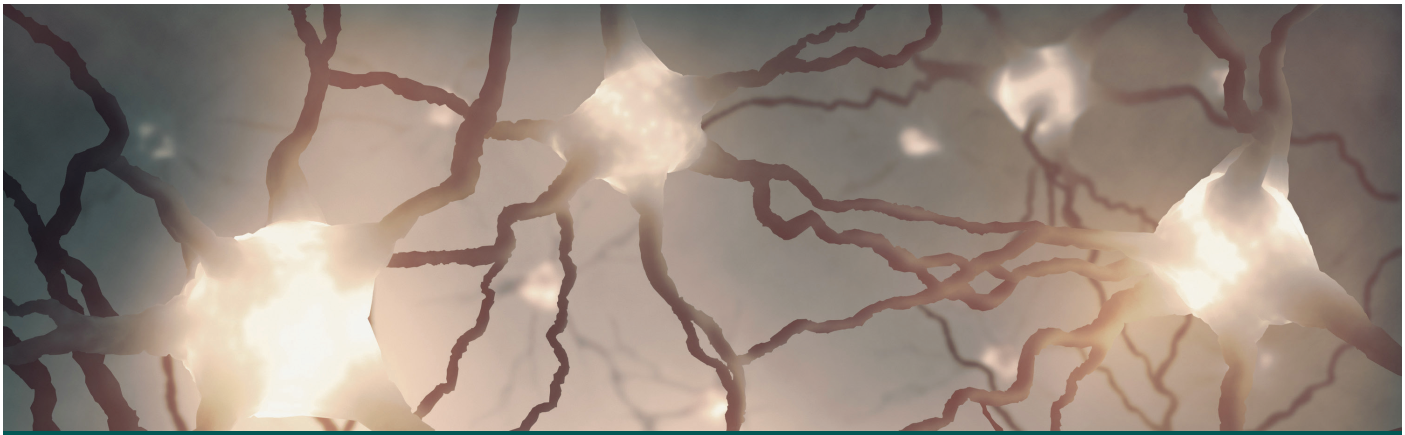

Exploring memory lane

Dr Simon J Thorpe and his collaborators are investigating the biological mechanisms that allow humans to recognise visual and auditory stimuli that they have not experienced for decades

Can you introduce the main aim of the M4 Project?

We're interested in understanding the remarkable ability humans possess to store memories that can last a lifetime. Our brains contain tens of billions of brain cells – neurons – that are linked together by connections called synapses. Each cortical neuron connects to thousands of other neurons, and it is generally assumed that memories are stored by modifying the strength of those connections. The real challenge is to understand how those modifications can still be intact decades later, despite the fact that the brain is continuously being rebuilt.

What prompted you to investigate how humans recognise past visual and auditory stimuli that have not resurfaced for decades?

One of the first challenges has been to prove beyond doubt that we can recognise a visual or auditory stimulus that could not have been reactivated for a long time. Most of us have had the experience of recognising an old television programme we believe we haven't seen since childhood. However, how can we be absolutely sure we didn't accidentally see it at some more recent point and have simply forgotten about it? To address this question, Christelle Larzabal, a doctoral student working on the project, has used the French National Audiovisual Institute (INA)'s superb archives to obtain the theme tunes of around 50 French TV programmes from the 1950s, 60s and early 70s that we know have never been rebroadcast. They are not on YouTube, nor available on DVD or video. We already have an example of someone, currently in their 60s, who can explicitly remember details such as the title of, or key character in, a TV programme they could not have seen for decades.

If we really are able to keep memories intact for several decades without reactivation, then this challenges current theories about how information is stored in the brain. Consider the problem of storing a complete memory trace in biological hardware. Most researchers would accept that the basic mechanism underlying the formation of memories involves modifying the strength of the synaptic connections between neurons. And it is generally believed that synaptic connection strengths are continuously modified by ongoing activity. How then could a particular pattern of connections be maintained over periods of several decades?

Why is the M4 Project's theory deemed highly controversial?

The idea that we have 'grandmother cells' is controversial and very few scientists take it seriously – at least in public! But, in our opinion, it is currently the only viable explanation for how our brains can keep memories intact for decades. If a neuron responded selectively to the *Mission Impossible* theme tune, for example, it could be used to store the long-term memory for that film. But if it also responded to a range of unrelated stimuli, each time those unrelated stimuli are shown, the original selectivity would be lost due to a spike-timing dependent plasticity mechanism. We make the equally controversial suggestion that as much as 90 per cent of our cortical neurons may be completely inactive; they effectively constitute a sort of 'neocortical dark matter' composed of neurons that are sitting around waiting for some long lost stimulus to reappear.

Is there potential for developing artificial systems that harness the brain's architecture for highly selective processing power?

The processing architectures we are proposing can be simulated on ordinary computer hardware. Back in 1999 we set up SpikeNet Technology, a company that develops bio-inspired algorithms for image processing and object recognition. We can harness the latest developments in graphic processing unit architectures to accelerate these algorithms, and we have a couple of students working to develop real time spike-based methods for auditory and visual processing. But the really exciting test is to develop specific hardware that can directly simulate synapses using simple electronic elements called memristors – effectively resistors that can be modified by learning.

How do you see your project's research progressing in the next five to 10 years?

Well, I'm very ambitious! I've got a long list of provocative claims that I want to test, and if any of them turn out to be true, then we will have made significant progress. But I wouldn't be at all surprised if things turn out differently to what we expected. That's what happens when you are exploring a new area of research – you have to be ready to come across results you can't explain. And often, you end up with more questions than you started with. But that's what makes science exciting!

Ten provocative claims

Researchers at the **Brain and Cognition Research Center** in Toulouse, France, are validating 10 provocative claims that, if proved correct, would significantly challenge current theories on the human ability to retain long-term memories

OUR ABILITY TO retain long-term memories has always been a puzzling phenomenon for scientists. Whether humans can indeed recall a memory from several decades ago still remains a matter of conjecture. It is known that people in old age are able to recognise visual and auditory stimuli from childhood, such as a tune or image. However, it is difficult to determine whether their memory is definitely from a long time ago or whether there has been an intermediary stage, where the same memory has resurfaced and the recognition arises from this newer memory.

THE M4 PROJECT

The M4 Project: Memory Mechanisms in Man and Machine was created in order to finally provide answers to this age-old quandary. A team of scientists led by Principle Investigator Dr Simon J Thorpe is exploring potential biological mechanisms that could allow long-term memories to remain intact without the possibility of reactivation. As Thorpe explains, the group has recently made some headway: "We have identified a mechanism involving the formation of highly selective neurons that are totally silent unless the original stimulus is presented again". By remaining silent, these neurons are effectively able to maintain their original selectivity indefinitely, until re-initiated by the original stimulus.

The M4 Project has been funded by the European Commission since May 2013. Its researchers are using an interdisciplinary approach to assess the neurological factors that affect long-term memory and are attempting to harmonise a wide range of methodological approaches, from novel protocols in psychology and neuroscience to computational modelling and hardware development. Their current work focuses on validating '10 provocative claims' about human sensory memories, and has produced some promising preliminary results.

GRANDMOTHER CELLS

When a memory is reactivated, neurons in the neocortex generate a series of electrical pulses, or 'spikes', which are initiated by the recognition of a familiar audio or visual stimulus. The theory of 'grandmother cells' refers to the hypothesis that some neurons may activate rarely, only triggering when they encounter a particular complex stimulus such as a concept or object – a familiar face, for instance. One of the provocative claims concerns the idea that old memories rely on the creation of these highly selective neurons. "If a neuron is selective enough," Thorpe posits, "it should never fire at all unless the original stimulus is presented again. And since synapses only change when there is a spike, this would allow the neuron to keep the trace stored during the original learning, even after several decades."

According to Thorpe, it is possible that higher-order association areas could contain tens of millions of such neurons, each tuned to particular sensory stimuli. This would mean that the brain effectively contains a 'neocortical dark matter' of inactive neurons that may not have fired for months, years or even decades. Such neurons would not exhibit any electrical activity, rendering them invisible to many of the techniques currently used to record brain activity. This is at present a hypothesis, and researchers at the M4 Project are working on providing evidence for its existence.

SPIKE-TIME DEPENDENT PLASTICITY

In the late 1990s, scientists discovered that if an input spike to a neuron occurs immediately before its output spike, then the input is strengthened. On the other hand, if an input spike occurs immediately after a neuron's output spike, the input is weakened. This process is called spike-time dependent plasticity (STDP). "STDP enables neurons to become selective to essentially any spatio-temporal pattern of incoming spikes if that pattern occurs repeatedly," asserts Thorpe, alluding to a key finding of the M4 Project team. If a neuron does not have spikes, the synaptic strengths will not be altered. This means that a highly selective neuron that never re-encounters its original stimulus will not fire any spikes, so there will be no changes in the synaptic weights. Therefore, neurons which remain completely silent would be able to maintain their selectivity forever.

Activating grandmother cells.

FINDING EVIDENCE

One single experience can provide a long-term memory. Often this experience will be revisited in dreams or by actively seeking it out, constituting an 'automatic memory formation'. Scientists at the M4 Project suggest that the strength of the memory increases proportionally with the number of repetitions. However, their latest experiments showed that even with two repetitions of a visual pattern, the memory trace can become robust. The researchers are now cross-referencing findings from behavioural tests with event-related potential recordings and functional magnetic resonance imaging, which will look at electrical activity within the brain and enable them to pinpoint neurological responses and changes.

The team is also using behavioural methods and functional imaging to investigate STDP and the precise neurological mechanisms that enable a memory to persist for decades. To this end, the researchers are proposing to record the electrical activity of individual neurons in certain patients with epilepsy. These particular patients do not respond to drug treatments and require surgery on the brain to alleviate their condition. In order to locate the section that is to be removed, electrodes are inserted in the brain to record neurological activity until an epileptic episode occurs. This also allows the neurons to be monitored whilst patients are exposed to auditory and visual stimuli, such as watching television and listening to music. It is possible at this point to record the activity of individual neurons, and Thorpe is excited about the prospects of this approach: "I can't wait to find out what happens when someone sees an old TV programme they haven't seen for decades!"

COLLABORATE TO INNOVATE

The clinical work with epileptic patients is reliant on collaboration between Emmanuel Barbeau, another researcher working on the M4 project, and Luc Valton, an epileptologist at the Pierre Paul Riquet hospital, which is conveniently based a few hundred metres from the laboratory. Indeed, strong working relationships with investigators at a range of institutions, including the Alternative Energies and Atomic Energy Commission (CEA), have enabled the team to explore a number of fascinating avenues of research.

With his colleagues at CEA, Thorpe is looking into whether STDP could be implemented using components called 'memristors' – semiconductor devices in which resistance can be changed by applying a voltage that exceeds a certain threshold. Thorpe elaborates: "The memristor research is one clear illustration of an area where collaboration is vital for us. No one at our institution has any expertise in developing specific electronic devices for imitating biological synapses. But we do have some clear ideas about what to do with such devices as soon as they become a practical reality". With such ambitions, it is clear that the M4 Project will be opening many doors on memory research.

TEN PROVOCATIVE CLAIMS

The M4 Project is working to validate the following claims:

1. Humans are able to recognise images and sounds they have not experienced for decades
2. Humans can recognise these stimuli after a long period of time without an intermediary 'reminder' period where the memory trace has been reactivated
3. Very long-term memories only occur if there has been an initial memorisation phase to strengthen the memory. The strength of a memory increases proportionally to the number of presentations
4. A permanent memory can be formed with as few as several tens of presentations
5. 'Attention-related oscillatory brain activity' aids the speed and efficiency of memory storage
6. Grandmother cells are used to store extremely long-term memories, as they are highly selective and lie dormant for an indefinite period of time
7. The neocortex partially comprises 'neocortical dark matter', where long-term memories are stored
8. Grandmother cells are created by using simple spiking neural network models with spike-time dependent plasticity and competitive inhibitory lateral connections
9. Neuron selectivity is achieved through binary synaptic weights that are either 'on' or 'off'. This simple mechanism accounts for the brain's ability to store very long-term memories
10. Artificial systems using memristor-like devices can be used to replicate these mechanisms. This provides the potential for new processing architectures which may replace current computing hardware

THE M4 PROJECT: MEMORY MECHANISMS IN MAN AND MACHINE

OBJECTIVE

To develop an understanding of the biological mechanisms that allow humans to store lifelong memories.

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Alternative Energies and Atomic Energy Commission (CEA), France

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SIMON J THORPE is Principal Investigator of the M4 Project. He completed his undergraduate degree in Psychology and Physiology at the University of Oxford, UK, where he also received his PhD in 1981. He became a CNRS researcher in 1983 and a founding member and Director of CerCo, a CNRS laboratory at the University of Toulouse, in 1993. SpikeNet Technology, a high-tech spin-off that develops real time image processing systems using bioinspired processing strategies, was set up by Thorpe in 1999 based on his experimental work, and won the Innovation and Future Prize from the Midi-Pyrénées Region in 2012.

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