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Sex differences in learning — shared principles across taxa

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Male and female brains exhibit differences in anatomy, neurochemistry and functional connectivity, all of which can influence behaviour. Flexibility through learning is an important aspect of behaviour. Learning enhances survival by allowing animals to modify their behavioural responses to a changing environment based on their previous experiences. However, despite its universality and physiological relevance, learned behaviour has been less well studied than innate behaviour within the context of sexual dimorphism. In this review, we provide a comparative overview of the cellular, molecular and evolutionary mechanisms underlying sex differences in several forms of learning across taxa.

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Introduction

Learning is a universal property of all animals and is defined as the ability to change behaviour based on previous experience. Innate behaviours, on the other hand, are those displayed by naïve animals without any prior experience and are considered to be genetically and/or hormonally encoded. Sexual reproduction imposes sex differences in anatomy, physiology and energy investment. It is therefore not surprising that most innate behaviours associated with reproduction, such as responses to pheromones, mating, egg laying and parental care, are sexually dimorphic (i.e. the behaviour is qualitatively or quantitatively different in males and females). For learned behaviour, however, it is perhaps harder to envisage how and why it should be subject to sexual dimorphism. Here, we will propose proximate (cellular and molecular) and ultimate (evolutionary) mechanisms by which sex differences in learning arise based on studies performed in a broad range of animals, from invertebrates to humans. We chiefly highlight recent findings and where possible, we refer the reader to excellent and comprehensive reviews on specific subjects.

As we will see, even innate behaviours can be flexibly modified by experience [1], and learning can be influenced by innate preferences. Thus, one mechanism underlying sex differences in learning is the interaction between circuits for sexually dimorphic innate behaviour and those for learning and memory. As learning enhances survival, it is under selective pressure. Therefore, sex differences in learning may also arise through sex differences in selective pressures associated with mating strategies and ecological constraints [2,3]. A third source of sexual dimorphism in learning is hormonal physiology. Hormones play a fundamental role not only in the organisation and activation of sexual characters, particularly in vertebrates, but also in the modulation of stress and cognition [4]. Intrinsic physiological differences can influence how well each sex performs a particular learning task or which strategy is employed by each sex to solve a task. Sex differences in strategy are particularly evident at the circuit and molecular level.

The intersection of circuits for innate and learned behaviour

Males and females of most species behave differently. Traditionally, studies of sensory processing and behaviour have made a strong distinction between innate and learned responses. Innate behaviour is viewed as genetically and/or hormonally encoded, and controlled by stereotypical, hardwired circuits that are distinct from those, more flexible circuits, dedicated to learning. Sex differences are most apparent in innate behaviours associated with reproduction such as courtship and mating. However, sexual dimorphism extends also to flexible behaviours that arise through previous experience and learning. Recent work, is beginning to show that the traditional conceptual and anatomical segregation between circuits for innate and learned behaviour may be an oversimplification, and that the interaction between these circuits often underlies sexually dimorphic learning.

Many innate, reproductive and social behaviours are mediated by pheromones. Pheromones have intrinsic rewarding or aversive value, and elicit approach or avoidance to regulate aggression, courtship and mating in a sexually dimorphic manner. These innate responses, however, are actually flexible and susceptible to modification by previous experience and associative learning. For example, the *Drosophila* male pheromone cVA

stimulates courtship in females but suppresses it in males [5,6]. These innate behavioural sex differences are mediated by an olfactory circuit consisting of Or67d sensory neurons and DA1 glomerular projection neurons, which make sexually dimorphic synapses to third-order interneurons in the lateral horn (LH), a processing centre for innate olfactory behaviour [7–9]. Behavioural responses to cVA can be modulated by experience in both females and males to refine mate choice and social learning. During mating, cVA is transferred from the male to the female, labelling the female as mated. For females, being exposed to cVA during mating results in decreased attraction to this pheromone and reduced sexual receptivity [10]. In males, courtship rejection from a mated female can enhance sensitivity and aversion to cVA, inhibiting subsequent attempts to court mated females [11•]. Courtship learning in males requires the activation of dopaminergic neurons in the γ lobe of the mushroom body (MB), a processing centre for learning and memory in the insect brain [11•]. These dopaminergic neurons are positive for the gene *fruitless*, which specifies most aspects of male courtship [12–14]. These studies demonstrate that innate olfactory preferences encoded in the LH can be broadly modulated through learning by neurons in the MB, demonstrating an interaction between brain regions dedicated to innate (LH) and learned (MB) olfactory processing. Indeed, recent work by the Jefferis group shows that there are functional connections from the MB to the LH that are required for aversive learning [15•]. These connections provide a neural substrate through which innate and learned sensory information may be integrated, potentially in a sexually dimorphic manner (Figure 1a).

The intersection between circuits for innate and learned behaviour is also observed in the mammalian reward system. The ventral tegmental area (VTA) is the source of dopamine signalling that conveys the rewarding or aversive motivational and reinforcing signals required for associative learning. Many inputs and outputs to the VTA display sexual dimorphism in anatomy and/or neurochemistry. The VTA itself, however, does not appear to be sexually dimorphic. A recent study [16•] found no sex differences in the gene expression profiles, number of connections or electrophysiological properties of dopaminergic neurons in the VTA of mice. How then is sex-specific motivation and reward implemented? One direct projection to the VTA comes from the medial preoptic area (mPOA) in the hypothalamus, a nucleus that regulates reproductive and social behaviours in a sexually dimorphic manner [17]. McHenry and colleagues recently identified a population of neurotensin-expressing neurons in the mPOA that are responsive to steroids, encode social odour cues and whose projections to the VTA promote reward and social attraction [18•] (Figure 1b). Together, these studies indicate that brain areas involved in reward and motivation, such as the VTA, do not need to be sexually dimorphic for sex differences in learning to arise. Instead, input to these regions from circuits that control innate reproductive and social behaviours can provide sex-specific valence and reinforcing qualities that may support sexually dimorphic learning.

Sex-specific neurons that are required for associative learning but not for innate sexual behaviours have recently been found in the nematode *Caenorhabditis elegans* [19•]. The male-specific MCM neurons (mystery cells of the male) are required for sexual conditioning, the learned association between an odorant or tastant, and the presence of mates [19•,20]. Sexual conditioning in male worms is reminiscent of the conditioned place preference that mice develop to a location where they have been exposed to the sex pheromone darcin [21]. Both sexes of *C. elegans* (males and hermaphrodites) can learn to associate a chemosensory stimulus with an aversive experience, such as starvation, and switch their chemosensory preferences from attraction to avoidance (reviewed in [22]). This aversive learning can be overridden by sexual conditioning only in males, however [20]. Such sexual dimorphism in learning has ethological relevance, as only males need to find mates in order to reproduce, while hermaphrodites, being somatic females that carry their own sperm, instead reproduce through self-fertilisation. The MCMs are the only male-specific neurons in a circuit for associative learning that is otherwise present in both sexes. However, just as the VTA receives sexually dimorphic inputs, some input circuits to the MCMs are sex specific and mediate sexually dimorphic innate responses to pheromones [19•,23,24] (Figure 1c).

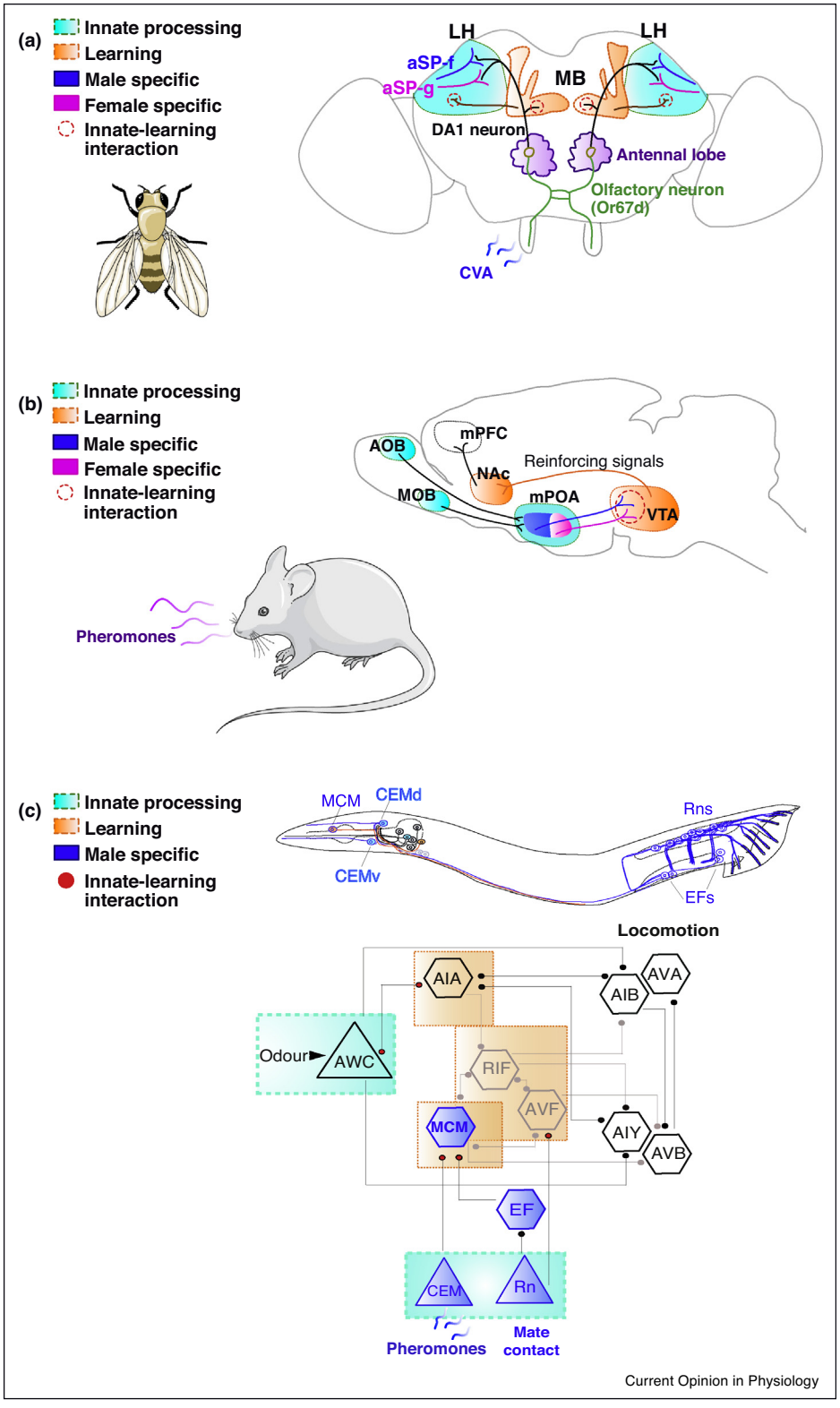
Some of the developmental mechanisms underlying *C. elegans* sex-specific learning have been identified. The MCM neurons are born during sexual maturation from differentiated glial cells. These glial cells are present in both sexes but act as neural progenitors only in males, and this is determined cell-autonomously by the glial cell's genetic sex [19•]. A role for genetic sex, independently of sex hormones, on brain specification and learning has also been revealed in vertebrates [25]. Furthermore, the addition of new neurons during sexual maturation in a sexually dimorphic manner appears to be a common underlying mechanism for regulating social learning across taxa [26,27].

By using ethologically relevant paradigms, the studies described here reveal that flexible, learned behaviour is strongly shaped by innate preferences that have been fixed in the genome through evolution.

Evolutionary pressures for sex differences in learning

The ecology of a species (distribution of food and mate resources, predators, *etc.*) imposes selective pressures that

Figure 1



The intersection of circuits for innate and learned behaviour in flies **(a)**, mice **(b)** and worms **(c)**. **(a)** Schematic representation of the sexually dimorphic circuit for 11-cis-vaccenyl acetate (cVA) detection in the fly brain. MB mushroom body; LH, lateral horn. **(b)** Schematic representation of a sexually dimorphic circuit for social odours in the mouse brain. AOB, accessory olfactory bulb; MOB, main olfactory bulb; mPOA, medial preoptic area; VTA, ventral tegmental area; NAc, nucleus accumbens; mPFC, medial prefrontal cortex. **(c)** Cartoon of a male worm and schematic

shape the species' behaviour and cognition [3]. Since reproductive strategies and lifestyle are often sexually dimorphic owing to anatomical and physiological constraints, each sex will be under distinct evolutionary pressures that can result in sex differences in learning. Learned behaviours that appear to be particularly subject to sex-specific evolutionary pressures are display and mate location [2].

The best studied learned display system is birdsong. Birds that learn and use songs for courtship and social interactions belong to three orders: parrots, hummingbirds and oscine songbirds. In most species, birdsong is displayed only by males, which learn their songs from adult tutors, normally their fathers. However, there are some species where mating couples form duets and both sexes sing and learn songs. The song nucleus was the first anatomical sexual dimorphism in the vertebrate brain to be linked to a sexually dimorphic learned motor behaviour [28]. The song nucleus is considerably larger in males of species in which only males sing; in duetting species the dimorphism is not as pronounced (for a recent review, see [29]). The anatomical sexual dimorphism of the song nuclei is paralleled by sex differences in expression of the *cntnap2* gene during development and in the adult [30]. CNTNAP2 has been implicated in human language, suggesting a conserved role for this gene in vocal processing [31].

Song perception is also sexually dimorphic. When hearing songs, female budgerigars (*Melopsittacus undulatus*) engage the caudomedial mesopallium (CMM) in both hemispheres, whereas males display right hemisphere dominant activation [32]. Thus, similar to humans, functional hemispheric asymmetries are found in the perception of vocalisations, but only in males. Songs have different rewarding properties for male and female zebra finches (*Poephila guttata*). These songbirds are both monogamous and gregarious, and singing plays both a sexual, pair-bonding role and a social, affiliative one. In males, songs from other males trigger dopamine release in the striatum and have reinforcing properties [33•]. For females, however, only songs from their mate, but not those from a stranger, will be rewarding. This process has been proposed as a mechanism for maintaining monogamy in a highly gregarious species [33•].

In species that are under scramble competition, navigational skills for finding food and mates are predicted to be under selective pressure. Navigational ability should therefore be higher in species or sexes that compete more strongly for resources and explore bigger areas of territory, as proposed by the range size hypothesis. This model has been used to explain the sexual dimorphism in navigational ability and hippocampus size observed in meadow voles (*Microtus pennsylvanicus*). Meadow voles are polygamous and males have a larger home range, encompassing the territories of several females, better navigational skills and a bigger hippocampus than females [34]. In contrast, monogamous species such as the prairie vole (*M. ochrogaster*) and the pine vole (*M. pinetorum*), in which males and females have similar home range sizes, do not display overt sex differences in spatial cognition or hippocampal size [34]. Range size, however, may not be the only variable in how the sexes use space, and even in monogamous species, there may be subtle differences in space usage and spatial cognitive demands. Indeed, a recent study by Rice *et al.* has shown that although male and female prairie voles learn at the same rate in a spatial location laboratory task, the water maze, males outperform females in spatial memory accuracy [35•]. Also in hummingbirds, which feed on nectar, sex differences in foraging strategies are correlated with sexually dimorphic cognitive abilities. Males are territorial and females are opportunistic, making rapid intrusions into male territories. Males are better than females at remembering nectar location and renewal rate but females have a larger hippocampal formation [36]. Larger hippocampal size may be adaptive since females, being opportunistic, may have larger home ranges. Together, these studies indicate that, for two important functions of the hippocampus — spatial location memory and navigation — navigational demands are more strongly correlated with larger size.

Social animals can learn new skills through interactions with or observations from other individuals in the group. Several studies have identified sex differences in such social learning. Female zebra finches copy new foraging strategies from male demonstrators whereas males do not [37]. Similarly, foraging information spreads faster through subgroups of female guppies (*Poecilia reticulata)* than through male subgroups [38]. Juvenile female blue tits (*Cyanistes caeruleus*) are also twice as likely to learn a new skill from a demonstrator than males [39], and so are juvenile female chimpanzees [40]. In these two species, females, but not males, disperse away from their group into a new one during sexual maturation. Thus, the female-biased learning has been attributed to the need to cope with novel physical and social environments at the stage of dispersion.

Finally, other physiological and lifestyle sex differences, such as nutritional needs and the feeding of offspring, may also generate sex differences in motivation that contribute to sex-biased learning. Nevertheless, sex

(Figure 1 Legend Continued) of a sexually dimorphic circuit for odour processing and learning in worms. Each neuron class is labelled by its three-letter code. Rn, ray neurons, CEMv (CEM ventral), CEMd (CEM dorsal).

differences in lifestyle do not always result in sex differences in cognition. Both male and sterile female-worker bumblebees forage for flowers, but males also need to search for mates. Males' mating needs, however, do not compromise their ability to learn visual floral cues for foraging, at which they are as proficient as workers [41]. It would be important to determine whether, despite the lack of sex differences in performance, male and female bumblebees employ distinct neural mechanisms for learning and foraging.

Sexually dimorphic associative learning and the effects of stress

Sex differences in associative learning and their underlying mechanisms have been extensively studied in rodents and humans, particularly with regard to the effects of stress on cognition. Here we summarise the main general ideas and latest progress, but for recent comprehensive reviews see [42–45]. Broadly speaking, females outperform males in fear conditioning and object location tasks, and males are better at navigation and spatial rotation. However, because of the intrinsic sex differences that exist in arousal, pain threshold and exploratory activity, the effects of sex on learning and memory are highly dependent on the particular behavioural paradigm that is tested.

Sex differences in learning are more prominent in fear-conditioning paradigms where the behaviour is an active response (such as startle or active avoidance) than in those that require passive responses (such as freezing) [46]. This may be because females react to fearful stimuli with more active behaviours than males [47•]. Circuits and cell types that favour the expression of active or passive fear responses have been recently identified in the central nucleus of the amygdala [48]. It will be important to determine whether the balance of these circuits is different in males and females.

Context-dependent fear-conditioning paradigms, in which the context where the conditioned stimulus (CS)-unconditioned stimulus (US) association occurs is taken into consideration, have been extensively used to investigate sexually dimorphic learning because of their relevance to psychiatric disorders such as post-traumatic stress disorder (PTSD). PTSD is characterised by the return of a fearful memory in a safe or neutral context, and is much more prevalent in women than men [49]. Recent studies in humans and rats have shown that females display higher fear generalisation (i.e. lower discrimination between dangerous (CS-US) and safe (CS-no US) contexts) [50,51] and earlier loss of the extinction memory (CS-no US) [46,52]. Some of the neural and molecular mechanisms underlying these sex differences are beginning to be elucidated in rodents. During fear memory retrieval, males and females engage different brain regions, the hippocampus (involved in contextual learning) and the basal amygdala (involved in processing fear and anxiety), respectively [51]. Additionally, during retrieval of the extinction memory, females display sustained activity of the prelimbic cortex (PL) [53], an area involved in the expression of conditioned fear [54]. Females also present higher methylation at the transcriptional start site of BDNF exon IV and reduced expression levels of this isoform in the infralimbic cortex (IL) [55], an area important for fear suppression and extinction [54]. Since BDNF enhances neural plasticity [56], reduced levels in the IL will impair fear extinction. High levels of circulating ovarian hormones also contribute to female fear generalisation and reduced extinction [50,52].

High oestrogen levels do not always have detrimental effects on learning [57], they do, however, make females more vulnerable to stress. In both classical and operant fear conditioning tasks, female rats outperform males and this is associated with peak levels of oestrogen during pro-oestrus [44]. Stress influences either sex differently depending on the type of learning. In classical conditioning tasks, stress impairs learning in females and enhances it in males, and this also depends on circulating hormone levels. In operant conditioning tasks, which require active avoidance, the effects of stress are reversed [58]. One possible reason for females performing better at operant tasks may be their intrinsic bias to respond to fear with active rather than passive behaviour. The effects of stress on learning require the hippocampus and the amygdala in both sexes but only the effects on females require the medial prefrontal cortex (mPFC) and its connections to the amygdala [59]. Importantly, transcriptome profiles in the mPFC are highly variable in females across the oestrous cycle [60]. Learning abilities and the effects of stress are mirrored by the formation of dendritic spines in pyramidal CA1 neurons of the hippocampus [61]. However, intrinsic, experience-independent sex differences in these neurons may already exist since oestrogen-dependent sexual dimorphism in dendritic morphology is observed when mouse hippocampal CA1 neurons are developed in culture [62].

The negative effects of stress on learning extend to other forms of memory. Recently, in a mouse genetic model for predisposition to stress, the BDNF Val66Me strain, only females displayed spatial memory impairment and this was dependent on circulating ovarian hormones. The hippocampal CA3 neurons of un-stressed BDNF Val66Me mice displayed gene expression profiles similar to the ones of wild-type mice exposed to acute stress, which importantly, differed greatly between the sexes [63].

Together, these studies indicate that males and females employ different behavioural and neural strategies to cope with fear and stress and this is, in part, due to differences in sex hormones. Since fear conditioning

paradigms have a strong stress component, it will be important to better dissect the contribution of sex differences in the stress response system from more specific sex differences in learning and memory.

Different mechanisms to achieve the same goal

Cognitive sexual dimorphism is not always manifested as differences in performance. Sometimes the sexes differ in the expression of a behavioural response, in the strategy employed to solve a problem or in the underlying neural and molecular mechanisms for learning and memory. In these contexts, dimorphisms in implementation may act to compensate for intrinsic physiological sex differences in order to maintain equal levels of performance [64].

Behavioural strategies and neural implementations

As already mentioned above, one clear example of sex differences in behavioural strategy is the expression of fear in rodents. Males tend to freeze while females tend to dart [47•]. Darting improves extinction learning in females [47•] and may act to compensate for their heightened arousal [42].

Males and females also employ different strategies for navigation. In our own species, males tend to navigate by allocentric processing (using absolute position), whereas female mainly use egocentric processing (position relative to oneself) [65,66]. When a navigational task relies on landmark-based orientation, sex differences in performance disappear. However, neural implementation remains dimorphic: males preferentially engage the left hippocampus and females, the parietal and PFC [67]. An early-stage component of navigation is the processing of surrounding scenes. In males, the parahippocampal place area (PPA), a cortical region involved in the presentation of the visuospatial structure of the scene, displays higher scene selectivity than in females and this is correlated with better self-reported navigational skills in males but not in females [68]. Navigation has elements of spatial rotation and working memory. Sex differences in navigational skills are thought to arise from differences in spatial rotation ability only [43]. However, a recent study has shown that working memory is also sexually dimorphic, with males outperforming females when the load or demands of the task are increased [69]. This suggests that sex differences in working memory may also contribute to sex differences in navigation. Navigational strategies are also sexually dimorphic in cuttlefish. Although no differences in learning rates are observed during navigation, mature males employ visual cues, whereas females and immature males employ motor responses that indicate whether they have turn left or right [70•], a strategy that displays some similarities with egocentric processing. In addition, mature males travel longer distances than females when tested in an open field [70•] posing the question of whether sex differences in navigational strategy may be linked to differences in home range size. Further evidence in support of the range size theory will need to come from field studies in the wild.

Sexually dimorphic neural implementation without differences in performance is also observed during episodic memory retrieval in humans. Males and females display different activity in the left parahippocampal gyrus (involved in the spatial processing of scenes) and the dorsolateral PFC (involved in temporal sequencing of events), respectively [71]. Differential neural activity may represent sex differences in encoding. Indeed, while males and females retain episodic memory at similar rates, women display a higher rate of acquisition [72].

Based on some fMRI studies [73,74], functional connectivity in the human brain appears to be broadly sexually dimorphic, which could potentially allow for widespread differences in neural implementation during a cognitive task. Ingalhalikar and colleagues have proposed that men display higher intra-hemispheric connectivity and reciprocal connections within subnetworks, whereas females display more interhemispheric connections and cross-subnetwork participation [73,74]. However, other studies find extensive overlap in the connectivity patterns of men and women and no consistency of female or male-typical connectivity within an individual's brain [75]. Together, these somehow contradictory studies underscore the challenge of extracting generalisations from heterogenous populations of complex organisms, such as humans.

Molecular mechanisms

In vertebrates, the largest sexual dimorphism in neurochemistry is found in the level of circulating sex hormones. Because of their role in the regulation of neurogenesis, plasticity, and learning and memory, sex differences in oestrogen levels underlie much of the sexual dimorphism observed in hippocampal and striatal learning in rodents (recently reviewed in [4,57,76]). It is important to note that males also synthesize oestrogens and these are found at high levels in the hippocampus [4]. Oestrogens promote synaptic plasticity and potentiation. The mechanisms underlying the potentiating effects of oestradiol (E2) on hippocampal CA1 glutamatergic transmission in each sex are different, however. Post-synaptic potentiation is mediated by the oestrogen receptor ER-β in males and by ER-1 in females, whereas the pre-synaptic effects are mediated by ER-α in males and by ER-β in females [77]. This is important because ER-α and ER-β receptors regulate the expression of different synaptic proteins [78]. The endocannabinoid system at hippocampal GABAergic, inhibitory synapses is also differentially regulated in

male and females through oestrogen-dependent and independent mechanisms [79].

Other molecular pathways differentially underlie memory formation in males and females independently of oestrogen signalling. These include synaptic kinases, such as Ca^{2+}/calmodulin kinase kinases α and β (CaMKKα and CaMKKβ), the transcription factor CREB, and the splicing factor SRp20, all of which are required in male but not female mice for spatial learning (reviewed in [80]). Recently, in a mouse genetic model of neurodevelopmental disorders associated with the human 16p11.2 deletion, hemizygous males but not females were found to be impaired in reward-directed learning [81•]. The defects were associated with male-specific increased activation of the ERK1 pathway in the striatum upon reward, and elevated expression of markers for striatal spiny D2 neurons, which inhibit undesired actions during goal-directed behaviour [81•]. These results suggest that there are sex differences in molecular mechanisms underlying natural reward processing and reinforcement in the striatum. It will be important to determine whether some of these sex differences in gene expression may be regulated by epigenetic mechanisms as seen for the BDNF locus and others [82]. Indeed, several histone-modifying enzyme-encoding genes on chromosome X, such as *Utx*, *Jarid1c* and *Usp9x* are expressed at higher levels in females than in males and this contributes to sex-dependent differences in learning through epigenetic regulation [80].

Concluding remarks

The work reviewed here demonstrates that sexually dimorphic learning is universal. Several common underlying principles can be found across species. One is the influence of circuits for innate behaviour on circuits for learning. Sex differences in innate motivational incentives and natural rewards often underlie sexually dimorphic learning. Secondly, many sex differences in cognition represent differences in expression, strategy or mechanisms to achieve the same goal without the need for differences in ability or performance. Finally, selective pressures on reproduction and/or lifestyle, which often differ between the sexes, may drive much of the sexual dimorphism in learning.

To fully understand the process of learning, we will need to investigate the neural mechanisms that can support it, the ecological pressures under which it evolved and the different forms by which it can be implemented in the sexes of a single species. More effort should be placed in integrating what we have learned from each of these different fields and approaches. In particular, the use of ethologically relevant or more naturalistic behavioural paradigms in combination with molecular and cellular analysis of circuit anatomy and function promises to shed valuable insight into the mechanisms underlying plasticity, from genome to behaviour.

Conflict of interest statement

Nothing declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.cophys.2018.05.004

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