Bachelor Thesis

Sex differences in addiction:

a study of the mesolimbic system, HPA axis and hormonal influences

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Abstract

Addiction is a complex condition encompassing psychological, physiological, and social components, characterised by compulsive engagement in rewarding stimuli despite negative consequences. This paper explores the complex interactions between addiction and sex differences, focusing on hormonal, neuroanatomical, and stress-related influences. Key findings reveal that addiction progression differs between men and women, with females exhibiting faster transitions from substance use to dependency, a phenomenon influenced by hormonal fluctuations such as estradiol (E2). Sex-specific variations in the mesolimbic dopamine system, prefrontal cortex, and amygdala further highlight the biological underpinnings of addiction. Additionally, stress, mediated through the hypothalamic-pituitary-adrenal (HPA) axis, emerges as a critical factor influencing all phases of addiction, from acquisition to relapse. Despite significant advances, inconsistencies in human studies and limitations in animal models highlight the need for more research into the hormonal and neural mechanisms that drive addiction. These insights emphasise the importance of developing tailored, sex-specific prevention and treatment strategies to address the complexities of addiction effectively.

Contents

1 Introduction

Addiction is a complex condition characterised by the compulsive engagement in rewarding stimuli, despite negative consequences. It is both a psychological and physiological phenomenon that affects the brain's reward system, leading to a cycle of dependency and often harm (Becker, 2017). Addiction comes in various forms, including substance use (e.g., drugs, alcohol) and behavioural addictions (e.g., gambling, internet use).
In 2022, the United States recorded nearly 108,000 drug overdose deaths, a figure that doubled since 2015 (CBS News, 2024). Between April 2022 and March 2023, approximately 290,635 adults in England were in contact with drug and alcohol services, a slight increase from the previous year (Adult Substance Misuse Treatment Statistics 2022 to 2023: Report, 2023). Of these, 48% sought treatment for opiate-related issues, while 30% were treated for alcohol-only problems. Notably, there was a rise in individuals entering treatment for crack cocaine and powder cocaine use, with new entrants for powder cocaine surpassing previous peak numbers.

The emergence of synthetic drug cocktails, such as "pink cocaine" or "tusi," has raised concerns, particularly in Latin America and Europe. Despite its name, this substance often contains little to no cocaine, instead comprising mixtures like MDMA, ketamine, and 2C-B, sometimes dyed with food colouring and flavoured. The unpredictable composition of such drugs poses significant health risks and has been linked to an increase in drug-related deaths (Adult Substance Misuse Treatment Statistics 2022 to 2023: Report, 2023). Substances like these are usually cheaper, making them even more accessible than conventional substances such as cocaine or heroin.

Addiction is complicated and diverse, however, some generalisations can be made. Substance use disorders exhibit sex differences in prevalence, substance preferences, and progression patterns (Becker et al., 2016). For instance, males are generally more likely to abuse alcohol and illicit drugs, while females are more likely to develop prescription drug addiction (Becker et al., 2016). In addition to substance use, behavioural addictions also show sex-specific patterns (Fonseca et al., 2021). Males are more likely to engage in problematic gambling and internet addiction, while females are more prone to compulsive shopping and eating disorders (Wong et al., 2016; Fonseca et al., 2021; de Mattos et al., 2016). These differences may stem from varying coping mechanisms, with females more likely to use addictive behaviours to regulate mood or stress (Fattore et al., 2014).

A trend observed in healthcare for the last few decades has focussed on the individualisation of healthcare. The shift from a generalised 'one size fits all' approach to more individualised care does imply that there is a necessity for understanding the differences between patients. One important distinction to make in this process is accounting for the sex of the patient. Understanding the sex differences in addiction is crucial for advancing both scientific knowledge and practical interventions. Firstly, men and women often exhibit distinct patterns in substance use, motivations, and consequences, which requires tailored approaches in prevention and treatment. Secondly, biological and hormonal differences between the sexes influence how addiction develops and progresses, underscoring the need for sex-specific research. Lastly, social and cultural factors play a crucial role in shaping substance use behaviours and access to care, making it essential to address these differences to achieve desired health outcomes. A comprehensive understanding of these differences and their implications on addiction-like behaviour is essential to properly address an issue as complex as addiction.

2 What is addiction?

Usage of substances or a particular behaviour does not equal addiction. A description of addiction is the change from positive reinforcement experienced from the effects of the substance, to negative reinforcement when the substance is not taken. Or in cases of behavioural addictions, when the behaviour has not or cannot be completed, such as gambling, sex or shopping.
Another characteristic change in addiction is the change from impulsive behaviour to compulsive behaviour (Uhl et al., 2019). Impulsive behaviour is often seen as repeated intoxication and positive reinforcement, substances get taken regardless of the known negative consequences (George et al, 2017). Compulsive behaviour is observed later, in the withdrawal and preoccupation phases.

Addiction is typically organised into three phases; acquisition/intoxication, withdrawal/negative effects, preoccupation/anticipation (George et al, 2017).
The acquisition phase is when the substance is first taken and the first associative mechanisms are activated. The main neurotransmitters here are dopamine and opioid peptides.
The withdrawal phase is when an association between the substance and a positive reward has been established. During this phase, in addition to dopamine and opioid peptides, other hormones and neurotransmitters also become involved. Stress hormones (CRF), norepinephrine and vasopressin all increase during this phase (Koob, 2009), and get released when the substance is not taken. The amygdala is also more involved during this phase, suggesting a more emotionally involved connection.
The final phase of preoccupation completes the transition from positive to negative reinforcement. Here, the amygdala and hippocampus are heavily involved. During this craving phase, the inhibitory function of the PFC has been shown to be decreased (Goldstein et al, 2012). This decreased inhibition is believed to be one of the main reasons for drug-seeking behaviour regardless of the negative consequences and has been associated with an increase of GABAergic and CRF activity (George et al, 2017). Some of these changes in the morphology of the brain and neurons has been partly attributed to Delta-FosB, a transcription factor that accumulates in the striatum and NAc after repeated substance exposure (Fluyau et al., 2024). This transcription factor is able to alter the morphology of the pathways in the brain, resulting in the addiction phenotype.

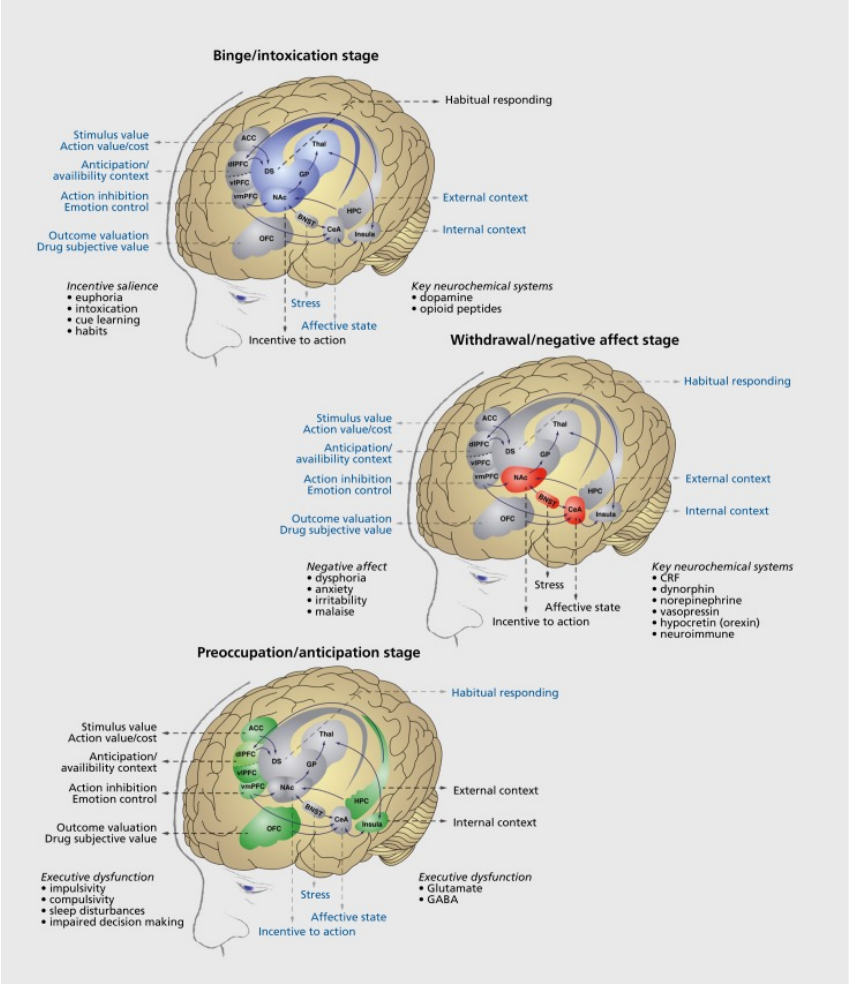

Figure 1: *This figure shows the pathways and their components during the different phases of addiction. Illustrating the pathways, associations and neurotransmitters per phase, we can see clear distinctions between the phases. A shift from positive association to habit forming and finally to dependence and preoccupation becomes clear. Adapted from: George, O., & Koob, G. F. (2017). Individual differences in the neuropsychopathology of addiction. Dialogues in Clinical Neuroscience, 19(3), 217–229. DOI: https://doi.org/10.31887/dcns.2017.19.3/gkoo*

3 Mechanisms of addiction

3.1 Mesolimbic system in addiction

The mesolimbic system is responsible for the engagement and reinforcement of rewarding feelings of pleasure (Alcaro et al., 2007). The dopamine (DA) neurons that start in the ventral tegmental area (VTA) and substantia nigra project to the forebrain (PFC, striatum, hippocampus and amygdala) (Kokane & Perrotti, 2020). This system is necessary for the basic actions needed for survival like feeding, mating or social interactions. The chronic use of drugs will result in enhanced activation of this system which can result in changes in the structure and function of these pathways.

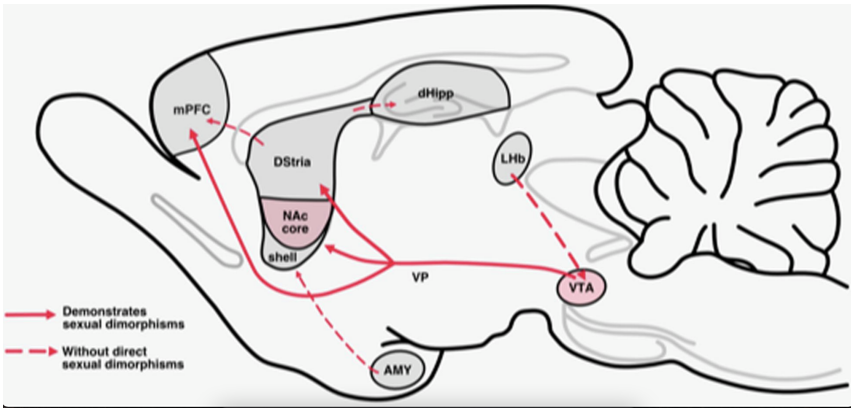

Figure 2: *Shows the mesolimbic reward pathway. Sex differences have been illustrated using solid arrows, whilst pathways without sexual dimorphisms are dotted. Adapted from: Kokane, S. S., & Perrotti, L. I. (2020). Sex differences and the role of estradiol in mesolimbic reward circuits and vulnerability to cocaine and opiate addiction. Frontiers in Behavioral Neuroscience, 14.* https://doi.org/10.3389/fnbeh.2020.00074

3.1.1 VTA in addiction

As mentioned before, the VTA is part of the mesolimbic system. Here it is involved in rewarding motivational processes, but is also involved in the mesocortical DA system, which is involved in working memory, drug-cue associations and its enforcement of drug use (Olivia et al., 2016). The VTA contains DA, GABA and glutamate neurons, where drug use changes the excitatory and inhibitory input on the DA neurons in the VTA (Olivia et al., 2016). GABA is the main inhibitory neurotransmitter (Jewett et al., 2023), whereas glutamate neurons have a mainly excitatory function (Zhou et al., 2014). Being able to influence both the inhibitory and excitatory pathways, the VTA is likely responsible for mediating the effects of substances (Olivia et al., 2016).

3.1.2 Striatum in addiction

The striatum consists of two parts, the dorsal striatum (DS) and the ventral striatum, also known as the nucleus accumbens (NAc) (Yager et al., 2016). The dorsal striatum can again be subdivided into the dorsomedial striatum (DMS), responsible for goal-oriented learning, and the dorsolateral striatum (DLS), necessary for stimulus-response learning. When the drug associated cues are established in between the NAc and the DS via intrastriatal connections, simple exposure to only the cue can activate the DS (Volkow et al., 2006). This highlights the importance of this area in all phases of addiction.
The NAc has two areas with different functions and connections. The shell mainly receives information from the limbic system, whereas the core receives its input from the motor system (Xu et al., 2020). Their outputs also differ, where the core mainly projects on the substantia nigra, the shell projects to the globus pallidus and the VTA (Xu et al., 2020; Ma et al., 2020). Regardless of the separation of their in- and outputs and the function of the shell and core, they do share important connections which could be involved in combining the different inputs to be converted to one output (van Dongen, 2008).

This difference in function is also seen in addiction. The core interacts mainly between the regions involved in motor function, so the output of behaviour. The shell interacts with the limbic system and autonomic system, suggesting regulation of reward and responses to stimuli (Xu et al., 2020). So, combined, the core and the shell control the engagement in and reinforcement of addiction-like behaviour, using these reward pathways (Meredith et al., 2008). Following this, it is understood that the NAc shell is mostly involved in short-term aspects of addiction such as reward, and the core is mostly involved in long-term behaviours.

3.1.3 Prefrontal cortex in addiction

The medial prefrontal cortex (mPFC) gets its input mainly from the VTA via dopaminergic projections, which activate the glutamate system in the PFC (Koob & Volkow, 2009). This activation triggers the activation of mesocortical dopamine neurons in the VTA, and the glutamatergic projections take control of the dopamine release in the PFC (Geisler & Wise, 2008). As the PFC also sends glutamatergic signals to the striatum, it has the ability to regulate conditioned responses to stimuli or other cues. Researchers have shown that under a period of drug abstinence, there is a strong increase in glutamatergic activation of the nucleus accumbens (Schofield et al., 2016). This highlights the importance of these pathways in regulation of cue-associated behaviours.

3.1.4 Hippocampus in addiction

The hippocampus is sometimes referred to as the 'flash drive' of the brain and is highly involved in learning and memory processing (Fogwe et al., 2023). In addiction, the hippocampus is involved in the formation of drug-cue associations and the reintegration of drug related memories. It has also been found responsible for the reinstatement of drug taking behaviour seen in relapse through these environmental cues (Kutlu & Gould, 2016; Xu et al., 2020).

3.1.5 Amygdala in addiction

The basolateral amygdala (BLA) is involved in the response to natural rewards, and therefore drug-associated cues also. The BLA receives dopaminergic inputs from the VTA and outputs to neurons in the NAc (Xu et al., 2020). Due to its position and connections between the DA input from the VTA and its output to the NAc and PFC, it is optimised for forming and maintaining associative memory functions. As the BLA receives inputs that have sensory information associated with them, BLA neurons encode emotionally significant information (Rosen et al., 2015; Rosenkranz & Grace, 2002).
Research has also shown that the amygdala is involved in the associative properties in opiate usage, where inactivation of the BLA led to the abolishment of the ability of drug-cues to reinstate a response (Fuchs & See, 2002). Increases in activity of the central amygdala (CeA) are related to the anxiety-like effects seen in acute withdrawal and increased drug intake associated with addiction (Koob & Volkow, 2009) and inactivation with DA antagonists led to abolishment of self-administering drugs (Caine et al., 1995).

3.2 HPA axis in addiction

Stress has long been known as a risk factor for addiction. Stress can come in many forms; social, physical, physiological or psychological stress can all influence our mood, wellbeing and behaviour (Scheiderman et al., 2008). The hypothalamic-pituitary-adrenal (HPA) axis is one of the most important pathways in the stress response (Karaca et al., 2021).

The stress response starts in the paraventricular nucleus (PVN) in the hypothalamus, where corticotropin releasing hormone (CRH) gets released upon a stressor (Herman et al., 2016). Areas involved in addiction such as the PFC, amygdala and hippocampus can all signal these stressors to the PVN (Nikbakhtzadeh et al., 2023). The CRH then gets transported to the anterior pituitary together with arginine vasopressin (AVP), where there is access to corticotrophs. Upon stimulation of CRH and AVP, the corticotrophs release adrenocorticotropic hormone (ACTH) into the adrenal glands where it promotes the synthesis of glucocorticoids (cortisol in humans, corticosterone in rodents) (Sheng et al., 2021). During chronic stress, the HPA axis is highly active, leading to an increase in the release of glucocorticoids (GC's).

Glucocorticoids can influence things like behavioural responses such as mood, immune function and decision making (Pan et al., 2023). Research has also shown that there is a correlation between the pathways of self-administration of substances and the release of glucocorticoids due to stress (Srinivasan et al., 2013). It has even been shown that in rodents, injections of antagonists of glucocorticoid caused a decrease in stress-induced relapse (Taslimi et al., 2018). It has been suggested that this role of stress in addictive behaviour could be due to the influence of the stress response on the formation of memories related to substance use experiences (Goldfarb et al., 2019).

4 Sex differences in the anatomy of addiction

4.1 Sex differences in the mesolimbic system

4.1.1 Sex differences in the VTA

The neurons in the VTA have been found to be different in males than females in multiple ways. Research has shown that sex and ovarian hormones (oestradiol) can influence the dopaminergic cells in the VTA (Wang et al., 2020; Johnson et al., 2019). It has also been found that female rats have a larger percentage of dopaminergic neurons in the VTA than males (Kritzer et al, 2008). More differences have also been found in the activity, distribution and size of the dopaminergic neuron populations (McArthur et al,, 2007; Kalamarides et al., 2023). Where females had lower GABA levels in the VTA than males when experiencing withdrawal from morphine exposure.

The baseline activity of the dopaminergic neurons in the VTA might be similar between male and female rats is nearly identical (Gillies et al., 2014; Locklear et al, 2016). But the level of oestradiol (E2) in the blood can influence the activity of the VTA dopaminergic neurons: Zhang et al. (2008) have shown that the firing rates of these neurons differ depending on the phase of the oestrous cycle. They showed that the firing rates are highest in oestrus, intermediate in diestrus and lowest in proestrus. In ovariectomised (OVX) rodents, replacement of E2 resulted in the increased DA activity and DA release (Calipari et al., 2017, Vandegrift et al., 2017). They showed that over the oestrous cycle, while the E2 increased, so did the inhibition in the OVX-E2 treated mice. Using fibre optic cables to measure the activity of neurons in the VTA, they showed that E2 administration lead to this increase in activity and release of DA. This ability of E2 to influence the dopaminergic VTA neurons suggests oestrogen receptors are involved and locally expressed (Milner et al., 2010; Kokane & Perrotti, 2020).

4.1.2 Sex differences in the striatum

In the striatum, the main neuron type is the GABAergic medium spiny neuron (MSN), making up about 95% of the neurons in this region (Matamales et al., 2009). These MSNs in the dorsal striatum can influence motor as well as cognitive functions via their projections (Haber, 2011). These neurons combine all of the inputs from different brain regions and determine the final output of the striatum (Yoest et al, 2015; Kokane & Perrotti, 2020).

Sex differences in the shell of the NAc are not very consistent or clear, likely due to interactions with other regions of the brain (Yoest et al, 2015; Kokane & Perrotti, 2020). The sex differences at the core of the NAc seem to be mainly controlled by influences on the characteristics of the neurons and striatal terminals (Wissman et al., 2011; Forlano & Woolley, 2009). Research also suggests that there are sexual dimorphisms in spine density, where females have a higher spine density and larger spine size in the MSNs of the core of the nucleus accumbens (Forlano & Woolley, 2009). This study also showed that there is no difference in the number of DA neurons.

4.1.3 Sex differences in the prefrontal cortex

One research group has also shown that under the female dependent subjects, a larger decrease was found in the volume of white cerebral matter and the lateral OFC (Rosetti et al., 2019). They

took magnetic resonance images (MRI) from cannabis users (n=129) versus controls (n=114). They found that overall, dependent females had a higher chance of reduction in the cerebrum white matter and the lateral OFC when compared to their controls. This difference was not observed in dependent males and their controls.
It has also been shown that the activity patterns between males and females differ. It was found that stimulation of the inferior gyrus, part of the PFC, was negatively correlated with cocaine use in females but not males (Cousijn et al., 2021). This suggests a sex-dependent connectivity in the PFC.

4.1.4 Sex differences in the hippocampus

Males generally have a greater absolute hippocampal volume than females, but when this is corrected for total brain volume this difference disappears (Tan et al., 2015). But when examining the regions of the hippocampus, clear differences emerge. For example, the posterior hippocampus has been found to be larger in females than males (Sacher et al., 2012), indicating sex dependent differences in the connectivity. Other research has shown that females tend to use more brain areas than males during spatial navigation tasks (Yagi & Galea, 2018). Females were found to use the prefrontal cortex more and the hippocampus less than males (Sneider et al., 2011), further supporting the idea that females have different connectivity when compared to males.

4.1.5 Sex differences in the amygdala

Researchers have found that amygdala volume was 6% lower in alcohol dependent males when compared to control males, which was not found in females (Grace et al., 2021). In male neurons in the central amygdala (CeA) were found to be more sensitive to inhibition by ethanol than female neurons (Logrip et al., 2018). This group also found that female neurons were inhibited by cortisol during a stress response, decreasing the effect of the ethanol. The overall decrease in amygdala volume has also been found to be greater in males than females in alcohol abuse (Topiwala et al., 2017). This suggests less activity and relative importance of this brain area in dependent males than dependent females.

4.2 Sex differences in the HPA axis

Multiple studies have shown that females have greater concentrations of ACTH and glucocorticoids upon exposure to acute stress and take longer to return to baseline levels than males (Green et al., 2016). It was also found that these increases in stress hormones were dose-related and significantly higher in females than males (Kuhn et al., 1997). Researchers have suggested that this could be due to sex differences in the PVN activity (Babb et al., 2013), although this remains elusive due to contradicting findings (Kokras et al., 2019). Another possible explanation for these sex differences could be the different levels of HPA-related gene expression in response to acute stress (Babb et al., 2013). They found that males typically had higher levels of CRH and AVP mRNA than females in the PVN (Green et al., 2016) and less of the ACTH precursor proopiomelanocortin (POMC) in the anterior pituitary (Iwasaki-Sekino et. al., 2009).
Although the precise mechanisms behind these sex-differences remain unclear, it is evident that these differences exist.

5 Sex differences in gonadal hormones

Sex hormones, including testosterone and oestradiol, are known to influence a wide range of behaviours and neural processes. These hormones play a role in modulating risk-taking, neural excitability, and substance use behaviours, often showing sex-specific effects (Martier et al., 2023).

5.1 Testosterone in addiction

It has been found that testosterone is linked to increased risk taking behaviour, even showing effects on gambling (Stanton et al., 2011) and even the economy (Cueva et al., 2015). This risk taking behaviour is associated with the intoxication stage of addiction (Brooks et al., 2019). Suggesting that testosterone may contribute to the earlier exposure to substances or addictive behaviours in males. However, it has also been found that testosterone and progesterone administration negatively affects cocaine consumption when self-administering in rodents (Mello et al., 2011). Thus, testosterone might cause earlier exposure to substances or addiction-like behaviour but dampen the effects of addiction at a later stage.

5.2 Oestradiol in addiction

Apart from the sexual dimorphisms in the anatomy, there is also an influence on the electrophysiological characteristics of the GABAergic MSNs by changes in E2 (Proano et al., 2018). They observed that the frequency and strength of the excitatory signals decrease during diestrus, while intrinsic properties such as resting membrane potential and input resistance change to increase the excitability of the neuron. During proestrus and estrus the opposite happens, where the intrinsic excitability decreases and the excitatory signals increase again. This suggests that lower E2 levels, as seen during diestrus, leads to activation of the MSNs, whilst higher levels of E2 induce the release of GABA (Proaño et al., 2018; Kokane & Perrotti, 2020).

In the nucleus accumbens, there are two types of dopamine receptors. The D1 receptors have an excitatory function for movement and reward (Kokane & Perrotti, 2020). D2 receptors are inhibitory on the globus pallidus. Overall it has been found that E2 can increase the turnover of dopamine in the brain of rodents (DiPaolo et al., 1985), that E2 increases the binding of dopamine to D2 receptors (Bazzett & Becker, 1994, DiPaolo et al., 1985) and can increase the density of the D2 receptors (Ferretti et al., 1992). Therefore it can be concluded that D2 receptor inhibition is influenced by the level of oestradiol, whereas there are nearly no differences for the functioning or number of D1 receptors (Ferretti et al., 1992).

It has been shown that females tend to progress through the stages of addiction more quickly than men (Becker, 2016). This has been shown to be true in self-administration experiments (Hu et al., 2003; Lynch Carroll, 2000), where male and OVX rats displayed an increase in acquisition of cocaine self-administration upon treatment with E2 (Hu et al., 2003; Jackson et al., 2005). And most other research also suggests that fluctuating E2 levels have an influence on the susceptibility to addiction (Towers et al., 2023).

To study this, animal models can be used to obtain insights that could not be obtained in humans due to ethical considerations. The estrous cycle in rodents is similar to that of humans,

although their cycle is much shorter. This leads to a quicker onset and decline of the blood plasma levels of the rodents when compared to humans, but the principle is the same (Pestana et al., 2022). The period of the estrous cycle in rodents takes about 5 days, whereas in humans this takes about 28 days.

5.2.1 Menstrual/oestrous cycle

The fluctuations in the sex hormone levels result in the brain also receiving these hormones in a cyclic manner. Therefore, the female brain does not always have a base-level of these hormones, but receives different levels of them depending on the oestrous phase (Kokane & Perrotti, 2020).

Phase	Description
Metestrus	This is the phase where the levels of progesterone (P4) and estradiol (E2) are typically low, allowing the cycle to restart again. This usually takes 24 to 48 hours and is followed by the diestrus.
Diestrus	This phase looks similar to metestrus but is characterised by a peak of oestradiol at the end of this phase. This peak is the sign that the cycle is going into the proestrus phase.
Proestrus	Here we see a clear increase in the levels of both progesterone and estradiol, leading to their peak. The rapid increase of both of these hormones is what will trigger ovulation. When estradiol begins to decline but progesterone is still high, ovulation is reached. The decrease in the levels of estradiol is what will lead the cycle into the estrus phase.
Estrus	Both E2 and P4 levels here are at their lowest. This will lead to the cycle restarting at the metestrus phase.

Table 1: **Estrous Cycle**

5.2.2 Menstrual cycle in humans

In humans, the menstrual cycle bears resemblance to the estrous cycle observed in rodents, wherein the hormonal levels of estradiol and progesterone show regular fluctuations over a duration of approximately 28 days. These hormonal variations serve to maintain the processes of ovulation and the onset of menses through similar physiological mechanisms (Pestana et al., 2022).

The follicular phase of the menstrual cycle spans a 10 to 12-day period and is characterised by the low levels of progesterone and a progressive increase in oestradiol concentrations, ultimately leading to a peak that triggers ovulation (Kokane & Perrotti, 2020). Subsequently, the luteal phase, extending for another 10 to 12 days, is marked by a gradual rise and subsequent decline in progesterone levels, along with a secondary gradual peak in estradiol. The onset of menses occurs when both E2 and P4 have reached their lowest point at the end of the luteal phase (Pestana et al., 2022).

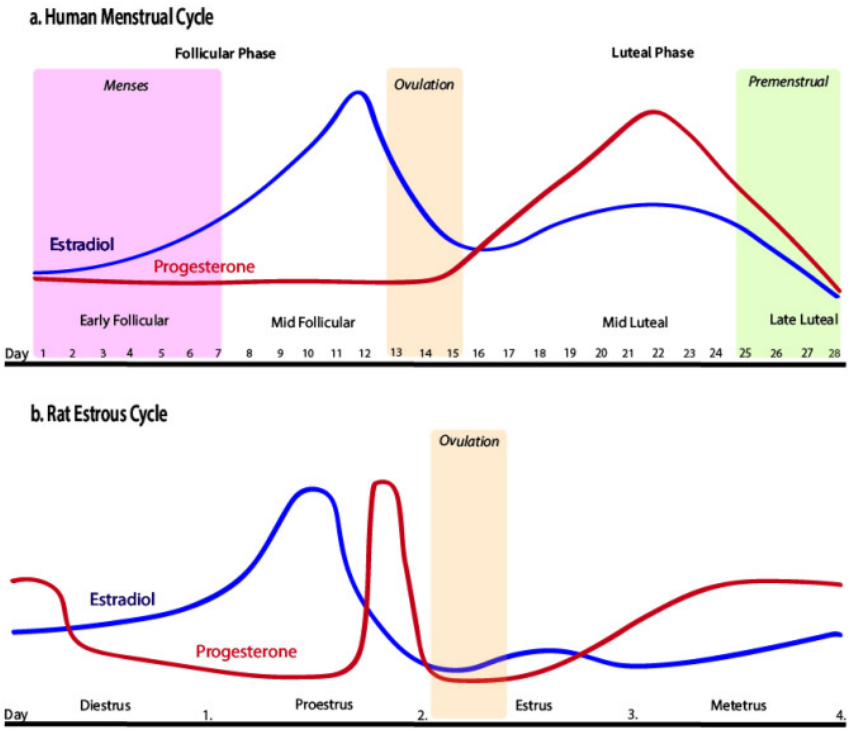

Figure 3: *Shows the menstrual cycle in humans and the estrous cycle in rodents. Due to their similarities in phases and the corresponding levels of hormones, this rodent model can be used to study the effects of the menstrual cycle. Adapted from: Pestana et al.,(2022). What pre-clinical rat models can tell us about anxiety across the menstrual cycle in healthy and clinically anxious humans. Current Psychiatry Reports, 24(11), 697–707.* https://doi.org/10.1007/s11920-022-01376-7

5.3 Hormones and the HPA axis

Some of the sex differences in the HPA axis can be explained by the circulating levels of gonadal hormones. Researchers often use gonadectomy (GDX) together with hormone replacement in order to study these effects. Most findings conclude that estrogens increase HPA activity whereas androgens decrease HPA activity (Goel et al., 2014). One of the supporting pieces of evidence is a decrease in ACTH and corticosterone levels in female GDX mice, where there was an increase observed in male GDX mice (Seale et al., 2004).

These results seem promising, but not all studies had the same results. Conflicting evidence has been found that seems to elude the opposite, with increases for males and decreases for females (Babb et al., 2013). Thus, the fluctuating levels of oestradiol during menstruation could influence the levels of glucocorticoids, increasing susceptibility to drug-taking behaviour.

6 Observed sex differences

6.1 Observed sex differences in the epidemiology of addiction

In alcohol consumption in men, they usually drink more, more often and more dangerously than women. Although, this gap is closing, especially in younger adults. And with women starting to drink at an earlier age this does not seem to slow down (Fonseca et al., 2021).
Like mentioned earlier, men are more likely to use substances, but women are closing the gap according to recent research (Fonseca et al., 2021). They found that there was a substantial increase in the cocaine consumption in women in Argentina and Bolivia. For opiods, researchers in the US also found that the addiction rate for heroin is increasing for women between 2007 and 2014 (Marsh et al., 2018). In this same study they also found that the onset of the addiction is different in women compared to men. Women are more likely to start with a legal prescription for pain relief than men (Marsh et al., 2018). One reason that was suggested is the increase in the amount of women that have experienced some form of trauma (Wilson & Widom, 2008).
Men and women have also been found to have different motivations for drug use. Men are more likely to first use substances due to peer-pressure or thrill-seeking. Women mostly use drugs as a coping mechanism to deal with issues like depression and anxiety (Fonseca et al., 2021). This could have societal factors, but might have an underlying biological basis.
When it comes to types of substances used, men are more likely to use alcohol and cannabis, whereas women are more likely to misuse prescription medications, like opioids and benzodiazepines (McHugh et al., 2022)

6.2 Observed sex differences in the advancement of addiction

Sex differences can be found throughout all phases of addiction, with different pathways and systems involved in each step

6.2.1 Acquisition

Binge-drinking is over 2.5 times more likely in men than in women (Keyes et al., 2008). Although, as mentioned previously, this gap is closing rapidly. When comparing two studies a decade apart, it was found that the number of days that people drink per month increased for women and decreased for men (Keyes et al., 2010).
Females also tend to start at lower doses than males do (Hopf & Lesscher, 2014). Social and cultural factors also have an influence on the acquisition of addiction (Becker et al., 2016). One example is peer pressure, often seen in adolescent males, which can increase the chances of the use of a substance and thus the probability of addiction. For females, trauma is often associated with substance use (Carter-Orbke et al., 2024).
In general, men have an increased probability of using drugs. However, men and women are equally likely to develop a substance use disorder (SUD) (Treatment Episode Data Set (TEDS): 2014, National Discharges From Substance Abuse Treatment Services). Women also go through the process of addiction faster, progressing more quickly from substance abuse to substance dependence faster than men do. This move from onset to addiction is also known as telescoping (Treatment Episode Data Set (TEDS): 2014, National Discharges From Substance Abuse Treatment Services). This phenomenon of faster telescoping in females is also seen in rodent studies (Radke et al., 2021). Where self-administration by female rodents of substances such as cocaine,

alcohol or amphetamines are observed to progress towards addiction faster than males (H. C. Becker, 2012; Hopf & Lesscher, 2014).

6.2.2 Withdrawal

This is where the addiction-like behaviour is really established and stabilised. Here, females tend to stabilise at higher doses than males (J. B. Becker et al., 2016), they also show more and greater side effects than males do. Seeking external or professional help is one of the first steps to break the typical progression seen in addiction. Here another difference can be observed, namely that females seek this help significantly more often (McHugh et al., 2017).
In the phase of withdrawal, a multitude of differences can be found between the sexes. Females during withdrawal will show more anxiety and mood swings during this phase. Meanwhile, males will exhibit more agitation and physical changes such as sweating during withdrawal (Fattore et al., 2008). Women have also been found to have more significant symptoms when trying to quit smoking than men (Becker et al., 2016). Thus potentially having more difficulty with abstinence.

6.2.3 Preoccupation

In this phase, women are more susceptible to stress and emotional triggers, leading to a higher likelihood of relapse when faced with difficulties or negative emotional states (J. B. Becker et al., 2016). Men may be more influenced by environmental cues and contextual factors, such as social settings where substance use is prevalent and have longer periods of abstinence (J. B. Becker et al., 2016).
Coping mechanisms during relapse also show sex-specific patterns. Women may lean towards internalising behaviour, using substances to mitigate feelings of depression or anxiety. Conversely, men might adopt externalising behaviour, using substances in response to external pressures or to enhance positive emotions (Flores-Bonilla, 2020).

6.3 Influence of the menstrual/oestrous cycle on addiction

So, there are fluctuations in E2 in female rats during the oestrous cycle, where E2 can influence brain areas involved in addiction-like behaviours. But how do these results reflect in the behaviour of women? It has been shown that the frequency of cigarette use increased in the premenstrual and menstrual phase when compared to the follicular, ovulatory and luteal phases (Snively et al., 2000; DeBon et al., 1995). In amphetamine studies, the effects of this substance was described as more intense in women in the follicular phase (Justice & de Wit, 2000) compared to women in the other phases of the menstrual cycle. In alcohol or cocaine related studies there were either no correlations found between the menstrual cycle of women and their substance intake (Carroll et al, 2015; Mello et al., 2007), or they contradict each other (Carroll et al, 2015; Lambeth et al, 2020).

However, in rodents such contradictions were not found. It was mentioned earlier that OVX females treated with E2 had increased acquisition of self-administration (Hu et al., 2003; Jackson et al., 2005), but other research has shown that the influence of E2 is dependent on organisation preceding puberty (Perry et al., 2013). They showed that perinatal hormone signalling (progesterone and oestradiol) renders the male brain insensitive to later exposure to oestradiol. Female rodents did not need this perinatal signalling for E2 to increase cocaine self-administration or

general intake (Perry et al., 2013). They also found a decreased effect of oestradiol in adult females treated with an oestradiol benzoate (EB) at the start of puberty, suggesting that E2 during puberty can masculinise the neurons that govern this behaviour. It was also found that untreated females had an increased motivation, while the pubertal treated E2 group had decreased motivation (J. B. Becker & Rudick, 1999; Perry et al., 2013). This suggests that oestradiol during puberty might influence motivational behaviour, but other factors determine the ultimate behaviour.

Oestradiol is able to increase this motivation for cocaine due to its effects on the striatum, where it causes a drug induced dopamine overflow (J. B. Becker & Rudick, 1999). But oestradiol is also involved in a negative feedback loop between the substantia nigra and the VTA (Torres-Hernandez et al., 2005; Zhang et al., 2008). This, together with the findings mentioned above, suggests that E2 together with other substances like progesterone feminise the full response in untreated rodents. In OVX+E2 treated mice, later E2 administration might only feminise the negative feedback loop, leading to reduced dopamine signalling and lower breaking points for cocaine administration (Perry et al., 2013; Zhang et al., 2008). Furthermore, research has shown that the oestrous cycle can influence hippocampal volume (Qiu et al., 2013), and long term memory (Warren et al., 1995).

6.4 Influence of stress on addiction

As mentioned previously, stress has been known as a risk factor for a long time. The overactivation of the HPA axis can cause increased risk taking due to the impairment of the PFC due to such high levels of cortisol (Carrion et al., 2011). This increased stress and impairment in decision making make the acquisition phase very susceptible to addiction. During the escalation in addiction, the sensitisation of the reward pathways due to stress may be one of the causes of the reinforcing effects of substance use (Sinha, 2008). It has also been implied that this is one of the mechanisms that cause the shift from positive to negative reinforcement, where the negative associations during periods of abstinence get reinforced due to the stress response (Sinha, 2024). Thus, stress is a risk factor for all phases of addiction, meaning the stress response could be a target for treatment in addiction.

7 Discussion and conclusions

The results of the research being done on sex-differences in addiction might not be very clear-cut, but does highlight the importance of these studies. Addiction is a complicated global health issue that has a multitude of societal, physiological and psychological factors that influence it. The findings described in this paper emphasise that addiction is not a uniform process, with individually unique patterns of progression, use and relapse in both men and women.

Epidemiological trends show that historically, men have higher rates of substance use, but this gap is closing rapidly, especially in younger generations. This shift is partly caused by changing social dynamics, with more women engaging in risk-taking behaviours at increasingly younger ages. There are also differences in the motivation for drug taking, where men use substances for thrill-seeking or due to peer-pressure, women most often take substances as a coping mechanism for emotional stress. These differences highlight the importance of considering sex when looking at prevention, intervention or treatment.

The progression of addiction is also distinguishable between men and women. Women tend to progress more rapidly from initial use to dependency, a process known as telescoping. This is most likely due to both biological and hormonal influences. Studies in both humans and rodents suggest that the female ovarian hormone oestradiol (E2) plays an important role in this accelerated process. It does so by modulating the mesolimbic dopamine system, heavily involved in the reward and reinforcement of behaviour.
In this mesolimbic pathway, there are also sexually dimorphisms. Key areas such as the ventral tegmental area (VTA), striatum and amygdala exhibit structural and functional variations between men and women. The striatum in females shows a higher spine density and greater sensitivity to oestradiol. These factors can enhance dopamine signalling and increase drug-seeking motivation. Similarly, differences in dopaminergic neurons in the VTA cause changes in response to signalling, which can explain some of the differences seen in addiction-like behaviour such as increased reinforcement and more intense substance cravings. Amygdala volume has been shown to decrease more in alcohol dependent males than in females.
Hormonal fluctuations further modulate addiction-like behaviours, especially in women. The oestrous and menstrual cycle, which regulate oestradiol and progesterone levels, influence drug-seeking and relapse likelihood. Studies in rodents have shown that oestradiol administration can cause increased addiction-like behaviours in OVX female rodents. This result was not found for untreated rats upon E2 administration. There are also findings that suggest that certain phases of the menstrual cycle are associated with increased substance use, although results are sometimes inconsistent. This highlights the importance of further research to disentangle these relationships.
Stress emerges as a critical factor in addiction, influencing all phases. The overactivation of the HPA axis, coupled with the modulation of stress hormones like cortisol, can impair decision-making and promote risk-taking behaviours. This vulnerability is heightened during the acquisition phase and remains significant during withdrawal and relapse, where stress-induced craving poses a substantial challenge to recovery. Furthermore, the role of stress in sensitising reward pathways underscores its importance in the progression of addiction.

Despite all the research mentioned in this paper, there are some limitations to this study. While rodent models offer valuable insights into addiction, the application to human addiction is limited by the physiological and behavioural differences. There have also been some inconsistencies found in studies on hormonal influences in humans, again showing that addiction is shaped by a complex network of factors. Future research should focus on the clarification of hormonal influences on addiction-like behaviour over longer periods of time. Including neuroimaging studies can be particularly useful for mapping the concentrations of hormones or neurotransmitters in different locations of the brain. This can help clarify the influence of hormones in real-time.

To conclude, a lot of research has been done into addiction and its prevention and treatment. This paper shows the importance of considering sexual dimorphism in addiction, highlighting the differences that can explain some of the differences seen between males and females in addiction. But, it also highlights the contradictions found and thus the need for more research in this field. To truly address addiction, the development of tailored, sex-specific prevention and treatment strategies should be incorporated that account for both biological and sociocultural influences.

8 References

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