

LEARNING, REMEMBERING AND FORGETTING IN THE MAMMALIAN BRAIN



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ABSTRACT

Education in its most general sense is a form of learning in which knowledge is imparted from one source to another. The delivery of education and the testing of its impact has been an ongoing human endeavour for many years and ideas on how to manage education have largely resulted from theories of education. The acquisition, storage and retrieval of learned behaviours result from brain activity. Using a variety of experimental approaches, studies in neuroscience have been considering the issue of the physiological mechanisms that mediate learning and memory formation and its retrieval. These studies are not only providing insight into the basic physiological and molecular mechanisms that underpin learning but also some surprising findings on the impact of the environment and presentation state on learning and recall of learned events. In this session, I will discuss current ideas of learning and memory formation in the mammalian brain and possible implications for education practice.

Learning is a lifelong process by which we acquire new facts and skills, or modify existing ones as a result of experience. It provides the knowledge and skills necessary to respond successfully to the challenges that we face throughout our life. Education, in a general sense, describes the delivery of learning in which knowledge is imparted from one source to another. The ability to learn is present in all living organisms but particularly in humans and primates. Learning requires first the understanding of novel situations and the formation of a response to these situations that leads to particular, desired outcomes. Secondly, the ability to respond appropriately in the future requires the storage of information that underpins this understanding, and its effective retrieval.

Thinking about the nature of memories, how they are formed and how we learn goes back to the time of the ancient Greeks. Aristotle placed the seat of thinking in the heart but had surprisingly modern ideas about learning: for example, he thought that learning resulted from an association of ideas. Learning and memory have until relatively recently been the exclusive province of philosophers, in large part due to the influence of René Descartes (1596–1650), a pivotal figure who separated the mind from the body. He described the body, including the brain and the entire nervous system, as one type of object (*res extensa*), with length and breadth that could be objectively measured and studied. In contrast, the mind was a fundamentally different substance (*res cogitans*), responsible for thoughts, desires and volition but with no physical structure and indivisible. As such, the mind was not amenable to experimental analysis. Descartes' ideas were a dominant influence on theories of the mind and effectively put the study of learning and memory out of the scientific arena.

It has long been known that all animals have a brain, and that the capacity to learn and remember is an integral part of their behaviour. But it had been taken for granted that humans were fundamentally different from animals. By the turn of the 20th century, it was well established that

activity within the central nervous system is the basis for higher cognitive function. The experimental study of learning and memory began in the late 19th and early 20th century, and owed a great deal to the writings of Charles Darwin, who appreciated that all behaviour must have a biological basis. The natural extension of this idea was that clues to human behaviour could be found by studying animals. Indeed, not long after the publication of the *On the origin of species* (1859), the first physiological studies of learning were conducted by the Russian psychologist Ivan Pavlov (1849–1936) who studied classical conditioning in dogs. Modern ideas about the biological underpinnings of learning and memory begin with the Spanish neuro-anatomist Ramón Y Cajal (1852–1934). Cajal discovered that the nervous system was composed of individual cells. These cells, called neurons, were separate entities and communicated with each other at specialised junctions, a finding for which he shared the Nobel Prize in Physiology or Medicine in 1906. In his Croonian Lecture, delivered to the Royal Society in 1894, Cajal described his findings that nerve cells form connections with each other, and suggested that learning may be due to changes in the strength or pattern of connections between neurons. This idea, that a modification of the connections between neurons is the basis for learning, was formalised by the Canadian psychologist Donald Hebb in his book *The organisation of behaviour* (1949). Hebb proposed that during learning, if a particular connection between neurons is repeatedly used such that activity in one cell drives activity in the other, the strength of the connection between these cells is strengthened. Evidence for an activity-driven change in synaptic strength was first demonstrated at synapses in the hippocampus in 1973 and called long-term potentiation (LTP – Bliss & Lømo, 1973). It was well known that the hippocampus played a key role in memory formation (Milner, Squire & Kandel, 1998), and the finding of LTP in the hippocampus set the scene for the biological study of memory formation and LTP, a form of synaptic plasticity that remains the main cellular mechanism for learning and memory formation (Bliss & Collingridge, 1993).

Memory is a word that is used in a number of different contexts. For scientists, memory typically refers to the ability to encode and store information. Memory can also refer to something that is stored in the brain or the experience of remembering something. As a biologist, in this review, I will use memory as the first of these and discuss our current understanding of memory encoding. Memories are also separated into two categories: procedural or implicit memory; and declarative or explicit memory. Implicit memory relates to those that involve changes in behavioural outcomes, such as learning to ride a bicycle or playing the piano. In contrast, explicit memories are those that relate to memories of events and episodes, and are the type we are most commonly aware of. Importantly, emerging literature is showing that both types of memory formation engage similar biological mechanisms, and have very similar time courses.

Memory formation is thought to result from changes in the strength of connections between neurons involved in particular circuits, and is known as synaptic plasticity. Over the last 20 years, studies in animals have led to very specific cellular and molecular models of learning and memory formation (Kandel & Pittenger, 1999). Many of these findings come from analysis of simple forms of learning such as spatial learning and Pavlovian conditioning. These studies have shown that learning and memory formation result from two forms of plasticity: synaptic plasticity and neurogenesis. Synaptic plasticity refers to changes in synaptic strength of connections in existing networks of neurons, by the process of LTP, and is initiated by the coincident activity of cells that are engaged in networks that process related ideas. Neurogenesis, by contrast, refers to the generation of new neurons and their integration into the existing neural circuitry (Ming & Song, 2011). How particular neurons are generated and when this process is initiated is less well understood but engaging either LTP or neurogenesis has effects on neural activity, and leads to functional outcomes in cognitive state and behaviour.

All learning results from the observation, manipulation and storage of information, and the long-term impact of any learning clearly depends on the efficacy and accuracy of recall. Different types of memory clearly engage different neural circuits (Squire, 1987), and studies over the last 20 years have established that memory formation proceeds in three phases: acquisition, storage and retrieval (McGaugh, 2002). The first step, acquisition of memory, is immediate and is thought to result from LTP at particular synapses. This initial memory then undergoes a process of consolidation and storage. Consolidation refers to the fact that memories are initially formed in a somewhat labile form, after which processes are initiated during which they are transformed to a different state and become long-term memories. Initial memory formation is initiated by local biochemical changes at synapses that are engaged during a particular learning experience. In particular, it is clear that these cascades require the activity of receptors called N-methyl-D-aspartate (NMDA) receptors that are activated by the neurotransmitter glutamate, and a rise in cytosolic calcium at the synapse (Collingridge & Bliss, 1987). This rise in calcium activates second messenger systems that result in strengthening of that synapse (LTP). However, this form of LTP is relatively brief, lasting from one to three hours. Activation of NMDA receptors also initiates a different set of signalling cascades that lead to changes in gene expression in the neurons involved, leading to long-lasting changes of synaptic activity. In areas of the brain such as the hippocampus, activation of NMDA receptors also initiates neurogenesis in which new cells mature and integrate into the existing neural circuits, and this activity is required during memory consolidation. Both animal and human studies have shown that memory acquisition and consolidation is highly dependent on the learner's mental and emotional state, the method of information presentation, how performance is reinforced and the environment in which the person learns. Thus, both memory formation and consolidation also respond to modulatory influences.

Memory recall is the retrieval of information that has been stored. Two types of recall are generally recognised: free and cued recall. Free recall refers to the situation where events are retrieved at random, whereas, in cued recall, particular events are retrieved in a particular order as a result of an external cue. As described above, memory storage is thought to require activity of particular neural circuits and changes in the strength of connections within these circuits. For some forms of memory, in particular simple forms of learning, it is now clear that during memory recall, presentation of the cue activates the same neurons (the 'engram') that were engaged during acquisition. Indeed, stored memories of a particular event can be revived by selective activation of neurons that were engaged during the acquisition phase.

Consolidation of memory is thought to result in a long-lasting, stable memory trace. But it has been known for many years that recall of stored memories can destabilise the stored memory and it undergoes a second round of reconsolidation. In recent years, this proposal has gained much traction in studies again using Pavlovian conditioning in which the underlying mechanisms have been examined. These studies suggest that after recall of a stored memory, biochemical changes in neurons that represent the stored memory are destabilised, and a second round of genetic changes are required for permanent storage. The reasons for this reconsolidation are not clear but it has been suggested that this mechanism provides the opportunity to update stored memories based on new information. These results also suggest that procedures may be able to be implemented that enhance the second round of consolidation, thus leading to better long-term storage of information. These results provide an explanation for how rehearsal (practice) improves memory.

Forgetting? Memory formation is thought to result from plasticity within the nervous system, and retrieval of these memories results from reactivation of the 'engram' that is laid down during memory consolidation. The question arises: is forgetting an erasure of this engram?

We all have had the experience when facts that appear to have been forgotten at some time can be remembered when circumstances change. Studies in animal models have also provided a possible explanation for these changes. In Pavlovian fear conditioning, a normally innocuous stimulus (the conditioned stimulus), such as a tone or light, is contingently paired with a noxious one (typically an electric shock, the unconditioned stimulus) so that the conditioned stimulus now predicts the onset of an aversive stimulus. After a number of conditional stimulus–unconditioned stimulus pairings, subjects come to respond to the conditioned stimulus with behavioural, autonomic and endocrine responses that are characteristic of defensive responses to a fearful stimulus (the conditioned response). This is a form of Pavlovian learning, and involves the storage of 'emotional' memories that are rapidly acquired and long-lasting (Maren, 2001). In this process subjects learn that encountering the conditional stimulus predicts an aversive outcome, is therefore dangerous and respond appropriately. But after the formation of this memory, subsequent repetitive presentations of the conditional stimulus, not paired with the unconditioned stimulus, break the previous association, and leads to a gradual reduction of the conditioned response through a process known as extinction. Thus, a memory that a particular conditioned stimulus was dangerous and predicted an aversive outcome was formed and consolidated. After extinction, it may appear that this memory has been forgotten, as the conditioned stimulus no longer evokes the original learnt response. But experiments have shown that, rather than being forgotten, recall of this original memory has only been inhibited. New learning has taken place that interferes with recall of the old association. Under different circumstances, the original memory can return. These experiments have focused on one form of simple learning, and show that memories that appear to be forgotten are in fact still intact. Similar mechanisms have been shown to operate for a variety of different memories suggesting that similar mechanisms may also be engaged for more complex memories.

In this brief review, I have described some of the cellular mechanisms that underpin memory formation, storage and recall. These findings come from experimental studies in animals coupled with molecular and genetic studies using simple learning paradigms where learning can be simply assessed. But in our daily lives and in education, we learn much more complex relationships and form complex memories. How these memories may be formed and whether they fit into the physiological structure I have described will require some understanding of how particular episodes are encoded at the neural level. It is clearly going to require a multifaceted approach in which experimental neuroscience collaborates with educators and psychologists. The Centre for the Science of Learning is a starting point to bring together these different disciplines. Similar activities are also supported overseas and present a bright future for this endeavour.

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