

**Allocution du Pr. Richard MORRIS**  
**Lauréat du Prix International 2019 de la Fondation Fyssen**

**Ecological psychology and spatial navigation**

Chers Président, membres du comité, Mesdames et Messieurs.

Je m'excuse de ne pas pouvoir être présent avec vous aujourd'hui. Je vous parle depuis Édimbourg en Écosse, ville de Marie reine des Scott qui était française. Je suis donc avec vous en esprit !

C'est pour moi un immense honneur que de recevoir ce prix cette après-midi. Merci. Alors que je vous fais face, je prends conscience que mes contributions scientifiques reposent sur les « épaules des géants », ces scientifiques, dont les découvertes, notamment en France, ont révolutionné les domaines de la psychologie écologique et de la mémoire spatiale.

Dans ce que je vais décrire aujourd'hui, je suis redevable aux membres de mon laboratoire qui ont réalisé la majorité des expériences. Ainsi, veuillez garder en mémoire que lorsque je dirai « je », il s'agit plutôt de « nous ». Et si je dis « nous », il faut comprendre « ils et elles ».

**La controverse et une histoire :**

Ce soir, je veux vous présenter une controverse ayant trait à la façon dont nous traitons la mémoire spatiale

Est-elle plutôt liée à la navigation spatiale ?

Ou - plutôt à la mémoire ?

Permettez-moi de vous présenter ce dilemme avec une histoire célèbre – en une livre de Dr. Frances Yates.

*“At a banquet, given by a nobleman of Thessaly named Scopas, the poet Simonides of Ceos chanted a lyric poem in honour of his host, but including a passage in praise of Castor and Pollux. Scopas meanly told the poet that he would only pay him half the sum agreed upon for the panegyric and that he must obtain the balance from the twin gods to whom he had devoted half the poem.*”

*"A little later, a message was brought in for Simonides that two young men were waiting outside who wished to see him. He rose from the banquet and went out, but could find no one..."*

*"... During his absence, the roof of the banqueting hall fell in, crushing Scopas and the guests to death beneath the ruins; the corpses were so mangled that the relatives who came to take them away for burial were unable to identify them.*

*"... But Simonides remembered the places at which they had been sitting at the table and was therefore able to indicate to the relatives which were their dead. The invisible callers, Castor and Pollux, had handsomely paid for their share in the panegyric by drawing Simonides away from the banquet just before the crash...."*

*"... And this experience suggested to the poet the principles of the 'art of memory' of which he is said to be the inventor.*

*"... Noting that it was through his memory of the places at which the guests had been sitting that he had been able to identify the bodies, he realized that orderly arrangement is essential for good memory."*

This story led to the development of the "method of loci" used by orators from Greek and Roman times to this day. What key points about memory does this story illustrate?

**First**, Simonides did not intend to remember the locations of the guests - it just happened. So much of memory is automatic.

**Second**, Simonides had a framework - a spatial framework - into which he slotted information, the names of the guests.

**And third**, Simonides didn't have to actually navigate spatially to remember who was where, but perhaps he did a mental walk in his mind?

I mention these three important points to contrast two separate intellectual traditions in ecological psychology, spatial memory and neuroscience.

**One tradition is that spatial memory provides a framework, a context or a schema with which we remember other things. These other things may be static landmarks or, as in the story, be images of people or events which are effortlessly set into a framework.**

The other view is that.

**This is that spatial memory is primarily about navigation - how we get from one place to another, from A to B, from our home to our place of work or around a building, and the different ways in which effective navigation through space can be achieved.**

**The central argument of this talk is that these two mental processes interact and overlap.**

The relation between them arises because the organisation of what we call 'episodic' or 'episodic-like memory' - the memory for the unique events of our lives - profits from recognising that the evolution of this form of memory in mammals emerged out of systems which evolved initially to help animals - including invertebrate animals - to find their way around.

## **NAVIGATION AND PATH-INTEGRATION**

Many scientists interested in spatial navigation have focused on how people and animals find their way around.

Take desert ants as an example. They forage from their burrows in the sand to find a food source that may be some distance away, meandering as they move around, and then they accurately and directly retrace their steps to home. It is an astonishing skill, a miracle to watch, and carried out by a process called "path-integration". This is a brain process mediated by some neural system that keeps track of the steps, twists and turns, taken by ants as they forage. That done, the little brain of the ant computes a return vector which the animals follow to get back to the safety of their burrow.

Path-integration is also used by rodents, and many other species, including ourselves. Most famous for their skills in navigation were the indigenous people of French Polynesia in the Pacific who took long voyages between islands by observing the stars, and by keeping track of the speed and direction of their boats. And they made corrections to their paths by cross-checking between these different sources of evidence.

France is one of the great nations of the world for sailing, which is my hobby, and many a famous French sailor such as Eric Tabarly, Bernard Moitessier and Mode Fontenoy will have used the same trick to help them plot their way - what we sailors call "dead-reckoning".

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However, the curious thing about path-integration or dead-reckoning is that, in principle, it gets you from A to B, and then maybe back to A again, without you actually knowing where anything is. Reflect on this for a moment. A tourist surrounded by skyscrapers and lost in New York may stop to ask a local person: "Where is the Empire State building?" Instead of answering with its address, the local will most likely say *"Hey, yeah, walk 10 blocks north, take a left, and then walk 5 blocks east - the Empire State building will be right in front of you"*. This works - but you still don't know where it is - only how to get there.

## **SPATIAL MAPS IN THE BRAIN**

During the latter part of the 20th Century, scientists began to turn their attention to how the mammalian brain such as ours mediates spatial navigation.

The human brain has billions of cells, each cell has thousands of connections from other cells, and thus the brain really is a massive connection machine. It's the brain that makes so much possible, perception, action, language, learning, social understanding – and navigation. All packed into 1.4 kg.

In Edinburgh, there is a tradition that new Professors must give a Public Lecture - a so-called 'Inaugural Lecture'. When I gave mine, I was blessed by my parents being present in the audience. They were proud, and I had a lot to thank them for. But also a lot to apologise for - all those moments in my childhood when I'd behaved like a complete idiot, apparently brainless. As I had recently served as a subject in a human brain imaging study, I thought I would show them the structural image of my brain that was taken during that study and given to me as a present afterwards.

I presented this image of my brain modestly to the audience, but specifically to my parents, as definitive evidence that I really did have a brain. Whereupon

my father - who had a great sense of humour - exclaimed loudly to the whole audience:

*"But, Richard, that picture is no evidence that your brain is actually working!"*

I was speechless, but the audience laughed and laughed. My father had once again put me in my place.

Our current understanding is that networks of brain cells represent experience in distinct ways, and these networks can change in response to experience. Such changes most likely occur at the connections - the synapses - that link one cell to another. This will be vital for the learning that underlies successful effective navigation.

Somewhere, buried inside the brain, your brain, my brain, is a spatial navigation system. We can see that system in action in the beautiful human imaging studies of navigation by taxi drivers in London conducted by Eleanor Maguire and Richard Frackowiack. Richard now lives in Paris with his wife Laura Spinney whom some of you may know as having written a beautiful book, called "Pale Rider", on the Spanish Flu Epidemic of 1918-1921. One hundred years on, it's a book that feels very timely.

One important brain network is the hippocampus, a beautiful structure embedded in the medial temporal lobe of the human brain and...

...connected by a myriad of different paths from upstream brain areas that pass information from sensory regions, and on to downstream brain areas which receive the product of hippocampal processing.

Fifty years ago, an American scientist working in London, John O'Keefe, did a remarkable experiment. Under anaesthesia, he inserted miniature electrodes into the hippocampus of laboratory rats and, having secured them with cement to the skull and allowed the animals to recover, he used them to record brain-cell activity as the animals moved around a familiar space. He saw cells in the hippocampus spiking, as we call it in the trade, that were finely tuned to the location of the animal, with different cells tuned to different locations. He recorded from hundreds of cells and consistently found the same pattern. He called them "Place Cells" and so began a field of research that he and others have developed considerably over the past 50 years.

That worldwide research effort led on to the discovery of new types of navigational cells in neighbouring brain regions, such as "head-direction cells" that represent where the body is pointing in space, and "grid cells" of the entorhinal cortex discovered by Edvard and May-Britt Moser that fire repetitively in beautiful hexagonal patterns and provide a metric for space.

Over recent years, astonishing new technologies have been developed that enable researchers to record not just from one cell, but from tens or even hundreds simultaneously. These have been used in the laboratories of Bruno Poucet and his colleagues in Marseilles, and elsewhere in France, in both navigational and memory tasks. These multiple single cell recording techniques are now being complemented by imaging techniques that can detect the transient movement of charged ions into and out of cells, such as calcium, and so enable visualization of hundreds of cells simultaneously and repetitively across days. In this way, contemporary neuroscientists are now spying on the brain at work. In Edinburgh, we're now using endoscopic Ca<sup>2+</sup> imaging in my laboratory and it is miraculous to watch it in action. As the animals move around, the computer screen is alive with first one group of brain cells firing and then a moment or two later a different group of cells fire. Fascinating, but a challenge to analyze mathematically.

For their amazing contributions on the cellular basis of this navigational system, John O'Keefe, and Edvard and May-Britt Moser were awarded the Nobel Prize in Physiology or Medicine in 2014. The Nobel Committee called it the "GPS System of the Brain" – tying it firmly to the navigational tradition.

## **GOING BEYOND CORRELATION TO CAUSAL ANALYSES**

These physiological approaches offered the very suggestive idea that there was a navigational system which knew about where the animal was, the metric of space through which it was moving, the direction of the head and body. John O'Keefe imagined that these cells fed into what he called a "cognitive map". A representation inside our brain of the ecology of space. And of course, a map is what you use to find your way around.

However, suggestive as this was, it was only correlational data concerning the relationship between behaviour and physiology. Statistical correlation is suggestive, indeed it can be tantalizing. But correlation can also be misleading making it not always easy to distinguish cause from effect.

One way to try and dig ourselves out of this problem is to perform interventions that disrupt the activity of the brain. These interventions are designed to stop the brain working properly - such as stopping place cells from firing. Had it been that place cells were merely an epiphenomenon, then disrupting their activity should have little effect on navigation. Are these, in Stephen Jay Gould's memorable phrase, like "the spandrels of San Marco in Venice" – not actually doing anything structurally. Conversely, if disrupting place cells were to affect the skill of spatial navigation, we navigators would have reached yet another way-point in a comprehensive scientific analysis.

## **THE WATERMAZE**

This was on my mind when I developed the open-field watermaze at the University of St Andrews which I later brought to Edinburgh. The idea was to develop a task that captured the essence of place cells - cells that fire at a particular position in space without regard to local cues.

In the watermaze, rodents swim around a large circular pool trying to find an escape platform located at a specific position:

- a platform that cannot be seen,
- is silent,
- offers no olfactory cues that can anyway be disrupted by swirling the water between trials, *and*
- a platform can be felt, but only after it has been found.

As a short film of the watermaze shows, rats can readily learn to do this and display the spatial knowledge they have acquired during learning.

In 1982, my group showed that damaging the hippocampus had a severe effect on this navigational learning. We published a paper entitled "place navigation impaired after hippocampal lesions" - set entirely within the navigational tradition. And we went on to show that interrupting the connections into and out of the hippocampus had similar disruptive effects on spatial navigation – these studies done with a French-Swiss scientist, Dr. Françoise Schenk. This reminds us that brain regions are not like the monastic monks of old - they do not work in isolation - but they are parts of extended networks that collectively enable diverse cognitive functions to be carried out.

I had the good fortune in my career for many other groups to take up the watermaze as a technique, and to use it imaginatively for research projects I would never have dreamed of. It became, for example, a task of choice for early work on animal models of neurodegenerative diseases such as Alzheimer's Disease – using mice that had been genetically engineered to express the very same genetic mutations as discovered in people with familial forms of this sad condition. Using the watermaze, my group was the first to reveal age- and disease related-dependent deficits in place navigation in the watermaze in these beta-amyloid over-expressing mice.

Even when they do learn, we also showed faster forgetting over a period of about a week - as in the work of Dr. Stephanie Daumas who now works in Paris. Her PDAPP animals learned more slowly but they could certainly learn. Their problem was that they forgot much faster. It's a big effect. Interestingly, Stephanie's work has been followed up by research clinicians in London who report that people with a familial mutation for beta-amyloid also show accelerated forgetting over 7 days.

This is a result of some practical importance as too many diagnostic tests for Alzheimer's try to get the clinical interview done quickly in a single visit to the clinic. I am now cautious of the wisdom of this as we are at risk for failing to see the cognitive benefits of new treatments because the cognitive tests may lack sensitivity to changes over time.

I also continued my work in basic discovery-oriented research. Specifically, I became interested in the idea that changing the strength of synaptic connections in the hippocampus – this shows its circuitry - could be the process of memory formation. Understanding how such changes come about mechanistically became a field in its own right after the discovery, in 1973, of Long-Term Potentiation - or LTP - by Timothy Bliss and Terje Lomo. Using a drug called AP5, which blocks the N-methyl-D-aspartate receptor sub-type of excitatory glutamate receptor in synapses, and which Graham Collingridge showed blocked the induction of LTP but not its expression, we decided in 1986 to test this drug in rats in the watermaze.

We observed, to a mixture of delight and relief, that when infused into the hippocampus, it also blocked place navigation while leaving other forms of learning intact. And it did it at a dose of the drug that blocked LTP in living animals.

This was, for me, one of the most exciting moments in my career.



The NMDA receptor – show here at nanoscale resolution - is an exquisite biophysical machine which can detect the conjunction of activity between two connected brain cells. It detects when one cell is talking to another *and* the other is listening to the first. This is precisely the kind of molecular conjunction machine that one would need for putting things together - the very associative process that is at the heart of learning and memory. Interestingly, here also, French scientists played the lead in the remarkable work of Professor Philippe Ascher and his colleagues on the biophysical characteristics of NMDA receptors.

These exciting findings led me on to a program of work extending over 20 years in which my laboratory tried to test the synaptic plasticity and memory hypothesis to destruction. The hypothesis has so far survived the onslaught.

We and other groups have used a variety of physiological, pharmacological and molecular-genetic procedures – notably in the work of the Nobel Laureate Susumu Tonegawa - to reveal that regulating synaptic plasticity in the hippocampus has a dramatic effect on spatial learning but leaves information already learned unaffected. The underlying mechanism is that the connections get stronger, or weaker, through the insertion or removal of specific receptors into synapses, and this mechanism is embedded within the circuitry of the hippocampus. Work by Dr Daniel Choquet in Bordeaux is leading the world in understanding how this happens.

This is just a start, and we now need to bring in all manner of other important dimensions - such as the contribution of inhibitory neurons during development and in adulthood as in the remarkable work of Professor Rosa Cossart - also from Marseilles.

## **A TURNING POINT**

At this time in my unfolding story, I became disenchanted by my exclusive focus on navigation to a static hidden object in a static location. The world isn't always like that. If I put my glasses down, I tend not to do so in the same place always. They get lost all over the house. The need to keep track of recent events is really important, especially in social situations. And it turns out that keeping track of recent events is not confined to humans but occurs in other vertebrates also.

Consider the intriguing observations of Serge Daan of Gröningen University who became interested in the patterns of circadian behaviour of flying kestrels. Kestrels like nothing more than a tasty little vole or mouse for their breakfast. Radio tracking of a number of individual animals over the summer months in northern Holland showed that if a kestrel caught a vole at one place in a field early one morning - it would tend to go back to that same place around the same time the next day. The location of capture drifted over days, of course, and with it the animal's memory of the most recent place where a prey animal had been found.

Catching a vole is not like seeing a landmark for navigation. Recognition memory won't help. It's an event. And events, unlike landmarks, do not leave any recognisable trace on the ground. When a kestrel returns to roughly the right place the next day, there are no local cues left by its success on the previous day - it can only be guided by its memory of where the event happened.

## **THE EVENT ARENA**

Accordingly, we tried to create a new animal model of this form of episodic-like memory - not using kestrels and voles - but rats and sandwells. The animals have to learn that food may be available in a sandwell that can occupy up to 49 places in a large arena, but that its location varies from day to day. We call this process 'everyday memory'. It is still an example of spatial memory, but the animal has to do something. He has to search around, and then dig, and then remember at which sandwell he dug up the food. Unlike just momentary inspection of static objects as happens in novel object recognition memory studies, there is a digging event and the animals seem to remember where that event happened.

Using the event arena, we have observed that the duration of the memory where the food was most found recently requires hippocampal synaptic plasticity, but how long it lasts depends on separate neuromodulatory signals mediated by a different neurotransmitter - dopamine - being released into the hippocampus. The first person to show the dramatic effects of blocking dopamine in the hippocampus in the event arena was a French scientist in my lab, Dr. Ingrid Bethus, who now works in Nice.

Memory lasts longer when something novel happens around the time of learning and this novelty effect may also be mediated by dopamine.

Evidence in support of this idea is the novelty effect can be mimicked by optogenetic activation of a catecholaminergic region of the brain called the locus coeruleus. Paradoxically, this has long been identified as a noradrenergic rather than a dopaminergic brain region, but it turns out that the action of a single enzyme in the axonal terminals of noradrenergic neurons can flip the terminals from releasing only noradrenaline to releasing both noradrenaline and dopamine.

We are still working on this puzzle and, frankly, not sure quite what is going on - but we speculate that it may have something to do with "flashbulb memory" such as remembering where one was and with whom during emotionally surprising events.

The textbook example of this is remembering the 9/11 tragedy in New York. Closer to home, remember back to the tragic terroristic attacks in Paris of a few years ago. Most of you listening will remember the shock and horror of what happened that day. The emotional surprise will, most likely, cause you also to remember many things that happened to you that very day. We can mimic that by shining a light into the locus coeruleus in conjunction with genetic technology.

## **TURNING THE MEMORY OF EVENTS INTO KNOWLEDGE**

There is one more twist to the argument I want to put before you.

Experiments in the event arena are giving us a neurobiological handle on this separate facet of how spatial memory works. Whereas, initially, the focus was on how to find one's way around, you'll appreciate that as the talk has gone on, the focus has shifted to how a stable spatial layout provides a framework for embedding and then remembering where events have happened during the day. And how surprise can make things more memorable.

Sometimes we keep the special memories of our lives as somewhat isolated memories. Like meeting one's partner, or getting married, or the birth of a child. For years afterwards, we can travel back in our mind's eye to those special moments.

But the additional twist is as follows. More frequently, we abstract generalities from our memory of events, forgetting the details and perhaps remembering only the gist of things, but somehow abstracting from our experience to develop a sense of how things fit together. This happens in school, in developing specialized knowledge such as professional skills at work, and in lots of other ways. These abstractions may begin by locating events in maps in the mind, but they develop into something much more than that - they are frameworks, or what many people have called "schemas" of knowledge.

The British psychologist Frederic Bartlett was one of the first to write about schemas, the Swiss psychologist Jean Piaget also, and more recently the American John Bransford - shown here against a backdrop of the now unfashionable Great Wall of China.

Together with Guillen Fernandez in Holland, I have been conducting human brain imaging studies of schemas using a technique called functional magnetic resonance imaging. One study looked at how people remember spatial frameworks and how a gradually developing but consistent framework made it much easier to learn new things than a framework which kept changing. And we did that study in both humans with brain imaging, and in rats trained in the event arena to learn paired-associates. In both cases, we saw interactions between the hippocampus and prefrontal cortex.

## **CONCLUSION AND IMPLICATIONS**

Ladies and Gentlemen, I have tried to take you on the intellectual journey over the nearly 40 years since the watermaze was developed. There have been two themes – spatial navigation and, second, the making, organizing and keeping of memories.

It's the hippocampus does both of these – it both helps us find our way around and it keeps track of the rich tapestry of the events of our day.

Are there wider ramifications of this scientific journey?

Yes – to this audience I want to stress the importance of curiosity-driven discovery-oriented research, can sometimes unexpectedly supplement other more translational approaches to the development of new medicines – such as for conditions like Alzheimer's Disease. We need to do both types of research.

And, second, with respect to memory I feel I must end on the fact that in this digital age, it is all too easy to become cognitively lazy and rely on the devices that we all have at hand. Need we bother to remember the layout of a city like New York or Paris now that Google Maps can do it for you? Why not take such knowledge out of the brain and put it in a machine?

Personally, I see storing things on my iPHONE as an adjunct rather than substitute for what I should remember. Fine for storing long website URLs or forgettable phone numbers, but it would be ridiculous to have to use one's phone in the kitchen at home to remember in which cupboard the salt or pepper has been stored. It would be ridiculous because it would be time-wasting and, anyway, the automatic binding of "what-and-where" precludes the necessity of us doing this.

So - ladies and gentlemen - let's all be proud of the mysterious stuff we have in our heads. Use your spatial frameworks. Find your own way around. Form mental models of the world around you. Keep using your hippocampus!

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