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_{H}2 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_{H}2 effector cytokine production, but not T_{H}1 or T_{H}17 effector cytokine production. The identification of preferentially expressed adaptors or post-translational modifications of DENND1B in T_{H}2 cells may further reveal how T_{H}2-polarizing conditions could regulate these yet-to-be identified mechanisms to confer T_{H}2 specificity.

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Street View of the Cognitive Map

Cian O’Donnell1 and Terrence J. Sejnowski2,3,*

1Department of Computer Science, Faculty of Engineering, University of Bristol, Bristol BS8 1UB, UK
2Howard Hughes Medical Institute at the Salk Institute for Biological Studies, La Jolla, CA 92037, USA
3Division 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 locations 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
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 Harley 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

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**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.

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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 White-lam, 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.

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Christian Fankhauser1,* and Alfred Batschauer2,*
1Centre for Integrative Genomics, Faculty of Biology and Medicine, University of Lausanne, 1015 Lausanne, Switzerland
2Faculty of Biology, Department of Molecular Plant Physiology and Photobiology, Philippus-Universität, 35043 Marburg, Germany
*Correspondence: christian.fankhauser@unil.ch (C.F.), batschau@staff.uni-marburg.de (A.B.)
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