////Title: How Memories are Made and Lost in the Brain

////Standfirst: Our brain forms long-term memories and stores information through synaptic plasticity, the ability of the connections between neurons to be strengthened or weakened over time. However, the exact methods through which synaptic plasticity is achieved by the brain remain largely unknown in the scientific community. Professor Don Kulasiri (Kuh-lah-si-ree) at Lincoln University, New Zealand, is using a mathematical modelling approach to shed light into this process. His findings are providing molecular insights into how memories can be strengthened or lost.

////Body text:
Our brain has a fascinatingly tremendous capacity to receive, encode, and store information. Stored information, known as memories, influence our actions, allow us to acquire knowledge, learn languages, form relationships, develop a personal identity, and so on. Thanks to memory, even certain sounds or smells can be associated with specific events. Remarkably, our brain begins forming memories from the womb, when an embryo is just 20 weeks old.

Different parts of our brain are associated with specific types of memory. For example, the almond-shaped set of brain neurons known as amygdala store fear and fear memories. The hippocampus – a seahorse-shaped brain component, stores events, facts, times, locations, associated emotions, and background information such as who, what, when, and where. It also enables us to recognise objects and people. Procedural memories, also known as motor skills, are stored in the cerebellum at the back of the brains. The front of the brains, the pre-frontal cortex, is linked to the memory of semantic tasks, meaning the ability to correlate new information to existing knowledge.

Sleep is vital for memory since it helps us store and retrieve long-term information. Exercising our brain also improves its capacity to store and recollect memories. It is recognised that thinking creates stronger connections between neurons in our brains. The more you think about an event, the more accurately you can remember it. Memory is thought to deteriorate with age. However, this is a false preconception as memory most likely diminishes in the elderly because they tend to exercise their brain less than their younger counterparts.

…

Scientists believe that memories are represented by an amazingly complex network of interconnected nerves in the brain. Nerves in close proximity are separated by junctions known as synapses. Synaptic plasticity is the process through which they communicate with each other by sending molecular signals. These signals are known as neurotransmitters, and they are taken up by adjacent neurons through signal receptors located on the cell surface. The number of surface receptors and the quantity of neurotransmitters in a junction determine how quickly and easily information can be transmitted from one nerve to another. Release of calcium ions from the neuron receiving information is also very important for inter-neuron communication. These parameters can change based on, for example, how much we exercise our brain. The ability of activity between neurons to change is known as synaptic plasticity and is one of the most important features of learning and memory.

Enhanced patterns of activity between neurons produce a long-lasting increase in signal transmission between them. This persistent strengthening of a synapse is known in neuroscience as long-term potentiation or LTP. Since memories are believed to be encoded by changes in synaptic strength, LTP is one of the most important tools our cells possess to enhance it.

A long-lasting decrease in communication between neurons is known as long-term depression or LTD. It is one of the methods our cells use to selectively weaken specific synapses. This is necessary to counteract continuous synapse strengthening by LTP, which would eventually reach a plateau and inhibit the formation of new memories and learning. Diseases associated with memory loss, such as Alzheimer's, are characterised by enhanced LTD or faulty LTP. In cases were ageing is associated with memory loss, LTD is also boosted.

…

Scientists have long been interested in uncovering what changes occur in our genes and proteins to drive synaptic plasticity. They have identified that the calcium/calmodulin-modulated MAP (map) kinase II (two) protein, or CaMKII (Kam-kinase-two), and the protein kinase A II, or PKAII, play important roles in learning and memory. They are, thus, often referred to as memory molecules. Their abundance inside cells increases during LTP. This is what causes a class of receptors, known as AMPA receptors, to accumulate on the surface of neural cells. It also causes the addition of phosphoryl molecules onto cell surface tunnels, known as ion channels. These phosphorylation events improve the permeability of ion channels and facilitate inter-neuron communication.

For the CaMKII protein to become more abundant and activated, calcium ions need to flow into the neurons through the N-methyl-D-aspartate or NMDA receptor. CaMKII also directly interacts with NMDA receptors as part of its activation cycle and binds to phosphoryl molecules. Such changes in the structure of CaMKII, known as transition states, are critical for prolonging its activation. All these processes occur slowly over hours or days. They take a long time and last for a long time, determining the duration of LTP and providing the means for long-term memory formation.

Despite years of research, our knowledge of the relationship between state transitions and LTP is limited. Professor Don Kulasiri at Lincoln University, New Zealand, has devoted many years to unravelling these mysteries. Thanks to his expertise in using computational modelling to study biological systems, he has been able to enhance our understanding of LTP and how it operates in health and disease.

…

Mathematical modelling uses known information to predict the outcome of an event. This form of science translates problems into mathematical formulas consisting of all the known parameters and components about a system and uses them to explain unknown components of that system. It is an indispensable tool for the natural sciences, such as physics, but also for the biological sciences.

Several years ago, Professor Kulasiri and his team developed a mathematical model based on differential equations that elucidated how synaptic strength builds up to form long-lasting memories. Their model took into consideration the CaMKII transition states, and the probabilities of CaMKII and NMDA receptor binding together. They found that CaMKII and NMDA receptor binding depends on the natural attraction between the two proteins, known as affinity, as well as on movement of CaMKII into a protein-dense region on the surface of the neuron receiving information, known as postsynaptic density. They also determined that binding of phosphoryl molecules to CaMKII is not necessary for CaMKII and NMDA receptor binding, but that it speeds up the binding process to facilitate LPT.

Dr Kulasiri's team then focused on another poorly understood area, namely, the importance of calcium ions in long-term potentiation and depression. They developed a new mathematical model that used calcium ion concentration, transition states of important proteins, and other essential features of the synaptic processes, as inputs. The proteins taken into consideration were calmodulin or CaM (Kam), PKA, CaMKII, PP2B, and PP1. The model developed by the New Zealand team was 20-times faster than any pre-existing model, which allowed it to complete a large volume of calculations in a short time.

They found that the CaM pool size was critical for coordination between LTP and LDP. This was a surprising finding that would need to be proven experimentally. They also found that the interplay between LTP and LDP depends on the relative activity strengths between the important proteins involved. For example, an increase in the activity of PP2B and a decrease in the activity of PKA and CaMKII enhanced LTD. In contrast, high levels of activation followed by slow deactivation of PKA and CaMKII promoted LTP.

Dr Kulasiri's team proceeded to investigate the relationship between synaptic plasticity and Alzheimer's disease – a condition characterised by gradual but permanent loss of memory and other cognitive abilities. It is known that the movement of calcium ions in and out of cells becomes irregular in Alzheimer's patients. This can occur even before any other symptoms appear and is believed to be an important factor in disease progression. Amyloid plaques, clumps of amyloid-β (beta) proteins, accumulate in the brain of Alzheimer's patients that can physically obstruct NMDA receptors and calcium ion movement, destroying communication between nerve cells.

The New Zealand team developed a mathematical model that mimics changes in amyloid plaques during Alzheimer's disease to further investigate how they are involved in disturbing communication between neurons. They discovered that NMDA receptors become overactivated in Alzheimer's disease due to higher levels of the neurotransmitter, glutamate. The latter is toxic to neurons and contributes to disease severity. Uptake of NMDA receptors within cells also leads to disruption of synapses because fewer interactions between CaMKII and NMDA receptors are allowed to form.

…

Collectively, this substantial body of research by Dr Kulasiri and his team has provided new and important knowledge about how synaptic plasticity is achieved in the healthy brain s well as neurological disorders such as Alzheimer's disease. Critically, this work may inform the development of therapeutic approaches aiming to prevent the loss of synapses and memory decline.

Meet the Researcher

Professor Don Kulasiri
Head, Centre for Advanced Computational Solutions (C-fACS)
Faculty of Agriculture and Life Sciences
Lincoln University
Canterbury
New Zealand

Contact

E: Don.Kulasiri@lincoln.ac.nz

W: https://www.lincoln.ac.nz/About-Lincoln/Staff-Profiles/?StaffID=Kulasiri%20Don

Key Collaborators
Yao He, Lincoln University, Christchurch, New Zealand
Jingyi Liang, Lincoln University, Christchurch, New Zealand
Sandhya Samarasinghe, Lincoln University, Christchurch, New Zealand

This SciPod is a summary of the papers 'Modelling the dynamics of CaMKII–NMDAR complex related to memory formation in synapses: The possible roles of threonine 286 autophosphorylation of CaMKII in long term potentiation', published in the Journal of Theoretical Biology, DOI:10.1016/j.jtbi.2014.11.001; 'Modelling bidirectional modulations in synaptic plasticity: A biochemical pathway model to understand the emergence of long term potentiation (LTP) and long term depression (LTD)', published in the Journal of Theoretical Biology, DOI:10.1016/j.jtbi.2016.05.015; and 'Computational investigation of Amyloid-β-induced location- and subunit-specific disturbances of NMDAR at hippocampal dendritic spine in Alzheimer's disease', published in the journal PLOS ONE, DOI:10.1371/journal.pone.0182743.