Examensarbete

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Sex-dependent differences in human reward processing: A systematic review

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Abstract

Much work has been done in the neuroscience of reward processing, such as; mapping brain areas, key neurotransmitters, and connectivity patterns related to different aspects of reward-related behavior. There are a lot of suggested behavioral and neural sex differences in reward processing, primarily based on animal studies of reward behavior. This review aimed to systematically review publications on human neurofunctional sex differences in reward processing, and provide a more stable footing for future research in the field. Two searches through Web of Science and Scopus for publications that combined neuroimaging with behavioral tasks for examining functional sex differences in neural reward processing. The searches produced nine studies (n=9) that were included after the screening process. There are significant differences between males and females in reward processing, specifically in the striatum, orbitofrontal cortex, prefrontal cortex, nucleus accumbens, and insula. However, the full extent of these differences, and the underlying causes, are still not clear. There is a lack of control for important confounding factors in the present field of sex differences in reward processing. Future research in this field has to consider all of the underlying factors that cause men and women to differ, such as the impact of gonadal hormone fluctuations and societal pressures. If these factors were taken into account, data of higher validity and generalizability could have been produced.

Keywords: reward-processing, sex-differences, dopamine, reward pathways, sex hormones.

Definitions and Abbreviations

PFC	Prefrontal Cortex: the front part of the frontal lobe.
OFC	Orbitofrontal cortex: area of the frontal cortex above the eye sockets.
VTA	Ventral tegmental area: group of neurons in the midbrain.
fMRI	Functional magnetic resonance imaging: brain imaging technique that measures functional changes related to blood flow.
PET	Positron emission topography: brain imaging technique utilizing radioactive tracers.
NAc	Nucleus accumbens: area of the forebrain that together with the olfactory tubercle form the ventral striatum.

Sexual Dimorphisms in Human Reward Processing: A Systematic Review

The processing of reward is a neurological function fundamental for survival. Reward-seeking behavior engages motivational and cognitive processes to obtain primary rewards such as food, water, and sex and secondary rewards such as money and social approval. Electrical self-stimulation rodent studies began to map out brain areas related to reward processing in the 1950s (Olds & Milner, 1954). Since then, the development of functional neuroimaging techniques has allowed researchers to examine changes in neuronal activity in vivo in response to experimental manipulations. One vital tool for investigating the neural activity related to reward processing is specific carefully designed behavioral tasks. Several studies have used behavioral research paradigms known to engage areas of the reward-processing system to explore reward-related neurological sex differences (Dumais et al., 2018; Warthen et al., 2020). One prevalent behavioral task for investigating the neural activity in reward processing is the monetary incentive delay task. The classical monetary incentive delay task combined with functional neuroimaging can quantify neural activity during rewarding and neutral cues. After subtracting neutral cues from the total activation, only activity related to reward anticipation remains (Lutz & Widmer, 2014). Variations of the monetary incentive delay task allow investigation of several processes related to reward, such as anticipation versus consumption, reward versus punishment, and reward learning (Lutz & Widmer, 2014). Furthermore, neuroscientific research on reward processing identified the neurotransmitter dopamine and several areas with a high affinity of dopaminergic neurons as what is now called the brain's reward system. Most of the dopamine is produced in the ventral tegmental area (VTA). From the VTA, dopamine is transported throughout the brain by four major dopaminergic pathways. Two of these pathways are heavily implicated in reward processing; the mesolimbic- and mesocortical-dopamine pathways (Iversen & Iversen, 2007).

The mesolimbic dopamine pathway starts in the VTA and projects dopamine to the nucleus accumbens (NAc) and the olfactory tubercle in the ventral striatum. The NAc receives input from the dopaminergic neurons in the VTA, glutaminergic neurons of the hippocampus, amygdala, and medial prefrontal cortex (Dhingra et al., 2021). These closely interconnected areas all work together in the learning, memorization, and feeling the sensation of reward stimuli that increase motivation to repeat rewarding behavior (Schultz, 2002). The mesocortical dopamine pathway begins in the VTA and projects dopamine to the cerebral cortex with extensive connections to the dorsolateral area of the prefrontal cortex (PFC). The mesocortical dopamine pathway is necessary for motivation, emotional response, and executive functions such as cognitive control (Dhingra et al., 2021).

The process of reward-related learning, from the neural perspective, begins with initial dopaminergic neural activations in response to the received reward but gradually

changes towards being activated by the conditioned stimuli that predict the reward instead. The dopaminergic response, thus, does not respond to reward unconditionally but is sensitive to the unpredictability of both the time and occurrence of reward (Schultz, 2002). In other words, receiving a reward activates an initial dopaminergic neuronal response, which pairs motivational salience and the feeling of wanting a reward. After learning what events and stimuli precede the wanted reward, the preceding events and stimuli generate reward-anticipation and become the actual trigger of the dopaminergic neuronal response.

Sex Differences

It is generally known that men and women experience differential development, starting as early as the fetal stage. Different sex chromosomes, prenatal gonadal hormones that interact with sex steroid receptors, and sex-specific gene expression cause sexually dimorphic bodies, brain regions, and neuro-circuitry (Cahill, 2006). Puberty further differentiates the development of men and women by a large influx of gonadal hormones, mainly testosterone in men and estrogen in women (Sisk & Foster, 2004). Both animal and human studies have identified several structural and functional sexual dimorphisms of the brain. Using techniques such as functional magnetic resonance imaging (fMRI) and positron emission topography (PET), anatomical and functional sex differences have been found in areas that are relevant to reward processing, such as the amygdala, hippocampus, anterior cingulate cortex, dorsolateral PFC, thalamus, hypothalamus, paracingulate gyrus, parietal lobe, and the caudate (Cahill, 2006; Dhingra et al., 2021; Goldstein et al., 2001; Kaasinen et al., 2001; Riccardi et al., 2011). Rodent studies have shown sex differences in functional dopamine signaling and concentration in the NAc, striatum, and VTA. Female rodents have been found to exhibit greater dopaminergic activation in response to rewards such as food and drugs (Becker & Chartoff, 2019; Becker & Hu, 2008; Becker et al., 2012). Sex differences in dopaminergic functioning are theorized to a large extent to be mediated by the effects of ovarian hormones, and estrogen was found to mediate drug sensitization and enhance dopamine release in the ventral striatum and NAc (Becker, 1999; Cahill, 2006). Since ovarian hormones constitute a significant part of the theorized dimorphisms, studies investigating reward processing should consider estrous cycle fluctuation effects.

Many psychiatric conditions such as schizophrenia, substance abuse, attention deficit hyperactive disorder, anxiety, and depression include the pathophysiology of the reward processing system. The psychiatric illnesses where the reward system is differentially affected also show differing occurrence rates and symptomology in females versus men (Chowdhury et al., 2019; Ramtekkar et al., 2010). Research on neurological sex differences could help us understand the nature of the most prevalent psychological disorders.

Much literature reports neurofunctional sex differences in rodents' reward systems, but how these findings translate to the human population is still debated. Research

of the functional sexual dimorphisms in the human reward systems could help develop treatment and prevention strategies for common neuropsychiatric disorders. This review aims to identify the sex-dependent functional differences in the human brain, specifically the striatum, insula, NAc, orbitofrontal cortex (OFC), and PFC, by reviewing evidence of studies combining functional brain imaging and behavioral tasks known to activate reward processing. This systematic review will be the first to gather available evidence on functional sex differences in the human reward system.

Methods

Search Strategy

The first searches were conducted on Scopus on the 8th of February 2022 and on Web of science on the 15th of February 2022. The following search string was used in Scopus: (reward OR dopamine OR addiction OR "substance-abuse") AND ("sex differe*" OR "gender differe*" OR "sex* dimorph*") (neuro*). The search was limited to only include publications in English within subject areas “neuroscience” and “Bioscience”, and exclude document types “book chapters”, “review”, “conference paper” and “editorial”. There was no limit on time period for the search. 212 results were found on Scopus using the search string. A similar search string was used for Web of science: (reward OR dopamine OR addiction OR "substance-abuse") AND ("sex differe*" OR "gender differe*" OR "sex* dimorph*") NOT (rats OR mice OR animals). This search string yielded 154 results. A second search was conducted to decrease the chance of overlooked essential publications. This search included the term “healthy” to exclude the large extent of publications that included subjects with abnormal brain functioning such as schizophrenia, depression, and brain damage. The terms “animal,” “rat,” and “rodent” were excluded to limit the search to human subjects. The second phase of publication searching was conducted on the 9th of March 2022. The search string used for the second Web of science search was: (reward OR dopamine) AND ("sex differe*" OR "gender differe*" OR "sex* dimorph*") AND (HEALTHY) NOT (animal* OR rat* OR rodent*). This search string yielded 114 results. For the second search on Scopus, the following search string was used: (reward OR dopamine) AND ("sex differe*" OR "gender differe*" OR "sex* dimorph*") AND (healthy) AND NOT (animal* OR rat* OR rodent*). This search was limited to document type "article" and " neuroscience " subject area. This search string yielded 117 results. The search results were exported to the Publish or perish software, and duplicates were identified by comparing DOI numbers and titles in excel for all four searches. Titles and abstracts were manually screened, and relevant publications were saved as full texts in folders. Saved full text was then read in full and deemed relevant or irrelevant using criteria developed using the PRISMA protocol. The search process in documented in detail in the PRISMA flow diagram (Moher et al., 2009) (Figure 1).

Inclusion Criteria

Studies were eligible for inclusion if the study: 1) Assessed neurofunctional gender differences directly related to the normal functioning of the human reward system within the specified brain areas; 2) Utilized functional neuroimaging paired with behavioral tasks relevant to reward processing; 3) Presented empirical data; 4) Was peer-reviewed; 5) Included participants that were healthy humans and of adult age (age >18); 6) Published in English.

Exclusion Criteria

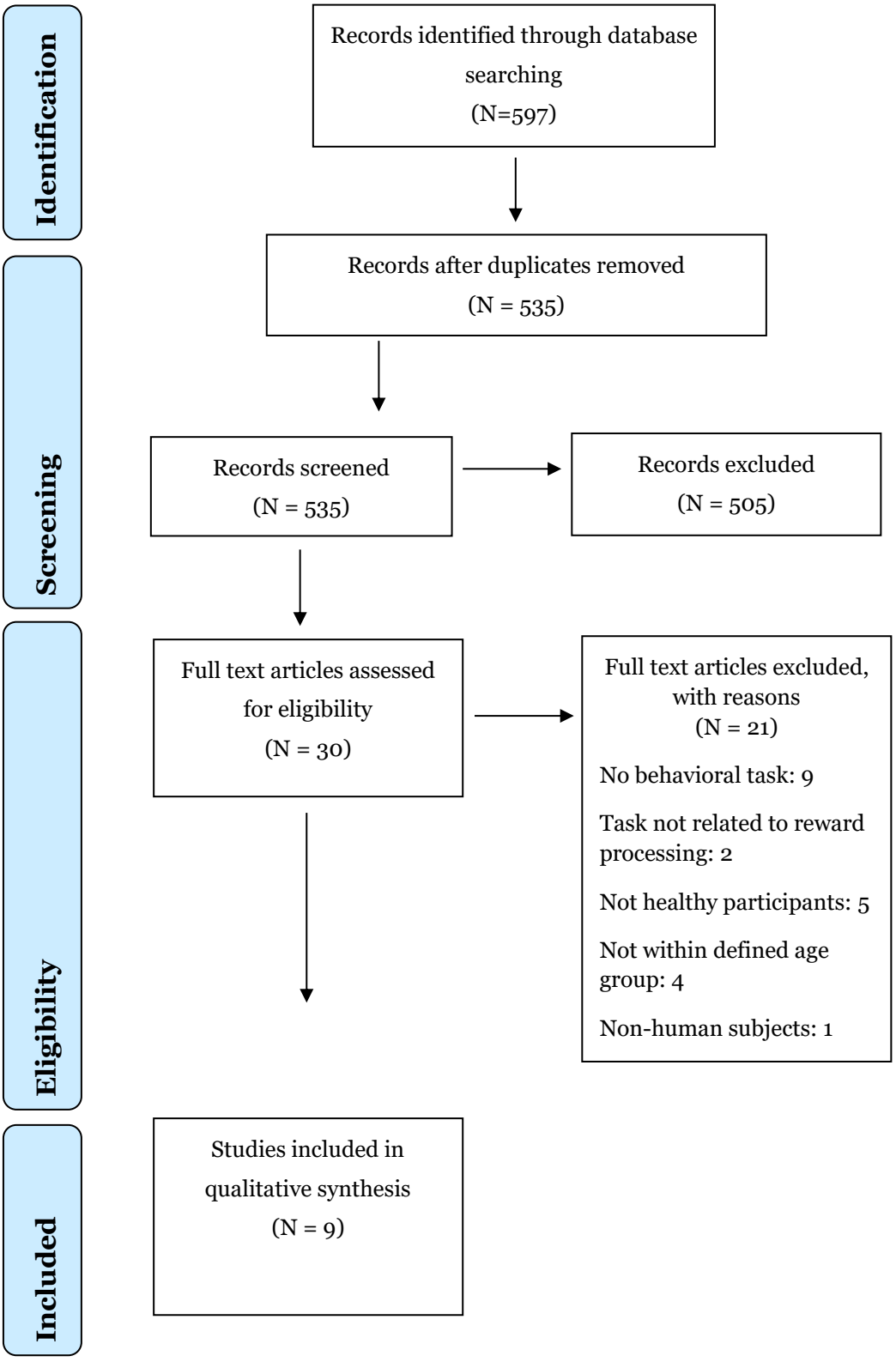
Studies were excluded if 1) The imaging technique used was not functional or not paired with a behavioral task relevant to reward processing. 2) The publication was a review article, meta-review, conference paper, or commentary. 3) The study utilized psychoactive substances.

Data Extraction

Information from the included publications was extracted and presented in a table in the results section. The data gathered was 1) Study sample data (e.g., number of participants, gender distribution, and mean age). 2) Information about study design (e.g., imaging techniques, behavioral tasks, and regions of interest) 3) General publication information (e.g., publication year, H-index, and impact factor).

Figure 1.

Standard Flow Diagram used to Document the Literature Search Process.



Note. PRISMA 2009 Flow Diagram (Moher et al., 2009).

Results

In the included nine studies, 810 participants were studied, of which 365 were males (45.06%) with a median age of 24.7 and 445 were females (54.93%) with a median age of 24.

Three types of behavioral tasks that are in some way related to reward processing were utilized in the nine studies reviewed—six studies utilized monetary rewards, either in a gambling setting or incentive delay task. One study used a desire-reason self-control task, and one used an interpersonal and intertemporal decision task. One study utilized a specialized computer game as the behavioral task. The primary imaging tool included in the studies was fMRI (n=8), with only one PET study.

Table 1.

Basic publication information and summarized results.

Study	Sample Data	Publisher Data	Imaging Type	Behavioral Task and Design	Regions of Interest	Results Summary
Barman et al., 2015	N = 63 32 males (mean age 25.6) 31 females (mean age 23.5)	Social Cognitive and Affective Neuroscience Impact Factor: 3.571 H index: 103	fMRI	Monetary/social incentive delay task Within subject and between group design	Ventral striatum, amygdala, fusiform face area, default mode network.	In women and, to a lesser extent in men, higher Autism-Spectrum Quotient was associated with increased posterior default mode network activation during social reward anticipation. During feedback a negative correlation of Autism-Spectrum Quotient and right amygdala activation in men only.
Dhingra et al., 2021	N = 63 36 males (mean age 38.3) 27 females (mean age 34.3)	BMC Neuroscience Impact Factor: 2.811 H index: 98	fMRI	Monetary Incentive Delay Task. Within subject and between group design	Bilateral OFC, visual cortex, ventral striatum, insula, medial frontal cortex, anterior cingulate gyrus	Men had higher sensitivity to rewards and losses. Women had higher sensitivity to punishment.
Diekhof et al., 2012	N = 32 16 males (mean age 24.7) 16 females (mean age 24.3)	Brain Research Impact Factor: 3.252 H index: 204	fMRI	Self-control. Desire-reason dilemma. Within subject and between group design	NAc, VTA, right ventral pallidum, anterior cingulate cortex, right putamen, left posterior OFC.	Males = increased and females = decreased NAc and anteroventral PFC connectivity ($p<0.001$). Main effect of gender in left superior temporal sulcus ($p<0.001$)

Study	Sample Data	Publisher Data	Imaging Type	Behavioral Task and Design	Regions of Interest	Results Summary
Diekhof et al., 2021	N = 172 (mean age 24) 61 males 111 females	Brain Structure and Function Impact Factor: 3.270 H index: 95	fMRI	Self-control task. Desire-reason dilemma. Within subject and between group design	Ventral striatum, anteroventral prefrontal cortex.	Association between a genetic predisposition in the dopamine system and a sex difference in reward related responding. genetic predisposition has a stronger impact on female than on male reward processing capacity. Women = activation in left ventral striatum during reward rejection ($p<0.05$). Men = Activation in left ventral striatum in desire-reason dilemma ($p<0.05$).
Dumais et al., 2018	N = 190 85 males (mean age 29.6) 95 females (mean age 29.6)	PLoS ONE Impact Factor: 2.74 H index: 332	fMRI	Incentive processing task. Within subject and between group design	Medial PFC, precuneus, parahippocampus, and lateral parietal lobe. e frontal eye fields, inferior precentral sulcus, dorsolateral PFC, middle temporal motion complex, and left superior parietal cortex. lateral PFC, anterior insula, middle frontal gyrus, and anterior inferior parietal lobe	Women have a pattern of neural activity indicative of enhanced attention to external valenced stimuli during the processing of reward and punishment. Women showed increased suppression of the default mode network and increased activation of the dorsal attention network compared to men.
Hoeft et al., 2008	N = 22 (ages 19-23) 11 males 11 females	Journal of Psychiatric Research Impact Factor: 4.9791 H index: 136	fMRI	Game or Control conditions Within subject and between group design	NAc, amygdala, OFC.	Men = greater activation in NAc ($p=0.047$) And right amygdala ($p<0.001$). Men ($p=0.026$) > Women ($p=0.019$) in left NAc – left OFC connectivity.
Martin-Soelch et al., 2011	N = 24 12 males (mean age 32.1) 12 females (mean age 33.5)	European Journal of Neuroscience Impact Factor: 3.115	PET	Slot-machine task. Within subject and between group design	Ventral striatum, Dorsal putamen, Middle caudate, dorsal caudate.	Significant bilateral mean binding potential reduction in women ($p<0.05$). In men the reduction reached significance only in the right ventral striatum ($p<0.05$).

Study	Sample Data	Publisher Data	Imaging Type	Behavioral Task and Design	Regions of Interest	Results Summary
		H index: 206				
Soutschek et al., 2017	N = 23 12 males / 11 female (Mean age 23.7)	Nature Human Behavior Impact factor: 5.78 H index: 46	fMRI	Interpersonal and intertemporal decision tasks /monetary Within subject and between group design	Striatum	The reward system is more sensitive to prosocial rewards in women than in men.
Warthen et al., 2020	N = 221 100 males (mean age 20.95) 121 females (mean age 20.41)	Social Cognitive and Affective Neuroscience Impact Factor: 3.571 H index: 103	fMRI	Monetary incentive task Within subject and between group design	Midbrain (ventral tegmentum, substantia nigra pars compacta), bilateral NAc, dorals anterior cingulate cortex, bilateral anterior insula.	Men exhibited greater responsiveness to stimulus salience in the NAc, midbrain, anterior insula and dorsal anterior cingulate cortex.

Note. fMRI= functional magnetic resonance imaging. OFC= orbitofrontal cortex. VTA= ventral tegmental area. PET= positron emission topography. NAc= nucleus accumbens.

Regions of Interest: Sex Differences in Reward Processing

All included studies investigated brain regions and networks known to be related to reward processing. The nine included studies provide data from 26*(shown in table 1) brain regions, the most prevalent being the striatum, followed by the insula, OFC, and PFC.

Striatum

In the fMRI studies that specified the striatum as a region of interest (n = 5), several significant sex differences were reported. Unpredicted rewards elicited striatal dopamine release in a larger area in women than men. Furthermore, the dopaminergic response occurred bilaterally in women, with a greater magnitude in the right ventral striatum. In contrast, men showed a lateralization effect with significant dopaminergic activation, limited to the right ventral striatum, during unpredicted reward (Martin-Soelch et al., 2011). During an interpersonal decision task, females elicited a more significant activation in the striatum than men when the choices related to prosocial rewards rather than selfish rewards (Soutschek et al., 2017).

Barman et al. (2015) found that compared to the anticipation of social reward, the anticipation of monetary reward elicited higher levels of striatal activation in men and

women, respectively. Using a Monetary incentive delay task, Dhingra et al. (2021) found that monetary rewards elicit higher activations of the ventral striatum but failed to find any significant sex differences in this area. Diekhof et al. (2021) compared men and women with low multilocus genetic composite scores in a desire-reason dilemma task. They found reduced suppression of activation in the bilateral ventral striatum and right VTA ($p < 0.05$) in women but not men during the rejection of rewards.

Orbitofrontal Cortex

Among the fMRI studies that specified the OFC as a region of interest (n=3), the findings indicate sexually differential activation in response to various reward-related tasks and stimuli. During a desire-reason dilemma in Diekhof et al. (2012) study, only men displayed a significant decrease in activation in the posterior OFC ($p<005$) and several other brain areas when rejecting conditioned rewarding stimuli and successfully resolving the dilemma. Hoeft et al. (2008) report that men, compared to women, display higher activation levels when contrasting game > control in the bilateral OFC during a computer game behavioral task. Furthermore, Hoeft et al. (2008) study further reported that males show significantly higher levels of functional connectivity between the left NAc and bilateral OFC ($p<0.05$). In contrast, females showed negative functional connectivity between the same areas ($p< 0.05$).

Using covariance analyses, when comparing men and females with age and reaction time differences as covariates, Dhingra et al. (2021) found sex differences in bilateral OFC activation ($p<0.05$) in monetary reward task paradigms (dollar win/loss > nil). Dhingra et al. (2021) report higher bilateral OFC activation levels in men than women ($p<0.05$) during monetary wins and losses. However, no significant sex differences were found by Dhingra et al. (2021) in their specified region of interest during reward anticipation.

Insula

The findings from the included studies, which specified the insula (n=3) either directly or as part of more extensive networks (e.g., the frontoparietal control network), report significant sex differences relevant for reward processing. When comparing men's and women's sensitivity to stimulus salience, men displayed significantly higher responsiveness to stimulus salience within the mesoaccumbal pathway and salience network, including the dorsal anterior cingulate cortex and dorsal and ventral insula ($p< 0.02$) (Warthen et al., 2020). When contrasting activation of the dollar vs. cent wins (wins vs. large wins) in men and women, a negative correlation of sensitivity for punishment score was found for women but not men in the right anterior insula, left superior frontal gyrus, and temporal gyrus (Dhingra et al., 2021). However, the same regions did not significantly correlate with sensitivity for punishment scores with losses in neither men nor women. Furthermore, men appeared to have higher neural sensitivity towards wins with sensitivity for punishment

scores, but this finding failed to reach statistical significance (p=0.06) (Dhingra et al., 2021). When Dumais et al. (2018) investigated frontoparietal network activations during behavioral reward and punishment tasks, no statistically significant sex differences were found (p>0.05).

Prefrontal Cortex

The included studies that defined the whole or specific regions of the PFC (n=3) report several functional sex differences. The PFC is large, complex, and has many subdivisions. This section will cover all mentioned region of interest and networks (E.g., the default mode network, dorsal attention network and frontoparietal network) that are related to the PFC and includes: anteroventral PFC, dorsolateral PFC, medial PFC and lateral PFC. Dumais et al. (2018) investigated the default mode network (including the medial PFC) during reward and punishment using an incentive processing task. Dumais et al. (2018) could show that during reward and punishment trials, women had more significant suppression of the default mode network than males (p = 0.004). However, women had greater dorsal attention network activation than men when comparing dorsal attention network (including the dorsolateral PFC) activation during reward (p = 0.008) and punishment (p = 0.017) trials. No significant sex differences in frontoparietal network (including lateral PFC) activations during behavioral reward and punishment tasks were found (Dumais et al., 2018).

Diekhof et al. (2012) discovered that men had a positive functional coupling between the right NAc and left anteroventral PFC during the dilemma using a desire-reason dilemma task. However, women had a non-significant decrease in the connectivity between the same regions (Diekhof et al., 2012). Diekhof et al. (2012) found that the functional connectivity between the NAc and anteroventral PFC was modulated by gender and context (p=0.05). A later study by the same author (Diekhof et al., 2021) found minor sex differences in a desire reason dilemma task. Males had a more robust recruitment of the anteroventral PFC, whereas women showed increased negative connectivity between the anteroventral PFC and the VTA. In the desire-reason dilemma, men had significant negative functional connectivity between the left ventral striatum (p<0.05) and the anteroventral PFC (p<0.005). Within the included sample of subjects with low multilocus genetic composite scores, women had more robust negative functional connectivity with the left anteroventral PFC in reward rejection tasks than men (p<0.05). However, women with high multilocus genetic composite scores had a more significant positive functional interaction between the right VTA and bilateral anteroventral PFC during the acceptance of rewards (p<0.05). However, no significant sex difference was found in a direct comparison of this aspect (Diekhof et al., 2021).

The NAc was specified as a region of interest in 3 studies included in this review. As previously mentioned, Hoeft et al. (2008) reported greater connectivity between the NAc and

OFC in males compared to females in their behavioral task (p=0.05). Furthermore, gender modulated task-related connectivity was also found between the NAc and anteroventral PFC (p<0.05), where men exhibited greater connectivity than females in the desire-reason dilemma (Diekhof et al., 2012). Males also showed increased responsiveness towards high- vs. low-stimulus salience in the NAc (P< 0.02) (Warthen et al., 2020).

Menstrual Cycle Phase Effects

Dumais et al. 2018 study was the only study that considered menstrual cycle phase effects. By categorizing women into two groups depending on where in the menstrual cycle they were. Women were assigned to the follicular phase group if the number of days since their last period was 1-12 (n=52); the rest of the women were considered to be in the luteal phase of the menstrual cycle (n=42). When the two groups' experimental data from the incentive processing and working memory tasks was compared, Dumais et al. (2018) did not find significant differences within the specified regions of interest.

Discussion

Summary of Main Findings

This systematic review identified functional sex differences within the reward processing system in the human brain. 26 neural locations were investigated by the nine relevant studies using within-subject and between-group design (mixed-factorial design).

The data suggest that men and women differ in their functional neurology within the reward processing system and networks, which is in line with previous findings in animal studies (Becker, 1999; Becker & Chartoff, 2019). fMRI studies reveal differences in connectivity and activation patterns in a wide range of areas during aspects of reward processing. Sensitivity to non-drug rewards (i.e., monetary rewards) in the striatum is positively correlated with higher fMRI blood-oxygen-level-dependent imaging responses and subjective ratings of pleasure to drug rewards (Crane et al., 2018). Striatal blood-oxygen-level-dependent responses can be seen as indicators of motivational salience, outcome magnitude, and probability of reward outcome (Fareri & Delgado, 2014). The found sex differences in striatal activation could be evidence for sexually differential salience attribution to the types of rewards. The PET study by Martin-Soelch et al. (2011) shows sex-specific asymmetry in the dopaminergic mesostriatal response to rewarding stimuli. Men appeared only to have significant dopamine release in the right ventral striatum during unpredicted rewards, at the same time, women were found to have significant dopamine release in both left and right ventral striatum with generally higher magnitude in the right (Martin-Soelch et al., 2011). The findings concluded that the degree of striatal dopaminergic asymmetry that favors the left hemisphere positively correlated with the behavioral traits of higher incentive motivation and approach behavior (Tomer et al., 2008). Sex differences in lateralization of striatal dopamine release in response to rewards suggest a sexually

dimorphic reward system in humans. This hypothesis could theoretically be tested by investigating statistics of the specific trait that seems to differ between the sexes.

On the one hand, data suggests that, generally, males and females have differing valance attribution towards the experimental stimuli since some of the data from the included studies suggest women be more sensitive to punishment and prosocial rewards (Soutschek et al., 2017) and men appear to be more sensitive to the reward-aspects of monetary wins and losses (Warthen et al., 2020). On the other hand, (Warthen et al., 2020) found no significant sex differences in stimulus valence (reward vs. punishment) ($p>0.05$).

Based on the data provided in this thesis, women generally find social rewards more motivationally salient and rewarding compared to men, who generally have higher salience attribution towards monetary rewards. However, the lack of neuroscientific data on gender differences within social reward processing weakens the strength of these conclusions.

Furthermore, the findings that men exhibit greater activation and functional connectivity in the mesocorticolimbic system during computer game play and the feedback of monetary wins and losses (Hoeft et al., 2008) may reflect a generally higher motivational state. The found lateralization of striatal dopamine release in reward responses speaks for a proclivity for higher motivational states that may help explain the statistical sex differences in gambling and drug addictions. However, there are lines of evidence that suggest a telescoping effect in women regarding addictive behavior and that the gender gap in addiction is narrowing (Zakiniaeiz & Potenza., 2018).

Limitations

Of the nine studies included in this review, only 1 study utilized some control for menstrual cycle and hormonal fluctuation variation (Dumais et al., 2018). Five of the nine studies recognize the absence of hormonal fluctuations and estrous cycle control as a potential confounding variable (Dhingra et al., 2021; Diekhof et al., 2012, 2021; Martin-Soelch et al., 2011; Warthen et al., 2020). Three of the nine studies fail to mention hormones or the estrous cycle (Barman et al., 2015; Hoeft et al., 2008; Soutschek et al., 2017).

Since cycle-dependent hormonal fluctuations affect dopamine signaling and release (Becker, 1999), and nearly all studies overlooked the potential impact, hormonal differences can account for some or most of the found sex differences in the reward system. Interestingly the only study controlled for menstrual cycle effects failed to find any significant effect. Importantly, however, the assessment of the menstrual cycle phase was an indirect measure using self-report and, therefore, vulnerable to reporting errors and self-report biases (Dumais et al., 2018).

Since the age of the participants was somewhat closely matched across all studies (20-34), along with the relatively small sample sizes, it might not be possible to generalize the findings to the entire population. Furthermore, even though the included studies examined

roughly the same region of interest, the behavioral tasks and measurements were focused on different aspects of reward-processing (anticipatory, preparatory, gain, loss, social-reward, incentive, valence). The strength of the conclusions of the summarized data is weakened due to the variability of the experimental manipulations and settings. It is also worth mentioning that there was no assessment of the included participants' gender identity. The neuroscience of gender identity is poorly researched (Kiyar et al., 2020), and the lack of control in this aspect may leave the gathered data vulnerable to unintended variability.

Societal and Ethical Aspects

The reported differences in male and female brains responses to reward stimuli suggests that males and females are generally differentially influenced by external factors such as stress, trauma, and pharmaceutical interventions. The environmental factors then have a differing effect on the neural plasticity throughout the lifetime of males and females, potentially leading to further sexually dimorphic brain function. However, this plasticity could also have the reverse effect, where differences in environment can shape the brain of one sex to more closely match that of the typical physiology of the opposite sex—adding the fact that many common neuropsychiatric conditions, such as substance abuse, anxiety, and depression are known to be related to abnormal and alterated reward system functionality. These lines of evidence provide valid grounds for further research on the efficacy and the need for differential psychological and medical treatments, learning, and encouragement. Furthermore, considering the findings and lack of knowledge on the long- and short-term neurological alterations caused by ovarian hormones (Lisofsky et al., 2016). There might be an urgent need to reevaluate the extent and amount of hormonal contraceptive prescriptions. The use of hormonal contraceptives (intrauterine devices and oral contraceptive pills) in the United States and Europe are extensive (approximately 25% of all women aged 15-49 (United Nations, 2019)), often used from the age of fifteen and is sometimes prescribed to children as young as twelve. This growing knowledge gives rise to potential major ethical issues within the pharmaceutical industry, medical society, and youth clinicians. Without reliable data from longitudinal within-subject studies, there is no way of knowing that the extensive use of pharmaceutical hormones does not negatively affect this significant portion of the female population.

Concluding Remarks

The data provided and examined in this review cannot explain the underlying causes of the differences in neurofunction and behavior. There is a lack of research in the neuroscience of healthy human sex differences; most publications have focused on animal models and abnormal brain functioning. It is clear that there are several significant differences between the sexes, and the neuroscientific literature confirms this. However, the extent and nature of the differences are poorly understood. Future research in this field has

to consider all of the underlying factors that make men and women differ (e.g., hormones and society) if they want to produce data of higher validity and generalizability. One important note is that; The value of a reward depends not only on its monetary value, quality, or aesthetic. Reward value is highly subjective and dependent on the individual receiving the reward. It is highly embedded in the context in which the reward is received and the preconceived notions of the reward's value. Since most studies in this review have focused on monetary rewards, the reported activational patterns and connectivity primarily reflect the salience and motivation for monetary gain and loss.

The most plausible explanation is that the reported sex differences arise due to several converging factors. Genetic factors, sex-specific socialization, sex-hormone influences, and cultural pressure are most likely culprits of the neurological and psychological differences between the sexes. As I see it, the studies investigating human sex differences are adding weights to different sides of a scale, balancing nature and nurture. It most likely will not tip anytime soon.

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