Modeling the role of acetylcholine and hippocampal theta rhythm in memory-guided behavior

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Lesions of the hippocampus and cholinergic blockade both impair performance in memory guided tasks. In my modeling work (Hasselmo, 1999; Hasselmo et al., 2002 a,b,c), physiological and anatomical data were used to constrain the structure of models of hippocampus and prefrontal cortex, to analyze the role of cholinergic modulation and theta rhythm oscillations in memory-guided behavior mediated by these structures. These models have been used to replicate aspects of human verbal memory function as well as rat spatial navigation. These simulations demonstrate the role of acetylcholine and theta rhythm oscillations in setting dynamics which serve to maximize the encoding and context-dependent retrieval of sequences of activity. Specific dynamical requirements include: 1.) Encoding of new information without interference from previously encoded information requires transitions between encoding and retrieval states (Hasselmo and Bower, 1993; Hasselmo, 1999; Hasselmo et al. 2002a), 2.) Selection of the correct movement based on memory of previous events in a specific task requires mechanisms for timing and synchronization of retrieval activity (Hasselmo et al., 2002b), 3.) Linking slow behavioral transitions to fast neuronal mechanisms of spiking and synaptic modification requires intrinsic mechanisms for maintaining sustained activity (Fransen et al., 2002). These neuronal mechanisms all appear to be associated with cholinergic modulation and theta rhythm in the rat hippocampus and prefrontal cortex. Loss of some of these properties can underlie the impairments of memory-guided behavior observed with cholinergic blockade or with fornix lesions which reduce hippocampal theta rhythm. Models have generated the prediction that cholinergic blockade should enhance proactive interference in paired associate memory tasks, which has been supported by experimental data (Atri et al., 2003). Models have also demonstrated how the same oscillatory variables that maximize memory-guided behavior also serve to simulate physiological data on neuronal spike firing and field potentials in the hippocampus.

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