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Mini-Review

Sex Differences in Animal Models of Decision Making

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The ability to weigh the costs and benefits of various options to make an adaptive decision is critical to an organism's survival and wellbeing. Many psychiatric diseases are characterized by maladaptive decision making, indicating a need for better understanding of the mechanisms underlying this process and the ways in which it is altered under 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 female subjects to determine whether sex differences exist and to identify the mechanisms that contribute to such differences. This Mini-Review begins 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 are then considered. The Mini-Review concludes with a discussion of the implications of sex differences in decision making for understanding psychiatric conditions.

Key words: delay discounting; intertemporal choice; risk; probability; dopamine

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 most individuals are able to calculate costs and benefits effectively to engage in adaptive choice behavior. However, multiple psychiatric conditions are characterized by maladaptive decision making. For example, individuals suffering from substance use disorders (SUDs) display heightened impulsive choice and risk-taking behavior. Most studies that have assessed relationships between decision making and psychiatric diseases such as SUDs have used only 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, although males have higher rates of drug dependence, females develop dependence more rapidly and are at greater risk for relapse (Lynch, 2006; Becker and Hu, 2008). Thus, although previous studies have been useful in beginning to understand how decision making can be altered in psychiatric diseases, those studies obviously are not representative of the entire population and are, therefore, limited in application.

The use of animal models of decision making (see Table I) 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 neurobiological mechanisms mediate these differences. This Mini-Review presents an overview of the current

SIGNIFICANCE:

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 Mini-Review discusses what is currently known about sex differences in animal models of decision making and considers possible explanations for such differences. The Mini-Review concludes by highlighting the requirement for inclusion of both male and female subjects to ensure that future scientific discoveries can be more readily translated to all human beings.

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

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

knowledge on sex differences in animal models of decision making and discusses 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 among options that differ in their time of arrival. These options usually differ in reward magnitude, so 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), 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. It is important to note that alterations in impulsive choice have been strongly linked with psychiatric diseases, such as SUDs (Coffey et al., 2003; Kirby and Petry, 2004; Johnson et al., 2015) and attention deficit hyperactivity disorder (Winstanley, 2011).

Although 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 shown a similar absence of sex differences (Carroll et al., 2009; Hamilton et al., 2011; Rosati and Hare, 2013; Latzman et al., 2015). 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, after 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 rats displayed greater impulsive choice than male LoS rats, whereas there were no sex differences in HiS rats (Perry et al., 2007). Overall, these studies indicate that, although females appear to be more impulsive than males under some conditions, additional work is required to expand on these findings. For example, individual differences in

impulsive choice at baseline or relationships between impulsive choice and other behavioral variables (Perry et al., 2007; Koot et al., 2009) 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 among 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 (rIGT) in which rats made discrete choices between a long-term advantageous option and a long-term disadvantageous option. 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, similarly to the human IGT, this decision-making task specifically measures the process by which subjects learn about the probability distributions of reward vs. punishment delivery across a 10-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 rIGT, 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, although 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 without regard to 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 rIGT to execute a decision; males appear to use more global information to make decisions and settle on their preference, whereas females use details obtained after assessment of both options to determine the most adaptive choice (as evidenced by their frequent 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 IGT than males (van den Bos et al., 2013b).

In a more recent study, Peak et al. (2015) used a different variant of the IGT, the rodent gambling task (rGT), to assess sex differences in decision making. In contrast to the rIGT, which has only 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 et al. (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 discussed above, the rIGT is conducted for 10 days, irrespective of meeting certain behavioral criteria on 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 among the different options. This is an important distinction because performance in the rIGT 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 rIGT consisted of quinine-treated sugar pellets, whereas the punishment used in the rGT was that of lost reward opportunity (a timeout period during which no new trials can be initiated). Finally, although the rIGT 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 that delivers a small, safe food reward and the other that delivers a large food reward accompanied by varying probabilities (ranging from 0–100%) of mild foot shock (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 that could not be explained by disparities in body weight influencing shock perception or by differences in reward motivation. Furthermore, 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 rIGT, in which females shifted between the advantageous and the disadvantageous options frequently. Similarly, the greater preference for the large, probabilistically punished reward in males seems inconsistent with their performance in the rIGT, 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 rIGT is that, similarly to the case of the rGT and rIGT, the tasks assess distinct components of decision making. Whereas the RDT is conducted until behavioral stability is obtained (~25–30 days), the rIGT 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, whereas performance in the latter assesses learning about reward–outcome 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 rIGT, however, rats must gather information about task contingencies as they proceed through the training. Indeed, in both the human IGT and the rIGT, females take longer than males to develop a preference for the most advantageous option (van den Bos et al., 2012, 2013b). Although this may manifest as greater risk-seeking compared with males, it may actually be reflective of females taking longer to learn about the probability distribution of outcomes because they must spend more time evaluating all of the options before deciding on 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 from 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 because it may help explain some of the well-described sex differences in psychiatric diseases (e.g., SUDs) 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 and colleagues (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-seeking 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. Furthermore, in some species, males are 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 on 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 and 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 because 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. These fluctuations in motivation for food and sex in females are modulated by estradiol, indicating that gonadal hormones can influence adaptive decision making (see 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). 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 required 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 it is difficult for them to inhibit this approach behavior (MacDonald, 2008). Although 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 rIGT (van den Bos et al., 2012). Conversely, Bjorklund and Kipp (1996) proposed that females must engage in more effortful control to ensure their reproductive success (Bjorklund and Kipp, 1996). For instance, to find the best possible mate, females must inhibit the tendency to choose the first mate available to secure a more optimal, long-term partner. Females must also exert effortful inhibitory control to prioritize the requirements of their dependent offspring over their own requirements. Finally, females must 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 rIGT and the RDT, females might be required to exert more inhibitory control 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 that 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 discussed above, 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 rIGT and RDT; not only did females in both tasks take longer to develop a preferential choice across sessions but they were able to shift their choices more rapidly among 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 rIGT, males quickly settled on the advantageous option early in training and persisted with this choice behavior throughout the duration of the rIGT. 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 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; Justice and de Wit, 1999; Quinones-Jenab et al., 1999; Evans et al., 2002; Festa and Quinones-Jenab, 2004; Jackson et al., 2006; Becker and Hu, 2008; Perry et al., 2013, 2015), 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). However, another study showed that, although 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 with 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 because it was reversed by administration of either high-dose estradiol or a combination of estrogen receptor (ER) α and ERβ agonists (although 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 have shown 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. Given this accumulated evidence, future studies should 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; Simon et al.,

2011; Orsini et al., 2015, 2016) and decreases impulsive choice in intertemporal decision-making tasks (Wade et al., 2000; Winstanley et al., 2003; van Gaalen et al., 2006; Setlow et al., 2009). Manipulations of dopamine receptors, either systemically or within a specific brain region, also affect decision-making behavior (St. Onge and Floresco, 2009; Simon et al., 2011; St. Onge et al., 2011; Stopper et al., 2013; Mitchell et al., 2014a; Di Ciano et al., 2015; Barrus and Winstanley, 2016). 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 et al., 1982; Robinson, 1984; van Haaren and Meyer, 1991). OVX females show little to no sensitization to these stimulants (Robinson et al., 1982; Robinson, 1984; van Haaren and Meyer, 1991; Sircar and Kim, 1999; Forgie and Stewart, 1994), but estradiol administration can restore normal behavioral sensitization to amphetamine (Peris et al., 1991; Forgie and Stewart, 1994). 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 not yet been tested, it is in line with previous work showing that males and females differ in their responses to dopaminergic 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 with castrated rats, and, after administration of estradiol, these receptors are rapidly downregulated in OVX females but not in 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 because this 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 Decision Making and Probabilistic Decision Making sections above), there is little information with regard to 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) after testing in the rIGT (van Hasselt et al., 2012). Specifically, c-fos expression in the lateral OFC was inversely correlated with the proportion of advantageous choices in the rIGT in females (this relationship was absent in males). Most studies that have investigated this question have used neuroimaging techniques in human subjects. In line 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 in 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 which yields a certain reward (safe choice) and two which may or may not yield a larger reward (uncertain choice). The authors found that the OFC in females was more dynamically engaged than that in males during task performance (Lee et al., 2009). Although 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. 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 latter 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 with regard to safe reinforcement. To the best of our knowledge, there are no data on whether these sex differences in OFC recruitment extend to intertemporal choice behavior.

Other neuroimaging studies have indicated that additional areas of the prefrontal cortex are recruited in a sex-dependent manner. Having used the Balloon Analog Risk Task, Cazzell et al. (2012) reported that, compared with 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. In another study, there were hemispheric differences in dlPFC activation between males and females in the IGT. Although there was increased activity in the *right* dlPFC in males relative to females, dlPFC activation was greater in the *left* dlPFC in females compared with males (Bolla et al., 2004). The insular cortex is also implicated in mediating risky choices in females but in not males (Lee et al., 2009). Using 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; for future research, it will 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 in females (Goldstein et al., 2001), is recruited in a sex-dependent manner during regulation of emotional memories (Cahill et al., 2001, 2004; Cahill, 2006; 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 basolateral amygdala increase choice of a large reward associated with greater probabilities of punishment (Zeeb and Winstanley, 2011; Orsini et al., 2015). 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). Overall, 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 results different from those in males, suggesting 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 because 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 (Shurman et al., 2005; H. Kim et al., 2007; Y.T. Kim et al., 2009; Struglia et al., 2011) and increased impulsivity (Ahn et al., 2011), is greater in males than in females (Abel et al., 2010). Greater risk taking and impulsivity are characteristic symptoms of attention deficit hyperactivity disorder (Evenden, 1999), which is diagnosed 10 times more frequently in males than in 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 SUDs (Carroll et al., 2004; Lynch, 2006; Becker et al., 2012), which have been shown in both preclinical and human studies to be associated with greater impulsive choice and risk-taking behavior (Bechara et al., 2001; Anker et al., 2009; Gowin et al., 2013; Mitchell et al., 2014a,b). 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 (Lynch, 2006; Bobzean et al., 2014). 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, most preclinical studies that have examined relationships between drug use and risk taking have used males exclusively. 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 under both normal and pathological conditions to determine whether tailored treatment is warranted for each sex.

CONCLUSIONS

This Mini-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 Mini-Review also illustrates that there are still large gaps in our knowledge and understanding of these sex differences, largely because of the paucity of studies in female subjects. In a climate in which sex-dependent psychiatric diseases such as SUDs 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 use only 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. 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 translational scientific discoveries.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

ROLE OF AUTHORS

CAO drafted the manuscript. CAO and BS revised and finalized the Mini-Review.

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