Synaptic plasticity and memory

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Changing synaptic connections between neurons is widely assumed to be the mechanism by which memory traces are encoded and stored in the central nervous system. In its most general form, the "synaptic plasticity and memory hypothesis" states that during formation of memories appropriate synapses undergo activity-dependent alterations, and that synaptic plasticity is both necessary and sufficient for the storage of information underlying the type of memory mediated by the brain area in which that plasticity is observed. This hypothesis has been formulated mainly from theoretical reasoning about the computational power of neural networks. Very recently, experimental evidence on this hypothesis has accumulated to an amount that can now be considered as increasingly evidential. Nevertheless, the question of how memories can persist despite ongoing synaptic plasticity is still unresolved. This "plasticity-stability dilemma" is lately becoming an important focus of research on synaptic physiology.

Introduction

The role of activity-dependent synaptic plasticity in learning and memory is a central issue in neuroscience (Martin et al., 2000). Most of the relevant experimental work concerns the possible role of long-term potentiation (LTP) in learning. The majority of studies focuses on N-methyl-D-aspartate (NMDA) receptor-dependent forms of LTP, which endows synaptic plasticity with properties like input-specificity and associativity

as well as persistence. These properties are often considered fundamental for storage mechanisms (Marr, 1971; Hopfield, 1982; Churchland and Sejnowski, 1992). The ultimate goal of research on synaptic plasticity is caricatured by the question: does LTP equal memory? Since Hebb's relatively simple hypothesis (Hebb, 1949), thinking about LTP's putative role in memory has moved to a set of more specific ideas about activity-dependent synaptic plasticity and the multiple types of memory that we now know to exist (Martin et al., 2000). These distinct hypotheses do, however, share a common core, which is called the “synaptic plasticity and memory hypothesis”.

Even if we accept this hypothesis, fundamental theoretical questions about synaptic plasticity and memory remain open. This is because, on the one hand, ongoing storage of new memories requires a high degree of susceptibility of synapses, i.e., synapses must always remain plastic at least to some degree. On the other hand, the retention of older memories demands a high stability of the underlying neuronal circuits, for example due to stable synapses or at least due to stable neural computations within the particular brain region of interest (despite a considerable amount of changes of its synaptic connectivity). The main challenge in building models of long-lasting memory, especially in cases where new experiences are continually generating new memories, is how to protect older memories against alterations induced by new experiences. This quandary is referred to as the “plasticity-stability dilemma” (e.g. Abraham and Robins, 2005).

In addition to persistent modifications of synapses, a variety of synapses in the central nervous system also exhibit fully reversible changes (Zucker and Regehr, 2002). Changes in response to prior activation that last at most for a few minutes are called short-term plasticity (STP). Two major forms of STP have been described: short-term depression goes along with an attenuation of the efficacy of synaptic transmission following the arrival of a spike whereas short-term facilitation describes an increase of the efficacy. In STP the efficacy of a synapse recovers within typically hundreds of milliseconds, but recovery time constants of minutes have also been reported. The computational role of STP in learning and memory is much less elaborated than, for example, the role of LTP.

Recent Advances

A specific type of problems within the framework of the plasticity-stability dilemma is that un-supervised forms of plasticity tend to run out of balance, and consequently lead to unstable neuronal networks. Thus, a mechanism is needed which maintains an appropriate level of total excitation within a network but still allows plasticity to occur. Theoretical and experimental work suggest that sliding plasticity-induction thresholds (BCM-model), synaptic redistribution and spike-timing dependent plasticity

(STDP) might help to overcome some of these problems (Abbott and Nelson, 2000). Recent studies have also found homeostatic mechanisms to be of importance for synaptic gain control (Burrone and Murthy, 2003): Work on the neuromuscular junction suggested that synapses respond to prolonged inactivity or hyperactivity with up- or down-regulation of synaptic inputs, respectively. Furthermore, data on spinal and cortical neurons demonstrated that alterations in overall network activity rescale synapses in a multiplicative or fractional manner (Turrigiano and Nelson, 2004). Such mechanisms allow cells to balance between inhibition and excitation and thereby prevent pathological states of hyper- or hypo-excitability of the network. Little is known, however, about the detailed subcellular mechanisms underlying the principles of neuronal homeostasis and its theoretical implications. Another solution to the plasticity-stability dilemma is to assure the persistence of neural computations in a network through multistable synapses where each synapse has a cascade of states with different levels of plasticity (Fusi, Drew and Abbott, 2005). In this way high levels of memory storage are combined with long retention times.

Experiments using conditional knockout strains of transgenic mice have revealed that ongoing NMDA-receptor-mediated processes do indeed operate to consolidate and retain memories over weeks and months (see e.g. Abraham and Robins, 2005). Conditional NMDA-receptor knockout during the first week following conditioning or training caused retrograde amnesia when measured approximately two weeks post-training. Even more strikingly, NMDA-receptor knockout for 30 days beginning six months post-training impaired the retention of conditioned memories. These intriguing experiments provide strong evidence that both the consolidation of memory in the early post-training period and the stable maintenance of remote memory require continued neural activity and NMDA-receptor activation. Insofar as this is indicative of ongoing synaptic plasticity, these findings appear to support the synaptic plasticity hypothesis for memory retention. However, they do not answer the question of whether the ongoing plasticity merely refreshes the weights for those synapses that were originally modified during initial memory storage, or whether there are more widespread changes in synaptic structure and function.

A deeper understanding of ongoing synaptic reorganization in the brain can only emerge from studies that take into account both the local plasticity rules and the representation of information in small neuronal networks. Recent experiments have indeed revealed the particular importance of the timing of pre- and postsynaptic spikes for the induction of long-term plasticity. “Critical windows” of spike timing, with precision on the order of milliseconds, have been found (see Bi and Poo, 2001 for a review). The precise profile of critical windows appears to depend on the synapse type; the underlying molecular mechanisms remain to be fully understood. Correlated spiking of pre- and postsynaptic neurons can result in strengthening or weakening of

synapses, depending on the temporal order of spiking. Such “spike timing–dependent plasticity” (STDP) of synapses, which has already been mentioned in the context of the plasticity-stability dilemma, is therefore likely to be significant for the development and functioning of neural networks.

Future Challenges

A major challenge to understanding human behavior is how the nervous system allows the learning of events that can occur over arbitrary time scales, ranging from microseconds to minutes, using a plasticity rule such as STDP, which operates on a fixed neuronal time scale on the order of milliseconds. Further research is needed to understand how those very different time scales can be bridged. It is therefore necessary to understand the interdependence of STP and LTP at the level of a single synapse, on the one hand, and the computational mechanisms that can combine the long time scales of STP with the much shorter time scales of the induction of LTP at the level of small networks, on the other hand.

LTP may serve a universal function in the encoding and storage of memory traces, but what gets encoded and how is an emergent property of the network in which this plasticity is embedded, rather than of the mechanisms operating at the synapse in isolation. For example, the character of information processing in the hippocampus is different from that in the amygdala and would remain so even if the mechanisms of plasticity utilized in each brain area were conserved. Understanding the role of synaptic plasticity in the central nervous system therefore requires a systems theory of at least small neuronal modules of the brain.

Progress in accepting or rejecting the synaptic plasticity memory hypothesis and in resolving the stability plasticity dilemma is hampered by our lack of knowledge about what and how information is represented as spike trains across pathways and recurrent neuronal networks of memory processing areas in the central nervous system. Therefore, for example, multiple single-unit recording in behaving animals together with powerful new data-analysis techniques and the possibility of combining these with pharmacological or genetic intervention will become more and more important. The sophisticated nature of the field means, however, that few laboratories can marshal the myriad of multidisciplinary techniques that are necessary to advance our understanding. Such diverse technological requirements dictate a collaborative approach, in which computational neuroscience is indispensable to provide a common theoretical background.

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