

## LEARNING AND MEMORY

## Friends show the way

Two competing theories of the operating mechanisms of the hippocampus in memory — the cognitive map theory and the relational theory — have been the subject of debate for many years. Writing in *The Journal of Neuroscience*, Kumaran and Maguire describe a functional MRI (fMRI) study during which participants carried out a novel cognitive task designed to resolve this issue, and report evidence in favour of the cognitive map theory.

According to the cognitive map theory, the hippocampus is specifically involved in creating and maintaining spatial maps of the environment. By contrast, the relational theory suggests that the hippocampus more generally processes associations and event sequences that are incorporated into a relational framework, with spatial navigation representing just one form of relational processing.

To test the relative strengths of these two theories, Kumaran and Maguire designed two parallel tasks to highlight brain activation in response to spatial and non-spatial (social) forms of relational processing. Participants were required to determine an optimal route either between friends' homes or between the friends themselves using social connections as navigational markers. These processes are conceptually similar in that, mathematically, they can be represented with nodes and edges, and form an interconnected network through which we can navigate and choose preferable routes.

The two behaviourally matched tasks elicited distinctly different patterns of fMRI activation. Importantly, the hippocampus was active in response to the spatial, but not the non-spatial, relational processing task — findings that are consistent with



the cognitive map theory of hippocampal operations.

This work helps to settle the long-standing debate between two competing theories of hippocampal functions in memory, and indicates that the role of the hippocampus in relational memory is specific to the domain of space. However, the relationship between hippocampal spatial memory operations and other forms of hippocampal-dependent memory, such as episodic memory, remains to be determined.

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### References and links

**ORIGINAL RESEARCH PAPER** Kumaran, D. & Maguire, E. A. The human hippocampus: cognitive maps or relational memory? *J. Neurosci.* **25**, 7254–7259 (2005)

## NEUROGENETICS

## A screening success

For many years, a major challenge for neuroscientists has been the identification of the proteins that are responsible for communication at synapses. Now, using a large-scale RNA

interference (RNAi) screen in *Caenorhabditis elegans*, Sieburth and colleagues have discovered more than 100 genes that are important for synaptic communication. This study was made possible through the work of Wang and colleagues — published in an accompanying paper in *Nature* — who developed the innovative technique that was used to screen for these genes.

*C. elegans* neurons are normally insensitive to RNAi screens. However, Wang and colleagues made the unexpected discovery that genes in the *C. elegans* homologue of the mammalian retinoblastoma pathway negatively regulate RNAi. They showed that mutations to several components of this pathway enhance the effectiveness of RNAi, probably because neurons and other mature cells revert to immature germline cells, which have a heightened sensitivity to RNAi.

Sieburth and colleagues used these mutant forms of *C. elegans* to systematically search for genes that are implicated in neurotransmission at the neuromuscular junction by screening for a reduction in acetylcholine secretion following RNAi. In total, they identified 185 genes, 132

of which had not previously been implicated in synaptic communication.

These researchers went on to categorize the functional profiles of the genes by analysing the patterns of reduced acetylcholine secretion. This revealed that the candidate genes are involved in a range of functions during synaptic transmission, including exocytosis, endocytosis, formation of the active and peri-active zones, vesicle transport, and neuropeptide modulation at the synapse.

In support of a role for the protein products of these genes in synaptic communication, Sieburth and colleagues showed that many of the proteins are located in either presynaptic or postsynaptic regions. Furthermore, they examined mutants from classic genetic knockout studies and confirmed that a subset of the proteins is involved in synaptic functions.

This collaborative work has not only led to an important step forward in the search for genes that regulate synaptic communication, but has also demonstrated the promise of this powerful genetic tool for tackling some unresolved questions in neuroscience.

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### References and links

**ORIGINAL RESEARCH PAPERS** Sieburth, D. *et al.* Systematic analysis of genes required for synapse structure and function. *Nature* **436**, 510–517 (2005) | Wang, D. *et al.* Somatic misexpression of germline P granules and enhanced RNA interference in retinoblastoma pathway mutants. *Nature* **436**, 593–597 (2005)

