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A journey from neocortex to hippocampus

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In the mid-1960s, it was generally agreed that the engram, the neural trace of previously experienced events, must be encoded by Hebb-like neurons in which synaptic efficacy could be modified by activity. Here, I describe my attempts as a PhD student at McGill University, Montreal, to find rules governing cortical plasticity in the neocortex, and having failed, why the hippocampus seemed to offer a far better prospect.

Keywords: neocortex to hippocampus; long-term potentiation; synaptic plasticity; Hebb; learning; memory

Sometime in the autumn of 1963 I went to see Ben Delisle Burns, then a professor in the Physiology Department at McGill University, Montreal, where I had taken my undergraduate degree, to talk about doing a PhD with him. 'There is one topic in which I am so passionately interested' said Burns, 'that if you come to my laboratory that is what I shall want you to work on'. His passionate interest—the neural basis of memory—was mine also. I signed up.

When I began my research in 1964, it was—then as now—widely, if not quite universally, assumed that the neural substrate of memory resided in the putative ability of cortical synapses to undergo long-term changes in efficacy as a result of particular patterns of activity. The synaptic theory of memory goes back at least as far as Cajal and Tanzi in the early part of the twentieth century, and is hinted at in the work of the nineteenth century psychologist William James. The first objective in the campaign to understand memory at the neural level was thus to identify synapses with the ability to sustain activity-dependent changes in efficacy for prolonged periods of time—in the limit, for the rest of the organism's life. David Lloyd in the 1940s (Lloyd 1949) and John Eccles in the early 1950s (Eccles & McIntyre 1953) had studied PTP in monosynaptic spinal pathways as a model for cortical plasticity, but by the early 1960s enthusiasm for PTP, like PTP itself, had waned; its time-course was simply too rapid to be useful. Burns expressed this disenchantment for existing models in his book on the properties of cortical ensembles published in 1958:

> Those mechanisms of synaptic facilitation which have been offered as candidates for an explanation of memory… have all proved disappointing.
>
> (Burns 1958, p. 96)

The mechanisms that Burns had in mind were PTP and reverberatory activity in self-re-exciting networks, a mechanism championed by Lorente de No in the 1930s and 1940s (Lorente de No 1939). The former was inherently too brief, and the latter was functionally too fragile to persist indefinitely.

The general frustration was echoed by Eccles a few years later at a meeting I shall return to below:

> Unfortunately, it has not been possible to demonstrate experimentally that excess use produces prolonged changes in synaptic efficacy.
>
> (Eccles 1966, p. 330)

Neurophysiologists have the option of turning to model neurons when the real things fail to please. Burns formulated a neural model of Pavlovian conditioning in which two cells A and B, A carrying the signal from the conditioned stimulus, and B the signal from the unconditioned stimulus, converged on a motor output cell M. Burns realized, like Konorski before him (Konorski 1948), that for conditioning to occur, the synaptic efficacy between B and M must be increased as a result of A and B being co-active. Sadly, he concluded, there was no evidence for 'such a peculiar property' (Burns 1958). Burns refers to his McGill colleague Hebb from time to time, but does not specifically mention his now famous 'neurophysiological hypothesis' (Hebb 1949):

> *When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.*[1], p. 62

It is strange now, writing at a time when Hebb's postulate must be the most quoted sentence in the literature of neuroscience, its only rival being Sherrington's magical metaphor of the brain as 'an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one',[2] to realise that neither Burns nor Eccles paid much attention to the neurophysiological postulate. Both, it is true, include Hebb with Ramon y Cajal, Tanzi and Konorski

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

as among those who had identified activity-dependent changes at the synapse as the probable neural basis for memory. But for Burns and Eccles, the 'Hebb' synapse was little more than a self-evident conceptual embodiment of PTP, which Eccles and Lloyd had studied in spinal reflexes. The problem with PTP was that, except in pathological conditions involving a period of sensory deprivation by cutting the dorsal root, its duration was hopelessly inadequate for memory functions. In fact, Hebb's postulate is a good deal subtler than a simple restatement of homosynaptic potentiation. The artful phrase 'fires or takes part in firing' allows an input to share in the effect produced by another input, and thus endows his rule with the important property of associativity. It is nevertheless odd that Hebb did not draw this specific conclusion, extending his model to three neurons, as Burns was to do a few years later.

So it was obvious, by the time I started my PhD with Burns in 1964, that while spinal cord pathways may have been easy to isolate, they did not contain the stuff of which memories are made. There seemed no option but to look for electrophysiological evidence for synaptic plasticity in the brain itself, despite the then unfathomed neural tangle of cortical networks. Burns taught me how to record from single units in undercut slabs of cortical tissue in the intact cat, a preparation he had developed with the idea of reducing spontaneous activity, so that the firing of the recorded cell was more closely under the control of the experimenter. Test shocks were delivered to a stimulating electrode placed nearby in the isolated slab, and I took as a measure of the 'conductivity' of the pathway the probability of the test stimulus eliciting an action potential from the cell I was recording from. My task was to see if I could produce long-lasting changes in conductivity by transient manipulations in the rate of stimulation. In some experiments, I had a second electrode, which allowed me to look for heterosynaptic effects. We were joined in the analysis of these experiments by the physicist Albert Uttley in whose division at the National Physical Laboratory in Teddington, near London, Burns and I had carried out the first experiments, and the results were published in 1968 (Bliss *et al.* 1968). I find the paper, with its heavy formalism, almost unreadable today. Moreover, the variability of the results and the generally polysynaptic nature of the responses conspired to make it impossible to draw any general conclusion about the rules governing activity-dependent changes at single synapses. Most experiments in which homosynaptic activity was briefly increased revealed an apparently anti-Hebbian reduction in 'conductivity' for a few tens of minutes (the duration of the effect limited by the length of time it was possible to hold the cell). Heterosynaptic stimulation led in most cases to facilitation of the homosynaptic pathway. However, the main conclusion I reached after devoting nearly 3 years to this approach was that it was misguided. The preparation was too complex; it was essential to simplify.

During this period, I had heard Eric Kandel give a sparkling talk at McGill University about his work with Tauc on synaptic plasticity in the sea slug *Aplysia* (Kandel & Tauc 1965). An animal with a nervous system consisting of a few nerve cells, each one identifiable from animal to animal, and a limited and reproducible behavioural repertoire, provided one clearly profitable way to simplify. But, perhaps as the result of my conventional English education, I preferred to stick to my own class, and so continued to work on mammals. It was while writing my thesis that I came across a book that would lead me in the direction of the hippocampus. In 1964 a conference on 'Brain and conscious experience' had been held, improbably, at the Vatican. The organizer was Sir John Eccles, who had won the Nobel Prize the year before, and who had long had an interest in the neural basis of memory. Among the speakers was Per Andersen, who had recently returned to Oslo after postdoctoral studies in Eccles' laboratory in Canberra, and who had steered Eccles towards the hippocampus, the detailed neural organization of which had been illuminated by the beautiful work of the Oslo school of neuroanatomists. In his chapter on memory in the proceedings of the Vatican conference—the book I had found in the library at McGill University—Eccles speculated on what it was about cortical synapses (the presumptive neural seat of memory) that made them (again, presumably) more plastic than spinal cord synapses (Eccles 1966). He drew attention to the spine apparatus, found in or at the base of spines on neocortical and hippocampal pyramidal cells, and quoted a speculation of Hamlyn's (1963) that these structures, more prevalent in pyramidal cells of the hippocampus and neocortex than in spinal neurones, might contribute to the cellular machinery of memory. But it was Andersen's chapter (Andersen 1966) that made the greatest impact. He emphasized the relative simplicity of the hippocampal neural architecture, and the readily interpretable field potentials that stimulation of its stratified axonal projections elicited. Here was a way of recording synaptic efficacy in an identified monosynaptic pathway with extracellular electrodes. A superior preparation in every way—and in a structure that I knew to be important for memory. This is another McGill connection. In 1954, the patient known in the neurological literature as H.M. had undergone a bilateral resection of the temporal lobes, including the hippocampal formation, in an attempt to control his intractable epilepsy. The operation had resulted in a profound and permanent anterograde amnesia. H.M. was unable to form new episodic memories. His case established the importance of the hippocampus in the formation of new episodic or declarative memories in humans (Scoville & Milner 1957). Later work showed that other forms of learning and memory (for example, working memory, conditioning, priming, skill learning) were largely intact, demonstrating the existence of parallel and independent memory streams.

H.M.'s amnesia had first been studied by the McGill psychologist Brenda Milner, and his case was well known and much discussed in the seminar rooms of Montreal. In the autumn of 1967, when I came to Mill Hill, London, to continue working with Ben Burns who had become Head of the Division of Neurophysiology at the National Institute for Medical Research the year before, I had reached the inescapable conclusion that the hippocampus was the structure in which to continue the pursuit of the plastic synapse. I contacted Per Andersen shortly afterwards, to visit his laboratory to learn about the technique of field potential recording. With this indispensable technique, only possible in structures like the hippocampus that possess a rigorously laminated neural organization,

synaptic responses could be monitored with extracellular recording electrodes. It was exactly what was needed to pursue changes in synaptic efficacy that, hopefully, might last for many hours.[3] The mnemonic engine of the brain was matched with the ideal technique for probing its mysteries. When Andersen heard of my reasons for wanting to work on the hippocampus, he told me that Terje Lømo, a PhD student in his laboratory, had discovered a phenomenon that would surely interest me. Lømo was writing his thesis, and had not had time to work on it further. If I came to Oslo, Andersen suggested, perhaps I might persuade him to take a break from writing? I made arrangements with an indulgent Medical Research Council to take a premature sabbatical, and a few months later, in the autumn of 1968, Terje Lømo and I did our first experiment together. We delivered a single tetanus to the perforant path, and the response to the test stimulus, reflecting the magnitude of the evoked synaptic response and therefore a measure of synaptic strength, was hugely potentiated. Over the following minutes the magnitude of the response dropped, as expected of PTP, but then levelled off well above the baseline. We watched with increasing excitement as the hours passed,[4] and the traces on our oscilloscope remained stubbornly elevated. We had confirmed what Lømo had found in 1966, and, unknown to me until I came to Oslo, had published in abstract form (Lømo 1966): tetanic stimulation of the perforant path leads to a persistent increase in synaptic efficacy. As I have said elsewhere, that experiment also engendered an equally persistent sense of amazement that 'such modest stimulation can produce so immediate, so profound, and so persistent an effect' (Bliss & Lynch 1988).

Lømo and I were aware of the significance of what we had seen, as was Per Andersen in whose laboratory the work was done and who did so much to encourage it. But we were careful not to claim too much for long-lasting potentiation, as we then called it. The last sentence of our paper attempts, in a flurry of clauses and subclauses, to emphasize that although we had found a cortical pathway in which changes in synaptic efficacy lasting for hours could be readily induced—clearly a good thing for a neural mnemonic device—our stimulus was wholly artificial, and we had no idea whether the effect that so delighted us did, in fact, play any part in the real life of the animal (Bliss & Lømo 1973). It is a salutary reminder of the difficulty of bridging the physiological and cognitive domains of enquiry that 30 years after writing that sentence we could rewrite it with almost equal validity today. We may suspect, but we do not know that LTP forms the neural basis of learning for any task in any animal. But perhaps a sub-Galilean murmur may be forgiven in this anniversary year: *surely, it must*.

ENDNOTES

[1]A Google search on 16 November 2001 produced 311 hits for 'Hebb's postulate' and 138 hits for 'Sherrington enchanted loom'.

[2]The italics are Hebb's. Switching to an italic font to notify the reader that the text so decorated constituted a significant statement was a technique introduced into popular literature by Stella Gibbons in Cold Comfort Farm (1932); its use by Hebb in his canonical postulate led to its adoption by at least one leading behavioural physiologists of the next generation.

[3]Or for many days. The technique was equally adaptable to awake animals that had been implanted with chronic recording and stimulating electrodes, as Tony Gardner-Medwin and I were to find after I had returned from Oslo (Bliss & Gardner-Medwin 1973).

[4]Persistent excitement is something of a contradiction in terms. LTP and the last day of a closely fought 5-day cricket match provide two well-documented counter examples.

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GLOSSARY

LTP: long-term potentiation
PTP: post-tetanic potentiation