

EUROBRAIN

Which way do I go?

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ARE MADE OF THIS
2 & 3 ASSOCIATIVE
LEARNING
IN THE SNAIL
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Always getting lost? The reason may lie in how well tuned a part of your brain called the hippocampus is to remembering directions.

Evidence shows that the hippocampus, a region deep inside the brain, plays an essential part in encoding memories. In a new study to determine the extent to which the hippocampus is also involved in remembering spatial cues, researchers from the Wellcome Department of Neurology at the University of London chose a particularly apt group of study subjects: London taxi drivers.

Uniquely among the world's big city taxi drivers, people who want to drive a taxi in London must first go through an intensive training period called "The Knowledge". During an average time of about two years, trainees must learn all the streets, alleyways, intersections, and thoroughfares of London – no small task.

The researchers used structural magnetic resonance imaging combined with a technology called "voxel based morphometry" to precisely measure the taxi drivers'

brains and compare them with non-taxi driving controls. Results showed that all this memorising of street corners and intersections resulted in a larger posterior hippocampus in the taxi drivers as compared to the average English Joe. The study was published in the March 14 issue of the *Proceedings of the National Academy of Sciences (USA)*.

The larger hippocampi among the taxi drivers, say the researchers, reveal a couple of interesting things about the brain. First, this research identifies, with a good degree of certainty, a specific hippocampal area, – the posterior hippocampus – as important for spatial orientation. But perhaps even more importantly, this study also shows that the hippocampus can change in response to experience, thus providing new details about the ways in which the brain is plastic and can undergo change in response to environmental demands.

By **Terri Rutter**, senior editor of *BrainWork*, a publication of the Dana Press


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Memories are made



Richard Morris

A small, darkened room in laboratories at Edinburgh University is almost entirely occupied by a large container lined with white cloth and filled with water. Under the cloth you can just make out the submerged shapes of platforms. This is Richard Morris's water maze. But he is not conducting aquatic experiments here; he is studying the basis of memory.

Memory is the remarkable in-built ability by which we process, store and retrieve information. Different types of memory are co-ordinated by distinct areas of the brain. Although there are different schools of

PROFESSOR PAUL BENJAMIN – ASSOCIATIVE LEARNING IN THE SNAIL THE SNAIL PROVIDES CLUES TO THE BASIS OF MEMORY

The humble snail is providing a unique means of studying the basis of learning. The University of Sussex have discovered. Snails are trained to respond to food and their behaviour can be monitored. With just a few hundred nerve cells found in the snail, the actions of molecules and cells to uncover the complex behaviour of the single cell.

A memory trace is formed in the neural circuit underlying feeding and ingestion. Electrical signals are recorded from single cells. These changes occur in differentiated with feeding. The memory trace is represented as a global pattern of electrical activity. Professor Paul Benjamin has found that the gas, nitric oxide (NO), is involved in memory.

"Snails are cleverer than you think", said Professor Benjamin. "One trial learning up to 20 days indicating that they are capable of long-term memory." Similar thought to underlie learning and memory in higher animals but the snail enables it in single identified nerve cells.

Professor Benjamin plans to incorporate this new knowledge into a computer simulation of the work of the snail.

de of this

thought over how and where memories are formed, broadly speaking, there are two sorts of memory. Motor and cognitive skills, such as riding a bicycle or executing a strategy, are termed procedural memory. In these, memory is intrinsic to performance and cannot be separated from it. Information about facts and events, people and places is variously called declarative or representational memory because it is represented in the brain in a manner that is independent of overt behaviour. Procedural memories seem to be both formed and stored in the

cortex; representational memories are formed through the interaction of subcortical and cortical brain areas, but probably also end up stored in cortex.

Professor Richard Morris is particularly interested in memory formation mediated by the hippocampus, a seahorse-shaped structure located deep within the medial temporal lobe of the brain. Theories abound, but his Hippocampal Research Group are investigating the idea that this structure plays a part in the “automatic recording” of ongoing events in the world around us. It retains traces of experience for a short period, allowing the opportunity for long-term memories to be created, and provides a framework for recalling memories as well.

“I think there is an automatic recording system that registers the events and details of our daily life and over which we have no control”, says Richard Morris. Even what appears to be inconsequential is recorded – provided we’ve attended to it. “For example, what did you have for lunch today? That’s easy to recall – and doesn’t require any of us to memorise effortfully as we eat it.” But such information is only held for a few days at most, providing the opportunity for memory consolidation into a more permanent form. The memory formation system has to decide what information is worth retaining and what is not.

The hippocampus adapts itself (a term known as plasticity) to enable us to hold on to large amounts of information indefinitely. We may subsequently dispense

with most of it, but we are presented with the opportunity to form lasting memories if it matters. Deciding whether something is useful for us to retain is the basis of knowledge and depends on our interests.

“If you are a lawyer, the court case of a young offender will be more meaningful to you than it would be to, for instance, an actor, whose priority may be to learn the lines of *Hamlet*”, says Professor Morris.

The inspiration for Professor Morris’s investigations into how memories are formed originated from research conducted in the 1970s in London when the existence of so-called “place cells” was established. By recording the activity of single nerve cells in rats, the researchers discovered that if a rat walked from one corner of a box to another, separate cells would start firing and transmitting messages as it moved, creating a sort of map and providing it with information about where it was.

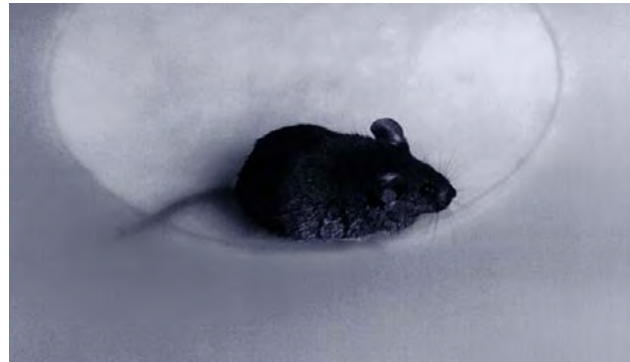
“Here in Edinburgh University, our job is to invent tools that give us a window into understanding the mechanisms of memory.

learning and memory, scientists at the stimuli so that their feeding behaviour. It is possible to combine studies of mechanisms of memory at the level of

tion. Following training, changes in the afferent sites in the nervous system associated with electrical activity at all levels of the system involved in the early stages of long term

learning is possible and they remember for large molecular and cellular changes are possible. This enables the researchers to study the detail

computer-based simulation of the feeding net-



Mouse on a platform of the water maze

We try to invent behavioural tasks that help us find out what animals learn and know about the world. The water maze is one example", explains Professor Morris, "and it enables various types of learning and memory to be studied simultaneously."

In its simplest form, a rat or mouse is placed in the pool, which is two meters wide, and has to swim around until it finds a hidden escape platform. The animal climbs on and can then try to work, by looking around the room, where the platform is located. By making the water opaque, it cannot see where the platform is hidden, but very quickly learns to find it. However, a rat with a damaged hippocampus has great difficulty in learning it.

To explore the importance of hippocampal plasticity, drugs called NMDA antagonists were administered which block the ability of connections between brain cells to change in efficacy. "The cells aren't damaged, they still fire nerve impulses, but they can't make new connections", says Richard Morris. His group has recently

found that these drugs impair the animal's ability to remember what it has done most recently, while leaving procedural learning intact. "It's as if, and perhaps we have, selectively interfered with the automatic recording system."

Neuroscientists, psychologists and psychiatrists are fascinated by the concept of memory. The research in Edinburgh is one example of the world wide effort not only to understand the extraordinary capacity of animals and humans to take in and select information, but also to find out what happens when the brain is damaged through injury or disease.

By **Elaine Snell**, EDAB, London

Forget your pain



In 1846, a revolutionary new drug was introduced at Massachusetts General Hospital (MGH) in the hopes of eliminating the pain associated with surgery: ether. Before then, the only “medicine” for patients about to go under the knife was a shot of whiskey and a “bite the bullet” command from the surgeon. Much has changed in the field of surgery since then, but how the body responds to pain has not.

“Under general anesthesia”, says Clifford Woolf, who directs neural plasticity research at MGH, “patients are not aware of pain during surgery, but their nervous systems are aware of it.” This, unfortunately, leads to post-operative pain and sometimes chronic pain.

His ultimate goal is not to eliminate pain outright, since the capacity to experience pain can have a protective value. “But persistent pain offers no biological advantage”, he says, “while causing undue suffering and distress.”

Before coming to Boston, Woolf spent twenty years at University College London, where he made important contributions to our understanding of lingering pain. In the 1980s, he showed that trauma at the periphery that results in tissue damage, such as burning a finger, can produce long-term changes in nerve cells in the brain and spinal cord.

“Like turning up the volume on the stereo”, he notes, “the [central nervous] system becomes sensitized; the pain threshold is lowered and reactions are exaggerated.”

Overly sensitive

Daniel Carr, a pain researcher at the Tufts-New England Medical Center, likens the response to “a post-traumatic stress phenomenon in the spinal cord, placing it in a hypersensitive state that persists long after [the painful] stimuli cease”.

In collaboration with Ru-Rong Ji of MGH, Woolf recently discovered that the perception of pain initiates, within a minute or so, the activation of proteins that play a pivotal role in causing persistent hypersensitivity.

The pain-triggered proteins, called ERKS (extracellular signal-regulated kinases), receive and respond to signals from outside cells. When ERKs in spinal cord neurons receive distress signals following the infliction of pain, they become activated. The “switched on” ERKs then induce changes in a distinct part of the cell’s surface, called the NMDA receptor. Ion channels, gateways to the cell that regulate electrical activity, open more readily in the altered receptors and stay open for long periods of time. This process renders the cells hypersensitive for tens of minutes or hours. Chronic pain may result from longer lasting – and perhaps even permanent – changes to genes in the nucleus of spinal cord neurons.

What you wish you could forget

Lingering pain, says Woolf, is like a bad memory that will not go away. In fact, at the most basic level, “remarkable similarities” are clear between the mechanisms

of pain and memory, including changes to the NMDA receptor. The connection makes sense from an evolutionary standpoint, he says. "To survive, even the simplest one-cell organism must react to the environment. As multi-cellular organisms evolved and developed nervous systems, it became important not only to detect hostile environments but also to remember."

Carr agrees that the parallels between pain and memory are striking: "If you make a checklist of the mechanisms involved in pain sensitisation and long-term potentiation" – the latter being the main theory of how neurons process a memory – "there is a tremendous amount of overlap. In lower animal forms, the two processes are indistinguishable."

Strategies against chronic pain

One strategy is to interrupt sensitisation before painful memories have a chance to form. This idea, called "preemptive analgesia", involves administering pain medication before surgery, not just during and after, in order to block the nerve pathway from the injured tissue to the spinal cord. "This approach doesn't cure a problem, but rather prevents a long-term difference from arising", says Carr.

The technique appears to work, at least in some cases: A 1998 report by Allan Gottschalk and colleagues at the University of Pennsylvania Medical School found that preemptive analgesia significantly reduced pain in patients who had their prostate glands removed.

Woolf and Ji are working on another approach with laboratory rats, blocking the action of ERKs to lessen the pain. This strategy would not be suitable for humans, as ERKs are present in every cell in the body and the side effects of deactivating them, en masse, could be substantial.

But Woolf believes this work will lead to therapies that are useful to humans: "We hope to find something special about the ERKs in the central nervous system that will enable us to target them without affecting every other cell", Woolf says.

By **Steve Nadis**, who writes about science and medicine from Cambridge, Massachusetts, USA.

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