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NEWS & VIEWS

BEHAVIOURAL NEUROBIOLOGY

Females can also be from Mars

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Is the preference to mate as a male or a female irreversibly set during development? Apparently not: a study in mice shows that pheromone perception determines how an adult female behaves sexually.

We perceive gender as a core characteristic, generally unwavering in almost any social context. So we regard gender differences in behaviour as reflecting irrevocable, pervasive differences in the adult brain of the two sexes[1], rather than the flip of a switch between male or female behavioural repertoires. But on page 1009 of this issue, Kimchi *et al.*[2] suggest that, in adult female mice, two crucial components of gender — partner preference and mating behaviour — are controlled by pheromone sensing*. Startlingly, genetic or surgical disabling of pheromone perception seems to switch on full-blown male mating behaviours in females. Together with a previous study[3], these experiments indicate that neural pathways responsible for male-typical sexual behaviour are present in the brains of females but lie dormant, and that it is the gender-specific processing of sensory information that determines the masculine or feminine nature of behaviour.

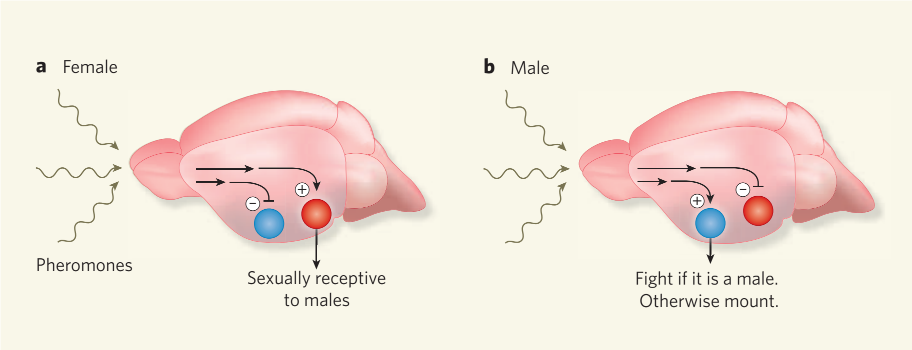

Figure 1 | A new model for the sexual differentiation of behaviour. The traditional view of sexual differentiation is that, during the development of the male brain, gonadal hormones induce the formation of neural centres controlling masculine sexual behaviours, and prevent the formation of neural centres for feminine behaviours[9]. Meanwhile, in females, feminine neural centres develop and masculine centres fail to form. Kimchi *et al.*[2] suggest a new model, in which neural centres controlling masculine and feminine behaviours form in both sexes during development. **a**, In adulthood, pheromonal cues in females activate the feminine sexual-behaviour centre (red) and inhibit the male centre (blue). **b**, The neural pathway for feminine sexual behaviour might also develop in male mice, but its activation is inhibited by pheromonal signals, preventing males from showing female-specific sexual behaviour. (Figure modified from Fig. 5 of ref. 2.)

Pheromones are olfactory cues that aid communication of the social and reproductive status of members of a species. In vertebrates, pheromones are recognized by neurons located in two sensory tissues in the nasal cavity, the main olfactory epithelium (MOE) and the vomeronasal organ (VNO)[4]. The MOE is essential for chemoinvestigation (such as anogenital sniffing), mating and aggressive behaviour[5,6], whereas the VNO is required for aggressive behaviour and for identifying the sex of conspecifics[7,8] — members of the same species.

Previous work[7,8] had shown that deletion of the gene encoding TRPC2, a cation channel expressed only in VNO neurons, profoundly diminishes pheromone-evoked activity in these neurons. Therefore, mutant mice lacking this gene offer a highly specific means of probing the behavioural effects of diminished pheromone sensation. Male mice lacking the *Trpc2* gene do not distinguish between males and females, mating with animals of either sex[7,8]. Moreover, in contrast to normal males, these mutant male mice do not fight with intruder males[7,8]. Such findings had suggested that the VNO recognizes one or more male pheromones that enable gender discrimination and elicit the appropriate behavioural response. Earlier work[7] had also shown that, unlike normal females, female mice lacking *Trpc2* do not display maternal aggression, failing to attack intruder males when nursing a litter.

Now, Kimchi *et al.*[2] find that *Trpc2*-deficient females also fail to distinguish between males and females among their conspecifics in terms of mating preference. Unexpectedly, however, they found that mutant females behave like *Trpc2*-deficient males, sniffing, pursuing and mounting mice of either sex. These behavioural responses do not result from a rewiring of neural circuits during development[2], because the authors found that normal females show similar indiscriminate, male-typical sexual behaviour when the VNO is surgically removed in adulthood. These findings suggest that the VNO detects pheromones that normally prevent female mice from displaying male-typical sexual behaviour (Fig. 1).

But *Trpc2* mutant female mice do not entirely resemble normal males in their behaviour. They also mate in a female-typical manner, bearing litters when co-housed with males. Moreover, unlike normal males, they do not attack other males[2,7].

Kimchi and colleagues' findings inform our thinking about the sexual differentiation of behaviour on various fronts. Several decades of research had led to a model in which male-specific mating behaviour was thought to be hardwired into the developing brain by steroid hormones secreted from the testes[9]. The subsequent post-pubertal rise in circulating gonadal steroid hormones was thought to activate neural pathways that mediate gender-typical courtship behaviour[9]. For example, testosterone is necessary both perinatally and in adulthood to ensure male-typical sexual behaviour in rodents.

Normal adult female mice show some degree of male sexual behaviour towards other females, especially if treated with testosterone[2,3], when they mount nearly as often as do females lacking *Trpc2*. But Kimchi *et al.*[2] found that female mice lacking *Trpc2* show male-type mating patterns even in the absence of externally administered testosterone. So it seems that sexual behaviour in females is regulated both by hormonal inputs and by gender-specific neural circuits that process pheromonal cues. In

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the absence of a functional VNO (as in *Trpc2*-deficient females), even low, female-typical levels of testosterone may suffice to permit high levels of male-typical behaviour.

Regardless of the mechanism involved, however, it seems that one or more male pheromones inhibit mice from mounting other male mice, and elicit aggressive behaviour in males. So when male or female mice cannot distinguish between the sexes, they initiate male-typical mating routines towards all conspecifics, presumably using pheromonal cues sensed by the MOE[5–8] (Fig. 1).

What does the work of Kimchi *et al.*, taken together with previous findings, tell us about the functional role of structural differences in the brain? As females can display male-type mating patterns, it seems unlikely that gender-specific effectors of mating patterns lie in neural structures that differ between the sexes, such as the medial amygdala, which integrates olfactory and pheromonal information, and the medial preoptic nucleus in the hypothalamus[1,10]. It is more likely that these sexually dimorphic regions are responsible for sex-specific changes in neural activity evoked by pheromones (Fig. 1). Such areas could also be where steroid hormones modulate the strength of male- or female-specific routines of sexual behaviour. Indeed most, if not all, of the sexually dimorphic structures in the brain express receptors for gonadal steroid hormones[10]. Perhaps such structures influence only those behavioural patterns, such as inter-male aggression and female sexual receptivity, that seem to be more robustly limited to one sex. Whatever the answer, the latest results suggest that sexual differentiation of neural circuits engaged by the VNO are crucial for the gender-typical display of behaviour in rodents.

Do Kimchi and colleagues' findings hold true for other organisms? Studies in the fruitfly *Drosophila* have shown that female flies genetically modified to express a male-specific messenger RNA — *fruitless*^{M} (*fru*^{M}) — engage in male-type courtship rituals with flies of either sex[11–13]. It is not known, however, whether the *fru*^{M} protein confers male courtship capacity on a female when it is present only in adulthood. This protein is expressed in several sensory structures and neuronal groups in the fruitfly brain, and probably influences male courtship behaviour at many levels. Nevertheless, as Kimchi *et al.* have found in mice, sexual behaviour in fruitflies seems to be governed by simple rules, with sensory information activating either male- or female-typical mating circuits[14,15]. Whether such simple rules dictate affairs of the human heart remains to be seen. ■

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THEORETICAL PHYSICS

A black hole full of answers

Jan Zaanen

A facet of string theory, the currently favoured route to a 'theory of everything', might help to explain some properties of exotic matter phases — such as some peculiarities of high-temperature superconductors.

How are heat and charge transported within a high-temperature superconductor? And what happens when heavy nuclei are torn apart to make the soup of elementary particles known as a quark–gluon plasma? In a paper published on the *arXiv* preprint server, Hartnoll *et al.*[1] show convincingly that the easiest insight into the superconductor problem, just as into the quark–gluon plasma[2,3], is to be had by looking at a black hole. Not any old black hole, of course, but a black hole in a negatively curved space-time with an extra dimension (Fig. 1).

What might sound like a theoretical physicist's idea of a bad joke could, in fact, be history in the making. The context is a highlight of string theory known as the anti-de-Sitter space/conformal field theory correspondence[4] — AdS/CFT for short — which demonstrates an intimate connection between Einstein's general theory of relativity and quantum physics. That it might also find use in such far-flung fields as superconductivity and the quark–gluon plasma is the stuff of physicists' dreams — the unifying power of physical laws as formulated in the language of mathematics.

Viewed as a whole, string theory amounts to a head-on attack on the incompatibility of general relativity and quantum theory, the two greatest accomplishments of twentieth-century physics. According to general relativity, space and time are dynamic entities, linked to matter and energy. By contrast, quantum physics tells us how matter and energy behave, but can only be formulated in a frozen space-time.

String theory is a collection of mathematical discoveries that might just offer a solution to this puzzle. But it has had a bad press of late. This is in part because its 40-year history is littered with claims that, if only we would stick to its true path of enlightenment, the answers to the big questions of physics would be just around the corner. Its failure to deliver on those promises and produce, so far, anything of consequence to experiment has become rather an embarrassment.

The AdS/CFT correspondence is a case in point. It is a fascinating mathematical result, uncovered by the Argentinian physicist Juan Martín Maldacena in 1997, but had seemed unrelated to anything that happens in or outside the laboratory. The correspondence predicts a universe governed solely by gravity, being in this regard rather like ours, with stars, black holes and all the other familiar trappings. The difference is that it has an extra, fourth spatial dimension (plus the normal one time dimension) and a negative (anti-de-Sitter) overall curvature, so forming a universe closed in on itself.

As it turns out, this world corresponds precisely to a non-gravitating universe of just three spatial dimensions filled with something similar to the quantum fields that describe the elementary particles in the standard model of particle physics. Thus, general relativity and quantum-field theory seem to be embedded deep inside the same structure. But try as they might, string theorists have not been able to find an AdS/CFT-like theory that impinges directly on the world we live in. Until now, that is.

Hartnoll *et al.*[1] use the AdS/CFT correspondence to illuminate the real-life problem of how heat and charge currents flow in a 'quantum liquid' of electrons. These quantum liquids are found in the metallic state of copper oxide (cuprate) superconductors above the transition temperature (T_c) below which they become superconducting (which is generally around 100 kelvin). In terms of quantum mechanics, these liquids are strange beasts. Somehow, the electrons manage to organize themselves in a quantum critical state, meaning that their collective quantum physics becomes scale-invariant — it looks the same, regardless of the time- and length-scales over which one observes the system[5]. High-temperature