

# Half a century of Hebb

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In 1949, Donald Hebb predicted a form of synaptic plasticity driven by temporal contiguity of pre- and postsynaptic activity. This prediction was verified decades later with the discovery of long-term potentiation, securing Hebb's place in the scientific pantheon. But the Hebbian synapse was just part of a broad and ambitious theory of the physiological basis of mind. What became of the rest of the theory?

Hebb believed that synaptic connections were the material basis of mental associations, but he went beyond the naive connectionism of behaviorists like J. B. Watson in two important respects. First, he argued that an association could not be localized to a single synapse. Instead, neurons were grouped in "cell assemblies," and an association was distributed over their synaptic connections. Second, Hebb rejected the notion that stimulus-response relationships could be explained by simple reflex arcs connecting sensory neurons to motor neurons. It was necessary to postulate "a central neural mechanism to account for the delay, between stimulation and response, that seems so characteristic of thought." Following Lorente de Nó, Hebb believed that sensory stimulation could initiate patterns of neural activity that were centrally maintained by circulation in synaptic feedback loops. Such 'reverberatory activity' made it possible for response to follow stimulus after a delay.

In short, Hebb argued for a 'dual trace mechanism' of memory. Reverberatory neural activity was the trace of short-term memory, whereas synaptic connections were the trace of long-term memory. Keeping this context in mind, it is worth re-examining how Hebb introduced his synapse:

*"Let us assume then that the persistence or repetition of a reverberatory activity (or 'trace') tends to induce lasting cellular changes that add to its stability. The assumption can be precisely stated as follows: When an axon of cell A is near enough to excite a cell B and repeatedly or*

*persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."*

I have emphasized the first sentence here, because it is very important, though not so well-known. It hypothesized a specific function for the Hebbian synapse: the conversion of short-term into long-term memory by stabilization of reverberatory activity patterns. Once such an activity pattern was stored in synaptic connections, thereafter it could be recalled repeatedly by excitation from sensory neurons, or from other reverberatory activity patterns.

In the past half century, what progress has been made in confirming or denying Hebb's theory? There have been three major steps in this direction: the first observations of delay activity, the discovery of long-term potentiation, and the first neural network models of delay activity. Starting in the 1970s, neurophysiologists began to address the question that fascinated Hebb: what happens in the brain during the time interval between stimulus and response? Fuster, Niki and their colleagues found that certain prefrontal cortex neurons could be active during delays of many seconds, and encode information about the preceding stimulus or the impending response. This delay activity provided, for the first time, a candidate for the 'reverberatory activity' of Hebb and Lorente de Nó. Also in the 1970s, neuroscientists began to study the phenomenon of long-term potentiation (LTP), following the initial work of Bliss and Lomo on hippocampal synapses. A crucial role of the NMDA receptor in LTP was revealed in the 1980s, providing the first insights into how temporally contiguous presynaptic and postsynaptic activity could lead to potentiation, as Hebb predicted. In the 1990s, the first neural network models of delay activity were introduced. In the preceding two decades, theorists had shown that a recurrent neural network could possess multiple stable states, which could be stored in the network by Hebbian synapses. These stable states, or dynamical attractors, were identified with delay activity patterns for the first time by Amit, Zipser and their colleagues. Their models can be counted as the first precise realizations of

Hebb's idea of reverberatory activity in a cell assembly.

Today the validity of Hebb's theory is still uncertain. Granted, the existence of the Hebbian synapse is not in doubt, but it is still unclear whether delay activity is truly reverberatory activity. If the neural network models are correct, then feedback loops are indeed the mechanism by which delay activity is maintained. This idea has been challenged, however, on the grounds that the persistence of delay activity is due to mechanisms that are intrinsic to single neurons, such as plateau potentials. Moreover, there is still no evidence that LTP stabilizes reverberatory activity, as Hebb postulated. In addition, Hebb's belief in just two memory traces may be incorrect. We know now that synaptic plasticity is not a unitary process, but rather many processes on different time scales. Besides LTP, there are shorter-lasting forms of plasticity like post-tetanic potentiation, augmentation, facilitation and depression. If these forms of synaptic plasticity are involved in memory, the number of memory traces will have to be increased.

Looking to the future, what strategy might definitively prove or disprove Hebb's theory? Here are some recommendations. First, study the simplest examples of neural activity that could possibly be 'reverberatory,' and focus on whether synaptic feedback loops are really involved. Choosing the simplest examples is essential, because it will be technically demanding to settle the mechanistic question of whether reverberatory activity actually exists. Second, investigate the role of LTP in these examples. Third, attempt to manipulate Hebbian synaptic plasticity *in vitro* so as to store reverberatory activity patterns as long-term memories in culture or brain slice preparations—a synthetic rather than analytic strategy.

Hebb's synapse is not his only legacy. Even after half a century, his theory as a whole is still inspiring, because it is a general framework for relating behavior to synaptic organization through the dynamics of neural networks. That is why further exploration of Hebb's ideas is a promising route for translating our accumulating knowledge about the molecular and cellular events underlying synaptic plasticity into a real understanding of learning and memory.

*For a more detailed history of these ideas, see Orbach, J. The Neuropsychological Theories of Lashley and Hebb (University Press of America, Lanham, 1998).*

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