from the Swedish population indicate that 4.3 % experienced gambling related problems to some degree, and 1.3 % were classified as problem gamblers (Public Health Agency of Sweden, 2023).

Sex differences in gambling behavior

Gambling and problem gambling has historically been, and continues to be, more prevalent among men than women (Calado & Griffiths, 2016). Recent estimates shows that among those who experience problem gambling in Sweden, 1.3 % are females and 3.0 % are males (Public Health Agency of Sweden, 2023). Previous research suggests several differences between men and women regarding gambling preferences, the progression of gambling problems, and associated comorbidities. Studies indicate that women tend to begin gambling later in life than men but experience a faster progression to disordered gambling (Grant et al., 2012; Syvertsen et al., 2023; Zakiniaeiz et al., 2017). Additionally, general sex differences in preferred gambling forms among problem gamblers have been observed. Men are more likely to engage in strategic forms of gambling, such as sports betting or poker, while women tend to prefer non-strategic, chance-based games like slot machines (Håkansson & Widinghoff, 2020; Merkouris et al., 2016; Stark et al., 2012). Notably, women who engage in electronic gaming machines (EGMs) have been found to progress more rapidly toward high-risk gambling than men (Syvertsen et al., 2023). Furthermore, women with gambling disorder exhibit higher rates of comorbid psychological distress, including depression and anxiety (Grant et al., 2012; Merkouris et al., 2016; Sundqvist & Rosendahl, 2019). It has been hypothesized that these behavioral patterns reflect sex differences in gambling motivations, particularly in relation to mood regulation (Marchica et al., 2020; Sacco et al., 2011; Syvertsen et al., 2023).

Models of problem gambling

The two most influential models developed to account for the multiple biological, psychological, personality, learning, and environmental factors contributing to the development of gambling disorder are the *Pathways Model* (Blaszczynski & Nower, 2002) and the *Biopsychosocial Model* (Sharpe, 2002). The pathways model was developed to explain the heterogeneity among individuals with gambling problems. It identifies three distinct subtypes of problem gamblers: *behaviorally conditioned, emotionally vulnerable,* and *antisocial/biologically vulnerable.* These groups differ in terms of the

etiological factors that contribute to problem gambling, including premorbid states, histories of poor coping and problem-solving skills, adverse family backgrounds, developmental life events, psychosocial functioning, and trait impulsivity profiles (Blaszczynski & Nower, 2002; Nower et al., 2022). Similarly, the Biopsychosocial Model outlines the biological, psychological, and social factors hypothesized to contribute to problematic gambling behavior. This model provides a comprehensive framework that acknowledges gambling as a multifaceted behavior shaped by individual and contextual factors, including the structural characteristics of gambling products (Sharpe, 2002). While the Pathways Model takes a categorical approach by focusing on individual differences, the Biopsychosocial Model is process-oriented, emphasizing reinforcement learning mechanisms in gambling behavior.

A common element in both models is the ability of gambling to engage the autonomic nervous system (ANS). Gambling can act as a form of positive reinforcement (increasing excitement) or negative reinforcement (relieving anxiety and stress) through physiological arousal, which interacts with individual biopsychosocial and etiological factors, shaping different pathways to problem gambling (Blaszczynski & Nower, 2002; Nower et al., 2022; Sharpe, 2002). Both models recognize the influence of multiple risk factors in the development of problem gambling, including biological predispositions and physiological arousal.

Autonomic nervous system responses

Central biological systems play a crucial role in psychophysiological responses associated with stress, arousal, and decision-making, enabling individuals to adapt to different situations. The ANS is a neural network that regulates reactivity in organ systems through neural circuits activated by emotional stimuli, making it fundamental to emotional responses. The primary functions of the ANS include maintaining homeostasis, activating bodily systems to mobilize resources for action, and deactivating these systems once action is no longer required (Levenson, 2014).

The ANS arises from preganglionic axons distributed across the spinal cord and brainstem, with most organs receiving dual innervation from both the *sympathetic nervous system (SNS)* and the *parasympathetic nervous system (PNS)*. These two branches often exert opposing effects, mediated by the release of different neurotransmitters. The main purpose of the SNS is to prepare the body for action by stimulating the release of norepinephrine. Preganglionic neurons originating in the spinal cord synapse onto postganglionic neurons in the periphery, which then project sympathetic signals to target tissues. The SNS activation produces autonomic and somatic responses such as pupil dilation, increased heart rate, electrodermal activity, and heightened respiration

(Ishikawa, 2023; Levenson, 2014). Emotionally or motivationally significant stimuli elicit projections from the sensory cortex and thalamus or memory-related hippocampal structures to the amygdala, which then engages additional brain regions involved in orienting responses, perceptual processing, and defensive or appetitive reflexes (Lang, 2014). In contrast, the PNS is primarily responsible for 'rest-and-digest' activities and exerts inhibitory effects through the release of acetylcholine, which decreases heart rate and skin conductance. However, ANS activity is not exclusively dominated by one branch, as co-activation of the SNS and PNS is often observed in response to emotional stimuli (Ishikawa, 2023; Levenson, 2014).

Measuring ANS activity in emotion research

Cardiovascular activity and *electrodermal activity (EDA)* are widely used psychophysiological measures due to their sensitivity to neurobehavioral processes (Berntson et al., 2007; Bradley & Lang, 2007; Dawson et al., 2007; Ishikawa, 2023). EDA is based on the phenomenon that the skin briefly becomes a better conductor of electricity when an individual is presented with an emotional stimulus. Research has shown that sweat gland activity at palmar and plantar sites is more closely related to emotional arousal than to thermoregulatory processes (Boucsein, 2012). The eccrine sweat glands, which are entirely controlled by the SNS, make EDA a direct and sensitive measure of sympathetic activation (Levenson, 2014). The degree of SNS activation determines sweat secretion, which in turn affects skin conductance. Increased activation leads to more sweat rising in the ducts, allowing electrical signals to pass through the stratum corneum, causing changes in *skin conductance response (SCR).* The amplitude of SCR is linearly related to the number of activated sweat glands (Boucsein, 2012). Electrodermal measurements are categorized as skin conductance level (tonic activity) and SCR (phasic activity). High sympathetic arousal corresponds to greater SCR amplitudes, with phasic SCR activity typically assessed within a predefined time window following an emotional stimulus presentation to evaluate arousal and attentional engagement to a specific event (Boucsein, 2012; Ishikawa, 2023).

The SNS and PSNS branches both innervate and exert control over the *cardiovascular system*, leading to complex interactions that serve as broader indices of autonomic regulation (Ishikawa, 2023; Levenson, 2014). The cardiovascular response to stressors triggers elevations in glucocorticoids and catecholamines, influencing adaptive physiological responses such as increased cardiac output, respiration, and blood flow redirection to the brain and musculoskeletal system (Berntson et al., 2007). Cardiovascular responses are commonly assessed using *electrocardiography (ECG)*, which records electrical potentials generated by cardiac muscle activity, producing the characteristic PQRST waveform. Several quantitative measures can be derived from ECG

recordings, including heart period, defined as the time interval (in milliseconds) between R-spikes, and *heart rate (HR)*, expressed in beats per minute (BPM) (Berntson et al., 2007).

Emotionally salient stimuli often elicit biphasic HR deceleration and acceleration responses. It typically displays a relatively prolonged cardiac deceleration immediately following the presentation of a novel stimuli. The early cardiac deceleration has been interpreted as an orienting response, a reflexive reaction to environmental changes that enhances attention toward appetitive or aversive stimuli. This response is thought to be mediated by fundamental motivational systems that evolved to facilitate survival by directing attention and mobilizing resources for appropriate behavioral responses (Bradley, 2009). The subsequent HR acceleration component primarily reflects arousal as a preparatory response to appetitive or defensive stimuli (Bradley, Codispoti, Cuthbert, et al., 2001).

Extensive psychophysiological research has sought to unravel the specificity of ANS patterns in predicting distinct emotional states (Lang, 2014). Studies of emotional picture processing have shown that aversive stimuli elicit strong HR deceleration and high SCR amplitudes, indicating coactivation of the SNS and PSN branches in situations requiring attention and action preparation. In contrast, pleasant stimuli evoke a smaller HR deceleration, followed by a more pronounced HR acceleration. Importantly, SCR responses, which are governed by SNS activity, do not differentiate between positive and negative stimuli but instead reflect overall arousal intensity, regardless of valence (Bradley, 2009; Bradley, Codispoti, Cuthbert, et al., 2001; Codispoti et al., 2001; Lang, 2014; Lang et al., 1993).

Sex differences in physiological responses to emotional stimuli have been documented in several studies. Research using electrophysiological measures suggests that women are more reactive to unpleasant or aversive visual stimuli, whereas men exhibit greater physiological responses to highly arousing visual stimuli (Bianchin & Angrilli, 2012; Bradley, Codispoti, Sabatinelli, et al., 2001; Kemp et al., 2004; Sarlo et al., 2005). In terms of physiological measures, women show greater HR deceleration and stronger startle reflexes in response to negative emotional images, while men display heightened HR acceleration and SCRs when viewing highly arousing content, especially of sexual nature (Bradley, Codispoti, Sabatinelli, et al., 2001). Greater HR deceleration to pleasant visual stimuli in females compared to males have also been reported (Bianchin & Angrilli, 2012). Neuroimaging studies show that men and women recruit different neurocircuitry depending on the emotional context, indicating marked sex differences in terms of perceptional performance, reactivity, emotion regulation and learning from emotional

experiences. This suggest that, men and women may apply different strategies during emotional processing in different contexts (Whittle et al., 2011).

ANS activity during gambling

Measures of ANS responses are widely used to examine emotional and cognitive processes during gambling and decision-making tasks. Based on early theories implicating arousal in the development of problem gambling (Blaszczynski & Nower, 2002; Brown, 1986; Sharpe, 2002), past research has utilized tonic measures to assess general arousal, with levels of ANS activity averaged across gambling sessions. The role of autonomic arousal during gambling is supported by early research reporting increased physiological arousal during gambling in problem gamblers compared to controls (Krueger et al., 2005; Ladouceur et al., 2003; Meyer et al., 2000; Meyer et al., 2004). Additionally, several studies have captured reliable increases in physiological arousal following winning events in various gambling situations (Coventry & Constable, 1999; Coventry & Hudson, 2001; Diskin & Hodgins, 2003; Moodie & Finnigan, 2005; Sharpe, 2004; Wilkes et al., 2010; Wulfert et al., 2008; Wulfert et al., 2005). These responses were manifested through tonic measures of heart rate, cortisol levels, and skin conductance levels. More recent research employing tonic cardiovascular measures of arousal (blood pressure) and subjective ratings of arousal, has also reported increased stimulatory effects following an online gambling challenge, with high recreational gamblers showing greater effects compared to non-gamblers (Miller & Gordh, 2021). Studies employing tonic cardiovascular measures of arousal have demonstrated similar arousing effects during gambling in both men and women (Coventry & Hudson, 2001; Miller & Söderpalm Gordh, 2022; Wulfert et al., 2008).

Since early research on tonic arousal during gambling, there has been growing interest in the emotional processing of gambling-specific cues. Consequently, an emerging body of research has employed phasic ANS measures to associate distinct physiological responses with specific gambling stimuli. Measures of SCR and HR are commonly used to capture distinct ANS responses during gambling, such as anticipatory responses or reactions to the reveal of gambling outcomes (Dixon et al., 2010; Lole et al., 2014; Lole et al., 2012). These physiological responses are also believed to play a role in cognitive processes such as working memory, attention, and decision making. They serve as indicators of both emotional response to, and anticipation of, an uncertain decision (Boucsein, 2012). Neural studies have reported greater emotional sensitivity to full-misses in females and greater sensitivity to reward in males (Dhingra et al., 2021; Garrido-Chaves et al., 2021; Grose-Fifer et al., 2014). However, possible sex differences in ANS responses during gambling remains understudied.

Genetics

Genetic information is encoded in a macromolecule called deoxyribonucleic acid (DNA), which is found in the nucleus of every cell in the human body. The entire complex of DNA is tightly bound to proteins called histones, which help form highly structured and condensed chromosomes. Upon fertilization, each parent contributes 23 chromosomes, resulting in a total of 46 chromosomes in human cells. As a result, our DNA contains duplicate copies of the same genes—one inherited from the mother and one from the father. The complete set of genetic material within an organism is known as the genome (Ferrier, 2014; McGuffin, 2002). DNA consists of two linked strands, each composed of a long chain of nucleotides. Each nucleotide contains one of four nitrogenous bases: adenine (A), guanine (G), cytosine (C), or thymine (T). These bases are attached to a sugar molecule (deoxyribose) and a phosphate group, which together form the backbone of the DNA, creating its characteristic double-helix structure. The bases on the two strands are connected by hydrogen bonds, forming complementary base pairs—adenine always pairs with thymine (A-T), and cytosine always pairs with guanine (C-G).

The central dogma of molecular genetics describes the flow of genetic information from DNA to ribonucleic acid (RNA) through a process called *transcription*, and from RNA to polypeptides (proteins) through a process called *translation* (Ferrier, 2014; McGuffin, 2002). During transcription, a strand of DNA serves as a template for the synthesis of RNA, which acts as a "working copy" of the genetic code. Genes encode several different types of RNA involved in protein synthesis: messenger RNA (mRNA), which contains the instructions for protein production; ribosomal RNA (rRNA), which forms ribosomes; and transfer RNA (tRNA), which facilitates the translation of mRNA into proteins. Genes that encode proteins must first be transcribed into mRNA, which carries genetic information from DNA to the ribosomes for protein synthesis. This process is initiated by transcription factors, proteins that bind to the promoter region of the gene to start transcription. The entire gene sequence is transcribed until RNA polymerase reaches a transcription termination site. The resulting mRNA then exits the nucleus and enters the cytoplasm, where it binds to ribosomes (Ferrier, 2014; McGuffin, 2002).

Protein synthesis, known as translation, occurs when the nucleotide sequence of mRNA is converted into a sequence of amino acids, forming a polypeptide chain (protein). A group of three nucleotides, called a codon, codes for a specific amino acid. Another RNA molecule, tRNA, is responsible for reading the codons on the mRNA and matching them with the corresponding amino acids. This ensures that the genetic information from DNA is accurately translated into a functional protein (Ferrier, 2014; McGuffin, 2002).

Only about 2% of the human genome is believed to encode proteins. DNA also contains other functional elements, including sequences that regulate transcription and replication, as well as sequences that can activate or inactivate genes. These functional regions are interspersed with long stretches of DNA that appear to have no known function. Although homologous chromosomes carry the same genes, they are not always identical. A DNA sequence located at a specific position on a chromosome is called a locus. If an individual has identical sequences at a given locus on both paired chromosomes, they are homozygous at that locus. Conversely, if an individual carries two different alleles at a given locus, they are heterozygous. One of the most common genetic variations involves single nucleotide differences at specific loci, known as single nucleotide polymorphisms (SNPs). If more than 1% of the population carries a different nucleotide at a particular locus, the variation is classified as an SNP and thereby show allelic variation. While many allelic variations have little or no impact on gene function, some result in observable traits, known as phenotypic variations (McGuffin, 2002).

The role of dopamine in gambling

The most extensively studied neural system related to problem gambling, is the dopamine system (Murch & Clark, 2016). However, the role of dopamine and reward processing in problem gambling is an ongoing debate. Some studies have shown increased striatal dopamine synthesis in pathological gamblers compared with healthy control subjects (van Holst et al., 2018). However, several PET studies reported no differences in baseline dopamine D2/D3 receptor binding between problem gamblers and controls (Boileau et al., 2013; Clark, Stokes, et al., 2012; Joutsa et al., 2012), although reduced dopamine receptor levels were correlated with mood-related impulsivity (Clark, Stokes, et al., 2012) and gambling severity (Boileau et al., 2013; Joutsa et al., 2012).

Function of the dopaminergic system has been associated with reward prediction during anticipation and response, learning mechanisms and motivational aspects of gambling (Balodis & Potenza, 2020; Clark et al., 2019; Grant et al., 2016; Linnet, 2020). Dopamine neurons are influenced by previous experiences of reward probabilities and show differential phasic responses between predicted and unpredicted rewards, which informs future reward predictions. This type of outcome evaluation is referred to as ‘reward prediction error’ and believed to be associated with the reinforcement learning of reward properties of a certain stimuli (Mikhael et al., 2022; Schultz, 1998, 2002, 2013; Starkweather et al., 2018). The defining feature of games of chance is that the reward is uncertain, and always comes as a surprise. Unpredictable monetary rewards are a potent form of positive reinforcement, and influential theories suggest that the addictive property of gambling lies in the anticipation and

expectancy coding of rewards, rather than responsivity to the actual reward delivery (Clark et al., 2019; Linnet, 2020; Zack et al., 2020).

Theories on incentive-sensitization suggests that repeated exposure promotes perceptual escalation of incentive salience of cues associated with the addictive product (Berridge & Robinson, 2016; Clark et al., 2019; Linnet, 2014, 2020; Robinson & Berridge, 1993; Robinson & Berridge, 2000, 2008; Sescousse et al., 2013; Zack et al., 2020). It is suggested that the repeated exposure to reward uncertainty in gambling situations may render the dopamine system sensitized and hyperreactive to cues associated with uncertain reward. This may lead to an escalation of reinforcement learning and motivation to gamble and evoke illusory predictions of future rewards, through powerful expectancy effects (Clark et al., 2019; Linnet, 2020; Zack et al., 2020). Several studies posits that problem gamblers may be hyperreactive to reward anticipation and gambling specific cues, which leads to increased incentive value and motivation to gamble. This may explain the process of increased attention and preoccupation in gambling (Clark et al., 2019; Linnet, 2020; Sescousse et al., 2013; Zack et al., 2020). Accordingly, studies have reported increased neural responses in striatal and cortical regions during anticipation of uncertain rewards in problem gamblers (Knutson, Adams, et al., 2001; Knutson, Fong, et al., 2001; Knutson et al., 2003; Knutson & Greer, 2008; Linnet et al., 2012; van Holst et al., 2012). However, contradicting results have also been reported, showing blunted responses during reward anticipation in prefrontal and striatal regions among pathological gamblers (Balodis et al., 2012; Choi et al., 2012; Luijten et al., 2017). These inconsistencies may partly stem from the heterogeneity in terms of the tasks included (van Holst et al., 2017). Furthermore, Linnet et al. (2011b) reported that striatal dopamine release, indicated by D2/3 receptor binding potentials, was associated with poor reward-related decision-making under uncertainty among pathological gamblers but better performance in healthy controls.

Polymorphic variants of the dopamine D2 receptor

Dopaminergic alterations, particularly in dopamine transporters and D2/D3/D4 receptors, are believed to play a crucial role in the development and maintenance of gambling disorder (Pettorruso et al., 2020). The dopamine D2 receptor system serves as a key regulator of dopamine transmission and is involved in shaping neural structures that mediate dopamine-related behaviors (Gallo, 2019; Pettorruso et al., 2020). One of the most widely studied SNP in addiction is the *Taq1A* (rs1800497) (Blum et al., 1995; Foll et al., 2009; Gorwood et al., 2012). The *Taq1A* genotype is located within the protein-coding region of exon 8 in the *ankyrin repeat and kinase domain containing 1 (ANKK1)* gene on chromosome 11 (Neville et al., 2004). This SNP results in an amino acid substitution, producing either the minor A1 allele or the A2

allele (rs1800497 - SNP - NCBI (nih.gov)). The minor A1 allele has been associated with reduced dopamine D2 receptor expression in striatal regions (Gluskin & Mickey, 2016; Hirvonen et al., 2009; Jönsson et al., 1999; Noble et al., 1991; Pohjalainen et al., 1998; Ritchie & Noble, 2003; Thompson et al., 1997). Early studies linked the *Taq1A* A1 allele to pathological gambling, with one study reporting its presence in 51% of pathological gamblers compared to 26% of controls (Comings et al., 1996). However, several association studies of pathological gambling and various candidate genes related to dopamine transmission have yielded mixed results (Comings et al., 2001; Gray & MacKillop, 2014; Lim et al., 2012; Lobo et al., 2015; Lobo et al., 2010).

A potential linkage effect has been suggested between the *Taq1A* genotype and other polymorphisms that influence dopaminergic signalling, such as the synonymous polymorphism *C957T* (rs6277) located in exon 7 of the *DRD2* gene (Doehring et al., 2009; Hirvonen et al., 2009; Klaus et al., 2021; Ritchie & Noble, 2003). The functionality of the allelic variants of this genotype remains debated. While Duan et al. (2003) reported reduced mRNA stability and lower dopamine D2 receptor synthesis in T carriers, Hirvonen et al. (2004, 2005) conversely found reduced striatal D2 receptor availability in C carriers. In a later study, Hirvonen et al. 2009 found that the C variant was associated with higher extrastriatal DRD2 availability in the cortex and the thalamus. These findings suggest that the *C957T* genotype may have differential functional effects in the cortex and the striatum. Despite these discrepancies, *Taq1A* and *C957T* serve as functional markers for the D2 dopamine receptor.

Few studies have explored gambling behaviors in relation to these genotypes. One study found increased reward related impulsivity during acute stress among *C957T* C carriers (White et al., 2009). Another study reported better memory for rewarding stimuli during an incentive delay task in both *Taq1A* A1 carriers and *C957T* C homozygotes (Richter et al., 2017). Moreover, pathological gamblers carrying the *Taq1A* A1 genotype displayed poorer performance in tasks measuring cognitive flexibility (Fagundo et al., 2014).

Additionally, some evidence reports sex differences in D2 receptor expression, although findings vary across brain regions and measurement methods. Studies have found higher baseline dopamine D2 receptor availability in females than in males across various brain regions (Karalija et al., 2021; Malén et al., 2022). Preclinical studies have also suggested a role for estrogen in modulating dopamine release and increasing the expression of dopaminergic DRD2 genes. However, the extent to which sex-related factors modulate human reward sensitivity remains inconclusive [see Diekhof (2018) for a review].

Structural characteristics in gambling

Most, if not all, forms of gambling comprise of distinct cognitive elements, including a decision-making phase (e.g., placing a bet or choosing a number/symbol in the game), an anticipation phase before the outcome is revealed, and finally, "the big reveal" of the result (Griffiths & Auer, 2013; Murch & Clark, 2016; Zack et al., 2020). Despite these shared characteristics, different forms of gambling vary significantly in terms of the probability and magnitude of wins, the level of player involvement and skill required, the interval between the stake and outcome, and the frequency of reinforcement. These structural characteristics influence the motivation to continue gambling and, consequently, the addictive potential of different gambling types (Griffiths & Delfabbro, 2001). To date, most experimental gambling studies have focused on the appetitive processing of reward outcomes. However, there is growing recognition of other cognitive constructs in reward-based decision-making, such as negative valence processing and the perception of "nearly winning" (Balodis & Potenza, 2020). From a psychological perspective, frequent gamblers are particularly prone to erroneous beliefs and cognitive distortions, such as impaired processing of randomness, the illusion of control, and loss-chasing. These distortions may lead them to overestimate their chances of winning, reinforcing continued gambling behavior. Research suggests that certain features of gambling games can manipulate players' perceptions of winning and facilitate development of irrational cognitions (Clark, 2010). EGMs, such as slot machines, are considered among the most addictive forms of gambling (Binde et al., 2017; Markham et al., 2015) due to their rapid, intensive, repetitive structure and intermittent random reward delivery, which maximizes outcome uncertainty. Slot machines incorporate several reinforcing features, including large early wins, bonus rounds, and near-miss outcomes, which encourage players to persist despite extended periods without rewards. This reinforcement pattern often results in prolonged gambling sessions (Delfabbro et al., 2023).

Near-misses

Certain gambling features that contribute to the reinforcement and facilitation of excessive gambling have received increased attention in gambling research. Among the most studied structural characteristics—common across various forms of gambling—are near-misses (Barton et al., 2017). These are defined as non-winning outcomes that come close to a win but ultimately fall short (Reid, 1986). The impact and addictive potential of near-misses are of particular interest since their occurrence can be manipulated and engineered modern gambling products' (Harrigan, 2008). Early theories suggest that near-misses encourage continued play and contribute to the addictive potential of gambling by creating a false sense of being close to a win, even though the actual

outcome is objectively equal to a regular loss. This notion is supported by studies demonstrating that moderate frequencies of near-misses lead to prolonged slot machine gambling (Cote et al., 2003; Kassinove & Schare, 2001; MacLin et al., 2007).

Research has found that near-misses are associated with heightened psychophysiological responses compared to full-misses. They are generally experienced as frustrating yet simultaneously increase the motivation to continue gambling (Clark et al., 2009; Qi et al., 2011; Billieux et al., 2012; Clark et al., 2012; Clark et al., 2013; Stange et al., 2016; Barton et al., 2017; Stange et al., 2017). Some researchers suggest that near-misses encourage persistent play by fostering a deceptive sense of control over the game (Billieux et al., 2012; Clark, Crooks, et al., 2012; Clark et al., 2009; Qi et al., 2011). Neuroimaging studies have shown that near-misses activate the striatal and insular brain regions in ways comparable to actual wins (Chase & Clark, 2010; Clark et al., 2009), with greater activations in these regions among problem gamblers (Chase & Clark, 2010; Dymond et al., 2014; Sescousse et al., 2016). Additionally, Ulrich et al. (2016) found that heightened SCRs to near-misses were linked to greater problem gambling severity. Other research shows that frequent near-misses are associated with persistent play, particularly in individuals with higher levels of impulsivity (Broussard et al., 2024).

While most studies report significant increases in ANS responses following near-misses, findings remain inconsistent regarding how near-misses compare to wins and full-misses, as well as how different physiological measures (e.g., SCRs vs. HR) capture these effects (Clark et al., 2012; Clark et al., 2013; Sharman et al., 2015, Dixon et al., 2011). One study found no difference in ANS responses between near-misses and full-misses (Lole et al., 2012). A systematic review of near-miss effects in slot machine gambling identified consistent patterns of increased desire to continue gambling and an overestimation of one's chances of winning following near-misses. However, the effects of near-misses on actual gambling behavior (e.g., betting patterns) and subjective valence ratings have yielded mixed results (Barton et al., 2017). Some subsequent studies failed to detect any subjective or behavioral effects of near-misses (Detez et al., 2019; Pisklak et al., 2020).

The effects of near-misses may also depend on whether they occur just before or after the winning position. Research using computerized slot machine tasks shows that near-miss outcomes where the reel stops one position before a win ('near-misses before') are associated with increased motivation to continue playing, whereas near-misses where the reel stops one position after a win ('near-misses after') tend to evoke frustration and decreased motivation (Clark et al., 2013; Sharman et al., 2015), along with large SCRs compared to 'near-misses before' and full-misses (Clark et al., 2013). One study also

reported lower ratings of perceived luck and decreased betting amounts following 'near-misses after', in a 'wheel of fortune' game (Wu et al., 2017). Additionally, neurophysiological studies have documented distinct event-related potential patterns in response to near-misses occurring before versus after the payline (Dores et al., 2020).

The findings outlined above highlight the complexity and variability of emotional responses in slot machine gambling, particularly concerning near-misses. However, inconsistencies in research findings raise concerns about the reproducibility of these effects. Addressing these inconsistencies is crucial, especially considering the ongoing replication crisis in psychology and neuroscience (Klein et al., 2018; Poldrack, 2019; Stanley et al., 2018).

Decision-making in gambling

Impairments in decision-making processes that lead to risky or unwise choices have been associated with substance use disorders and behavioral addictions (Bickel et al., 2018; Koffarnus & Kaplan, 2018). Individuals with gambling disorder often exhibit deficits in motor inhibition, working memory, planning, cognitive flexibility, and decision-making (Hodgins et al., 2011). Gambling can be considered an optimal example of a risky decision-making. During gambling, individuals must navigate risk-reward trade-offs, like many real-life decisions with elements of uncertainty and ambiguity. As a result, gambling games provide a valuable paradigm for neuroscience research on decision-making (Clark, Averbeck, et al., 2013; Winstanley et al., 2016). Decision-making in gambling can involve different levels of uncertainty—where probabilities are either explicitly known (decision-making under risk) or unknown (decision-making under ambiguity) (Brand et al., 2007; Dunn et al., 2006; Guillaume et al., 2009; Maia & McClelland, 2004). One of the most widely used and ecologically valid measures of decision-making under uncertainty, particularly in addiction and gambling disorder research, is the Iowa Gambling Task (IGT) (Bechara et al., 1994; Brevers et al., 2013; Linnet, 2013).

IOWA Gambling Task (IGT)

The IGT is a well-established experimental paradigm designed to simulate real-life decision-making scenarios involving varying degrees of risk and reward. It was originally developed to evaluate decision-making impairments in patients with lesions in the ventromedial prefrontal cortex (VMPFC). These patients exhibit no apparent deficits in working memory, attention, or cognition, but show significant impairments in decision making (Bechara et al.,

1994; Bechara et al., 1999; Bechara et al., 1997; Bechara et al., 2000; Bechara et al., 1996).

During the task, participants select cards from four different decks, each containing monetary rewards and occasional losses. The decks differ in terms of their long-term gain probability. Two of the decks (A and B) are disadvantageous, offering large immediate rewards but are offset by large occasional losses, ultimately leading to a net monetary loss over time. The other two decks (C and D) are advantageous, providing smaller frequent gains but even smaller losses, resulting in an overall monetary profit. The probabilities and risks associated with each option are unknown to the participants (Bechara et al., 1994). Therefore, they must progressively learn to favor long-term gains over short-term rewards based on the reward and loss feedback obtained throughout the task (Brand et al., 2007). Bechara et al. (1997) introduced self-reports to assess participants' awareness of the appropriate strategy in the task. Their findings suggested that implicit learning occurs before participants consciously recognize the best strategy. Some participants performed well without fully understanding the task at a conscious level, while poor performers continued to choose disadvantageously, sometimes even after becoming aware of the correct strategy (Bechara et al., 1997).

Theories suggest that decisions are guided by emotions and "gut feelings" during the early trials (decisions under ambiguity), and as the task progresses, decisions become more explicit and deliberate as participants gain conscious awareness of the risks and rewards (decisions under risk) (Brand et al., 2006; Brand et al., 2007; Dunn et al., 2006; Guillaume et al., 2009; Maia & McClelland, 2004). However, these early assumptions have been revised, with research indicating that implicit and explicit processes do not operate independently during the task. Instead, IGT performance appears to be more complex, involving an interaction between emotional guidance and cognitive resources, with considerable variability between individuals (Buelow & Blaine, 2015; Wood & Bechara, 2014).

Several studies report that individuals suffering from gambling disorder shows impairments in decision-making on the IGT compared to healthy controls (Brevers et al., 2012; Cavedini et al., 2002; Ciccarelli et al., 2016; Goudriaan et al., 2006). Brevers et al. (2012) also found that problem gambling severity was associated with poorer decision-making under ambiguity but not under risk, suggesting that problem gamblers may be particularly vulnerable to impaired decision-making in uncertain conditions. Moreover, research has identified associations between impaired decision-making on the IGT, cognitive distortions, and problematic alcohol use among adolescent problem gamblers compared to non-problem gamblers (Ciccarelli et al., 2016). Furthermore, dopamine release in the ventral striatum has been correlated with

disadvantageous IGT performance (Linnet et al., 2011b), and excitement levels in individuals with gambling disorder (Linnet et al., 2011a).

Several studies have highlighted sex differences in IGT performance within healthy populations. Males generally outperform females across 100 trials, in terms of advantageous choices. These differences have been linked to various factors, including sex-related functional asymmetries in the VMPFC and amygdala (Weller et al., 2010) and variations in sensitivity to the frequency of gains and losses (van den Bos et al., 2013). A recent meta-analysis confirmed this trend (Zanini et al., 2024), underscoring the importance of considering sex as a contributing factor in IGT performance.

The somatic marker hypothesis (SMH)

The somatic marker hypothesis (SMH) was developed to explain the role of emotions in decision-making. First formulated by Damasio (1994) in *Descartes' Error*, the hypothesis builds on his earlier work examining the consequences of VMPFC damage (Damasio et al., 1991). Damasio (1994) argued that decision-making impairments observed in patients with VMPFC lesions result from an inability to utilize emotional biasing signals—termed *somatic markers*—when pondering uncertain choices. This hypothesis was supported by early research demonstrating that healthy participants generated anticipatory skin conductance responses (aSCRs) during the Iowa Gambling Task (IGT), while individuals with VMPFC damage failed to develop such responses. These patients exhibited poor task performance, repeatedly selecting disadvantageous options. The lack of aSCRs in VMPFC patients was interpreted as an insensitivity to future outcomes and an inability to predict long-term rewards and punishments (Bechara et al., 2000; Bechara et al., 1996).

The SMH proposes that physiological and affective changes experienced during various life events are encoded in memory and subsequently serve as implicit knowledge that guides decisions, especially in situations where the risks and probabilities associated with a choice are uncertain (Bechara and Damasio, 2002; Bechara and Damasio, 2005). According to this model, decision-making in complex and uncertain environments is influenced by biasing physiological signals regulated by neural structures within the brain's emotion-processing circuitry (Bechara & Damasio, 2005). Studies suggest that emotional feedback processing and implicit guidance predominantly occur during the early trials of the IGT, when subjects make decisions under high levels of uncertainty (Maia and McClelland, 2004; Dunn et al., 2006; Brand et al., 2007; Guillaume et al., 2009). A meta-analysis confirmed the role of aSCRs in predicting IGT performance but concerns regarding methodological inconsistencies and publication bias were raised (Simonovic et al., 2019).

It has been proposed that deficits in somatic marker functioning may contribute to an increased vulnerability to addictive disorders. This hypothesis is supported by evidence of impaired emotional processing and decision-making among individuals with substance use disorders, as well as abnormal activity in neural circuits integral to emotional information processing, including the VMPFC, amygdala, striatum, anterior cingulate cortex, and insular/somatosensory cortices (Bechara & Damasio, 2002; Bechara et al., 2002; Olsen et al., 2015; Verdejo-Garcia & Bechara, 2009). Some argue that somatic markers may be involved in both maintenance and development of both substance-use disorders and behavioral addictions, including gambling disorder (Olsen et al., 2015; Verdejo-Garcia & Bechara, 2009). However, few studies have employed psychophysiological measures to directly assess somatic marker activity in individuals with gambling-related problems. One study found that pathological gamblers, compared to controls, exhibited both lower performance and diminished somatic markers—specifically, attenuated aSCRs and reduced heart rate variability—prior to making disadvantageous choices in the IGT. These findings suggest that individuals with gambling disorder may experience impaired risk evaluation and attentional bias during decision-making under uncertainty (Goudriaan et al., 2006).

Furthermore, the influence of somatic markers on decision-making in the IGT is thought to be associated with neurotransmitter activity within cortical and subcortical brain regions. Serotonin and dopamine are considered two of the primary neuromodulators involved in somatic marker activity and performance on the IGT (Bechara & Damasio, 2005; Li et al., 2010). One study investigated the impact of genetic variations in the serotonin transporter gene-linked polymorphic region (*5-HTTLPR*) on decision-making in the IGT. The findings revealed a significant effect of this genotype on decision-making processes, with nearly half (42%) of the observed effect being mediated by enhanced somatic markers (Miu et al., 2012).

In the context of gambling, the concept of reward prediction error highlights the crucial role of dopaminergic pathways in learning to anticipate future rewards (Mikhael et al., 2022; Schultz, 1998, 2013; Starkweather et al., 2018). This mechanism aligns with the somatic marker hypothesis, as fluctuations in dopamine activity influence the reinforcement of advantageous or disadvantageous decision-making patterns (Li et al., 2010). Given the fundamental role of uncertainty in both gambling behavior and decision-making within the IGT, understanding individual variations in dopamine function in relation to somatic markers and decision-making is of particular interest in this thesis.

Contributions of preclinical research

The use of animal models has been critical for advancing knowledge of the neurobiology of gambling disorder. Preclinical studies on animals have provided important insights into the mechanisms underlying gambling addiction, including behavioral inhibition, risk-taking, probabilistic discounting, working memory, incentive salience, motivation, and near-miss processing (Nautiyal et al., 2017). Both humans and animals are sensitive to reward size and probability and exhibit similar preferences and biases in choice behavior (Heilbronner, 2017). Several rodent tasks that seek to simulate different aspects of human decision-making have been developed (de Visser et al., 2011; Izquierdo et al., 2019; Izquierdo et al., 2012; Winstanley & Floresco, 2016). The use of such models, in combination with pharmacological and lesion-based methodologies, allows for carefully controlled experimental conditions that are not feasible in human research, thereby providing critical complementary knowledge on the neurobiological underpinnings of gambling disorder (P. J. Cocker & C. A. Winstanley, 2015; Potenza, 2009; Winstanley et al., 2016). Gambling-related behaviors and decision-making in various rodent gambling tasks have been linked to several monoaminergic systems, with dopamine receiving significant attention in this context. Animal studies examining behavioral changes related to D2 receptor modulations in various gambling-like tasks have yielded mixed results. Some studies have reported win-like responses to near-misses in rats performing a rodent slot machine task, with this effect being enhanced following administration of a dopamine D2 agonist (Winstanley et al., 2011). The blockade of D2 receptors has been found to decrease risk-based decision-making in some studies (Zeeb et al., 2009), whereas other studies have reported an increase in risk-taking behavior following D2 receptor blockade (Georgiou et al., 2018; Ishii et al., 2015; Jenni et al., 2017). Additionally, some studies have found no effect of D2 receptor blockade on decision-making in various gambling- and risk-related tasks (Cocker et al., 2014; Di Ciano et al., 2015; Larkin et al., 2016; Stopper et al., 2013; Zeeb et al., 2015).

Rat Gambling Task (rGT)

Many of the earliest paradigms developed to model gambling-like behavior in animals were designed based on the IGT (Rivalan et al., 2009; van den Bos et al., 2006; Zeeb et al., 2009). The Rat Gambling Task (rGT), developed by Zeeb et al. (2009), is commonly referred to as the rodent analogue of the IGT. It was originally designed to assess gambling-like decision-making processes and to specifically investigate the effects of pharmacological and other manipulations on decision-making. The rGT is conducted in an operant box featuring four choice options that provide nutritional rewards (sugar pellets) to simulate wins and time-out periods of varying lengths to mimic losses. The

rats have limited amount of time (30 min) to maximize the number of pellets. Similar to the IGT, each choice is associated with different reward/loss probabilities and can be categorized as either advantageous or disadvantageous based on long-term payout potential. The four options are labeled P1, P2, P3, and P4, corresponding to the number of pellets associated with each choice. P1 is associated with fewer rewards but also less punishing time-outs, thus considered a 'safe' option. P2 is the most advantageous choice, yielding the highest number of pellets across a session. In contrast, P3 and P4 are considered risky options, as they provide occasional large rewards but are offset by prolonged time-out penalties, resulting in lower number of pellets across a session. As in the IGT, successful performance in the rGT requires subjects to evaluate probability distributions over multiple trials and adjust their choices based on the reward/loss feedback accumulated throughout the task.

Studies have shown that rats generally develop stable preferences for the most advantageous options, which provide smaller but more frequent rewards, over the disadvantageous options that offer larger rewards but result in greater net losses (Zeeb et al., 2009; Zeeb and Winstanley, 2011; Barrus et al., 2015; Barrus and Winstanley, 2016; Tjernström et al., 2022), similar to the assumptions of healthy human individuals performing the IGT (Bechara et al., 1997). However, studies formally comparing interspecies data on the IGT and rodent analogues are scarce, but important to improve the translational validity of information that may help unravel the complex processes of decision-making and generate clinical advances (Potenza, 2009).

Differential sensitivity to gambling in relation to decision-making

The gene-environment interaction research field in psychiatry, has traditionally been dominated by the diathesis-stress framework, where certain genotypes are assumed to confer increased risk for adverse outcomes in a stressful environment (Dick, 2011; Manuck & McCaffery, 2014). The diathetic approach and focus on identifying inherent vulnerability factors have naturally surrounded the gambling research field, characterized by overwhelming implications of dopamine function and influential hypotheses regarding incentive-sensitization processes in gambling behavior (Berridge & Robinson, 2016; Clark et al., 2019; Linnet, 2014, 2020; Robinson & Berridge, 1993; Robinson & Berridge, 2000, 2008; Sescousse et al., 2013; Zack et al., 2020). Some theories have further suggested that biological inherent individual factors may account for vulnerability toward engaging in addictive behaviors, which may be exacerbated by environmental factors, such as exposure to the addictive element (Leyton & Vezina, 2013, 2014). In contrast to the diathesis-stress

framework, the concept of biological sensitivity to the environment has been presented and relates to two complementary theories: *biological sensitivity to context theory* and *differential susceptibility theory* (Belsky & Pluess, 2009; Ellis et al., 2011). These theories suggest that certain candidate genes that interact with environmental events do not confer a risk for behavioral or psychiatric disorders but rather seem to alter the sensitivity to the environment per se both regarding positive and negative influences (Belsky & Pluess, 2009; Ellis et al., 2011). Specifically, certain susceptibility genes associated with monoaminergic neuromodulators (such as dopamine and serotonin) might involve differential susceptibility to environmental factors (Belsky & Pluess, 2009; Åslund & Nilsson, 2018). This may include experiences of emotional responses to gambling, i.e, certain genotypes might confer differential sensitivity and response activity in the autonomic nervous system in response to gambling stimuli. The present thesis adopts these theories by exploring relationships between dopamine-related candidate genes and ANS responses to gambling and decision-making in a non-clinical sample of young adults.

Rationale of the thesis

The reported findings outlined above show that the emotional responses associated with gambling outcomes, and especially the effect of near-misses, is lacking in consistency. Improving reproducibility are of great concern given the replication crisis within the field of psychology and neuroscience (Klein et al., 2018; Poldrack, 2019; Stanley et al., 2018). In addition, while prior research has shown that near-misses can activate the brain's reward system and influence physiological responses (Clark, Crooks, et al., 2012; Clark et al., 2009; Clark, Liu, et al., 2013; Sescousse et al., 2016), there is limited knowledge about sex differences in these reactions. Most of the experimental gambling research has historically used male samples only, mainly due to higher prevalence of gambling among men. Genetic markers, such as polymorphisms in the dopamine D2 receptor (*Taq1A* and *C957T*), have been linked to variations in reward processing and decision-making, and may affect the brain's sensitivity to gambling related cues, but their interaction with ANS responses has not been extensively studied. Moreover, gene-environment interactions may play a crucial role in how genetic predispositions manifest in certain gambling and decision-making situations. Differential ANS response sensitivity during gambling and decision-making as a function of dopamine D2 receptor genotypes may thus be modulated by previous exposure to gambling activities. Furthermore, human and animal models provide complimentary insights on the psychobiological underpinnings of decision-making, but cross-species comparisons are lacking.

This thesis aims to address these knowledge gaps and hypotheses by investigating how ANS responses are influenced by near-misses, thus increasing reproducibility by replicating the design of a previous study on the near-miss effect. In addition, it will also investigate how sex may impact these effects. Furthermore, it examines decision-making in both humans and animals performing gambling tasks to identify similarities and differences in strategies. It also takes on an exploratory approach by investigating the relationship between dopamine-related polymorphisms, ANS responses, and decision-making, and whether these putative interactions are further influenced by previous gambling exposure.

By integrating physiological, behavioral and genetic perspectives, this thesis contributes with further insights into individual differences in the emotional, attentional and motivational processing during gambling, with possible implications regarding the impact of gambling characteristics and susceptibility characteristics during gambling.

Research aims

The overall aim of this thesis was to explore underlying mechanisms contributing to individual differences in autonomic responses (SCR and HR), subjective perceptions, and decision-making during simulated gambling tasks, including candidate gene-environment interactions and translational considerations.

The specific aims of the included studies were:

Paper I: To investigate autonomic responses and subjective ratings generated by win, near-miss and full-miss outcomes in a slot machine task, focusing on the differential effects of two subtypes of near-misses. A second aim was to investigate sex differences in physiological and subjective responses to gambling outcomes.

Paper II: To explore individual decision-making strategies among humans in the IOWA Gambling Task (IGT) and rats in the rat Gambling Task (rGT).

Paper III: To investigate the relationship between single nucleotide polymorphic variants of the *DRD2* and *ANKK1* genotypes and autonomic responses during anticipation and slot machine outcomes. A second aim was to investigate candidate gene-environment interactions (cG×E) of genotypes and real-life gambling frequency on autonomic responses during slot machine gambling, as well as possible sex differences.

Paper IV: To investigate candidate gene-environment interactions (cG×E) of single nucleotide polymorphic variants of *DRD2* and *ANKK1* genotypes and previous exposure to gambling on decision-making performance in the IOWA Gambling Task, as well as interactions with somatic marker activity. A second aim was to explore possible sex differences.

Methods

Experimental study in human subjects

Participants

The papers included in this thesis reports data from an experimental study at Västmanland County Hospital, Västerås, Sweden. Participants were recruited from a large cohort study of young adults born in 1997 and 1999 (Survey of Adolescent Life in Västmanland, SALVe Cohort). The SALVe Cohort study was initiated in 2012 and follow-up questionnaires are distributed every 3rd year until 2032. The data collection for the experimental study was derived from the 2015 wave 2 of the SALVe Cohort and started in the fall of 2017. Participants who had provided a saliva sample for DNA extraction in the cohort wave 2 were eligible for inclusion (N = 1248). In order to maximize the number of gamblers in the study all cohort participants scoring ≥3 on the Problem Gambling Severity Index (PGSI) (Ferris & Wynne, 2001), were asked to participate. The PGSI is a 9-question screening tool that assesses problem gambling during the past 12 months (scores: 0-27). In the next step, individuals were included in a randomized order and stratified based on age and sex to increase the probability of normally distributed variables. The data collection was finalized in the spring of 2019 having reached a final sample of 270 volunteers (140 women, 130 men, age 18–22 years) (Figure 1).

None of the participants reported any current or previous history of gambling disorder diagnosis. The level of problem gambling according to PGSI scores were categorized according to the following cutoffs: 0 = non-problem gambler, 1-2 = low-risk gambler, 3-7 = moderate-risk gambler, ≥8 = problem gambler (Public Health Agency of Sweden, 2010). According to the PGSI self-reports 20 participants were considered as low risk (2 females, 18 males), 14 as moderate risk (3 females, 11 males) and 1 male was considered a problem gambler.

To assess generalizability of the included sample, participants of the experimental study (N = 270) were compared to the larger cohort (N = 1215) in terms of socioeconomic status (parents' monthly income), origin (parents born in/outside Scandinavia), and self-reported symptoms on the Adult ADHD Self-Report Scale (Kessler et al., 2005), Depression Self-Rating Scale (Svanborg & Ekselius, 2003), and the Adult Anxiety Scale-15 (Spence, 2017).

There were no differences in socio-economic status ($p = 0.690$) or origin ($p = 0.893$) between the participants in this study and the cohort. Independent samples t-test showed no significant differences in terms of self-reported symptoms of depression ($p = 0.961$) or ADHD ($p = 0.543$), but the sub-sample of the experimental study had significantly lower levels of self-reported symptoms of anxiety compared to the cohort ($p = 0.015$).

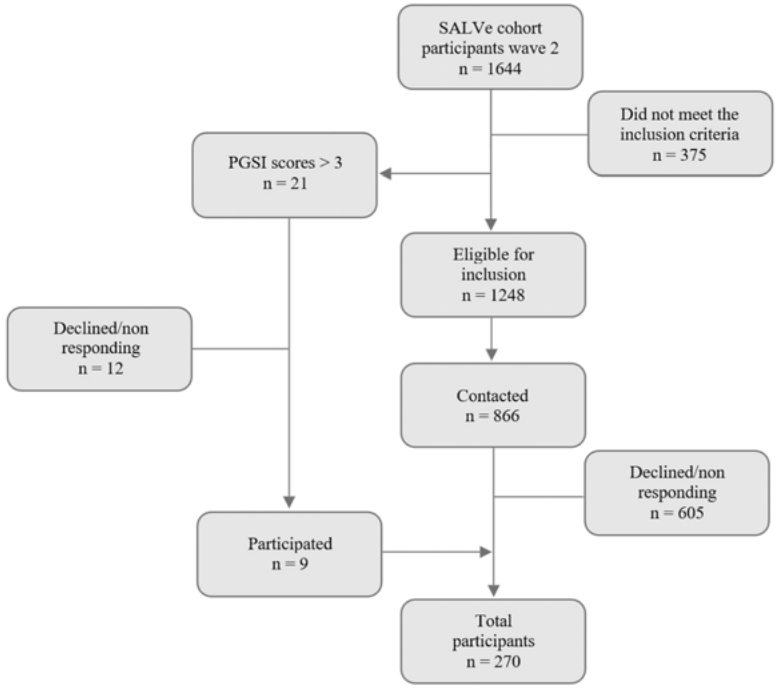

Figure 1. Inclusion procedure: total sample of participants included in the experimental session.

Experimental procedure

Before arriving to the experimental session, participants completed a web-based questionnaire on use and extent of gaming, alcohol use, drug use, and self-rated symptoms of attention-deficit/hyperactivity disorder, depression, and anxiety. During the individual experimental sessions participants performed several tasks with simultaneous recordings of psychophysiological responses. Upon arrival, written informed consent was obtained from all participants after they had received detailed information on the procedures by the examiner. Then, the sensory system electrodes for recordings of electrodermal activity (EDA) and electrocardiograms (ECG) were attached, and the session was initiated. Before engaging in the computerized tasks, the participants completed a web-based questionnaire on gambling, gaming, personality traits, sleep habits, sensory processing sensitivity, and positive/negative affect.

Thereafter, the participants performed four computerized cognition tasks, a semi structured diagnostic interview on internet gaming disorder, and a semi structured interview on problematic substance use and/or other excessive behaviors (e. g. social media use, shopping, food habits, exercise, porn, alcohol, drugs etc.). In connection with the interviews the participants had a short break with refreshments before starting the last part of the session, including three gambling tasks (slot machine gambling task, IGT and Cambridge Gambling Task). Participants were reimbursed a gift card of 1000 SEK for participation in the entire session. To increase their investment in the gambling tasks, the participants were informed that they could receive additional gratification on each gambling task, depending on their performance (maximum of 200 SEK/gambling task). The data collection was finished in June 2019.

Measurements

Slot machine gambling task

The first gambling task, administered to the participants after the break, was the slot machine gambling task based on the task used in previous research by Clark et al. (2009; 2012; 2013) and (Sescousse et al., 2016). Graphics and sounds were modified to resemble an internet casino environment. The task displayed two reels with six different symbols each, and a payline across the center (Figure 2). Participants were required to select a symbol on the left reel, and then spin the right reel. After pressing the 'SPIN' button, the reel spun for 3 s and then slowly decelerated to a standstill during an interval of 2.8 – 6.0 s, producing a total anticipation interval of 5.8 – 9.0 s. Two matching symbols aligned horizontally on the payline when the right reel stopped, resulted in a 'win' outcome. This was also followed by a short melody, applause, and the messages "Jackpot!" (5 s) and "You won 100 SEK" (4 s) displayed on the screen. The task also generated two types of near-miss outcomes depending on whether they stopped one position before ('near-miss before') or after ('near-miss after') the payline. Any other outcomes were termed 'full-misses'. All non-win outcomes were followed by a sound indicating a loss followed by the message "No win" (4 s) displayed on the screen. Next, the participants subjective experiences during the task were rated on three questions following each trial (no time limit): "How pleased are you with the result?", "How much do you want to continue to play?", and "How do you rate your chances of winning?" This also allowed recovery time of the ANS responses.

The participants performed three practice trials followed by the main session with 60 trials. The task took approximately 30 min. Unknown to the participants, the task was standardized with a fixed distribution and order of outcomes, to allow comparisons of individual responses for each gambling outcome. The proportions of gambling outcomes were 10 'wins', 10 'near-misses before', 10 'near-misses after' and 30 'full-misses'. The standardized

distribution of outcomes resulted in the maximum additional reimbursement of 200 SEK for each participant.

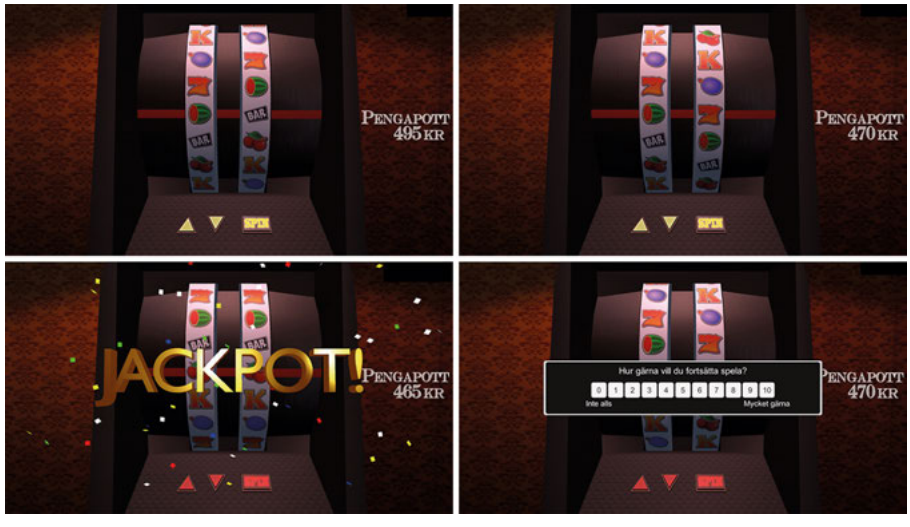

Figure 2. Screen display of the computerized slot machine gambling task, including 'near-miss after' (top left), 'near-miss before' (top right), win (bottom left), and subjective ratings (in swedish) (bottom right).

IOWA Gambling Task

The following gambling paradigm was the IGT originally developed by (Bechara et al., 1994). A computerized version modified in terms of graphics and sounds resembling an internet casino environment was administered (Figure 3). The task presented a screen display of four card decks that differed in terms of their monetary win/loss contingencies, and consequently their long-term gain probabilities. The participants were instructed to try to maximize their total profit as much as possible through repeated selections of cards across 100 trials. Participants could switch between each deck as many times as they pleased. Two of the decks were advantageous (C + D) and two were disadvantageous (A + B) with regards to their long-term monetary outcomes. Starting the task, the participants had no knowledge on the win/loss probabilities associated with each deck, and the only information they received was that some decks were better, and some were worse. Hence, they must rely on implicit learning through reward/loss feedback, and progressively develop preferences for the long-term advantageous options in favor of the riskier immediate rewards, which also resulted in higher long-term monetary net gain. Following deck choice, a card containing gains and losses was revealed which either added a positive amount or subtracted a negative amount from the total earnings. The outcome reveal was followed by 8 s time-interval before the start of the next trial, to allow recovery of the ANS responses. The net gain or

loss of each card generated either a winning or losing sound. The continuously accumulated amount of wins and losses were displayed on two bars at the top of the screen. A screen display of the task is presented in Figure 3. The participants started the trial with a virtual loan of 2000 SEK and could win a maximum of 200 SEK (gift card) depending on their performance on the task. The virtual net profits were converted accordingly: profits <100 SEK = 0 SEK, profits between 100 and 1,000 SEK = 100 SEK (≈ 10 €), and profits >1,000 SEK = 200 SEK (≈ 20 €).

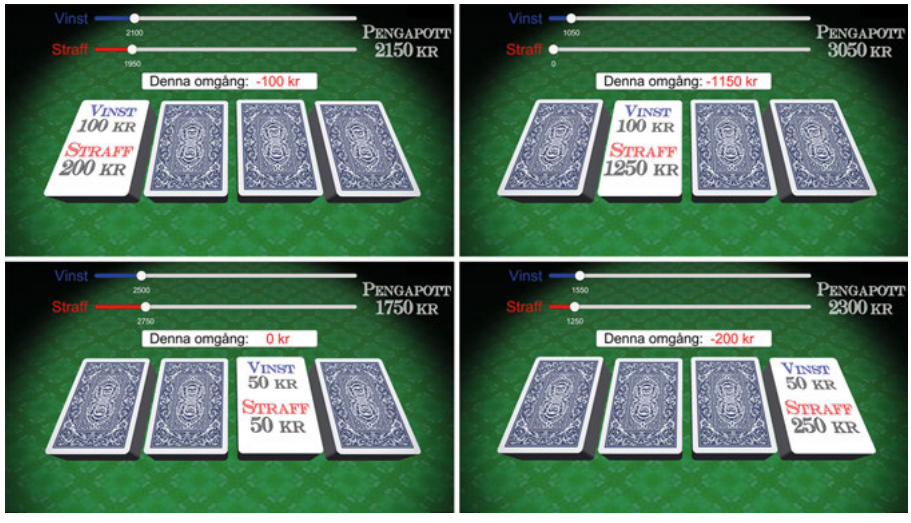

Figure 3. Screen display of the computerized IGT (in Swedish) including outcome examples of deck A (top left), B (top right), C (bottom left), and D (bottom right). Two bars displayed the accumulated wins (in blue) and losses (in red) at the top of the screen, and total earning (in SEK) displayed to the right.

Psychophysiological measures

During the entire experimental sessions, participants were equipped with several electrophysiological sensors. Autonomic responses were measured thru EDA and ECG. Sensory data were recorded with Biopac Systems MP150 (Biopac Systems, Goleta, CA, USA). The Biopac system was connected to the task computer, which in turn was connected to a second computer running *Acqknowledge* v5.0.1 to event-mark the psychophysiological responses using digital channels. The equipment used for the skin conductance recordings were two grounded Ag–AgCl electrodes (Biopac EL507 with a BN-PPGED amplifier module, sample rate 62.5, constant voltage 0.5 V, low-pass filter 3.0 Hz, high-pass filter DC). The electrodes were attached to the thenar and hypothenar eminences of the non-dominant hand, and a 0.05 M NaCl electrolyte paste GEL101 was used.

For the ECG recordings, three disposable grounded Ag–AgCl electrodes (Biopac EL504, with a BN-RSPEC module, sample rate 2000, low-pass filter 35 Hz, high-pass filter 1 Hz) were used. The electrodes contained liquid

hydrogel (4% NaCl) and were attached to the right shoulder and grounded to the eighth rib on the left and right side. In *Acqknowledge,* the EDA signal was transformed into micro siemens (μS), and the ECG signal was converted into heart rate (HR) in beats per minute (bpm). Due to seasonal changes, the room temperature ranged from 20°C to 32°C (M = 25.5°C) and the humidity from 20% to 58% (M = 41%) across the sessions.

Previous gambling exposure

Participants also reported gambling frequency during the past 12 months via 4 items (During the past 12 months, how often have you gambled with money on…? 1) online poker, casino or similar?; 2) poker, casino or similar, but not online?; 3) electronic gambling machines/slot machines, but not online?; 4) sports betting?). Choice categories for each item ranged between 0-8. Summary scores were calculated to index the total level of gambling frequency (possible range: 0-32). Continuous measures of 'gambling frequency' based on the self-reported gambling frequency summary scores were used as covariates in Paper III. In paper IV, participants with self-reported gambling frequency summary scores ≥ 1, were categorized as 'gamblers', and those with scores < 1 were categorized as 'non-gamblers'. Level of problem gambling based on self-reported PGSI scores and gambling frequency summary scores are presented in Table 1.

Table 1. Level of problem gambling (PGSI) and previous gambling experience including forms of gambling, distributed among males and females.

	N (%)	**Males (%)**	**Females (%)**
PGSI			
Total score ≥1	35 (13.0 %)	30 (23.1 %)	5 (3.6 %)
Levels*			
Non-problem gambler	235 (87.0 %)	100 (76.9 %)	135 (96.4 %)
Low-risk gambler	20 (7.4 %)	18 (13.8 %)	2 (1.4 %)
Moderate-risk gambler	14 (5.2 %)	11 (8.5 %)	3 (2.1 %)
Problem gambler	1 (0.4 %)	1 (0.8 %)	-
Previous gambling experience			
Total score (≥ 1)	84 (31.1 %)	65 (50.0 %)	19 (13.6 %)
Online casino			
Score (≥ 1)	41 (15.2 %)	35 (26.9 %)	6 (4.3 %)
Land-based casino			
Score (≥ 1)	43 (15.9 %)	40 (30.8 %)	3 (2.1 %)
Land-based EGM			
Score (≥ 1)	16 (5.9 %)	10 (7.7 %)	6 (4.3 %)
Sports betting			
Score (≥ 1)	47 (17.4 %)	38 (29.2 %)	9 (6.4 %)
Total	270 (100 %)	130 (100 %)	140 (100 %)

*PGSI cut-off scores: 0 = non-problem gambler, 1-2 = low-risk gambler, 3-7 = moderate-risk gambler, ≥8 = problem gambler (Public Health Agency of Sweden, 2010).

Genotyping

Molecular genetics technology employs polymerase chain reaction (PCR) to detect and manipulate small DNA fragments in the laboratory. This process involves amplifying DNA using primers—single-stranded DNA molecules that are complementary to the target sequence. When heated, the DNA double helix unwinds, and as the mixture cools, the primers anneal to the single-stranded genomic DNA through base pairing. This cycle repeats multiple times, exponentially increasing DNA concentration by 10^5- to 10^6-fold, thereby facilitating the detection of polymorphisms through various genotyping techniques (McGuffin, 2002).

Saliva samples (200 μL) for the genotyping procedure were collected using the Oragene® DNA self-collection kit (Ottawa, Ontario, Canada) using a silica-based extraction method (Kleargene™, LGC, Biosearch Technologies). Genotyping analyses of all the SNPs (*Taq1A/rs1800497* A2 > A1 and *C957T/rs6277*C > T) were performed using the Kbioscience Allele-Specific Polymorphism assay based on competitive allele-specific PCR and bi-allelic scoring (LGC®, England). Allele discrimination was completed using SNPviewer®. Genotype frequency and distribution are presented in Table 2.

Table 2. Descriptives of genotype distributions.

Gene	Polymorphism (SNP)	Allele	Allele frequency	Hardy-Weinberg equilibrium	Allele frequency	
			N		N	
					Females	***Males***
ANKK1	*Taq1A*	A1:A1	13		5	8
	(rs1800497)	A1:A2	94		57	37
		A2:A2	160		76	84
	Missing data		3		2	1
	Total		267	0.865	138	129
DRD2	*C957T*	T:T	66		38	28
	(rs6277)	T:C	132		66	66
		C:C	70		35	35
	Missing data		2		1	1
	Total		268	0.810	139	129

Rat experimental study

Animals

The sample included in the animal experiment were 72 outbred male Lister Hooded rats (HsdOla:LH, Envigo, Horst, the Netherlands), delivered at 5-6 weeks. The rats were food restricted to 85 % of their free feeding weight during testing. Their body weight was closely monitored to ensure that the food restriction was properly carried out. The rats were pair-housed in cages with

wood chip bedding, paper sheets and a wood tunnel for enrichment purposes. The animals were handled and habituated to the experimenter prior to the behavioral testing. A detailed description of the animal housing and environmental conditions is reported in Tjernström and Roman (2022).

Rat Gambling Task (rGT)

Rats performed the rGT in five-hole operant chambers (34 × 33 × 33 cm) placed inside ventilated sound attenuating cabinets (56 × 56 × 70 cm; Med Associates, Inc.). Inside the chambers there were four response holes and a food tray, which were equipped with stimulus lights and photo beams to record the rat's responses. Sucrose pellets (45 mg) were delivered through a pellet dispenser connected to the food tray (Sandown Scientific, Middlesex, UK).

Following a habituation period in the chambers on 2 daily 30-minute sessions, the rGT training schedule based on Zeeb et al. (2009) was initiated. The first part of the training procedure in the operant chambers teaches the rats that a nose-poke in a response hole leads to a reward. Next, to ensure exploration of all choice options, the rats undergo a forced choice training for 7 weeks in which only one of the response holes at a time were lit and delivered pellets or time-outs. Following this period, the rats explore all choice alternatives of the rGT procedure in which free selections of the response holes can result in either a pellet reward or a time-out punishment.

During the rGT, rats choose between the four response holes (P1, P2, P3 and P4) associated with different number of reward pellets, length of time-out periods, and reward/punishment probabilities. The different options and their associated probabilities were: *P1* = 1 pellet (90 % chance) and 5 s time-out; *P2* = 2 pellets (80 % chance) and 10 s time-out; *P3* = 3 pellets (50 % chance) and 30 s time-out; *P4* = 4 pellets (40 % chance) and 40 s time-out. The rat initiated a trial by a response in the illuminated food tray, followed by a 5 s inter-trial-interval before a choice could be made. Any response attempt made during this time (premature response) the rat had to wait 5 s before starting a new trial. Similarly, if the rat did not make a response within 10 s (omission) a new trial was initiated. The rGT was performed on 30 min sessions for five consecutive days for 5 weeks. A detailed description of the experimental procedures is reported in Tjernström and Roman (2022).

Data processing and statistical analysis

Software's

The software for the human experimental gambling tasks was developed by Motion Control in Västerås AB and the Academy of Innovation, Design, and Engineering at Mälardalen University, for the purpose of the current research

during 2016-2017. The psychophysiological data were recorded with Biopac System MP150 (Biopac Systems, Goleta, CA, USA). The data was exported to MATLAB and the *Ledalab* software package was used for data processing (www.ledalab.de). Moreover, the chambers used in the rat experimental study were controlled by software written in Med PC (Med Associates, Inc.). All statistical analyses were performed using IBM SPSS Statistics (v26 and v28) and Microsoft Excel. Graphs were created in GraphPad Prism 9.

Data processing of the psychophysiological measures

Following an initial quality assessment of the physiological data several exclusion criteria were established, which are specified below. A continuous decomposition analysis of the EDA signal was performed in *Ledalab* to separate skin conductance data into continuous signals of tonic and phasic activity. In the slot machine task, SCR amplitudes were calculated for 1) stimuli onset of the anticipation response (pressing the SPIN-button), and 2) stimuli onset for wins, near-misses and losses (outcome delivery as the reel stops). SCRs were computed as the maximum SCR amplitude (minimum criterion 0.05 μS) within 1-4 s post stimulus onset (gambling outcome), minus the baseline value 1 s pre stimulus onset. In paper I, SCR amplitudes were logarithmically transformed (ln(SCR.amp +1)) to normalize the data. However, this did not significantly impact the results and original SCR amplitude measures were used in the succeeding studies (Paper III and Paper IV). In Paper IV, anticipatory SCRs (aSCRs) during the IGT were calculated as the maximum SCR amplitude detected between the start of a trial to card selection (minimum criterion 0.05 μS).

The HR response (in bpm) was calculated for every half second, 0–8 s post-stimulus onset. All of the gambling outcomes were followed by a biphasic HR response, comprising an initial deceleration phase followed by a subsequent acceleration phase. HR summary measures for each gambling outcome were computed as the initial deceleration component (the minimum 0–3 s post-stimulus value, minus the baseline value 1 s pre-stimulus average HR) and a subsequent acceleration component (the maximum 2–6 s post-stimulus value, minus the deceleration component) (Hodes et al., 1985).

Subsequently, a low-pass filter was applied to the skin conductance data, removing any frequencies above 1.0 Hz, and the data was exported to MATLAB, using the *Ledalab* software package (www.ledalab.de).

Exclusions

Paper I

In the slot machine SCR analysis, 69 participants were excluded due to missing data or recording artifacts arising from excessive movement, electrode

detachment or technical failure of the recording equipment. Unfortunately, this excluded all the participants who had scored 'high' on PGSI from the 2015 SALVe cohort wave 2. Proportions of healthy individuals who show zero SCRs to emotional stimuli are common in healthy populations (Venables & Mitchell, 1996). Participants were considered non-responders and excluded if they had zero SCRs to ≥50% of the winning outcomes, resulting in the exclusion of 23 participants. In total, 178 participants (females = 94, males = 84) were included in the SCR analysis in Paper I.

In the slot machine HR analysis, two participants were excluded because of heart arrythmia, and four were identified as outliers based on high bpm compared with the group mean (>2.5 SD), leaving 264 participants (females = 136, males = 128) in the HR analysis in Paper I. One participant was excluded from all analyses because of technical failure in all recordings, leaving 269 participants (females = 139, males = 130) in the analysis of subjective ratings in Paper I.

Paper II

The IGT relies on explorations of the different options to guide decisions on the task. Due to repeated selections from one single deck across the task, 6 participants were excluded from the IGT analysis, leaving a total of 264 human participants (females = 138, males = 126) in Paper II. As for the rGT, two rats had missing values in week 5, leaving 70 male rats in the analysis of end performance.

Paper III

The exclusion criteria due to technical failure, heart arrythmia and outliers in the ECG and EDA recordings described in Paper I, also applied in Paper III. However, non-responders were not excluded in Paper III since potential absence of responses were of interest in terms of genetic influence on gambling responsivity. According to self-reports 14 participants used antidepressants (such as selective serotonin reuptake inhibitors; serotonin, and norepinephrine reuptake inhibitors; tetracyclic piperazine-azepine; and/or bupropion). These were excluded in the analyses due to possible mediating effects on dopaminergic signaling and potentially automatic processing through SCRs and HR. In total 190 participants (females = 102, males = 88) were included in the SCR analysis, and 251 (females = 127, males = 124) were included in the HR analysis. In addition, some participants had missing genetic data (Table 2), resulting in different numbers of participants in the respective analytic models.

Paper IV

Participants with missing data in the EDA recordings attributed to recording noise, excessive movement, electrode detachment or technical failure during the IGT, were excluded in Paper IV (N = 72). As in Paper II, 6 participants

were also excluded due to repeated selections from one single deck across the IGT task. Participants who used antidepressants (such as selective serotonin reuptake inhibitors; serotonin, and norepinephrine reuptake inhibitors; tetracyclic piperazine-azepine; and/or bupropion) were also excluded due to potential mediating effects on dopaminergic signaling and SCRs (N = 14). In total 181 participants (females = 99, males = 82) were included in the final analysis. In addition, some participants had missing genetic data (Table 2), resulting in different numbers of participants in the respective analytic models.

Statistical analysis

Paper I

Repeated-measures analyses of variance (ANOVA) were used to analyze summary measures for the subjective ratings and physiological responses, with significance threshold set at $p < .05$, and Huynh–Feldt and Greenhouse–Geisser corrections used. Post hoc tests included Bonferroni corrections. The first set of analysis explored differential responses in the overall sample with three within-subject factor levels (wins, near-misses, and full-misses). Separate models were conducted for SCR, HR and subjective ratings measures. Secondly, the effects of near-miss subtypes were explored using a three-within-subject factor ANOVA model ('near-misses before', 'near-misses after' and full-misses) for SCR, HR and subjective ratings. Next, sex differences were investigated in two steps. First, female, and male responses were explored separately with a repeated measures ANOVA model with three within-subject factor levels (wins, near-misses, and full-misses), divided by sex. Subsequently, sex differences in the responses to different gambling outcomes were explored with separate two-way ANOVA models for each gambling outcome. Effects (η_p^2) in the ANOVA models were estimated according to the following: small = 0.01, medium = 0.06 and large = 0.15 (Cohen, 2013). Due to the small number of participants scoring above the risk level on the PGSI, no adjustments were made for problem gambling in the analyses. The sample size provided sufficient statistical power to detect a minimal effect size of d = 0.3 ($\eta_{p2} \approx 0.02$) in the analysis of sex differences (140 females/130 males).

Paper II

Human and rat group performance was assessed using normative scoring approaches (Bechara et al., 2000). Calculations of scores were performed by taking selection from the advantageous choices minus selections from the disadvantageous choices [IGT: (C+D) - (A+B), and rGT: (P1%+P2%) - (P3%+P4%)] across the entire tasks (IGT: 100 trials and rGT: 25 days). To standardize and enable comparisons, percentages (%) of choice scores were used for both tasks. Choice scores were also calculated for each 20-trial block across 100 trials in both tasks, and per week (5 days) across the testing period of the rGT. Repeated-measures ANOVA were used to analyse

changes in choice scores over blocks and weeks, with significance threshold set at $p < 0.05$, and Huynh-Feldt and Greenhouse-Geisser corrections used. Post-hoc tests included Bonferroni corrections.

Humans and rats end performance were assessed according to their choice scores during the last phase of the tasks. The last 40 trials (trials 61-100) were considered end performance for humans in the IGT (commonly termed decisions under risk) (Brand et al., 2007). The last week (5 days) were considered end performance for the rats in the rGT. Performance was assessed according to the following criteria: choice scores > 0 = advantageous, choice scores < 0 = disadvantageous.

Finally, individual choices during end performance among humans and rats were explored by the formation of subgroups for each choice. Subjects with a mean +1 SD of the percentage in each choice category were defined as 'extremes'. This was computed for choices during trials 61-100 of the IGT, and during the last week (5 days) of the rGT. The significance threshold was set at $p < 0.05$.

Paper III

Linear regression analyses using Generalized Linear Models (GLM) were conducted to investigate associations and interactions between independent variables of genotypes, sex, gambling frequency, and dependent measures of ANS responses to slot machine stimuli. Models of main effects (adjusted for 'sex' and 'gambling frequency') of genotypes on ANS responses were conducted, using 3 ANS measures (SCRs, HR acceleration, HR deceleration) and 4 dependent outcome variables (anticipation, wins, near-misses and full-misses). Two-way interaction models were also conducted to investigate cG×E interactions (genotype*gambling frequency), as well as interactions with sex (genotype*sex). Finally, three-way interactions were performed by including 'sex' in the cG×E model (genotype*sex*gambling frequency).

In the regression models, the minor and heterozygote alleles were compared against the major allele of each gene. We explored the effects of genotypes using three allelic levels of homozygous major, heterozygous, and homozygous minor alleles. To improve power, particularly in the interaction analyses, we also grouped individuals carrying the minor allele, including both homozygotes for the minor allele and heterozygotes, thereby exploring the effect of homozygotes for the major allele versus *presence of the minor allele* (*Taq1A* = A2:A2 vs. A1:A1/A1:A2, *C957T* = C:C vs. T:T/T:C). A significance threshold of 0.05 was used.

Paper IV

As in Paper II, decision-making in the IGT task was assessed by normative net-scoring approaches [(C + D) – (A + B)] (Bechara et al., 2000), and reported decision-making patterns block-wise (net-scores each 20-trial blocks)

and during end-performance (net-scores during trials 61-100). Summary measures were calculated for anticipatory SCRs overall.

A repeated-measures ANOVA with Huynh-Feldt and Greenhouse-Geisser corrections was conducted to assess changes in patterns of net-scores and aSCRs across the tasks. Repeated measures ANCOVA models were also conducted to explore the influence of 'sex' and 'gambling exposure' on aSCR and net-score changes across the task. Post-hoc comparisons included Bonferroni corrections.

Linear regression analyses using Generalized Linear Models (GLM) were used to analyze associations and interactions between net-scores genotypes, and aSCRs. Outcome measures of net-scores during end performance were used in the following regression models. We explored associations between 1) genotypes and net-scores, 2) genotypes and SCRs and 3) SCRs and net-scores, including adjustments for sex in the respective models. Next, two-way interaction analyses were conducted to test cG×E interactions (genotype*gambling exposure), and interactions between genotypes and aSCRs (SCRs*genotype), on net-scores.

Finally, three-way interactions were conducted to analyze interactions between 1) genotypes, gambling exposure and aSCRs (genotype*gambling exposure*aSCR), and 2) genotypes, sex and aSCRs (genotype*sex*aSCR), on net-scores. To improve power, homozygotes for the minor allele was combined with the heterozygote group (*Taq1A* = A2:A2 vs. A1:A1/A1:A2, *C957T* = C:C vs. T:T/T:C). The significance threshold was set at $p < 0.05$.

Ethical considerations

The participants were derived from the SALVe cohort study with approval from the Ethical Review Board of Uppsala (dnr 2012/187). The current experimental study received specific ethical approval from the Ethical Review Board of Uppsala (dnr 2016/569), with an extended approval (dnr: 2019-01368). The animal experiment was approved by the Uppsala Animal Ethical Committee (permit number 5.8.18-00833/2017). Guidelines of the Swedish Legislation on Animal Experimentation (Animal Welfare Act SFS 1998:56 and Animal Welfare Act SFS 2018:1192), and the European Union Directive on the Protection of Animals Used for Scientific Purposes (Directive 2010/63/EU), were followed. All human participants received written information about the study, as well as detailed information on the procedures by the examiner upon arrival to the experimental session. Written informed consent was obtained from all participants. The participants were informed that participation was voluntary, and that all data would be kept confidential. All studies included in this thesis were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).

The experimental study did not include individuals under the age of 18, which is the legal age for gambling in Sweden. In accordance with the ethical approval, the project did not include those with a previous or current gambling disorder, to not impose a risk of increasing severity of existing gambling problems. Hence, all participants who were willing to participate were asked upon invitation if they had ever been diagnosed or treated for gambling disorder. None of the participants reported any current or previous history of gambling disorder diagnosis. The study allowed inclusion of participants with previous experiences of gambling and self-reports of sub-clinical criteria for problem gambling according to the PGSI index. However, the gambling paradigms were simplified compared to real-life gambling, with low levels of risk investment, and therefore unlikely to induce any harm to the participants. Sensitive information regarding problematic substance-use or other excessive behaviors were provided by the participants through web-based questionnaires and semi structured interviews. If indications of mental ill-health arose during the experimental session, the participants were referred to appropriate health-care systems or support organizations by the examiner. Each individual experimental session took approximately 4-5 hours. Given the extensive time of the experimental sessions, all participants received a gift-card compensation to cover loss of income and travel expenses.

Results

Paper I: ANS responses to slot machine stimuli

Wins, near-misses and full-misses

Comparing the ANS responses to slot machine outcomes revealed greater SCRs and HR deceleration for wins compared with both near-misses and full-misses (all $p < 0.001$). Near-misses elicited greater SCRs and HR deceleration than full-misses ($p < 0.001$, $p < 0.001$, respectively). Near-misses also elicited the largest HR acceleration compared with both wins and full-misses ($p < 0.001$, $p < 0.001$, respectively), but HR acceleration did not differ between wins and full-misses. Subjective ratings of 'pleased with result', 'continue to play', and 'chance of winning' were greatest following wins (all $p < 0.001$), with no significant differences between near-misses and full-misses (Table 3).

Table 3. Subjective ratings and psychophysiological responses on the slot machine task [mean (SD)]

	Wins	Near-misses	Full-misses	Post-hoc comparisons
ANS responses				
SCRs	0.60 (0.30)	0.37 (0.18)	0.32 (0.16)	Win>NM>FM
HR acceleration	11.46 (4.31)	12.55 (4.37)	11.75 (3.82)	Win<NM>FM
HR deceleration	4.48 (2.38)	4.03 (2.03)	3.72 (1.75)	Win>NM>FM
Subjective ratings				
Pleased with result	8.23 (1.98)	1.58 (2.14)	1.58 (2.11)	Win>NM≈FM
Continue to play	4.82 (3.05)	4.13 (2.92)	4.11 (2.88)	Win>NM≈FM
Chance of winning	3.14 (2.41)	2.75 (2.23)	2.70 (2.17)	Win>NM≈FM

Post hoc threshold = $p < 0.05$.

Near-miss subtypes

'Near-misses after' elicited greater HR acceleration than both 'near-misses before' ($p = 0.040$) and full-misses ($p < 0.001$). 'Near-misses before' elicited larger HR deceleration than 'near-misses after' ($p < 0.001$) (Figure 4). There was no significant difference in SCRs between the two near-miss subtypes. Results also revealed higher perceived chance of winning and motivation to play following 'near-misses before' compared with 'near-misses after' ($p = 0.002$, $p < 0.001$, respectively) and full-misses ($p = 0.021$, $p < 0.001$, respectively). Specifically, 'near-misses after' resulted in lower ratings of 'continue

to play' compared with both full-misses ($p < 0.001$) and 'near-misses before' ($p < 0.001$). 'Near-misses before' resulted in slightly higher ratings of 'pleased with result' than 'near-misses after' ($p = 0.040$).

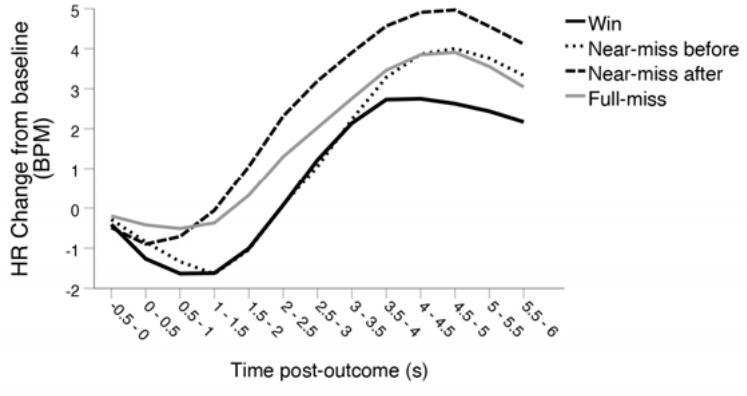

Figure 4. Changes in HR, with mean bpm for every half-second bin (from 1 s pre-outcome to 6 s post-outcome), following gambling outcomes; wins, 'near-misses before', 'near-misses after' and full-misses. Reference line indicates baseline responding, calculated as mean bpm − 1 to 0 s (y-axis). Stimulus outcomes occurring at 0 (x-axis).

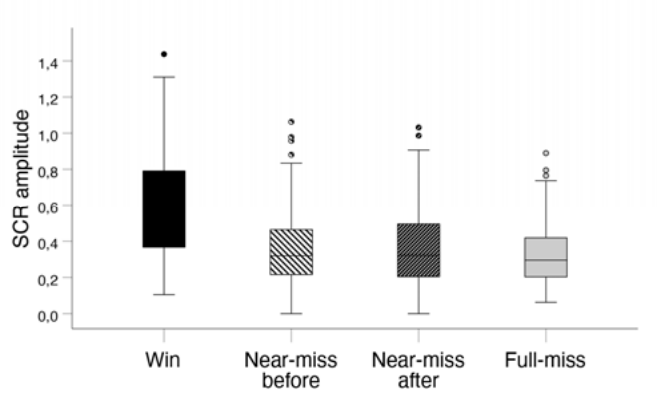

Figure 5. Mean SCR amplitudes (ln(SCR.amp + 1)) following gambling outcomes; wins, 'near-misses before', 'near-misses after' and full-misses. *Error bars:* 95% CI.

Sex differences

Subgroup analysis showed greater SCRs for wins compared with near-misses and full-misses in both females and males (all $p < 0.001$). Near-misses elicited greater SCRs than full-misses among females ($p < 0.001$) but not among

males. Females showed no differences in HR deceleration in response to any of the different outcomes. Males showed the largest HR deceleration following wins, and greater HR deceleration for near-misses than full-misses (p = 0.028) (Table 4). For both females and males, wins elicited the highest ratings on 'pleased with results', 'continue to play' and 'chance of winning' (not significant in males), but there were no differences between near-misses and full-misses (Table 4).

Comparing male and female responses to each gambling outcome revealed that females had slightly larger SCRs than males following wins (p = 0.039). SCRs following near-misses and full-misses did not differ between males and females. There were no sex differences in HR acceleration or deceleration following any of the gambling outcomes. Females scored slightly higher than males on 'continue to play' following wins (p = 0.022). Ratings for 'continue to play' following near-misses and full-misses did not differ between males and females. There were no sex differences in the ratings for 'pleased with result' or 'chance of winning' following any of the gambling outcomes (Table 4).

Table 4. Significant results of sex differences in ANS responses and subjective ratings (ANOVA).

	Mean (SD)		**ANOVA (*p*)**	**Effect size (η_p^2)**
	Females	Males		
SCR				
Wins	0.64 (0.31)	0.55 (0.28)	***F* = 4.315, *p* = 0.039**	**0.024**
Near-misses	0.39 (0.19)	0.35 (0.16)	$F = 2.289$, $p = 0.132$	0.013
Full-misses	0.32 (0.16)	0.33 (0.16)	$F = .356$, $p = 0.552$	0.002
*Post hocs**	**Win>NM>FM**	**Win>NM≈FM**		
HR deceleration				
Wins	4.23 (1.83)	4.75 (2.83)	$F = 3.171$, $p = 0.076$	0.012
Near-misses	4.06 (1.85)	4.00 (2.21)	$F = .055$, $p = 0.815$	0.000
Full-misses	3.84 (1.72)	3.59 (1.78)	$F = 1.311$, $p = 0.253$	0.005
*Post hocs**	**Win≈NM≈FM**	**Win>NM>FM**		
HR acceleration				
Wins	11.48 (4.07)	11.44 (4.57)	$F = .006$, $p = 0.939$	0.000
Near-misses	12.27 (4.25)	12.85 (4.50)	$F = 1.145$, $p = 0.286$	0.004
Full-misses	11.66 (3.85)	11.85 (3.79)	$F = .171$, $p = 0.679$	0.001
*Post hocs**	Win<NM>FM	Win<NM>FM		
Continue to play				
Wins	5.23 (3.03)	4.38 (3.02)	***F* = 5.291, *p* = 0.022**	**0.019**
Near-misses	4.34 (2.85)	3.91 (2.99)	$F = 1.471$, $p = 0.226$	0.005
Full-misses	4.29 (2.81)	3.91 (2.96)	$F = 1.169$, $p = 0.280$	0.004
*Post hocs**	Win>NM≈FM	Win>NM≈FM		
Chance of winning				
Wins	3.25 (2.24)	3.03 (2.59)	$F = .526$, $p = 0.469$	0.002
Near-misses	2.62 (2.02)	2.88 (2.45)	$F = .906$, $p = 0.342$	0.003
Full-misses	2.64 (2.01)	2.78 (2.35)	$F = .271$, $p = 0.603$	0.001
*Post hocs**	**Win>NM≈FM**	**Win≈NM≈FM**		

*Post hocs** = Differences in responses to each outcome based on repeated measure ANOVA models among females and males separately. *Significance* = $p < 0.05$. *Effect size* = partial eta squared (η_p^2).

Paper II: Decision-making in humans and rats

Overall performance and choice progression

Across the IGT, there was an increase in choice scores from block 1 to block 3 ($p < 0.001$), but no significant difference between block 3 and 4 or blocks 4 and 5, indicating an overall stabilization of performance during the final two blocks (trials 61-100). In the rGT, there was an increase in scores from block 1 to 2 ($p < 0.001$), but no significant increases in scores between blocks 2, 3, 4, and 5. Average choice scores were also calculated for each week that the rats underwent testing in the rGT, showing a significant increase in choice scores from week 1 to week 2 ($p < 0.001$). Comparing choice score progression during the first 100 trials in both rGT and IGT revealed a significant difference in choice scores for all blocks ($p < 0.001$) (Figure 6).

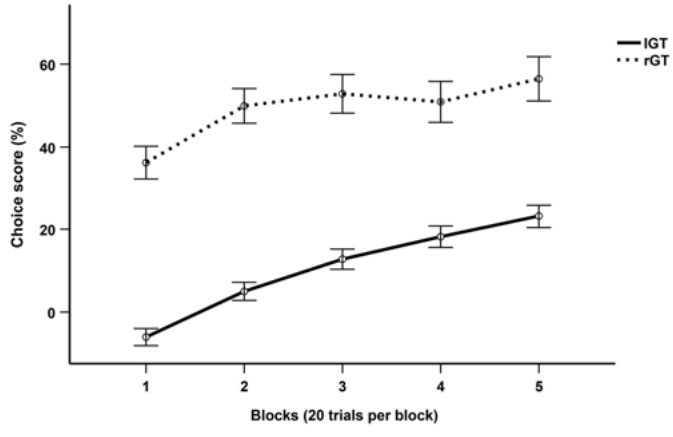

Figure 6. Mean choice score per 20-trial block across the first 100 trials of the rGT and IGT. *Mean ± 1 standard error (SE).*

Patterns of separate choices in the IGT indicated a trend toward the advantageous decks (C + D) away from the disadvantageous decks (A + B) over the course of the task. Choice patterns during the first 100 trials in the rGT, indicated an increasing preference for P1 and relatively stable choice levels for P2, P3, and P4. Average choices over the 25 days of rGT showed a preference for P1 during the first 6 days but shifted towards P2 from day 7 until the end of the rGT (Figure 7).

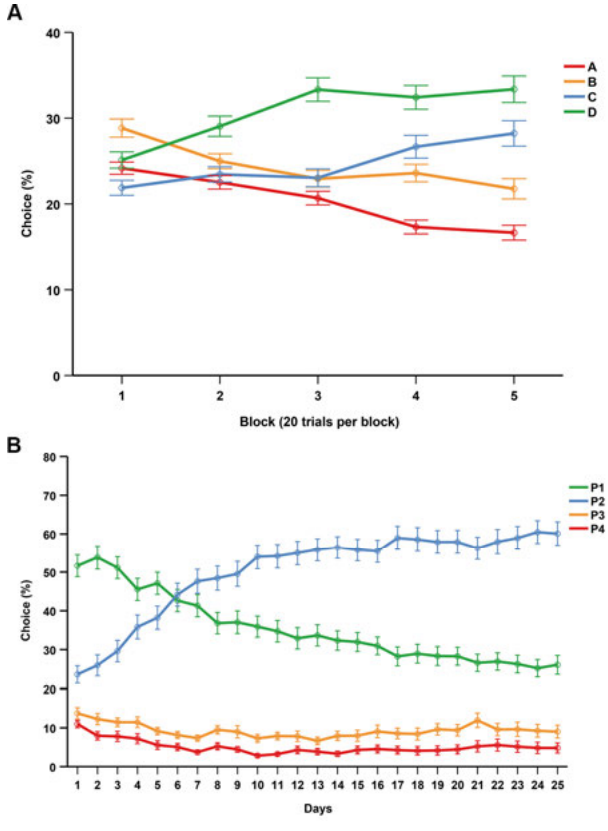

Figure 7. Average deck choices (%) per 20-trial blocks over the entire session of the IGT (A) and for each day that the rGT was performed (25 days) (B). *Mean ± 1 standard error (SE).*

Decision-making during end performance

In the IGT, decision-making during end performance was assessed using choice scores during trials 61–100 based on previous analysis indicating stabilization in overall choice scores during the final two blocks. In the rGT, choice scores across the last 5 days of the task, i.e., the last week, was considered end performance. Most human participants developed a preference for the advantageous decks (N = 166, 62.9%). However, a noteworthy proportion of participants did not (N = 98, 37.1%). Most individuals in the rGT developed a preference for the advantageous choices (N = 66, 94.3%). Only, four subjects preferred the disadvantageous choices (N = 4, 5.7%).

Subgroups of 'extreme' individuals in each choice during end performance were identified using the mean + 1 SD of the percentages in each separate choice option. Individuals below the threshold of +1 SD in all choices were considered intermediates. Two individuals in the IGT had a high frequency of choice in both A and B, while two individuals in the rGT had a high frequency

of choice in both P1 and P3. These were categorized as intermediates in the respective task (Figure 8). The proportion of individuals in the IGT categorized as extremes in each choice option was A: N = 38 (14.4%), B: N = 31 (11.7%), C: N = 27 (10.2%), and D: N = 37 (14.0%). A noteworthy proportion were considered intermediates: N = 129 (48.9%). The proportion of individuals in the rGT categorized as extremes in each choice option were P1: N = 7 (10.0%), P2: N = 11 (15.7%), P3: N = 9 (12.9%), and P4: N = 9 (12.9%), and intermediates: N = 32 (45.7%).

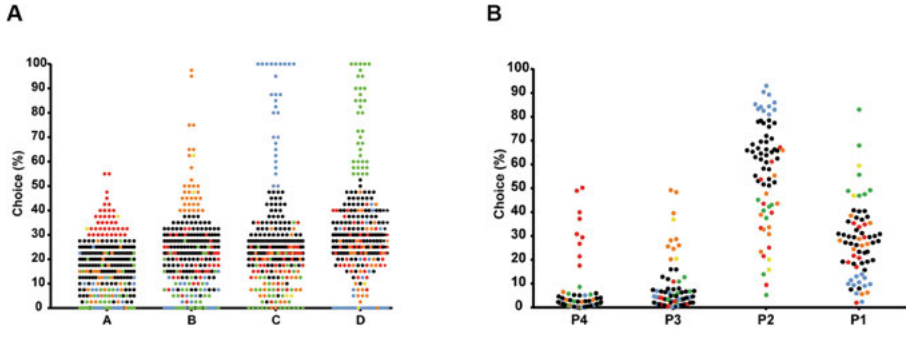

Figure 8. Scatterplots of the percentage of individual deck choices during trials 61-100 in the IGT (A), and during week 5 of the rGT (B). 'Extreme' individuals above mean ± 1 SD in each choice are coloured as follows; IGT (A) A-red, B-orange, C-blue, D-green, high in both A and B-yellow, intermediates-black; rGT (B) P4-red, P3-orange, P2-blue, P1-green, high in both P1 and P3-yellow, and intermediates-black.

To allow comparison, extreme individuals in each choice option were categorized into subgroups of 'good,' 'intermediate,' and 'poor' decisionmakers. In the IGT: high in A + high in B = poor, high in C + high in D = good, intermediates = intermediates. In the rGT: high in P3 + high in P4 = poor, high in P1 + high in P2 = good, intermediates = intermediates. The two individuals categorized as high in both A and B in the IGT were considered 'poor.' The two individuals categorized as high in P1 and P3 in the rGT were considered 'intermediates.' There were no differences in choice scores between the subgroup of good decision-makers in the IGT, good decision-makers in the rGT, and intermediates in the rGT. However, intermediates in the IGT had significantly lower choice scores than intermediates in the rGT ($p < 0.001$), and poor decision-makers in the IGT had lower choice scores than poor decision-makers in the rGT ($p < 0.001$) (Figure 9).

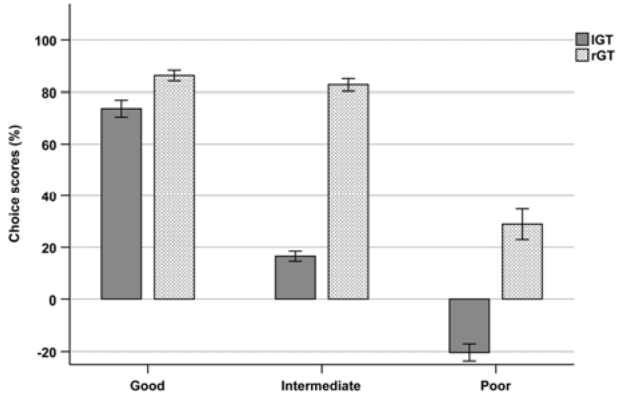

Figure 9. Mean choice scores of each subgroup (good, intermediate and poor) during trials 61–100 of the IGT and the last 5 days of the rGT.

Paper III: cG×E on ANS responses to slot machine stimuli

Influence of gambling frequency

There were significant sex differences in the level of gambling frequency (p <0.001), with higher scores among males (M = 1.81, SD = 2.69) than females (M = 0.24, SD = 0.81). Higher levels of gambling frequency were associated with smaller SCR responses to wins (p = 0.021). There were no associations between gambling frequency and SCR responses during anticipation or to near-misses or full-misses. There were no significant associations between gambling frequency and HR acceleration to any gambling stimuli. However, a higher level of gambling frequency was associated with smaller HR deceleration to full-misses (p = 0.017).

Influence of genotypes

Larger anticipatory SCRs and larger SCRs to wins were observed in *Taq1A* A1:A1/A1:A2 carriers compared to A2:A2 carriers (p = 0.018, p = 0.003, respectively). There were no significant associations between *Taq1A* variants and changes in SCRs to near-misses or full-misses. Larger anticipatory SCRs and SCRs to full-misses were seen in *C957T* T:C allele carriers compared to C:C carriers (p = 0.009, p < 0.001, respectively). No significant associations were shown between *C957T* variants and changes in SCRs to wins or near-misses. There were no significant associations between *Taq1A* or *C957T* and HR responses to any gambling stimuli.

Interactions between genotypes and sex

There was an interaction between *Taq1A* variants and sex on anticipatory SCRs ($p = 0.027$). Subgroup analyses divided by sex revealed larger anticipatory SCRs in A1:A1/A1:A2 carriers compared to A2:A2 carriers among males ($p = 0.013$), but not among females (Figure 10A). There was also an interaction between *Taq1A* variants and sex on SCRs to wins ($p = 0.004$), with significantly larger SCRs to wins in A1:A1/A1:A2s compared to A2:A2 among males ($p = 0.009$), but not among females (Figure 10B). Figure 10 illustrates the level of SCRs for *combined groups* of *Taq1A* alleles, clustered by sex.

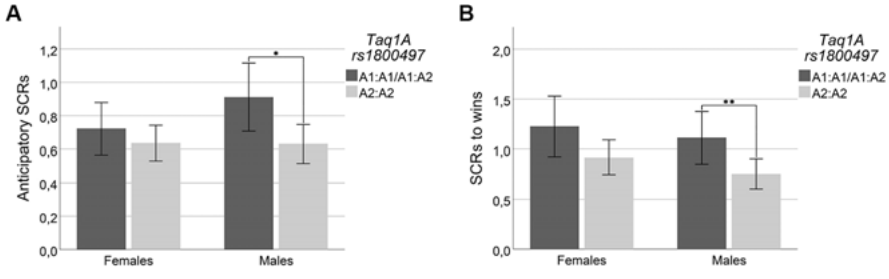

Figure 10. Illustration of sex differences in SCRs by genotype variants. A) SCRs during anticipation among *Taq1A* variants clustered by sex. B) SCRs to wins among *Taq1A* variants clustered by sex. *Error bars:* 95% CI.

There was an interaction between *C957T* variants and sex on anticipatory SCRs ($p = 0.007$), and SCRs to full-misses ($p = 0.003$). Subgroup analyses showed significantly larger anticipatory SCRs and SCRs to full-misses in male heterozygotes compared to male C:Cs ($p = 0.004$, $p = 0.004$, respectively), while such differences were not significant in females (Figure 11). No other interactions were observed. Figure 11 illustrates the effect of *C957T* heterozygotes by displaying SCRs for *three alleles*, clustered by sex.

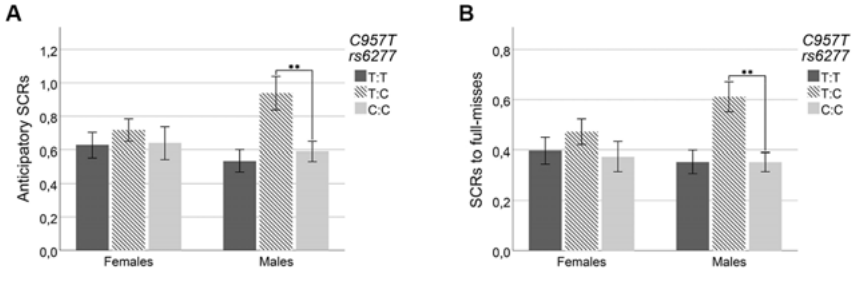

Figure 11. Illustration of sex differences in SCRs by genotype variants. A) SCRs during anticipation among C957T variants clustered by sex. B) SCRs to wins among C957T variants clustered by sex. *Error bars:* 95% CI.

cG×E of genotypes and gambling frequency

There was an interaction between *Taq1A* variants and gambling frequency on anticipatory HR deceleration responses. Specifically, A1:A1/A1:A2 carriers showed decreased anticipatory HR deceleration responses with increased level of gambling frequency ($p = 0.037$) (Figure 12). Furthermore, there was an interaction between *Taq1A* variants and gambling frequency on HR acceleration responses to wins, showing decreased HR acceleration to wins with increased level of gambling frequency among A1:A1/A1:A2 carriers ($p = 0.019$). No further interactions were shown between *Taq1A* variants and SCRs or HR responses to slot machine stimuli. Figure 12 illustrates HR responses in *dichotomized groups* of *Taq1A* alleles.

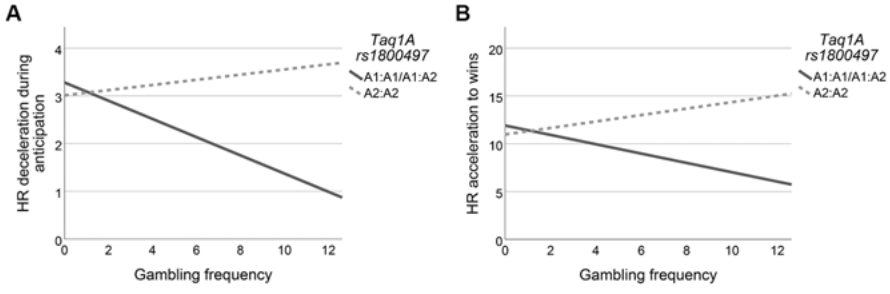

Figure 12. Illustration of GxE interactions on HR responses. A) Interactions between *Taq1A* variants and previous gambling frequency on HR deceleration during anticipation. B) Interactions between *Taq1A* variants and previous gambling experience on HR acceleration to wins.

Paper IV: cG×E on decision-making and the influence of somatic markers

There was a significant difference between males and females in terms of gambling exposure ($\chi(1) = 23.978$, $p < 0.001$), with 40 male (48.8 %) and 15 female (15.2 %) 'gamblers'.

Block-wise changes in net-scores and aSCRs

There was a significant increase in net-scores from block 1 to block 2 ($p < 0.001$), and from block 1 to 5 ($p < 0.001$), but the differences between blocks 2 and 3, 3 and 4, 4 and 5 did not reach statistical significance. Results also showed a decrease in aSCR from block 1 to block 2 ($p < 0.001$), but no significant differences between blocks 2, 3, 4 and 5. Based on these results trials 61-100 (end performance) were used as outcome variable and aSCRs during trials 1-40 (decision-making under uncertainty) were used as covariates in the following analyses.

Females had lower net-scores than males during end performance ($p = 0.007$). There was a difference in aSCRs during the uncertainty phase based on gambling exposure, with larger aSCRs in 'non-gamblers' compared to 'gamblers' ($p = 0.018$) (Figure 13). There were no differences in net-scores based on gambling exposure, and no sex differences in aSCRs during uncertainty.

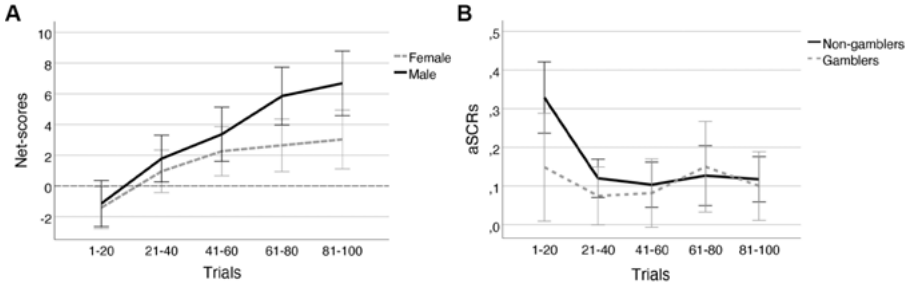

Figure 13. Changes in mean net-scores and aSCRs between 20-trial blocks. A) Block-wise net-scores in females and males. B) Block-wise aSCRs in 'non-gamblers' and 'gamblers'. *Error bars:* 95% CI.

cG×E of genotypes and gambling exposure on decision-making

There was an interaction between *Taq1A* genotypes and gambling exposure on net-scores ($p = 0.021$) (Figure 14A). Subgroup analyses were performed to test associations between genotypes and net-scores in 'gamblers' and 'non-gamblers', separately. An unadjusted model initially showed lower net-scores in A1:A1/A1:A2 carriers compared to A2:A2 carriers among 'gamblers' ($p = 0.029$), but not among 'non-gamblers'. However, these results were not significant when adjusting for sex. There was also an interaction between *C957T* genotypes and gambling on net-scores ($p = 0.038$) (Figure 14B), with lower net-scores in C:C carriers compared to T:T/T:C carriers among 'gamblers' ($p = 0.014$), but not among 'non-gamblers'.

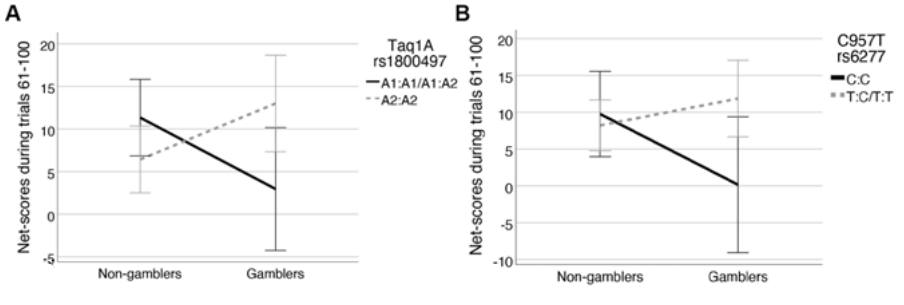

Figure 14. Illustrations of interactions between *Taq1A/C957T* genotypes and previous gambling exposure on net-scores during trials 61-100. A) Interactions between *Taq1A* variants and previous gambling exposure on net-scores. B) Interactions between *C957T* variants and previous gambling exposure on net-scores.

Interactions between genotype, aSCRs and gambling exposure on decision-making

Firstly, there was an interaction between *Taq1A/C957T* and aSCRs on net-scores during end performance. Specifically, *Taq1A* A1:A1/A1:A2 carriers had higher net-scores with larger aSCRs compared to A2:A2 carriers (p = 0.049), and *C957T* C:C carriers had higher net-scores with larger aSCRs compared to T:T/T:C carriers (p = 0.013). Secondly, there was a three-way interaction between *C957T* genotypes, gambling exposure and aSCRs on net-scores (p = 0.008). Subgroup analyses revealed that C:C carriers had higher net-scores with larger aSCRs compared to T:T/T:C carriers among 'non-gamblers' (p = 0.013), but this effect was not seen among 'gamblers' (Figure 15). Furthermore, no significant interaction between *Taq1A* genotypes, gambling and aSCRs on net-scores was observed.

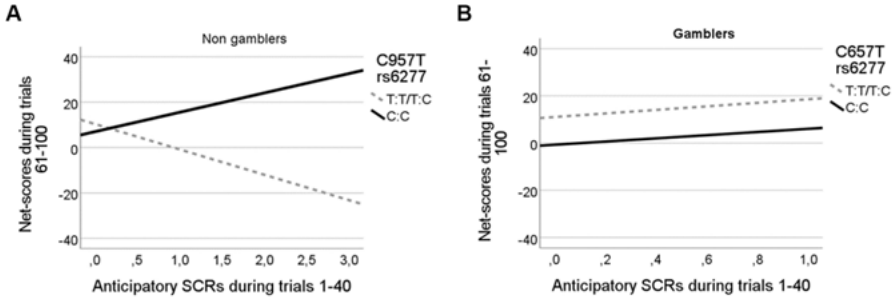

Figure 15. Illustrations of interactions between *C957T* genotypes and aSCRs on net-scores during trials 61-100, separated by previous gambling exposure. A) Interactions between *C957T* variants and aSCRs on net-scores in 'non-gamblers'. B) Interactions between *C957T* variants and aSCRs on net-scores in 'gamblers'.

Interactions between genotype, aSCRs and sex on decision-making

There was a three-way interaction between *C957T* genotypes, aSCRs and sex on net-scores (p = 0.031), but no significant group differences were shown in the post hoc analysis when including Bootstrap. However, subgroup analysis separated by sex showed higher net-scores with larger aSCRs in male C:C carriers (p = 0.027), but this effect was not observed in females. There was no significant interaction between *Taq1A* genotypes, sex and aSCRs on net-scores.

Discussion

The overall aim of this thesis was to investigate the underlying mechanisms contributing to individual differences in emotional responsivity, subjective perceptions, and decision-making during two gambling tasks. This was achieved using objective measures of physiological responses, biological markers, and behavioral data during simulated gambling. The included papers aimed to address gaps in the literature and contribute incremental yet meaningful insights through both replication and exploratory approaches. The key findings support the near-miss effect in gambling (Paper I) and suggest cGxE interactions and differential sensitivity during the anticipation and receipt of monetary rewards (Paper III), as well as during decision-making (Paper IV) in various gambling tasks. Additionally, translational perspectives are explored by comparing decision-making strategies in humans and rats (Paper II).

The effect of near-misses and near-miss subtypes

As expected, the arousing and motivational effects of wins during simulated slot machine gambling were confirmed, aligning with models of arousal in gambling (Blaszczynski & Nower, 2002; Brown, 1986; Sharpe, 2002). These autonomic nervous system (ANS) responses were unsurprising and may be attributed not only to the excitement of winning but also to the visual and auditory sensory feedback associated with this outcome. This feedback is likely to activate enhanced attention orienting, as indicated by the HR deceleration response (Bradley, Codispoti, Cuthbert, et al., 2001; Codispoti et al., 2001).

Beyond this general finding, near-misses elicited larger ANS responses overall, indicating both enhanced attention orienting and arousal compared to full-misses, consistent with previous research (Clark, Crooks, et al., 2012; Clark, Liu, et al., 2013). The distinct psychophysiological response patterns between near-misses and full-misses suggest differences in emotional processing, despite both outcomes being objectively equal in terms of monetary value. This aligns with theories proposing that near-misses can generate win-like responses, potentially contributing to the misuse potential of gambling (Griffiths, 1993; Parke & Griffiths, 2006; Reid, 1986). However, subjective

perceptions of near-misses were not supported by trial-by-trial subjective ratings of motivation, satisfaction, or perceived chances of winning, as observed in other studies (Clark et al., 2009; Qi et al., 2011; Clark et al., 2012). Interestingly, differences in subjective ratings and ANS responses emerged when distinguishing between two near-miss subtypes—those occurring before versus after the payline. Large HR acceleration, accompanied by low ratings of pleasure and motivation, suggested that 'near-misses after' were primarily associated with negative affect, such as regret or frustration (Amsel, 1958; Dixon et al., 2013). In contrast, 'near-misses before' appeared more encouraging, as indicated by higher ratings of motivation, satisfaction, and perceived chances of winning. The results further extend previous findings by showing that 'near-misses before' were associated with a higher perceived chance of winning compared to both 'near-misses after' and full-misses, along with enhanced attention orienting, as indexed by HR deceleration responses. This highlights the potentially motivational properties of this near-miss subtype. However, visual inspection of the change in beats per minute (bpm) from pre-outcome to post-outcome (Figure 4) suggests that the HR deceleration response is initiated during the gradual slowing of the reel before the outcome is revealed, possibly reflecting an anticipatory response. It remains unclear why this was not observed in previous studies by Clark et al. (2012; 2013), but subtle differences in the temporal resolution of the stimuli across tasks may be a contributing factor.

Nevertheless, these motivational and affective responses align with theories suggesting that different near-miss subtypes evoke distinct upward counterfactual thinking patterns—additive and subtractive (additive and subtractive) (Clark, Liu, et al., 2013; Sharman et al., 2015; Wu et al., 2017). These patterns are believed to influence emotion and motivation (Epstude & Roese, 2008; Markman & McMullen, 2003; Roese & Olson, 1993). Near-misses overall may be perceived as "almost hitting the jackpot" and cause players to mentally simulate a better outcome. Specifically, near-misses where the reel stops just before the winning position may lead players to mentally simulate a trajectory toward a winning outcome, thereby increasing motivation to continue gambling (additive upward counterfactual). In contrast, near-misses where the reel stops just after the winning position may instead induce a subtractive upward counterfactual, in which the player mentally reverses the outcome, leading to feelings of frustration and regret (Clark, Liu, et al., 2013; Markman & McMullen, 2003; Sharman et al., 2015; Wu et al., 2017). Paper I provides further support for these theories, emphasizing the multifaceted nature of near-misses in generating "mixed emotions" depending on their characteristics. However, it should be noted that the mean levels of the subjective ratings were generally low, yielding small effect sizes. It is important to consider the repetitive nature of these ratings, which may affect their ability to reliably capture subjective experiences during the task. While ANS responses offer objective

measures of emotional processing in gambling, the challenge remains in effectively operationalizing higher-order cognitions associated with these physiological responses using subjective and behavioral measures (Lang, 2014; Levenson, 2014).

Since the publication of Paper I, a recent study conducted a series of conceptual replications examining the impact of near-miss outcomes in a three-reel online slot machine simulation, assessing subjective ratings (motivation, valence) and two behavioral measures (gambling speed and bet size). The findings showed some similarities with previous research but also notable deviations. Specifically, while near-misses differed from full-misses across all measures, near-misses were generally rated more positively and led to increased bet sizes and faster gambling speeds compared to full-misses (Palmer et al., 2024). This contrasts with prior research suggesting that near-misses are typically experienced as aversive and frustrating while still increasing motivation to continue gambling (Billieux et al., 2012; Clark, Crooks, et al., 2012; Clark et al., 2009; Qi et al., 2011; Stange et al., 2017; Stange et al., 2016). Moreover, the study did not find reliable differences between the two near-miss subtypes (Palmer et al., 2024). These inconsistencies raise questions about the impact of subtle variations in experimental design, further suggesting that near-misses may elicit either aversive or appetitive states depending on contextual factors. Slot machines with two versus three reels may induce different levels of anticipation, as three-reel tasks involve sequential symbol stops, potentially increasing reward expectancy and anticipation compared to two-reel tasks, where anticipation is driven primarily by the deceleration of a single reel (Palmer et al., 2024).

Taken together, the findings indicate that near-misses evoke conflicting aversive and appetitive emotions, influenced by their temporal placement relative to the winning line and the broader anticipatory context. This complexity complicates interpretations of the near-miss effect in gambling behavior, highlighting its psychological intricacies. However, the results clearly demonstrate a distinction between how near-misses and full-misses are processed, reinforcing concerns about the potentially harmful effects of near-misses. From a public health perspective, these effects warrant careful consideration in the regulation of both land-based and online casino gambling.

Comparing decision-making strategies in humans and rats

Decision-making strategies among humans in the IOWA Gambling Task (IGT) and rats in the Rat Gambling Task (rGT) were compared in Paper II,

revealing differences in overall performance, choice progression and end performance between the two species. While the overall results confirmed the typical decision-making patterns commonly reported separately in each species, some deviations were observed.

In the IGT, performance was characterized by both exploration and learning, as indicated by increasing net scores and a gradual shift in preference toward the two advantageous choices over the disadvantageous ones across the task. This aligns with theories suggesting that participants initially engage in exploratory behavior (decisions under uncertainty) before transitioning to more conscious and deliberate decision-making (decisions under risk) in the later stages of the task (Brand et al., 2007; Dunn et al., 2006; Guillaume et al., 2009; Maia & McClelland, 2004). In contrast, rats displayed relatively stable preferences for advantageous choices throughout the task. However, a shift in choice preference was observed after day 7, transitioning from the safe but less strategic choice (P1) to the most strategic choice (P2). Notably, the weekly progression of choices is not typically reported in rGT research, and some inconsistencies exist in the early literature (Zeeb et al., 2009; Zeeb & Winstanley, 2011). Additionally, prior studies have reported different rankings of choices during final performance. A meta-analysis of 211 rats (all trained in the same lab) identified a P2>P3>P4>P1 ranking (Barrus et al., 2015), while other studies reported P2>P3>P4>P1 (Barrus & Winstanley, 2016) and P2>P1>P4>P3 (Baarendse et al., 2013). Therefore, reporting choice progression throughout the rGT may provide valuable insights into the influence of strain differences or training protocols on baseline performance and choice development.

Considerable variability in IGT performance among healthy individuals has been reported in previous studies, reflected in divergent net scores, differences in exploratory tendencies, and varying learning rates (Barnhart & Buelow, 2022; Bull et al., 2015; Steingroever et al., 2013). The present study compared a population-based human sample with genetically diverse outbred Lister Hooded rats, revealing individual differences in choice preferences across both groups. In both species, individual choice patterns at the end of the task showed that participants developed preferences for a single option or a combination of options, with extreme decision-makers present for each option. However, notable differences emerged in the overall distribution of choices, particularly in the number of intermediate decision-makers in the IGT versus the rGT. Analyses of inter-individual variability in single choice preferences are uncommon in both the IGT and rGT but may offer important insights into the complex processes underlying individual decision-making. Categorizing participants as advantageous or disadvantageous decision-makers based on standard scoring approaches may lead to overly broad classifications, overlooking individuals with highly distinct choice patterns. Therefore, both

human and preclinical research would benefit from more detailed analyses of individual choice behaviors rather than relying solely on net-score or choice-scoring methods.

Procedural differences

The rGT is often presented as the rat analogue of the IGT, but notable procedural differences may account for the discrepancies in choice progression and performance levels between rats and humans in these tasks. Key differences include: (1) the effects of rGT pre-training, (2) the number of trials administered, (3) the probabilistic structure of the tasks, and (4) the frequency and magnitude of wins and losses associated with each choice.

First, according to standard rGT procedures, rats undergo training in operant chambers, including a forced-choice phase before the task begins. This pre-training establishes choice preferences early on, which then stabilize as the task progresses. In contrast, human participants in the IGT receive only brief verbal instructions and have no prior knowledge of the win/loss contingencies associated with each deck. These differences likely contribute to the distinct learning rates observed between species (Zeeb et al., 2009). Additionally, the multiple testing sessions in the rGT allow for the stabilization of choice preferences, making it possible to identify pronounced risk-taking profiles. In contrast, because the IGT is typically completed in a single session, trial-and-error learning may continue beyond the first 100 trials for some individuals. This is supported by studies showing that increasing the number of trials in the IGT improves performance, particularly among participants who initially exhibit disadvantageous decision-making (Buelow et al., 2013; Bull et al., 2015; Steingroever et al., 2013).

Beyond differences in learning conditions, the probabilistic structures of the tasks also diverge. In the rGT, the rewards and losses associated with each choice occur randomly within probabilistic schedules. In contrast, the IGT follows a fixed sequence in which large losses occur after a predetermined number of trials. Research has shown that altering the order of decks in the IGT can influence task performance (Fellows & Farah, 2005). Moreover, differences in win/loss frequency and magnitude between the IGT and rGT result in discrepancies in risk/gain potential over the short and long term. As a result, humans and rats may base their decisions on different experiences and perceptions of each option. Specifically, in the rGT, choice P1 is considered a safe but non-strategic option in the long run, as it yields small rewards and infrequent small losses, suggesting risk-averse decision-making (de Visser et al., 2011). This type of choice is not directly represented in the IGT, and it remains unclear whether the most strategic choice in the rGT (P2) and the advantageous choice in the IGT (Deck C or D) reflect similar underlying

decision-making processes. While repeated selection of P2 in the rGT likely indicates a reward maximization strategy, it is uncertain whether repeated choices of Deck D in the IGT—which features relatively small and infrequent losses—reflect the same strategy or are driven by loss aversion. Overall, the procedural differences between the IGT and rGT likely contribute to variations in learning, choice perception, and the underlying decision-making mechanisms in humans and rats, including whether decisions are guided by implicit learning or explicit knowledge.

Modelling risky or ambiguous decision-making?

The procedural differences between the IGT and rGT are highly relevant for interpreting the decision-making processes involved in these tasks. They also make the IGT and rGT suitable for studying different aspects of risky and ambiguous decision-making. The IGT allows for the examination of how decisions evolve from exploration to exploitation over the course of the task. In contrast, the repeated daily sessions of the rGT result in relatively stable choice preferences, making it more suitable for investigating pronounced risk profiles. In the IGT, some individuals may become aware of the choice contingencies toward the end of the task, whereas others may continue learning on a trial-by-trial basis even after 100 trials (Balodis et al., 2006; Buelow et al., 2013; Bull et al., 2015; Steingroever et al., 2013). This study focused on the final 40 trials as an indicator of decision-making during end performance. However, since the IGT does not distinguish between learning deficits and a preference for risk, poor performance in the final trials could reflect either risky decision-making strategies, difficulties in recognizing choice contingencies, or impaired implicit guidance.

These considerations raise further questions about the applicability of both tasks in assessing gambling behavior in real-world settings. Both the IGT and rGT can measure an individual's ability to discriminate between choice options that vary in reinforcement contingencies and to inhibit responses to immediate large gains in favor of long-term profits. However, the tasks structures are highly simplified and do not resemble any commercial form of gambling. Additionally, they lack several psychological features linked to problematic gambling behaviors, such as near-misses (Chase & Clark, 2010; Dymond et al., 2014; Sescousse et al., 2016), and high sensory stimulation (Dixon et al., 2014; Loba et al., 2001). Nevertheless, research has shown that problem gamblers display impairments in decision-making during the IGT (Brevers et al., 2012; Cavedini et al., 2002; Ciccarelli et al., 2016; Goudriaan et al., 2006), suggesting that the task can model certain features related to disordered gambling.

A broader challenge in animal models is the representation of rewards and losses. While money serves as a secondary or conditioned reinforcer in humans, nutritional rewards in animal models are primary reinforcers. The motivational value of money is highly subjective, whereas food motivation in rodents is influenced by hunger and satiety (de Visser et al., 2011). Consequently, differences in reward types may affect baseline motivational levels between humans and rats. Critically, representing 'loss' in animal models poses a particular challenge. Other rodent gambling tasks have used bitter-tasting quinine pellets (van den Bos et al., 2006) or electric foot-shock punishments (Simon et al., 2009) as aversive outcomes. The time-out periods used in the rGT most closely resemble losses in the IGT, as they restrict the number of trials and the amount of food pellets earned throughout the task (Rivalan et al., 2009; Zeeb et al., 2009). However, because sugar pellets are consumed immediately in the rGT, it is not possible to deduct previously obtained rewards, unlike monetary losses in the IGT (Winstanley et al., 2016).

Despite these challenges, animal models continue to provide valuable insights into the neural mechanisms underlying reward processing, risk-taking, and compulsive behavior, thereby informing treatment approaches for gambling disorders. However, careful task design and interpretation are essential to ensure meaningful comparisons between animal and human gambling behaviors.

Differential sensitivity to gambling stimuli and decision-making

Papers III and IV explored the relationships between single nucleotide polymorphic variants of the *DRD2* and *ANKK1* genotypes and ANS responses during the slot machine gambling task and decision-making in the IGT, while also considering previous exposure to gambling. This thesis presents preliminary cG×E effects of *Taq1A/C957T* genotypes and gambling exposure on ANS responses to slot machine stimuli (Paper III) and decision-making performance in the IGT (Paper IV).

A key challenge in interpreting these findings lies in the operationalization of emotional responses as measured through SCRs and HR changes. ANS activity is driven by both cognitive and affective processes, including attentional and perceptual processing as well as emotional responses to stimuli (Ishikawa, 2023). According to existing literature, increased SCR amplitude reflects emotional intensity and attentional engagement, HR deceleration indicates attentional orienting, and HR acceleration is primarily associated with emotional reactivity (Bradley, 2009; Bradley, Codispoti, Cuthbert, et al., 2001; Codispoti et al., 2001; Lang, 2014; Lang et al., 1993). Based on these

principles, a few interpretations regarding the differential emotional impact during the tasks can be made.

First, considering the main effects of genotype, allelic variants (*C957T* CC and/or *Taq1A* A1) associated with reduced striatal D2 receptor density (Gluskin & Mickey, 2016; Hirvonen et al., 2004, 2005; Hirvonen et al., 2009; Ritchie & Noble, 2003) were linked to increased attentional orienting during anticipation and heightened emotional reactivity to reward delivery in simulated slot machine gambling (Paper III). Additionally, these variants were associated with enhanced decision-making performance via emotional reactivity under uncertainty (i.e., somatic markers) in the overall sample (Paper IV). The findings from Papers III and IV suggest that these genotypes may contribute to differential ANS sensitivity to gambling cues and gambling-related decision-making. In the context of simulated slot machine gambling, the effects of the *C957T* variants were primarily driven by heterozygosity, complicating interpretation. The C allele of *C957T* has been linked to reduced D2 receptor density in the striatum (Hirvonen et al., 2004, 2005) but higher D2 receptor availability in the cortex and thalamus (Hirvonen et al., 2009). It is possible that the influence of this genotype on ANS responses during gambling reflects region-specific functional differences in D2 receptor regulation. However, further research is required to clarify the mechanisms underlying these effects.

Secondly, when accounting for previous gambling exposure, low to moderate exposure was associated with reduced reward responses in the slot machine task and blunted anticipatory responses during uncertainty in the IGT, consistent with studies reporting blunted neural reward responses (Balodis et al., 2012; Choi et al., 2012; de Ruiter et al., 2009; Reuter et al., 2005) and reduced somatic markers in problem gamblers during the IGT (Goudriaan et al., 2006).

The incentive-sensitization theory suggests that repeated exposure to addictive stimuli, such as gambling, increases the incentive salience of gambling cues over time (Berridge & Robinson, 2016; Clark et al., 2019; Linnet, 2014, 2020; Robinson & Berridge, 1993; Robinson & Berridge, 2000, 2008; Sescousse et al., 2013; Zack et al., 2020). Our interaction models further suggest that these effects may be particularly pronounced in individuals carrying dopaminergic genotypes associated with reduced dopamine D2 receptor availability, contributing to differential sensitivity to gambling cues and decision-making under uncertainty. Interestingly, the observed genotypic influences on emotional processing and decision-making during the tasks reversed when controlling for gambling exposure. Individuals carrying the *Taq1A* A1 allele with a history of gambling showed reduced attentional orienting during anticipation and diminished reward responses in the slot machine task. Additionally, carriers of the *Taq1A* A1 and *C957T* C alleles with prior gambling exposure demonstrated poorer decision-making in the IGT. While larger somatic

markers were generally associated with better decision-making in *Taq1A* A1 and *C957T* C carriers, this relationship was not observed in individuals with previous gambling exposure.

Given the relatively low frequency and intensity of gambling exposure in the sample, these findings should be interpreted cautiously. In the slot machine task, the inverse relationship between gambling exposure and ANS responses in *Taq1A* A1 carriers may reflect reduced incentive salience toward simplified slot machine cues in this subgroup. In the IGT, poorer decision-making and null effects of somatic markers in carriers of the low D2 expressing alleles previously exposed to gambling, along with overall blunted aSCRs in individuals previously exposed to gambling, may relate to reduced incentive salience or attentional bias during decision-making under uncertainty. These preliminary findings require replication in larger, well-powered studies.

Although participants generally exhibited elevated ANS responses to near-misses (Paper I), no significant *Taq1A* or *C957T* genotype effects were observed for ANS responses to near-misses. Furthermore, no cG×E interactions were found in relation to near-miss processing. Few studies have examined the role of dopaminergic function in near-miss processing. One study reported blunted striatal activations to near-misses and full-miss outcomes in gamblers compared to non-gamblers, suggesting that repeated near-misses experiences may lead to decreased responses in dopamine-rich brain regions over time (Worhunsky et al., 2014). However, Sescousse et al. (2016) found increased striatal activation to near-misses in gamblers, with no significant modulation by dopamine D2 receptor antagonists. Overall, further research is needed to explore dopaminergic mechanisms underlying emotional responsivity to near-misses, which signal the absence of reward while still maintaining incentive salience.

The role of somatic markers

There were no significant associations between aSCRs and decision-making during end performance in the overall sample, challenging the SMH as a general predictor of decision-making in non-clinical samples. While there is broad consensus that somatic markers, as indexed by aSCRs, play a significant role in shaping decision-making in the IGT (Simonovic et al., 2019), their precise interpretation and timing remain subjects of debate. The fundamental premise of the SMH suggests that bodily responses precede cognitive awareness (Bechara, 2004). However, methodological inconsistencies across studies—including variations in physiological measures and IGT protocols—complicate its validation (Simonovic et al., 2019). Additionally, uncertainties remain regarding whether somatic markers differentiate between advantageous and disadvantageous deck selections. Previous research has yielded mixed

findings: some studies report increased somatic markers preceding disadvantageous decks (Bechara et al., 1999), while others suggest heightened responses before advantageous decks (Tomb et al., 2002) or propose that somatic markers simply reflect general anticipatory responsivity that facilitates attention under uncertainty (Simonovic et al., 2019). Moreover, early studies posited that somatic markers develop gradually over the course of the task as a result of implicit learning from previous outcomes (Bechara & Damasio, 2005). In contrast, later research suggests that emotional feedback processing and implicit guidance predominantly occur during the early trials of the IGT, when participants make decisions under high level of uncertainty (Brand et al., 2006; Brand et al., 2007; Dunn et al., 2006; Guillaume et al., 2009; Maia & McClelland, 2004). Findings from the present study support this perspective, revealing increased anticipatory responses during the early trials that declined as the task progressed. However, our study did not distinguish between responses preceding advantageous and disadvantageous decks. Future research should incorporate this distinction to further elucidate the precise mechanisms by which somatic markers shape decision-making.

Although previous studies have reported altered responsivity in samples of carefully screened pathological gamblers (Goudriaan et al., 2006), such deficits may stem from the duration and clinical severity of gambling disorder, with potential implications for the maintenance of problematic gambling behaviors (Olsen et al., 2015). Since the present study examined a young, non-clinical sample with moderate gambling exposure, the findings suggest differential sensitivities in decision-making processes before the onset of clinical symptoms. However, whether these effects contribute to increased susceptibility to problem gambling in emerging adulthood remains an open question, warranting further investigation in larger, highly powered samples.

Sex differences

Results suggest increased emotional reactivity and motivation following slot machine wins among females compared to males (Paper I). Two-way interaction models further indicate sex differences in the relationship between genotypes, emotional responses to slot machine stimuli, and decision-making under uncertainty. However, the response patterns do not suggest opposing genetic effects between males and females. Instead, genotypic differences were more pronounced and statistically significant only in males, leading to an observed interaction effect. The most notable findings include large anticipatory responses and heightened reactivity to full-misses in the slot machine task among male *C957T* heterozygotes, as well as large anticipatory responses in male carriers of the *Taq1A* A1 allele (Paper III). Additionally, the impact of aSCRs on IGT performance appeared more pronounced in male *C957T* C:C

carriers, although Bootstrap estimates failed to detect significant group differences, questioning the robustness of these findings (Paper IV).

Sex differences in emotional processing represents some of the most robust sex stereotypes in affective research (Plant et al., 2000; Timmers et al., 2003). While some evidence indicates sex differences in emotional perception, reactivity, regulation, and learning, findings remain inconsistent (Whittle et al., 2011). Additionally, lack of methodological standardization in psychophysiological research complicate interpretations and inferences regarding sex differences in emotional processing (Bianchin & Angrilli, 2012). In the context of gambling, previous studies have reported greater emotional sensitivity to rewards in males compared to females (Dhingra et al., 2021; Garrido-Chaves et al., 2021; Grose-Fifer et al., 2014), contrasting the results of Paper I. Some research suggests that estrogen modulates dopamine release and D2 gene expression, but sex differences in reward sensitivity remain inconclusive and may involve multiple factors, including genetic, hormonal, environmental, developmental, and socialization influences [see Diekhof (2018) for a review]. The observed sex differences in the present study may be attributed to differences in dopaminergic gene expression. It may also have been caused by variations in gambling experience, given the significantly higher gambling frequency in males within the sample. Consequently, potential effects in females may have gone undetected due to insufficient statistical power. Additionally, SCR is a complex measure sensitive to environmental factors such as season and time of the day, particularly among females (Venables & Mitchell, 1996).

Results reflect the complex biases associated with sex, which are expressed at psychophysiological, behavioral and neurobiological levels through:

1. Sex differences in autonomic nervous system (ANS) responses and self-reported motivation following rewards observed in the present study,
2. Higher IGT net-scores in males, consistent with both the present findings and previous research (Zanini et al., 2024), and
3. Potential sex differences in DRD2 gene expression (Diekhof, 2018; Diekhof et al., 2021).

While establishing causal relationships between these factors is beyond the scope of this study, the present findings have important implications for understanding sex differences in gambling behavior. Males and females typically exhibit distinct motivations for gambling and differing trajectories of problem gambling progression (Håkansson & Widinghoff, 2020; Merkouris et al., 2016; Syvertsen et al., 2023). These differences may, in part, be linked to neurophysiological variations affecting responses to gambling stimuli and gambling behavior. Moreover, studies comparing decision-making in male and

female rats remain scarce (Orsini et al., 2016), representing a critical area for further preclinical research. Taken together, the current study underscores the necessity of considering sex differences in research on emotional processing in gambling-related contexts.

Methodological considerations

This thesis included a relatively large sample of young adults for this type of experimental setting, with an evenly distributed subset of males and females, recruited from a community-based cohort. In Paper I, the sample size provided sufficient statistical power to detect a minimal effect size of d = 0.3 ($\eta_{p2} \approx 0.02$) in the analysis of sex differences (140 females/130 males). Participants did not differ significantly from the SALVe cohort in terms of socioeconomic status (parents' monthly income), origin (parents born in or outside Scandinavia), or self-reported symptoms of ADHD and depression, suggesting that the sample was fairly representative of an average population of young adults in Sweden. However, participants in the experimental study reported significantly lower levels of anxiety symptoms compared to the broader cohort.

Paper I replicated previous findings on ANS responses to near-misses (Clark, Crooks, et al., 2012; Clark, Liu, et al., 2013) using a highly powered design. This represents a valuable contribution to the field, particularly in light of the replication crisis and the growing emphasis on reproducibility in psychology and neuroscience (Klein et al., 2018; Poldrack, 2019; Stanley et al., 2018). Nevertheless, several limitations of this thesis must be addressed.

Validity of gambling tasks

Significant attention was given to the experimental setup, physiological measurements and methodological design of the gambling tasks. Despite these efforts, certain limitations should be acknowledged. The slot machine task used in Paper I and Paper III was simplified compared to contemporary real-life slot machines, which typically feature multiple reels and allow multiple betting styles (Dixon et al., 2010). As a result, the ecological validity of the procedure may require further consideration. However, in more complex tasks, the near-miss effect becomes more difficult to conceptualize due to the increased potential for close-call outcomes (Palmer et al., 2024). Additionally, different forms of gambling may appeal to different individuals, given the heterogeneity among problem gamblers and their motivations for gambling—whether for stress relief or excitement and thrill (Blaszczynski & Nower, 2002). Due to the diversity and complexity of real-life gambling, no single human or animal task can fully capture all aspects relevant to problem gambling (Winstanley et al., 2016).

Furthermore, participants completed several other tasks before engaging in the gambling tasks as part of a larger experimental session. This sequence may have influenced their level of investment and motivation, potentially leading to boredom or disinterest. Nevertheless, the cues presented in the computerized slot machine still elicited differential phasic autonomic nervous system (ANS) responses, reinforcing the validity of a laboratory setting in detecting distinct emotional reactions to gambling-related stimuli.

Another concern in Paper I is the reliance on participants' subjective ratings for each trial. These ratings do not constitute direct behavioral measures, and their ability to reliably capture cognitive processing—such as motivation and perceived chances of winning—may be questioned. However, the significant, albeit small, variations observed in subjective ratings analyses suggest a pattern of differential cognitive processing of gambling outcomes, particularly near-miss subtypes. Developing reliable methods to assess subjective perceptions during gambling is crucial, as supplementing self-report measures with physiological data can help delineate the psychological processes that accompany objective measures of ANS activity (Clark & Goudriaan, 2018).

Sample size and power

The limitations of Papers III and IV primarily concern power issues in the two-way and three-way interaction models. Despite efforts to recruit a large number of gamblers and achieve a balanced sample of females and males, the final sample size was limited due to the exclusion of a substantial proportion of participants caused by technical failures in the EDA recording equipment. Unfortunately, this exclusion encompassed all participants with higher Problem Gambling Severity Index (PGSI) scores, who had originally been included to increase the number of gamblers and reduce the risk of zero inflation. Consequently, the final sample consisted of a relatively low frequency of individuals with gambling experience, most of whom were classified as being at a low to moderate subclinical risk for problem gambling. In Paper III, significant two-way interactions were observed only in the heart rate (HR) response measures but not in skin conductance responses (SCRs), possibly due to the exclusion of numerous participants from the SCR analyses. A stronger link between genotypes, gambling exposure, and autonomic nervous system (ANS) responses may be more apparent in more balanced subgroups of frequent gamblers, evenly distributed across allelic variants. Additionally, the significantly higher level of prior gambling experience among males in the current sample likely interfered with our analyses on sex differences.

Sample size and power issues are a common concern in gene-environment interaction studies and are frequently debated (Duncan & Keller, 2011). However, the current study employed an experimental design incorporating

objective, carefully monitored physiological and behavioral measures. This approach helps mitigate issues associated with self-reports, which are introspective, often retrospective, and susceptible to various biases, such as demand characteristics and social desirability (Clark & Goudriaan, 2018). Compared to cGxE studies relying on questionnaire data, the study design presented in this thesis offers greater precision and control over variable assessment (Moffitt & Caspi, 2014).

We also acknowledge the importance of addressing multiple testing issues. Papers III and IV involved multiple testing across several outcome variables of interest. While multiple testing corrections, such as the Bonferroni correction, are crucial in confirmatory studies to control the experiment-wise error rate and ensure valid conclusions, statisticians argue that such corrections significantly increase the risk of Type II errors (Perneger, 1998). This can be counterproductive in exploratory studies (Bender & Lange, 2001), as the reduction in statistical power following such corrections may prevent the detection of true associations. In an exploratory setting such as ours, where multiple hypotheses emerge in a data-driven manner, multiple testing corrections do not effectively resolve the challenge of drawing valid inferences (Bender & Lange, 2001). In line with this reasoning, crude p-values were applied in Papers III and IV, given their exploratory nature and primary goal of hypothesis generation. However, it is important to emphasize that the results are preliminary and require further high-powered confirmatory studies for validation.

Considerations of confounding factors

The limitations of all papers also extend to the control of other factors which may have impacted the results. Although, participants of Paper III and IV who used antidepressant were excluded, the studies did not account for other potential mediators of ANS activity, such as hormonal levels, environmental conditions, psychiatric diagnoses, mood or personality traits (Boucsein, 2012). In Paper II, both males and females were included in the human sample, whereas only male rats were used. Research on the IGT generally indicates that females tend to perform worse and exhibit a bias toward low-loss frequency decks compared to males (van den Bos et al., 2013). Furthermore, Paper II compared a population-based human sample with genetically diverse outbred Lister Hooded rats, introducing individual differences in both groups. However, individual variation is inherently greater within the human sample due to differences in life experiences and environmental influences, which may have further contributed to the observed behavioral differences.

As previously noted, gambling exposure among the subgroup of participants with gambling experience was generally low, making it difficult to draw conclusions regarding the impact of this environmental factor in the present

sample. Additionally, gambling exposure in this sample may co-occur with other confounding variables, such as alcohol use, personality traits, anxiety, depressive states, or other undetermined factors that were not controlled for in this thesis.

The effects of the investigated genotypes on ANS responsivity followed similar trends in both the slot machine task and the IGT, enhancing the reliability of their main effects. However, various polymorphisms in genes related to other monoaminergic functions have also been implicated in gambling disorder (Grant et al., 2016), with research suggesting the potential additive effects of multiple candidate genes involved in dopamine, serotonin, norepinephrine, and GABA functioning (Comings et al., 2001). Particularly, the serotonergic system has been linked to reward system function through complex regulatory interactions with dopamine (Courtiol et al., 2021). Previous studies have also demonstrated a significant impact of the *5-HTTLPR* polymorphism on decision-making in the IGT (Ha et al., 2009; Miu et al., 2012).

Conclusions

Results from this thesis support the near-miss effect and indicate differential emotional processing of gambling stimuli and during decision-making, as a function of dopamine D2 receptor genotypes.

Paper I confirms that near-misses elicit different autonomic nervous system (ANS) responses compared to regular full-misses, thereby supporting theories on the near-miss effect in gambling. Given the need to improve reproducibility in experimental research, these findings are particularly valuable. From a public health perspective, these effects should be considered in gambling regulation policies aimed at harm prevention in both land-based and online casino gambling.

Paper II represents an initial attempt to explore the similarities and differences in reward-based decision-making processes between the IGT and its rodent analogue, the rGT. Procedural differences between the tasks suggest variations in the extent to which rats and humans rely on explicit knowledge versus implicit guidance when making decisions in the respective tasks. Since animal tasks aspire to simulate human decision-making, interspecies comparisons of learning patterns, choice progression, and individual choice preferences are crucial from a translational perspective. Drawing inferences from both human and animal studies requires careful methodological considerations regarding the extent to which these tasks capture similar psychological constructs relevant to real-world gambling behaviors.

Paper III and Paper IV provide preliminary evidence that functional markers of the D2 dopamine receptor are associated with differential ANS sensitivity to slot machine gambling cues and rewards, as well as anticipatory responses linked to implicit guidance during decision-making under uncertainty. These relationships were also influenced by previous gambling exposure and sex, potentially indicating differential susceptibility to gambling stimuli. However, potential gene-environment interactions between genetic predispositions and gambling exposure in shaping emotional responses and decision-making require further investigation in well-powered studies to substantiate this hypothesis.

The conceptualization and development of ecologically valid gambling paradigms, along with reliable measures that capture cognitive and motivational processes during gambling, are crucial for understanding the mechanisms underlying individual differences in problematic gambling behavior. Furthermore, this thesis underscores the need to consider sex differences in research on emotional processing in gambling-related contexts. Additionally, further research is needed to disentangle the functional mechanisms underlying individual differences reported in this thesis and how they may promote appetitive behavior in a gambling context.

Svensk sammanfattning

Spelproblem leder till lidande för individer och stora kostnader för samhället och utgör ett folkhälsoproblem i Sverige och globalt (Public Health Agency of Sweden, 2023; Wardle et al., 2024). Trots att ökat spelande och exponering för spel kan leda till kontrollförlust, förklarar detta inte fullt ut varför vissa individer utvecklar spelproblem, medan det för andra förblir en harmlös fritidssysselsättning. Teoretiska modeller för uppkomsten av spelproblem betonar samspelet mellan biologiska förutsättningar och miljöfaktorer (Blaszczynski & Nower, 2002; Sharpe, 2002). Spelandets beroendepotential har delvis sin grund i dess förmåga att aktivera responser från det autonoma nervsystemet (Brown, 1986). Dess påverkan varierar dock mellan olika spelformer och kan vara särskilt framträdande vid specifika strukturella element och utfall. Upplevelser av så kallade *nära-vinster* tros ha en stark inverkan på spelmotivation genom att manipulera känslan av framgång i slumpmässiga spel (Griffiths, 1993). Beträffande biologiska förutsättningar spelar även dopaminsystemets funktion en central roll genom att signalera förväntad belöning och förstärka spelbeteenden. En genetisk markör som har associerats med spelproblem (Comings et al., 1996) är en polymorfism i genen *ankyrin repeat and kinase domain containing 1* (*ANKK1*), känd som *Taq1A* (Blum et al., 1995; Foll et al., 2009; Gorwood et al., 2012). En polymorfism i den intilliggande *dopamin D2 receptor* (*DRD2*) -genen, *C957T*, utgör liksom *Taq1A* en funktionell markör för dopamin D2-receptorn (Hirvonen et al., 2009). Interaktionen mellan biologiska, psykofysiologiska och beteendemässiga faktorer kan undersökas med hjälp av experimentella metoder. Djurmodeller spelar också en viktig roll i att förstå de underliggande mekanismerna bakom spelbeteende (Winstanley et al., 2016), men det saknas formella jämförelser mellan människor och djur i tester som påstås mäta liknande beteenden.

Mot denna bakgrund var det övergripande syftet med denna avhandling att undersöka autonoma responser, subjektiva upplevelser och beslutsfattande vid spel om pengar. Detta inkluderade effekten av *nära-vinster*, samt individuella skillnader i känslighet för spelstimuli och beslutsfattande utifrån genetiska markörer för dopamin D2-receptorn, med hänsyn till tidigare spelande och kön. Även translationella perspektiv behandlades.

Avhandlingens fyra delstudier baseras på data från en experimentell spelstudie vid Västmanlands sjukhus i Västerås. En subgrupp av unga vuxna födda 1997 och 1999 (n = 270), som tidigare deltagit i en större kohortstudie i Västmanland, genomförde ett antal speltester samtidigt som deras fysiologiska responser (hjärtfrekvens och hudkonduktans) mättes. Denna avhandling inkluderar data om autonom och subjektiv responsivitet i *Slot Machine Gambling Task* samt beslutsfattande och autonom responsivitet i *Iowa Gambling Task* (IGT). Vid jämförelser mellan människor och djur inkluderades även data från vuxna utavlade hanråttor (n = 72) som genomförde *rat Gambling Task* (rGT).

Studie I undersökte deltagarnas fysiologiska responser och subjektiva upplevelser av olika utfall i *Slot Machine Gambling Task*. Specifikt jämfördes reaktioner på vinster, förluster och *nära-vinster*, där vinstsymbolen stannar endast en position från vinstlinjen. Resultaten visade att upplevelsen av *nära-vinster* gav upphov till starkare autonoma responser än vanliga förluster. En distinktion kunde även ses mellan olika typer av *nära-vinster*, beroende på om vinstsymbolen stannade före eller efter vinstlinjen. *Nära-vinster efter* orsakade frustration och negativ affekt, medan *nära-vinster före* upplevdes som mer motiverande. Gällande könsskillnader uppvisade kvinnor starkare hudkonduktansresponser och högre motivation att fortsätta spela efter vinster jämfört med män.

Studie II jämförde deltagarnas val och beslutsfattande i IGT med råttors strategier i en preklinisk version av testet – *rat Gambling Task* (rGT). Resultaten visade skillnader i människors och råttors övergripande beslutsfattandeförmåga, hur valen utvecklades över tid och individuella val mot slutet av testerna. Beteendemönstret bland deltagarna i IGT kännetecknades av utforskande och inlärning samt individuell variation mot slutet av spelet, medan råttorna visade relativt stabila preferenser för de fördelaktiga alternativen genom hela testet. Procedurskillnader i testerna, såsom träningsprotokoll, antal omgångar samt sannolikhet och storlek på vinster/förluster, kan bidra till skillnader i implicita och explicita beslutsfattandestrategier. Dessa tester lämpar sig därför för att studera olika aspekter av beslutsfattande.

Studie III och IV undersökte relationer mellan genotyper av dopamin D2-receptorn och autonoma responser under slotmaskinspelet samt beslutsfattande i IGT. Resultaten visade att individer med genotypen *Taq1A* A1, associerad med lägre densitet av D2-receptorer, uppvisade ökad förväntansrespons och emotionell intensitet vid vinster i slotmaskinspelet. Dessa individer, inklusive bärare av *C957T* C-varianten, visade även en koppling mellan beslutsfattande och autonom förväntansrespons i IGT, där starkare responser var associerade med mer fördelaktiga val. Deltagare med tidigare spelvana uppvisade generellt lägre responser efter vinster i slotmaskinspelet samt lägre förväntansresponser i IGT. Gen-miljöinteraktionsmodeller visade ett omvänt förhållande

mellan genotyp och autonoma responser vid hänsyn till tidigare spelande. Tidigare spelande hos individer med *Taq1A* A1-varianten var kopplat till lägre förväntansresponser och vinstresponser i slotmaskinspelet. Dessutom var tidigare spelande hos individer med *Taq1A* A1 och *C957T* C-varianten associerat med sämre beslutsfattande i IGT. Kopplingen mellan högre förväntansresponser och förbättrat beslutsfattande observerades inte hos deltagare med tidigare spelvana.

Ur ett folkhälsoperspektiv bör *nära-vinster* beaktas i regleringen av spel, då denna avhandling, tillsammans med tidigare forskning, visar att sådana utfall aktiverar autonoma nervsystemet och hjärnans belöningssystem på ett sätt som skiljer sig från vanliga förluster. Framtida studier bör utveckla speltester med hög ekologisk validitet och reliabla mått på subjektiva upplevelser och spelbeteende för att med bättre precision kunna utvärdera den psykologiska och beteendemässiga effekten av *nära-vinster* och dess beroendepotential.

Translationella slutsatser från människa-djur-studier kräver noggrant övervägande av metodologiska likheter och skillnader i testprotokoll. IGT ger insikt i hur individer utvecklar beslutsfattande under osäkerhet, medan rGT resulterar i mer stabila strategier och tydliga riskprofiler. Framtida IGT och rGT studier bör också överväga individuella skillnader i beslutsfattande snarare än enbart medelvärdesberäkningar av sammanslagna val.

Slutligen indikerar resultaten att individuell variation i känslighet för spelstimuli och beslutsfattande kan bero på genetiska faktorer som påverkar dopaminfrisättningen i hjärnan. Dess påverkan tycks även modifieras av tidigare spelvana, men på grund av låg spelvana i den aktuella studiepopulationen bör dessa resultat ses som preliminära och i behov av replikering för att fastställa potentiella gen-miljöinteraktionseffekter. Resultaten från delarbetena i denna avhandling betonar även att könsskillnader bör beaktas i forskning kring emotionella reaktioner i spel.

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