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Sex differences in behavioral strategies: avoiding interpretational pitfalls

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Despite ample evidence for sex differences in brain structure and function, our understanding of the neurobiological basis of behavior comes almost exclusively from male animals. As neuroscientists move to comply with recent NIH mandates that biomedical researchers include both sexes in their studies, the ways we interpret outcomes in classic rodent behavioral models deserve closer scrutiny and more nuanced evaluation. In this mini-review, we highlight recent sex differences papers in learning, decision-making, and spatial navigation paradigms that underscore the distinctions between cognitive capabilities versus behavioral strategies that may confer unique benefits to males and females.

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Introduction

Neuroscientists have studied animal behavior in laboratory settings for over a century, leading to an ever-increasing understanding of the relationship between structure, physiology, and function in the mammalian brain. In particular, rodent behavioral models have provided key insights into the neural basis of dozens of complex processes, including learning, decision-making, stress coping, aggression, and substance abuse. However, because the vast majority of behavioral neuroscience research has been conducted in males [1], we inarguably (and regrettably) know much more about the male brain than we do about the female brain. In a recent attempt to rectify this imbalance across biomedical research, the NIH implemented a policy that requires funded researchers to consider sex as a biological variable (SABV) and include subjects of both sexes in all experiments [2]. Despite some resistance [3,4], this initiative is likely to succeed in illuminating aspects of brain function that are common to both sexes, as well as those that are sexually dimorphic [5]. Information of either kind can be useful to basic and translational scientists alike, but it is critical — especially in behavioral research — that we interpret potential sex differences in outcome measures thoughtfully.

When we conduct behavioral experiments, we are, in essence, asking animals to tell us what the situation we have placed them in means to *them*. In many cases, the animal might engage any number of responses, and it is up to us to determine what each one means to *us*. When males and females differ quantitatively in the outcome measures that we have defined, it is important to consider whether these differences reflect true disparities in, for example, cognitive ability or emotional state, or rather a qualitative difference in behavioral strategies, which may optimally serve the potentially discrete needs of each sex. In this review, we discuss recent studies that highlight this distinction, and emphasize the need for thorough, careful behavioral analyses as more neuroscientists begin to incorporate SABV into experimental design.

Sex differences in common behavioral models

How do animals process information about threatening environments and stimuli? Although it is not necessarily surprising to learn that males and females might behave differently in response to stressful events, a nuanced understanding of how and why these differences exist is only just starting to emerge. A recent paper from Tronson and colleagues [6•] nicely demonstrates that after classical context fear conditioning, female mice are more likely than males to show a generalized freezing response in a novel context. This was true even with prior exposure to the shock-associated context, which appears to help *refine* the distinction in male mice (i.e., reduce generalization). These behavioral differences were associated with discrete recruitment of major brain regions — while hippocampal activity was greater in males, females selectively showed activation of the basal amygdala in both contexts. These data could suggest that female mice are unable to discriminate meaningful contexts, but it may instead indicate that after a traumatic experience, treating new environments with extra caution is evolutionarily beneficial to females. Although examining this sex difference in a more naturalistic setting will be necessary to appropriately test this hypothesis, experimenters using classic Pavlovian approaches should consider that elevated context generalization in female mice may not reflect a cognitive deficit, but instead a strategy to reduce risk to the animal's life.

This latter interpretation is supported by impressive new work by Pellman *et al.* [7••], who employed a 42-day 'closed economy' system to examine sex differences in foraging strategies when the foraging environment is risky. Here, male and female rats lived in a 2-chamber home cage in which the nesting side was safe, but eating and drinking required traveling to a foraging arena that randomly delivered foot shocks. After 2 weeks of chamber acclimation without shocks, the authors observed the change in animals' behavior as they learned that they would have to endure shocks in order to forage. Although both sexes reduced the time they spent in the foraging chamber during the 2-week shock period, males compensated by increasing their meal size, while meal size decreased in both intact and ovariectomized females, resulting in reduced overall food consumption and arrested weight gain. In the final 2 weeks, the shocks were terminated so that the authors could observe extinction. Males rapidly increased time spent in the foraging arena, while foraging time in females climbed much more slowly. Together, these data could be interpreted as evidence for impairments in cognitive flexibility or extinction learning in females, but they may instead reflect sex differences in strategy. Specifically, they suggest that females will select general safety over metabolic needs, preferring to avoid a potentially risky environment at the cost of blunted weight gain — even when the risk is no longer there. By contrast, males appear to adapt their feeding efficiency in order to maintain steady weight gain. Although the putative evolutionary value of these sexually divergent strategies is difficult to assess in a controlled laboratory setting, it is clear that males and females weigh foraging in risky environments differently. Importantly, the longitudinal design of this study is noteworthy and laudable, because it allows unique insight into complex behavioral strategies over time, rather than capturing a brief snapshot of behavior, as is true of most paradigms.

Our lab has also found that females are more likely to engage active behaviors to avoid potential threats. As we recently reported [8•], a subset of female rats in a cued fear conditioning paradigm exhibited escape-like 'darting' behavior in response to the conditioned stimulus. These animals subsequently demonstrated enhanced extinction retention, suggesting that darting may reflect an adaptive mechanism that promotes cognitive flexibility [9]. One alternate interpretation could be that because they are smaller, female rats perceive the conditioning chamber as larger and therefore the threshold for 'predator imminence' [10] is shifted, thus increasing the likelihood of an escape response instead of freezing. This explanation is unlikely for a few reasons. First, within a large cohort ($n = 58$) of females, there was no relationship between body weight and darting prevalence ([8•], *Author Response [viewable in online version at eLife]*). Second, the observation that animals are more likely to engage escape responses in larger spaces has only been reported in environments much larger than our chambers (e.g. a hallway, as in [11]). A more recent attempt to observe this phenomenon in standard chambers that differed in size by a factor of 3 ($\sim$15 × 23 cm vs. 15 × 71 cm) failed to find an effect of chamber size on innate fear behavior [12]. Together, these findings support the idea that darting during classical cued fear conditioning is a sexually dimorphic strategy to promote escape. The fact that it both appears only in females and is advantageous for extinction in the long term may seem contradictory to clinical reports that women are more susceptible to post-traumatic stress disorder [13,14]. However, resilient and vulnerable individuals can be found in most populations [15] and the absence of darting in males does not necessarily mean that they lack their own strategies and mechanisms for improving long-term outcomes. As we also recently reported [16], successful extinction retrieval in males (but not females) is correlated with a unique morphology in prefrontal-amygdala circuitry. Although the incidence of darting was not associated with the estrous cycle, there is evidence that circulating ovarian hormones can influence fear learning and extinction (nicely reviewed in [17]). The key message to our work is that if only freezing were measured, darters would have been assumed to be cognitively impaired at forming a CS-US association. This is clearly not the case, and therefore freezing alone is likely an insufficient measure of fear learning and responding, especially in female rats. A more comprehensive examination of animals' behavioral repertoires during classic tasks will be critical as we move to more thoroughly understand how each sex processes threatening stimuli.

Sex differences in risk evaluation can also be observed in models that more explicitly test decision-making. In an elegant set of experiments, Orsini *et al.* [18] used a 'risky decision task' (RDT) to examine how male and female rats weigh reward and punishment against each other. In this task, animals chose between receiving a safe, small food reward, or a large food reward that was intermittently punished with a shock. The authors then observed changes in animals' choices as they varied the likelihood of the shock. Although both males and females reliably chose the large reward when there was no chance of receiving punishment, females quickly switched to the small reward as shock probability increased. By contrast, males maintained high levels of large reward choice, even when shock was guaranteed. To rule out the possibility that their effect was due to greater pain thresholds in males due to their size, the authors recalibrated the intensity of the shock according to each animal's weight, and obtained the same results. Similar to the work described above by Pellman *et al.*, these findings suggest that females will select a behavioral strategy that