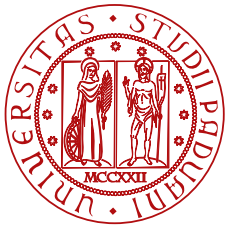

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Gambling and Testosterone: from animals to humans

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ABSTRACT

Gambling disorder is a psychiatric condition characterized by a dependence on gambling. Patients with this disorder experience a strong attraction to gambling and feel unable to control their gambling behaviour, despite the negative consequences that may result, such as financial, family, and social problems. In recent years, studies have focused on understanding the causes of gambling disorder and possible therapeutic strategies. Some studies have examined the relationship between testosterone and risk propensity in gambling, to understand the hormone's role in gambling addiction. Testosterone is known to influence human behaviour, including motivation and risk propensity. Some studies have shown that testosterone can increase risk propensity and motivation to seek large rewards, increase perseverance in gambling, underestimate risks, and reduce the sense of punishment caused by monetary loss. It is possible to compare the differences in key behaviours and verify whether there is an effect of testosterone on risk propensity in gambling, both in human and animal models. These studies on animal models can be useful for understanding human behaviour and gambling addiction. Indeed, gambling is considered here as a form of behaviour motivated by the search for rewards, with a compulsive character, and that is repeated despite losses in the long run. Findings on animal models suggest that testosterone could influence this behaviour, contributing to the facilitation of various sub-components identified within the disorder in humans. In conclusion, studies on animal models suggest that testosterone may influence risk propensity in gambling, but further research on human models is needed to confirm this relationship. The aim of the thesis is to analyse all relevant and recent literature on the topic and see how this hormone may influence gambling behaviour, using different techniques and methods. We will introduce the literature which assessed testosterone and gambling in humans, and then try to integrate the inconsistencies found through animal models, or just confirm previous findings. The idea of using animal models can be a strength, establishing the relationship between a hormone and a behaviour, whose cross-species validity could give solidity to the hormonal theory.

Contents

1 Introduction

1.1 Pathological Gambling: Definition and characteristics

Pathological gambling previously called pathological gambling and classified as an impulse control disorder in DSM-III and DSM-IV, has recently been reclassified as an addictive disorder in the DSM-5. It is a disorder that involves gambling behaviour characterized by an inability to resist the urge to gamble, despite the negative consequences that the gambling may have on the player's life and the lives of those around them. It has a prevalence of 0.5-2.0 percent across the world. It is recognized as a prototypical "behavioural addiction" [83]. Numerous studies have investigated personality traits that may predispose individuals to develop pathological gambling. The cognitive aspects include deficits in aspects of impulsivity, sensation seeking, inhibition, working memory, planning, cognitive flexibility, and time management/estimation have been reported in individuals with gambling disorder compared to healthy volunteers [91] [102] [18] [51] [65] [19] [13]. Individuals with gambling disorder also tend to prefer small immediate rewards rather than larger delayed rewards, to the detriment of long-term task outcomes (i.e., they show abnormally elevated 'delay discounting') [191]. Gambling disorder is often associated with features of compulsivity [176], as individuals who start gambling have inefficient inhibition and are not able to interrupt behaviour. Indeed, individuals with gambling disorder often score high on the Padua Inventory, a measure of compulsivity [25] [116] and display marked response perseveration [176] [141] and difficulties with cognitive flexibility [130][108]. Although the pathophysiology of GD is not fully understood, there appears to be broad consensus that number of cores

phenotypes are involved, including increased impulsive behaviour, risky decision making, increased sensation seeking, the presence of cognitive distortions, increased compulsivity, and altered reward sensitivity. All these phenotypes can be readily modelled in rodent paradigms with good construct and face validity. Reliability of these paradigm won't be discussed, as it would request a whole another research. Many reviews, however, evidence the cross validity of these measures [183] [121].

1.2 Testosterone

Testosterone is a steroid hormone primarily produced by the testicles in men and the ovaries in women, although it is also synthetized in small amounts in the adrenal glands of both sexes. Testosterone plays an important role in the development and growth of male sex organs, such as the prostate and testicles, but is also involved in muscle growth, sperm production, mood regulation, and increased libido. Testosterone is also responsible for the appearance of secondary male characteristics, such as facial and body hair growth and deepening of the voice. Testosterone is lipophilic and non-polar, and thus it can pass through the blood–brain barrier and then the plasma membrane of cells to bind with androgen receptors in the cytosol. This ligand–receptor complex then dimerizes, is phosphorylated, and translocate to the cell nucleus, where the DNA-binding domain binds to a specific sequence of DNA called the hormone response element and acts as a transcription factor [142]. Testosterone also has an impact on risk propensity. Numerous studies have shown that testosterone levels are related to the tendency to take risks. In general, it has been observed that men with higher levels of testosterone tend to behave more aggressively and competitively and engage in risky behaviours [211]. However, the correlation between testosterone and risky behaviours is not linear. In other words, extremely low or high levels of testosterone do not necessarily indicate risky behaviour [161] [172]. Moreover, there are many subtypes of risky behaviours, and they may be differentially influenced [22]. Additionally, risky behaviour is not solely dependent on testosterone but is influenced by many other factors, such as personality, environment, culture, and other biological mechanisms [84]. Aim of this review is to show relevant information about financial risk taking, as a predictor of gambling disorder. Testosterone plays an important role in reward and risk mechanisms that serves as the basis for its significance in reward-risk assessment [87] [8] [145]. Animal studies have identified androgen receptors in almost all reward- and risk-dependent neural structures. Furthermore, through the modulation of both

dopamine and GABA, Testosterone can elicit reward-motivated behaviour [156] [20]. Importantly, gambling male prevalence rate is five times the female rate [2] and this may be explained by the influence of gonadal hormones in risk preferences.

1.3 Methods

For this literature review, we conducted a systematic search using various databases, including PubMed, Google Scholar, and Zendy. We used the keywords "testosterone," "risk-taking behaviour," "pathological gambling", "animal studies" "androgen receptors", to find relevant articles. Studies on both humans and animals were included. Most of the existing literature on the administration of exogenous testosterone on risk-taking behaviour pertains to rodent models. Both the effects of exogenous administration (which exhibit the transient effect of testosterone on cognitive functions) and studies on the correlation with endogenous levels, including indices of prenatal and pubertal exposure, were considered. Financial investments tasks were considered in this study as a reliable source of information about gambling behaviour. In this latter way, we expect to find the relationship between the hormone and the effects of pathology. Also, studies on gonadectomized rats where included, as they represent with good reliability organizational effect of hormones on behaviour. Studies that focused on the construct validity of the animal models compared to humans will be not faced, as it has already been proved widely [185] [122].

2

Testosterone and financial risk taking

2.1 Overview on the main results

Here we present briefly experiment and theories made in the past few years, with the help of the literature on the argument. Studies on human have utilized cognitive assessment for Gambling (IGT, BART) endogenous level of testosterone analysis, 2D to 4D digit ratio, and testosterone administration. The outcomes have been varied, with some indicating a modest but notable connection to our hypothesis, while others revealing no correlation at all. We will refer also to theories elaborated out of the results from experimental data: the dual hormone hypothesis (testosterone-cortisol ratio), the winner-loser effect (the transient change of testosterone after a win influencing future wins), and the various environmental factors influencing the results.

One of the differences between men and women is in levels of testosterone. Gender and age have also been shown to relate to risk preferences: men have a higher preference for risk taking than women and the preference for risk taking decreases with age [58] [55]. These findings contribute to the growing body of research exploring gender differences in decision-making. They suggest that females may exhibit a more cautious approach, prioritizing safe outcomes and avoiding potential losses. We also add to the various elements of our analysis a study published by Kanayama [99]. The study examined the correlation of disturbs between anabolic use and other traits of personality and disorders. The study found a significant correlation with other substance abuse disorder, and social misconduct during childhood. Both terms correlate with pathological gambling in terms of the relation with impulsivity, de-

lay discounting, sensitization to rewards. Steroid use has been also associated with gambling disorder [147]. Moreover, a study issued in by Fadoua [68] examined the relationship between basal testosterone and a questionnaire assessing the propensity to risk. Results found there was a positive relationship between testosterone and risk propension, and that males were more willing to take risk. Op de Macks et al. [53] studied the effect of sex hormones on monetary reward processing in teens, showing that younger subjects tend to take far more risks than either children or adults. Risk-taking preference appears to peak at age 14 [36], and, according to Laube et al. [107], this effect occurs in part because of a large influx of sex hormones such as testosterone that influence striatal activity. To add more information, adolescents exhibit higher rates of gambling disorder than other age group [193] when both testosterone level are at the maximum, and the development of prefrontal and orbitofrontal cortex is uncompleted [54].

2.1.1 Evidence from endogenous testosterone levels

Many studies assessed the relation between testosterone current levels and subsequent financial risk-taking behaviour. One of the first studies from Coates et al. [43] measured endogenous testosterone levels and testosterone variations in a group of male traders. Results showed that trader's morning testosterone level predicts his day's profitability. This suggest that higher testosterone contributed to economic return, specifically by increasing risky decision making. A study coming from Apicella [7] demonstrated that salivary levels of testosterone correlate positively with risk taking in an investment task for real monetary payoffs. The results from Apicella suggest that a man with a testosterone level one standard deviation above the mean invests 12 percent more than a man with an average testosterone level. The study also shows that there is a positive correlation between facial masculinity and risk taking, which is known to be a proxy of pubertal exposure to testosterone. Sapienza [154] showed that only among women testosterone correlate positively with risk taking. In is important to notice, however, that in comparably low concentrations of salivary testosterone the gender difference in risk aversion disappeared, suggesting that testosterone has nonlinear effects on risk aversion regardless of gender. Stanton, Liening and Schultheiss [165] conducted a correlational study on the effects of endogenous testosterone on choices in the IGT. In this study, IGT performance was measured over 5 blocks, and the number of advantageous deck selections increased over time ($p < .001$). The results showed that high-testosterone women and high-

testosterone men made riskier choices than their low-testosterone counterparts of the same sex, and this effect was pronounced in women. Thus, high levels of testosterone are associated with willingness to incur greater risk in both sexes. High level testosterone participants failed to show significant progresses as the task progresses, compared to low level testosterone participants. This relationship was particularly consistent during the final block of the experiment. These findings suggest that the impact of testosterone on behavioural decision-making may be influenced by its detrimental effects on cognitive flexibility and stubbornness. Studies involving testosterone-treated rats have demonstrated deficits in various forms of cognitive flexibility, such as reversal learning and extra-dimensional set-shifting [188] [202] [112]. Schipper [158] used Holt-Laury lotteries, and tested risk taking for gains and losses, the salivary testosterone and cortisol in 200 subjects (males and females). In males, salivary testosterone is negatively correlated with risk aversion for gains. It means that men with high testosterone were willing to gamble more in order to get the riskier reward. Moreover, females demonstrated to be significantly more risk averse in both domains, compared to males. It has been also proved that salivary testosterone influences intertemporal discounting rate and testosterone levels, in females [56]. While some studies which found a positive correlation between testosterone and risk taking, some has showed no significance [5] [66], [157], or non-linear correlation [165]. For example, a Study by Blanco et al. [5] found that a sample of problem gamblers had testosterone levels were similar in problem gamblers and a healthy control group. This finding regarding males contradicts other studies that have associated higher testosterone levels with increased sensation seeking, aggression, and risky behavior. However, the author proposed that impulsivity is a multifaceted trait comprising various components, suggesting that testosterone may not directly influence the specific gambling behaviors associated with risk-taking. Contrasting results may be derived by the complex interaction between testosterone, personality traits and behaviour. A review by Jennifer Kuratha et al. [106] examined the relationship between personality traits and endogenous testosterone. They found small correlations between risk-taking constructs and testosterone (r=0.12), thus suggesting that endogenous testosterone may influence, or may be influenced by personality traits, thus adding another variable that may account for the contrasting results. Takahashi [172] noted how testosterone may enhance financial risk taking only in low impulsive, and high impulsive people, but the people in between were not particularly affected. Many characteristics were not considered those studies, inner motivation, cortisol, dopamine activity and environmental factors about the

challenge, which is known to exert a role on financial risk taking. Plus, the ratio of rewards/punishments, gambling tasks used, were not standardised: this may have confused results.

2.1.2 Testosterone administration

Testosterone can have transient effect by binding to the androgen receptor in the brain. Many studies have pointed out how testosterone can influence the dopaminergic activity of the VTA [31], nucleus accumbens [195] prefrontal area [75] and orbitofrontal area [114], thus interacting with areas that results correlated with risky decision making. Therefore, a few studies have been conducted to assess the effect of testosterone on financial risk taking, with interesting results. A study by Goudriaan et al. [82] administered both an aromatase inhibitor (Letrozole 2.5 mg) and estradiol to a group of 20 healthy males, for 7 days. Three neurocognitive measures of risk taking were used: Balloon Analogue Risk Task (BART), Game of Dice Task (GDT), and Iowa Gambling Task (IGT). The high testosterone group showed an increase in risk-taking on the BART, suggesting a particular role of testosterone in risk making under unknown probabilities. Testosterone instead did not affect GDT and IGT, which are task of risk under known probabilities. A study by Hermans et al. (2010) used functional magnetic resonance imaging (fMRI) to investigate the effects of testosterone administration on neural activity in terminal regions of the mesolimbic pathway. In a placebo-controlled double-blind crossover design, 12 healthy women received a single sublingual administration of 0.5 mg of testosterone. During MRI scanning, participants performed a monetary incentive delay task, which is known to elicit robust activation of the ventral striatum during reward anticipation. Results show a positive main effect of testosterone on the differential response in the ventral striatum to cues signalling potential reward versus non-reward. Notably, this effect interacted with levels self-reported intrinsic appetitive motivation. Cueva et al. [49] analysed 142 people participating in an experimental asset market. The administration of testosterone shifted response towards riskier investments. Cueva hypothesized that testosterone influenced risk taking by improving optimism about future price changes. A similar experiment by Nadler et al. [120] has confirmed the previous results: testosterone administration generated larger and longer-lasting bubbles by causing high bids in an experimental asset market. In a study conducted by Wu et al. [204], the researchers examined how testosterone affects loss chasing, which refers to an increase in subsequent gambling after experiencing a loss.

Using a computerized gambling task, they assessed risk-taking and loss chasing behaviour. Interestingly, the administration of exogenous testosterone did not have an impact on the proportion of risky choices in the female participants. However, when participants received a testosterone, they exhibited significantly less loss chasing effect, meaning they were less likely to select the risky option following losses rather than after gains. This finding, according to the author, supports the hypothesis that testosterone administration reduces sensitivity to losses in the gambling task, as placebo participants fail to adjust their risk-taking behaviour in subsequent trials after experiencing losses. In another study conducted by Wu et al. [203], it was observed that higher levels of testosterone in circulation were positively associated with impulsivity. The objective of the study was to examine the impact of testosterone administration on impulsivity using an intertemporal choice task, wherein participants had to choose between smaller-sooner rewards and larger-later rewards. The study included 111 healthy young male participants who were randomly assigned to receive a single dose of 150 mg testosterone gel or a placebo in a double-blind, placebo-controlled setup. The decision-making task was performed by the participants 180 minutes after the administration of the substance. The results, based on both model-free (indicated by a higher indifference point) and model-based (indicated by a steeper discounting rate) parameters, revealed that testosterone administration increased impulsive choices. This finding supports the hypothesis that the introduction of exogenous testosterone leads to an increase in impulsivity among healthy young males in a laboratory setting. A study of Carriere et al. [41] explored testosterone as an emerging modulator of impulsivity and risk in problem gambling and confirmed the previous results. They used differentially different drugs treatment for opiate disorders, and measure how they modulated gambling activity. Results explain the efficacy of naltrexone, opiate receptor antagonist, in blocking gambling craving through resetting opiate-testosterone signalling modulating behavioural and cognitive impulsivity, decision-making and reward-punishment sensitivity in GD. Another study from Schaefer et al. [157], used the Columbia Card task, which measures distinctively gain amount, loss amount, and the probability of losing—in both a dynamic, more affective ("hot") and a static, more deliberative ("cold") decision-making context. They tested 80 females with testosterone administration and found no effect on risk taking, in both conditions. These results are consistent with previous findings that testosterone does not significantly influence fundamental risk preferences [26] [209]. It may be possible that testosterone influences some making risk-related subdomains but does not alter specifically risky

decision making in any context. An experiment from Bird [23] indicated that testosterone administration down-regulated task planning ability and inhibition but had null effects for economic decisions on the IGT. An extensive review from Stanton et al. [166] examined all the previous data and pointed out the main problems of the previous research: small sample size, rough ways to analyse testosterone concentrations (for example, salivary testosterone). He then proceeded to test and confirm hypothesis about testosterone role in risky decision making. Firstly, he tested the effect of testosterone administration on risk-taking and loss aversion (for the task, see Tom et al. [178]) in a double-blind, within-subjects, placebo-controlled, crossover experiment within men. First experiment found no actual relation between testosterone administration and risk aversion. Second study tried a more broadly measure of risk taking (BART) and a larger sample size (N= 121). Study 2 provided evidence that contradicted Study 1 by showing that testosterone increased loss aversion and did not predict any risk-taking behaviour. Study 3 tested the correlation between endogenous levels of testosterone and a wide range of economic behaviour and preferences, including risk taking, financial anxiety, temporal discounting in economic decision making, and impulse buying tendencies. Cortisol was measured in order to check for Dual hormone Hypothesis (see below). Testosterone was measured with liquid chromatography tandem mass spectrometry (LC-MS/MS). Test used were BART, Monetary Choice Questionnaire, Risk-taking task, Financial Anxiety Questionnaire, Impulse Buying Questionnaire. Results suggested that testosterone administration was not significantly correlated with economic behaviours and preferences in men and women. The extensive study failed to correlate any subscale of risky financial decision making to cortisol or testosterone level.

2.1.3 2D:4D digit ratio as a measurement of the organizational effect on testosterone, and its relationship with risk taking

The ratio between the length of the index finger (2D) concerning the length of the ring finger (4D) of a palm, is known as second to fourth digit ratio (2D:4D). The length ratio of the second digit shows the quantity of male hormone, to which an individual is exposed prenatally [94]. The shorter the 2D:4D ratio, the higher was the testosterone exposition. Many studies have used 2D to 4D trying to link the androgenization with the effect on the brain on financial risk taking. Though this is an imprecise way to calculate testosterone exposure in the utero, it has given to a good consistence of results. Coates et al. [43] sampled 49 male traders

and tested them for 2D:4D ratio and their performance in a "noisy" and "high frequency" gambling task. The results showed that prenatal testosterone influenced positively risk taking and enhanced the people's performance on the trading floor. Evans et al. [66] tested 67 males with IGT, assessing risk preferences, endogenous testosterone levels and 2D:4D. They found that prenatal androgen exposure affects the performance in IGT, by increasing risk taking. Instead, current testosterone did not predict gambling performance. Garbarino et al. [76] confirmed that low 2D:4D in financially motivated decision-making tasks significantly riskier options, in both males and females (N=152). They stated that the digit ratio partially explains the variation in risk-taking between the sexes. In another experiment [167] 2D:4D, rel2 and risk-taking behaviours across five domains were measured: financial, social, recreational, ethical, and health. A composite measure of risk-taking across all five domains revealed that both rel2 and 2D:4D were negatively correlated with overall risk-taking in both male sub-samples. No significant correlations were found in the female sub-samples. Also, Finley et al. [71] showed that low 2D:4D accounted for the differences in self-reported questionnaire for financial risk taking and gamble, supporting the previous results found. The research of Xie et al. [205] finds that, in line with previous research, male participants exposed to prenatal testosterone took more risk. In addition, they divided risk taking into three subdomain which shed new light on gender differences in risk attitudes. Firstly, the degree of testosterone that men are exposed to in utero correlates with riskier decisions in later life. Prenatal hormone may lead to more risk taking by influencing loss aversion. A study by Texeira et al. [174] tried to determine if 2D:4D ratio influences the amount of money gambled in disadvantageous choice. The results confirm the 2D:4D ratio is one of the main factors biological for explaining the behavioural differences between genders and testosterone exposure, and loss aversion. Secondly, testosterone exposure was associated with more optimism and overweighting of small probabilities of chances under time pressure for male participants, relative to female participants. Optimism and self perception of power may be an important factor in biasing gamblers into continuing playing. A study from Barel et al. [15] proposed association between power and optimism, and their role as moderators of the relation between 2D:4D and financial risk taking, a model differentiating men and women is suggested for better understanding the complex interplay between biological and personality markers. For men with higher testosterone, lower power and lower optimism are experienced as motivators for action to gain power and status, which in turn is translated into risky behaviours. By contrast, for women who generally tend to avoid financial risk taking,

higher optimism and higher power, coupled with higher levels of testosterone result in risky behaviours. Risk taking may be influenced by status. Ronay and von Hippel [152] have examined the relationship between high power and low power status, coupled with 2D:4D and risk propensity in BART. Results shows that low 2D:4D is predictive risk only in low induced status. While most studies have confirmed the negative association between the digit ratio and the preference for risk taking [76] [167] [8] [15] [71] [205], Some experiment exhibit null correlation between the two [171] [7] [38] [125] [138]. Negative correlations were not present.

2.1.4 Reward seeking vs status seeking, and environmental variables

It is also relevant to pinpoint the relation between non-social economic risk taking and risk taking in a money dependent status seeking motivation. The data indeed highlights the relations between testosterone administration and status seeking risk economic behaviour. It is shown that testosterone may reduce the amount of anti-social cheating behaviour in a social context while asserting dominance [92]. Also, as suggested before, Ronay et al. [151] tried to determine if low or high induced status could determine the influence of testosterone on risk taking in a BART task. The results showed that testosterone could induce risk taking only in low status subjects. This adds more information to the issue, suggesting that risk taking may be a biological tactic to gain status, triggered on by testosterone levels [184]. Another recent study showed that testosterone enhances preferences for high-status products relative to low-status products [123]. Additionally, research has also implicated approach-motivation and reward in how testosterone affects impulsive behaviour [61] [193] [203], and competitiveness [62]. Van Honk et al. [92] administered sublingual 0.5-mg single-dose testosterone in a crossover, double-blind, placebo-controlled, within-subjects design. Interestingly, testosterone administration in an experimental game of poker in this game of bluff poker significantly reduces random bluffing, as well as cold bluffing, while significantly increasing calling (in this way a disadvantageous option is chosen, according to the Nash equilibrium). Our data suggest that testosterone in humans primarily motivates for reputable status seeking, even when this elicits behaviours that are economically disadvantageous to find those mechanisms as evolutionarily conserved through the mammalians. Other studies linked testosterone with implicit need for power, dominance, rule, sensation seeking [117] [175] [64]. This could be congruent with the gambling behaviour, as people see money as an attainment of power. On the other hand, testosterone may

influence personality traits [172] [168] [23] and approaches to task learning [202]. Indeed, it might appear that testosterone reduces aspects of cognitive flexibility, to favour a 'win at all costs' approach to maximize gains. To our knowledge, no published studies have evaluated the effects of high-dose testosterone on progressive ratio (PR) schedules of reinforcement for food or drug reward. There are however, many examples of effort discounting tasks proving that testosterone may decrease effort discounting [59] [188] [134] and predict persistence in unsolvable puzzles tasks [192]. The results may be beneficial in understanding how testosterone may impair cognitive function. Interestingly, Stanton et al. [165] noted how testosterone group failed to learn task and improve performance by choosing the right option in IGT task. Moreover, Odlaug et al. [130] observed how gamblers' cognitive flexibility tends to be impaired. Recently, Riva et al. [149] have directly tested whether anthropomorphic primes influenced slot machine gambling. Corroborating previous qualitative reports, their pilot study indicated that regular slot machine players anthropomorphized slot machines more than nonregular players. In three subsequent experiments, participants were assigned to two groups who played an authentic internet slot machine game. Players who were primed with an anthropomorphized description of the slot machine game placed more bets (i.e., more spins), gambled for longer, and ultimately lost more money than players who read a neutral description of the slot machine. This may suggest that a factor of competitiveness towards a "human" machine could trigger inner mechanism of competitiveness, leading people to be more involved in the game. To sum up, the data outlined here suggest that either status, motivation to win, and competitiveness towards an anthropomorph competitor, may be a predictor of subsequent gambling behaviour. These are important variables possibly enlightening the difficult relationship between testosterone and behaviour. Future work might also benefit from adopting measures of reward sensitivity and approach motivation to the gambling experiments.

2.1.5 Testosterone to cortisol ratio

The dual-hormone hypothesis claims that more risk-taking may be explained by high testosterone in combination with low cortisol. Many studies considered the relevant effect of cortisol on testosterone decision making, since it is shown that it may have an inhibitory effect on risk taking [127] [118] [52]. The theory suggests that status-seeking behaviours are to be expected among individuals with simultaneously high testosterone and low cortisol. A study from Nofsinger et al. [126]

examined the role of testosterone, cortisol, and the dual-hormone hypothesis on financial choices and outcomes during two single-decision points, portfolio formation (asset allocation) tasks, and one multi-point portfolio rebalancing task. Those tasks meant to simulate market investing, as they were using a simulation of a financial trading simulation software. They found that higher levels of testosterone increase financial risk-taking, whereas higher levels of cortisol decrease financial risk-taking. The biggest risk taking was in subjects with high testosterone to cortisol ratio. A recent study by Kuin et al. [105] assessed the testosterone to cortisol ratio in a sample of prisoners, comparing them to cold executive functions, and hot executive functions (EF). Cold executive functions refer to logical and strategic cognitive processes such as planning and reasoning, whereas 'hot' EF include affect-driven cognitive processes, such as intuitive risk-taking in decision making. The results showed that prisoners tend to show more problems in hot EF (they take more risk in decision making and learn less from errors) than non-prisoners. These problems are not clearly related to characteristics of aggression in this sample of prisoners. An interesting preliminary finding in line with our expectations is that, despite the lack of a direct relationship between hot EF and aggression, both factors were positively correlated to having a combination of high endogenous testosterone and low cortisol levels. This is one of the first studies to have assessed all these factors altogether in one forensic sample. A study from Kohne [103] tested the endogenous testosterone level, relative to risk taking in a BART, in a group of adolescents and adults. Regarding the dual-hormone analysis, the combination of low cortisol and high testosterone was found to increase the parameter risk preference in both men and boys. This study indicates that the effects of testosterone combined with cortisol are similar in adults and boys. Increased testosterone, or reduced cortisol/testosterone ratio, has been related to low impulse control [139], but rats treated with testosterone chose a larger, delayed reward compared to controls [201]. Another relevant study come from Cueva et al. [49]. They found contrasting result comparing to the dual-hormone hypothesis: no significant evidence associated endogenous testosterone levels with trading behaviour in multi-person markets. On the other hand, exogenous levels had a causative role on risk taking. Cortisol level, instead, was associated with willing to risk in men, but not in women. This according to the author, is consistent with some data referring to gender differences in the perception of stress [182] [110] [146]. It is likely that behaviour in this environment is contingent on a greater number of factors than in the simpler tasks previously used to investigate the connection between testosterone and risk taking. Altogether,

the results point towards a positive relation between testosterone and risk taking, though ulterior work is needed to correctly address contrasting results.

2.1.6 Winner-loser effect

Another important area of work regards study of transient testosterone levels in response to wins, as a predictor of future risk taking [9] [82] [44] [40] [166]. Coates et al. [44] proposed a hypothesis, by reviewing previous data, comprehending his experiment on London traders [43]. They suggested that irrational exuberance observed during market bubbles is mediated by testosterone, and the change in testosterone levels following a win could predict future behaviour and risk taking. Coates measured the testosterone and cortisol levels of 17 male London traders over the course of 8 consecutive business days. Daily testosterone was significantly higher on overperforming days [43]. Then they hypothesized that winning is likely to enhance testosterone levels, and future risky decision making. A study of Carney et al. [40] tested if power poses increased testosterone and risk taking. They also tried risk taking when facing losses, and willingness to compete predicted that posing in high-power nonverbal displays (as opposed to low-power nonverbal displays) would cause neuroendocrine and behavioural changes for both male and female participants: high-power posers experienced elevations in testosterone, decreases in cortisol, and increased feelings of power and tolerance for risk; low-power posers exhibited the opposite pattern. In short, posing in displays of power caused advantaged and adaptive psychological, physiological, and behavioural changes, and these findings suggest that embodiment extends beyond mere thinking and feeling, to physiology and subsequent behavioural choices. Apicella et al. [9] tried to determine if changes in testosterone following monetary wins and losses influence future financial risk taking. They collected saliva samples prior to and at the end of a competitive interaction and then assessed risk preferences in behavioural economics task. The authors reported that irrespective of randomly assigned competition outcome, men (n = 49) for whom testosterone concentrations increased in response to the competition, were less risk averse compared to men for whom testosterone concentrations decreased. Testosterone changed effectively between win and losses, and testosterone changes after the competition were positively correlated with monetary risk taking. Whilst both increased risky choices, only testosterone increased optimism [86]; cortisol did not [49]. Geniole et al. [78] conducted a meta-analysis that reflects the heterogeneity of winner-loser effect findings in studies, collectively involving more than 2500

participants. These authors found that winners of a competition tend to experience modest increases in testosterone, compared to losers (d = .22 for women, d = .23 for men), and that the winner-loser effect is strongest for studies conducted in naturalistic settings like sports venues (d = .46), compared to studies conducted in laboratories, for which the winner-loser effect was weak (d = .08). To confirm the role of this environmental variables, some studies have highlighted that significant involvement in competition has been proved to have a role in post-win enhance in testosterone levels [1]. According to Page et al. [136], win-based testosterone increases could be helpful in attaining short term financial trading gains, but in the long run, foster over-confidence and larger, riskier bets with lower risk-reward trade-offs. Given that surprisingly few researchers have sought to explore whether the winner loser effect applies to gambling, even a basic understanding of how gambling wins and losses can cause marked fluctuations in testosterone has not been established. A recent experiment by Ferrari et al. [70] tried to determine if the winner loser effect could apply to slot machine gambling behaviour. Participants played at a slot machine, one of the most common machine tasks. No effect of winning on testosterone level was found, indicating that testosterone change from pre to post-gambling was similar for both winners and losers. Moreover, baseline cortisol did not influence testosterone change. The anthropomorphising effect on the machine, also, did not predict cortisol levels. According to the author, the absence of evidence about the change in testosterone/cortisol levels following a win may be accounted for the lack of inner motivation of the participants. Anthropomorphising alone did not predict for subsequent engagement, as predicted by previous models [149]. It remains possible that changes in testosterone within the context of competition serves to rapidly modulate ongoing social behaviour. This effect modulation on gambling can be predictive of compulsive continued gambling behaviour, and could lead to inefficient pattern of functioning, since the probability of successive bets is independent. This also refer to a gambler fallacy: gamblers indeed perceive the non-triviality of subsequent gambles. Their shift in behavioural pattern towards riskier bets may then be beneficial and lead to disadvantageous choices. Thus, more study on the transient change in testosterone levels in subjects affected by gambling disorder could be useful to explain better some compulsory mechanism which describes this disorder.

3

Evidence from animal models

3.1 Behavioural evidence

To sum up the literature about testosterone and risk taking in humans, general finding outlines a weak, constant correlation between testosterone and economical risk taking. Inconsistency in results may be derived by the inability to consider manipulate organizational effect of testosterone over the long run, imprecise measures of assessment of prenatal testosterone exposure 2D:4D, and environmentally and personality traits that can interact in a nonlinear way with testosterone function. One example is the influence of status, gender identities, personality traits, engagement, motivation. Both the dual hormone hypothesis and the winner lose effect yielded contrasting results, failing to give an unequivocal explanation on the matter. Also, standardized experiments were not re-tested to check for their reliability, and the various modelling and variable differently administered make impossible to gain reliable, specific conclusions about the matter. In this context, animal models result very valuable because of their inner manipulation of the variables. We will concentrate our aim on rodents' models because most experiments on decision making and testosterone are based on rodents. The manipulation of testosterone in rodents model involves administration of androgens, which can outline transient effect, and gonadectomy, which refers mostly to organizational post-natal effects. We find them a valuable instrument to disambiguate the transient vs organizational effect of testosterone on our issue. We will therefore discuss, in order, main tests used for assessing gambling performance, evidence from testosterone treatment on

rats, and then organizational effect of the hormone on their behaviour. Toward this endeavour, researchers have leveraged the ability of rats to perform complex cognitive tasks in order to model cost/benefit decision making. Findings from studies using such tasks have recapitulated various aspects of human risk-taking behaviour (exaggerated preference for risky options), including the increased risk-taking following drug exposure [24] [45] [69] [119]. Results from gambling tasks shows how rodent males tend to be more risk taking than females in a effort discounting task [134].

TABLE I. Sex Differences in Commonly-Used Decision-Making Tasks in Rodents

Task	Task measure	Sex tested	Sex differences	References
Rat Iowa Gambling Task	Learning about probabilities of different reward outcomes	Males and females	Males develop preference for the advantageous option more quickly than females	van den Bos et al., 2012
Rat gambling task	Choice of optimal (more reward, less timeout, punishment) over suboptimal options	Males and females	Females develop preference for the advantageous option more quickly than males	Peak et al., 2015
Risky decision-making task	Choice of small reward vs. large reward associated with probabilistic footshock	Males and females	Females show greater preference for small, "safe" reward	Orsini et al., 2016
Delay discounting	Choice of small immediate vs. larger delayed rewards	Males and females	Females tend to be more impulsive than males	Eubig et al., 2014; Koot et al., 2009; Lukkes et al., 2016; Perry et al., 2007
Probability discounting	Choice of small, guaranteed vs. large, probabilistic rewards	Males only	Unknown	St. Onge and Floresco, 2009
Effort discounting	Choice of small, low-effort vs. large, high-effort rewards	Males and females	No direct comparison between sexes	Uban et al., 2012; Floresco et al., 2008
Rat Balloon Analog Risk Task	Learning about the probability distribution of avoiding risk and obtaining rewards	Males and females	No sex differences	Ashenhurst et al., 2012

Figure 3.1: A table reviewing the main tasks utilised for rodent gambling analysis [134]

In a study conducted by Bayless et al. [17], the researchers aimed to explore sex differences and the role of neonatal testosterone in prefrontal cortex-dependent impulsive choice behaviour in prepubertal rats. Male and female prepubertal rats were subjected to a delay-based impulsive choice task, where impulsive choice was defined as selecting an immediate small food reward over a delayed large reward. In the first experiment, examining sex differences, it was found that male rats made significantly more impulsive choices compared to female rats. In the second experiment, investigating the organizational effects of testosterone, female rats treated with neonatal testosterone displayed significantly more impulsive choices than control females, and their performance resembled that of control males. The third experiment aimed to determine whether the effect of testosterone on performance was attributed to androgenic or estrogenic actions through the conversion of testosterone to estradiol. Male rats treated with the aromatase inhibitor formestane, which blocks the conver-

sion of testosterone to estradiol, as well as females treated with the non-aromatizable androgen dihydrotestosterone and females treated with estradiol during the neonatal period, all exhibited significantly more impulsive choices compared to control females. Their performance was like that of control males. These results indicate that male pubertal rats exhibit increased impulsive choice behaviour compared to females, and this sex difference is a result of the organizational actions of testosterone during the neonatal period. Furthermore, this effect can be attributed to both androgenic and estrogenic actions. Another rodent model (rIGT) simulates the human Iowa gambling task (IGT); it involves subjects making a series of card choices from four decks, resulting in either winning or losing hypothetical money. Unbeknownst to the subjects, two decks are considered "risky," associated with potential large wins but also larger losses, leading to debt. The other two decks are deemed "safe," offering smaller wins but negligible losses. Over 100 trials, healthy subjects tend to develop a preference for the safe decks. However, individuals with Gambling Disorder (GD) maintain a preference for the risky decks, leading to a build-up of debt. The validity of this test has been confirmed through various experiments [28] [29] [185] [150] [37]. Wallin Miller et al. [189] explored the effects of anabolic-androgenic steroids (AAS) on decision making using a rodent model of the Iowa Gambling Task (rIGT). The Iowa Gambling Task is adapted for rodents to assess their ability to make advantageous choices and learn from rewards and punishments. As hypothesized, testosterone altered decision making on the rIGT, significantly increasing selection of the most disadvantageous lever (L4), compared to vehicle-treated controls. This altered choice behaviour was due to diminished loss sensitivity, as testosterone significantly decreased the lose shift ratio. These effects were specific to the decision-making task and did not affect general cognitive performance or motor function. Similar research points in the same direction. Compared to control rats, testosterone-treated rats were significantly more likely to choose the large reward despite an effort cost, delivery delay, or pairing with a footstock [201] [47] [188]. Another study by Tan et al. [173] studied the effect of Toxoplasma Gondii infection on risk tolerance using a BART task. As Toxoplasma Gondii is a well-known for enhancing testosterone synthesis, experiment wanted to check for the levels of testosterone and the risk tolerance of male Wistar rats. Results showed that testosterone levels lead to enhanced risk taking in Wistar rats. Thus, testosterone decreases sensitivity to these costs, which is consistent with increased sensitivity to reward magnitude. Wallin et al. [188] [187] tested, in 2 separated experiments, probability and effort discounting, reversal learning and set shifting in rats. Rats were

chronically treated with 7.5mg/Kg testosterone. Specifically, testosterone increases aversion to uncertainty but decreases sensitivity to the output of effort for reward. On the other hand, testosterone impaired both reversal learning and set shifting, thus favouring previous maladaptive choices. Notably, rats sensitive to dopamine in the nucleus accumbens, and AAS alter accumbens dopamine receptor expression, causing rats to work harder to obtain the reward thus confirm the previous results on these effects. The negative relation between testosterone increases and aversion to uncertainty is not congruent with previous results on the RDT [47]: however, the probabilistic ratio used in the 2 experiments were different, so a steeper discounting ratio can impair results. Also, rats were not assessed with cortisol concentration, that can influence risk taking and inhibit testosterone function. Impulsive action is another component that is important to assess, as it is correlated with gambling behaviour [113]. Mainly, it is measured in tests of premature responding and behavioural inhibition. In humans, go/no-go and stop signal tasks (SST) are used, and GD individuals show deficits in performance on these neurocognitive tests. In rodents, impulsive action is commonly tested in operant behaviour paradigms, including differential reinforcement of low-rate responding (DRL), go/no-go, and 5-choice serial reaction time task (5-CSRTT). So, when it comes to actual assessment of gambling induced behaviour induced by testosterone in animal models, also measure of impulsivity and motor risk taking in results as a decisive predictor of the behaviour. A study [135] assessed the performance of orchiectomized rats in an open field task, compared to control. Results showed that orchiectomized rats were significantly less prone to explore the open field, compared to control. This result highlights the possible role of risk propension, in animal models. Another study showed that in females, removal of ovarian hormones increased choice of large, high-effort options, and acute administration of estradiol reversed this effect [47] [187] Recent insight from animal models comes from Cooper et al. [47] who investigated the effects of AAS on impulsive behaviour and risk assessment in a rodent model. Impulsivity here incorporates at least three components including impatience, reduced response inhibition (motor impulsivity), and increased risk-taking [67] [60] [198]. In the present model, 7.5 mg/kg of testosterone treatment was administered. Previous studies on both animals and human models have investigated on the effect of testosterone treatment on aggression. This aggression, though, is aware of environmental cues [78]. The result of the experiment shows that testosterone increases instrumental responses in rats when greater rewards co-occur with a greater risk of punishment, in a probabilistic discounting paradigm. Other experiments failed to

reproduce the same results. A study by Dokovna et al. [57] examined physical vs cognitive discounting task in male rats with administered testosterone. While previous studies showed that physical effort is influenced by the dopaminergic activity and thus testosterone, the present study failed to find results which correlate with steroid administration. However, this could have been influenced by the discounting rate of the effort task, which was very high, and the setting of the experiment as a measure of cognitive effort, as it could have reached a physical threshold. When considering decision-making behaviour, it is apparent that both testicular and ovarian hormones may contribute to such behaviours in males and females, respectively. Consequently, distinct sex-typical decision-making phenotypes can emerge, with females tending to exhibit risk aversion and males displaying risk-seeking tendencies. Evidence has indicated that circulating gonadal hormones mediate sex differences in risky decision-making [140] [190]. To directly investigate this hypothesis, Orsini et al. [133] conducted a study examining the effects of testosterone and estradiol administration in gonadectomized (GDX) male and female rats, with the expectation that removing gonadal hormones would disrupt choice behaviour and hormone administration would reinstate it. The studies mentioned by Islas-Preciado et al. [95] and Ishii et al. [93] Buelow and Barnhart [35] suggest that females tend to display greater risk aversion and sensitivity to losses compared to males in decision-making tasks. Islas-Preciado et al. [35] found that females exhibited a stronger preference for a smaller but certain reward over a larger but uncertain reward, especially when the probabilities of receiving the reward were low. This risk aversion in females was primarily attributed to their heightened sensitivity to losses. After experiencing a reward omission, females were more likely to shift their preference towards the small, certain reward. Similarly, Ishii et al. [93] observed a greater sensitivity to loss in females using a different variation of a rodent gambling task. This further supports the idea that males and females may process and utilize salient information related to risks and outcomes in decision-making differently [79] [109]. The findings of the study demonstrated that gonadal hormones, to some extent, mediate the sex-typical patterns of risky decision-making in both males and females [6] [88] [133] [181]. Specifically, ovariectomy (OVX) increased risk-taking in females, while orchidectomy (ORX) decreased risk-taking in males. Importantly, these effects were not attributable to differences in shock reactivity or food motivation. Collectively, these data establish a causal role for gonadal hormones in regulating risk-taking behaviour and highlight the capacity of estradiol to promote risk aversion in both sexes.

3.2 Neural underpinning of the gambling behaviour

In humans, deficit on the IGT is seen with neurological damage to brain regions including the OFc, mPFC, and amygdala, anterior cingulate cortex, tegmental area and ventral striatum, suggesting these areas are important for optimal decision making [143]. Animal studies have shown indeed that selective inactivation of those areas impair decision making on a rodent version of gambling tasks, increasing selection of the disadvantageous option [207] [208] [8] [129] [16]. The neurobiology of the brain response to testosterone is less well understood, but recent work has shown that administration of testosterone is associated with increases in the differential brain response to stimuli associated with rewards and appetitive goal attainment in ventral striatum during reward anticipation [87]. Research of Orsini et al. [134] pointed out that D1 receptors may influence appetitive reward sensitivity towards a greater effort. Testosterone can augment D1 receptors in the ventral striatum, enhancing the perception of the reward in comparison to the effort. Testosterone is also known to reduce coupling of orbitofrontal cortex with amygdala [196]. Therefore, it is possible that testosterone influences risk taking behaviour by altering activity within these regions and positively biasing predictions about the likelihood of future events, an effect reminiscent of our expectation-based pathway of testosterone action [15] [128] [163]. Similar results involve tegmental are in reward sensitivity [104] [46] and tegmental area activation induce greater motivation to earn money [4]. It is noteworthy that areas involved in gambling addiction the one in which Testosterone binds to the androgen's receptors. Research in animal models has identified extranuclear androgen receptors in the hippocampus, amygdala, hypothalamus, prefrontal cortex and tegmental area [155] [156] [31]. These extranuclear androgen receptors are well positioned to regulate rapid membrane and cytoplasmic signalling in axons and dendrites [155] [114] and DNA activity [21]. These mechanism of regulation of androgens could represent one of the causation factors of successive gambling behaviour, and impairment of subsequent executive function [177] [6]. If testosterone is to bias the reward system, then there must be a link between this system and the areas of the brain (e.g., amygdala, hypothalamus, septum) responding to testosterone, and its influence on midbrain dopaminergic neurons might be one way for this to happen. Studies using rodent models and brain lesion techniques have elucidated the specific roles of certain brain areas in gambling behavior. Rats with permanent lesions in the basolateral amygdala (BLA) have been shown to exhibit increased preference for the large, risky reward, indicating heightened risk-taking

behavior compared to rats in the control group [207] [132] [133] [89]. Importantly, control experiments have revealed that this increased risk-taking is not attributed to insensitivity to punishment but rather to an enhanced sensitivity to reward. These findings, along with other research studies [81] [73] [197] [199], highlight the crucial role of the BLA in integrating reward-related information with the OFC and other brain structures. As such, it would appear that the BLA plays an important role in mediating decision making when potential costs (delays, uncertainty) are highly salient. The functioning of amygdala, however, is to facilitate and integrate classical conditioning patterns, and need the integration of a bigger cognitive pathway. Utilizing rodent models, Garzola et al. [77] identified the BLA-orbitofrontal cortex (OFC) pathway as particularly relevant in studying gambling disorder. This pathway plays a significant role in rodent models of gambling disorder, shedding light on the neural mechanisms underlying this condition. Several studies have implicated the nucleus accumbens (NAc) in influencing choices towards more probabilistic rewards [39] [112] [206]. Moreover, Nac is more activated in the presence of a reward [53] [30], and studies show how testosterone influence the ability of Dopamine in the Nac to track risk preferences during risk-based decision making [170] [74]. It has been demonstrated that testosterone can influence the dendritic concentration within the nucleus accumbens [180]. Experimental evidence suggests that testosterone can modulate dopaminergic activity in the NAc by altering receptor expressions [59] and influencing the effort-reward tradeoff in an effort discounting task using rat models. Furthermore, a study conducted by Kelishani et al. [100] investigated the role of androgenic steroid influence on decision making and the density of dendritic spines in the nucleus accumbens. The findings indicated that testosterone tends to reduce the number of dendritic spines present in the nucleus accumbens. The effects of testosterone on two different types of decision-making processes, probability Discounting (PD) and effort Discounting (ED), may vary depending on specific regions within the nucleus accumbens (Acb). The core of the Acb (AcbC) appears to primarily influence ED behavior, while the shell of the Acb (AcbSh) is more involved in PD behavior. When the AcbC is inactivated or not functioning properly, individuals tend to show a decreased preference for larger rewards that require higher effort (ED behavior), but it does not significantly impact their PD behavior. In contrast, when the AcbSh is inactivated or impaired, individuals tend to exhibit a reduced preference for larger but uncertain rewards (PD behavior), while their ED behavior remains unaffected [80] [169]. Another potential role of dopamine is interesting to be assessed. There are different dopamine receptors in the brain, and

they seem to jointly modulate decision making in different ways. A study aimed to investigate the specific relationship between D2 and D4 receptors and their modulation of reward response during near-winning trials. The administration of a D2 agonist in our rodent model resulted in an increased tendency to misinterpret near misses as wins. D2 receptors encompass both D3 and D4 receptors. D3 receptors are predominantly found in the dorsal striatum and nucleus accumbens, while D4 receptors are primarily located in frontal cortical regions associated with higher-order cognitive processes and inhibition. Polymorphisms in D4 receptors have been linked to various impulse-related disorders. After isolating the effects of D3 and D4 receptors, it was observed that a D4 receptor antagonist counteracted the detrimental effect of quinpirole (a dopamine agonist) on the rodent task, restoring performance to baseline levels in the relevant task (referred to as rSMT). Interestingly, D2 and D3 receptors did not show a significant correlation with gambling behaviour. D4 receptors are more densely present in the striosomal compartment of the striatum, as well as in the amygdala and hippocampus. There is an overlap between the activated areas associated with near-miss stimuli and the role of D4 receptors. Activation of D4 receptors can modulate the influence of inputs from the basolateral amygdala and ventral tegmental area on pyramidal neurons in the prefrontal cortex (PFC). mPFC lesions are known to impair decision making in a rodent making task by choosing the highest reward/risky option [137]. In summary, D4 receptors improve performance by inhibiting responses to salient but irrelevant stimuli. This finding aligns with the theory of cognitive flexibility. Another study by Floresco et al. (2006), demonstrated that D4 receptor activity mediated set shifting, a cognitive process involving flexibility in task performance. Jenni et al. [97] discovered that manipulating DA receptors in the medial prefrontal cortex (mPFC) had distinct effects, like those observed in the medial orbitofrontal cortex (OFC), on risk-taking behaviour during the probability discounting task. Specifically, they found that blocking D1 receptors (D1Rs) in the medial OFC led to a decrease in risk-taking, while blocking D2 receptors (D2Rs) in the same region resulted in an increase in risk-taking. Further analyses demonstrated that the impact of D1R blockade was specifically attributed to an amplified sensitivity to negative feedback. Furthermore, there is evidence suggesting that genetic factors play a role in influencing gambling behaviour, particularly in pathological gamblers. Genetic differences and abnormalities have been identified in individuals with pathological gambling, indicating a potential genetic component in this behaviour. Several studies have demonstrated that gambling behaviour has a moderate level of heritability. In line with this, a

study conducted by Wagels et al. [186] investigated the relationship between carriers of the MAOA s phenotype, testosterone administration, and fMRI activation during the Balloon Analogue Risk Task (BART). The MAOA gene is involved in the metabolism of neurotransmitters such as dopamine, norepinephrine, and serotonin, which are implicated in reward processing and impulsivity. The study aimed to examine how variations in the MAOA gene and testosterone levels might impact brain activation patterns during a risky decision-making task. The experiment revealed that individuals carrying the MAOAs phenotype were more prone to engaging in risk-taking behaviour. Furthermore, they exhibited increased susceptibility to the effects of testosterone on risk-taking behaviour. Notably, the MAOA phenotype itself did not exhibit any direct relationship with testosterone levels. Consistent with previous findings, MAOA s carriers displayed significant BOLD activity in the anterior insula, a brain region known to be involved in risk decision-making [164]. This suggests that MAOAs carriers may have a reduced inclination towards harm avoidance, which subsequently increases their propensity for engaging in risky behaviours [34]. It suggests that individuals with the MAOAs phenotype may exhibit distinct patterns of risk-related decision-making and underscores the importance of considering multiple factors when examining the influence of testosterone on behaviour. The variable results observed in the relationship between testosterone and risk-taking behaviour may be attributed to other factors that influence the role of testosterone. These factors can vary from experimental settings to other genotypic conditions, which can potentially modulate the influence of testosterone on behaviour. It has been proposed that optimism could exert a role on gambling, in animal models [148]. Interestingly, optimism was related specifically to enhanced activation of anterior cingulate cortex (ACC), which is involved in predicting the future and processing of self-referential information; and the inferior frontal gyrus (IFG), involved in response inhibition and processing relevant cues. Recent studies have outlined how testosterone can cause optimistic behaviour and sense of agency, which could lead people to be risk takers [194]. Overall, these studies provide valuable insights into the intricate interplay between genetic factors, brain activation, hormone levels, and risk-taking behaviour. Multifactorial analysis involving brain data imaging, and genetic studies, is needed to further assess the role of hormone of financial risk taking.

4

Considerations and Future Works

In this review, we outlined consistent data on the transient and organizational effect of testosterone on risky decision making, which may explain the disparity across sex and the effect of testosterone in risky decision making. It is known that exposure to testosterone in specific periods can change significantly the androgen receptors density and activity in hippocampus and the ventromedial areas [131] and transient testosterone may cause inhibitor control on pain [50]. These changes may affect also how processing information is affected by sex, as male and female have a different way to process information [79] and there is a different degree of activation in males and females during reward and punishment [109]. Yet it is difficult to determine, some studies have shown a different pattern of activation during probabilistic decision making between sexes [162] [160] [48]. Females tend to be generally more risk aversive in many subdomains of risk. One possible evidence comes from the fact that they are specifically more sensitive to aversive stimuli and punishment [42], coherent with a greater activation of the mPFC [96]. Evidence suggests that female rats take longer to select punished rewards and acquire instrumental avoidance learning faster than males. This happens even if punishment is delayed [111]. Also, there is an increased tendency in females to shift their choice after encountering an occasional loss, showing major sensitivity to punishment [95]. In Uban study [181], it is shown that females show more effort discounting, tough stress effect was not considered in this experiment. The effect of stress on cognitive performance shows gender-specific differences, with variations observed between males and females [115] and stress can impair significantly effort discounting [33] [32] [159]. This can outline different behavioural response to stimuli. Pellman [140] tried to determine the will-

ingness to take food in a rodent task with a variable shock punishment. Different evolutionary tactics were used: while men stayed longer and longer on the task, to gather the most amount of food, and gained weight, females tended to become underweight and to avoid the shock punishment by risking less. This could reflect some evolutionary tactic that is represented even if the pathological gambling, thus leading to maladaptive behaviour from both sides. These distinction, however, could not be caused by testosterone, but by both estradiol, organizational effect of estradiol during development, or organizational effect of chromosomes. Estradiol was not addressed in this discussion, but many studies link the hormone to aversion to risk. Moreover, the relationship between gambling disorder and cognitive bias differs for men and women [98], and there are different reward sensitivity neural pattern activation in males and females [109] when assessing for uncertain outcomes. These elements should be addressed in order to understand what specific patterns lead to the disadvantageous choices, and how these cognitive biases are intertwined with the different cognitive biases. Indeed, since the cognitive resources utilised are different, we expect to see a different interaction of androgens on the rewarding properties of the stimuli. This may suggest an analysis with different gambling tasks at the same time, could shed light on the different biases, across sex, that lead to the disadvantageous choices. By exploring the dynamics of gambling behaviour in relation to fixed losses, researchers can shed light on the underlying mechanisms that drive perseveration and risk-taking in pathological gamblers. This approach would contribute to a more comprehensive understanding of the complex nature of gambling-related decision-making. On the other hand, effect of current testosterone has yet to be established. Islas-Preciado et al. [95] has indeed noted that gonadectomy doesn't change risk taking in males in the short term, despite males showing greater risk taking that males. It seems that the role of transient testosterone on risky behaviour is significant, but many environmental variables must come into act to activate the risk bias: motivation, competitiveness, status inducing win.

Further insights about the relation between personality traits and androgens effect and financial decision making can come if reinforcement sensitivity theory applied to gambling disorder. El Ahdab et al. [63] examined the possible relation between the Behavioural activational system (BAS) and testosterone. BAS is based on reinforcement sensitivity theory of personality of Jeffrey Gray (RST). RST involves 3 core mechanisms that influences sensitivity to reward, punishment, and motivation. BAS involves motivation to reward, approach behaviour and impulsivity. It is represented as a striatum-thalamus-neo-cortex network [144]. BAS have

also been proven to influence gambling tasks [101] [14]. The review showed that testosterone is likely to have an activating effect of the BAS, thus enhancing BAS system reactivity to reward, and gambling behaviour. It instead had no effect on the BIS system. Hermans et al. [87] noted how testosterone activated BOLD fMRI response in the ventral striatum. Activation on the ventral striatum was predictive of increasing risk taking in a monetary incentive delay task, but only in low BAS subject. Higher BAS score was not influenced by testosterone. RST theory can be another way to conceive the relationship between testosterone and risk taking and can explain the contrasting results found during the years. The division between a reward dependent mechanism and the aversive stimuli, by identifying the physical distinct pattern of neural activation approach in those 2 constructs, and their relation with personality characteristics, could disambiguate some results found in gambling behaviour [101]. It is also noteworthy to consider the "cognitive flexibility domain" as a component exerting role on gambling usage. As explained before, has been shown as a component which can interact with stubbornness and compulsive behaviour, and inhibition [188] [202] [112]. In the work of Hauger et al. [85] Stroop color word interference test, trail making test, and the stop signal task were used to assess this executive function. Results showed that testosterone treated rats' performance was significantly impaired. These studies have been confirmed by Wood study on rats [202], which showed that chronic administration of testosterone impairs cognitive performance in a biconditional discrimination task (Stroop test). Chronic high-dose testosterone reduced performance in this task. Moreover, nucleus accumbens has been proven to influence cognitive flexibility, and be impaired by testosterone [72] and gonadectomized rats have increased behavioural flexibility [179]. Gonadectomized rats shows also a major mPFC dopaminergic activity, and this may influence cognitive inhibition during planning and set shifting tasks. This demonstrates the potential for testosterone to impair executive function in humans. Specifically, behavioural flexibility has yielded consistent results to be influenced by testosterone, and it is correlated as predictive of problematic gambling [210]. Furthermore, it is crucial to consider that most gambling games involve fixed losses over the medium to long term. The studies we have examined primarily focus on situations where participants choose between a safe and certain reward versus an uncertain one. However, in the case of pathological gamblers, this choice does not manifest in real-time decision-making. Therefore, although the assessment of pathological gamblers' decision-making tendencies may be reliable, it can potentially confound data when combined with other variables. To disambiguate this factor,

further studies should investigate perseveration and the phenomenon of financial loss chasing in gambling contexts. Specifically, testing in situations where fixed losses are involved could provide valuable insights into the inclination of gamblers to persist in their behaviours despite negative consequences.

Compulsive gamblers often exhibit a heightened sensitivity to rewards and a diminished sensitivity to losses. This characteristic behaviour may be attributed to elevated levels of testosterone and reduced levels of cortisol. Current research suggests that cortisol is associated with increased sensitivity to losses and decreased sensitivity to rewards, whereas testosterone is linked to heightened reward sensitivity and reduced loss sensitivity [129]. However, it is important to consider that additional studies have shown that decision-making performance of male and female subjects is differently affected by stress, social context, and trait anxiety. For example, studies have found that men are less prone to acute stress following a loss [183] [182] [29] [28]. Moreover, while acute stress increases risk-taking in men, it leads to more risk-aversive or task-focused behaviour in women [182] [110] [146]. Testosterone is also proven to inhibit stress on males [3]. The interplay between testosterone and cortisol is complex, as testosterone can inhibit cortisol production through HPA axis inhibition, while cortisol can inhibit testosterone production via HPG axis inhibition. Consequently, testosterone and cortisol levels may exhibit inherent correlations and jointly influence the assessment of rewards and risks in individuals with compulsive gambling tendencies [129]. In addition, studies have found that an increased perception of control over emotions in men compared to women may contribute to men's higher engagement in gambling compared to women [200]. Testosterone levels have been shown to enhance the perception of control and the sense of agency [182] [27] [194]. Consequently, these findings suggest that male subjects may be more vulnerable to developing pathological gambling due to differences in information processing related to decision-making and perceived control over emotions. Furthermore, it is important to consider the influence of genes on sex chromosomes, which can impact brain development, function, and behavior independently of gonadal hormones. Genetically modified mouse models have been developed to differentiate between the effects of gonadal hormones and sex chromosome complement on physiological and behavioral outcomes in both males and females [10] [11] [12]. Utilizing these animal models will be valuable in determining whether sex differences in risk-based decision-making can be attributed to differences in sex chromosome complement [10] [11] [12]. The results from animal models point out that organizational effect can be more predictive of risky decision making,

compared to transient effects. This is congruent with the action of testosterone on the brain, which influences mainly genomic mechanisms over the long term [133].

Additionally, it should be noted that testosterone administration in human models is subject to health concerns, which can contribute to inconsistencies in research results. This limitation highlights the importance of utilizing animal models, as they allow for higher dosages of testosterone administration. In the context of studying pathological gambling, there is a lack of research specifically focusing on the gambling performance of anabolic-androgenic steroid (AAS) users. AAS users experience both transient elevations in testosterone levels and the long-term organizational effects of steroid use. This aspect becomes particularly important in investigating the relationship between testosterone and pathological gambling. Some evidence suggests that AAS users exhibit increased risk-taking behaviour [124], although it is important to consider that this may be a causal effect of steroid use rather than solely a consequence of testosterone elevation [189]. An extensive study by Sagoe et al. [153] identified an association between AAS abuse with frequency of gambling behaviour, and measures of impulsivity and sensation seeking. Impulsivity measures were categorized into two components: desire for novelty and intensity. Notably, the AAS has a more pronounced impact on the intensity of stimuli. This aligns with previous findings from studies involving both animals and humans, which highlight the role of testosterone in influencing sensitivity towards rewarding outcomes. However, it is crucial to exercise caution as sensation seeking, a construct associated with all forms of drug abuse, including AAS, may be more closely linked to the overall pattern of drug abuse rather than specifically to a propensity for financial risk. Moreover, drug usage among AAS is often heterogeneous, and different androgens and drugs can have different effect on behaviour [90]. To develop a deeper comprehension of the interplay between testosterone, AAS use, and pathological gambling, future research should investigate the specific effects of testosterone usage on gambling behavior, as evidence tell that addressing this gap in future research would be valuable. Moreover, it is important to acknowledge that pathological gamblers operate in an open world where they can be influenced by various environmental cues, unlike controlled laboratory experiments.

Although the overall big data on the relationship between testosterone and gambling suggests a causative role, the effects in humans are often inconsistent. This inconsistency may be attributed to the non-linear and organizational effects of testosterone during development, particularly in relation to risk-taking behavior. Animal studies have provided more conclusive evidence, supporting the idea

of organizational effects of testosterone and highlighting the importance of transient testosterone. The data indicate that testosterone primarily influences risky decision-making through organizational mechanisms, leading to long-term effects across different subdomains of decision-making tasks. Notably, testosterone has produced the most consistent effects on loss aversion, delay discounting, probabilistic discounting, and effort discounting. These effects may contribute to a 'win at all costs' mindset, where individuals are more likely to face challenges and persist in their behavior to obtain rewards, without fully considering potential losses, suffering, or stress. While this does not necessarily result in overall cognitive deficits, it becomes problematic in the context of gambling games such as slot machines and scratch cards, where losses are fixed in the long run. The traits and perseveration induced by testosterone may lead to maladaptive decision-making in such contexts.

Conducting further studies on the diverse environmental factors that impact motivation, engagement, competitiveness, and the anthropomorphization of the gambling experience is crucial. It has been vastly established testosterone effect on competitiveness and status seeking. The hypothesis behind this analysis is that, as money is general seen as a sign of power and status, testosterone may influence economic behaviour by increasing the willingness to take risk in order to obtain money. This hypothesis may help explain the contrasting results observed in human studies, where monetary rewards are often absent, potentially influencing motivation levels. Conducting additional investigations on all the above-mentioned variables will contribute to a comprehensive understanding of the intricate interplay between testosterone and gambling. This field of research holds promise for shedding light on both clinical implications and macroeconomic investment behaviour.

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