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Long-term potentiation and memory

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The discovery of long-term potentiation (LTP) transformed research on the neurobiology of learning and memory. This did not happen overnight, but the discovery of an experimentally demonstrable phenomenon reflecting activity-driven neuronal and synaptic plasticity changed discussions about what might underlie learning from speculation into something much more concrete. Equally, however, the relationship between the discovery of LTP and research on the neurobiology of learning and memory has been reciprocal; for it is also true that studies of the psychological, anatomical and neurochemical basis of memory provided a developing and critical intellectual context for the physiological discovery. The emerging concept of multiple memory systems, from 1970 onwards, paved the way for the development of new behavioural and cognitive tasks, including the watermaze described in this paper. The use of this task in turn provided key evidence that pharmacological interference with an LTP induction mechanism would also interfere with learning, a finding that was by no means a foregone conclusion. This reciprocal relationship between studies of LTP and the neurobiology of memory helped the physiological phenomenon to be recognized as a major discovery.

Keywords: long-term potentiation; learning; memory; spatial memory; watermaze

1. PERSPECTIVES ON MEMORY OF 1973 AND 2003

The perspective that we have of memory systems in 2003 is radically different from that prevailing in 1973. We now know of several interdependent brain systems that mediate different types of memory and, within these, the distinctive processes of memory encoding, storage, consolidation and retrieval (Schachter & Tulving 1994, pp. 269–310). These include explicit (declarative) and implicit (non-declarative) systems, and various sub-systems such as those responsible for spatial, episodic and semantic memory on the one hand, and for skill learning and priming on the other. These distinct brain systems have different operating characteristics, distinct patterns of cerebral localization and network architecture, and subserve discrete aspects of cognitive function. In 1973, by contrast, we had little more than a suspicion that learning involved both associative and non-associative mechanisms, and that short- and long-term memory were likely to be mediated by different neuronal mechanisms. The range of behavioural tasks at our disposal to study learning was equally limited, ranging from the word-list learning tasks of the 'verbal learning' era of human psychology through to operant schedules, alleyways and simple mazes for animals.

Observations about human global amnesia were emerging, starting with the seminal observations on patient H.M. (Scoville & Milner 1957). Following a medial temporal lobectomy for the relief of epilepsy, this now extensively studied patient was found to have intact short-term memory, reasonable memory for information acquired earlier in his life, but an apparent inability to form new long-term memories after the operation. Brenda Milner later advanced what she referred to as a 'consolidation' account in which the hippocampus, this being the brain area most clearly damaged, was held to be critical for transferring information from short- to long-term memory (Milner 1966).

This proposal was not without its problems. First, it was already apparent to Milner by 1970 that H.M. could learn and retain motor skills. Thus, some information was getting through to long-term memory. Second, it was apparent that other amnesic patients, notably those with damage to the mamillary bodies and dorso-medial thalamus, presented with a very severe retrograde amnesia. This led Warrington & Weizkrantz (1968) to advance the then controversial idea that at least some of the memory problems of amnesic patients were due to a failure of retrieval rather than of consolidation. Their argument was that their patients were failing to remember events that, before the onset of their amnesia, they could clearly recall—events such as marriage and the birth of their children. This profile cannot be due to a failure to assimilate information into the long-term memory, but could perhaps be due to dysfunctional retrieval processes.

Neuropsychological studies on animals were proceeding with a range of tasks that, surprisingly, revealed little or no deficits in learning when experimental lesions were made to the hippocampus. This led some researchers to wonder if rodents, and even primates, were different from people for the neuroanatomical organization of the mechanisms of learning. At the same time, a revolution was happening in animal learning theory with old behaviourist concepts about the determinants of classical and instrumental conditioning, dating back to Pavlov and

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

Thorndike, in the process of being swept away. New ideas were emerging out of some ingenious experiments, such as Kamin's discovery of 'blocking' (Kamin 1968) and Rescorla's studies of 'contingency effects' in conditioning. These led to a radical new *zeitgeist* beginning with the Rescorla–Wagner theory, in which conditioning was held only to occur when the US that followed the CS was unexpected (Rescorla & Wagner 1972). Although immensely influential in psychological circles, then and to this day, this departure from the notion that the mere coincidence of CSs and USs was all that mattered for associative learning did not impact substantially on physiologists. Later, mathematical modelling of Hebbian and other learning rules contributed to the developing sense that there must be multiple types of learning and memory with different functions.

2. THE CHANGING PERSPECTIVE AROUND 1973

Several developments led to major changes in the way that the neurobiology of learning and memory was studied in mammals. Numerous papers had an impact, but that impact differed across the various scientific sub-cultures examining the neurobiology of memory. Examples include McGaugh's advocacy of post-training drug administration protocols to explore the neuropharmacology of memory consolidation (McGaugh 1966), Marr's theory of archicortex (Marr 1971), the development of new one-trial recognition memory paradigms for primates (Gaffan 1974; Mishkin & Delacour 1975) and the introduction of the radial maze as a way of looking at short- and long-term spatial memory simultaneously (Olton & Samuelson 1976).

However, I believe that it was physiological findings that really changed the scene: O'Keefe and Dostrovsky's discovery of place cells in the hippocampus (O'Keefe & Dostrovsky 1971) and Bliss and Lømo's detailed description of long-lasting potentiation (Bliss & Lømo 1973). Over the next decade, as these findings were reproduced by others and the properties of LTP began to be documented, attention in the learning and memory community began to turn from merely asking where learning happened in the brain to identifying the physiological events that might trigger the 'growth process' at neuronal connections that Hebb (1949) had predicted, and the nature of the representations once formed.

3. THE WATERMAZE

I first met Lynn Nadel and John O'Keefe in 1973. They told me about place cells and emphasized the need for new ways to study spatial learning. I was impressed by the assertion that was later to become the first two sentences of their 1978 book: 'Space plays a role in all our behaviour. We live in it, move through it, explore it, defend it' (O'Keefe & Nadel 1978). I carried out my last behavioural experiment in an operant chamber in 1972 and have never been tempted back into the world of response rates and schedules of reward and punishment. Instead, I tried to re-invent tasks reminiscent of an earlier era of animal learning in which navigation through extended space was critical, but in a manner that better fitted the new physiological findings. A key issue for me was that place cells

Figure 1. The watermaze. A rat stands on the hidden escape platform inspecting distal cues. After very limited amounts of training, the animal learns to navigate relatively directly to this location in space from any starting point.

fired where they did irrespective of local cues—they could not be strictly sensory cells, whether unimodal or polymodal, they had to depend on some kind of memory processing. However, I also wanted to study the possible relationship between learning and plasticity, rather than just spatial perception and representation. To achieve this, I reasoned, I had to get rid of local cues completely but in a true learning task.

Upon joining the University of St Andrews in Scotland in 1977, I was assigned laboratory space outside the Department in the remarkable but somewhat antiquated Gatty Marine Laboratory located on the West Sands of St Andrews' north facing, and often bleak, shoreline. It was a slightly strange place to work, quite apart from not infrequently having to battle my way down the path along the shore through the winds of a northerly winter gale that had blown in from Russia. Once indoors, I got to my laboratory past tank after tank of sea creatures of various shapes and forms, some of whom might have been the subject of Adrian Horridge's recently completed studies of invertebrate interneurons (Horridge 1968). One day, it occurred to me that rats might be able to learn while swimming and that this might help solve the local cue problem. I wondered if they could escape from water onto a platform that was hidden beneath the water surface and so was neither visible, audible, offered no olfactory cues and could not be identified using somatosensory cues until after the animal had already successfully navigated to it. This might be the solution to the local cue problem.

The first 'watermaze' was built from hardboard and yacht resin by myself with the help of Chris Barman, an animal technician. We completed it in the workshop over the weekend, these being the days when staff still had access to workshops at weekends and Health and Safety Officers were still over the horizon. To my amazement and delight, the rats learned the task very quickly (figure 1). I ran some essential control conditions and a paper on 'place navigation' followed soon (Morris 1981). The observation that this type of learning is severely impaired by hippocampal lesions was made a year later (Morris *et al.* 1982). We tracked the animals by tracing a path with a felt-tip pen onto clear film that we had taped over a video monitor. A year or so later, the British Broadcasting Corporation (BBC) introduced the BBC Computer with

128 K of memory and an easily learned software language called BBC Basic. Some colleagues and I wrote a little program and, using a commercially available tracking device that John O'Keefe had used to track place cell firing, we were soon able to track the paths of the swimming rats directly. This was a revelation for, to my knowledge, studies of spatial learning had hitherto relied on observer reports. It was a small step towards better objectivity.

4. USING THE WATERMAZE TO STUDY LONG-TERM POTENTIATION AND MEMORY

I presented these findings at what came to be known as the 'Schloss Hippocampus' meeting of 1982. This was a meeting at a castle in southern Bavaria owned by the Max-Planck Society at which, in the views of many, the hippocampal field was to change direction irrevocably (Siefert 1983). Until then, work had been very much on the 'septo-hippocampus' with particular emphasis on the cholinergic and other inputs from the midbrain. It was at this meeting that many in the field first heard Carol Barnes describe her tantalizing observations that the persistence of LTP correlated with the persistence of memory in her circular arena task (Barnes 1983), although a journal paper had appeared earlier (Barnes 1979). While there, I met Gary Lynch who mesmerized us all with his remarkable observations on LTP. These included his work confirming the homosynaptic nature of the synaptic change when studied in hippocampal slices *in vitro,* the role of calcium in LTP induction, and the structural changes in spines viewed at the electron microscopic level (Lynch *et al.*, 1983*a*,*b*). It was immediately apparent that LTP was much more than a persistent change in synaptic efficacy induced by tetanic stimulation, as Bliss & Lømo (1973) had described 10 years earlier. It was also a change that was associated, at the point of induction, with an ionic current different from that used to mediate normal synaptic transmission and a change expressed in a manner that could have the very storage capacity required of the network model of Marr (1971) incorporating the Hebb synapse. The following year, Lynch & Baudry (1984) produced their remarkable *Science* paper in which glutamate receptors (*sic*.) were inserted into membranes to express the enhanced synaptic efficacy. If this concept has a contemporary ring to it, bear in mind that the paper is now nearly 20 years old. It is not always cited as often as it should be, perhaps because a cardinal plank of their evidence turned out to be changes in glutamate transport rather than in the expression of the synaptic receptor. However, the idea of a simple postsynaptic mechanism to express the change in synaptic weights had already emerged. Current debates on AMPA receptor trafficking have not moved on conceptually so very far from these early ideas, even if the techniques available now are spectacular by comparison to what was around then.

I resolved to go and work with Lynch and was fortunate to be able to do so in 1984, courtesy of a Medical Research Council Fellowship scheme that released University teaching staff to focus on research for a while. In this, and many other ways, I owe a great deal to the MRC. Lynch's laboratory was then working on a range of projects, including a serine protease inhibitor called leupeptin that was thought to inhibit the proteolytic mechanism that he and Michel Baudry had implicated in the glutamate receptor insertion process. In laboratory experiments on olfactory learning conducted in the Irvine laboratory, I had mixed success, possibly because we were using the very discrimination learning tasks that were proving insensitive to hippocampal lesions in rats and primates. Ursula Staubli was later to have success in using this drug to block LTP (Staubli *et al.* 1988), but its effects on learning were generally quite modest, even in the watermaze (Morris *et al.* 1987). However, while in Irvine, and contrary to the 'house rules' that reflected the friendly rivalry between the Lynch and Cotman laboratories, I discussed these experiments with Eric Harris, then a postdoc with Carl Cotman. He drew my attention to the recently published paper by Collingridge *et al.* (1983) on the role of the NMDA-receptor in LTP and the drug AP5. Sadly, it was time to go home, but Gary and I discussed some experimental options for when I got back to my laboratory.

Upon returning to St Andrews, Jeff Watkins at Bristol University kindly made available a small supply of the racemic mixture of an NMDA-antagonist (D,L-AP5) and I began work. At that point, no one knew whether AP5 would work *in vivo* or, indeed, be very effective in crossing the blood–brain barrier. Its structure did not augur well in this regard. Accordingly, using the same ICV minipump procedure that had been tried in Irvine with leupeptin, I did some acute *in vivo* experiments on dentate LTP. These experiments were exactly as Bliss & Lømo (1973) had carried out long before, but now in the rat rather than the rabbit and after chronically infusing D,L-AP5 or saline for several days. The blockade of LTP *in vivo* was complete, across a range of test pulse intensities, and without any apparent effect on baseline synaptic transmission. I was amazed and excited.

The obvious next step was to try this in swimming rats and, to my delight, Elizabeth Anderson and I found that rats treated with the drug were unable to learn the reference memory spatial version of the watermaze. Those given saline or the inactive isomer, L-AP5, were unimpaired. Strangely, we did not work with D-AP5 at that stage. I cannot remember why. Concerned that the deficit with D,L-AP5 might be sensory in nature, I deliberately tried the very discrimination tasks that animals with hippocampal lesions can learn and I observed, now with a mounting sense of disbelief, that they could. Both behavioural experiments were replicated 'blind'. Thus, chronic intraventricular infusions of D,L-AP5 at a dose sufficient to block LTP *in vivo*, without affecting fast synaptic transmission in the hippocampus, caused an apparently selective impairment of hippocampal-dependent place navigation (figure 2). The animals could see, could move around properly and could learn another equally difficult task, but they could not find their way in a task that needed place cells and apparently required NMDA-receptor-dependent LTP. Gary Lynch came to St Andrews to help write the paper that was published in 1986 (Morris *et al.* 1986). In the same year, McNaughton *et al.* (1986) took a complementary step forward by establishing the causal role of activity-dependent synaptic enhancement in learning in a different way. They observed that prior physiological saturation of LTP impaired subsequent spatial learning. This was to prove a controversial finding, but

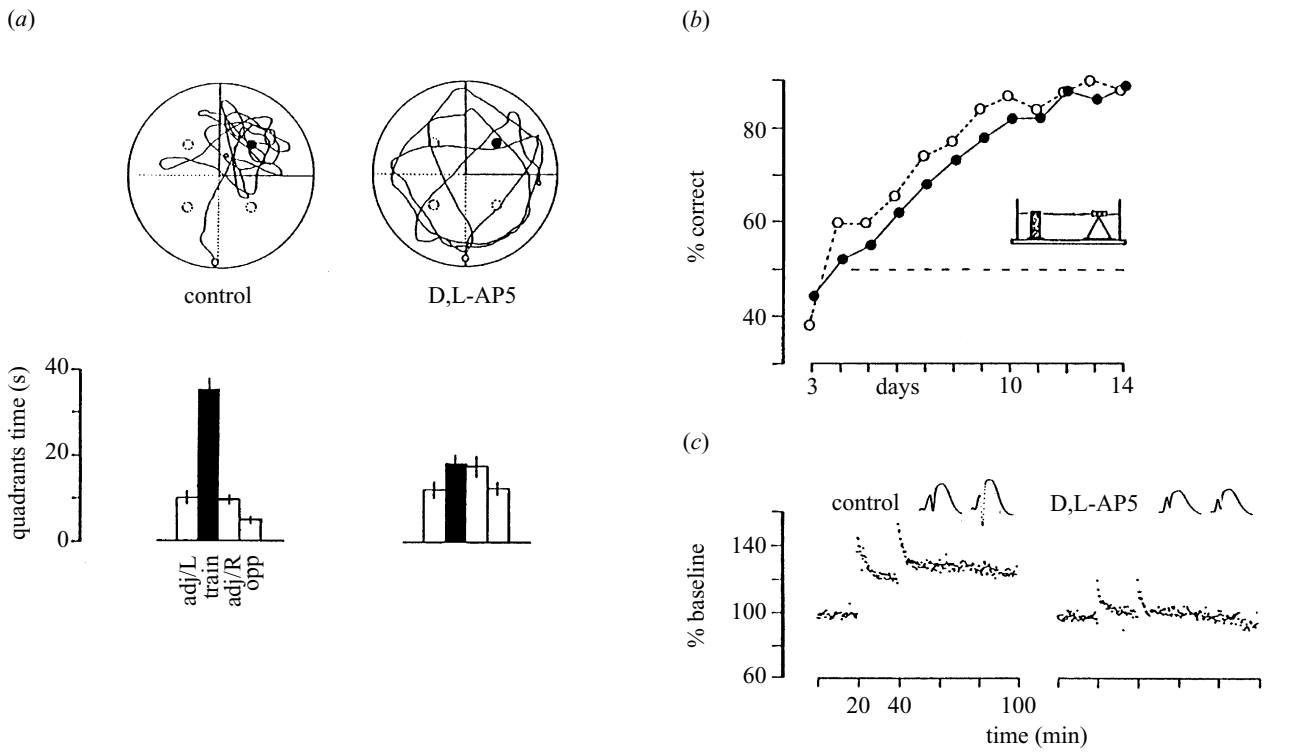

Figure 2. The role of NMDA-receptors in spatial learning. (*a*) An original drawing of the first set of probe test data obtained in the watermaze after chronic infusion of D,L-AP5. (*b*) Normal visual discrimination learning, a task unimpaired by hippocampal lesions. Control represented by open circles; D,L-AP5 infusion results represented by filled circles. (*c*) LTP of f-excitatory post-synaptic potential. Chronic intraventricular infusion of D,L-AP5 blocks dentate gyrus LTP *in vivo*.

one for which Bruce McNaughton and his colleagues were later vindicated (Moser *et al.* 1998).

5. REFLECTIONS

LTP might have turned out to be a physiological curiosity. It might have been a physiological phenomenon that displayed persistence of a duration commensurate with it being a basis for learning, but unrelated to the actual mechanisms used by the brain. However, there are now two primary reasons for thinking that synaptic plasticity and memory are intimately intertwined (Martin *et al.* 2000; Martin & Morris 2002). First, a generation of work on the physiological properties and cell-biological mechanisms reveals it to possess many other important characteristics of a memory mechanism. The discovery of Bliss & Lømo (1973) did indeed unleash a scientific party as Andersen notes (Andersen 2003). Second, LTP and long-term depression have now been shown to meet at least three of the four criteria that need to be met to establish it as a mechanism that is both 'necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed' (Martin & Morris 2002, p. 609).

(i) Changes in synaptic weights are detectable after learning.
(ii) Interfering with (or altering) the mechanisms responsible for the induction and expression of synaptic plasticity does indeed interfere (or alter) the rate of learning in a variety of relevant learning paradigms.
(iii) Altering the pattern of synaptic weights after learning also affects the ability of animals to remember a previous learning experience.

The fourth criterion, surely not yet met, is mimicry: were it feasible to alter the pattern of synaptic weights in a network in an appropriate manner, the animal should behave as if it remembered something that, in practice, had not happened. Tim Bliss calls this the 'Marilyn Monroe' criterion. This weakness of the available data apart, a rich array of physiological, pharmacological, molecular engineering and other techniques, allied to behavioural studies, have now tightened up the link between activity-dependent synaptic plasticity and memory to a point where it is reasonable to set aside a scientist's natural scepticism about the central principle.

I was lucky in several ways. I entered the field at a time of great change, and was in a position to profit from the important foundations laid by others. I met several key individuals who advised and very generously helped me, particularly in giving me the opportunity to travel abroad and work in a very exciting laboratory at a critical time. Finally, I also had the good fortune to hold my first university lectureship in a Department with no laboratory space. I love walking along the beach in St Andrews and I look up wistfully at the dark and somewhat forbidding grey, stonewalls of the Gatty Marine Laboratory with secret affection.

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GLOSSARY

AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid
CS: conditioned stimulus
ICV: intracerebroventriculae
LTP: long-term potentiation
NMDA: *N*-methyl-D-aspartate
US: unconditioned stimulus