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."

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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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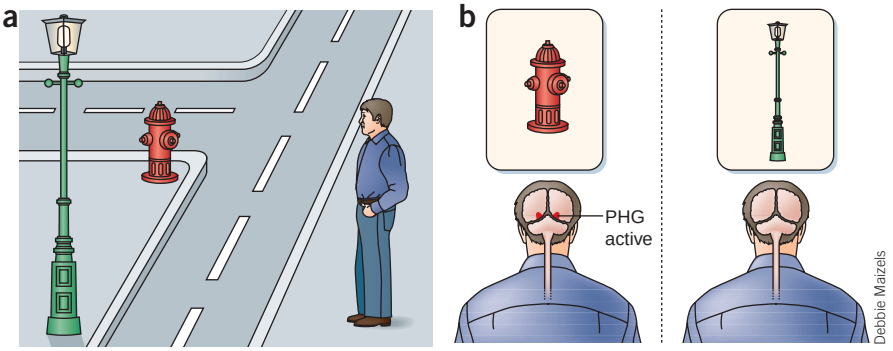

Figure 1 When exploring a new environment, although we might consciously pay attention to lots of interesting landmarks, the parahippocampal gyrus (PHG) is more discerning, and signals only those landmarks that have particular use in aiding navigation. This brain region responds to landmarks such as those at road junctions (hydrant in this example) and other points in the environment where we have to make navigational decisions.

this fine-tuned landmark processing seems to be the parahippocampal gyrus.

In the authors' cleverly designed yet simple experiment, volunteers were shown a film of a route through a virtual reality museum that they were instructed to learn. The museum contained landmarks consisting of objects on tables, positioned at two types of junctions, either points where a navigational decision had to be made, or at simple turns where no decision was required. Volunteers were then scanned using functional magnetic resonance imaging (fMRI) during an old/new recognition test in which the landmarks from the museum and new landmarks were shown from a canonical perspective on a white background. The authors found that the parahippocampal gyrus was more active for landmarks that had been seen at decision points compared to those that had been seen at simple turns. This result suggests that the brain is able to rapidly associate behavioral relevance with a landmark after just one exposure, and the parahippocampal gyrus can make it available at a later point in time without access to the original environmental context. This mechanism, in which the association with navigational relevance can be made despite a change in perspective, would be very useful for successful and flexible navigation[1].

One potentially serious confounding factor could be that subjects pay more attention to the landmarks at junctions, meaning the reported effects could be due to greater attention during learning. However, the authors addressed this concern. Half the landmark objects were toys, and subjects were instructed that the museum tour they had to learn was for children and so they needed to pay particular attention to the toys. Unsurprisingly, this manipulation resulted in speeded responses for the toys and faster responses for toys at decision points. Critically, however, there was no interaction in terms of the neural responses; toys at decision points were not associated with greater activity in the parahippocampal gyrus compared with non-toys at decision points. Thus, the neural response to navigationally relevant landmarks cannot be explained simply by subjects paying more attention to them during travel along the route. That parahippocampal activity was not influenced by selective attention is consistent with findings in another domain. The amygdala's response to emotional material is also impervious to the effects of selective attention[10] (but see ref. 11). Although some aspects of cognition are clearly modulated by attention, we might speculate that functions fundamental to surviving in the real world, such as navigation and interpreting emotions in other people, can be independent of attention.

If attention does not modulate the parahippocampal response to landmarks seen at junctions, does memory for the landmarks correspond with this brain response? Recognizing previously seen landmarks would be expected to improve navigation performance, informing the navigator that they had previously visited a place. However, the new results[9] suggest that this is not the means by which the parahippocampal gyrus contributes to navigation. Its role seems to be the automatic detection that a landmark is useful and informative for navigation. By using a recognition task, the authors were able to compare the response to remembered decision-point landmarks with that to forgotten ones. Parahippocampal response to decision-point landmarks was found to be independent of explicit memory. In other words, the association between relevance and the landmarks was established whether or not the subjects consciously remembered the navigationally useful landmarks.

From this, the authors suggest that during navigation, the parahippocampal gyrus stores the navigational relevance of a landmark that is automatically activated once the landmark is encountered again. Although this experiment cannot determine if the parahippocampus is responsible for encoding navigational relevance (as scanning occurred only during the recognition memory test), or indeed stores the landmark representation, the findings strongly suggest that reactivation of landmark representations involves this brain region and is automatic. Automaticity is at odds with the declarative memory theory that purports that medial temporal lobe memory retrieval depends on conscious awareness[12]. However, before doubt can be cast on that theory, it will be necessary to know if the explicitly forgotten but nevertheless navigationally relevant landmarks are actually useful for guiding navigation behavior at a later point in time. That is, does the parahippocampal activity have true functional significance? Additionally, it will be important to track the process from the beginning, that is, to scan during encoding, considering both explicit and incidental learning and the concomitant responses in the parahippocampal gyrus.

Exciting findings such these from Janzen and van Turennout[9] typically pose as many questions as they answer. To maintain experimental control, the subjects did not actively navigate in the virtual reality environment under their own volition, but rather passively viewed footage of navigation. The setting of a virtual museum was very simple and sparse, and lacked the complexity and richness of a real environment. Exactly how their findings speak to the free exploration, multiple competing landmarks and greater variety of decision points that characterize the real world is unclear. If—as the new data[9] seem to suggest—the parahippocampal gyrus signals useful navigational information, one might expect to see parahippocampal activity associated with better chosen routes during active navigation. However, a recent fMRI study using a much more complex and interactive virtual reality town found the parahippocampal region to be active independent of whether the routes chosen were good or bad[13].

Clearly the precise role of the parahippocampal gyrus in navigation is still unclear. We also still have much to learn about how it interacts with the hippocampus, thought to be the storehouse of the flexible 'cognitive map' of the large-scale spaces that we frequent[14]. The current study suggests a plausible basis on which we might start to reconsider that relationship. It may be that navigation, ubiquitous and of high survival value, is subserved by an efficient and cooperative brain system in which the parahippocampal gyrus selects information that maximally benefits the functioning of the hippocampus.

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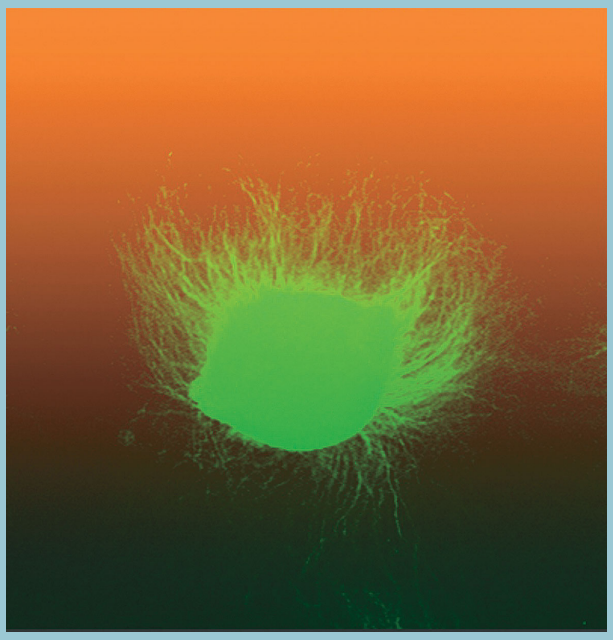
Assaying axon sensitivity

Molecular gradients are thought to guide axons to their proper targets. However, to properly understand both the function of graded axon guidance cues *in vivo*, as well as their downstream signaling mechanisms, we need to know just how sensitive axons are to these gradient cues. Better still, to study this guidance precisely, we also need to be able to quantitatively control molecular gradients. Now, on pages 678–682, Geoffrey Goodhill and colleagues report a new technique that allows for the efficient generation of precise and reproducible gradients of diffusible molecules. They use this technique to show that growth cones of developing axons are capable of detecting a concentration difference as small as about one molecule across their spatial extent, but that this sensitivity exists only across a small range of ligand concentrations.



The authors established molecular gradients by 'printing' drops of solution onto the surface of a thin collagen gel. Based on the mechanics of diffusion, the shape and steepness of the gradient can be controlled, and the actual concentration gradients produced by this method can be measured quantitatively with fluorescence imaging. Their gradient generation method allows for the generation of large numbers of identical gradients that require only limited quantities of chemotropic molecules. Moreover, the gradients were stable for at least a day after generation. This technique could also be used to generate gradients of multiple factors with different shapes and arbitrary spatial relationships.

The authors then used this technique to study the response of rat dorsal root ganglion axons by culturing explants (see image) in a three-dimensional collagen gel with an exponential concentration gradient of nerve growth factor. They found that developing axons are more sensitive to guidance factors than previously thought, and that a concentration difference as small as 0.1% across the growth cone can direct neurite outgrowth, making neuronal growth cones among the most sensitive concentration-sensing devices known. The paper provides a powerful new technology that can be applied to quantitative studies of other biological processes controlled by molecular gradients, such as cell migration. It may also be useful for designing guidance factor–based therapies for axonal regeneration following injury.

This paper also inaugurates the Technical Report format for *Nature Neuroscience*. This new section is meant for primary reports of new techniques that are likely to be influential in neuroscience research. These reports are formatted like Articles, but do not require a new biological discovery to prove the usefulness of the technique, and they are reviewed primarily on the strength of the method and its broad applicability.

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