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Long-term Potentiation as a Possible Associative Memory Mechanism in the Brain*

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Long-term potentiation (LTP) is a lasting increase in the strength of neuronal connnections resulting from brief high-frequency activity of input fibres. Its properties include persistence, input specificity, associativity and cooperativity. LTP meets Hebb's postulated requirements for an associative memory mechanism, and has formal similarities to behavioural learning paradigms such as classical conditioning. A selection of combined behavioural/electrophysiological experiments are reviewed which support the possibility that LTP normally occurs when animals learn. On the basis of these findings it is suggested that LTP is, at a minimum, an information storage mechanism characteristic of many neurones and at best, one that may be important for the acquisition and/or retention of certain learned behaviours.

Background: The model system approach to memory mechanisms

Despite the intense efforts made by behavioural neuroscientists to determine how the nervous system generates behaviour and cognition, our understanding of brain function at this level clearly lags far behind our understanding of function at more reductionist levels. While we are in fact beginning to develop a rather detailed picture of the neural basis of simple sensations and movements, we have as yet only modest understanding of the neural basis of the more complicated, and more interesting, mental faculties such as perception, emotion, cognition.

One recent growth area has been the study of brain mechanisms of information storage. Just as the study of memory has long been a major focus of traditional psychology, so it has always been a subject of great interest to neuroscientists. One advantage in studying memory mechanisms is that at least they involve by definition changes that last over time. This means that a researcher has time to look around in the brain (a reasonable first place to look) to determine what and where any neural changes take place. This approach has limitations, however, since it is likely that the brain changes brought about by an animal learning a task will be so subtle that finding and observing them seems rather improbable. Indeed it has been suggested that any changes that are detectable with current techniques are almost certainly too gross in nature to represent the storage of specific pieces of information (McNaughton, 1983). This state of affairs dictates that researchers employ other strategies to study memory storage mechanisms.

One prominent research question is: *where* does memory storage take place? Indeed this line of research has a long history, involving innumerable animal experiments (e.g., Lashley, 1950) and studies of patients with brain damage with a variety of

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etiologies (Squire, 1987). Some progress has been made in the analysis of brain circuits critical for the *process* of storage or consolidation of certain types of long-term memory (e.g., declarative memory; Squire & Zola-Morgan, 1988). However the sites of storage remain poorly delineated, most likely because they are widely scattered throughout many areas of the brain.

The other major research question is: what neural change or changes underlie memory storage, regardless of location, and how do they come about? This may seem a hopelessly ambitious task, given the above comments regarding our lack of knowledge about where in the brain to look, plus the improbability of identifying the biochemical and physiological events specific to the memory storage process. The current solution, in studies of vertebrates anyway, is to take a model system approach. Here a small area of brain can be studied in intense detail. Ideally this area contains only two or three prominent populations of neurones, with one or two of them serving as inputs to one other output population. (Because the neurones are connected by specialized contact areas called synapses, the input neurones are termed presynaptic and the output neurones are termed postsynaptic.)

In the model system sensory stimulation is replaced experimentally by electrical stimulation of the presynaptic neurones. The activity of the postsynaptic neurones in response to this patterned input may be thought of as the 'behaviour' of the system. A major advantage of this approach is the ability to study in detail how and why neuronal behaviour changes in response to a brief 'experience'. The major disadvantage is that there is no guarantee that such a model will relate to learning and/or memory storage that normally results from a real sensory experience.

Long-term potentiation

A number of neural pathways have been studied as model memory systems, but this review will focus on the phenomenon of long-term potentiation. In the late 1960's, long-term potentiation (LTP) was discovered in hippocampal pathways (Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973; Lomo, 1966), and LTP in the hippocampus remains the most successful and well studied model to date. In this paper I will review the properties of LTP, and discuss why it has generated such interest as a putative neural mechanism of information storage in the brain.

A typical LTP experiment is conducted as follows. A series of low frequency test pulse stimuli (e.g., 1/10 sec) are applied to an input pathway and the resulting response by the postsynaptic neurones to each stimulus (i.e., the evoked potential) is recorded and measured. Normally there is very little variability in the responses to these baseline test stimuli. Then a few very brief bursts of high-frequency stimulation (e.g., 400 Hz for 25 ms) are generated in the input pathway (the 'experience') followed by a resumption of the low frequency test pulses. The postsynaptic cells demonstrate 'memory' for this 'experience' by showing responses to the test pulses after high-frequency stimulation that are potentiated compared to the baseline responses (Fig. 1). This change is very reliable and extremely robust.

Properties of long-term potentiation

LTP exhibits four prominent properties that have established it as a major candidate memory mechanism: Persistence, input specificity, cooperativity and associativity.

The first property of LTP to attract attention was its persistence. Depending on the exact parameters and number of repetitions of the high-frequency stimulation, enhanced responding lasts from several days to many weeks (Barnes, 1979; Douglas & Goddard, 1975; de Jonge & Racine, 1985). Studies of LTP persistence (in rats and rabbits) have so far always found an eventual decay back to baseline (Racine, Milgram & Hafner, 1983). Thus LTP appears to be a lasting, but not permanent, change although it may be that the right parameters of stimulation have not yet been tried. It is important to note that there is no evidence that LTP is the result of neural pathology. Rather it appears to be a normal property of the cells under study.

The second property of interest is the input specificity of LTP. This is investigated by employing two independent inputs (i.e.

input pathways) to the same postsynaptic neurones (Fig. 2). It is found that high-frequency stimulation of one input produces LTP confined to that input, as long as the second input is quiescent during the high-frequency stimulation (Andersen, Sundberg, Sveen, & Wigström, 1977; McNaughton & Barnes, 1977). Thus LTP is input specific, that is, it does not generalize to other inputs contacting the same neurones. Indeed the quiescent input may even be depressed in function, which could represent the neural equivalent of a forgetting process (Abraham & Goddard, 1983; Levy & Steward, 1979). Input specificity is also indicative of the locus of change being confined to the synaptic contacts between the pre- and postsynaptic cells. If the postsynaptic cells changed at any other site (dendrites, cell bodies or axons) one would expect them to become more responsive to all inputs, that is, the control input as well as the stimulated one. Clearly input specificity improves the information storage capacity of neurones and is a necessary component of a sophisticated memory mechanism.

Cooperativity and associativity are related properties in that they both show that LTP results from an interaction between coactive input fibres. Cooperativity refers to the fact there is a threshold strength of stimulus (and therefore a threshold number of activated fibres) for LTP to be induced

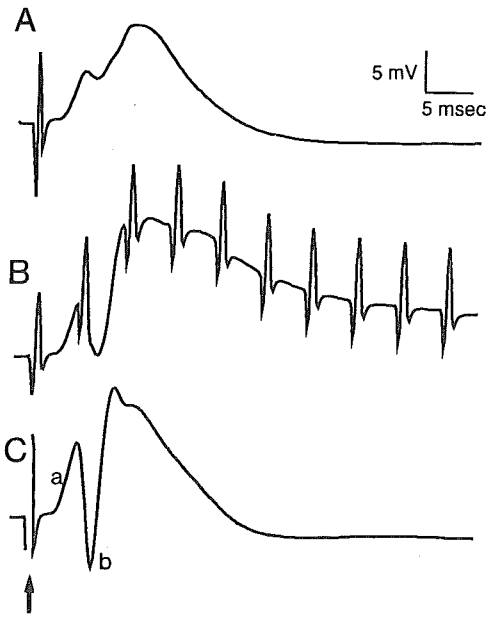

Figure 1. Typical evoked responses recorded before (A), during (B) and 30 min after (C) 400 Hz stimulation of the entorhinal cortex input to the dentate gyrus of the hippocampus. Note the increased initial positive slope of the population synaptic potential (component a) and the increased height of the negative-going population spike (component b, indicative of the numbers of postsynaptic cells firing) that occurs after high-frequency stimulation (compare response C to response A). Arrow indicates time at which the stimulus is delivered to the input. Waveforms in A and C are averages of 10 responses to test pulse stimulation; waveform in B is the response to a single 10 impulse train, of which several are required in order to induce LTP. All responses were recorded from a single unanaesthetized rat.

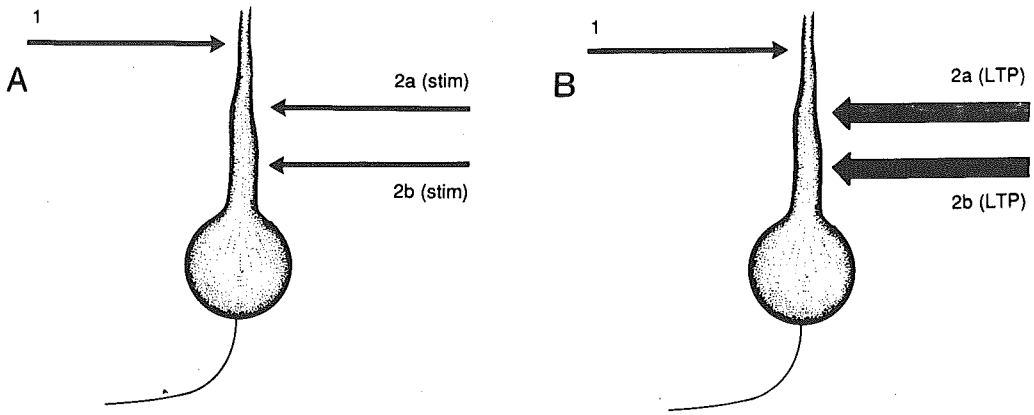

Figure 2. Schematic diagram of a simple circuit showing input specificity and cooperativity. Inputs 1, 2a and 2b to the postsynaptic cell by themselves contain too few fibres to induce LTP. Combined high-frequency stimulation (stim) of inputs 2a and 2b induce LTP in these pathways (cooperativity) but not in quiescent input 1 (input specificity). A, B show the relative synaptic strengths of the inputs (by arrow thickness) before and after LTP induction, respectively.

(Fig. 2). High-frequency stimulation of insufficient numbers of fibres, no matter how often repeated, will not induce LTP (McNaughton, Douglas, & Goddard, 1978). This suggests that a cooperative interaction between input fibres is required for LTP. Although the critical number of fibres is unknown and almost certainly varies with specific experimental protocols, in the normal paradigm it appears to be about the same number as that required to cause the postsynaptic cells to fire action potentials (McNaughton et al., 1978).

Associativity refers to a form of cooperativity between two anatomically separate inputs to the postsynaptic cells, one strong input (involving many fibres and thus above LTP threshold) and one weak (involving only a few fibres, Fig. 3). High-frequency stimulation of the weak input alone will not induce LTP, but pairing it with high-frequency stimulation of a strong input will then generate LTP in the weak input as well (Barrionuevo & Brown, 1983; Wigström & Gustafsson, 1983). Forward pairing (weak followed by strong) is more effective than backward pairing, but the optimal interaction occurs with simultaneous pairing (Levy & Steward, 1983; Gustafsson & Wigström, 1986).

Evaluation of long-term potentiation as an associative memory mechanism

At this stage let us pause and consider how well the properties of LTP dovetail with our expectations of an associative memory mechanism. On the positive side, LTP shows persistence, input specificity and associativity. It is a property of neurones widely distributed throughout the forebrain (Racine et al., 1983), and appears to be localised to the synaptic junctions between neurones. It has been observed in a variety of vertebrate species, including man (Haas, Greene, Heimrich, & Xie, 1988). There is also evidence that spaced tetanization episodes give better LTP induction than massed episodes (Larson, Wong, & Lynch, 1986). These characteristics are in concordance with assumptions often made in theoretical models of memory formation. For example, Donald Hebb (1949) postulated a mechanism for information storage whereby synaptic strengthening would occur for any inputs, but only those inputs, which repeatedly took part in firing postsynaptic cells. (This is an associative memory model since coactivity in many input fibres is normally required for postsynaptic cells to fire.) This memory mechanism is central to Hebb's influential neuropsychological concept of cell assemblies, both for their construction and for their serial chaining into phase sequences. The similarities between Hebb's hypothetical memory mechanism and the hippocampal LTP described above are so great that synapses showing such LTP are now known as Hebbian synapses (Kelso, Ganong, & Brown, 1986), and form the basis of subsequent elaborations of Hebb's theory (Goddard, 1980).[1]

It is interesting to note at this point that the network theories of Hebb and others have recently been upgraded through the introduction of 'parallel distributed processing' network models, or 'adaptive neural networks' (Rumelhart, McClelland, et al., 1986). Such models are receiving enormous attention because of their potential ability to provide an interface between basic neuroscience and cognitive psychology. Despite the improved organisational features these models incorporate, they are 'adaptive' (i.e. capable of learning) because logical equivalents to modified Hebbian synapses remain fundamental features of the connections between the network elements (e.g., McNaughton & Morris, 1987).

It is equally important to note that the LTP properties listed above also show formal similarities to the properties of associative conditioning at a behavioural level, particularly classical conditioning (Levy & Steward, 1979). The associativity experiments can be viewed, for example, in the following way. A weak or innocuous CS (weak input) normally generates a weak re-

[1]Strictly speaking this is a bit generous, since we know that Hebb's requirement for postsynaptic cell firing is not necessary for LTP (Douglas, Goddard, & Riives, 1982). However since the general level of postsynaptic depolarization *is* critical to LTP induction (Gustafsson, Wigström, Abraham, & Huang, 1987), the phenomenon clearly is subsumed within the spirit of the Hebbian rule.

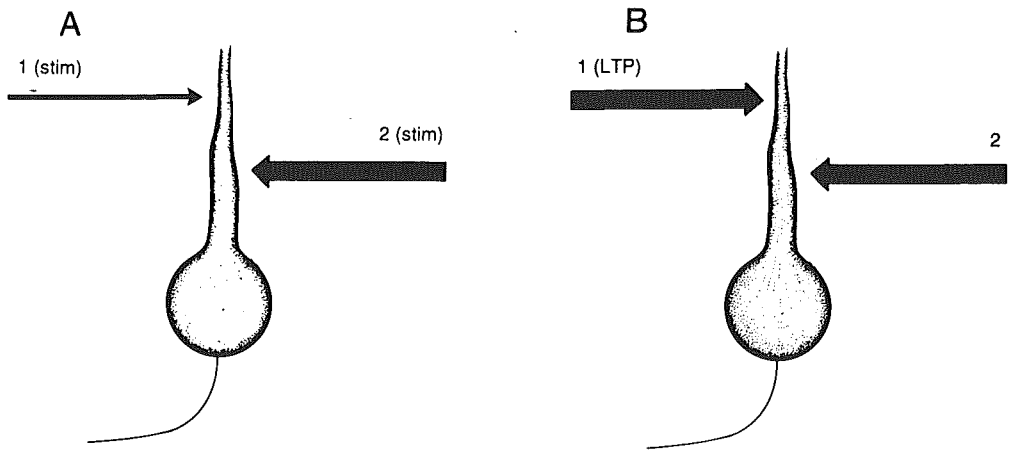

Figure 3. Schematic diagram of a simple circuit showing associativity. Input 1 contains too few fibres to induce LTP by itself. High-frequency stimulation (stim) of strong input 2 simultaneously with weak input 1 induces LTP in input 1. LTP may also occur in input 2 if not previously established to a saturation level. A, B show the relative synaptic strengths of the inputs (by arrow thickness) before and after LTP induction, respectively.

sponse. However after a number of temporal pairings of the CS with a salient, reinforcing UCS (strong input), the subsequent response to the CS alone is strengthened.[2]

On the negative side, LTP does not show such features as permanence or input (stimulus) generalization, nor the same optimal interstimulus intervals (e.g., as in classical conditioning) that are prominent features of associative learning. The lack of the latter two features in the LTP model is probably not crucial. After all, LTP is studied within the confines of a simple model system, and it would be rather surprising if all behavioural features were present in the model. One expects that activity within other relevant brain circuits, and its timing within these circuits, will determine many of the animal's learning characteristics. The impermanence of LTP could be more worrisome. However, memory for behavioural tasks has often been shown not to be permanent in many animal experiments (e.g., Zornetzer, Abraham, & Appleton, 1978). Further, it may be that human memories themselves are more transient than they appear (perhaps requiring repeated recall to maintain apparent permanence). On the other hand LTP may be a mechanism only for holding information over a relatively short period of time. This latter idea has some appeal. The hippocampus, for example, is currently viewed as a temporary or working memory store for various kinds of information, rather than the actual site of long-term memory storage (Olton, Wible, & Shapiro, 1986; Rawlins, 1985). Certainly human amnesics suffering from hippocampal damage, either alone or in combination with damage to other structures, show primarily anterograde amnesia (Squire, 1986). Pretraumatic memories remain largely intact, implying that final (permanent?) storage occurs at other sites.

[2]Whether the strong input is actually carrying 'reinforcement' information from an overall brain function point of view is immaterial to the argument at hand; furthermore, a comparison could equally be made with the association of conditioned stimuli in the standard sensory preconditioning learning paradigm.

Recent progress

With the above phenomenology having been worked out by the early 1980's, LTP research has since progressed in two additional general directions: 1) toward investigations of the cellular and molecular mechanisms underlying LTP and 2) toward a consideration of the possible relevance of LTP to the behaviour of normal animals.

Cellular mechanisms

While we have much yet to learn about the neural mechanisms responsible for

LTP, two pieces of the puzzle are already clearly in place. First, LTP appears to result largely from an increase in the amount of transmitter released from the presynaptic terminals (Dolphin, Errington, & Bliss, 1982). Second, the properties of input specificity, cooperativity and associativity all appear to be explained by the involvement of N-methyl-D-aspartate (NMDA) neurotransmitter receptors that are resident on the postsynaptic neurones (Wigström & Gustafsson, 1985). The details of this receptor action plus recent advances at subcellular and molecular levels of investigation have been extensively reviewed elsewhere (Collingridge & Bliss, 1987; Landfield & Deadwyler, 1988; the interested reader may also wish to note that a non-associative form of hippocampal LTP has now been discovered, Nicoll, Kauer, & Malenka, 1988). An important element of this research, however, has been the development of a number of drugs that selectively prevent the activation of NMDA receptors by the neurotransmitter, and thereby prevent LTP induction (Abraham & Mason, in press; Collingridge, Kehl, & McLellan, 1983). These pharmacological compounds represent tools which can be used to assess the extent to which NMDA receptors, and presumably therefore LTP, participate in the brain activities mediating specific behavioural changes.

Behavioural relevance

The relevance of LTP to normal behaviour has been studied rather independently of the mechanism experiments. Psychologists want to know in what way LTP in a model system is relevant to what really happens in the brain during memory storage. Or is LTP merely a physiologically interesting but biologically unimportant property of some nerve cells, useful only in keeping a large handful of neuroscientists gainfully employed? Morris and Baker (1984) describe four general experimental approaches being used to address this nagging question: The correlational approach, the prior LTP approach, the prior learning approach and the blockade/facilitation approach. All of these experimental designs are in fact correlational in nature, and thus none of them will be able to provide a definitive answer. A convergence of the results from such experiments, however, would considerably strengthen the case for a role for LTP in normal behaviour. Below I will briefly review examples of each of these approaches.

Correlational Approach

One of the earliest tests of the behavioural relevance of LTP was a correlational experiment conducted by Barnes (1979), who compared hippocampal LTP induction with spatial maze learning and memory abilities in middle-aged and senescent rats. The task apparatus was an elevated circular platform with numerous holes spaced evenly near the outer perimeter of the platform. Rats were trained to find the hole that led to a darkened escape chamber. (This task was chosen because the hippocampus is thought to be involved in normal spatial learning.) Barnes found that senescent and middle-aged rats could escape from the platform equally well once found, but that old rats took longer and made more errors in finding the goal over a series of training trials than the middle-aged rats. These same rats showed a similar pattern of results when given tetanic stimulation to a hippocampal pathway. LTP was induced equally well in both groups, but it decayed more rapidly following repeated high-frequency stimulations in the senescent rats. Remarkably, there was also a significant correlation of LTP and spatial behaviour *within* groups. For example, among just the middle-aged rats, poorer learners also tended to show poorer LTP induction and relatively faster LTP decay.

Prior Learning Approach

A second approach involves training animals on a behavioural task and looking for increased evoked potentials characteristic of LTP in hippocampal pathways. In one such study (Skelton, Scarth, Wilkie, Miller, & Phillips, 1987), rats were trained on a variable interval 2 minute schedule wherein a tone was used to signal the period that a response would be reinforced. Other rats received the same number of food pellets noncontingently. When hippocampal evoked potentials were examined in each

rat 22 hr following each training session, the average response amplitude was observed to grow with the learning of the operant conditioning task. This enhancement of the evoked potential persisted for at least 10 days following the termination of behavioural training.

In a related experiment (Sharp, McNaughton, & Barnes, 1985), rats were maintained in stimulus impoverished housing for several weeks. This was done in the hope that potentiated synapses would decay to a low strength level, thereby improving the chance of detecting an increase in synaptic strength suggestive of LTP. The animals were then placed for several days in a stimulus enriched environment that included contact with a variety of objects plus other rats. As predicted, hippocampal evoked potentials gradually grew in amplitude over several days, and the decay of this increase after the animals' return to the impoverished environment paralleled the decay of LTP (Sharp, Barnes & McNaughton, 1987). A more definitive demonstration that these evoked potential increases are due to LTP would be obtained, however, if these increases were shown to be prevented by the NMDA antagonists which specifically block LTP induction.

Prior LTP Approach

Experiments taking the 'prior LTP' approach have obtained apparently mixed results. LTP induction has been shown to enhance acquisition of a classical conditioned eyeblink response in rabbits (Berger, 1984) and acquisition of hippocampal stimulation as a conditioned stimulus in rats (Skelton, Miller, & Phillips, 1985). On the other hand, Barnes and colleagues have found that induction of LTP to a saturation level impairs performance of rats on spontaneous T-maze alternation as well as spatial memory in the circular maze task (Barnes, 1979; McNaughton, Barnes, Rao, Baldwin, & Rasmussen, 1986). Although apparently contradictory, these results could be interpreted as showing that performance of tasks requiring simple transmission of information through hippocampal circuits, for example, the conditioning tasks, will be facilitated when transmission is improved by LTP induction. However performance of tasks requiring storage of spatial information through subtle increases of synaptic strength at selected sites in the hippocampus, will be impaired when a large percentage of synapses has been arbitrarily driven to a saturation level before any training begins (Barnes, 1988).

Blockade/Facilitation Approach

The final experimental design involves comparing treatments that block or facilitate LTP with their effects on performance of some task. Laroche and Bloch (1982) observed that post-trial midbrain reticular formation stimulation improved avoidance conditioning and enhanced the rise in hippocampal unit activity in response to tone-shock pairings. Similarly, such stimulation enhanced the induction of LTP. Using the reverse approach, Morris, Anderson, Lynch, and Baudry (1986) employed an NMDA antagonist compound to block LTP in the hippocampus, and examined its effects on two different behavioural tasks. The drug, at doses shown to completely block hippocampal LTP induction, also disrupted animals' ability to remember the location of a hidden escape platform in a water maze task. On the other hand, animals were unimpaired in their performance of a visual discrimination task. The block of NMDA receptors and LTP induction in the hippocampus has effects on the performance of these two particular tasks virtually identical to the effects of destroying the hippocampus. Unfortunately, a number of questions remain regarding this particular experiment, such as 1) whether the drug exerted its spatial memory impairment effect by acting on other brain structures, 2) whether the drug exerted its effect by altering some characteristic of neural function other than LTP (cf., Abraham & Kairiss, 1988), and 3) whether the failure to affect visual discrimination performance reflected a failure of the drug to reach the visual cortex.

Another example of the correspondence of LTP blockade and memory performance centres on the use of drugs which block the synthesis of proteins. Such drugs have long been used in animal learning experiments

because they have the interesting property of selectively impairing long-term memory on a wide variety of tasks (Dunn, 1980). Initial learning and short-term memory for these tasks are unaffected. These findings have contributed significantly to multiple-process theories of animal memory. They also support the intuitively appealing idea that memory storage involves changes in the structural and/or enzymatic properties of nerve cells, changes that will almost certainly entail an altered make-up or distribution of cellular proteins. It is noteworthy, therefore, that the persistence of LTP past a few hours also appears to depend on new protein synthesis (Krug, Lossner, & Ott, 1984; Otani, Marshall, Tate, Goddard, & Abraham, in press). As in the memory experiments (Barondes & Cohen, 1968; Montarolo, Goelet, Castellucci, Morgan, & Kandel, 1986), a narrow time window is involved in that protein synthesis must occur during the first 15 minutes following high-frequency stimulation for LTP to become long-lasting (Otani et al., in press).

Summary

As discussed previously, none of the experimental designs or specific results described above represents a definitive demonstration that LTP normally occurs in mammalian brain and, if so, whether it has anything to do with information storage. On the other hand, one can not help but be impressed by the array of experimental data being generated which point to such a role for LTP. Certainly the properties of LTP are strikingly concordant with the expectations of an information storage mechanism from both theoretical and behavioural perspectives. Furthermore the LTP effect is so robust and reliable that it is clearly a fundamental feature of the way in which limbic and cortical neurones function. Because of these facts the question of whether LTP normally occurs in neurones appears to be trivial (even though it may not be trivial to conclusively demonstrate). More to the point are questions about the behavioural and neural circumstances that are favourable for LTP induction, and how such LTP modifies the activity of the neural networks, and thence of the organism, in which it occurs.

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