The search for real-life long-term memory traces and their stability and malleability in the mammalian brain

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We investigate molecular, cellular, and system mechanisms of learning and memory in the mammalian brain. We do this by studying rats and humans. In all our studies, we consider learning and memory as multilevel processes, which should be examined in real-world contexts. At the same time, these contexts should still enable reproducible, controlled experimentation, using tools of state-of-the-art brain research.

We are particularly interested in the processes and mechanisms that support encoding of unique one-time events into memory; in the processes that stabilize such memory into a long-term form ("consolidation"); in the persistence of memory traces over a long period of time; and in the retrieval and post-retrieval fate of memory items, including remodeling, extinction, suppression and forgetting. We hold the premise that although one-shot memories may be retrieved to some degree even years or decades after their encoding, they are malleable throughout. In our research program we wish to understand the processes and mechanisms of both the persistence and the malleability.

In our studies of brain substrates of human memory, we employ several paradigms that examine episodic memory. One set of studies uses movies (both commercial and custom made movies, created specifically for use in memory studies) as stimulus material, in order to mimic content and conditions of information processing leading to memory formation in real life. Memory is then tested hours, days, weeks or months later, by computerized interactive questionnaires that sample memory for movie events at high resolution and also tap into self-evaluation of recollective abilities ("metamemory"). By gauging memory performance parameters, we find that memory dissociates into "long-term" (up to a few weeks) and "remote" (longer than a few weeks). In parallel, we use functional magnetic resonance imaging (fMRI) to monitor changes in hemodynamic brain activity while the participants encode or retrieve the memory of the movie. We find, for example, that activity in brain areas previously known to support emotion and social information processing predicts successful encoding of ongoing episodes.

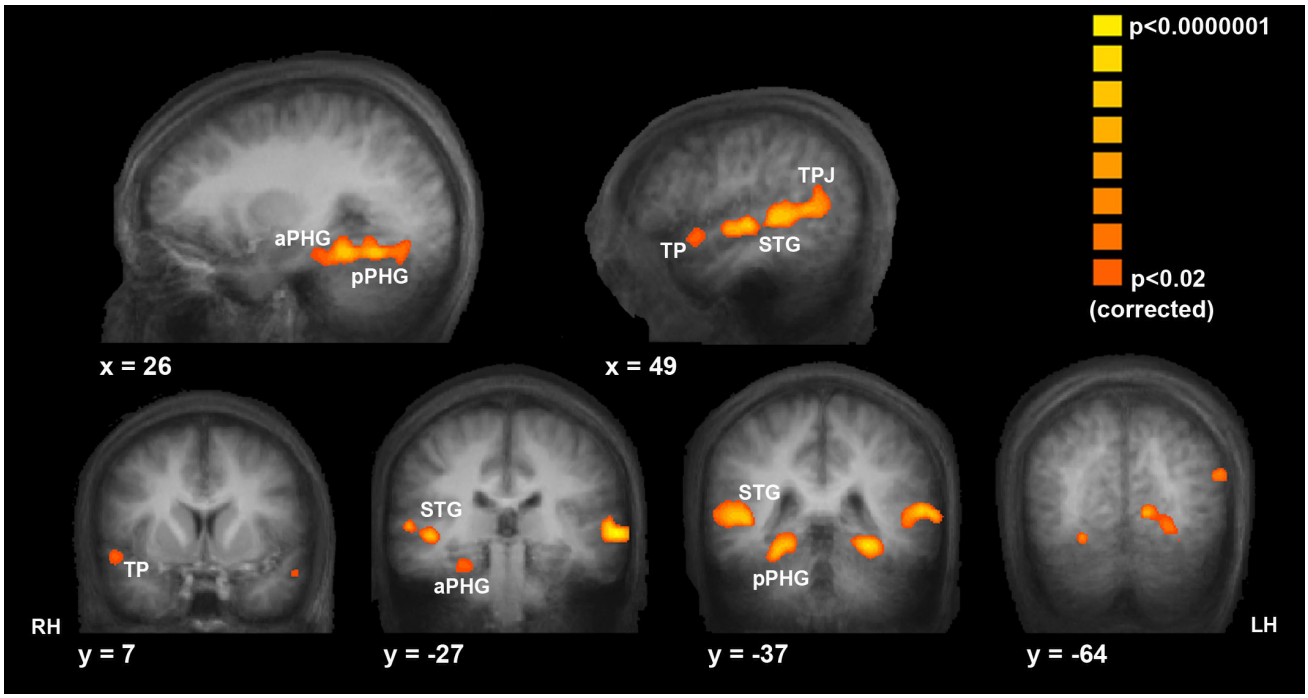

Fig. 1. *A brain network engaged in social and emotional processing is also required for long-term memory of audio-visual narratives. Subjects were scanned while watching a 27 min movie inside the MRI scanner. They returned for a memory test 3 weeks later and according to their performance a subsequent-memory inter-subject correlation (SM-ISC) analysis was performed. Overlaid on an average anatomical image of the 12 subjects are brain areas (orange) showing significantly higher correlation across subjects while viewing movie segments that were later remembered, compared with movie segments that were not remembered. This network includes brain regions known to support memory encoding, like anterior and posterior parahippocampal gyrus (aPHG, pPHG), as well as brain regions not previously found in memory studies. These regions, which were previously found to support emotion and social information processing, include temporal-parietal junction (TPJ), superior temporal gyrus (STG) and temporal pole (TP). (Hasson, Furman et al., 2008.)*

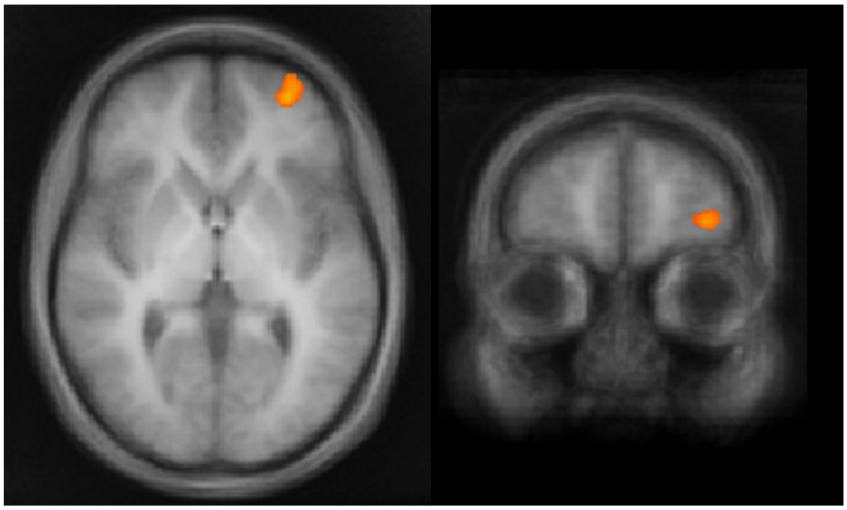

Fig. 2. *The left rostrolateral prefrontal cortex seems to be able to veto memory retrieval in subjects susceptible to post-hypnotic amnesia (PHA). Subjects who were either susceptible or non-susceptible to posthypnotic amnesia viewed a custom-made documentary movie describing the daily life of a young woman. A week later they were induced into a hypnotic state in the MRI scanner and received a post-hypnotic suggestion to forget the movie. When tested on movie details, memory in susceptible participants was suppressed to chance-level performance, accompanied by increased activation in the left rostrolateral prefrontal cortex. The memory returned to normal upon subsequent cancellation of the post-hypnotic amnesia suggestion. (See Mendelsohn et al., 2008.)*

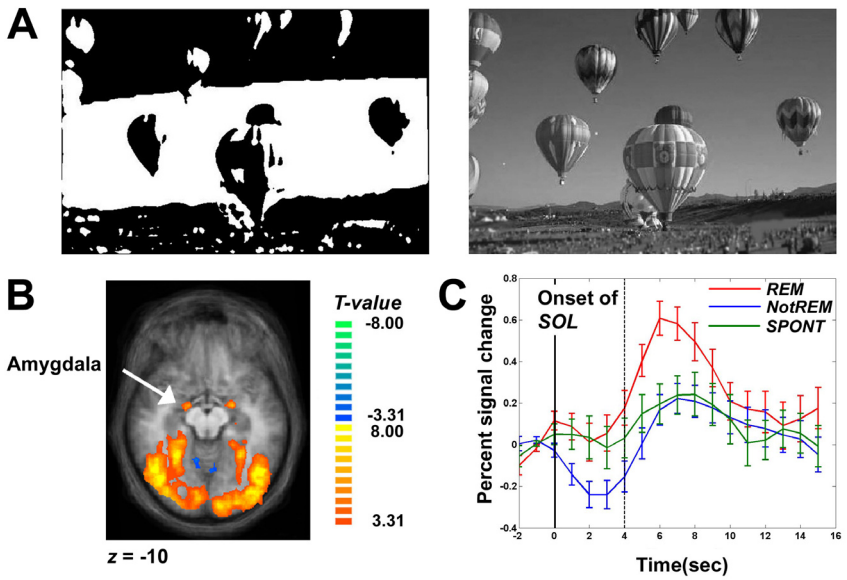

Fig. 3. *Activity in left amygdala predicts one-shot perceptual learning of camouflage images. (A) A camouflage image and its solution. (B) Neural activity in visual areas, lateral frontal areas and bilateral amygdala is elevated during viewing of the solution to camouflages, when compared to a baseline condition (viewing a blank screen). (C) Activity in left amygdala predicts subsequent memory of camouflage solution. Subjects were scanned while they viewed camouflages and their solutions, returning one week later for a memory test. Amygdala activity during viewing of subsequently remembered solutions (REM, red) was significantly higher than activity during viewing of solutions to images not remembered later (NotREM, blue), or during viewing of solutions to images that were spontaneously identified (SPONT, green). (Ludmer, Dudai & Rubin, in preparation.)*

We have recently used the unique tool of hypnosis in a related movie-memory paradigm, as a tool for studying mechanisms of memory suppression in highly-hypnotizable individuals which are susceptible to a suggestion to forget specific information once hypnosis is terminated (this reversible suggestion results in post-hypnotic amnesia, PHA). We found that suppression of memory performance for movie items in these individuals correlates with heightened activity in a specific prefrontal cortex area. We propose that this area serves to support pre-retrieval monitoring which can either promote or veto retrieval at an early stage. It is noteworthy that such vetoing may play an intriguing role in a spectrum of common and less-common emotive and cognitive pathologies.

Another on-going study investigates real-life memory by engaging subjects in real-world staged activities that they later recall while undergoing fMRI scanning. This study indicates, for example, that in real life, memory for temporal order of events decreases much more quickly than memory for event content. We are now searching for the brain circuits that underlie this differentiation.

Further studies in human subjects include the investigation of rapid, single-shot learning of camouflage image solutions, and investigation of the contribution of emotional arousal, as measured by galvanic skin response (GSR) and other physiological measures, to the consolidation and retrieval of memory.

In the only non-memory project in our lab (though memory might be integrated into this project as it unfolds), we study the brain mechanisms of courage in humans. Here we combine behavioral studies and functional neuroimaging of the mechanisms that permit the brain to overcome sustained fear, using a rather unique experimental procedure (which we leave undisclosed to ensure that new participants enjoy the surprise, not only the challenge).

In our persistent and multi-faceted investigation of the mechanisms of long-term memory in the rats' brain, we have recently found that rather unexpectedly, an enzyme must remain persistently active to keep memory going in neocortex for at least several months. This result is unpredicted by textbook accounts of the mechanisms of long-term memory. The enzyme is the atypical protein kinase PKMzeta, and it is required to keep remote taste associations in the insular cortex (which contains the taste cortex). Application of a selective inhibitor of this kinase, called ZIP, into the insular cortex, appears to rapidly erase the memory. In these studies we use conditioned taste aversion (CTA), a paradigm of single-trial learning during which a rat learns to associate a novel taste with transient malaise. This paradigm has been used extensively in our laboratory in recent years to elucidate molecular and cellular mechanisms of encoding, consolidation, extinction and reconsolidation of memory. Current work in our lab now attempts to target PKMzeta-related mechanisms to achieve memory enhancement, rather than erasure.

Selected publications

Eisenberg M, Kobilo T, Berman DE and Dudai Y (2003) Stability of retrieved memory: Inverse correlation with trace dominance. *Science*, 301, 1102-1104. [PDF]

Dudai Y and Eisenberg M (2004) Rites of passage of the engram: reconsolidation and the lingering consolidation hypotheis. *Neuron*, 44, 93-100. [PDF]

Dudai Y and Carruthers M (2005) The Janus face of Mnemosyne. *Nature*, 434, 567. [PDF]

Morris RGM, Inglis J, Ainge JA, Olverman HJ, Tulloch J, Dudai Y, and Kelly PAT (2006) Reconsolidation of spatial memory: differential sensitivity of distinct spatial memory tasks to local inhibition of protein-synthesis in dorsal hippocampus following memory retrieval. *Neuron*, 50, 479-489.[PDF]

Furman O, Dorfman N, Hasson U, Davachi L, and Dudai Y (2007) They saw a movie: Long-term memory for an extended audiovisual narrative. *Learning & Memory* 14, 457–467. [PDF]

Shema, R., Sacktor, TC., and Dudai, Y. (2007) Rapid erasure of long-term memory associations in cortex by an inhibitor of PKMzeta. *Science* 317, 951-953. [PDF]

Mendelsohn A, Chalamish Y, Solomonovich A, and Dudai Y (2008) Mesmerizing memories: Brain substrates of episodic memory suppression in posthypnotic amnesia. *Neuron* 57, 159-170. [PDF]

Hasson U, Furman O, Clark D, Dudai Y, and Davachi L (2008) Enhanced inter-subject correlations during movie-viewing correlates with successful episodic encoding. *Neuron* 57, 452-462. [PDF]

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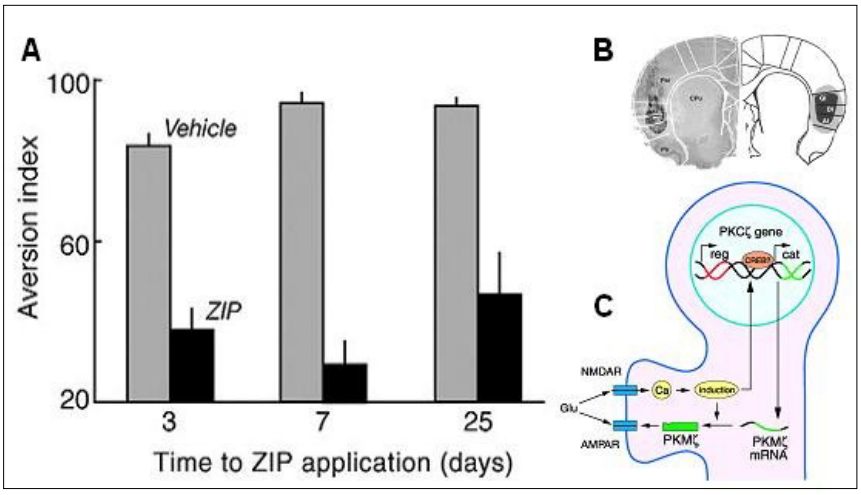

Fig. 4. *Long-term memory is rapidly erased by a single application of the PKMzeta inhibitor ZIP into insular cortex of the rat. (A) The inhibitor was microinfused at the indicated times after taste aversion training. Memory loss was observed in all groups. (The lower the aversion index, the weaker the memory.) In other experiments, memory was instantaneously erased even 3 months after learning. (B) A coronal section of the rat brain, depicting the taste cortex. (C) Model of synaptic changes assumed to subserve memory, adapted from studies of hippocampal long-term potentiation (LTP). Activation by the neurotransmitter glutamate (Glu) of the NMDA receptor (NMDAR) triggers increased synthesis of PKMzeta mRNA. The translated PKMzeta protein then potentiates AMPA receptors (AMPAR)-mediated transmission (the model in C is adapted from Hernandez et al, JBC 2003, 278, 40305; for the data from which A and B panels are adapted, see Shema et al., 2007).*