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In search of the Engram: Brain Mechanisms of Consolidation, Remodeling, and Extinction of Memory

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We investigate molecular, cellular, and system processes and mechanisms of learning and memory in the brain. We are particularly interested in the processes and mechanisms that convert memory into a long-term form (consolidation), and in the post-retrieval fate of memory items, including remodeling and extinction. For example, we wish to know how the brain decides whether an unfamiliar sensory item is to be stored or just ignored; how experience influences the manner in which information is perceived and processed; whether long-term memory is stable over time and use; and whether one could target an item in memory for specific erasure. Among other findings, we have recently unveiled a new rule that determines the stability of retrieved memory items. Our studies relate to the theoretical understanding of brain function, as well as to clinical issues, such as the pathology and treatment of certain memory and anxiety disorders.

One chapter in our research program focuses 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 analysis of the mechanisms of long-term memory and its fate after retrieval. In certain conditioning paradigms, information on taste can be associated with a reinforcer even hours later. 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). 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 organization and function.

Another chapter in our research program focuses on pharmacological and behavioral aspects of acquisition, consolidation, activation and extinction of memory in a small fish, medaka. This species provides an opportunity to study primitives of memory processes and mechanisms in a vertebrate brain with only rudimentary telencephalon and no neocortex. The medaka is also highly suitable for neurogenetic analysis.

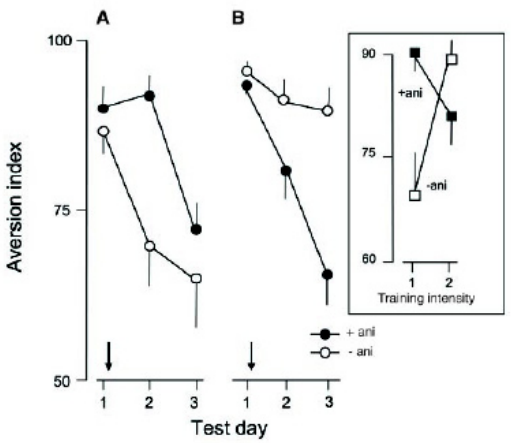

Fig.1 *Winner may lose it all: Effect of the protein synthesis inhibitor anisomycin, which blocks consolidation of long-term memory, on the extinction of aversive taste memory, as a function of the intensity of training. A. After a single training trial, the memory extinguishes readily; microinfusion of anisomycin into the taste cortex immediately after retrieval (arrow) blocks extinction. In contrast, after two training trials (B), the trace becomes much more resistant to extinction, and the effect of anisomycin after retrieval is now reversed: it causes amnesia of the original memory. These and additional findings in rat and fish have led us to conclude that among multiple associations of a memory item, the one that retains or gains control over behavior after retrieval, is also the one that undergoes a renewed consolidation process (reconsolidation), in which it becomes susceptible to change, including suppression or even erasure.*

Fig.2 *New worlds: In a rule learning paradigm designed to investigate consolidation, remodeling and extinction of human memory, subjects are presented on the computer screen with an unfamiliar virtual world, in which they have to paint a room using acts and tools never used in the real world. This is done to ensure that all the subjects are naive in the experimental setting at the beginning of the experiment. The rules then change unexpectedly.*

Yet another chapter in our research program deals with human memory. Here, again, we are interested in the acquisition, consolidation, and the post-retrieval fate, including forgetting, of the memory trace. Our studies on humans employ a combination of psychophysical method and functional neuroimaging. In particular, we use and develop paradigms of emotional priming (in collaboration with Dr. Talma Hendler, Ichilov Medical Center, Tel-Aviv), tinnitus (ear-ringing) and its anxiety and memory components (in collaboration with Dr. Amnon Shapira, Barzilai Hospital, Ashkelon), rule memory in a virtual world, and fast perceptual learning (insight, in collaboration with Dr. Nava Rubin, New-York University).

In both animal and human studies, we maintain close collaborations with several research centers worldwide, and particularly with New York University. We share collaborative multinational research grants with Dr. Joseph LeDoux (NYU), Dr. Karim Nader (McGill), Dr. Randolf Menzel (Berlin), and Dr. Richard Morris (Edinburgh).

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