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The Making of a Memory Mechanism[1]

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Abstract. Long-Term Potentiation (LTP) is a kind of synaptic plasticity that many contemporary neuroscientists believe is a component in mechanisms of memory. This essay describes the discovery of LTP and the development of the LTP research program. The story begins in the 1950's with the discovery of synaptic plasticity in the hippocampus (a medial temporal lobe structure now associated with memory), and it ends in 1973 with the publication of three papers sketching the future course of the LTP research program. The making of LTP was a protracted affair. Hippocampal synaptic plasticity was initially encountered as an experimental tool, then reported as a curiosity, and finally included in the ontic store of the neurosciences. Early researchers were not investigating the hippocampus in search of a memory mechanism; rather, they saw the hippocampus as a useful experimental model or as a structure implicated in the etiology of epilepsy. The link between hippocampal synaptic plasticity and learning or memory was a separate conceptual achievement. That link was formulated in at least three different ways at different times: reductively (claiming that plasticity is identical to learning), analogically (claiming that plasticity is an example or model of learning), and mechanistically (claiming that plasticity is a component in learning or memory mechanisms). The hypothesized link with learning or memory, coupled with developments in experimental techniques and preparations, shaped how researchers understood LTP itself. By 1973, the mechanistic formulation of the link between LTP and memory provided an abstract framework around which findings from multiple perspectives could be integrated into a multifield research program.

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Introduction

The research program dedicated to Long-Term Potentiation (LTP) and its potential role in learning or memory is among the most prolific, well-funded and controversial in contemporary neuroscience. LTP is a long-lasting and use-dependent increase in the efficacy of a synapse, and many contemporary neuroscientists (perhaps most) believe that LTP is a crucial component in mechanisms of memory.[2] Others are doubtful, believing that the link between memory and LTP has yet to be demonstrated, that the link has been refuted, or that LTP can be produced only under contrived experimental conditions that never occur in the normal working brain.[3] Regardless of who is right, the LTP research program – including both enthusiasts and detractors – has been a dominant research program in the neurosciences for nearly thirty years, and its development in many ways reflects the development of contemporary neuroscience generally. It is therefore surprising that the history of the LTP research program has yet to be told.[4] This paper describes the origins of the LTP research program, including the discovery and characterization of LTP, its association with learning or memory, and the integration of different fields[5] and perspectives[6] into a multifield project that is still growing over 30 years later.

Philosophers of neuroscience have tended to view the LTP research program through the lens of intertheoretic reduction. Bickle,[7] for example, has asserted that the LTP research program has effected an "accomplished psychoneural reduction" of memory consolidation to synaptic changes. Churchland and Sejnowski[8] see the development of this research program as involving the eliminative "coevolution" of theories in different sciences. Much the same point was made by Ken Schaffner[9] in his discussion of Kandel's work on learning in the Aplysia. History is a useful corrective for

[2] Stevens, 1998.

[3] See, e.g., Shors and Matzel, 1997; Sanes and Lichtman, 1999.

[4] See Bennett, 2001, Ch. 10 for a panoramic history of the published literature on LTP. The present essay expands and corrects Bennet's paragraph-length discussion (211) of the early history of the research program.

[5] See Darden and Maull, 1977; Darden, 1991.

[6] See Wimsatt, 1974.

[7] Bickle, 1998.

[8] Chuchland and Sejnowski, 1992.

[9] Schaffner, 1993b.

this narrow focus on reduction, with its emphasis on relationships among the meanings of theoretical terms. In particular, the historical details help us to recognize that the researchers coalescing into the LTP research program often had different instrumental and explanatory objectives, different experimental systems, different techniques, different pedagogical backgrounds and even different views about the very nature of explanation. In tracking this history, we are forced to expand the dimensions along which we can understand how varied perspectives are combined into multifield research programs in the process of building a theory. To the extent that the development of the LTP research program is representative of changes elsewhere in neuroscience and beyond, this historical account may direct our attention to previously neglected aspects of theory building and scientific change generally.

I begin with a brief sketch of contemporary perspectives on LTP, its mechanisms and its putative link to memory. I then describe the earliest reports of synaptic plasticity in the hippocampus, a brain region now associated with memory. I show that hippocampal synaptic plasticity was first encountered as a laboratory tool and then sporadically reported as an experimental curiosity. In the following section, I argue that synaptic plasticity was not discovered in the search for a memory mechanism, as many have assumed; rather, researchers were investigating the hippocampus because of its clinical relevance to the etiology of epilepsy and because it was a good experimental model for studying the neurophysiological organization of the cortex. I then turn my attention to the link between synaptic plasticity and memory, showing how this old idea was preserved through work in mathematical biophysics and its interface (largely through John Eccles) with electrophysiological research and theoretical work on the foundations of neuroscience. This link between plasticity and learning or memory was formulated in at least three different ways through the 1960's. The link was formulated reductively (claiming that plasticity was identical to learning), analogically (claiming that plasticity was an example or model of learning), and mechanistically (claiming that plasticity was a component in learning or memory mechanisms). In the next section, I describe how LTP specifically came to be characterized as researchers worked to develop techniques for producing and detecting it more reliably and while they struggled to justify the measures produced by those techniques. By 1973, LTP was situated within an explanatory project of discovering neural mechanisms of memory. In the final section, I show how his mechanistic view of the link between LTP and memory clearly defined the goals for the research program and created a framework onto and around which the findings of diverse fields and perspectives could converge.

Admittedly, this account of the origins of the LTP research program is skeletal. First, it is focused exclusively on the earliest phase of the

research program, spanning roughly from 1950 to 1973. There is considerable historical work to be done tracing its subsequent development. Second, the present account is drawn from primary sources and interviews. Since each is prone to systematic forms of distortion, there is a real possibility that the narrative will have to be significantly revised or expanded with new historical data. Third, the narrative is unabashedly "internalist;" it is primarily focused on the development, transmission and justification of commitments concerning the character of LTP, its explanatory relevance and the experimental techniques used to study it. Some of LTP's scientist detractors attribute the success of the research program to the sociology of contemporary neuroscience. Such charges have yet to be evaluated and will not be evaluated here. However, the present sketch will provide a useful backdrop for future efforts to understand the impact social factors on the research program's development.

LTP in Contemporary Perspective

Publication on LTP has increased geometrically over the last three decades[10] and, according to one recent estimate,[11] accounts for roughly four papers per day. One contemporary neuroscientist has praised recent work on LTP as a first step toward the "dream of neurobiology ... to understand all aspects of interesting and important cognitive phenomena – like memory – from the underlying molecular mechanisms through behavior."[12] There are many helpful reviews of LTP, its different types, its mechanisms, and its relationship to learning and memory.[13] Yet a brief sketch of a standard variety of LTP will introduce some of the research program's vocabulary and some of the metascientific concepts used below to describe its history.

LTP is the persistent enhancement of synaptic transmission in response to rapidly repeated stimulation. The neurons composing the brain are connected to one another at, and interact across, synapses. At chemical synapses (there are electrical synapses as well, but they are not a part of this story), neurons interact by passing chemical transmitters, typically from the presynaptic to the postsynaptic cell. Transmitters are released from the axon (the giving end) of the presynaptic neuron when an action potential reaches the axon's end. The transmitters traverse the synapse and bind to receptors on the dendrites (the receiving end) of the post-synaptic cell. The receptors (at least those

[10] Sanes and Lichtman, 1999.

[11] Malenka, 1999.

[12] Stevens, 1996, p. 1147.

[13] See e.g., Bliss and Lynch, 1988; Tsumoto, 1990; Bliss and Collingridge, 1993; Malenka, 1995; Squire and Kandel, 2000.

with which we are here concerned) act as gates for ion channels through the post-synaptic neuron's membrane. These channels allow ions to cross the cell membrane, and, because ions are charged, this flux of ions constitutes a flow of current across the membrane. This current alters the electrical potential of the post-synaptic cell. In excitatory synapses, the post-synaptic cell is "depolarized" from its resting state by the flow of ions. In inhibitory synapses, different ions "hyperpolarize" the receiving cell, decreasing the likelihood of an action potential. I will confine my attention to excitatory synapses, which have played the most significant role in the history of LTP.

LTP was initially encountered in the hippocampus. Potent evidence for association of the hippocampus with memory came from the patient, H.M., whose intractable epilepsy led him to assent to an experimental surgery involving the bilateral removal of his hippocampus. Brenda Milner's psychological evaluation of H.M. revealed that the surgery had resulted in tragically thorough amnesia for facts and events experienced after the surgery. [14] His memory for skills and his memory for events prior to the surgery were relatively unimpaired (excepting a loss of memories for facts and events just prior to the surgery). Subsequent animal studies have produced similar results.[15] A transverse section of the hippocampus, with its characteristic tri-synaptic excitatory loop, is shown in Figure 1a. As labeled in that figure, this loop runs from the perforant path fibers coming from the entorhinal cortex, through the granule cells (○) of the dentate gyrus, and from there to the pyramidal cells (△) of the cornu Ammonis region (labeled CA1 and CA3). LTP has been reported in each of these synapses and in the synapses of many other brain regions besides. The remainder of this diagram focuses on LTP produced by stimulating the fibers of the perforant path and recording from the granule cells in the dentate gyrus.

In Figure 1b (top), LTP is represented as a persisting enhancement of the post-synaptic response to the same pre-synaptic electrical signal following repeated use of the synapse. The top line represents stimuli delivered to the presynaptic cell; the bottom line records the post-synaptic response. At the beginning of the experiment (in the first third of the diagram), a test stimulus to the presynaptic cell produces a regular depolarization of the postsynaptic cell (i.e., an excitatory post-synaptic potential, or EPSP). The experimental intervention (in the middle third) involves applying a tetanus (rapid and repeated stimulation) to the presynaptic cell. Following this intervention (in the last third), the same test stimulus produces a much greater EPSP than before. This facilitation lasts well beyond the intervention, and may last for hours, days or weeks, as shown in Figure 1b (bottom). Figure 1c illustrates

[14] Scoville and Milner, 1957.
[15] See e.g., Mishkin, 1978.

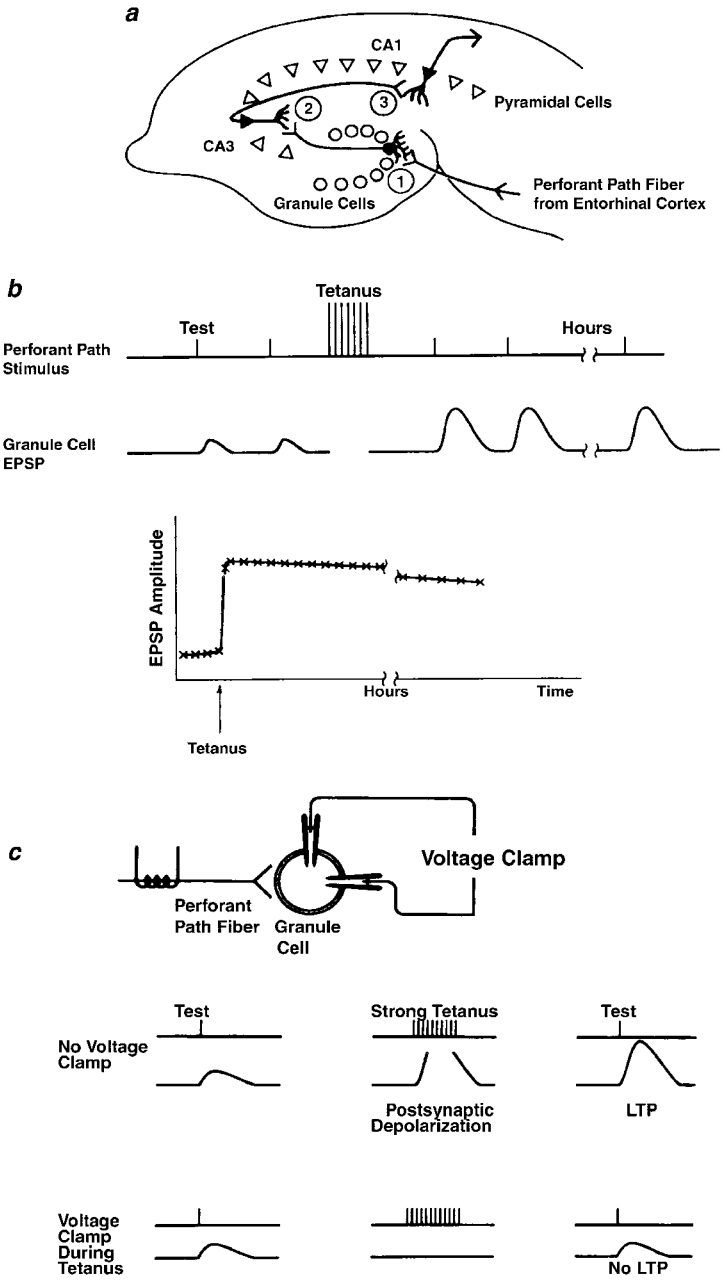

Figure 1. An overview of hippocampal LTP. (a) Transverse section of the hippocampus revealing its excitatory tri-synaptic loop. (b) LTP in the synapse between the perforant path fibres from the entorhinal cortex and the granule cells of the dentate gyrus. (c) Absence of LTP when the post-synaptic cell is voltage clamped to prevent tetanus-induced depolarization. Figure from Levitan and Kaczmarek (1991).

the "cooperative" nature of LTP. The top record is the same as described in Figure 1b. In the bottom record, the post-synaptic cell is "voltage clamped" during the tetanus (in the middle), meaning that voltage changes are prevented by a balancing external source of current. LTP is not induced in the absence of post-synaptic depolarization (in the last third). Such experiments suggested that LTP is cooperative; that is, it requires the simultaneous activation of both pre- and post-synaptic neurons.

Much of the LTP research program has been driven by the goal of describing the mechanisms for inducing and expressing LTP. In describing the mechanism for a phenomenon (like LTP), one describes the entities and activities in the mechanism and shows how those components are organized (spatially, temporally and interactively) to produce that phenomenon.[16] Although the mechanisms of LTP are quite controversial, a simple sketch of the less controversial components of the LTP induction mechanism will suffice to introduce some basic themes.

The hippocampal synapses that exhibit LTP use glutamate (i.e., glutamic acid, a ubiquitous amino acid) as a neurotransmitter. With each action potential, glutamate is released from the presynaptic cell and binds to receptors on the postsynaptic cell. One type of postsynaptic glutamate receptor in the hippocampus is the NMDA receptor (for N-Methyl D-Aspartate, a chemical agonist or stimulator with a high affinity for this receptor). When glutamate binds to NMDA receptors, they change their conformation, exposing a pore through the membrane. If the postsynaptic cell remains polarized (as in Figure 1d), the channel remains blocked by large, positively charged Mg^{2+} ions. If the postsynaptic cell is depolarized, the Mg^{2+} ions float out of the channel, allowing Ca^{2+} to diffuse into the cell. (This aspect of the mechanism is thought to explain the cooperative nature of LTP). The rising intracellular Ca^{2+} concentrations then set in motion a biochemical cascade, eventually producing three sorts of changes in the synapse.In the short term, the cascade is thought to increase in the number or sensitivity of AMPA receptors (for alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, a pharmacological agonist). AMPA receptors are also glutamate receptors, but they selectively regulate the flow of sodium (Na^{+}) and potassium (K^{+}) ions, thereby directly influencing the voltage across the post-synaptic cell's membrane. These local changes in the number of receptors in the dendrite are thought to account for the rapid induction of LTP. In the long term, the Ca^{2+}-stimulated biochemical cascade (triggered by the opening NMDA receptors) leads to the production of proteins in the postsynaptic cell body. These proteins have been connected with a number of changes in the post-synaptic cell, including changes in the shape or number of dendritic spines (receptor-

[16] See Machamer, Darden and Craver, 2000; Craver and Darden, 2001.

rich buds on dendrites), the activation of dormant AMPA receptors, and changes in the conductance through AMPA receptor channels. Some suspect that there is also a presynaptic component of the LTP mechanism, mediated by nitric oxide (NO) released from the post-synaptic cell and traversing backwards across the synapse, whereby, for example, the presynaptic cell increases its probability of releasing neurotransmitters with each new action potential.

LTP is now commonly believed to be a component in the mechanisms of spatial memory – roughly, the ability to learn and remember how to navigate novel environments. The link between LTP and spatial memory is now commonly described as mutlilevel.[17] Although the term "level" is used somewhat carelessly, the levels in this description can be understood as levels of mechanisms: that is, the items at lower levels are parts of the items at higher levels and the lower level parts are organized together (spatially, temporally and interactively) to produce the higher level activities or behaviors.[18] As currently understood, there are roughly four levels in the LTP-spatial memory hierarchy.

At the top of this hierarchy is an organism engaging in some spatial memory task, such as foraging for food or, as is more common in the laboratory, searching for a hidden platform beneath the surface of an opaque liquid in a circular pool (the "Morris water maze," which normal mice are quite good at solving). Because researchers only recently began to associate LTP with memory, as opposed to learning, I will use the disjunction "learning or memory" to refer to this component of the theory surrounding LTP. One level down are the components of the spatial memory mechanism, including the formation of "spatial maps" in the hippocampus. Specific cells in the hippocampus (known as "place cells") fire preferentially when an organism enters a given location in the maze in a particular orientation.[19] The resulting map, if measured with multiple electrodes at once, can be used to predict the path of the organism through its environment.[20] The third level down includes LTP and other mechanisms of spatial map formation in the hippocampus. And finally, bottoming out the hierarchy, are the molecular mechanisms of LTP described above.

Although the evidence supporting this multilevel picture is disputed, numerous experiments have been designed to test the postulated links among these different levels. Perhaps the most impressive evidence, if not the most compelling, has come recently from experiments intervening to delete or

[17] Stevens, 1996.
[18] See Wimsatt, 1976; Craver, 2001; Craver, in press.
[19] O'Keefe and Dostrovsky, 1971.
[20] Wilson and McNaughton, 1993.

alter the NMDA receptor. In mice, delayed knockouts of the genes for the NMDA receptor (after normal development is complete) have been reported to eliminate LTP, distort spatial maps and leave mice swimming randomly through the Morris water maze.[21] Similarly, altering the proportion of NMDA receptor sub-types in hippocampal place cells has been shown, under certain circumstances, to enhance spatial memory in mice.[22]

The Protracted Origins of the LTP Research Program

Kandel and Squire offer an account of LTP's history so representative of common wisdom that it will serve nicely as a foil for the account to be developed below:

> In 1973 Tim Bliss and Terje Lømo working in Per Andersen's laboratory in Oslo, Norway, made a remarkable discovery. Aware of Brenda Milner's insight about the role of the hippocampus and the medial temporal lobe in memory storage, they attempted to see whether the synapses between neurons in the hippocampus had the capability of storing information. To examine this possibility, they purposely carried out a quite artificial experiment. They stimulated a specific nerve pathway in the hippocampus of the rat and asked: Can neural activity affect synaptic strength in the hippocampus? They found that a brief high-frequency period of electrical activity (called a tetanus) applied artificially to a hippocampal pathway produced an increase in synaptic strength that lasted for hours in an anaesthetized animal and would, if repeated, last for days and even weeks in an alert freely moving animal. This type of facilitation is now called long-term facilitation, or more commonly, *long-term potentiation*.[23]

This passage introduces some of the central figures in our story, including Per Andersen (in whose Oslo laboratory much of the story is set), Terje Lømo (Andersen's first graduate student), Tim Bliss (Andersen's post-doc) and Brenda Milner (who performed the first psychological evaluations of H.M.). Yet this passage is a scientific argument rhetorically packaged as history; it is more compelling than accurate. For example, Bliss and Lømo used rabbits as experimental organisms (not rats), and the rabbits *were* anaesthetized (Bliss and Gardner-Medwin[24] did the experiments in unanaesthetized rats). It should

[21] McHugh et al., 1996.
[22] Tang et al., 1999.
[23] Squire and Kandel, 2000, pp. 110–111.
[24] Bliss and Gardner-Medwin, 1973.

also be noted that Terje Lømo published abstract-length reports of the same phenomenon in 1966, before having met Tim Bliss, and again in 1971. Most importantly, however, this rational reconstruction (as Lakatos[25] would call it) leaves out most of the interesting experimental and explanatory refinements that are crucial for understanding the origin and development of the LTP research program.

While there is much to recommend 1973 year as a defining moment in the LTP research program (as I discuss in the final section), neurophysiologists produced and reported tetanus-induced hippocampal synaptic plasticity over a decade before Lømo's first abstract. In the 1950's and 1960's the ability to produce tetanus-induced changes in hippocampal synapses was familiar as a laboratory tool. Prior to the development of hippocampal slice preparations in the early 1970's[26] hippocampal neurophysiologists experimented *in vivo*. The anesthesia, the blood loss and the repeated electrical intervention weakened the cell's electrical responses, and experimenters had strong incentives to collect as much data as they could before the experimental preparation failed. Perhaps out of frustration, they learned that they could "give new life" to the electrical signals by "turning the stimulus rate knob to a higher frequency for a few seconds."[27] Tetanus-induced hippocampal synaptic plasticity had thus been "observed" in the sense that it was recognized as a regular and repeatable phenomenon that could be used to extend the life of an experimental preparation. It was not yet in view as an activity of synapses.

Scattered reports of hippocampal synaptic plasticity can be found as early as 1956. John Green and Ross Adey report that year that: "A short high frequency burst of stimuli would potentiate responses evoked at 1/sec. for a few seconds up to a few minutes depending on the duration of the burst."[28] Per Andersen, in his dissertation, reports a tetanus-induced increase in amplitude and reduction in latency for the population potential lasting up to 6 minutes in both commissural-to-CA1[29] and commissural-to-CA3 synapses.[30] Soon after, Andersen (collaborating with his adviser, Birger Kaada, and Helge Bruland[31]) reported "post-tetanic potentiation" of septo-hippocampal connections lasting 5–10 minutes. Finally, Pierre Gloor et al., mention post-tetanic potentiation of perforant path synapses in the dentate gyrus lasting for a "fairly long period."[32] Each of these papers mentions

[25] Lakatos, 1971.
[26] Skrede and Westgard, 1971; Schwartzkroin and Wester, 1975.
[27] Andersen, 1991, p. xiv.
[28] Green and Adey, 1956, p. 250.
[29] Andersen, 1960a, p. 191.
[30] Andersen, 1960b, p. 216.
[31] Andersen, Bruland and Kaada, 1961.
[32] Gloor, Vera and Sperti, 1964, pp. 358–361.

potentiation of non-negligible duration in hippocampal synapses following tetanic stimulation. Yet these authors treat the phenomenon merely as an experimental curiosity, worthy of mention but not detailed exploration or discussion.

The "long-lasting potentiation" reported by Bliss and Lømo in 1973 is arguably different from the phenomenon (or phenomena) in these early reports. The primary difference is duration. None of the above authors describe a potentiation lasting longer than a few minutes, and there is no indication that the authors tried to extend it further. Many of these authors categorize the observed synaptic plasticity either as post-tetanic potentiation (PTP), a short-lasting form of plasticity first reported by Lloyd,[33] or as frequency potentiation (FP), enhancement of a synapse taking hold during the tetanic stimulation. But one should not place too much emphasis on theoretical vocabulary in trying to track the conceptual developments in this early period. LTP predates its name, the name predates the acronym, and there was neither a standardized language for describing the phenomenon nor a canonical account of how it should be characterized until much later. Bliss and Lynch trace the language of LTP as follows:

> Although the expression long term potentiation, introduced by Douglas and Goddard (1975), is generally used to describe the subject of this chapter, there are a number of other terms with a minority following: the compelling merits of enhancement, and its more recent variants, long-term enhancement, and long-term synaptic enhancement, are clear to McNaughton (1983). Long-lasting potentiation was favoured, after long debate, by Bliss and Lømo (1973) but these authors, in their search for grammatical purity, failed to anticipate the inevitable adoption of an acronym, and, too late, found themselves unable to pronounce LLP without sounding as if they required urgent assistance. Similarly, E, though stylish, is perhaps on the short side, LTE demands unprecedented powers of articulation, and LTSE has yet failed to find a public champion. Compared to rivals such as these, LTP positively trips off the tongue, and for this sound reason has, as we say, been generally if not universally adopted.[34]

In fact Bliss and Lømo do occasionally use the term, "long-term potentiation,"[35] even if they favor, "long-lasting potentiation." Douglas and Goddard[36] use "Long-Term Potentiation" in their title but favor "post-tetanic

[33] Lloyd, 1949.
[34] Bliss and Lynch, 1988, p. 3.
[35] Bliss and Lømo, 1973, pp. 331 and 350.
[36] Doublas and Goddard, 1975.

potentiation" in the body of the text. The earliest use of the acronym, "LTP," is by Dunwiddie, Madison, and Lynch[37] who, along with other members of the Psychobiology Department at the University of California, Irvine, made a most conspicuous effort through the late 1970's to standardize the research program's vocabulary. FP, PTP, and LTP were not clearly distinguished from one another *in common parlance* until well into the 1970's. As late as 1975, for example, Douglas and Goddard,[38] who certainly should have known better if anyone should have, repeatedly describe Bliss and Lømo[39] as having demonstrated "post-tetanic potentiation" (i.e., PTP) in the hippocampus. Similar confusion surrounds the precise definition of LTP, which has been under revision since the 1970's and, indeed, remains the subject of debate at present.[40] So deciding when it was LTP that researchers observed and reported requires the *post hoc* application of conceptual categories and descriptive vocabularies that were quite fluid in this early period.

But our topic is not the discovery of LTP, and so there is no need to tidy up these ambiguities. Our project is to track how the integration of perspectives from different fields transformed these early reports of an experimental tool or curiosity into a robust and explanatorily relevant phenomenon. In order to understand this historical trajectory, we need to ask why researchers were investigating the hippocampus and how hippocampal synaptic plasticity (and later, unambiguously, LTP) came to be linked to learning or memory. The answers to these questions are surprisingly distinct.

Hippocampal Connections

Why were these researchers so interested in the hippocampus? An obvious suggestion, explicit in the foil history above, is that researchers were interested in the hippocampus because of its potential role in memory. On this account, the conceptual association between hippocampal synaptic plasticity and memory was automatic; synaptic plasticity was discovered in the search for a memory mechanism. This explanation, while plausible, hides a complex set of stages through which researchers formulated the conceptual association between hippocampal synaptic plasticity and learning or memory (discussed in the next section). In fact, the hippocampus was not generally associated with learning or memory until the late 1970's. None of the early reports of hippocampal synaptic plasticity refer to a memory role for the hippocampus.

[37] Dunwiddie, Madison and Lynch, 1978.
[38] Douglas and Goddard, 1975.
[39] Bliss and Lømo, 1973.
[40] See, e.g., Sanes and Lichtman, 1999; Shors and Matzel, 1997.

And finally, there are better explanations for neurophysiological interest in the hippocampus. Or so I will argue.

It is prima facie quite plausible that these electrophysiologists were drawn to the hippocampus because of its link with learning or memory. Precedent for this association can be found in the 19th Century anatomical work of Gottfried Treviranus,[41] in the primate lesion experiments of Brown and Schäfer,[42] and in the work of Bechterew[43] at the turn of the 20th Century. Many also point to Klüver and Bucy's[44] report of "psychic blindness" following temporal lobe lesions as precedent for a learning or memory link.[45] Directly prior to the first reports of tetanus-induced plasticity in the hippocampus, Penfield[46] reported that he could induce vivid apparent memories in brain surgery patients by stimulating their temporal lobes. And finally, it was 1957 when Scoville and Milner, following up on Penfield's preliminary studies of unilateral hippocampal lesions, published the results of several bilateral hippocampal lesions, including the case-study of H.M..

However, the link between the hippocampus and learning or memory in these pioneering anatomical studies is more vivid in retrospect than it must have been at the time. Treviranus' (1816–1821) suggestion is highly speculative, claiming only that the organ must be involved in some "higher" mental function, "perhaps memory."[47] Brown and Schäfer's experiments involved extirpation of the bulk of the temporal lobe, and although they do report that "the movements are slow, the senses dulled, the memory very defective, and the disposition changed," they attribute these changes to "vascular disturbances" that must have affected "other portions of the brain."[48] Klüver and Bucy similarly removed the entire temporal lobe, and memory deficits are not included in their account of what is now called Klüver – Bucy syndrome. Penfield's stimulation studies were similarly spread out over the entire temporal cortex. (See Figure 2 in which the stippled region represents what he calls "memory cortex;" note that the region labeled "hippocampus" is not stippled.) Finally, Scoville and Milner recognized that the localization of H.M.'s deficit was complicated by the nonspecificity of the lesion. The surgery removed only the anterior portion of the hippocampus, and, in addition, much of the hippocampal gyrus and the amygdala. It was not

41 Treviranus, 1816–1821.
42 Brown and Schäfer, 1888.
43 Bechterev, 1900.
44 Klüver and Bucy, 1939.
45 For a detailed discussion of 19th and 20th Century precedents, see Finger, 1994.
46 Penfield, 1952.
47 In Meyer, 1971.
48 Brown and Schäfer, 1888, p. 327.

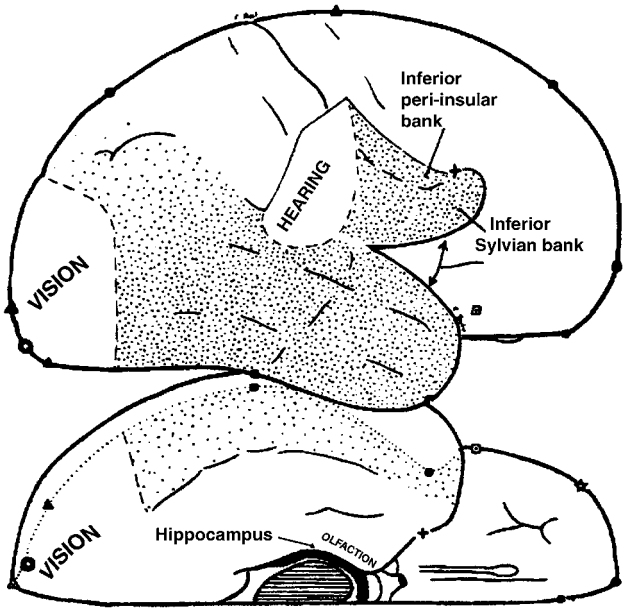

Figure 2. Wilder Penfield's "memory cortex." Stippled areas represent locations which when stimulated evoked reports of apparent memories. Drawn from Penfield (1952).

until much later, arguably until Mishkin's hippocampal lesions in monkeys,[49] that the memory hypothesis was on reasonably solid epistemic footing.[50] The memory hypothesis is more visible in retrospect (i.e., to those trained with this link in mind) than it was to mid 20th Century anatomists and physiologists.

The hippocampus was not generally linked to learning or memory in the 1950's. Six years before the first mention of hippocampal synaptic plasticity, Karl Lashley published the highly influential conclusion of his failed search for the engram (or memory trace): "This series of experiments has yielded a good bit of information about what and where the memory trace is not. It has discovered nothing directly of the real nature of the engram. I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning just is not possible. It is difficult to conceive of a mechanism that can satisfy the conditions set for it. Nevertheless, in spite of such evidence against it, learning sometimes does occur."[51] Researchers associated the hippocampus with other functions.

[49] Mishkin, 1978.

[50] See Milner, 1996; Squire, 1996.

[51] Lashley, 1950 reprinted in Cummins and Cummins, 2001, p. 347.

Broca,[52] Ferrier,[53] and Hughlings Jackson[54] suggested olfaction. Alf Brodal correctly declared in 1941 that nearly every textbook at the time introduced the hippocampus as an olfactory region.[55] Papez[56] and MacLean,[57] following Klüver and Bucy,[58] linked the hippocampus with emotions and autonomic regulation. Hippocampal stimulation was correlated with sleep and respiration,[59] staring and "apparent bewilderment,"[60] sexual behavior,[61] and salivation, chewing behavior, and fear.[62] This may explain why those who first reported synaptic plasticity in the hippocampus failed to cite any reports linking the temporal lobes to learning or memory. It may also explain why they refused to speculate as to the "true role"[63] of the hippocampus, and why they claimed that, "many more physiological and behavioral studies will be needed before any systematic correlation with the anatomical structure can be attempted."[64] As of 1951, Birger Kaada, Andersen's adviser, could correctly claim that "The functional role of the hippocampus is still completely obscure."[65]

If researchers weren't exploring the hippocampus because of its role in learning or memory, then why were they? There are several possible explanations. Both neurologists and neurophysiologists (often overlapping categories) explored the hippocampus because of its etiological link to epilepsy. Clinicians sought to control epilepsy (this motivation at least partly explains both Penfield's stimulation studies and H.M.'s surgery). Neurophysiologists viewed epilepsy as an experimental model for studying normal and pathological electrical activity in a well-defined neural network. The analogy between "kindling" (the facilitation of seizure discharge after repeated daily electrical stimulation) and the mechanisms thought to underlie tetanus-induced plasticity was a central motivation for continuing to explore the phenomenon.[66]

52 Broca, 1878.
53 Ferrier, 1886.
54 Hughlings Jackson, 1889.
55 Brodal, 1947, p. 180; see Wood and Craver, forthcoming.
56 Papez, 1937.
57 MacLean, 1954.
58 Klüver and Bucy, 1958.
59 Kaada and Jasper, 1952.
60 Andy and Ackert, 1955.
61 Kim, 1960.
62 Green and Adey, 1956.
63 Green and Adey, 1956.
64 Cragg and Hamlyn, 1957.
65 Kaada, 1951, p. 15.
66 See, e.g., Goddard, MacIntyre and Leech, 1969; Douglas and Goddard, 1975.

Others saw the hippocampus as a convenient and useful experimental model in which to combine anatomical and neurophysiological perspectives. By the 1950's, such reputed anatomists as Ramon y Cajal[67] and Lorente de Nó[68] had used Golgi's silver impregnation method to characterize the cytological structure of the hippocampus and had detailed its extrinsic connections with other brain regions.[69] Compared to other brain regions, the rodent hippocampus is large and readily accessible to electrodes inserted through the skull, making it attractive for *in vivo* neurophysiological research. Researchers in the 1950's and 1960's, much more than now, were inclined to describe the hippocampus as a relatively simple, primitive and stereotyped cortical structure that might provide clues as to the working of more complex cortical areas. For example, Andersen refers to the primitive structure of the hippocampus in justifying the inference from the physiological organization of the hippocampus to forms of organization in "more complex parts of the cerebral cortex."[70] The simplicity of the cytoarchitectural organization of the hippocampus allowed researchers to study monosynaptic connections, and its layered organization made it useful for inferring the behavior of single neurons and synapses from the behavior of populations of neurons.[71]

Oslo was especially well staffed in the 1960's for integrating anatomical and neurophysiological perspectives on the hippocampus.[72] Andersen's interest in the hippocampus (and so Lømo's as well) is at least partly explained by the influence of two senior colleagues in Oslo: Theodore Blackstad and Alf Brodal. Blackstad used Nauta's[73] terminal degeneration techniques to characterize the neurons of the hippocampus and their synaptic connections.[74] This work, in Andersen's words, "revealed a suitable substrate for a neurophysiological study."[75] Alf Brodal, to whom Andersen acknowledges an extensive intellectual debt, was a vocal advocate of understanding the brain by first understanding its wiring diagrams. As Brodal retrospectively explained:

> [My career] has chiefly been devoted to attempts to disentangle, experimentally, selected parts of the vast and complicated network of fiber

67 Ramon y Cajal, 1911.
68 Lorente de Nó, 1934.
69 See Meyer, 1971.
70 Andersen, 1960b, p. 179.
71 This inference is defended by Andersen et al., 1971a.
72 See also Cragg and Hamlyn, 1957, pp. 482–483.
73 Nauta and Gygax, 1954.
74 See e.g., Blackstad, 1956, 1958.
75 Andersen, 1960a, p. 179.

> connections in the brain, to determine what one may call its 'wiring patterns.' The complex and yet extremely orderly arrangement of this pattern is indeed fantastic and has never ceased to amaze me. After more than thirty years of occupation with this subject, I am more convinced than ever that the knowledge of the structure of the brain in its minutest details is a prerequisite for meaningful interpretations of observations in all other fields of the neurosciences.[76]

Andersen's neurophysiological approach was intended to complement the anatomical emphasis on structure (revealing locations, connections, distances, and cell morphology) with an investigation of the neurophysiological activities by which these wiring diagrams work. Lømo, representing a third generation of Oslo hippocampal researchers, gives full voice to this perspective on the utility of the hippocampus as a model:

> The dentate area of the hippocampal formation is a structurally primitive part of the cortex. The cell bodies of its main cellular components, the granule cells, are densely packed in one thin layer. The dendrites ascend to the cortical surface through the molecular layer which is practically devoid of nerve cell bodies. The molecular layer contains, in addition to the granule cell dendrites, afferent pathways to the granule cells, each terminating at a different level. A main afferent input is the perforant path. Arising in the entorhinal cortex, it activates the granule cells by way of synapses *en passage* restricted to the middle third of the dendritic tree (Nafstad, 1967). This is a mode of termination characteristic of many cortical afferents. After removal of the overlying neocortex, there is easy access in the rabbit to the perforant path as well as to its region of termination in the dentate area. For these reasons, the dentate area was chosen as a suitable region in which to study cortical synaptic mechanisms and organization.[77]

Concerns about experimental accessibility, simplicity and analogical extension to other, more complex, brain regions motivated Oslo neurophysiologists to explore the hippocampus. To summarize: The learning or memory centered explanation for neurophysiological interest in the hippocampus must be supplemented (if not replaced) by explanations in terms of its clinical relevance to epilepsy, its experimental accessibility to neurophysiological manipulation and its utility as an experimental system for combining anatomical and electrophysiological techniques in a simplified and well-

[76] Brodal, 1992, p. 123.
[77] Lømo, 1971, p. 19.

characterized cortical circuit. The LTP research program grew out of the integration of different fields (anatomy, neurology and neurophysiology) and experimental perspectives (e.g., silver impregnation, terminal degeneration, recording of hippocampal field potentials) in a convenient and tractable experimental system (the rodent hippocampus). The integration of these fields and perspectives using the hippocampus as an experimental model did not center upon identifying or associating the terms or concepts from their respective theoretical vocabularies but rather involved the use of different techniques to reveal different aspects of the neural organization in the hippocampus, often for different explanatory and instrumental ends.

The linkage of hippocampal synaptic plasticity with learning or memory requires a separate explanation. Reductive models of explanation and scientific change do accurately characterize one time-slice of this development. But they fail to reveal most of what is interesting in the historical episode.

Linking Synaptic Plasticity and Learning or Memory

The link between synaptic plasticity and learning or memory developed through the integration of more speculative theoretical neuroscience and mathematical biophysics with the emerging understanding of the electrophysiological properties of neurons and synapses. John Eccles was a central figure in this integration, but his efforts were frustrated by the absence of evidence for the existence of synaptic changes that could plausibly fill the speculative role mapped out for them. Andersen's post-doctoral Rockefeller fellowship with Eccles is a plausible point of contact between Eccles' integrative project and Oslo's anatomical and physiological research on the hippocampus. Shortly after returning to Oslo, Andersen began collaborating with Lømo (his first graduate student), and promptly published the first paper linking specifically hippocampal plasticity (reported merely as a curiosity in Andersen's thesis) and learning. In tracing these connections, the role of interfield integration in shaping the LTP research program is again apparent. As this integration proceeded, the very nature of the link between synaptic plasticity and learning had to be revised. At times, learning was to be understood by *reducing it* to changes in the efficacy of synapses. At others, synaptic plasticity was seen as *an example of* or as *analogous to* learning. Only later (circa 1973) did plasticity come clearly into view as a component in a multilevel memory mechanism (see the final section).

The idea that learning or memory might be explained by changes in neural connections is roughly as old as the idea that the brain is composed

of neurons. Finger discusses this speculative theoretical tradition at length.[78] Several types of synaptic changes were put forward as hypothetical explanations of learning or memory. One popular hypothesis appealed to "neural amaeboidism" or "neurobiotaxis," variously understood as the growth of new synapses, swelling or retraction of axons and dendrites, and the growth and retraction of glial cells in synapses. Forms of neural amaeboidism were endorsed by Hermann Rabl-Rückhard, Eugenio Tanzi, Raphaël Lépine and Mathias Duval. Sigmund Freud in his so-called "Project for a Scientific Psychology,"[79] speculated that memories could be formed by the "facilitation" of "cathexis" across "contact barriers" between neurons. By the early 20th century, advocates of synaptic hypotheses included Ramon y Cajal,[80] who endorsed a glial hypothesis, and Ariens Kappers.[81] Charles Sherrington,[82] who coined the term "synapse," endorsed a synaptic learning hypothesis, and Jerzy Konorski[83] coined the term "synaptic plasticity" in the mid 20th Century to describe his account of language learning.

Still, in the 1950's learning or memory was largely regarded as a black box and as inexplicable in terms of a simple synaptic mechanism. Lashley declared the results of his search for the engram, "incompatible with theories of learning by changes in synaptic structure," noting that, "integration cannot be expressed in terms of connections between specific neurons."[84] J.Z. Young claimed in his 1951 Croonian Lecture that "The most obvious failure of current neurophysiological theory is in providing an account of the changing potentialities or plasticity of the nervous system."[85] Kandel and Spencer, in a 1968 review that forcefully defended "cellular connection hypotheses," complained that: "We have only begun to formulate with any degree of precision the fundamental questions regarding the neural mechanisms of learning."[86] Leiman and Christian's list of "proposed memory mechanisms" (shown in Table 1) surveys the field as of 1973.

They characterize their list as "composed of tantalizing hunches which occasionally verge on plausible models."[87] It is perhaps a testimony to the state of the science at this time that Hydèn's hypothesis that memories were encoded in RNA, and corresponding work on cannibalistic learning in

[78] Finger, 1994.
[79] Freud, [1895] 1954.
[80] Ramon y Cajal, 1911.
[81] Kappers, 1917.
[82] Sherrington, 1906.
[83] Konorski, 1948.
[84] Lashley, 1950, p. 176.
[85] In Eccles, 1953, p. 193.
[86] Kandel and Spencer, 1968, p. 69.
[87] Leiman and Christian, 1973, p. 126.

Table 1. Lieman and Christian's list of proposed memory mechanisms

Samples of Proposed Memory Mechanisms			
Structure modifications	Reference	Process modifications	Reference
Birth of neurons	Altman, 1966	Facilitation of synapses with successful use	Hebb, 1949
Directed growth of nerve processes and creation of synapses	Ariens Kappers, 1917	Frequency tuned nerve membranes	Landauer, 1964
Axon terminals swell during activity	Eccles, 1953	Long-term posttetanic potentiation	Eccles, 1953
Spine apparatus storage	Hamlyn, 1962	Perineuronal pattern recognition	Adey, 1969
Glial storage	Galambos, 1961	Facilitation of synapses with disuse	Sharpless, 1964
Destruction of synapses	Ranck, 1964	Turning off synapses	Young, 1966
Death of neurons	Dawkins, 1971	Coherence of population activity	John, 1967
		Heterosynaptic activity	Burke, 1966
		Tuning motor system to sensory frequencies	Loeb, 1902
		Neural holograms	Pribram, 1966
		Residual excitation in neurons	Ebbecke, 1919

planaria, could gain wide assent in the learning or memory field (and the popular press) despite the poor quality of the science.[88] One cannot simply assume that researchers in the 1950's viewed synaptic plasticity as the only, or even the most plausible, hypothetical explanation of memory.

Among mathematical biophysicists, however, synaptic accounts of learning fit well within a reductive framework for explanation in neuroscience. Within such a framework, explaining a psychological phenomenon involved establishing (or assuming) the *identity* of psychological and neurophysiological phenomena and showing that descriptions of the relationships among psychological states could be mapped (perhaps via deduction) onto descriptions of the relationships among neurons.[89] Although advocates of reductionism in the philosophy of science typically concede that their models

[88] Olby, unpublished.

[89] See Nagel, 1961. Schaffner, 1969 and 1993a revised and extended Nagel's model. His approach has been adopted by Churchland, 1986.

are mere regulative ideals and so poor descriptions of scientific practice,[90] many mid 20th Century brain scientists were in fact articulating their explanations in a form very much like the classical model of reduction. Consider how McCulloch and Pitts describe "A Logical Calculus of the Ideas Immanent in Nervous Activity:"

> The "all-or-none" law of nervous activity is sufficient to insure that the activity of any neuron may be represented as a proposition. Physiological relations existing among nervous activities correspond, of course, to relations among the propositions; and the utility of the representation depends upon the identity of these relations to relations among the propositions. To each reaction of any neuron there is a corresponding assertion of a simple proposition. This, in turn, implies either some other simple proposition or the disjunction or the conjunction, with or without negation, of similar propositions according to the configuration of the synapses upon and the threshold of the neuron in question. [91]

In this explanatory schema, propositions are identified with "all or nothing" action potentials, and the inter-relationships among action potentials in a network are identified with complex propositions (e.g., conjunctions, disjunctions, and negations) and with inferences among propositions (e.g., from the activation of two propositions separately to the activation of their conjunction). The identities are explicit, and the connection between the psychological (propositional) and the neural is direct; there are no levels of organization intermediate between them.

Oppenheim and Putnam, in their reductionist manifesto, "Unity of Science as a Working Hypothesis," cite McCulloch and Pitts (and other mathematical biophysicists) as showing that phenomena at the "level" of the whole organism (psychology) could be reduced (in the technical sense sketched above) to phenomena at the "level" of cells: "In terms of such nerve nets it is possible to give hypothetical micro-reductions for *memory, exact thinking, distinguishing similarity or dissimilarity of stimulus patterns, abstracting* of 'essential' components of a stimulus pattern, recognition of shape regardless of form and of chord regardless of pitch, . . . *purposeful behavior* as controlled by negative feedback, *adaptive behavior*, and *mental disorders*."[92] Although McCulloch and Pitts are not directly concerned with learning or memory, their reductive explanatory schema was adopted by many learning or memory researchers. Synaptic learning hypotheses can be found, for example, in

[90] See e.g., Schaffner, 1974; Churchland, 1986.

[91] McCulloch and Pitts, 1943 reprinted in Cummins and Cummins, 2000, p. 352.

[92] Oppenheim and Putnam, 1953, p. 20; italics in original.

the networks of Brindley,[93] Gardner-Medwin,[94] Hebb,[95] Marr,[96] and Rosenblatt.[97] Variants on this theme were also proposed by Hilgard and Marquis[98] and Rashevsky,[99] who posited self-reexciting loops of excitation in chains of neurons, and Shimbel,[100] who identified reduced thresholds in post-synaptic cells with learning. These learning hypotheses are often represented diagrammatically as networks of synapses, each labeled with a different component of learning. Figure 3, taken from Gardner-Medwin's discussion of synaptic changes in learning, explicitly represents neural activity as the conditioned stimulus (CS), the unconditioned stimulus (UCS) and the response (R).[101] Despite differences in the details of these models, the overall explanatory project reflects the reductive program that McCulloch and Pitts so clearly express.

The mathematical biophysicists provided mathematical demonstrations that synaptic activities (and related changes) *could possibly* account for features of learning or memory. Yet it remained to be shown that the nervous system *could actually* change in the way required by these abstract and purely hypothetical demonstrations. The integration of this abstract theoretical speculation with detailed physiological work on the electrical properties of neurons was enthusiastically promoted by John C. Eccles. Eccles reports that he came "under the spell of the synapse"[102] as an 18- year-old medical student in Melbourne, an interest that was no doubt fostered during his Rhodes Scholarship with Charles Sherrington (from 1928–1930).[103] In his *Neurophysiological Basis of Mind*,[104] Eccles introduces the electrical and chemical properties of neurons, including the ionic components of the resting and active neural membrane potential, of excitation and inhibition, and of transmission across synapses. His integration of electrical and chemical findings concerning neurons culminates in the suggestion that "plasticity" in synapses might help to understand "learning, conditioning, and memory."[105] His reductive convictions are most fully expressed in his *Physiology of the*

93 Brindley, 1969.
94 Gardner-Medwin, 1969.
95 Hebb, 1949.
96 Marr, 1970.
97 Rosenblatt, 1962.
98 Hilgard and Marquis, 1940.
99 Rashevsky, 1938.
100 Shimbel, 1950.
101 Gardner-Medwin, 1969.
102 Eccles, 1992, p. 159.
103 Sherrington, 1906.
104 Eccles, 1953.
105 Eccles, 1953, p. 193.

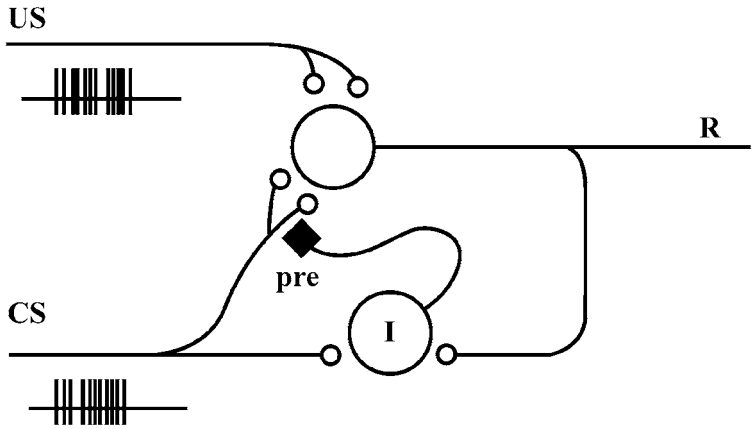

Figure 3. A reductive model of classical conditioning. Accompanying text reads: "A network showing the basic property of classical conditioning when it receives inputs of bursts of spikes. Two or more excitatory synapses (hollow circles) impinging on a cell must be active nearly simultaneously for the cell to fire. Thus cell I fires only if both R and CS are firing. The black square represents a (presynaptically) fatigable axo-axonic inhibitory synapse which after activation by a single spike prevents the adjacent excitatory synapse being effective for a period comparable with the length of an input burst. The inhibitory synapse fatigues if its axon from cell I fires several bursts. A burst of spikes at CS produces only one spike at R unless bursts at CS have previously been paired with bursts at US so as to fatigue the modifiable synapse." Redrawn from Gardner-Medwin, 1969.

Synapse,[106] the final chapter of which undertakes to redefine "descriptive" elements of Pavlov's psychology (e.g., classical conditioning) not in terms of Pavlov's physiological theory (couched in the vocabulary of irradiating waves from different brain centers) but rather in a language more appropriate to the neurophysiological properties of neurons (articulated in a vocabulary of synapses, excitation, and inhibition). The chapter is composed almost entirely of a fascinating translation table between the terms in these corresponding vocabularies. Although Eccles refers to his physiological explanations as "mechanisms" the overall character of the project is classically reductive, mapping the descriptive terms from one vocabulary into those of another. (In fact, Eccles' table exhibits both an instance of elimination, with neurophysiology replacing Pavlovian physiology, and an instance of smooth reduction, with neurophysiological terms being identified with descriptive psychological terms.)

Yet the reductive associations between synaptic changes and learning could only be sustained if synaptic changes have the properties appropriate to such an explanatory role. In 1953, Eccles reviewed a number of known

[106] Eccles, 1964.

changes in mono- and poly-synaptic reflexes and in peripheral neuromuscular junctions. None of these was entirely satisfactory as a plausible explanation for even simple forms of learning. For example, Eccles discusses PTP (post-tetanic potentiation), a form of plasticity in the spinal cord first reported by Lloyd,[107] as a possible explanation. However, Eccles and Lloyd's PTP was unattractive because it required physiologically implausible stimulus conditions to produce fairly short-lasting potentiation. As of 1965, for example, an "ultra-late" form of PTP lasting "an hour or longer" could be produced by stimulating a cell up to 500 times per second for half an hour or longer.[108] These stimulus rates are well beyond those normally observed in the CNS, the duration of the effect is hardly impressive in comparison to the duration of memories or learned responses, and the location in the spinal cord certainly makes any direct link with complex forms of learning implausible (even if the link with simple kinds learning might apply). As a result, PTP seemed implausible, even to its discoverers, as a neural explanation for learning or memory.

In the effort to integrate the perspectives of the neurophysiologist with those of the biophysicist, researchers had to rethink the nature of the link between synaptic plasticity and learning or memory. Researchers came to view plasticity as a simple example of learning or memory (i.e., as itself a kind of learning or memory) or as an analogue of learning or memory (i.e., something that could act as an experimental model for the study of learning or memory). Eccles himself occasionally spoke this way; he claimed that "... disused synapses are capable of 'learning' to operate more effectively as a result of intensive presynaptic stimulation."[109] Andersen and Lømo, in their report of a novel form of plasticity in the hippocampus to be discussed below, describe their phenomenon as "an indication of a simple learning process in a cortical synaptic system"[110] and "an example of primitive synaptic learning."[111] Roughly contemporaneously, Graham Goddard argued that kindling is "analogous to learning" in that it is a "relatively permanent change in behavior that depends upon repeated experience."[112] Although researchers in this period are not entirely consistent in their description of the link between plasticity and learning, there is clearly a trend in the 1960's to characterize synaptic plasticity as a kind of, an analog of, or as a

[107] Lloyd, 1949.

[108] Spencer and Wigdor, 1965, p. 278.

[109] Eccles, 1953, p. 209.

[110] Andersen and Lømo, 1967, p. 410.

[111] Andersen and Lømo, 1967, p. 406.

[112] Goddard, 1967, p. 102. Curiously, Goddard explicitly notes that kindling could not readily be produced in the hippocampus or the entorhinal cortex. The analogical link with learning is reasserted by Goddard, McIntyre and Leech, 1969, p. 328.

model of learning rather than as a reductive explanation. This more relaxed formulation of the link could be sustained even in the absence of evidence for physiologically plausible and relevant forms of synaptic plasticity.

Despite its implausibility as an explanation of complex forms of learning or memory, Eccles hoped to extend his research on PTP from the spinal cord into the brain. He wrote: "If it can be established that, in this simplest synaptic system, excess activation gives a prolonged increase in synaptic efficacy, experimental investigation could be extended to the more complex polysynaptic pathways, and, finally to pathways in higher levels of the nervous system."[113] This goal could not have been lost on Andersen during his Rockefeller Fellowship with Eccles in Canberra. In the second year of that fellowship, Eccles shared the 1963 Nobel Prize with Hodgkin and Huxley for work on electrical mechanisms in neurons and synapses. Although Andersen's post-dissertation work in Canberra was dedicated to working out inhibitory connections in the wiring diagram of the hippocampus,[114] it was soon after Andersen's return to Oslo that he again began exploring the curious plasticity of hippocampal synapses reported in his dissertation. This time, he had Lømo to help.

After completing medical school in Oslo and an internship at Pisa's Institute for Physiology, Lømo returned to Norway in 1964 to work with Andersen. With Andersen on the neurophysiological setup and Lømo working the electrodes in the experimental system, the two produced several papers on hippocampal neurophysiology. One of these, a little noticed paper delivered in Hakone, Japan in September of 1965, reports a long-lasting form of hippocampal synaptic plasticity and contains the first clear link between specifically hippocampal synaptic plasticity and learning.[115] Although they admit that the duration of the phenomenon, like PTP, is "too short to account for the plastic changes in a neural circuit that might take place in learning processes of a higher kind,"[116] they suggest, as noted above, that it might be an "example of primitive synaptic learning."[117] At no point do Andersen and Lømo discuss a potential role of the hippocampus in memory; instead, the link relies on an analogy between synaptic changes (long-lasting effects of repetitive stimulation) and learning.

The goal of forging an explanatory link between plasticity and learning or memory still resonated in the background of neurophysiological research in the 1960's. This goal received highly visible support from Eric Kandel

113 Eccles, 1964, p. 257.
114 Andersen, Eccles and Løying, 1963, 1964a, 1964b.
115 Published as Andersen and Lømo, 1967.
116 Andersen and Lømo, 1967, p. 410.
117 Andersen and Lømo, 1967, p. 411.

and Alden Spencer's[118] influential argument for what they call "cellular-connection hypotheses." They frame the argument by dividing the history of neurophysiological approaches to learning into two camps: those advocating cellular-connection hypotheses, and those advocating a gestalt-based (and Lashley-influenced) "aggregate-field" hypothesis. The latter, "emphasizes the global aspects of neuronal activity and minimizes the importance of individual neurons and specific neuronal interconnections."[119] Their argument for cellular-connection hypotheses is methodological:

> . . . neurophysiology is still confronted with opposing cellular and field theories of learning, neither of which has critical empirical support. In fact, we have only begun to formulate with any degree of precision the fundamental questions regarding the neural mechanisms of learning. Nevertheless, there is a general feeling that some early solutions to this problem are not out of reach. At present, methodological rather than conceptual factors limit an adequate appraisal of these opposing theories. We believe that cellular-connection hypotheses are useful because they can often be rigorously tested with current techniques. By contrast, aggregate-field hypotheses rarely can be tested because there are few interpretable indices of the global properties of the nervous system.[120]

They argue, explicitly, that neurophysiologists should search under the lamp-post because that is where the light is bright, a common strategy in neurobiology and biology generally.[121] Echoing Eccles' general strategy, Kandel and Spencer show how cellular hypotheses could be integrated with what was then known about the electrical and chemical properties of neurons. They then review different known varieties of synaptic changes (including growth at the neuromuscular junction, PTP and others), and different techniques for studying learning and memory in different experimental systems. Kandel and Spencer thus articulated a theoretical hypothesis and described a variety of experimental techniques for testing it in different experimental systems. This paper, which was widely read, reasserted the goal of finding an explanatory link between synaptic plasticity and learning. It contributed to the climate within which LTP would come to be seen as a significant explanatory advance.

In conclusion, the link between hippocampal synaptic plasticity and learning or memory was not the automatic consequence of having discovered

[118] Kandel and Spencer, 1968.
[119] Kandel and Spencer, 1968, p. 66.
[120] Kandel and Spencer, 1968, p. 69.
[121] See Weber, 2001.

plasticity in the search for a memory mechanism. Instead, this association took form gradually through the integration of different perspectives from different fields and involved the reformulation of the link between plasticity and learning or memory. Learning had been associated with synaptic changes in the theoretical writings of many of the central figures of 19th and early 20th Century neuroscience, and these speculative hypotheses were preserved in the work of the mathematical biophysicists, who demonstrated how such changes might plausibly account for different types of learning. By the mid 20th Century, researchers (Eccles chief among them) began to search for known types of plasticity in the nervous system, driven by the reductive goal of identifying learning or memory with long-lasting changes to neural connections. But known forms of plasticity were physiologically implausible, located in the wrong places, and of too short a duration to shoulder this explanatory burden. Some researchers came to think of known forms of plasticity as analogs or models of learning. Andersen's work with Eccles is at least part of the explanation for how this theoretical tradition entered the Oslo anatomical and physiological program focused on the hippocampus. And Kandel and Squire's methodological review created a climate within which explanatory cellular-connection hypotheses could be received (if not especially well at first). As we will see in the next section, LTP came to be characterized in such a way that it could plausibly satisfy the short-comings of previous neurophysiological explanations of learning or memory.

Characterizing LTP

The discovery of LTP proper (as opposed to less protracted forms of hippocampal synaptic plasticity) is often attributed to Lømo's 1966 abstract for the Scandinavian Physiological Society. In that brief report, Lømo describes a use-dependent increase of "synaptic efficiency" that "may last for hours."[122] Lømo first encountered the phenomenon accidentally while investigating frequency potentiation in Andersen's laboratory.[123] His abstract does not address the potential relevance of the extended duration for learning or memory and, as an abstract, contains minimal detail about the experimental preparation, about the stimulus conditions or about the character of the phenomenon itself. LTP's transformation from an experimental curiosity, as Lømo presents it, into a plausible component in the explanatory store of the neurosciences required considerable work to characterize the phenomenon and to shore up and defend the experimental techniques used to induce and

[122] Lømo, 1966, p. 277.
[123] Lømo, personal communication.

detect it. The complexity of these tasks deterred Lømo from exploring LTP in his dissertation.

When Lømo returned to the phenomenon in 1968, he and his collaborators had to try to convince others that LTP was not an experimental artifact, that it could be reproduced reliably, and that it could be characterized with some degree of precision. These tasks were constrained and driven by the electrophysiological evidence, by developments in experimental technique, and, not insignificantly, by the goal of characterizing the phenomenon in such a way that it could plausibly provide an explanation for learning or memory. Each of these three factors interacted with the others in the process of shaping the research program's understanding of LTP.

Detailed work on LTP did not resume until 1968, when Bliss came to Oslo from the National Institute for Medical Research in Mill Hill, London. Bliss had recently completed his Ph.D. at McGill University, then home to Gloor, Hebb, Milner and Penfield. This context no doubt contributed to Bliss' interest in neurobiological explanations of learning or memory. Bliss' initial interest in neuroscience traces to a summer job as an elevator operator in Banf. The tedium of the job afforded him the opportunity to read Rashevsky's *Mathematical Biophysics*,[124] prompting Bliss to shift his attention to the biophysics of nerve cells. In his graduate work, Bliss studied under B.D. Burns, who believed that memories might be formed in reverberating cortical circuits set up by changes in "synaptic resistance."[125] Bliss used neurophysiological techniques to search for synaptic plasticity in Burns' simplified experimental model: a surgically isolated portion of feline somatosensory cortex maintained with intact circulation. Burns' experimental model was temperamental and difficult, and although Bliss did manage to produce long-lasting changes in the conductivity of cortical pathways, the complexity of the cortical synaptic connections kept him from investigating the effect in a monosynaptic pathway and so from pinpointing the synapse as the locus of plasticity.[126]

While writing his thesis, Bliss discovered a collection of essays from a 1964 meeting at the Pontifical Academy of Science. The volume, edited by Eccles, contained an article by Andersen[127] demonstrating the utility of the hippocampus as a simplified model for studying cortical neurons and synapses – and monosynaptic pathways specifically. In the commentary appended to this article, Eccles mentions (without citation) evidence from ablation and stimulation studies connecting the hippocampus to memory. In

[124] Rashevsky, 1938.
[125] Burns, 1958.
[126] See Bliss, Burns and Uttley, 1968.
[127] Andersen, 1966.

reading this exchange, Bliss recognized that he could use the hippocampus to investigate plasticity in monosynaptic pathways. Bliss contacted Andersen and explained both his interest in the neural basis of memory and his desire to work in the hippocampus. Soon after, Andersen, the hippocampus and Lømo's preliminary results attracted Bliss to Oslo. Bliss and Lømo, who shared a sense of humor, nocturnal work habits and a fondness for the Beatles, quickly took up LTP as a side project.

It was during Bliss' stay in Oslo that he and Lømo collected the data reported in the 1973 *Journal of Physiology* paper – the paper commonly cited as the discovery of LTP on the grounds that this is the first paper to characterize LTP clearly and in detail.[128] LTP's transformation from a curiosity to a component in the explanatory store of the neurosciences involved: (1) extending LTP's duration, (2) pinpointing its stimulus conditions and the nature of the induced potentiation, (3) taming its variability, and (4) justifying experimental techniques and introducing new experimental preparations. Consider these in turn.

Bliss and Lømo were particularly interested in LTP's duration. They hoped that they could extend it to a point that LTP could plausibly be relevant to learning or memory in whole organisms (as opposed to synapses). As noted in the previous section, other known forms of synaptic plasticity (such as PTP and FP) were of too short a duration to plausibly explain learning or memory. In the hippocampus in particular, Andersen and Lømo[129] had reported a maximum duration of "a few minutes," and early reports of plasticity in the hippocampus had reported nothing lasting longer than ten minutes. Bliss and Lømo[130] remember fondly the mounting giddiness as, hour by hour late into the night, they returned to an experimental preparation that continued to exhibit a potentiated response to the test stimulus.

In the course of this early work, LTP came to be described in terms of three parameters, each reflecting the behaviors of populations of neurons.[131] These were: (i) the increased amplitude of the population spike (i.e., the extracellular measurement of the synchronous firing of post-synaptic cells), (ii) the reduced latency of the population spike (the time between the stimulus and population spike), and (iii) the increased amplitude of the excitatory post-synaptic potential following the stimulus. This initial characterization of the phenomenon was subsequently revised through the 1970's and 1980's. Like concern for the duration of the LTP phenomenon, these subsequent revisions were guided in part by the search for features of the phenomenon that could

[128] Bliss and Lømo, 1973.
[129] Andersen and Lømo, 1967.
[130] Personal communication.
[131] See Lømo, 1966, 1967.

be suggestively associated with features of learning or memory. Andersen and his collaborators in Göteborg, Sweden,[132] for example, argued that LTP was produced only at stimulated synapses, giving LTP the kind of specificity that one might expect for learning or memory (especially if one assumes a local coding scheme). McNaughton and his colleagues[133] demonstrated that LTP required "cooperative" activation of the pre and post-synaptic neurons, corresponding to Hebb's[134] learning rule and to associationistic conceptions of learning or memory. In this way, the characterization of LTP was guided by its putative link with learning or memory.

Well before these later developments, perhaps the most significant threat to the research program was LTP's experimental variability. The effect varied from subject to subject and in the same subject over time; several subjects failed to exhibit LTP at all. All three parameters (i, ii, and iii above) were potentiated in only 29% of the experiments, only one of the parameters (reduced latency) appeared in over 50% of the trials, and only 26% of the trials exhibited any of the three effects 30 minutes after the stimulus. This variability (which Bliss and Lømo explicitly discuss)[135] threatened to render LTP too sporadic to be of any physiological relevance, too irregular to be the product of any physiological mechanism, and too unstable to be fruitfully studied in the laboratory. Reducing or otherwise coping with variability was therefore a major challenge for the young research program.

Efforts to reduce this variability span the early history of LTP. For example, Douglas and Goddard[136] argued that the variability was partly a byproduct of long experimental sessions and consequently altered the stimulus for LTP in two ways. First, they switched the stimulus from a monophasic pulse to a diphasic pulse, thus reducing tissue damage and consequent experimental artifacts. Second, whereas Bliss and Lømo had often repeated stimulus trains 30 minutes after the initial stimulus, Douglas and Goddard delayed the repeat stimulus until 24 hours. They justified this decision on the basis of the hypothesis that LTP and kindling have similar mechanisms and that kindling was most effectively produced at a 24 hour delay. Variability of the phenomenon thus exerted pressure to change experimental techniques to produce it more reliably; and these experimental changes in turn altered the way researchers understood LTP.

While in Oslo, Bliss conducted two other sets of experiments, one to justify the use of population recording techniques in the hippocampus and

[132] Andersen et al., 1977.
[133] McNaughton, Douglas and Goddard, 1978.
[134] Hebb, 1949.
[135] Bliss and Lømo, 1973.
[136] Douglas and Goddard, 1975.

the other to further characterize the laminar architecture of the hippocampus. The first set, carried out with Andersen and Knut Skrede, aimed to correlate population measures in the hippocampus (such as those in i, ii, and iii above) with measures from single neurons. This correlation had been assumed in the previous work of Eccles, Andersen and Lømo, and it was crucial for establishing that the effect they were detecting could be interpreted as a change in the strength of individual synapses (making LTP a property of individual synapses rather than populations). Andersen, Bliss and Skrede argued that the amplitude of the spike produced by the synchronous discharge of a homogeneous cell population (like those in the major regions of the hippocampus) is an algebraic sum of the individual action potentials of the discharging cells in that population. This correlation could then be used to justify inferences from measures of the population spike to the activities of individual cells.[137]

The second set of experiments argued that the excitatory activity in transverse sections of the hippocampus could be regarded as "independent functional units."[138] This finding allowed researchers to construct a novel *in vitro* experimental preparation, the transverse hippocampal slice. As developed in Andersen's laboratory by Skrede and Westgard,[139] this preparation exploited the laminar architecture of the hippocampus by sectioning it in such a way as to (more or less) preserve its functional circuits in thin slices (like the transverse section shown in Figure 1a). By 1975, Schwartzkroin and Wester,[140] also working in Andersen's laboratory, had shown that LTP could be induced in transverse slices. As a result of this experimental development, researchers no longer had to keep experimental subjects alive during their experiments, they could easily see (with the help of a microscope) where they were inserting their electrodes, and they could readily introduce pharmacological agents and ionic changes simply by changing the composition of the bath. This development made experiments on hippocampal anatomy and physiology easier to conduct, less fragile than in *in vivo* preparations, and less costly in animal life. At the same time, the transverse slice preparation removed the slice from its context in the hippocampus and the rest of the brain, thereby raising questions about the physiological relevance of findings in the slice to the activities of an intact brain. Given the wave of research on the molecular mechanisms of LTP made possible by the slice preparation, this experimental development certainly rivals any theoretical or conceptual

137 Andersen, Bliss and Skrede, 1971a.

138 Andersen, Bliss and Skrede, 1971b.

139 Skrede and Westgard, 1971. The idea of recording from hippocampal slices was initially developed by Chris Richards at Mill Hill in London (Lømo, personal communication), although Richards used longitudinal rather than transverse slices. Bliss and Richards had tried and failed to produce LTP in longitudinal slices.

140 Schwartzkroin and Wester, 1975.

advance in the extent to which it fueled the subsequent growth of the LTP research program.

Bliss returned from Oslo to London in the Fall of 1969. Lømo followed soon after, taking a temporary position at University College in the department of Bernard Katz and Ricardo Miledi. Andersen (personal communication) had hoped that Lømo would master the techniques for quantal analysis of neurotransmitter release (allowing one to track changes in neurotransmitter release from the pre-synaptic cell) and then return to Oslo to apply those techniques to investigate the mechanisms of LTP. (Such experiments would later become a sub-industry within the LTP research program). Lømo did continue to work on LTP weekly with Bliss at Mill Hill. However, the variability that had plagued them in Oslo was somehow even worse in London (prompting them to joke that perhaps the Norwegian rabbits were simply smarter than their Brit counterparts). In part out of frustration with this variability, Lømo soon abandoned LTP altogether in favor of research on the electrical determinants of muscle properties. This work gained more immediate attention than LTP, and Lømo, who had a strong desire to make a name for himself independently of his collaborators, ultimately chose this as a more promising direction for his career.

As Lømo was developing his new research interests, Bliss began a brief collaboration with Tony Gardner-Medwin, a theoretically and computationally minded neurophysiologist at University College. The collaboration aimed at showing that LTP could be induced in unanaesthetized animals. Gardner-Medwin was in many ways well-suited to research on LTP. First, as noted previously, he had an interest in mathematical biophysics and, in particular, in the role of synaptic plasticity in memory.[141] Gardner-Medwin was very much aware of neurophysiological evidence concerning plasticity, and suggested reasonably that empirical evidence (of the sort produced by Bliss in his dissertation)[142] could ultimately trump his theoretical speculation about which types of synapses might be present in the brain and about what they might be capable of doing if joined into networks. Second, and perhaps most important, Gardner-Medwin had experience recording from the brains of awake and behaving rabbits. His experience with this preparation, as we will see in the next section, helped the research program to address one central objection to the LTP-learning link.

We have seen that, in the late 1960's, the LTP phenomenon was under construction. Experimenters had to find ways to extend its duration, to characterize its parameters, to reduce its experimental variability and to develop, justify and interpret new experimental techniques and preparations. This

[141] See Gardner-Medwin, 1969.
[142] Bliss, Burns and Uttley, 1968.

dynamic interplay of experimental techniques, empirical constraints, and the constraints of an emerging theory around LTP requires careful attention by anyone trying to capture the epistemological structure of the origins of the LTP research program. The linkage of hippocampal synaptic plasticity with learning or memory led researchers to extend the duration of the phenomenon. The need to reduce experimental variability altered the techniques for inducing LTP *in vivo*. And finally, the development of the hippocampal slice led researchers to ask new questions with pharmacological and electrophysiological techniques that could not so much as come into view before. Experimental techniques and preparations were a crucial arena for the integration of fields and perspectives in the history of the LTP research program.

LTP as a Memory Mechanism

In 1973, the experimental efforts in Oslo and London appeared in three full-length papers. Bliss and Lømo's collaborative work appeared back to back with Bliss and Gardner-Medwin's in the *Journal of Physiology*. A third paper, written by Bliss but bearing all three names, was presented at a conference on "Macromolecules and Behavior" at the University of Birmingham. This last paper displays considerably more interpretive bravado (and considerably less data) than the others. These three papers display the combined integrative work described in preceding sections (the integration of anatomy, mathematical biophysics, neurophysiology and theoretical neuroscience) and bring several other fields and perspectives into the mix as well (most notably biochemistry, psychology and neurology).

These papers also clearly articulate a new vision of the explanatory goals of the LTP research program. By extending the duration of LTP relative to other forms of plasticity, the three came to see LTP not as identical to, an example of, or analogous to learning, but instead as a component of a multilevel learning or memory mechanism.[143] This largely implicit reconfiguration of the explanatory objectives of the research program guided subsequent research by clarifying two basic research goals, both involving the integration of levels in this multilevel picture: first, to discover the lower level mechanisms that produce LTP, and second, to evaluate the role of LTP in higher level learning or memory mechanisms.[144] Both goals are still being pursued

[143] Discussions of mechanisms and their role in scientific integration can be found in Bechtel, 1988; Bechtel and Richardson, 1993; Machamer, Darden and Craver, 2000; Craver and Darden, 2001. The process integrating scientific fields is discussed in Darden and Maul, 1977 and Darden, 1991.

[144] See Craver, 2001, Section 4.

nearly 30 years later. In pursuit of each, the search for mechanisms provided an abstract structure of components organized together at multiple different levels that could be filled in and elaborated with findings from different fields and perspectives.

The first, downward looking, goal in this explanatory framework was to describe the mechanisms of LTP. Bliss and Lømo dedicate their entire discussion section to sorting out the "mechanisms which might be responsible for long-lasting potentiation."[145] They consider three: changes in tonic excitability of the post-synaptic cell, changes in the effects of the test stimulus on the pre-synaptic cells, and changes in synaptic efficacy. After ruling out the first two of these and thereby arguing by elimination for the relevance of synaptic mechanisms, they then consider possible schematic mechanisms within the synapse, including: "an increase in the number of terminals invaded by the constant test volley, an increase in the amount of transmitter released per synapse, an increase in the sensitivity of the post-synaptic junctional membrane, or a reduction in the resistance of the narrow stem by which spines are attached to the parent dendrite."[146] They "have no evidence which could distinguish between these various possibilities,"[147] but they nonetheless place considerable emphasis on the discovery of a mechanism for LTP and make this an explicit focus for future research.

The search for the lower level mechanisms of LTP brought with it at least three important consequences for the development of this fledgling LTP research program. First, the existence of a stable mechanism composed of known components could compensate for LTP's experimental variability. Even though the phenomenon was difficult to produce even under artificial experimental conditions, the fact that it was produced at all pointed to the existence of mechanisms in the synapse that might be regularly exploited in the normal (non-experimental) working of the synapse. Given the existence of a mechanism, variability might be blamed on artificial experimental techniques rather than the phenomenon itself, and researchers could set about refining those techniques to engage the mechanism under the conditions resembling those in the unperturbed brain. Second, the search for mechanisms helped to integrate LTP together with other accepted components, especially what was then known about the electrical and chemical properties of neurons and synapses. The ability to integrate LTP with other known features of neurons and synapses gave it added credibility relative to alternative mechanisms, such as those listed in Table 1.

[145] Bliss and Lømo, 1973, p. 350.
[146] Bliss and Lømo, 1973, p. 352.
[147] Bliss and Lømo, 1973, p. 352.

Third, and perhaps most important, the search for lower level mechanisms of LTP could foster growth in the research program by accommodating the perspectives of multiple fields. The findings in these varied fields and from these different perspectives added their own constraints on the mechanism of LTP.[148] Different perspectives could explore, for example, different components of the mechanism, different properties of those components, different activities in which those components engage or different forms of organization among them. Gary Lynch epitomizes the interdisciplinary spirit that followed in the wake of Bliss and Lømo's publication. Lynch encountered the hippocampus early in his career during work on the homeostatic mechanisms of hunger, thirst and behavioral arousal, and his interest in the hippocampus carried him into multidimensional studies of the anatomy, biochemistry, pharmacology, physiology and psychological relevance of the hippocampus and its subregions. Lynch and his colleagues pioneered the biochemical investigation of LTP, finely manipulating known presynaptic mechanisms[149] and applying pharmacological agonists and antagonists[150] to probe receptor subtypes on the post-synaptic cells. With the development of the slice preparation, these types of experiments proliferated, providing fertile ground for those who would combine electrophysiological and biochemical manipulations to explore the mechanisms of LTP.

The second goal sketched in the 1973 papers was to show that LTP was situated within (and so explanatorily relevant to) higher level mechanisms. In arguing for the explanatory relevance of LTP to memory, Bliss, Lømo and Gardner-Medwin appeal to LTP's duration, to the theoretical plausibility of synaptic plasticity as a potential memory mechanism, and, now for the first time, to a possible role of the hippocampus as an intermediate level in the mechanisms of memory. In both of the *Journal of Physiology* papers, the authors are timid concerning the relationship between LTP and memory. The first paper ends with a sentence nearly unreadable in its caution:

> The interest of these results derives both from the prolonged duration of the effect, and from the fact that an identifiable cortical pathway is involved. The perforant path is one of the main extrinsic inputs to the hippocampal formation, a region of the brain which has been much discussed in connexion with memory (Douglas 1967; Olds 1972). Our experiments show that there exists at least one group of synapses in the hippocampus whose efficiency is influenced by activity which may have occurred several hours previously – a time scale long enough to be potentially useful for information storage. Whether or not the intact

148 See Craver and Darden, 2001.

149 See Dunwidie, Madison and Lynch, 1978; Dunwidie and Lynch, 1979.

150 See e.g., Lynch, Gribkoff and Deadwyler, 1976.

> animal makes use in real life of a property which has been revealed by synchronous repetitive volleys to a population of fibres the normal rate and pattern of activity along which are unknown, is another matter.[151]

Bliss and Gardner-Medwin appeal directly to the potential relevance of LTP to memory in motivating the second paper. In that paper, they use Gardner-Medwin's technical expertise recording from awake and behaving animals to induce LTP in unanaesthetized rabbits. They thereby demonstrated that LTP could be induced in neurons that were not in a "depressed unphysiological state,"[152] and that "since the phenomenon is present in healthy unanaesthetized animals it is at least possible that its mechanism could underlie some form of plasticity under normal conditions in the hippocampus."[153]

In the third paper, Bliss admits to having, "no evidence one way or the other" that LTP "has anything to do with memory."[154] Still the laxity of a conference paper in comparison to a published journal article afforded Bliss the elbow room to begin to sketch the theoretical superstructure that would frame the LTP research program in detail. Bliss appeals to a diverse literature in support of a hippocampal link with memory, including psychiatric case studies,[155] ablation studies,[156] electroencephalography,[157] and biochemical research.[158] He also appeals to a broad theoretical literature linking synaptic plasticity to memory. Brindley,[159] Eccles,[160] Gardner-Medwin,[161] Hebb,[162] and Marr[163] are all cited in the introduction. This synthesis of the literature appeals to diverse fields and different kinds of evidence to situate the LTP phenomenon into a memory mechanism.

What is significant about this argumentative structure is not the certainty that it confers upon its conclusion; that question is still being debated. What should capture our attention instead is the way that this argument carved out a theoretical space that could accommodate researchers from many different fields using different experimental techniques in different organisms

151 Bliss and Lømo, 1973, p. 355.
152 Bliss and Gardner-Medwin, 1973, p. 371.
153 Bliss and Gardner-Medwin, 1973, p. 373.
154 Bliss, Gardner-Medwin and Lømo, 1973, p. 195.
155 Douglas, 1967; Milner, 1970.
156 Grastyan and Karmos, 1962.
157 Elazar and Adey, 1967; Vinogradova et al., 1970.
158 Hydén, 1973.
159 Brindley, 1969.
160 Eccles, 1953.
161 Gardner-Medwin, 1969.
162 Hebb, 1949.
163 Marr, 1970.

to address similar or theoretically related questions. The Eccles-inspired view of LTP *as* a form of learning in the synapse did not contain within it the seeds of this sort of multifield research program. As is common in research reports, however, Bliss explicitly hides the structure of the reasoning in order to frame the research as a case of predict-and-test science: "From a neurophysiological point of view, a first step in establishing whether any particular part of the brain is directly involved in the process underlying memory (that is, whether it is involved in the storage, and not merely the transmission of learned information) is to look for evidence of synaptic plasticity."[164] It is perhaps this passage that led Squire and Kandel, and so many others besides, to mischaracterize this historical episode. But we now know that LTP was not discovered in the search for a memory mechanism; instead, memory and the hippocampus were enlisted in the attempt to argue for the explanatory relevance of LTP, however vaguely, to memory. To point this out is not to cheapen their accomplishment, but rather to highlight more accurately just how significant their vision was for the subsequent development of the LTP research program.

Conclusion

The making of LTP was a protracted affair. Hippocampal synaptic plasticity began as a laboratory tool, slowly emerged as an experimental curiosity, gradually took shape as a reductive explanation or primitive example of learning, and was then, by the mid 1970's, reinterpreted as a component in a memory mechanism. This historical trajectory was shaped in part by changes in vocabulary (e.g., distinguishing FP, LTP and PTP) and by changing relations between distinct vocabularies (e.g., Eccles' reductive tables). Yet other aspects of this story cannot be understood in this way. The integration of perspectives in this episode was also achieved through the combination of two or more techniques to reveal different aspects of the same phenomenon, the development and refinement of new experimental techniques, the choice of experimental systems and model organisms and, finally, the struggle to articulate the very nature of a neurobiological explanation of learning or memory. Recognizing these diverse factors is a first step away from the foil history of LTP, which depicts the making of LTP as "predict-and-test" science driven by the goal of uncovering ever-deeper "levels" of explanation. A great deal of historical work remains to be done both to elaborate this sketch and to unravel the factors influencing the subsequent growth of the LTP research program into one of the most powerful in contemporary neuroscience. Likewise, a

[164] Bliss, Gardner-Medwin and Lømo, 1973, p. 193.

great deal of scientific work remains to be done both to understand what an ideally complete neurobiological explanation of learning or memory would look like and to envision and develop the kinds of experimental techniques that would show convincingly that such an explanation had been achieved. Perhaps this scientific work might be aided by thoughtful completion of the historical.

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