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Review

On the role of receptor–receptor interactions and volume transmission in learning and memory

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ABSTRACT

Learning and memory seem to be inherent to a biological neural network. To emerge, they need an extensive functional connectivity, enabling a large repertoire of possible responses to stimuli, and sensitivity of the connectivity to activity, allowing for the selection of adaptive responses. According to the classical view about the organization of the CNS, the connectivity issue is realized by the huge amount of synaptic contacts each neuron establishes, while the adaptation of the network to specific tasks is obtained by mechanisms of activity-dependent synaptic plasticity. The discovery of direct receptor–receptor interactions at the level of the plasma membrane and the existence in the brain of two main modes of communication, the wiring transmission (such as the synaptic transmission) and the volume transmission (based on the diffusion of signals in the extracellular space), provided a broader view of the functional organization of the CNS with potential important consequences on the understanding of learning and memory processes. Owing to receptor–receptor interactions clusters of receptors, the receptor mosaics (RM), can be formed at the plasma membrane where they can work as collective functional units. As a consequence, the connections between the cells become themselves networks (molecular networks) able to adapt their function according to the stimuli they receive. Learning, therefore, can occur also at the level of RMs. Thus, memory formation seems not only to be a distributed process, but also to follow a hierarchical morpho-functional organization. Furthermore, the combination of the two different forms of transmission could allow processes of correlation and coordination to be established between networks and network elements without the need of additional physical connections, leading to a significant increase of the degrees of freedom available to the CNS for learning.

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Abbreviations: BN, Boolean network; CNS, central nervous system; DA, dopamine; ECM, extracellular matrix; ECS, extracellular space; EEG, electroencephalogram; GPCR, G-protein-coupled receptor; LTD, long-term depression; LTF, long-term facilitation; LTP, long-term potentiation; RM, receptor mosaic; RRI, receptor–receptor interaction; TM, transmembrane domain; VT, volume transmission; WT, wiring transmission

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1. Introduction

Learning may be described as the mechanism by which new information about the world is acquired, and memory as the mechanism by which that knowledge is retained (Lynch, 2004). Memory is usually categorized as being declarative or explicit, i.e. involved in the conscious recall of facts and events, and non-declarative or implicit (such as learned motor skills) whose recall is always unconscious.

One of the most compelling and fascinating problems in neuroscience is no doubt to identify the mechanisms underlying learning and memory and despite the great deal of progress made in the past few decades (see Kandel, 1979; 2001; 2005), it remains a significant challenge.

Human studies demonstrated that explicit memory strongly depends on the integrity of the temporal lobe and of the hippocampus (Squire et al., 1984; Clark et al., 2002), while it is acknowledged that several areas of the brain (see Lynch, 2004 for a review) play a part in consolidation of other forms of learning/memory. For instance, the acquisition of motor skills and habits and the memories associated with such skills (procedural memories) relies on the integrity of the striatum and the cerebellum (Gabrieli et al., 1998; Hermann et al., 2004). Moreover, several lines of evidence indicated that the association between the conditioned and unconditioned stimuli occur in the amygdaloid nuclear complex (Johnsrude et al., 2000; Goossens and Maren, 2001) and the activation of the amygdala was shown to be closely correlated with memory for both aversive and pleasant stimuli (Hamann et al., 1999), a task in which are involved also the mesencephalic dopamine (DA) neurons (Schultz, 2002).

Learning and memory functions, however, are present in almost all the animals: implicit memory is probably the only type of memory observed in lower invertebrates, whereas explicit forms of memory can be recognized in vertebrates. Furthermore, the basic processes involved in memory encoding and maintaining resulted highly conserved through evolution and experiments in animal models from *Aplysia* and *Drosophila* to mouse and rat, were found of a great importance for the investigation of the molecular mechanisms based on memory formation and consolidation in the human brain (Barco et al., 2006).

In other words, learning and memory phenomena seem to be inherent to neural systems, although these systems can differ from each other markedly. Thus, the differences, at the molecular, cellular and anatomical levels, probably reflect the wealth of possible instantiations of two learning and memory universals (Hebb, 1949; Marom and Shahaf, 2002):

- (a) an extensive functional connectivity that enables a large repertoire of possible responses to stimuli; and
- (b) sensitivity of the functional connectivity to activity, allowing for selection of adaptive responses.

According to the classical view about the functional organization of the CNS, the connectivity issue is realized by the huge amount of synaptic contacts each neuron establishes, while the adaptation of the network to specific tasks is obtained by mechanisms of activity-dependent synaptic plasticity, triggered by the interaction with the external world to modulate the strength of the synaptic connections (Kandel, 1979; Malenka and Nicoll, 1999).

Starting from the 1980s, a broader view of the morpho-functional organization of the CNS was proposed by Agnati and Fuxe (Agnati and Fuxe, 1984; Agnati et al., 1986, 1995) based on the existence of two main modes of communication in the CNS: the ‘wiring transmission’ (WT), and the ‘Volume Transmission’ (VT). WT is characterized by a structurally well-defined channel (a “wire” i.e., a *private communication channel*), connecting a source with its targets (Agnati et al., 2006). The synaptic transmission between neurons is the most important example of WT in the CNS. VT, on the other side, is based on an extracellular transmission among all types of cells in the brain. Thus, VT takes place by using the ECS as a *non-private communication channel*, and represents the three-dimensional diffusion of signals for a distance greater than the synaptic cleft (see also Agnati et al., 1994; Agnati et al., 2007-this issue; Fuxe et al., 2007-this issue). Nicholson’s (1988) work provided strong experimental support for VT in the brain and also characterized the physical features of the process (Nicholson, 2001). Different classes of VT signals have been identified and include chemicals, such as neurotransmitters (Sem’yanov, 2005), ions (Sykova, 1992), gases (Gally et al., 1990) and enzymes (Vergnolle et al., 2003; Wang and Reiser, 2003), as

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