Memory concepts - 1993. Basic and clinical aspects
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DISCUSSION : Biological Memory Models

Moderator: Terrence J. Sejnowski
Computational Neurobiology Laboratory, The Salk Institute for Biological Studies, San Diego, California, U.S.A.

Introduction

"Learning" is a term used to describe a wide range of adaptive animal behaviors. The focus of studies on the neural substrates for these behaviors is generally at the cellular and molecular levels. An animal's behavior, however, is the result of its entire central nervous system interacting with the environment, and there are many levels of organization between the molecular and systems levels, as shown in Fig 1 [1]. We need to understand each of these levels and how they are interrelated to fully understand the fundamental basis for learning and memory. I summarize here some challenging problems and recent progress toward a new synthesis of how, and why, animals learn.

At what levels have common principles of learning and memory been found across species? Yadin Dudai (this volume) presented evidence for common intracellular signaling pathways that may underlie changes in the responsiveness of neurons in flies, slugs, and mammals. Eric Kandel and his colleagues have suggested that these pathways form an "alphabet" of molecular mechanisms that are preserved throughout phylogeny, just as the mechanisms for generating action potentials, first uncovered in the squid, appear to be universal [2]. This possibility was strengthened by the discovery that learning mutations in *Drosophila* affect the same molecules that important for learning in *Aplysia* (Kandel, this volume). Davis (this volume) has shown that some of these molecules are also expressed in the mushroom body, an interesting region of the insect brain that is particularly well developed in social insects. Nature tends to be conservative, but innovations do occur. The NMDA receptor, which mediates one form of long-term potentiation in vertebrates, is such an evolutionary innovation, although precursors of this receptor may be present in invertebrates [3].

A well-studied form of learning in humans is the recali-

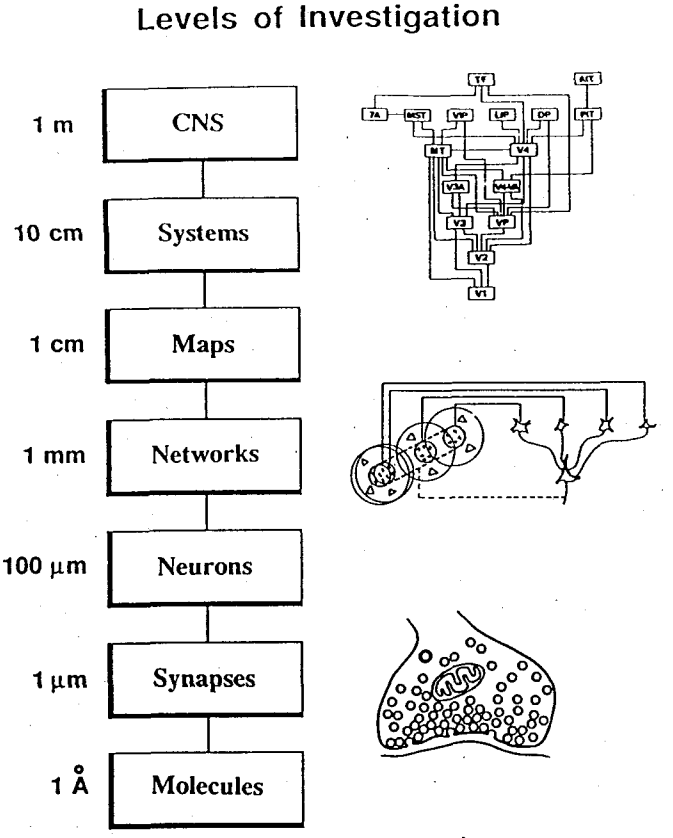

Figure 1: Levels of investigation in the nervous system. The spatial scales at which anatomical organizations can be identified varies over many orders of magnitude. Icons to the right represent structures at distinct levels: (top) a subset of visual areas in visual cortex; (middle) a network model of how ganglion cells could be connected to simple cells in visual cortex, and (bottom) a chemical synapse.

bration of visuo-motor coordination (Glickstein, this volume). We should expect the locus of learning to be widespread in the brain, even for this relatively simple form of adaptation. There has been a vigorous debate regarding the anatomical structures where the adaptive changes occur in the vestibulo-ocular reflex, which helps to stabilize images on the retina during head movements (Ito, this volume). Synapses in both the cerebellum and brainstem may be involved and there is evidence for both locations [4]. It generally has been assumed that the long-term gain changes of the vestibulo-ocular reflex must be at synapses,

but an alternative possibility has recently been suggested that involves changes in the time courses of neural responses [5]. The dynamics of neural networks opens up new ways to look at old problems.

Universal learning principles may also arise at the level of neural systems. Survival depends on learning and memory in the context of perception and action. Rewarding sensory stimuli such as food and water strongly affect behavior; other sensory stimuli, through contingent association, can also modify behavior. We have recently developed a systems-level model of predictive learning based on the regulation of learning and memory by diffuse ascending neurotransmitter systems, arising from a relatively small number of neurons in the brainstem, which project throughout large regions of the forebrain [6, 7]. These include the noradrenergic system arising from the locus coeruleus, the serotonergic projections from the Raphe nuclei, a histaminergic system arising from the hypothalamus, and dopaminergic projections from the substantia nigra and the ventral tegmental area. Similar diffuse neurotransmitter systems are found in invertebrates that may also regulate learning and memory.

A single neuron has recently been identified in honeybees which may be homologous in function with the dopaminergic neurons in the ventral tegmental area of vertebrates. Called VUMmx1, this octopaminergic neuron projects axonal arborizations widely throughout the entire bee brain. Intracellular recordings from VUMmx1 support its role in mediating reinforcement learning [8, 9]. When paired with sucrose, an odor that previously had no effect on proboscis extension reliably elicits extension. Hammer has shown that the firing of VUMmx1 by current injection can substitute for sucrose in a conditioning experiment: after pairing of VUMmx1 activation, the odor by itself subsequently elicits proboscis extension. Thus, the activity of VUMmx1 can substitute for the reinforcing stimulus.

Dayan and Montague have recently modeled the foraging behavior of bees using reinforcement learning [10]. The model is based on the principle of prediction by temporal differences [11, 12]. There is a central role in the model for VUMmx1, which is

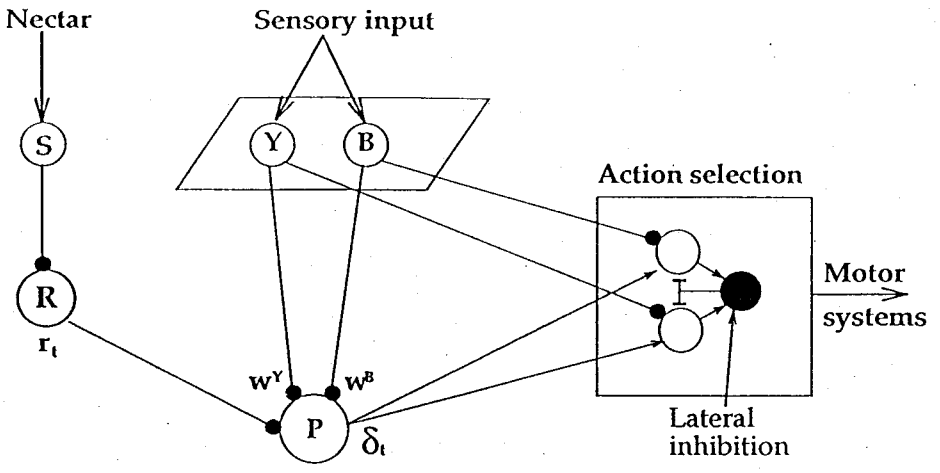

Figure 2: Neural architecture for a model of bee foraging. Predictions about future expected reinforcement are made in the brain using a diffuse neurotransmitter system. Sensory input drives the units B and Y representing blue and yellow flowers. These units project to a reinforcement neuron P through a set of plastic weights (filled circles w^B and w^Y) and to an action selection system. S provides input to R and fires while the bee sips the nectar. R projects its output r_t through a fixed weight to P. The plastic weights onto P implement predictions about future reward and P's output is sensitive to temporal changes in its input. The outputs of P influence learning and also the selection of actions such as steering in flight and landing. Lateral inhibition (dark circle) in the action selection layer performs a winner-takes-all. Before encountering a flower and its nectar, the output of P will reflect the temporal difference only between the sensory inputs B and Y. During an encounter with a flower and nectar, the prediction error δ_t is determined by the output of B or Y and R, and learning occurs at connections w^B and w^Y. These strengths are modified according to the correlation between presynaptic activity and the prediction error δ_t produced by neuron P. Before encountering a flower and its nectar, the output of P will reflect the temporal difference only between the sensory inputs B and Y. During an encounter with a flower and nectar, the prediction error δ_t is determined by the output of B or Y and R, and learning occurs at connections w^B and w^Y. These strengths are modified according to the correlation between presynaptic activity and the prediction error δ_t produced by neuron P. Simulations of this model account for a wide range of observations of bee preference, including aversion for risk (from reference 10).

responsible for predicting the reward value of incoming sensory stimuli (Fig. 2). If an odor, for example, temporally precedes the delivery of nectar, then through a predictive form of the Hebbian learning algorithm, the inputs to VUMmx1 are strengthened (Fig. 3). This learning algorithm is Hebbian since it depends on the conjunction of pre- and postsynaptic activity [1]; however, the postsynaptic activity is not the summed synaptic input, but the prediction error, calculated as the time derivative of the summed input, including input from the unconditioned reward stimulus. This form of Hebbian synaptic plasticity is predictive

PREDICTIVE HEBBIAN SYNAPSE

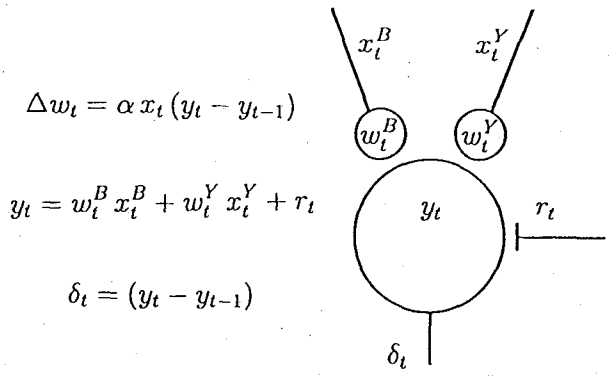

Figure 3: Learning algorithm for a predictive hebbian synapse. The goal of the neuron is to predict the reinforcement signal, r_t, by changing the weights, w_t, on the sensory inputs. The summed input to the cell is y_t and the output of the cell is its time difference, δ_t. The hebbian algorithm for the change in a weight Δw_t depends on the conjunction of the recent presynapatic activity for input x_t and the output of the cell. This is a causal algorithm because of the difference: the reinforcement r_t at time t is compared with the sensory input at the previous time step. The changes in the strength of the weight drive this difference to zero, so that the weights become a prediction of future reinforcement associated with the sensory input (from reference 10).

in the sense that only sensory inputs that occur before a reinforcing stimulus are strengthened; this temporal asymmetry is a hallmark of classical conditioning and has been demonstrated elegantly in bee learning [13]. This model accounts for a large number of behavioral experiments on bee learning, including risk aversion behavior [14].

Recordings from single neurons in the ventral tegmental area of primates have uncovered firing patterns to rewarding stimuli that are analogous to those found in VUMmx1 in bees [15, 16]. Early in learning, these dopaminergic neurons fire reliably to reward, but later in learning they no longer respond directly to the reward; instead they respond to the earlier sensory stimuli that reliably predict the reward. This is what a predictive Hebbian learning rule (Fig. 3), which modifies the inputs to these neurons, would produce and underlies the models explanation for blocking and secondary reinforcement in classical conditioning. The outputs from dopaminergic neurons in the ventral tegmental area, which project to the nucleus accumbens

and to the prefrontal cortex, may therefore carry information about predicted error of the reward value of the sensory stimuli. To complete the comparison with VUMmx1 in bees, it has recently been shown that stimulation of the VTA can substitute for reward [17]. Predictive Hebbian learning may be a universal mechanism that is important for orienting animals to stimuli that lead to future reward. The brain may be organized to make predictions about the importance of sensory stimuli for survival in an uncertain world and use these predictions to act appropriately. This principle provides computational explanations for many otherwise puzzling facts about learning and the brain from the molecular to the systems levels.

The development of the nervous system also offers important clues to learning since many of the same mechanisms that organize neural interactions during development are also used, in modified forms, in adult brains. In particular, the same diffuse ascending systems, such as the noradrenergic and cholinergic projections, used to regulate learning in the adult are also essential for the neural plasticity observed during development. A second common theme is the use of correlated neural activity for the precise development of maps between visual areas [18]. Hebbian synaptic plasticity may be used to refine the topography of visual maps [19] and to form the properties of cortical neurons [21]. The variety of cortical areas and response properties of cortical neurons may depend on gating of the learning by diffuse neurotransmitter systems [6, 7, 22] and changes in the visual inputs that occur at birth [23]. The development of auditory maps of space in owls is a favorable model system for studying map registration between the visual and auditory systems (Brainard, this volume). Advances in our knowledge of how developmental programs specify neural pathways and determine cellular interactions should be of great importance for understanding how adaptive changes occur in mature brains.

Despite all we have learned about learning and memory, there are important pieces still missing from the puzzle. All of the speakers in this session relied on behavioral data together with the anatomical substrate to provide a systems-level framework within which to study learning. There is, however, a large gap

between behavioral observations and data showing correlations with learning at the cellular and molecular levels. In particular, there is a major link missing at the network level, which is characterized by highly interacting populations of neurons (Fig. 1). New experimental techniques are needed to explore the network gap and new models are needed that provide insights into the properties of interacting neural populations. Our models of classical conditioning in bee foraging and the development of neocortex are steps in these directions [6, 7, 10].

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