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Poster presentation

Why are pyramidal cell firing rates increased with aging, and what can we do about it?

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Altered neuronal morphology and electrophysiological function in aged primates are correlated with cognitive deficits [1]. Recent experimental studies of young and aged layer 2/3 pyramidal neurons of the prefrontal cortex (PFC) of rhesus monkeys show an age related increase in both the somatic input resistance and action potential (AP) firing rate [1]. Aged cells display fewer apical dendrites, and reduced spine numbers, although the average spine in an aged cell is larger [2]. Figure 1 compares the morphology and firing patterns for typical young (left column) and aged (right column) pyramidal cells from the PFC of rhesus monkeys [2], illustrating that an aged cell fires at a higher frequency for the same 2s current injection (380 pA) at the soma, despite being similar in overall size and morphology to the young cell.

Through compartment modeling of these neurons, we extract aspects of altered morphology and electrophysiology that are central to age-related deterioration in cognitive function. We explore homeostatic mechanisms that can compensate for this deterioration partially or completely. To quantify homeostatic trade-offs between morphology and electrical function, we have designed morphologic metrics that include spine surface area, numbers of apical and basal dendrites, and volume of the soma, while active channel metrics are characterized by their maximal conductances, kinetics, and spatial distribution. By utilizing the concept of normalized sensitivity [3,4], the effect of perturbations in these metrics on neuronal function characterized by AP firing rate, somatic input resistance, AP firing rate adaptation, electrotonic lengths, and transfer impedance, is determined in terms of unitless measures (sensitivities). By nature, unitless measures allow direct quantitative comparison between parameters as different as branch diameter (μm) and channel densities (mS/cm^2). Our preliminary investigations and experimental evidence of an age related increase in slow Afterhyperpolarization (sAHP) and hyperpolarization activated cation (H) channel densities, suggest sev-

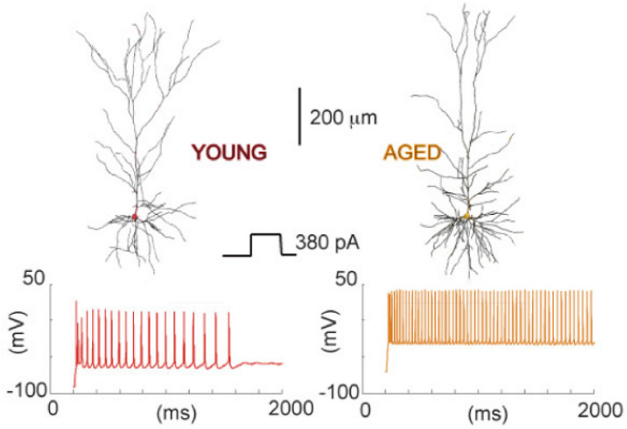

Figure 1
LAYER 2/3 NEURONS.

eral alternative hypotheses regarding altered neuron function with age. The increased sAHP, for example, could reflect a compensatory mechanism acting to minimize the firing rate increases that accompany morphologic change, or it may be an epiphenomemon of altered calcium influx observed in normal aging. Our analytical techniques allow us to predict the functional consequences of these alternatives. We also predict biologically realistic mechanisms, involving combinations of morphologic and active membrane properties, that either subserve altered neuron function, or are compensatory in nature. Using these techniques, we identify compensatory mechanisms that can restore cellular function of aged neurons to normal levels, despite the significant morphologic changes that characterize normal aging.

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