Summary

In primates, normal aging is accompanied by loss of short-term or working memory and decline in memory-related cognitive abilities [1,2]. The prefrontal cortex (PFC) has a major role in the execution of working memory. Execution of a memory task in the PFC is mediated by an increase (or decrease) of action potential (AP) firing rates during more than one epoch (e.g. during cue, delay and/or response periods) [3]. Morphometric studies of pyramidal neurons from PFC have shown no significant neuronal loss with age, but subtle morphologic changes including a significant decrease in the extent of dendritic trees and significant decreases in spine densities and numbers [4,5]. Computational studies have shown that neurons with different dendritic geometries can exhibit different profiles of AP firing patterns [6,7]. Consequently, the changes observed in dendritic geometries with age could cause altered AP firing patterns.

Recent in-vitro electrophysiological studies in layer III pyramidal neurons from PFC of macaque monkeys have shown a significant age-related increase in input resistance and in AP firing rates during somatic current injections [8]. We hypothesize that both the age-related decrease in spine densities and numbers, and the reduced dendritic branching patterns, particularly in the proximal apical tree, will increase the input resistance to a given somatic current injection, resulting in increased AP firing rates.

To address this hypothesis, pyramidal neurons from layers 2/3 of prefrontal cortex of young (< 10.2 years) and aged (> 19.2 years) macaque monkeys were electrophysiologically characterized and reconstructed in 3D. Computer simulations were performed to fit experimentally recorded APs, by adjusting the densities of active ion channels known to exist in these neurons. To test the effect of age-related decreases in spine densities on AP firing rates, spine shapes were extracted from a 2-dimensional image of a neocortical layer III neuron, and those spine shapes were added to the reconstructed neurons according to their actual spatial distributions. Using these constrained computational models, we demonstrate how the individual morphologic changes related to dendritic branching, tapering and spine densities may alter neuronal excitability with age. The observed change in AP firing rates might impair the normal neuronal response during a working memory task, and as a result perturb the retention of short-term memory.

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