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Network effects of age-related NMDA reduction in a model of working memory

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Specific cognitive deficits in working memory tasks are associated with normal aging in humans and nonhuman primates, even in the absence of pathologies such as Alzheimer's disease. Because normal aging does not involve widespread neuron death or gross morphological degeneration, the cause of these deficits remains unclear, although subtle anatomical and physiological effects are likely to play a causal role [1]. NMDA glutamate receptors in spines mediate synaptic communication and are critical in long-term potentiation (LTP) and learning. NMDA's dependence on postsynaptic depolarization has been proposed to enhance network stability through synaptic bistability [2]. Reduced NMDA expression is associated with aging in macaque monkeys and rats [3].

Combining single cell and network modeling methods, we investigated the hypothesis that decreased synaptic NMDA conductance is sufficient to cause network-level deficits in "discrete-attractor" working-memory tasks.These tasks can be modeled with a network of recurrently connected model neurons in which the synapses are tuned according to a Hebbian pattern, so that synaptic reverberation enables the network to store and respond to specific input patterns [4]. Such a network was constructed using multiple instances of a branched multicompartment model of an electrophysiologically characterized layer 2/3 neocortical pyramidal neuron from prefrontal cortex (PFC) of a young macaque monkey. The neuron was imaged at high resolution using a confocal laser scanning microscope; images were reconstructed using custom-developed software (VIAS) which generated a morphologically accurate model for the NEURON simulation system [5,6]. Passive cable parameters and active channel conductances were then fit to a range of sub- and super-threshold voltage responses [7]. Reduction in NMDA expression at the spines was modeled in the context of a simulated working memory task to quantify the stability of stored patterns in the network and the robustness of task function to perturbation of network parameters. Results are presented in a "stability manifold" framework which permits a global assessment of functional impairment over a range of network parameters [8]. Principal component analysis of the manifold generated vectors that quantify the stability variation over the network's parameter space; the directions and relative sizes of these principal components reveal which parameters can "trade off" against each other, suggesting possible avenues for network-level homeostasis. This approach allows quantitative investigation of the mechanistic link between a known molecular-level symptom of normal aging and one type of functional cognitive defect.

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