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Commentary on **Tracey J. Shors & Louis D. Matzel (1997) Long-term potentiation: What's learning got to do with it? BBS 20:597–655.**

Abstract of the original article: Long-term potentiation (LTP) is operationally defined as a long-lasting increase in synaptic efficacy following high-frequency stimulation of afferent fibers. Since the first full description of the phenomenon in 1973, exploration of the mechanisms underlying LTP induction has been one of the most active areas of research in neuroscience. Of principal interest to those who study LTP, particularly in the mammalian hippocampus, is its presumed role in the establishment of stable memories, a role consistent with "Hebbian" descriptions of memory formation. Other characteristics of LTP, including its rapid induction, persistence, and correlation with natural brain rhythms, provide circumstantial support for this connection to memory storage. Nonetheless, there is little empirical evidence that directly links LTP to the storage of memories. In this target article we review a range of cellular and behavioral characteristics of LTP and evaluate whether they are consistent with the purported role of hippocampal LTP in memory formation. We suggest that much of the present focus on LTP reflects a preconception that LTP *is* a learning mechanism, although the empirical evidence often suggests that LTP is unsuitable for such a role. As an alternative to serving as a memory storage device, we propose that LTP may serve as a neural equivalent to an arousal or attention device in the brain. Accordingly, LTP may increase in a nonspecific way the effective salience of discrete external stimuli and may thereby facilitate the induction of memories at distant synapses. Other hypotheses regarding the functional utility of this intensely studied mechanism are conceivable; the intent of this target article is not to promote a single hypothesis but rather to stimulate discussion about the neural mechanisms underlying memory storage and to appraise whether LTP can be considered a viable candidate for such a mechanism.

LTP – A mechanism in search of a function

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Abstract: Shors & Matzel (1997) suggest replacing the question "Is LTP a mechanism of learning?" with "Is LTP a mechanism of arousal and attention?" However, the failure of experiments to verify the LTP-learning hypothesis may arise not because it is untrue, but because in its current guise, it is not properly testable. If so, then the LTP-attention hypothesis is untestable, as well.

The hypothesis that links LTP to the mechanisms of learning is now a quarter of a century old. Shors & Matzel's (S&M's) (1997) target article, a broad-reaching and well-written review of the evidence to date, argues persuasively that there is still no reason either to accept or reject it outright. The response from the commentators supports this uncertainty, some agreeing that support for the hypothesis is indeed weak, others arguing that the right experiments have not yet been done. This leaves behavioural physiologists in something of a quandary. Should we press on, continuing to try many and various different ways of tying the two phenomena together for perhaps another quarter of a century, or should we follow S&M's advice and abandon the learning hypothesis, replacing it instead with something new, such as arousal or attention?

Clearly, the current approach to tackling the LTP-learning question has been unsuccessful in resolving the question and so the answer to the first question is "no." However, we should look carefully at the underlying reasons before we make the mistake of stumbling down another, equally stony path of investigation in pursuit of the neurobiological mechanisms of arousal. That so much hard work and so many experiments have failed to confirm a hypothesis that remains widely believed should raise a warning flag that it might be not the hypothesis but rather the means of testing it that is flawed.

At this point it is worth reiterating the well-worn point that LTP is an *experimental* phenomenon. Its study has uncovered some intricate synaptic machinery that probably does exist to change connection strengths between neurons. However, we should not make the mistake of confusing the question of what this synaptic modifiability does for an animal with the (methodologically easier) question of what *LTP* does for an animal. To keep this point in the foreground, therefore, it is useful to distinguish between LTP, on the one hand, and the putative phenomenon of naturally occurring synaptic modification (SM) on the other. LTP has been put forward as a model of naturally occurring SM, but it is *not the same thing.* Therefore, the question "Is LTP a mechanism of learning?" is really two questions: (1) Does SM underlie learning? and (2) Is LTP a good model of SM?

The study of model systems like LTP can be a useful tool in neu-

robiology, because it enables experimenters to isolate the phenomenon of interest and explore it in the laboratory. However, when study of a model fails to confirm a hypothesis, it may be that the hypothesis is wrong, but it may also simply be that the model is unsuitable. In the case of LTP, Shors and Matzel argue that the hypothesis is wrong and we should therefore find a different one. However, it is also possible that the hypothesis (that SM is the mechanism of learning) is correct but the model (LTP in a given pathway) is wrong. For example, it may be that the synaptic changes of LTP are not identical to those of SM, the differences contributing to the experimental results. Perhaps the pathway in which LTP was evoked was not that involved in the learning of the task, or perhaps the method of inducing LTP (with theta-burst or paired or tetanic or primed burst stimulation or whatever) did not mimic naturally occurring conditions. The list goes on.

The inevitable conclusion is that although the SM-learning hypothesis might have been supported by a large number of positive correlations between the properties of LTP and those of learning, a failure to find such correlations, or at least to find them reliably, cannot be construed as evidence that the hypothesis is wrong. This is because not enough is known about the system we are investigating to know whether LTP is a good model of it. It follows from this argument that the worst possible course of action would be to throw into the pool yet another hypothesis, about a process that is even less understood and less well localised than learning. There is no point in using LTP as a model for arousal, or anything else, if the process it is supposed to model has not even been partially characterised.

How better to characterise learning? The top-down approach would be to break it up into its simplest components and find out where in the brain these occur, using pharmacological and lesion techniques. The bottom-up approach would be to observe the behaviour of single neurons to see what they actually do when learning occurs. This means knowing what the neurons represent, what the animal learned, what the neurons learned (and for an individual neuron, this may not be the same thing), and whether the cell-to-cell communications changed after the process occurred. If the learning event involved a change in the connection strength between a pair of neurons, then, and *only* then, should our wealth of knowledge about LTP be brought into play.

In short, then, we should not throw away LTP as a model of learning-related synaptic change until its suitability has been discredited. Rather, we should set it aside while we better characterise the processes underlying learning, and this means discovering (a) where they happen, and (b) under what conditions. Until synaptic strength changes can be observed to participate directly in a given process, any attempts to postulate an underlying LTP-like mechanism can only be speculative.

LTP and reinforcement: Possible role of the monoaminergic systems

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Abstract: The absence of a clear influence of the responses modified by new connections created by LTP on the development of these connections casts doubt on an essential role of LTP in learning and memory formation without any association with reinforcement. The evidence for the involvement of the monoaminergic systems in synaptic potentiation in the cerebral cortex during learning is adduced, and their role in reinforcement system function is discussed.

I share Shors & Matzel's (1997t) doubts about the role of long-term potentiation (LTP) in memory trace formation and with Latash's (1997) more radical criticism of the concept of LTP as a key function in memory trace formation. It seems rather strange that this idea arose at all and persisted so long without any association with the concept of reinforcement. Some further considerations support the above doubts.

As a result of evolution, memory has developed as a mechanism of adaptation to the environment in which an animal must choose the behavioral responses useful for its survival and avoid making harmful ones. The memory trace, consisting of new connections in the cortex, is formed under the influence of continually arriving information about the consequences of the animal's behavior, together with an estimate of its usefulness or harmfulness. So there must be mutual relations between new connection formation in the cerebral cortex and the animal's behavior: The potentiation of available connections and the formation of new ones influence the behavioral responses, and the estimate of the results of the animal's behavior in turn exerts an effect on the formation of new connections and the modulation of existing ones. In the event of LTP, however, relations of this sort are only unidirectional. LTP creates new connections, acting on the animal's behavior, but any obvious mechanism for the reverse influence of these new or modified responses on forming the above connections is absent. Therefore, because these connections occur independently of the maintenance of the animal's optimal behavior, it seem highly improbable that LTP is important in memory trace formation.

According to the general synaptic theory of learning and memory, as well as the physiology of higher nervous activity, it is reinforcement that provides brain structures (including the cerebral cortex) with information about the usefulness or harmfulness of each behavioral response. The great diversity of learning networks (e.g., McCulloch & Pitts 1943; Rosenblatt 1962) constructed on this basis have been able to elaborate the requisite reactions in response to rather complicated forms of conditioned signals.

This raises the question: What transmits the information about the consequence of an animal's behavior to its cortex and influences synaptic potentiation in the cerebral cortex at learning? A possible participation of the monoaminergic systems of the brain was postulated in the middle 1970s (Freedman et al. 1977; Libet et al. 1975; Zhadin 1977).

Support comes from a variety of evidence:

(1) the association of monoaminergic nucleus activity with the reinforcement system (Gromova 1980);

(2) the diffuse distribution of monoaminergic fibers from certain local nuclei throughout the brain, in particular, over the whole cortex (Ungerstedt 1971);

(3) the unique chemistry of monoaminergic synapses, not found among cortico-cortical synapses or among internal connections in other structures of the brain (Ungerstedt 1971);

(4) the difference between the monoaminergic systems hypothetically associated with positive and negative reinforcement (Gromova 1980);

(5) the special structure of the monoaminergic synapses in the cerebral cortex; they have only presynaptic components, without any postsynaptic ones, and saturate all the cortical extracellular space with corresponding monoamine upon excitation of these synapses, providing an easy access to the monoamines for all the cortico-cortical synapses (Beaudet & Descarries 1978).

This all provides grounds to believe that it is the monoaminergic systems that promote the proper changes in efficacy of cortico-cortical synapses depending on the previous state of these synapses for the time period between the conditioned stimulus and response, as well as on the quality of reinforcement (positive or negative) at learning (Zhadin 1987; 1991; 1993).

According to our mathematical model (Zhadin 1987; 1991; 1995; Zhadin & Bakharev 1987), the prolonged action of positive reinforcement induces gradual transitions in relatively highly excited neurons in the cortex to their extremely high excitation levels and of less excited ones to complete inhibition, with occasional possible spontaneous transitions of the cells from one of these extreme levels to the other. The long-term negative reinforcement causes gradual transitions of both the relatively active and less ex-