Neurophysiological data and modeling support a role for theta rhythm in the encoding and context-dependent retrieval of sequences.

Michael E. Hasselmo, Department of Psychology Center for Memory and Brain, Boston University, 2 Cummington St., Boston, MA, 02215, hasselmo@bu.edu. http://people.bu.edu/hasselmo

Lesions of the fornix reduce the amplitude of hippocampal theta rhythm and impair performance in memory guided tasks including delayed spatial alternation and spatial reversal. Using a combination of neurophysiological experiments and computational modeling (Hasselmo et al., 2002a,b,c, Hyman et al., 2003; Wyble et al., 2000), I have proposed potential functional roles of hippocampal theta rhythm in these tasks. Here I will present a combined model of the hippocampal formation and prefrontal cortex which guides movements of a virtual rat in virtual spatial tasks, using representations of current and prior state to obtain goal directed selection of next action.

My modeling work demonstrates specific dynamical requirements which serve to maximize the encoding and context-dependent retrieval of sequences of activity. 1.) Encoding of new information without interference from previously encoded information requires transitions between encoding and retrieval states (Hasselmo et al. 2002a), which may be enhanced by modulatory changes in synaptic transmission during the theta cycle (e.g. Wyble et al., 2000; Molyneaux and Hasselmo, 2002), and modulatory changes in the induction of LTP (e.g. Pavlides et al., 1988; Hyman et al., 2003), 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 in the hippocampus (Hasselmo et al., 2002b; Hasselmo, submitted), in which interactions of forward associations and the reverse spread of context selects specific sequences for retrieval. These neuronal mechanisms appear to be associated with theta rhythm in the rat hippocampus, entorhinal cortex and prefrontal cortex. Loss of some of these properties may underlie the impairments of spatial alternation and reversal learning observed with fornix lesions.

This modeling effectively links neurophysiological data to the functional role of theta rhythm oscillations. The same oscillations that maximize memory guided behavior in the spatial alternation task also serve to simulate data on neuronal spike firing and field potentials in the hippocampus, including 1.) the phase relationships of synaptic currents during theta rhythm (Brankack et al., 1993; Buzsaki, 2002), 2.) the context-sensitivity of neuronal firing ("splitter cells") during spatial alternation (Frank et al., 2000; Wood et al., 2000), 3.) the phenomenon of theta phase precession of place cells (O'Keefe and Recce, 1993; Skaggs et al., 1996; Huxter et al., 2003), and 4.) the selective changes in theta phase precession across different trials on the same day (Mehta et al., 1997; Mehta et al., 2002).

Hasselmo, M.E., Bodelon, C. and Wyble, B.P. (2002a) A proposed function for hippocampal theta rhythm: Separate phases of encoding and retrieval enhance reversal of prior learning. *Neural Computation* 14: 793-817.

Hasselmo, M.E., Hay, J., Ilyn, M. and Gorchetchnikov, A. (2002b) Neuromodulation, theta rhythm and rat spatial navigation. *Neural Networks*, 15: 689-707.

Hasselmo, M.E., Cannon, R.C. and Koene, R.A. (2002c) A simulation of parahippocampal and hippocampal structures guiding spatial navigation of a virtual rat in a virtual environment: A functional framework for theta theory. In: Witter, M.P., Wouterlood, F.G. (eds.) *The parahippocampal region: organisation and role in cognitive functions.* Oxford University Press: Oxford. pp. 139-161.

Hyman, J.M., Wyble, B.P., Goyal, V., Rossi, C.A., Hasselmo, M.E. (2003) Stimulation in hippocampal region CA1 in behaving rats yields LTP when delivered to the peak of theta and LTD when delivered to the trough. *J. Neurosci.* 23(37):11725-31.

Molyneaux B.J. and Hasselmo, M.E. (2002) GABAB presynaptic inhibition has an in vivo time constant sufficiently rapid to allow modulation at theta frequency. *J. Neurophysiol*. 87(3): 1196-1205.

Wyble, B.P., Linster, C. and Hasselmo, M.E. (2000) Size of CA1 evoked synaptic potentials is related to theta rhythm phase in rat hippocampus. *J. Neurophysiol*. 83(4):2138-2144.