Sex differences in behaviour and relevant neural substrates

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Organisational/activational effects of sex hormones:

Which statement is correct?

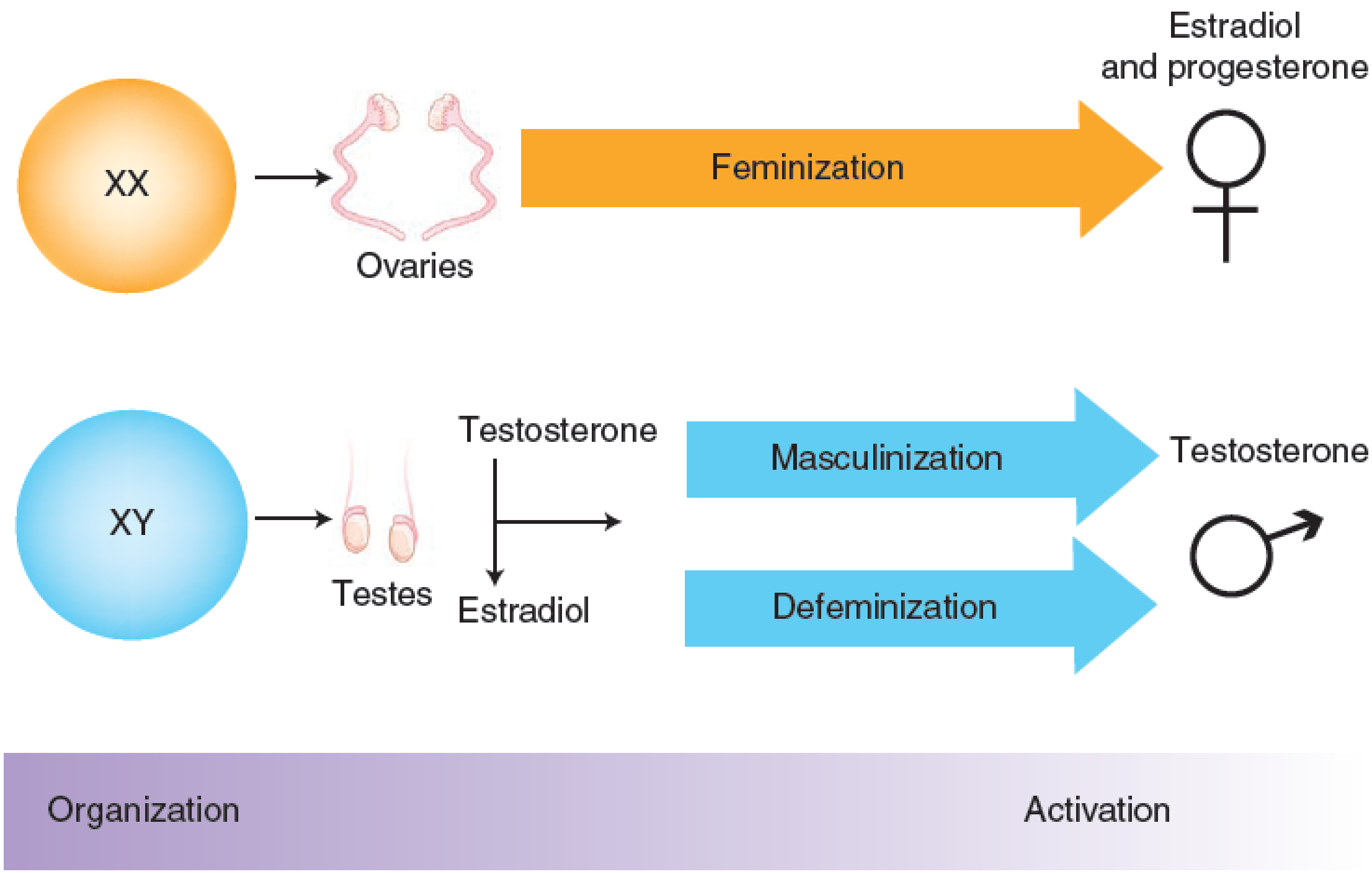
a) Organisational effects occur only during critical periods.

b) Activational effects occur only during critical periods.

c) Organisational effects are typically reversible.

d) Activational effects are permanent.

Sex differences in brain and behaviour – organisational/activational theory



Taken from McCarthy & Arnold(2011) *NatureNeurosci* 14:677

Excellent overview in: Arnold (2009) The organizational-activational hypothesis as the foundation of for a unified theory of sexual differentiation of all mammalian tissues. *Horm Behav* 55:570-578.

Sex differences in behaviour and cognition: some introductory remarks

•"[Sex differences refer to a difference] between the average male and the average female. Most behaviors show considerable overlap for males and females; in fact, the range of differences within each sex usually is larger than the average difference between the sexes . . . Therefore, identification of a sex difference acknowledges mean differences, but may allow one to predict very little about a specific individual's performance on the basis of sex alone."

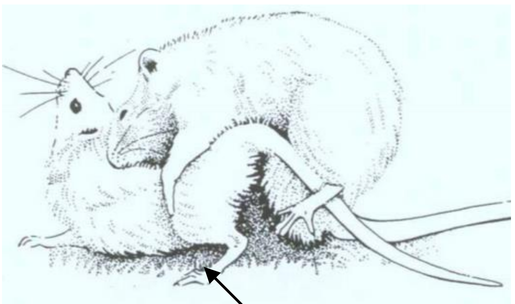
•"The largest behavioral sex differences are seen in *sexual orientation* and *core sexual identity* [in humans]; however, even these differences are not absolute [in humans]."

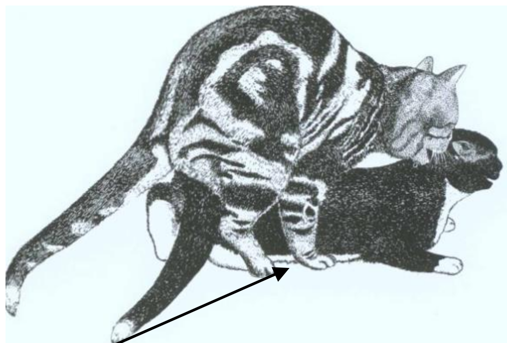
•"Sex differences in other behaviors are less marked than those in core sexual identity and orientation."

• Determinants of sex differences in behaviour and cognition:
-Sex genes, activity of different sex hormones, and environment/experience are all factors that differ between males and females. During development and adulthood, these factors interact in their effects on the brain to result in sex differences in behaviour.
-Sex differences in behaviour may be partly mediated by sexual dimorphisms in the brain or CNS (and there is good evidence for this with respect to some sexual behaviours).
-Alternatively, sex differences in behaviour may result from the exposure of identical (i.e., sexually homomorphic) brain substrates to female or male sex hormones and female or male experiences ('cultural factors').

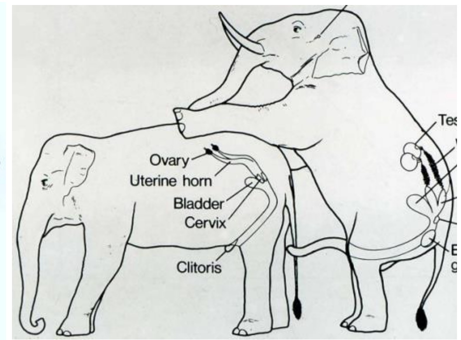
Citations from Collaer & Hines, 1995, Psychol. Bull. 118:55

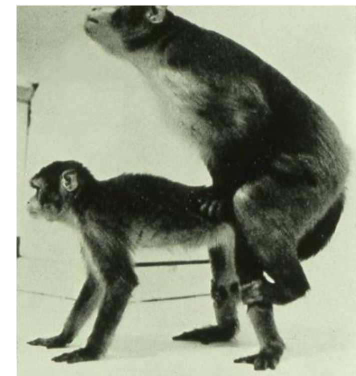
Mating behaviour





Lordosis response





Hormonal control and relevant neural sexual dimorphisms?

Heterosexual mating behaviour in mammals

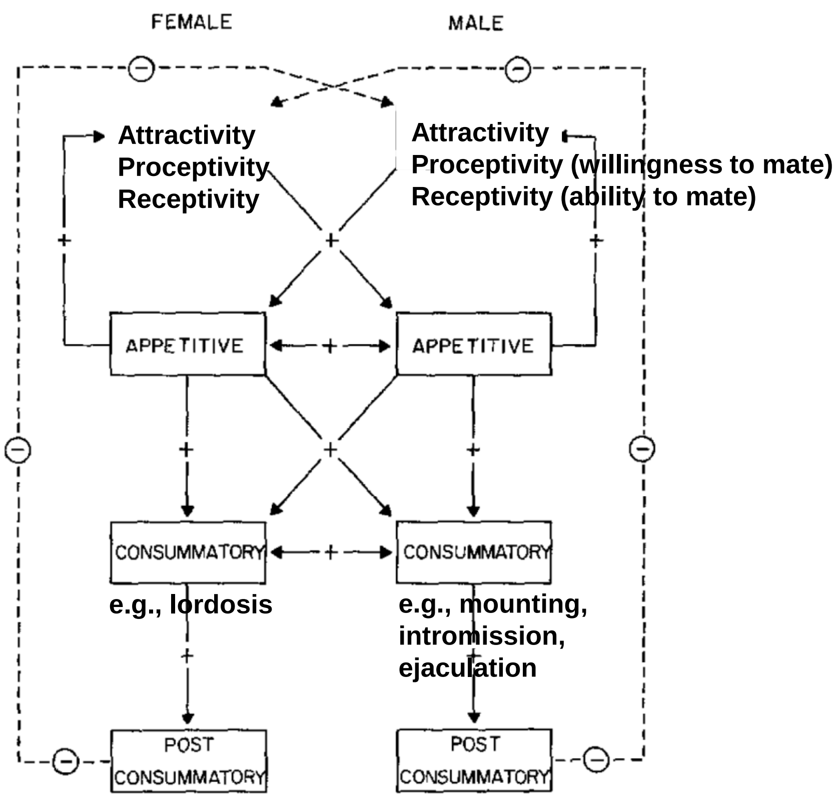
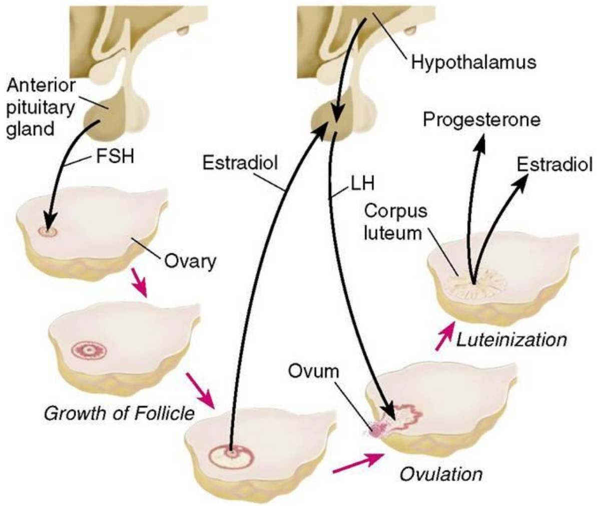


Fig. 1. Successive phases and reciprocal interrelations in heterosexual mating. (1) Partner's attractivity stimulates appetitive behavior which has four effects. Display of appetitive behavior enhances the general attractiveness of the performer, elicits complementary appetitive responses by the partner, evokes consummatory behavior by the partner, and produces feedback stimuli leading to initiation of consummatory behavior by the performer. (2) Execution of consummatory behavior has two effects. It stimulates the occurrence of consummatory responses by the partner and produces feedback effects leading to the postconsummatory phase or state in the performer. (3) The postconsummatory phase is associated with temporary loss or reduction in the performer of responsiveness to the stimuli which initially contributed to sexual attractivity of the

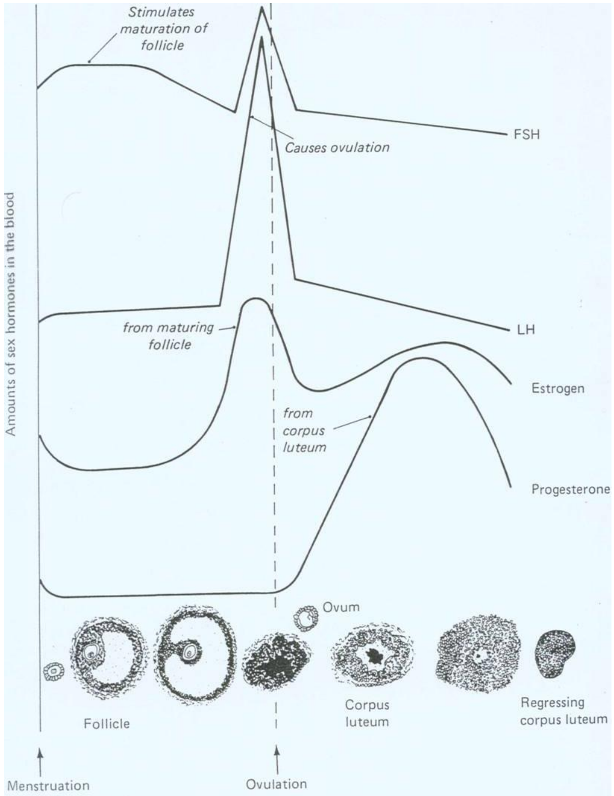
Beach, 1976, *Horm. Behav.* 7:105

Reproductive and hormonal cycles in female mammals



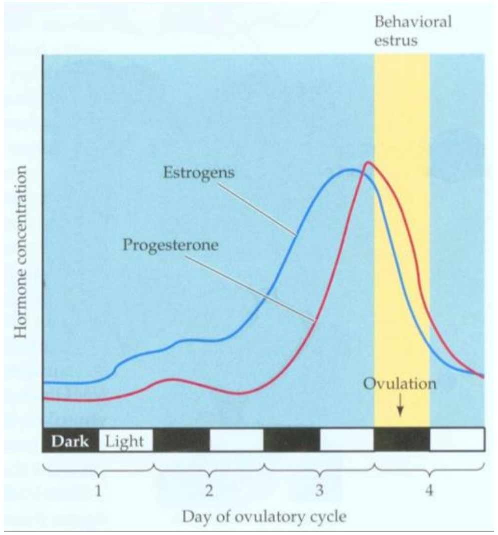
(Cycle repeats unless eggs are fertilised, and the resulting embryo secretes hormones that interrupt the cycle and maintain pregnancy.)

Human menstrual cycle



(Monthly growth and loss of uterus lining.)

Rat estrous cycle

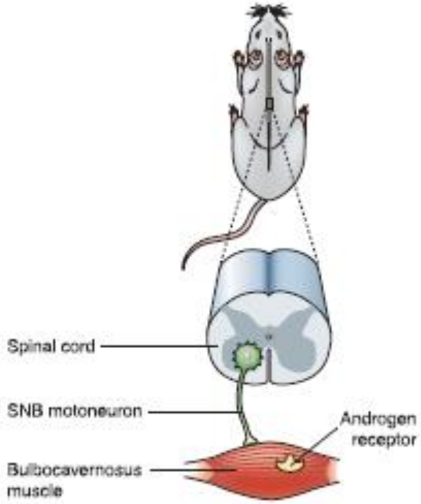


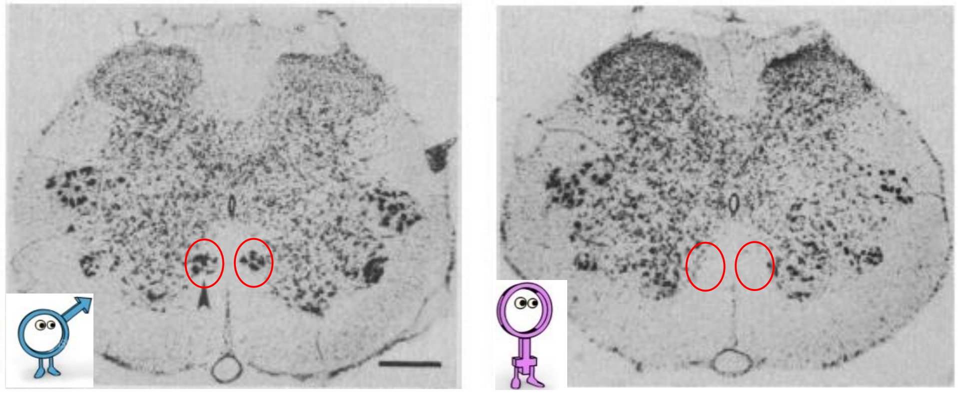
(No monthly growth and loss of uterus lining.)

- Pregnancy only possible during a certain time of the cycle around ovulation (when estrogen and progesterone levels are high).
- Female sexual behaviour is linked with the reproductive cycle and controlled by the hormonal fluctuations.
- Females can mate only during a certain time of the cycle around ovulation (behavioural estrous), except for primate females who can mate any time. However, even in primates attractiveness, receptivity, and proceptivity appear to be modulated by the hormonal cycle.
- Hormonal cycles may also influence behavioural, cognitive, and affective functions that are not directly related to reproductive behaviour.

Spinal mechanisms relevant to male copulatory behaviour in rats

Spinal nucleus of the bulbocavernosus (SNB)

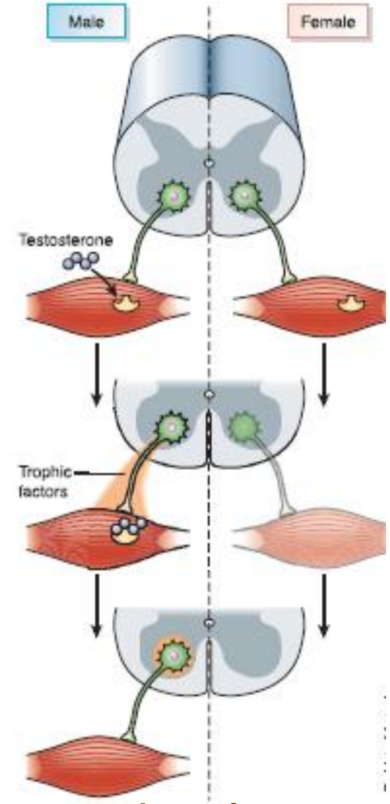




Breedove & Arnold, 1980, Science 210:564

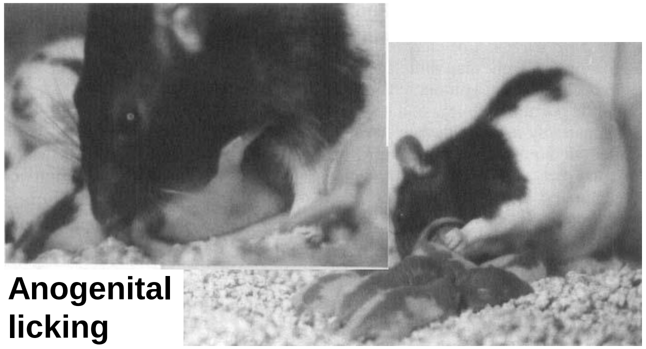
•Collection of motor neurons in the lower lumbar spinal chord; controls the bulbocavernosus muscle at the base of the penis.
•These motoneurons and muscles are necessary for normal penile reflexes that are important for successful copulation (Monaghan & Breedlove, 1992, *Brain Res* 587:178)
•They are absent or substantially reduced in size/number in adult females as compared to males.

Direct masculinising effects of testosterone



Morris et al., 2004, *Nature Neurosci.* 7:1034

Interaction of ‘nature’ and ‘nurture’: testosterone exerts some masculinising effects on SNB and sexual behaviour via the rat mother



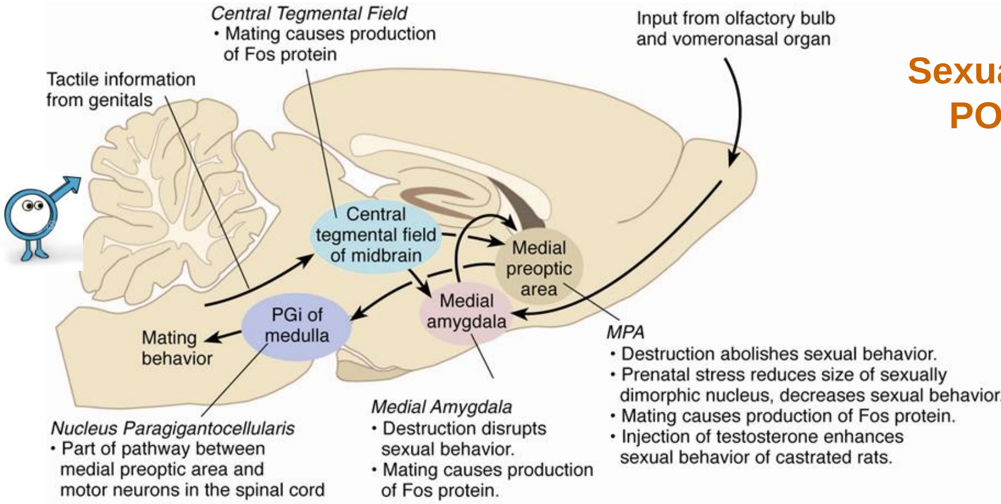
Anogenital licking

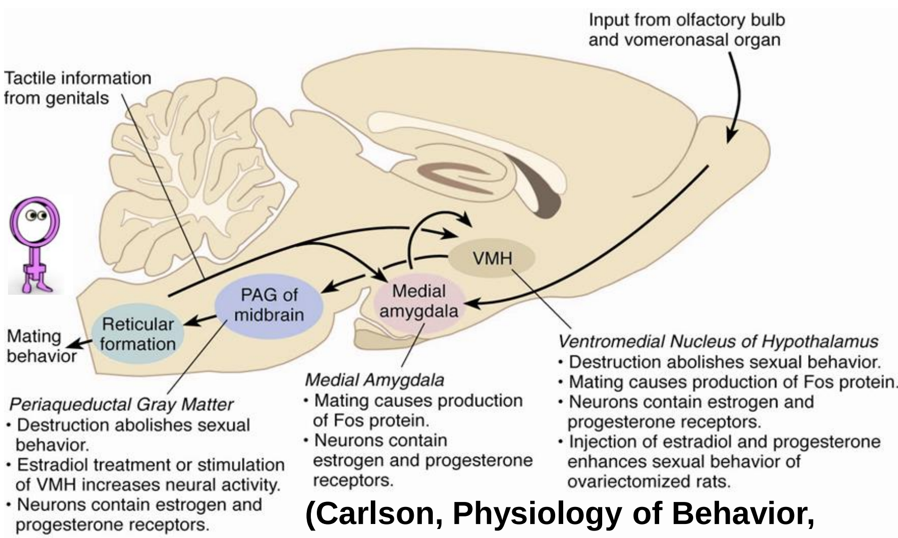
•Rat mothers are stimulated to lick their male pups more often than their female pups because of testosterone in urine.
•Such anogenital licking contributes to normal male sexual behaviour in the adult and to a normal number of SNB neurons.

Moore, 1992, *Ann. N. Y. Acad. Sci.* 662:160

Brain mechanisms relevant to mating behaviour in rodents

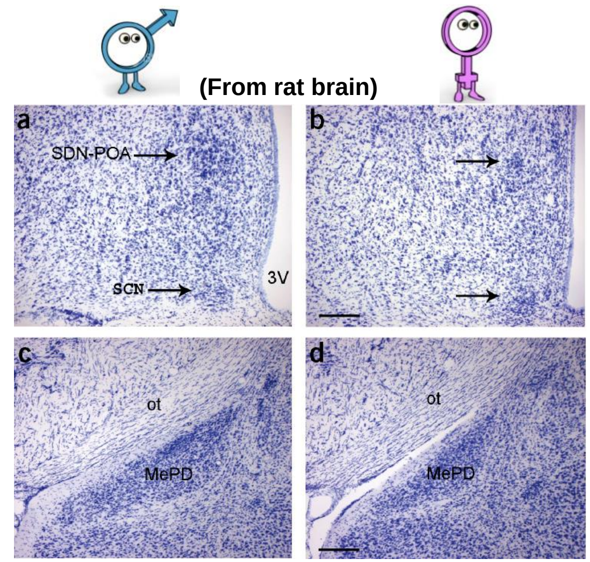
"Sex circuits"





(Carlson, Physiology of Behavior, Fig. 10.15 and 17)

Sexually dimorphic nucleus of the preoptic area (SDN-POA) and posterodorsal medial amygdala (MePD)



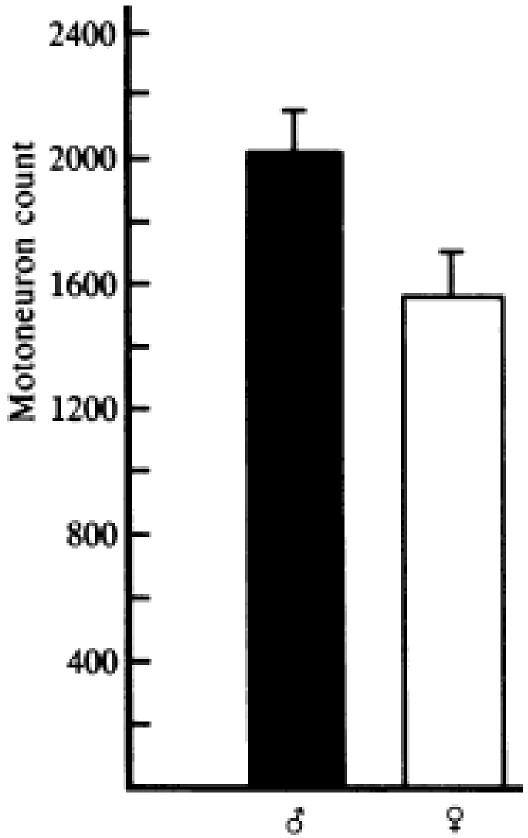
Morris et al., 2004, *Nature Neurosci.* 7:1034.

•SDN-POA is masculinised by testosterone during a critical perinatal period.
•MePD volume and cell size depend on testosterone action in adulthood.

•These circuits contain sex hormone receptors, and these are critical for sexually dimorphic mating behaviour: testosterone for male behaviour, estradiol and progestorone for female behaviour.
•Several components of these circuits are sexually dimorphic (for recent overview compare Shah et al., 2004, *Neuron* 43:313).

Sexual dimorphisms in human homologue to rodent spinal nucleus of the bulbocavernosus (SNB)

Ventrolateral (VL) cell group of Onuf's nucleus in the human spinal chord

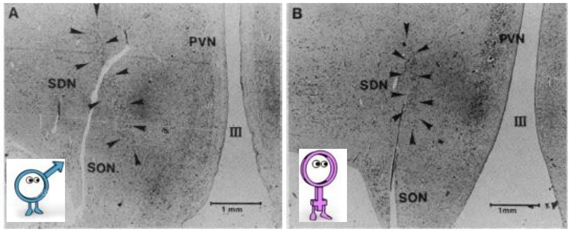


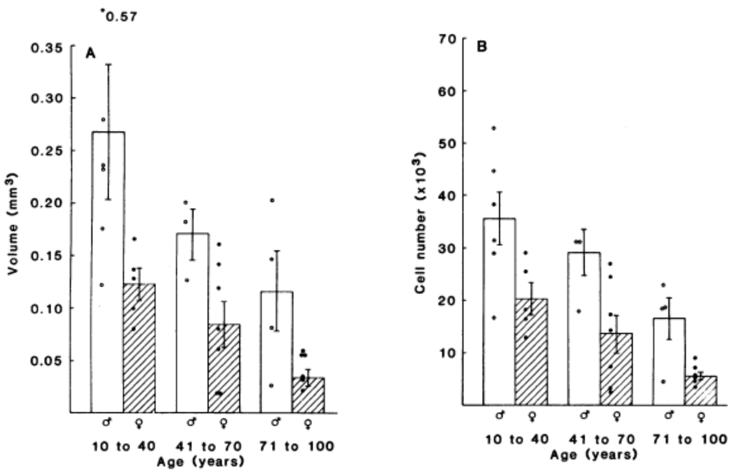
Forger & Breedlove, 1986, *Proc. Natl. Acad. Sci. USA* 83: 7527

Sexual dimorphisms in human preoptic area (POA) of the hypothalamus

Fliers & Swaab, 1985, *Science* 228:1112

•One nucleus in the POA of hypothalamus was larger in volume and cell number in males than in females.
•Hence, authors named the nucleus SDN.



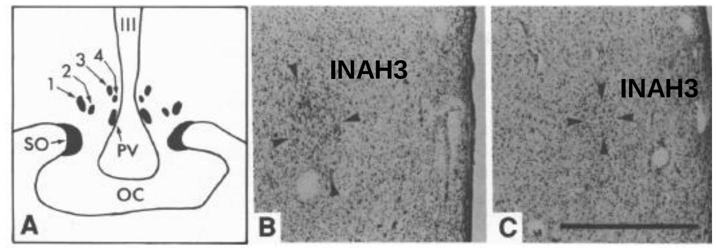


Allen et al, 1989, *J. Neurosci.* 9: 497

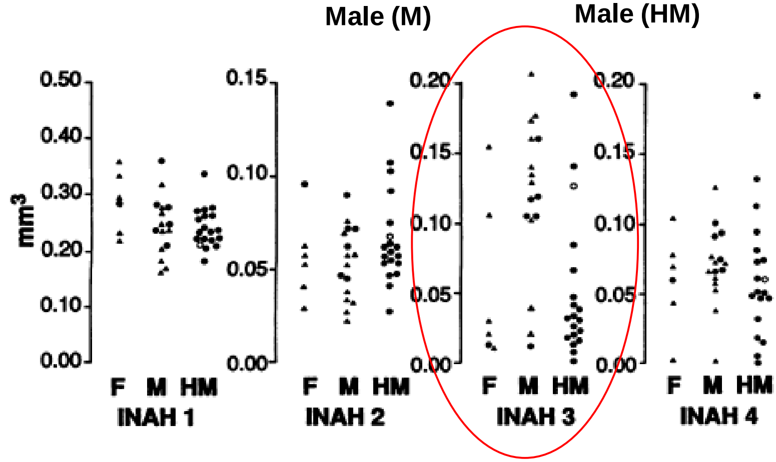
•Studied four nuclei in the POA, which they named interstitial nuclei of the anterior hypothalamus (INAH) 1-4.
• INAH1 corresponded to SDN of Fliers&Swaab (1985), but did not differ between sexes. INAH4 also did not differ.
•INAH2 and 3 were larger in men than in females.

LeVay, 1991, *Science* 253:1034

•Found no significant sex differences in INAH1,2, and 4.
•Replicated that INAH3 was larger in heterosexual men than in women.
•Found additionally that INAH3 did not differ between homosexual men and heterosexual women.



Heterosexual Male (M)
Homosexual Male (HM)



F=heterosexual female
M=heterosexual male
HM=homosexual male

Mating behaviour and relevant neural sexual dimorphisms - conclusions

•Sexual dimorphisms exist in CNS regions that have been implicated in sexually dimorphic mating behaviour (based on studies in rodents). This is consistent with the idea that neural sexual dimorphisms may contribute to behavioural sexual dimorphisms.

•Moreover, in line with the organisational hypothesis, some aspects of sexually dimorphic mating behaviour and relevant neural sexual dimorphisms have been shown (in rodents) to involve organising effects of sex steroids during critical developmental periods.

•In other brain regions that are critical for sexually dimorphic mating behaviour in rodents (e.g., ventromedial nucleus of hypothalamus which is critical for female lordosis), neural sexual dimorphisms have not (yet) been shown. However, these regions contain sex hormone receptors the stimulation of which is critical for the sexually dimorphic behaviour (activational effects of sex hormones).

•There have been recent discoveries indicating additional mechanisms that may mediate sexually dimorphic mating behaviour (Kimchi et al., 2007, *Nature* 448:1009; Dulac & Kimchi, 2007, *Curr. Opin. Neurobiol.* 17:675; Arnold, 2009, *Horm. Behav.* 55:570).

Other behavioural and cognitive functions . . . and relevant brain sexual dimorphisms?

Sex differences in aggressive behaviour

- Aggressive behaviour involves threat or attack on other individuals.
- While aggression is not a unitary concept, some aspects of aggression are strongly related to reproductive behaviour (e.g., competition for mating partner, protection of offspring).
- In rodents, it has been shown that these aspects of aggression are mediated by brain regions that overlap with regions implicated in reproductive behaviour; they are sex dependent and under the influence of sex steroids (there is particularly strong evidence for a role of testosterone).

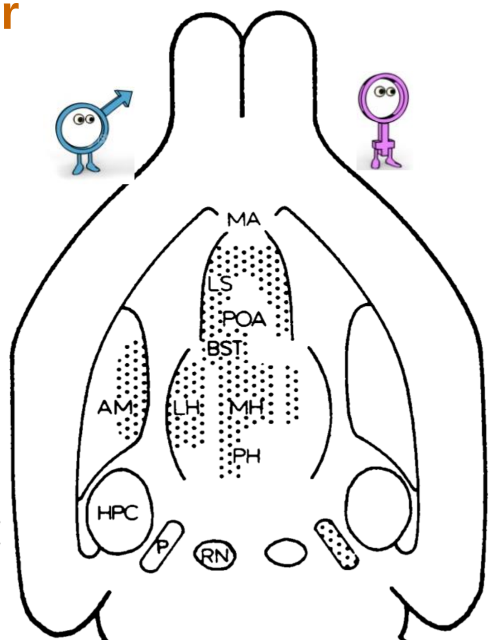


FIG. 6. A schematic horizontal brain section. Stippling indicates regions that appear to modulate hormone-dependent aggression in male (left) and female (right) rats. AM, amygdala; BST, bed nucleus of the stria terminalis; HPC, hippocampus; LH, lateral hypothalamus; LS, lateral septum; MA, medial accumbens; P, peripeduncular nucleus; PH, posterior hypothalamus; POA, preoptic area; RN, red nucleus.

Arnold et al, 1993, *Neurosci. Biobehav. Rev.* 16: 1992

- In humans, there is evidence for some aspects of aggression being sexually dimorphic.

One exemplar finding: Effect sizes of differences in ratings of aggression and competitiveness based on questionnaire responses

Measure	M vs. F	HsF vs. HtF	HtM vs. HsM	HtM vs. HtF
Physical aggression	.21	−.07	.38	.31
Verbal aggression	.26	−.14	−.05	.11
Interpersonal competitiveness	.29	.15	.22	.45

Statistically significant

HtM=heterosexual male
HsM=homosexual male
M=male

HtF=heterosexual female
HsF=homosexual female
F=Female

Gladue&Bailey, 1995, *Psychoneuroendocrinology* 20: 1995

- Testosterone has been suggested to contribute to these sex differences by acting on the brain, and some direct evidence supports this suggestion (Pasterski et al., 2007, *Horm. Behav.* 52:368). (However, other factors might also contribute, for example that men are – on average – physically stronger than women.)

Sex differences in cognitive functions

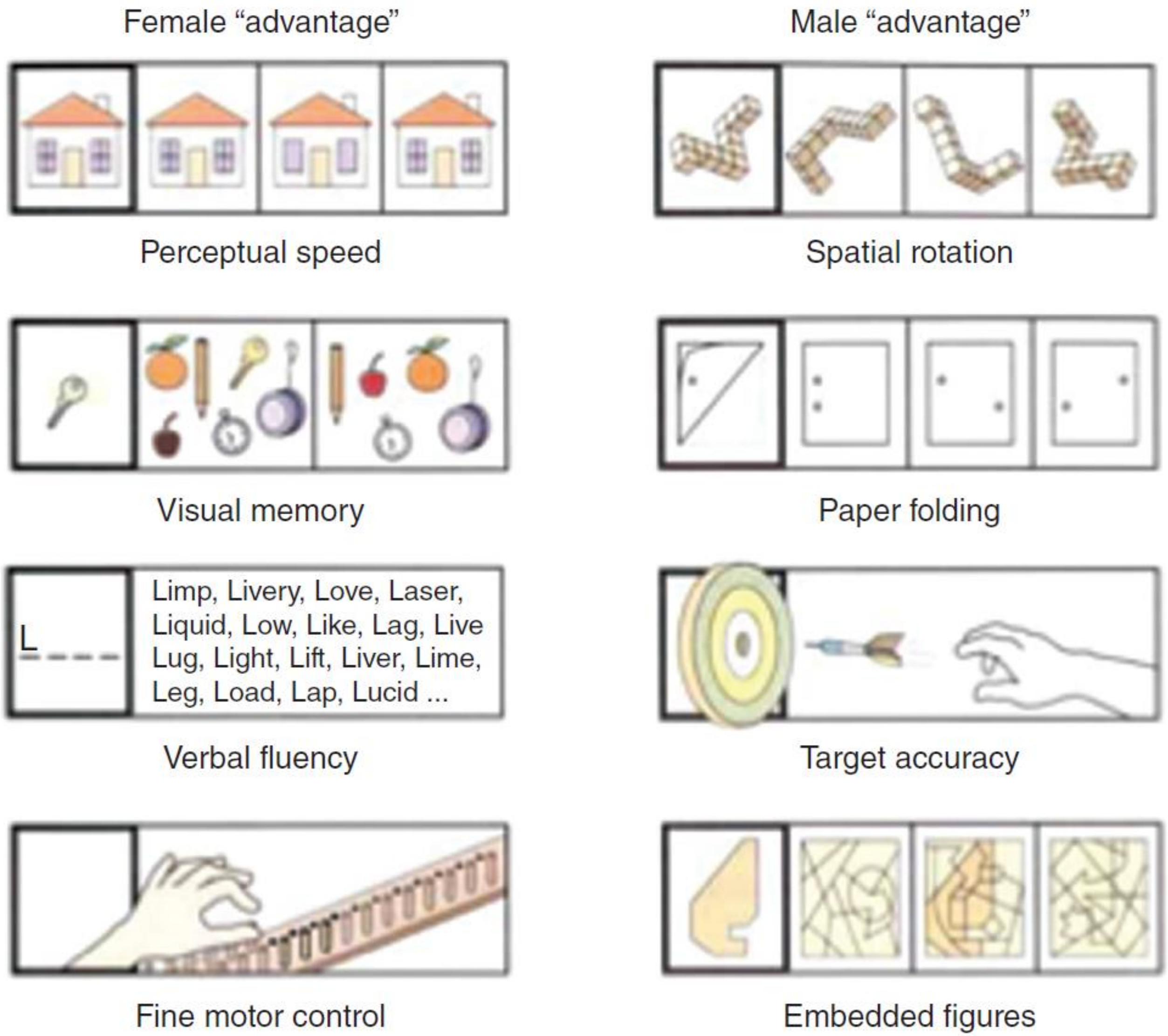
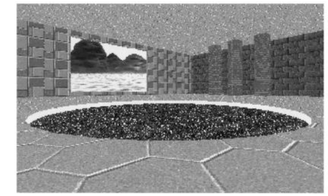


Figure 1 Tasks favoring women or men. On average women show superior performance in tasks requiring perceptual speed, verbal fluency, visual memory, and fine motor skills compared to men. However, men tend to do better than women on spatial tasks such as the mental rotations test, the paper-folding test, embedded figures, and have better target accuracy even when accounting for sports history. Figure adapted from Figures 1 and 2 with permission from Kimura 1992 (328).



Place learning and navigation

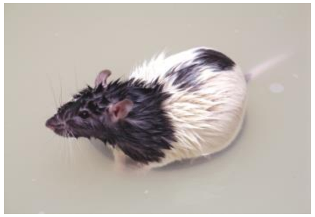
Figure taken from:
DK Hamson et al, 2016,
***Compr Physiol* 6:1295**

Sexual dimorphism in place learning and navigation and relevant neural substrates

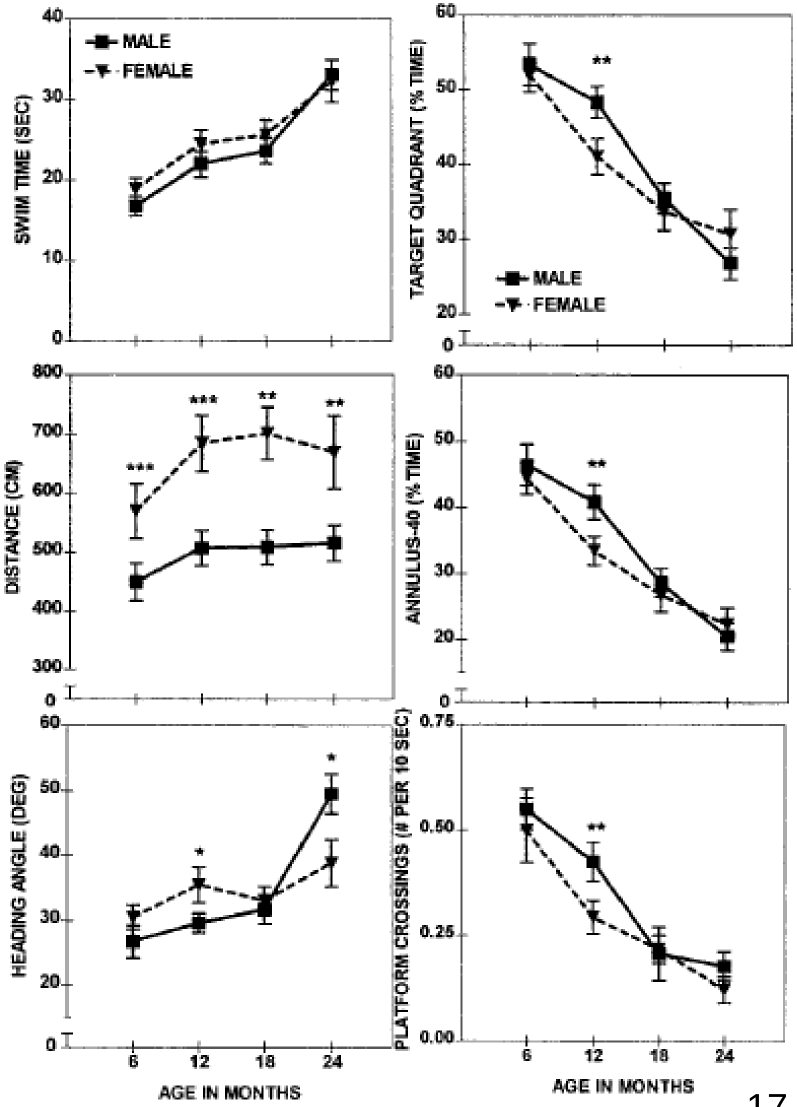
•One of the more consistent sexual dimorphisms in behavioural and cognitive abilities in humans and rodents is a male advantage in place learning and navigation (Astur et al., 1998, *Behav. Brain Res.* 93:185; Moffat et al.,1998, *Evol. Hum. Behav.* 19:73; Jonasson et al., 2005, *Neurosci. Biobehav. Rev.* 28:811).

Better place learning and navigation in males than in females – Exemplar study in rats (Markowska, 1999, *J. Neurosci.* 19:8122)

Watermaze

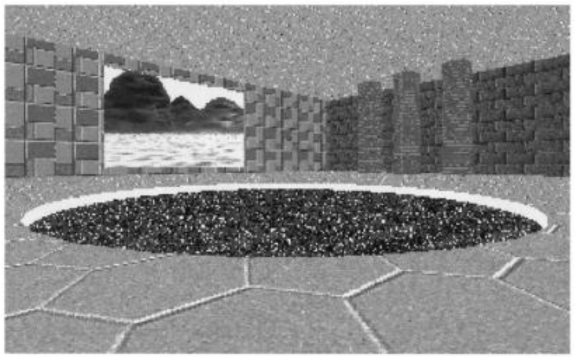


Performance measures

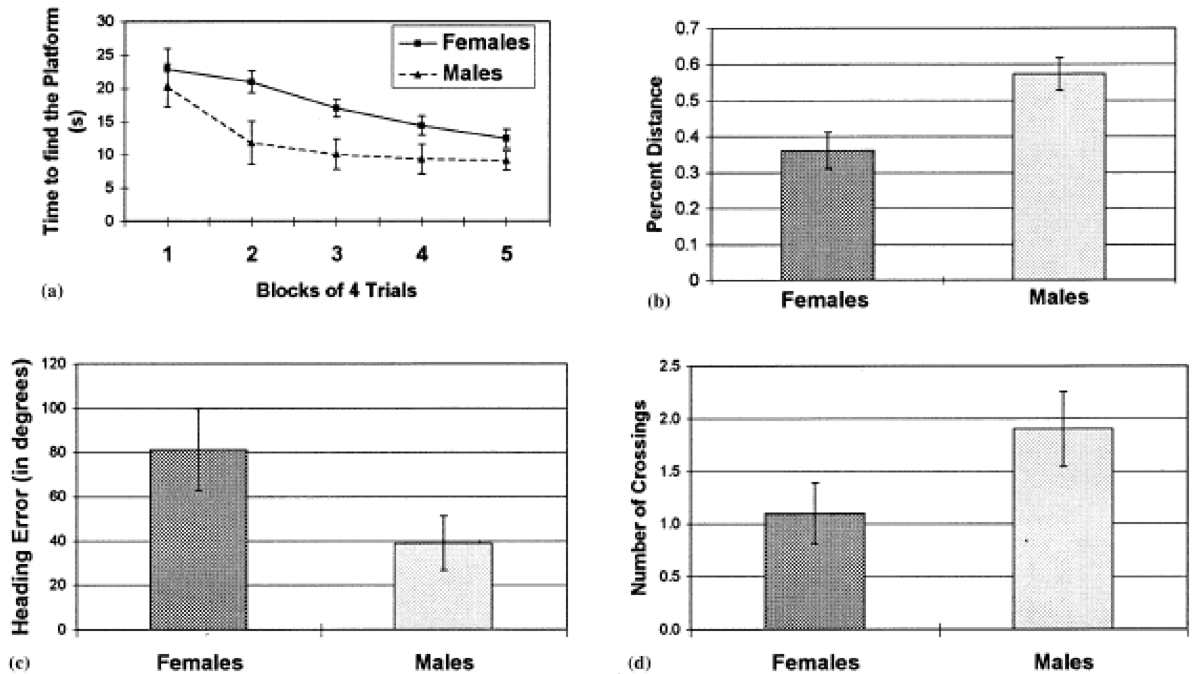


Better place learning and navigation in males than in females – Exemplar study in humans (Astur et al., 1998, *Behav. Brain Res.* 93:185)

Virtual watermaze



Performance measures



Sexual dimorphism in place learning and navigation and relevant neural substrates

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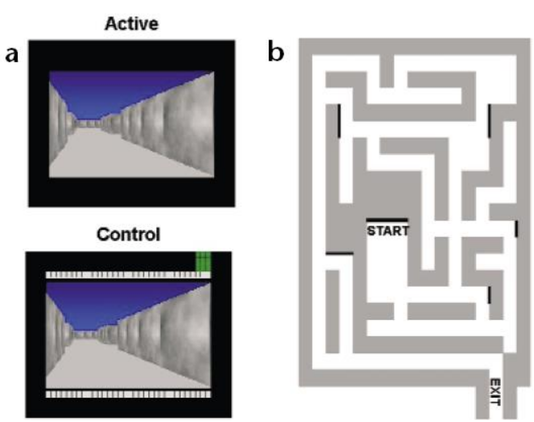
•From prairie voles, there is evidence that such differences might have evolved due to ecological pressures (they only exist in polygamous species in which males range more widely than females in the field) and correlate with a larger hippocampus (a structure that is critical for spatial learning) in males (Jacobs et al., 1990, *Proc. Natl. Acad. Sci. USA* 87:6349).

•Sex differences in the hippocampus have also been found in rats (Madeira & Lieberman, 1995, *Prog. Neurobiol.* 45:275), and men (for review, see Goldstein et al., 2000, *Cereb. Cortex* 11:490) (even though in rodents, the hippocampus tends to be larger in males than in females, whereas in humans the opposite is the case!). Origin of these sex differences is not clear.

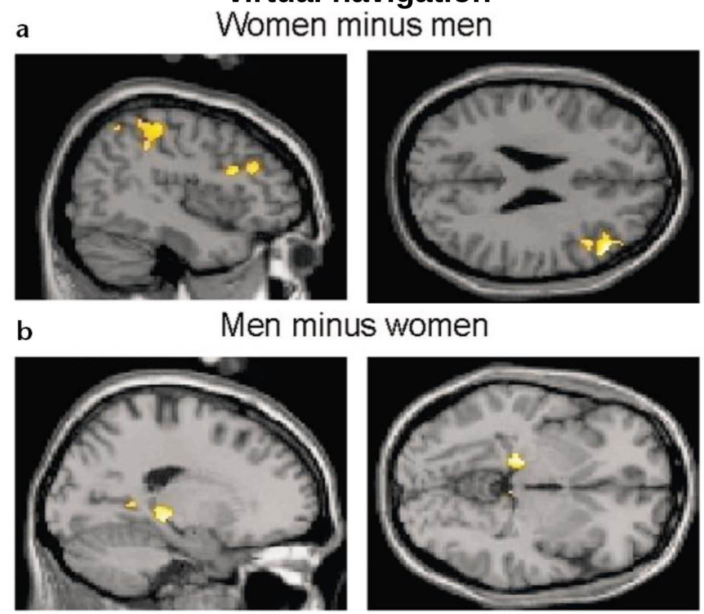
•A human fMRI study suggests that men may use their hippocampus more than women in order to navigate a (virtual) maze:

Virtual maze



Gron et al, 2000, *Nature Neurosci.* 3:404

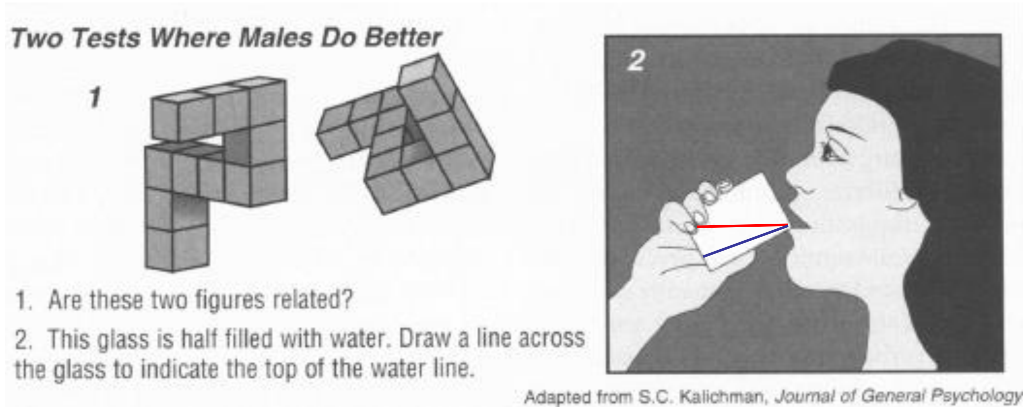
Sex differences in regional 'activation' during virtual navigation



Fronto-parietal activation

Left hippocampal activation

Sex differences in mental rotation and water jar task



Taken from Holden (1991) *Science* 253 :959

Exemplar study (Gladue & Bailey, 1995, *Psychoneuroendocrinology* 20:487)

- **Mental rotation**: 20 items with two correct and two incorrect choices each; 1 point per correct choice; maximum score 40.
- **Water jar task**: 10 items, consisting of jar tilted at different angles; subjects required to draw water line assuming jar is half full; maximum score 10 correct (drawn line within 5 deg of accurate water level).

Means

Measure	HsF	HtF	HsM	HtM
Mental Rotations	12.6 ± 1.2	16.6 ± 1.1	18.6 ± 1.1	20.6 ± 1.1
Water Jar	5.6 ± .48	6.0 ± .47	6.8 ± .47	7.9 ± .46

Effect sizes

	M vs. F	HsF vs. HtF	HtM vs. HsM	HtM vs. HtF
Mental rotations	.52	−.15	.05	.32
Water jar	.40	.05	.20	.38

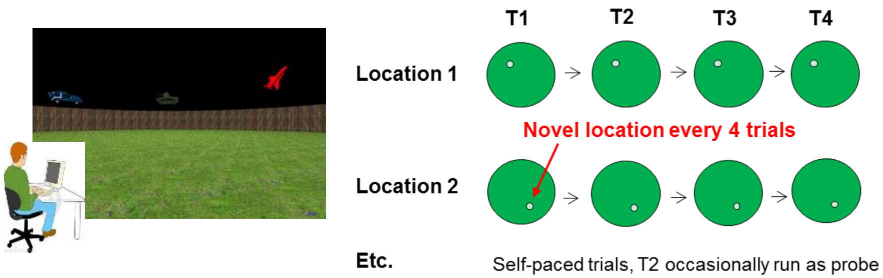
Statistically significant

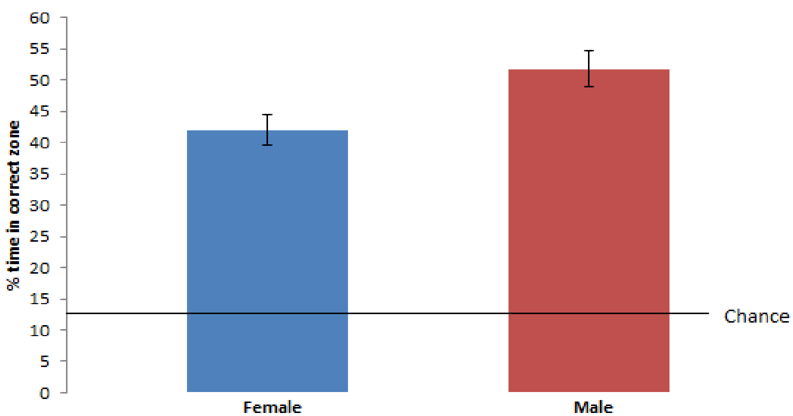
HtF=heterosexual female
HsF=homosexual female
F=Female

HtM=heterosexual male
HsM=homosexual male
M=male

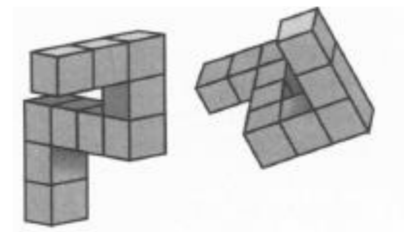
Sex differences in rapid place learning and mental rotation

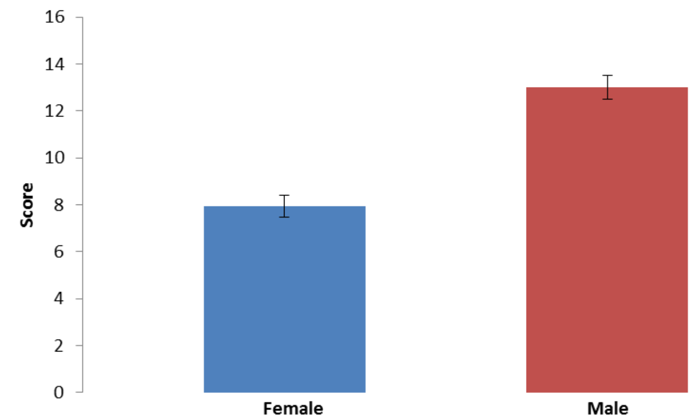
Rapid place learning in virtual environment





Mental rotation test





- 60 females, 63 males – large sample size giving about 80% power to show signficant difference with an effect size of 0.5 (note: many published studies are underpowered)

- Although men were on average better on both tests, performance measures on place learning and mental rotation test did not significantly correlate ($F_{1,121}$=2.11, p=0.15, r=0.13). This implies that sex differences on these two tests are likely to rely on different neuro-psychological mechanisms (also compare Astur et al., 2004, Behav Brain Res 151:103-115)

Final year project 2014/15, Replication 1 in Buckley & Bast, 2018, *Hippocampus* 28:796-812

Cognitive sex differences between the average female and average male allow only very limited predictions concerning cognitive abilities of individuals!!!

If men are on average better on a rapid place learning or mental rotation test with an effect size (Cohen's d) of 0.5, this means that for any randomly picked male the probability of him being better on these tasks than any randomly picked female is 64%.

If there is no average sex difference, the probability is 50%.

Concerning effect sizes and their interpretation compare:
Coe, R. (2002). It's the effect size, stupid: What effect size is and why it is important. EducationOnline, http://www.leeds.ac.uk/educol/documents/00002182.htm

Sex differences in brain sites not primarily associated with sexual behaviour

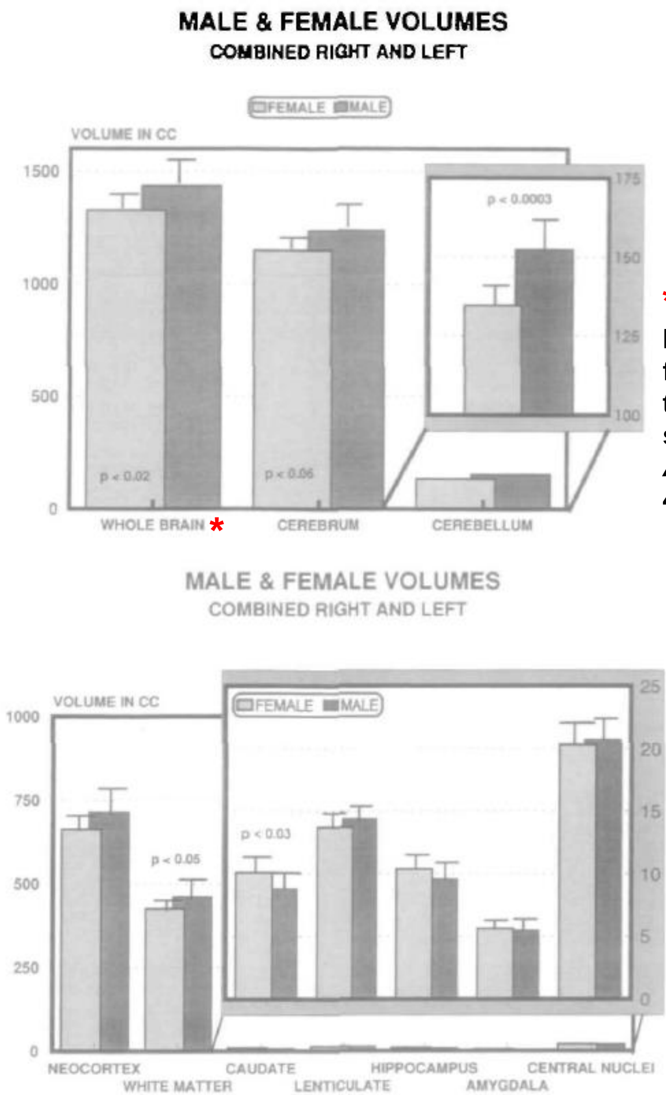


Figure 7. Graphic representation of male and female whole brain (A) and structural (B) mean volume differences. The error bars represent 1 standard deviation from the mean

* **Brain weight is also higher in males than in females (both in absolute terms and relative to body size) (see Breedlove, 1994, *Ann. Rev. Psychology* 45:389).**

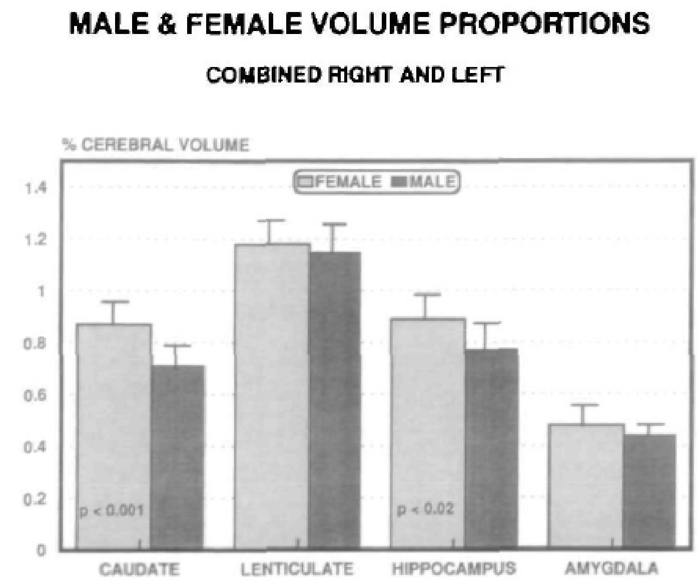


Figure 8. Graphic representation of male and female mean volume proportion differences for representative structures. The error bars represent 1 standard deviation from the mean.

If these neuroanatomical sexual dimorphisms contribute to sex differences in behaviour and cognition is not known.

Filipek et al, 1994, *Cereb. Cortex* 3:404

Sex differences in the incidence of neuropsychiatric diseases

Table 2. Lifetime and 12-Month Prevalence of UM-CIDI/*DSM-III-R* Disorders*

	Male				Female				Total			
	Lifetime		12 mo		Lifetime		12 mo		Lifetime		12 mo	
Disorders	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Affective disorders												
Major depressive episode	12.7	0.9	7.7	0.8	21.3	0.9	12.9	0.8	17.1	0.7	10.3	0.6
Manic episode	1.6	0.3	1.4	0.3	1.7	0.3	1.3	0.3	1.6	0.3	1.3	0.2
Dysthymia	4.8	0.4	2.1	0.3	8.0	0.6	3.0	0.4	6.4	0.4	2.5	0.2
Any affective disorder	14.7	0.8	8.5	0.8	23.9	0.9	14.1	0.9	19.3	0.7	11.3	0.7
Anxiety disorders												
Panic disorder	2.0	0.3	1.3	0.3	5.0	1.4	3.2	0.4	3.5	0.3	2.3	0.3
Agoraphobia without panic disorder	3.5	0.4	1.7	0.3	7.0	0.6	3.8	0.4	5.3	0.4	2.8	0.3
Social phobia	11.1	0.8	6.6	0.4	15.5	1.0	9.1	0.7	13.3	0.7	7.9	0.4
Simple phobia	6.7	0.5	4.4	0.5	15.7	1.1	13.2	0.9	11.3	0.6	8.8	0.5
Generalized anxiety disorder	3.6	0.5	2.0	0.3	6.6	0.5	4.3	0.4	5.1	0.3	3.1	0.3
Any anxiety disorder	19.2	0.9	11.8	0.6	30.5	1.2	22.6	0.1	24.9	0.8	17.2	0.7
Substance use disorders												
Alcohol abuse without dependence	12.5	0.8	3.4	0.4	6.4	0.6	1.6	0.2	9.4	0.5	2.5	0.2
Alcohol dependence	20.1	1.0	10.7	0.9	8.2	0.7	3.7	0.4	14.1	0.7	7.2	0.5
Drug abuse without dependence	5.4	0.5	1.3	0.2	3.5	0.4	0.3	0.1	4.4	0.3	0.8	0.1
Drug dependence	9.2	0.7	3.8	0.4	5.9	0.5	1.9	0.3	7.5	0.4	2.8	0.3
Any substance abuse/dependence	35.4	1.2	16.1	0.7	17.9	1.1	6.6	0.4	26.6	1.0	11.3	0.5
Other disorders												
Antisocial personality	5.8	0.6	...	...	1.2	0.3	...	...	3.5	0.3	...	...
Nonaffective psychosis†	0.6	0.1	0.5	0.1	0.8	0.2	0.6	0.2	0.7	0.1	0.5	0.1
Any NCS disorder	48.7	0.2	27.7	0.9	47.3	1.5	31.2	1.3	48.0	1.1	29.5	1.0

**UM-CIDI indicates University of Michigan Composite International Diagnostic Interview; NCS, National Comorbidity Survey.*

†Nonaffective psychosis includes schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and atypical psychosis.

•Affective disorders (with the exception of mania) and anxiety disorders are more prevalent in women, substance abuse disorders and antisocial personality disorder are more prevalent in men (Table, Kessler et al., 1994, *Arch. Gen. Psychiatry* 51:8).

• Autism-spectrum disorders are more prevalent in males than in females (mean ratio ca. 4:1; Fombonne, 2005, *J. Clin. Psychiatry* 66 (Suppl. 10):3). (This finding has prompted the Extreme-Male-Brain Theory of Autism; see Baron-Cohen et al., 2005, *Science* 310:819).

Sex differences in behaviour and cognition: interaction of nature and nurture

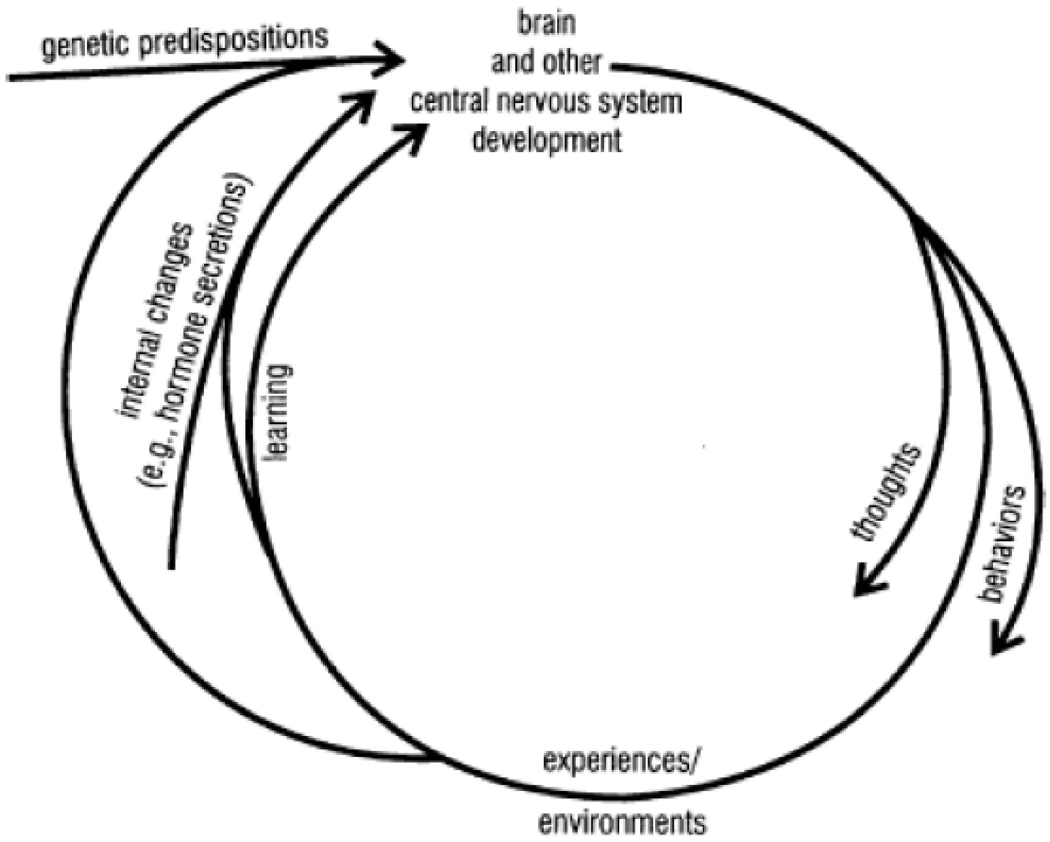


Fig. 8. Biopsychosocial model showing how genes, hormones, and experiences alter brain development and how individuals select experiences from the environment based on their predilections and past experiences, thus also altering the size and connectivity of their brains. In this model, nature and nurture exert reciprocal effects on each other. From Halpern (2000).

Taken from Halpern et al (2007) *Psychological Science in the Public Interest 8* (1):1-51.

Science faculty's subtle gender biases favor male students

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Despite efforts to recruit and retain more women, a stark gender disparity persists within academic science. Abundant research has demonstrated gender bias in many demographic groups, but has yet to experimentally investigate whether science faculty exhibit a bias against female students that could contribute to the gender disparity in academic science. In a randomized double-blind study (*n* = 127), science faculty from research-intensive universities rated the application materials of a student—who was randomly assigned either a male or female name—for a laboratory manager position. Faculty participants rated the male applicant as significantly more competent and hireable than the (identical) female applicant. These participants also selected a higher starting salary and offered more career mentoring to the male applicant. The gender of the faculty participants did not affect responses, such that female and male faculty were equally likely to exhibit bias against the female student. Mediation analyses indicated that the female student was less likely to be hired because she was viewed as less competent. We also assessed faculty participants' preexisting subtle bias against women using a standard instrument and found that preexisting subtle bias against women played a moderating role, such that subtle bias against women was associated with less support for the female student, but was unrelated to reactions to the male student. These results suggest that interventions addressing faculty gender bias might advance the goal of increasing the participation of women in science.

gender disparity in science (9–11), and that it "is not caused by discrimination in these domains" (10). This assertion has received substantial attention and generated significant debate among the scientific community, leading some to conclude that gender discrimination indeed does not exist nor contribute to the gender disparity within academic science (e.g., refs. 12 and 13).

Despite this controversy, experimental research testing for the presence and magnitude of gender discrimination in the biological and physical sciences has yet to be conducted. Although acknowledging that various lifestyle choices likely contribute to the gender imbalance in science (9–11), the present research is unique in investigating whether faculty gender bias exists within academic biological and physical sciences, and whether it might exert an independent effect on the gender disparity as students progress through the pipeline to careers in science. Specifically, the present experiment examined whether, given an equally qualified male and female student, science faculty members would show preferential evaluation and treatment of the male student to work in their laboratory. Although the correlational and related laboratory studies discussed below suggest that such bias is likely (contrary to previous arguments) (9–11), we know of no previous experiments that have tested for faculty bias against female students within academic science.

If faculty express gender biases, we are not suggesting that these biases are intentional or stem from a conscious desire to

PSYCHOLOGICAL AND COGNITIVE SCIENCES

Sex differences II: sex differences in behaviour and relevant neural substrates – selected overviews

***Textbook chapters*:**

Carlson NR (any recent edition) The physiology of behavior. Chapter 10 (Reproductive behavior) and 11 (part on Aggressive behavior).

***Review articles*:**

Breedlove (1994) Sexual differentiation of the human nervous system. *Ann Rev Psychol* 45:389-418.

Kimura (1996) Sex, sexual orientation and sex hormones influence human cognition. *Curr Opin Neurobiol* 6:259-263.

Cahill (2006) Why sex matters for neuroscience. *Nature Rev Neurosci* 7:477-484.

Arnold (2009) The organizational-activational hypothesis as the foundation of a unified theory of sexual differentiation of all mammalian tissues. *Horm Behav* 55:570-578.

Further reading:

Halpern et al. (2007) The science of sex differences in science and mathematics. *Psychological Science in the Public Interest* 8(1):1-51.

Sex differences II: sex differences in behaviour and relevant neural substrates – Some questions for revision

• In which type(s) of behaviour are sex differences most pronounced?

• What are the two principle types of effects by which sex hormones may contribute to sex differences in behaviour?

• What evidence is there for the idea that sex differences in the CNS contribute to sex differences in behaviour?

•What other mechanisms apart from sexual dimorphisms in the CNS may contribute to sex differences in behaviour and cognition?