with risk for Crohn's disease. The current paper by Yang et al. makes a link between *DENND1B* polymorphisms and increased eosinophilic inflammation, thereby offering a potential explanation of why *DENND1B* might also be related to this disease of the intestinal mucosa. Indeed, recent studies identified an important contribution of eosinophils and T_H2 immunity to the pathogenesis of Crohn's. Therefore, it will be important to study the mechanistic involvement of DENND1B in this disease. More generally, there are 18 human DENN domain-containing proteins and their alternative spliced variants. Missense mutations, chromosomal translocations, and altered levels of expression have been described in association with neurological disorders, ocular disorders, and cancers (Marat et al., 2011). The experimental data provided by Yang et al. offer a framework by which other DENN-domain-containing proteins may regulate yet-to-be identified receptor systems to maintain homeostasis that, when dysregulated, contributes to disease. Moreover, this paradigm further

illustrates how alterations in duration and/or subcellular localization of signaling may alter biological consequences to contribute to disease pathogenesis.

In conclusion, Yang et al. help to unravel some of the mysteries surrounding the contribution of *DENND1B* to asthma pathogenesis. However, some important questions are still open, such as the implication of *DENND1B* deficiency in other challenge models in vivo (e.g., worm or viral infections) and whether DENND1B and Rab35-mediated internalization of the TCR mainly affects degradation or recycling away from the immunological synapse. However, the most interesting question that remains is why the DENND1B pathway is specifically regulating T_H2 effector cytokine production, but not T_H1 or T_H17 effector cytokine production. The identification of preferentially expressed adaptors or post-translational modifications of DENND1B in T_H2 cells may further reveal how T_H2-polarizing conditions could regulate these yet-to-be identified mechanisms to confer T_H2 specificity.

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Street View of the Cognitive Map

Cian O'Donnell[1] and Terrence J. Sejnowski[2,3,*]
[1]Department of Computer Science, Faculty of Engineering, University of Bristol, Bristol BS8 1UB, UK
[2]Howard Hughes Medical Institute at the Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[3]Division of Biological Sciences, University of California, San Diego, La Jolla, CA 92161, USA
*Correspondence: sejnowski@salk.edu
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To understand the origins of spatial navigational signals, Acharya et al. record the activity of hippocampal neurons in rats running in open two-dimensional environments in both the real world and in virtual reality. They find that a subset of hippocampal neurons have directional tuning that persists in virtual reality, where vestibular cues are absent.

The hippocampus is a brain structure crucial for both memory and spatial navigation. For the past four decades, the dominant theory for the role of the hippocampus in spatial navigation has been that certain hippocampal neurons, called "place cells," are active selectively when animals or people occupy certain loca-

tions in space and act as the building blocks for a cognitive map (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). Although this theory has been hugely successful—John O'Keefe was awarded the 2014 Nobel Prize in Physiology or Medicine for this work, along with May-Britt and Edvard Moser—three

challenges to this model have lurked in the shadows, all of which feature in a new study from Acharya et al. (2016) in this issue of *Cell*.

First, the cognitive map theory rests upon the idea that place cells encode spatial location and little else. However, various data have mounted to suggest
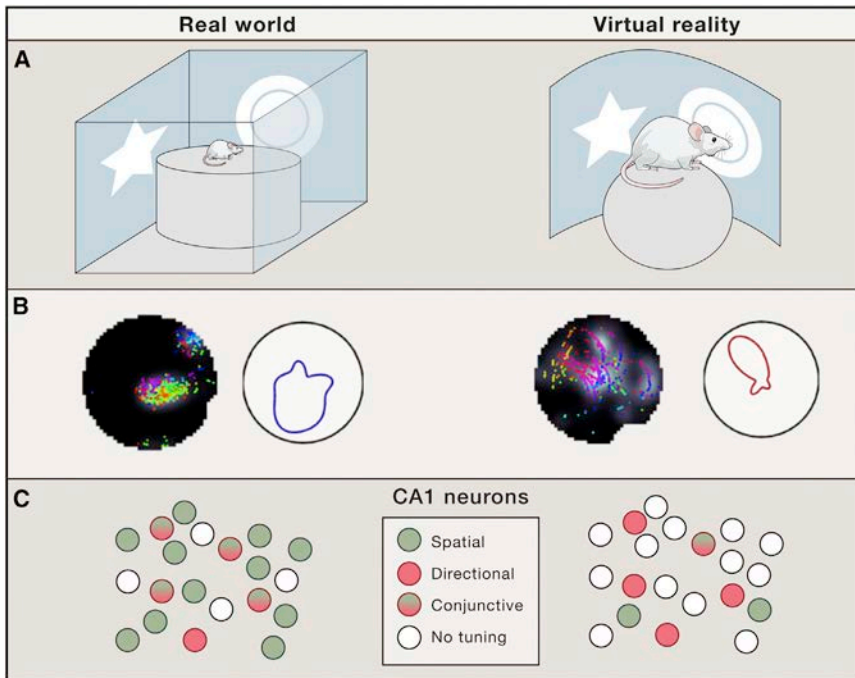
Figure 1. Hippocampal Neurons in a Real-World Environment and in Virtual Reality
(A) Schematic diagram of experimental recording set up. A rat is allowed to explore either a circular platform in the real world (left) or on a rotatable ball in virtual reality while head-fixed (right).
(B) Firing properties from one example neuron recorded while the rat explores in the real world (left) and another example neuron recorded in the virtual reality setup (right). The black circles represent the spatial environment the rat could explore, and colored dots represent the locations that the rat occupied when the neuron fired. The open circles represent the directional tuning curve of the same cells in polar co-ordinates. Figure adapted from Acharya et al. (2016), Figures 1 and 2.
(C) Schematic diagram of the approximate relative proportions of hippocampal CA1 neurons showing spatial tuning (green), directional tuning (magenta), conjunctive tuning (green and magenta), or no tuning (white) in the real world (left) and virtual reality (right) experiments.

that place cell firing is influenced by a host of other high-level variables, such as the shape of the environment, running speed, time elapsed during a run, and even the current goal of the task (reviewed by Hartley et al., 2014). In addition, and more controversially, place cells have been reported to be tuned to low-level properties such as the direction the animal is facing (McNaughton et al., 1983). Interestingly, this directional tuning was even reported in the original place cell study by O'Keefe and Dostrovsky (1971), but the field later came to the conclusion that this effect was simply an artifact of the analysis methods (Muller et al., 1994). The purported lack of directional information in the hippocampus proper was puzzling because such signals are believed necessary for the hippocampus to accurately track the animal's location.

A second difficulty for the cognitive map theory is that it is almost exclusively based on data recorded from rodents. In contrast, hippocampal recordings from other mammals such as bats, monkeys, and humans have either found strong directional tuning in addition to spatial selectivity (in the case of bats) (Rubin et al., 2014) or a paucity of cells showing place field responses at all (in the case of monkeys and humans) (Rolls, 1999). Instead, hippocampal neurons in primates typically appear to act more like "spatial view" cells: active when the animal or person is looking at a particular place or object but irrespective of their own location in their environment (Rolls, 1999), which implies an egocentric reference frame rather than an allocentric one.

A third paradox has been that rodent place cells can show strong directional selectivity when a rat is let run in familiar one-dimensional linear tracks or mazes. Confusingly, however, the same place cells that show directional selectivity in

such circumstances don't seem to care about the animal's direction when the rat is let forage in an open two-dimensional environment (Muller et al., 1994).

Acharya et al. (2016) set out to resolve these questions by analyzing activity of hippocampal neurons recorded from rats as they explored two-dimensional space in two complementary scenarios (Figure 1A): first on a real world platform and second in a virtual reality setup in which the rat is actually head-fixed but can navigate a virtual world projected on a screen in front of the rat by running on a rotatable Styrofoam ball. The wall cues in the virtual reality were made to match the wall cues in the real world. The key dissociation between the real-world and virtual environments is that in the real world both visual and vestibular cues are informative as the rat runs around, whereas in virtual reality, vestibular cues should be minimized since the rat is head-fixed while visual cues are preserved.

These experiments lead to two central findings. First, a subset of roughly 25% of hippocampal neurons show directional tuning in two-dimensional open field real-world environments (Figure 1B, left). The authors suggest that the reason they find directional tuning where many others have not is because they use a rich visual environment and more sensitive analysis methods. Second, this directional tuning is preserved in virtual reality (Figure 1B, right), implying that vestibular signals are not necessary to generate directionality. Indeed, further experiments in which the experimenters manipulated the virtual reality visual cues demonstrate a causal role for vision in the process.

These findings on the directional tuning properties of hippocampal neurons are especially striking because of the complete differences with the spatial tuning properties of the same population of neurons. A previous study by the same authors had found that, unlike the directionality tuning, place cell firing is substantially degraded in virtual reality two-dimensional environments (Aghajan et al., 2015). Also, the subset of neurons that show spatial tuning (~75% in real-world, ~12% in virtual reality) seem to be statistically independent of the subset of neurons that show head-direction tuning (~25% in both cases) (see

Figure 1C). Finally, certain place cells that had two firing fields even show different directional tuning in each field. Hence, directional tuning appears to be mechanistically distinct from spatial tuning in hippocampus.

A possible explanation for the discrepancy between the results in the virtual reality and in the real world is the presence of odor cues to which rats are particularly sensitive that are absent in the virtual reality. Odors are strong cues that could override visual cues in determining the place tuning of a hippocampal neurons. This could be tested by introducing virtual odors within the virtual environment to see how they affect the response to visual stimuli.

What are the implications for the field? A first challenge will be to figure out the mechanistic origin of this head-direction signal. As discussed above, it appears to be dissociated from the spatial signals that drive place cells. Also, since the canonical head direction nuclei show strong vestibular dependence (Stackman and Taube, 1997), a different directional information pathway may be involved. Second, it is unknown whether or how this hippocampal CA1 head-direction information is used by downstream neural circuits. This will be especially important to understand given CA1's role as the primary output station of the hippocampus. Third, these findings prompt a revision of the cognitive map theory. What is the computational role of these conjunctive place-direction signals for spatial navigation?

This study has uncovered a new level of complexity in the firing patterns of neurons in the rat hippocampus that ultimately will give us a deeper understanding of its function. There may be another Nobel Prize up the road for whoever makes this discovery.

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Shadow on the Plant: A Strategy to Exit

Christian Fankhauser[1,*] and Alfred Batschauer[2,*]
[1]Centre for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne, 1015 Lausanne, Switzerland
[2]Faculty of Biology, Department of Molecular Plant Physiology and Photobiology, Philipps-Universität, 35043 Marburg, Germany
*Correspondence: christian.fankhauser@unil.ch (C.F.), batschau@staff.uni-marburg.de (A.B.)
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The light spectrum perceived by plants is affected by crowding, which results in the shade avoidance syndrome (SAS). Findings presented by Pedmale et al. bring cryptochromes to the forefront of SAS and elucidate a fascinating molecular crosstalk between photoreceptor systems operating in different wavebands.

Plants convert light into chemical energy through photosynthesis. This process is fundamental for the existence of life on our planet. The two extreme conditions, full sunlight and low light, are harmful to plants. High light intensity causes photodamage through formation of reactive oxygen species (ROS) or by direct damage of DNA and other cellular compounds through UV-B absorption. These types of damage can be prevented, at least in part, by formation of sunscreen pigments, movement of leaves and chloroplasts reducing the light exposed area, inactivation of ROS, or repair of DNA-lesions. In contrast, low light reduces the capacity for photosynthesis, which may ultimately lead to plant starvation. Such low light conditions are particularly harmful under foliar shade, where photosynthesis-driving wavebands (red and blue light) are preferentially filtered out compared to green and far-red light. Under a canopy, the red/far-red (R:FR) ratio is about 0.15 or lower, in open stands 1.15 or higher. Sun-loving plants respond to such conditions by the so-called shade avoidance syndrome (SAS).

SAS includes several morphological alterations to escape low light such as enhanced growth of the stem, upward direction of leaves, etc. Pioneering work by Harry Smith and coworkers revealed that phytochrome photoreceptors (phy) are essential for the SAS (Smith and Whitelam, 1997). These photoreceptors are well suited to detect R:FR ratio because the tetrapyrrole chromophore in phytochrome exists in two interconvertible forms. Upon light absorption, the inactive red-light absorbing form (Pr) is converted to the physiologically active far-red