HHS Public Access

Author manuscript

J Neurosci Res. Author manuscript; available in PMC 2017 July 02.

Published in final edited form as:

J Neurosci Res. 2017 January 2; 95(1-2): 260–269. doi:10.1002/jnr.23810.

Sex Differences in Animal Models of Decision-Making

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Abstract

The ability to weigh the costs and benefits of various options in order to make an adaptive decision is critical to an organism's survival and well-being. Many psychiatric diseases are characterized by maladaptive decision-making, indicating the need to better understand the mechanisms underlying this process and the ways in which it is altered in pathological conditions. Great strides have been made in uncovering these mechanisms, but the majority of what is known comes from studies conducted solely in male subjects. In recent years, decision-making research has begun to include females to determine whether sex differences exist and to identify the mechanisms that contribute to such differences. This review will begin by describing studies that have examined sex differences in animal (largely rodent) models of decision-making. Possible explanations, both theoretical and biological, for such differences in decision- making will then be considered. The review will conclude with a discussion of the implications of sex differences in decision-making for understanding psychiatric conditions.

Keywords

delay discounting; intertemporal choice; risk; probability; dopamine

Introduction

To make a decision, one must consider several variables before taking action. Information about the risks and rewards associated with each option must be integrated with internal cognitive and motivational drives as well as the environmental context in which the decision is made. This process happens on a daily basis and the majority of individuals are able to effectively calculate costs and benefits to engage in adaptive choice behavior. However, there are multiple psychiatric conditions that are characterized by maladaptive decision-making.

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Role of authors

CAO drafted the manuscript. Both CAO and BS revised and finalized the manuscript.

For example, individuals suffering from substance abuse disorders (SUD) display heightened impulsive choice and risk-taking behavior. To date, the majority of studies that have assessed relationships between decision-making and psychiatric diseases such as SUD have only used male subjects; however, there is well-established evidence that the incidence and presentation of many of these pathological conditions differs between sexes (McCarthy et al. 2012). For instance, while males have higher rates of drug dependence, females develop dependence more rapidly and are at greater risk for relapse (Becker and Hu 2008; Lynch 2006). Thus, although previous work has been useful in beginning to understand how decision-making can be altered in psychiatric diseases, it is obviously not representative of the entire population and is therefore limited in its application.

The use of animal models of decision-making has allowed researchers to begin to address these gaps in knowledge. Using these models, scientists can answer fundamental questions about whether males and females differ in decision-making processes and what the neurobiological mechanisms are that mediate these differences. This review will present an overview of what is currently known about sex differences in animal models of decision-making and discuss the implications of these findings for understanding sex differences in psychiatric disease.

Sex differences in animal models of decision-making

Intertemporal decision-making

One form of decision-making that is commonly assessed in the laboratory is intertemporal choice, which refers to choosing between options that differ in their time of arrival. These options usually differ in reward magnitude and as such, decisions often consist of choosing between a small reward available after a short delay and a larger reward available after a long delay. Consequently, this behavior provides a measure of impulsivity ("impulsive choice"), or the extent to which an individual is willing to wait to procure a greater reward, and reflects the degree to which the delay diminishes (or "discounts") the subjective value of the larger reward. Typical intertemporal decision- making performance in such a "delay discounting task" manifests as a decrease in the choice of larger, delayed rewards in favor of smaller, more immediate rewards as the delays increase in duration. Importantly, alterations in impulsive choice have been strongly linked with psychiatric diseases, such as SUD (Coffey et al. 2003; Johnson et al. 2015; Kirby and Petry 2004) and attention deficit hyperactivity disorder (Winstanley 2011).

While this form of decision-making has been well studied in males, it has not been as thoroughly characterized in females, and in the studies that have been conducted, the results are not always transparent. For example, in one of the earliest animal studies assessing sex differences in impulsive choice, Perry et al. (2008) tested male and female rats in an "adjusting delays" intertemporal choice task (in which the delay to the large reward was adjusted based on the rat's previous choices) and found that choice behavior did not differ between sexes. More recent studies have replicated this lack of sex differences in impulsive choice in both rats and mice using delay discounting tasks in which the delays shift systematically within a test session (Doremus-Fitzwater et al. 2012; Eubig et al. 2014; Hamilton et al. 2015; Lukkes et al. 2016), and several studies in monkeys have found a

similar absence of sex differences (Carroll et al. 2009; Hamilton et al. 2011; Latzman et al. 2015; Rosati and Hare 2013).Within some of the rodent studies, however, there were more nuanced behavioral differences between males and females, suggesting that there may be subtle sex differences in intertemporal decision-making. For instance, Eubig et al. (2014) reported that following acute administration of amphetamine, females were quicker to initiate trials and displayed more impulsive choices than males. In another study, males and females were characterized as “flat” or “steep” discounters based on their task performance; “steep” female discounters displayed a greater reduction in their preference for the large, delayed reward than their male counterparts at longer delays (Koot et al. 2009). Age of testing may also be critical in detecting sex differences; Lukkes et al. (2016) reported that adolescent females displayed less impulsive choice than adolescent males. Finally, Perry et al. (2007) showed that in rats selectively bred to be high saccharin (HiS) or low saccharin (LoS) preferring, female LoS displayed greater impulsive choice than male LoS whereas there were no sex differences in HiS rats (Perry et al. 2007). Together, these studies indicate that although females appear to be more impulsive than males under some conditions, further work is needed to expand upon these findings. For example, individual differences in impulsive choice at baseline or relationships between impulsive choice and other behavioral variables (Koot et al. 2009; Perry et al. 2007) may be critical determinants of sex differences that could have implications for differential vulnerability of females and males in the development of psychiatric diseases.

Probabilistic decision-making

Many decisions involve making choices between options that differ in both their expected rewards and their potential for accompanying negative consequences. There are several different animal models of such probabilistic decision-making, all of which assess the extent to which the probability of an adverse consequence discounts the value of a rewarding outcome. These models have been instrumental in demonstrating sex differences in probabilistic decision-making, although these differences appear to depend on both the task and the type of adverse consequence involved. In an initial study examining sex differences in probabilistic decision-making, van den Bos et al. (2012) used a rodent version of the Iowa Gambling Task (r-IGT), in which rats made discrete choices between a long-term advantageous option and a long-term disadvantageous option (van den Bos et al. 2012). The former consisted of frequent small food rewards (sugar pellets) and infrequent punishments in the form of quinine- laced sugar pellets. In contrast, the disadvantageous option consisted of occasional large food rewards intermixed with frequent punishments. Importantly, similar to the human Iowa Gambling Task (IGT), this decision-making task specifically measures the process by which subjects learn about the probability distributions of reward vs. punishment delivery across a ten day period (i.e., the transition from uncertainty to risk). Although both males and females chose the advantageous option over the disadvantageous option to the same extent by the end of the r-IGT, males developed this preference more rapidly than females. In addition, as the rats progressed through the task, males continued to choose the advantageous option irrespective of whether they were rewarded or punished on the previous trial. This suggests that males learned quickly that while punishment could occur, the advantageous option was the better choice in the long term. Females, however, tended to shift their choice to the disadvantageous option regardless of whether they were

rewarded or punished for choosing the advantageous option. Importantly, choice behavior in females did not seem to be modulated by estrous cycle. Overall, these differences suggest that males and females use distinct information gathering strategies in the r-IGT to execute a decision: while males appear to use more global information to make decisions and settle on their preference, females use details obtained after assessment of both options to determine the most adaptive choice (as evidenced by their constant switching between the advantageous and disadvantageous options). These findings in rats are consistent with those in humans, which show that females take longer to develop a preferential strategy in the Iowa Gambling Task (IGT) than males (van den Bos et al. 2013b).

In a more recent study, Peak et al. (2015) used a different variant of the Iowa Gambling task (the rodent gambling task; rGT) to assess sex differences in decision- making. In contrast to the r-IGT, which only has two options from which to choose, the rGT consists of four options that differ in both reward (and punishment) probability and reward magnitude. Over multiple training sessions, rats learn that of the four options, one is the most advantageous in the long term and one is the most disadvantageous in the long term. Contrary to the results of the van den Bos (2012) study described above, Peak et al. (2015) showed that females developed optimal choice behavior more rapidly than males. The differences in the outcomes of these two experiments are likely due to differences in the decision-making tasks employed, and consequently may have significant implications for how males and females process different types of probabilistic decision-making. As mentioned above, the r-IGT is conducted for ten days, irrespective of meeting certain behavioral criteria upon completion, whereas the rGT conducted by Peak et al. (2015) occurred in multiple phases to facilitate learning of the task contingencies. Specifically, rats were trained to learn the different reward- punishment contingencies in a forced choice version of the rGT in which they experienced only one option at a time. Only after rats were trained in this version of the rGT (7 consecutive days) did they move on to the free choice rGT in which they could choose between the different options. This is an important distinction as performance in the r-IGT may more closely model uncertainty (involving an unknown probability distribution) whereas performance in the rGT may more closely model risk (involving a known probability distribution) given the greater opportunities for learning in the latter task. In addition, the punishment used in the r-IGT consists of quinine-treated sugar pellets whereas in the rGT, the punishment is that of lost reward opportunity (a timeout period during which no new trials can be initiated). Finally, while the r-IGT involves choosing between two options, the rGT consists of calculating the optimal choice among four options that differ in both probability of reward delivery and reward magnitude. It is therefore conceivable that males and females learn about and process information about the rewards and probabilities inherent to the tasks differently depending on the structure of the decisions and the types of adverse consequence involved.

To complicate matters further, our laboratory recently evaluated sex differences in a third probabilistic decision-making task (the “Risky Decision-Making task”, RDT) involving varying probabilities of explicit physical punishment (Orsini et al. 2016). In this task, rats make discrete choices between two levers, one which delivers a small safe food reward and the other which delivers a large food reward accompanied by varying probabilities (ranging from 0-100%) of mild footshock (Simon et al. 2009). Female rats showed a significantly

greater preference for the small, safe reward than male rats (Orsini et al. 2016), a difference which could not be explained by disparities in body weight influencing shock perception nor by differences in reward motivation. Further, choice behavior in this task in females was not modulated by estrous cycle. On the surface, it seems as though the greater preference for the "safe" option in females conflicts with their performance in the r-IGT, in which females shifted between the advantageous and disadvantageous options frequently. Similarly, the greater preference for the large, probabilistically punished reward in males seems inconsistent with their performance in the r-IGT, in which males settled on the advantageous reward more rapidly than females. One difference that could account for this discrepancy is the type of punishment involved (quinine-laced food vs. shock). An alternate, and equally appealing, explanation for these conflicting effects of sex on decision-making in the RDT and r-IGT is that, similar to the case of the rGT and r-IGT, the tasks assess distinct components of decision-making. Whereas the RDT is conducted until behavioral stability is obtained (~25-30 days), the r-IGT is conducted for a predetermined duration (10 days), irrespective of whether behavior is stable at the completion of training. Thus, performance in the former likely reflects informed choice and behavior driven by risk, while performance in the latter assesses learning about the reward-outcomes contingencies (taxing uncertainty to a greater extent). These distinct components of decision-making may therefore recruit different strategies to make decisions. In the RDT (and the rGT), rats must rely on their knowledge of task contingencies to make an adaptive choice. In the r-IGT, however, rats need to gather information about task contingencies as they proceed through the training. Indeed, in both the human IGT and r-IGT, females take longer than males to develop a preference for the most advantageous option (van den Bos et al. 2013b; van den Bos et al. 2012). While this may manifest as greater risk-seeking compared to males, it may actually be reflective of females taking longer to learn about the probability distribution of outcomes as they need to spend more time evaluating all of the options before deciding upon the most optimal. Consistent with this notion, female rats took longer to reach stable performance than males in the RDT (Orsini et al. 2016). They also omitted significantly more trials than males, which could be viewed as another strategy to evade punished outcomes, albeit different than actively avoiding the punished option by choosing the safe option. It is therefore critical that researchers recognize that males and females may use different strategies to make probability-based decisions as it may help explain some of the well-described sex differences in psychiatric diseases (e.g., SUD) in which altered decision-making plays a prominent role.

Potential explanations for sex differences in decision-making

Evolutionary and behavioral mechanisms

In a recent review, Cross, Coping and Campbell (2011) proposed a theoretical account for the well-established observation in human studies that females are more impulsive than males, an explanation that may be extended to understanding such differences in other forms of decision-making (e.g., probabilistic decision-making). They posited that differences between men and women in reward sensitivity, punishment sensitivity, and effortful control can explain sex differences in impulsivity (Cross et al. 2011). Deeply rooted in evolutionary theory, these authors suggest that each of these components contributes differently to ensure

the reproductive success of men and women. For example, men may be more risk-taking because they are hypersensitive to reward and hyposensitive to punishment. Across the animal kingdom, males' reproductive success frequently depends on competition with other males to obtain mates and rise in social hierarchy. Further, in some species, males were traditionally responsible for securing food and resources in the face of potential danger. In contrast, females tend to be hyposensitive to rewards and hypersensitive to punishment. This may derive from the fact that the reproductive success of females often depends on avoiding harm and death not only for their sake, but also for their offspring. Because the young of many species depend more heavily on mothers than fathers, the energy expenditure for females is greater and thus limits the number of offspring. Hence, it may be advantageous for females to avoid harm and injury to increase their offspring's chances of survival.

It is important to consider that motivation for reward, be it food or a mate, does differ between males and females, which can influence the choices they make and thus their reproductive success (Yoest et al. 2014). In contrast to males, females are motivated for different rewards depending on their sexual receptivity. Females are motivated to find a mate and reproduce only when conception is likely; this increase in sexual motivation, however, is accompanied by a decrease in motivation for food (Fessler 2003). Yoest et al. (2014) argue that these parallel changes in motivation for food and sex ensure reproductive success for females as less time spent finding food and eating means that more time can be devoted to finding an optimal mate and reproducing when chances of conception are high. Interestingly, these fluctuations in motivation for food and sex in females are modulated by estradiol, indicating that gonadal hormones can influence adaptive decision-making (see further discussion below under 'Biological Mechanisms').

Differences in effortful control between males and females can also have a large impact on their reproductive success (Cross et al. 2011). Behaviorally defined, effortful control refers to "the ability to inhibit a dominant response and perform a subdominant response" (Cross et al., 2011, p. 102). It is through effortful control that organisms can regulate impulsive choice and risk-taking to be able to make adaptive decisions that promote long-term survival. MacDonald (2008) argued that effortful control was necessary to inhibit innate and automatic responses that had evolved over time, such as behaviors related to mate selection. For example, the drive for intrasexual competition is so strong in males that is difficult for them to inhibit this approach behavior (MacDonald 2008). While this might predict greater impulsive behavior in males, which is not necessarily consistent with preclinical and clinical literature, it does align with the fact that males tend to be more risk-seeking than females (Orsini et al. 2016) and are quicker to develop a preference for the more advantageous option in the r-IGT (van den Bos et al. 2012). Conversely, Bjorklund and Kipp (1996) proposed that females have to engage in more effortful control to ensure their reproductive success (Bjorklund and Kipp 1996). For instance, in order to find the best possible mate, females must inhibit the tendency to choose the first mate available so as to secure a more optimal long-term partner. Females must also exert effortful inhibitory control to prioritize the needs of their dependent offspring over their own needs. Finally, females need to inhibit behaviors that would place themselves or their offspring in danger. Again, this theory of increased inhibitory control in females does not readily explain sex differences in intertemporal choice, but could account for differences observed in probabilistic decision-

making. For example, in both the r-IGT and RDT, females might need to exert more inhibitory control so as to evaluate all available choices rather than quickly developing a preference for one option, as is the case with males. In the RDT in particular, poor inhibitory control in males might explain their willingness to endure physical punishment to obtain the larger reward. Together with differences in reward and punishment sensitivity, variations in effortful control between males and females may thus be differentially adaptive for each sex; however, it is noteworthy that these differences may also predispose men and women to different psychiatric diseases.

Another potential interpretation of the observed sex differences in decision-making, which is not mutually exclusive from those discussed above, is that females may be more flexible and exploratory in their behavior than males (Koot et al. 2009). As mentioned in previous sections, males and females appear to employ different strategies in making decisions. Males may initially use an exploratory strategy to determine the most advantageous option, but then switch to a strategy of exploitation to take advantage of this option (Koot et al. 2009; van den Bos et al. 2013a). In contrast, females may more readily shift between exploration and exploitation, allowing them to gather more information about each of the options. This theory can account for sex differences observed in the r-IGT and RDT: not only did females in both tasks take longer to develop a preferential choice across sessions, they were able to more rapidly shift their choices between the options within a session. In contrast, in the RDT, males began each session by choosing the large reward option and continued to do so throughout the sessions, even when the probability of punishment was high. In the r- IGT, males quickly settled on the advantageous option early in training and persisted with this choice behavior throughout the duration of the r-IGT. Similarly, Koot et al., (2009) reported that, in contrast to males, females that discounted delays steeply shifted their preference to the smaller, more immediate reward at longer delays. Notably, these differences in strategy utilization could also support the reproductive success of each sex, suggesting an evolutionary basis for the divergence in approach tactics.

Biological mechanisms

Given the wealth of evidence demonstrating that behavioral responses to drugs of abuse vary across the estrous cycle (Becker 1999; Becker and Hu 2008; Evans et al. 2002; Festa and Quinones-Jenab 2004; Jackson et al. 2006; Justice and de Wit 1999; Perry et al. 2013; Perry et al. 2015; Quinones-Jenab et al. 1999), it is conceivable that fluctuations in ovarian hormones in females may contribute to sex differences in decision-making. Evidence for this supposition, however, is mixed. Decision-making performance does not vary across the estrous cycle in females in either the RDT (Orsini et al. 2016) or the human IGT (van den Bos et al. 2013b). Interestingly, however, another study showed that while choice performance in an effort discounting task (in which rats decide between a small, low-effort reward and a large, high-effort reward) did not vary across the estrous cycle in intact females, it was affected by ovariectomy (OVX) (Uban et al. 2012). Compared to sham controls, OVX females exhibited an increase in choices of the large, high-effort reward. This increase appeared to be at least partially mediated by estradiol and estrogen receptors, as it was reversed by administration of either high dose estradiol or a combination of ERα and ERβ agonists (although interestingly, ERα and ERβ agonists administered alone had the

opposite effect in OVX rats). These findings provide initial evidence that female gonadal hormones can affect decision-making, although it is unclear whether this extends to intertemporal or probabilistic decision-making. Notably, several recent studies showed that systemic administration of testosterone can modulate male rats' performance in the RDT, an effort discounting task, and a probability discounting task (in which subjects choose between a small guaranteed reward and a large reward associated with varying probabilities of omission (Cooper et al. 2014; Wallin et al., 2015), hinting that hormones can influence other forms of decision-making. Based on this accumulated evidence, it will be important in future studies to more rigorously determine how gonadal hormones impact decision-making, perhaps by manipulating hormone levels rather than passively tracking estrous cycle.

Although it has not yet been thoroughly investigated, the sex differences in, and effects of hormonal manipulations on, decision-making described above may be attributable in part to interactions between gonadal hormones and dopamine signaling (Becker and Hu 2008). Indeed, performance in many if not all preclinical models of decision-making is sensitive to dopaminergic manipulations. For example, systemic administration of amphetamine decreases preference for the large, risky reward in the RDT (Mitchell et al. 2011; Orsini et al. 2015; Orsini et al. 2016; Simon et al. 2011) and decreases impulsive choice in intertemporal decision-making tasks (Setlow et al. 2009; van Gaalen et al. 2006; Wade et al. 2000; Winstanley et al. 2003). Manipulations of dopamine receptors, either systemically or within a specific brain region, also affect decision-making behavior (Barrus and Winstanley 2016; Di Ciano et al. 2015; Mitchell et al. 2014a; Simon et al. 2011; St Onge et al. 2011; St Onge and Floresco 2009; Stopper et al. 2013). Over a decade of research has shown that females are more sensitive to dopamine-induced changes in behavior and that estradiol seems to play a large role in this effect (Becker and Hu 2008; Becker et al. 2012). For example, intact females show greater behavioral sensitization to amphetamine and cocaine than males (Becker et al. 1982; Robinson 1984; Robinson et al. 1982; van Haaren and Meyer 1991). OVX females show little to no sensitization to these stimulants (Forgie and Stewart 1994; Robinson 1984; Robinson et al. 1982; Sircar and Kim 1999; van Haaren and Meyer 1991), but estradiol administration can restore normal behavioral sensitization to amphetamine (Forgie and Stewart 1994; Peris et al. 1991). Interestingly, amphetamine administration causes a greater decrease in choice of the large, "risky" reward in the RDT in females relative to males (Orsini et al. 2016). Although the role of estradiol in this effect has yet to be tested, it is consistent with previous work showing that males and females differ in their responses to dopamine manipulations. This could be due to basal differences in extracellular levels of dopamine, dopamine receptor levels, and/or autoreceptor control, all of which are modulated by estradiol (Becker and Hu 2008; Becker et al. 2012). For example, males have more dopamine D1 receptors in the striatum relative to either intact or OVX females (Hruska et al. 1982). In contrast, there are no sex differences in levels of dopamine D2 receptors in the striatum of intact males and females (Levesque and Di Paolo 1990). However, there is greater D2 binding in OVX rats compared to castrated rats, and upon administration of estradiol, these receptors are rapidly downregulated in OVX females but not castrated males (Bazzett and Becker 1994). In light of these findings, it will be important to determine how gonadal hormones interact with dopamine signaling during decision-making as it could reveal mechanisms underlying the observed sex differences.

Despite the wealth of studies that have documented sex differences in decision- making at the behavioral level (see Intertemporal and Probabilistic Decision-making sections above), there is little information regarding the neural mechanisms that might underlie these differences. The only animal study conducted to date showed that the orbitofrontal cortex (OFC) is differentially activated in males and females (as assessed with c-fos expression) following testing in the r-IGT (van Hasselt et al. 2012). Specifically, c-fos expression in the lateral OFC was inversely correlated with the proportion of advantageous choices in the r-IGT in females (this relationship was absent in males). The majority of studies that have investigated this question have used neuroimaging techniques in human subjects. Consistent with findings from van Hasselt, these studies also show that the OFC is differentially recruited for males and females in various types of decision-making tasks. For example, in the human IGT, the OFC is activated more robustly in males than females (Bolla et al. 2004). Another study used the Risky Gains Task to assess sex differences in neural activation during decision- making. In this task, participants choose among three options, one of which yields a certain reward (safe choice) and two that may or may not yield a larger reward (uncertain choice). The authors found that the OFC in females was more dynamically engaged than males during task performance (Lee et al. 2009): while there were no correlations between neural activity and behavior in males, there was a negative correlation between neural activity in the OFC and choice of the uncertain reward when preceded by a punished outcome (i.e., no reward delivery) and a positive correlation between OFC neural signal and choice of the uncertain outcome when preceded by a uncertain, but unpunished, outcome. Interestingly, in a recent study (Crowley et al. 2015), males had greater OFC activation than females prior to making safe choices in another risk-based decision-making task. These last two studies suggest that the OFC in females may be more selectively tuned to process punishment and uncertainty whereas the OFC in males may be more selectively recruited to process information regarding safe reinforcement. To our knowledge, there are no data on whether these sex differences in OFC recruitment extend to intertemporal choice behavior.

Other neuroimaging studies have reported that additional areas of the prefrontal cortex are recruited in a sex-dependent manner. Using the Balloon Analogue Risk Task, Cazzell et al. (2012) reported that, compared to males, females had greater activation of the dorsolateral prefrontal cortex (dlPFC) in both hemispheres specifically during periods in which they experienced loss of monetary rewards. Interestingly, in another study, there were hemispheric differences in dlPFC activation between males and females in the IGT. Whereas there was increased activity in the *right* dlPFC in males relative to females, dlPFC activation was greater in the *left* dlPFC in females compared to males (Bolla et al. 2004). The insular cortex is also implicated in mediating risky choices in females, but not males (Lee et al. 2009). In the Risky Gains Task, Lee et al. (2009) showed that signal intensity in the insula was positively correlated with the number of choices of the uncertain outcome in female subjects when this choice type was followed by another choice of the uncertain outcome. Given the insula's role in encoding of aversive information and anticipated risk (Naqvi et al. 2014), it is conceivable that in females the insula is part of a network with the OFC and dlPFC that processes risk of uncertainty and punishment-related information associated with choices. All of the aforementioned studies are limited, however, in that they are correlational

in nature; it will hence be useful to employ animal models to address the causal role of activity in these systems.

Brain regions that are known to be sexually dimorphic are involved in various forms of decision-making. For example, the amygdala is larger in males than females (Goldstein et al. 2001), is recruited in a sex-dependent manner during regulation of emotional memories (Cahill 2006; Cahill et al. 2001; Cahill et al. 2004; Kilpatrick et al. 2006), and is critically involved in both intertemporal and probabilistic decision-making tasks. Lesions of the basolateral amygdala in male rats cause an increase in impulsive choice (Winstanley et al. 2004). Similarly, in the rGT and RDT, lesions of the BLA increase choice of a large reward associated with greater probabilities of punishment (Orsini et al. 2015; Zeeb and Winstanley 2011). In contrast, in a probability discounting task, temporary inactivation of the basolateral amygdala causes male rats to decrease their choice of the large, uncertain reward (Ghods-Sharifi et al. 2009). Together, these studies show that the amygdala is a key brain region in regulating adaptive decision- making. Given its sexually dimorphic structure and function, it stands to reason that the same manipulations of the amygdala in females may yield different results than those in males and thus suggests that the amygdala may contribute to sex-dependent differences in decision-making.

Clinical implications

Understanding the precise mechanisms underlying sex differences in decision- making may have significant clinical implications as many psychiatric diseases that are characterized by maladaptive decision-making are sex-biased. The prevalence of schizophrenia, which is associated with poor performance in the IGT (Kim et al. 2007; Kim et al. 2009; Shurman et al. 2005; Struglia et al. 2011) and increased impulsivity (Ahn et al. 2011), is greater in males than females (Abel et al. 2010). Greater risk-taking and impulsivity are characteristic symptoms of attention deficit hyperactivity disorder (Evenden 1999), which is diagnosed ten times more frequently in males than females (McCarthy et al. 2012). Anorexia nervosa is 13 times more prevalent in females than males (McCarthy et al. 2012) and is associated with pathological risk aversion (Kaye et al. 2013). Finally, there are considerable sex differences in SUD (Becker et al. 2012; Carroll et al. 2004; Lynch 2006), which has been shown in both preclinical and human studies to be associated with increased impulsive choice and risk-taking behavior (Anker et al., 2009; Bechara et al. 2001; Gowin et al. 2013; Mitchell et al. 2014a; Mitchell et al. 2014b). Thus, differences in decision-making between males and females could be linked to each sex's predisposition to specific psychiatric conditions. For instance, the fact that female rats choose the small, safe reward more than males in the RDT (Orsini et al. 2016) could suggest that a similar behavioral phenotype in women renders them more vulnerable to development of eating disorders. Alternatively, it is possible that psychiatric diseases could impact decision-making in one sex more than the other. As an example, females, who at baseline appear to be more risk-averse (i.e., prefer options that are not associated with risk of punishment) than males, are quicker to escalate their drug use, progress from recreational drug use to dependence more rapidly, and are more vulnerable to relapse (Bobzean et al. 2014; Lynch 2006). Hence, it is possible that females are more sensitive to the effects of chronic drug use on decision-making than males. Consequently, females may display an increase in risky behavior associated with drug abuse, such as

escalation of use and relapse. To date, however, the majority of preclinical studies that have examined relationships between drug use and risk-taking have exclusively used males. For example, Mitchell et al. (2014a) demonstrated that chronic cocaine self-administration causes an increase in risk-taking in the RDT in male rats. It is possible that females would show a different behavioral trajectory (e.g., more rapid transition to a risk-seeking phenotype) than males in this same experimental design. Overall, this underscores the importance of studying the mechanisms underlying decision-making in both males *and* females in both normal and pathological conditions to determine whether tailored treatment is warranted for each sex.

Conclusions

This review outlines clear sex differences in decision-making, which may be due to different strategies that have evolved to ensure the reproductive success of each sex; however, this review also illustrates that there are still large gaps in our knowledge and understanding of these sex differences, largely due to the paucity of studies in female subjects. In a climate in which sex-dependent psychiatric diseases such as SUD and post-traumatic stress disorder are on the rise, it is exceedingly important that resources are devoted to research that addresses these major gaps in knowledge. The recent mandate by the National Institutes of Health that requires the inclusion of sex as a biological variable has brought this issue to the forefront of the neuroscience research community (Clayton and Collins 2014). Specifically, this new policy requires strong justification from the literature and/or preliminary data to only use one sex, clearly indicating that there should be few excuses for not including both sexes in a research program. Resistance to such efforts will only impede scientific discoveries that could benefit the health of both men *and* women. Thus, it is our hope that such mandates, in addition to educating the scientific community through lectures and publications, will encourage researchers to embrace the inclusion of both sexes in studies of decision- making to produce more representative and translatable scientific discoveries.

Acknowledgments

Supported by NIH DA036534 (BS) and a Thomas H. Maren Fellowship (CAO)

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Significance Statement

Many psychiatric diseases affect one sex to a greater extent than the other. A common feature across these diseases is that decision-making abilities are impaired. Thus, sex differences in decision-making may contribute to the differential development or presentation of psychiatric diseases. This review discusses what is currently known about sex differences in animal models of decision-making and considers possible explanations for such differences. The review concludes by highlighting the need for inclusion of both male and female subjects to ensure that future scientific discoveries can be more readily translated to all human beings.

Table 1

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