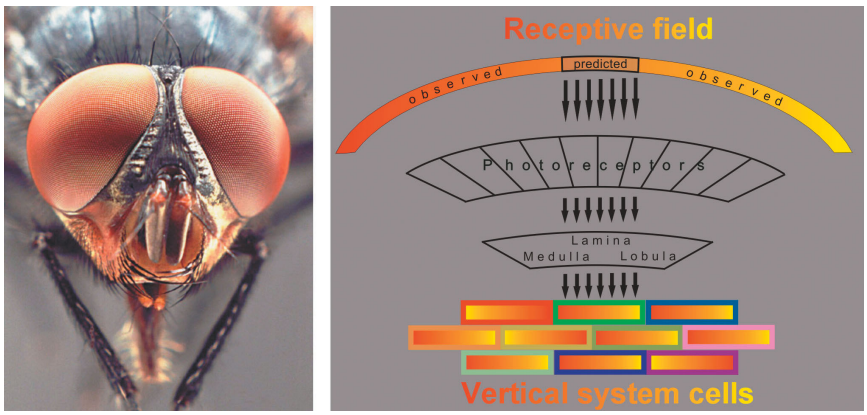


**Figure 1** A fly's eye is built from many single facets, each of them possessing its own lens and photoreceptors. The latter send axons toward three successive layers of neuropil—the lamina, medulla and lobula complex—such that neighborhood relationships (retinotopy) are preserved (arrows in **b**). Part of the lobula complex contains a group of identifiable interneurons, the tangential cells, which respond to motion in a directionally selective way. A subset, the vertical system (VS) cells, respond to patterns of motion. Unexpectedly, the receptive field of each VS cell extends well beyond its dendritic arbor.

and an electrical synapse between cell X and VS7/8. The frequency of synaptic inputs, but not the membrane potential of VS 7/8, could be increased by depolarizing current injection in HSN. This indicates that another neuron, which generates spikes, intervenes between HSN and VS7/8 (as a gap junction would transmit a sustained depolarization). A similar reasoning is applied for the connection between VS1 and VS7/8. In this case, inhibition is visible between the cells, and the frequency of synaptic inputs decreases with depolarizing current injection. It turns out that inhibition from VS1 confers upward sensitivity on VS7/8, for that part of the visual field served by VS1. Thus, the receptive field of VS7/8 contains three spatially separated directional vectors: one upward, one downward and one horizontal, concentrically arranged around a point that becomes a center of rotational specificity.

These results go a long way toward explaining how the VS cells achieve their visual tuning—they get a basic form of direction selectivity from their mainstream inputs, and then elaborate it to a more sophisticated form by network interactions among the neighboring cells of the lobula plate. But the data say little about the next question, which is how these properties combine to be useful to the fly. A signal from VS7/8 is an ambiguous signal. From the output of the VS cell, an observer (say, a neuron farther down the line) cannot tell whether something moved upward in front of the fly or downward behind the fly. If the 'something' is a fly swatter, the ambiguity could be unfortunate. Thus, the VS cells are poorly suited for detecting small objects; as has long been recognized, their main role is navigation during flight. But even for flight it is hard to completely rationalize the VS cells' selectivity. The VS7 cell would respond well to the rotational motion called 'roll'—the type of visual flow field generated when the fly banks during a turn. However, some of the VS cells are tuned for off-axis rolls, and it is not clear what flight maneuver could generate these rotations. Also, most flight paths mix the rotational visual input with very strong translational inputs from the fly's overall motion forward, up or down. Generalized, this is a central issue for all sensory systems, because monkeys and humans have complex but ambiguous receptive fields deep in their sensory systems just as flies do. To understand the steps that lead from lobula plate cells to accurate flight will be a challenge with broad rewards.

1. Haag, J. & Borst, A. *Nat. Neurosci.* **7**, 628–634 (2004).
2. Krapp, H.G., Hengstenberg, B. & Hengstenberg, R. *J. Neurophysiol.* **79**, 1902–1917 (1998).



# Brain gender: prostaglandins have their say

Erich N Ottem, Damian G Zuloaga & S Marc Breedlove

**New findings reveal that steroid hormones masculinize some aspects of the rat brain via prostaglandins. Blocking prostaglandin synthesis with drugs like aspirin can interfere with sexual differentiation of the brain and impair sexual behavior later in life.**

*Different though the sexes are, they intermix. In every human being a vacillation from one sex to the other takes place, and often it is only the clothes that keep the male and female likeness, while underneath the sex is the very opposite of what it is above.*
*–Virginia Woolf, Orlando, p. 133 (1928)*

Scientists, the ultimate voyeurs, have been striving to peer not only beneath clothes, but well beneath the skin to ask how men and women come to be different. We know from studies in non-human mammalian models that the gonads are important during the perinatal period, when testes secrete hormones such as testosterone to masculinize the body, while in females, the absence of steroid secretions from ovaries permits the body to develop feminine traits. We have known for almost half a century that the same testicular steroids that masculinize the body can also masculinize the brain and therefore behavior in mammals[1].

But if testosterone is the executive barking out orders ("Be a man!"), we would like to identify the underlings who scurry around to implement them. In other words, which genes are being regulated in which cell populations, and what are the molecular consequences of those changes? Amateau and McCarthy[2] now show that steroids can masculinize the perinatal rat brain by inducing the production of prostaglandin-E2 ($PGE_2$).

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Indeed, they found that inhibitors of this pathway (including aspirin) impair male sexual behavior later in life.

The authors examined a portion of the brain that has long been a hotbed of sexual neurobiology research—the preoptic area (POA). This region within the anterior hypothalamus is crucial for regulation of hormone secretion, and has been implicated in both female and male sexual behavior. Lesions of the POA disrupt ovulatory cycles in females and abolish copulatory behavior in males. Previous searches for possible sexual dimorphism in the brain also revealed a subregion of the POA—the sexually dimorphic nucleus of the POA (SDN-POA)—that is distinct in Nissl stains and many-fold larger in volume in males than in females[3].

Amateau and McCarthy used levels of spinophilin (a protein highly expressed in dendritic spines) as a measure of the masculinizing effects of steroids on sprouting of dendritic spines in the POA. They found that treatment of newborn male rats with indomethacin, an inhibitor of cyclooxygenase-2 (COX-2), the rate-limiting enzyme for $PGE_2$ synthesis, reduced the number of spines and levels of spinophilin in the POA. It also greatly reduced occurrence of male copulatory behaviors later in adulthood. Perinatal treatment of males with a less potent COX-2 inhibitor, aspirin, given to their mothers during pregnancy and lactation, also diminished adult copulatory behavior, albeit transiently. We do not know exactly how much aspirin the mothers ingested, as it was placed in their drinking water (one 81-mg baby aspirin per half-liter), but it is likely comparable to the dose a human would take for a headache.

Conversely, providing exogenous $PGE_2$ to newborn female rats short-circuited the system, masculinizing their brains without the need for steroids. $PGE_2$ therefore seems both necessary and sufficient for the masculinization of some aspects of morphology and function in the POA. $PGE_2$ manipulations had no effect on spinophilin expression in the hippocampus, so the effect seems to be specific to brain regions prominently engaged in sexual differentiation. These data suggest a new and unexplored mechanism, downstream from gonadal steroids, that directs sexual differentiation of the brain.

Given their freewheeling ideas about gender, Virginia Woolf's famous Bloomsbury group might not have been surprised about one aspect of sexual differentiation of the brain—estrogen, the 'feminine' hormone crucial for female reproduction, also serves to masculinize the brain of male rats. The

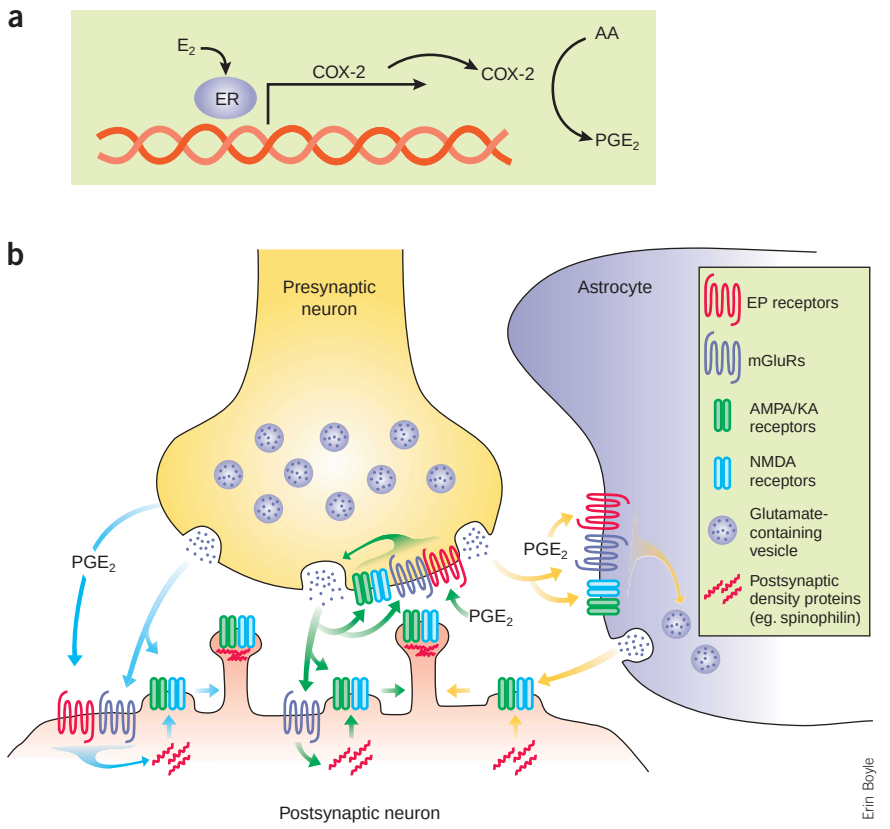


**Figure 1** Alternative mechanisms for estrogen-induced masculinization of the rat brain through prostaglandins. (**a**) Estradiol (E2) interacts with estrogen receptors (ER), which are expressed in many neurons and glia, and could directly (as shown here) or indirectly increase the expression of cyclooxygenase-2 (COX-2), the rate-limiting enzyme for the production of prostaglandin-$E_2$ ($PGE_2$) from arachidonic acid (AA). (**b**) Newly formed $PGE_2$ could promote dendritic spine formation by at least three different pathways. $PGE_2$ and glutamate of presynaptic origin (blue arrows) may activate various prostaglandin receptors (EP) and glutamate receptors on the postsynaptic target to initiate new spine formation. $PGE_2$ could also act on presynaptic EP receptors (green arrows) to augment glutamate release, thereby promoting new spine formation in the postsynaptic cell. Alternatively, $PGE_2$ may trigger glutamate release from nearby glia to induce spine formation (yellow pathway). In each case, the postsynaptic cell assembles various proteins, including spinophilin, to support the new spines.

males' testes primarily secrete testosterone, but in the brain, a portion of that testosterone is converted to estradiol by a single reaction catalyzed by the enzyme aromatase. (Other androgens are similarly converted into other estrogens.) The estrogens then bind to estrogen receptors—not androgen receptors—to masculinize brain morphology and behavior. Research has shown this in several ways; for example, treating newborn female rats with estrogen causes them to behave in a masculine fashion in adulthood and also causes them to have a large SDN-POA[3]. Amateau and McCarthy found that $PGE_2$ was just as effective as estrogen at inducing spine formation in the POA. Thus, coupled with the demonstration that perinatally blocking $PGE_2$ demasculinizes the brains of males, the findings suggest that $PGE_2$ acts downstream from estrogen to masculinize the rat brain.

An important question is whether the authors inadvertently altered steroid production or metabolism when they manipulated $PGE_2$. In that case, they would simply have found a complex way to manipulate perinatal steroids. But assays of testosterone a few days after the $PGE_2$ treatment and at maturity gave no evidence that circulating steroids differed between experimental and control animals. Furthermore, the overall volume of the SDN-POA was unaffected by $PGE_2$ manipulations. This is reassuring, as it indicates that the manipulations did not affect gonadal testosterone secretion or hypothalamic aromatase activity, because either would have affected SDN-POA volume. It is also curious, however, because it suggests that although

$PGE_2$ mediates estrogenic masculinization of dendritic spine formation in the POA, it cannot account for masculinization of the volume of the SDN-POA. Presumably steroids call for a different set of underlings, not $PGE_2$, to enlarge SDN-POA volume.

As with any new finding, a host of questions arise. For example, which cells are responding to the estrogen to induce $PGE_2$ production? There are plenty of hypothalamic neurons with estrogen receptors, so either the postsynaptic neurons forming the spines or their presynaptic partners might be the ones that detect estrogen and trigger some chain of events leading to increased $PGE_2$. No synapse in the CNS is ever very far from a glial cell, and many glia possess estrogen receptors[4], so it is also possible that a nearby astrocyte might respond to estrogen and release $PGE_2$. For that matter, it is possible that some relatively distant neuron is affected by estrogen and changes its activity so that, several synapses away, $PGE_2$ emerges.

Not knowing which cells respond to the steroid hormone seems to be a large gap in the story. For all our information about how steroids affect the developing brain morphologically and functionally, there is no evidence to show whether in these instances steroids affect neurons or glia (or even connective tissue). Once we learn where estrogen acts to induce $PGE_2$ production, we can then investigate the mechanism by which $PGE_2$ boosts dendritic spine formation. Is $PGE_2$ acting on the postsynaptic neuron forming the spine, its presynaptic partner, or through some third party such as a nearby glial cell or a distant neuron that affects electrical activity in the POA? As with estrogen receptors, mapping the distribution of $PGE_2$ receptors (EP) provides little help, as they seem to be almost everywhere. Furthermore, there is evidence that the transmitter glutamate and its numerous receptors may interact with $PGE_2$ to regulate development of the POA. For example, pharmacological blockade of AMPA receptors blocks the ability of $PGE_2$ to increase spinophilin in the POA[5]. $PGE_2$ also induces $Ca^{2+}$-dependent glutamate release from astrocytes, but only if AMPA and metabotropic glutamate receptors (mGluRs) are activated[6]. Glutamate receptors and a host of second messengers have been implicated in dendritic spine formation[7], and new evidence suggests that astrocytes are capable of vesicular release of glutamate[8]. Thus, the list of interactions that may occur during estrogen-induced, $PGE_2$-mediated brain masculinization suddenly suffers from an embarrassment of riches (**Fig. 1**).

These results also raise the question of whether widespread use of COX inhibitors such as indomethacin or aspirin may affect sexual behavior in humans. Although it might be tempting to try to relate these results to sexual orientation, the authors did not examine any measures of sexual orientation (such as partner preference). However, there was a distinct dampening of masculine performance in male rats exposed to COX inhibitors, indicating a reduced libido. Could a pregnant woman seeking relief from migraine through one of these drugs inadvertently hinder the masculinization of her fetal son's brain? Certainly these unexpected results reinforce the notion that pregnant women should strive to avoid ingesting any drugs, however benign they are thought to be today. Even now there may be some husband out there saying, in effect, "Sorry, dear, not tonight. My mother had a headache 30 years ago."


1. Phoenix, C.H., Goy, R.W., Gerall, A.A. & Young, W.C. *Endocrinology* **65**, 369–382 (1959).
2. Amateau, S.K. & McCarthy, M.M. *Nat. Neurosci.* **7**, 643–650 (2004).
3. Gorski, R.A., Harlan, R.E., Jacobson, C.D., Shryne, J.E. & Southam, A.M. *J. Comp. Neurol.* **193**, 529–539 (1980).
4. Jordan, C.L. *J. Neurobiol.* **40**, 434–445 (1999).
5. Amateau, S.K. & McCarthy, M.M. *J. Neurosci.* **22**, 8586–8596 (2002).
6. Bezzi, P. *et al. Nature* **391**, 281–285 (1998).
7. Cohen-Cory, S. *Science* **298**, 770–776 (2002).
8. Montana, V., Ni, Y., Sunjara, V., Hua, X. & Parpura, V. *J. Neurosci.* **24**, 2633–2642 (2004).


# A 'landmark' study on the neural basis of navigation

Hugo J Spiers & Eleanor A Maguire

**How does the brain learn the relevance of landmarks at key decision points? An imaging study now shows that the parahippocampal gyrus responds to the navigational relevance of landmarks, even those that were not remembered.**

There is scarcely any place on earth where we humans have not stepped. As a species, navigation is part of our nature and has been crucial to our adaptation and survival. Even now, a sizeable chunk of our day is spent trying to get to from place to place, whether to work, home, school or the store. We have all experienced the annoyance of taking the wrong route, leading at best to wasted time and at worst to dangerous situations. To avoid becoming lost in the wrong part of town, objects along a route must quickly be identified and stored in memory as landmarks to later guide the traveller. Where a path divides, we must make a decision, and a mistake here could be particularly costly. Therefore, learning the relevance of landmarks at decision points would seem to be crucial.

Neuropsychological and neuroimaging research has shown that the hippocampus and parahippocampal gyrus are vital in allowing us to navigate in new environments[1,2]. The parahippocampal gyrus in particular has been implicated in the encoding of landmarks[3] and object-place associations[4], as well as in the processing of scene details[5,6] and layouts[7]. Despite the empirically demonstrated[8] usefulness of landmarks at decision points, however, we know nothing about how the brain handles this important information.

Now, in this issue, Janzen and van Turennout[9] demonstrate that the parahippocampal gyrus responds to the navigational relevance of landmarks (**Fig. 1**). What is particularly exciting about their study is that the parahippocampal response was selective. Activity in this brain region increased only for landmarks at decision points, and not for other landmarks even though they were as well or better remembered. More interesting still, the parahippocampal signal was apparent even when the navigationally relevant landmarks were lost to conscious awareness. Thus, Janzen and van Turennout[9] provide a significant insight into the dynamics of our navigation system. The brain identifies landmarks at key decision points, it does so automatically, requiring just one exposure, and the locus of

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