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Focus on females: A less biased approach for studying strategies and mechanisms of memory

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Abstract

Recent work on sex differences in learning and memory has demonstrated that females and males differ in cognitive and behavioral strategies, as well as neural mechanisms required to learn, retrieve and express memory. Although our understanding of the mechanisms of memory is highly sophisticated, this work is based on male animals. As such, the study of female memory is narrowed to a comparison with behavior and mechanisms defined in males, resulting in findings of male-specific mechanisms but little understanding of how females learn and store information. In this paper, we discuss a female-focused framework and experimental approaches to deepen our understanding of the strategies and neural mechanisms engaged by females (and males) in learning, consolidation, and retrieval of memory.

Despite the large number of studies on learning and memory and underlying neural mechanisms, a surprisingly small proportion of these focus on how females learn and remember information. Given the fundamental role of neuronal plasticity in the brain, together with the conservation of these mechanisms across species [1], the overwhelming assumption for many years has been that the mechanisms underlying memory formation would be largely independent of sex. However, chromosomal and hormonal influences during development result in divergent neural circuits and structures [2,3] that together with hormonal milieu during adulthood, drive sex differences in a wide range of behaviors and neural functions [4,5]. Sex differences are evident in a number of memory tasks in performance (e.g., verbal memory), cognitive strategy (e.g., spatial memory), and/or circuit and molecular mechanisms (e.g., fear conditioning) (for review see [••6,7]). More importantly, women and men are differentially vulnerable to disorders of memory including post-traumatic stress disorder [8], Alzheimer's Disease and other dementias [9], and learned aspects of addiction [10]. Understanding the neural mechanisms underlying learning and memory in both females and males is critical for identifying risk factors and developing sex-specific interventions and treatments for these disorders.

The goal of studying sex differences in memory is to identify what information females and males are learning, the strategies by which each sex solves memory tasks, and the similar

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and distinct neural (circuit, systems, and molecular) mechanisms underlying acquisition, consolidation, retrieval and post retrieval memory processes. However, our extensive knowledge of basic mechanisms of memory garnered over decades of research in male animals has narrowed the question of sex differences to a comparison of behavior and mechanisms in females with those defined in males, thereby constraining our understanding of memory in females [5,11]. In this paper, we discuss recent findings from fear conditioning and approaches to advance the study of learning and memory in both females and males.

Studying sex differences in memory

There are two interrelated approaches that dominate the study of sex differences in memory: (1) Selection of memory tasks that show clear sex differences in performance, and comparing the strategies, circuits and molecular mechanisms engaged by each sex; and (2) Identifying neural circuits and molecular mechanisms well known for their role in memory in males and examining the role of these mechanisms in females.

(1) Searching for sex-specific mechanisms where there are sex differences in memory performance

Utilizing sex differences in performance on memory tasks to examine sex differences in underlying mechanisms of learning and memory is an appealing place to start. Under parameters where males form robust context fear memories and females do not, only males show increased activation of memory-related signaling pathways during consolidation, including the extracellular regulated protein kinase 1/2 (ERK1/2) [12]. Even when both sexes acquire context fear conditioning, females do not engage the same signaling pathways as males [13–16]. Although these studies identify differences in behavior and signaling in the hippocampus, they fail to identify what information females are learning and the mechanisms by which females store memory.

Where sex differences in memory performance are more nuanced, studies of neural mechanisms are more informative. For example, females show more generalization between fear-associated contexts [••17,18] and differential activation of amygdala and hippocampus during retrieval [••17]. Together these findings suggest that females are not only using different neural circuit and/or molecular mechanisms during memory processes, but that different mechanisms are engaged because *what information* is retrieved is somewhat different in females compared with males. Accordingly, in cued fear discrimination tasks females initially show better discrimination between shock-paired and unpaired cues [19,20] but greater generalization after extended training [21]. This suggests that how these fear and “safety” memories are encoded, and what information is retrieved fundamentally differs between females and males.

Focusing on tasks that have clear sex differences in memory performance has had some success in identifying sex differences mechanisms of memory, but there are major limitations to this approach. First, sex differences in behavior do not necessarily represent differences in underlying neural mechanisms, and the lack of differential behavioral outcomes doesn’t rule out differences in mechanism [11,22]. Thus focusing on memory

tasks that show striking differences in performance on memory tasks will fail to identify sex differences in neural mechanisms that mediate converging memory processes and behavioral responses. For example, both men and women show strong acquisition of fear conditioning, and activation of the canonical fear circuit (notably hippocampus and amygdala) [23,24], but women show greater activation of amygdala, medial prefrontal cortex, dorsal anterior cingulate cortex, and less retrosplenial cortex activation compared with men [25]. Second, the reliance of exploiting differences in behavioral performance assumes that females have the same conditioned responses (CR) as males. Yet recent work demonstrates sex differences in fear CRs. For example, in cued fear conditioning both male and female rats show freezing behavior, but females also show more rapid, active, "darting" responses to a conditioned fear stimulus [••26]. In fear potentiated startle, in which mice show an exaggerated startle response in the presence of a cue paired with footshock, females show slower extinction and less retention compared with males, in direct contrast to comparison experiments using a freezing CR that show faster extinction and greater retention by females [27,28]. Thus despite the apparent advantages of directly comparing females to males on memory performance, this approach fails to identify what females are learning, and how females are storing memory.

(2) Focusing on "known" memory-related mechanisms

The second approach to studying sex differences in mechanisms of memory has focused on brain regions and molecular mechanisms of memory that are well established in males, and testing whether these circuits and mechanisms are similarly required for memory in females. For example, in studies of fear conditioning, the canonical neural circuits including hippocampus and amygdala are well established in males [23,24]. Nevertheless, we have recently shown that although cFos activation is similar between the sexes during consolidation, during retrieval of context fear conditioning, females show more cFos activation in basal amygdala, whereas males show more activation in dorsal hippocampus [17]. Differential activation of amygdala and hippocampus between females and males have also been demonstrated in higher firing rates, number of spines, excitatory input, and LTP in amygdala [29,30], and weaker LTP in the hippocampus [31–33] of females.

At a molecular level, using signaling pathways known for their role in male memory as a starting point has identified both molecular mechanisms that are common to both sexes (e.g. PKA and Akt) as well as male-specific mechanisms (e.g., including CaMKKα/β, *cfos*, *bdnf*), even under conditions of context fear conditioning where both sexes acquire robust memory [13–16]. This suggests that both females and males recruit a set of basic memory mechanisms during consolidation, but with differential activation of a subset of sex-specific pathways and processes. Studies on transgenic animals generated based on mechanisms established males have identified both similarities and differences in mechanisms required for memory in females. For example, in GluA1 knockout mice, both sexes show deficits in spatial memory, but only males exhibit impairments of context fear conditioning [34]. Given the importance of AMPA receptor activation and trafficking to memory formation, and the importance of GluA1 in particular [35], this is a surprising and striking finding, yet it only tells us another male-specific mechanism. In mice with CREB mutations, both females and males show deficits in long-term memory for tone- and context fear conditioning, and for

Morris Water Maze [36]. Nevertheless, sex differences in the role of hippocampal CREB in memory are observed in other studies, where males show reduced activation of CREB [37] and females show greater susceptibility to disruptive effects of more subtle manipulations of CREB [38]. That cyclic AMP (cAMP)-related signaling may be differentially required for memory in females compared with males is supported by the finding that mutations of PDE4 (3′,5′-cAMP-specific phosphodiesterases) result in enhanced LTP in male, but not female mice [39]. Targeting mechanisms required for memory in male animals has successfully identified mechanisms that are required for memory in both sexes, as well as male-specific mechanisms. This approach, however, fails to identify mechanisms recruited by females but not males.

Starting with a male-centric hypothesis and targeting known sex differences in performance or mechanisms of memory established in males can never identify female-specific mechanisms of learning and memory. More insidious, this male-centric approach comes with the central assumption that females are doing fundamentally the same thing as males, just more- or less- well. Questions of sex differences commonly framed as “(how) are females are different from males?” assume males are “normal” and females as somehow “less than normal”. In order to move forward, we need to reframe this question from a direct comparison between the sexes towards a female-centered view in order to identify *what* females are learning, *how* they are storing and retrieving memories, and thus determine *where* they differ from males.

Strategies to move beyond female *vs* male comparisons in learning and memory research

1. Identification of behavioral and cognitive strategies used by females (and males) in memory tasks

It is becoming apparent that behavioral and cognitive strategies preferentially engaged during memory tasks differ between the sexes. In addition to the well-known sex differences in spatial strategies [••40,41], recent work has highlighted that females and males differ in how they solve a variety of tasks [••17, ••26, ••42], suggesting that what information is learned and retrieved, and the behavioral response to fear-associated memory is not identical. To understand sex differences in learning and memory, we need to determine what CRs are most appropriate, and systematically assess the cognitive strategies used by both sexes — even when using the same CR — before we can adequately interpret sex differences in circuits and mechanisms underlying memory.

We have many tools to look beyond the level of responding in order to determine how animals are learning or remembering a given task. For example, in context fear conditioning, the concept that male rodents are learning a conjunctive context representation that gets associated with the aversive footshock, rather than associations between individual contextual elements with footshock was empirically established [43–47]. Similarly, role of hippocampus in context fear conditioning, and the conditions under which context fear conditioning can be hippocampus-independent in male rodents was established over many years [43,48–50]. Applying a similar rigorous and systematic experimental approach to

learning and memory in females is essential for understanding what females are learning, what information is preferentially retrieved, and what behavioral responses to measure.

2. Female-focused approach

In order to validate tasks for females, identify whether the same CRs are appropriate measures of memory, and determine how females are solving memory tasks, there needs to be a shift away from a purely male-centric lens, towards a focus on females. This approach has some notable successes in identifying female-specific mechanisms of memory. For example, a body of work has examined the roles and molecular mechanisms of gonadal hormones on memory function in females ([5, ••51,52], and reviewed in this issue [53]). Importantly, these findings have profound insights for mechanisms of memory and synaptic plasticity in females and in males [••54].

Another female-focused approach is targeting circuits, pathways, and genes identified as having sex-specific activation or expression in human studies. In women, but not men, a polymorphism of pituitary adenylate-cyclase activating polypeptide receptor type 1 (PAC1R), increases risk for some symptoms of post-traumatic stress disorder [55]. Following these findings, recent work has identified PAC1R in prefrontal cortex as a female-specific mechanism for trace fear conditioning [••56]. Similarly, by focusing on sex differences in cholinergic signaling [57], a recent study has identified a differential role of cholinergic signaling in retrieval of memory in females and males, with inhibition of nicotinic acetylcholine receptors resulting in decreased freezing in males and increased freezing in females [58]. Targeting genes, neurotransmitter systems, and neural circuits known to exhibit sex differences in non-mnemonic tasks will be a powerful way to study sex differences, and specifically identify female-specific mechanisms underlying memory formation, consolidation, and retrieval.

3. Exploratory research and screening tools

The lack of molecular and neural targets identified as potentially important for memory in females is a current limitation to applying a female-focused approach. In order to effectively move away from the male-centric approach to studying memory, we need to use exploratory approaches to identify female-specific mechanisms. Screening of molecular pathways and neural circuits has had success in males, identifying distinct temporal and transcriptional patterns and epigenetic modifications between tasks [59–61] and brain regions activated during retrieval of a recent versus a remote fear memory [62]. Exploratory approaches used together with brain regions previously identified as critical for memory will serve as a way to rapidly advance the identification of novel female-specific mechanisms.

There are some successes in females using an exploratory approach: by systematically examining neuronal activity within the basolateral and lateral amygdala — nuclei known for their critical role in fear conditioning — one recent study demonstrated higher baseline firing rate and more dendritic spines in the basal and lateral nuclei of the amygdala of females, associated with greater cue-dependent fear in females compared with males [29]. Another study demonstrated that female mice with the Val66Met BNDF polymorphism show impaired CA3-dependent object place memory, whereas males exhibited intact

memory [63]. These findings demonstrate a differential role of function and gene expression in females and males thus highlighting the importance of exploratory research in both sexes.

Exploratory research to determine what transcriptional, signaling, and neural loci are activated in females during learning, memory consolidation, and memory retrieval will be critical for identifying mechanisms and circuits that are not engaged by males. Recent advances in sequencing [64] and technologies for quantifying brain-wide activation (e.g., CLARITY; [65,66]) provide powerful, broad-based screening methods. Applying these tools in both sexes will identify novel mechanisms of learning and memory processes, additional targets for female-centric approaches to studying sex differences in memory, and insights into possible cognitive strategies engaged by females in learning and memory tasks.

Conclusion

Given sex differences in susceptibility to memory-related disorders including post-traumatic stress disorder, Alzheimer's Disease and other dementias, understanding how both females and males learn, store, and retrieve memories is critical for developing novel treatments, preventive strategies, and identifying at-risk individuals. However, with the influx of new data on females and memory, in part as a consequence of NIH Sex as a Biological Variable initiative, it is clear a simple comparison of females to males on behavioral response or neural mechanism is not sufficient to identify and interpret how females and males solve problems of memory. Shifting toward a female-focused study of memory and its mechanisms, validating behavioral tasks in females, and utilizing exploratory approaches will be critical for reframing the question from "how are females different from males?" to "how are females (and males) solving this task?" and towards a new conceptual framework for understanding of how both sexes learn, encode, and retrieve memories.

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HIGHLIGHTS

- Direct comparisons between sexes fail to detect female-specific memory mechanisms
- Females and males differ in behavioral and cognitive strategies in memory tasks
- Appropriate behavioral measures are key for studying what females are learning
- Exploratory approaches are necessary to identify female-specific memory mechanisms
- A female-focused approach is necessary for novel insights into learning and memory