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The taste of memories: Mechanisms of learning, memory and forgetting in the mammalian brain

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Objectives of Research

We investigate molecular, cellular, and system mechanisms of learning, short-term memory, consolidation, persistence and extinction of long-term memory in the mammalian brain. We also try to understand how the brain decides whether an unfamiliar sensory item should be stored in memory or just ignored. In most of our studies we concentrate on taste memory in the rat. Rats acquire information about taste very rapidly, hence the temporal window of acquisition and consolidation of memory can be well delineated. The information is then robustly retained over time, thus enabling longitudinal analysis of the mechanisms of long-term memory. In certain taste conditioning paradigms, information on novel taste can be associated with a reinforcer even hours after the first encounter with that stimulus. This permits investigation of acquisition of stimulus attributes in the absence of confounding exogenous reinforcers (i.e., 'incidental' learning, a very common but hardly understood type of learning in mammals). Furthermore, rats are amenable to molecular, cellular, neuroanatomical and behavioral analysis, thus permitting a concerted analysis of learning and memory of ecologically meaningful tasks at various levels of biological organization and function.

Role of the insular cortex and the amygdala in taste learning

We have established that the insular cortex, which includes the taste cortex, is obligatory for normal learning of tastes. The amygdala, a brain region involved in emotional memory, is also obligatory for the encoding of taste memories. Such learning can be inhibited by blocking cholinergic or glutamatergic transmission during conditioning but not afterwards. The gustatory thalamus, the gateway of taste information to the cortex, is also under study.

Novel tastes activate intracellular signaling cascades

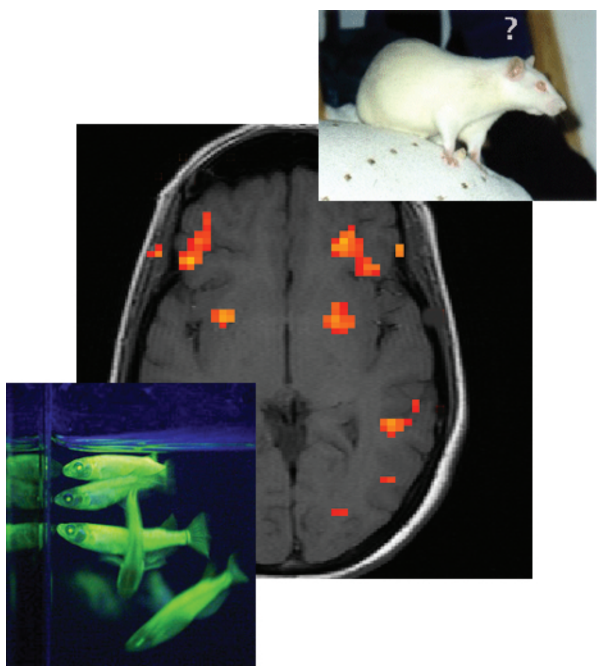
We found that when rats sample an unfamiliar taste, elements of mitogen-activated protein kinase (MAPK) cascades are specifically and differentially activated in the insular cortex. This activation, which can be blocked by a specific inhibitor, is obligatory for the formation of long-term taste memory. Furthermore, the activation of MAPKs cascades induces the activation of downstream nuclear targets such as the transcription factor Elk-1. We are also developing new behavioral paradigms, including context-dependent conditioning, to study how different memory representations could be subserved by a differential activation of the transcription factor CREB.

Glutamate, acetylcholine, and dopamine are important for MAPK and Elk-1 activation

We also set out to investigate which neurotransmitter systems mediate the information about taste and its unfamiliarity in the taste cortex. We found that glutamatergic, as well as cholinergic and dopaminergic transmission, is obligatory for long-term taste memory and taste-dependent MAPK and Elk-1 activation in cortex. Other neuromodulatory systems are also investigated.

Memory updating requires de novo protein synthesis

Once stored, long-term memories can be modified, or 'updated', by a 'relearning' process. We have recently found that the process of memory extinction, in which long-term taste memories are modified as a result of retrieval in the absence



of reinforcement depends on the synthesis of new proteins in the insular cortex and amygdala. This process does not seem to require the activation of MAPK cascades, but depends on β-adrenergic transmission.

The representation of taste and novelty by neuronal activity in the gustatory cortex

We search for the neuronal code(s) of familiar vs. unfamiliar taste in the insular cortex by recording multiple single units from the freely moving rat. We wish to establish which brain areas contribute to the signaling of unfamiliarity in the brain, and how neuronal cells adjust their activity to accomplish this task. (This project is in collaboration with Dr. Ehud Ahissar.)

The role of telencephalon in learning and memory

We investigate the phylogenetic contribution of the telencephalon to learning, consolidation and retention of memory in the teleost fish Medaka (*Orysias latipes*), which is also suitable for neurogenetic analysis.

Reading through a mirror

Human memory is also investigated in our laboratory. A major distinction in human memory is between declarative versus procedural systems. While improved performance in simple perceptual and motor skill tasks seems to reflect only procedural knowledge, it is not clear which memory systems are involved in the long-term memory of higher-level skills, such a reading. We are studying the acquisition and consolidation of skill in reading mirror transposed material, using psychophysics and functional neuroimaging (fMRI), to get a better understanding of the mechanisms involved in the consolidation of human memories. (This project is in collaboration with Dr. Avi Karni.)

Selected Publications

Dudai, Y. (1997) How big is human memory, or, on being just useful enough. Learning & Memory 3, 341-5.

Dudai, Y. (1997) Time to remember. Neuron, 18, 179-182.

Rosenblum, k., Berman, D. E., Hazvi, S., Lamprecht, R., and Dudai, Y. (1997) NMDA receptor and the tyrosine phosphorylation of its 2B subunit in taste learning in the rat insular cortex. J. Neurosci. 17, 5129-5135.

Lamprecht, R., Hazvi, S., and Dudai, Y. (1997) cAMP response element-binding protein in the amygdala is required for long- but not short-term conditioned taste aversion memory. J. Neurosci. 17, 8443-8450.

Berman D. E., Hazvi, S., Rosenblum, K., Seger, R. and Dudai, Y. (1998) Specific and differential activation of mitogen-activated protein kinase cascades by unfamiliar taste in the insular cortex of the behaving rat. J. Neurosci. 18, 10037-10044.

Dudai, Y. (1999) The smell of representations. Neuron 23, 633-635.

Lamprecht, R., and Dudai, Y. (2000) The amygdala in conditioned taste aversion: It's there, but where. In: The amygdala (Aggleton J, ed), Oxford University Press, Oxford, pp 331-351.

Dudai, Y., and Morris, R.G.M. (2000) To consolidate or not to consolidate: what are the questions? In: Brain, Perception, Memory. Advances in Cognitive Sciences (Bolhuis J.J. ed), Oxford, University Press, Oxford pp. 149-162.

Dudai, Y. (2000) The shaky trace. Nature 406, 686-687.

Berman D. E., Hazvi, s., Neduva, V. and dudai, Y. (2000) The role of identified neurotransmitter systems in the response of the insular cortex to unfamiliar taste: activation of ERK1-2 and formation of a memory trace. J. Neurosci. 20, 7017-7023.

Berman, D.E., and Dudai, Y. (2001) Memory extinction, learning anew, and learning the new: dissociations in the molecular machinery of learning in cortex. Science 291, 2417-2419.

Dudai, Y., (2002) Memory from A to Z. Keywords, concepts and beyond. Oxford, University Press (in press).

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