

AGE-RELATED COGNITIVE IMPAIRMENTS CORRELATE WITH CHANGES IN NEURONS OF PREFRONTAL CORTICAL AREA 46 OF THE RHESUS MONKEY

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In normal aging monkeys, area 46 of the prefrontal cortex (PFC) shows no detectable loss of cortical neurons or volume, though there is an increase in dystrophic myelinated fibers and a loss of subcortical white matter. Nevertheless age-related impairments in cognitive functions of the PFC begin in middle age. In behaviorally characterized monkeys, we used DT-MRI scans to assess long white matter tracts, in vitro whole cell slice neurophysiology to assess neuronal function, post-mortem on-the-slide ligand binding to evaluate serotonergic (5-HT) and nicotinic cholinergic (nACh) receptors and quantitative spatial analysis to assess microcolumnar organization. The DT-MRI scans revealed significant age-related loss of fractional anisotropy in the cingulum bundle, superior longitudinal fasciculus and anterior corpus callosum which correlated with age-related cognitive decline. Neurophysiological analysis of layer 2-3 pyramidal cells indicated that basic membrane properties were unchanged while membrane input resistance is increased, the balance of excitation and inhibition is altered and action potential firing frequency is enhanced. These physiological findings demonstrate profound alterations in the functional responsiveness of healthy neurons and the alterations in firing frequency were significantly related to cognitive impairment. Analysis of receptors demonstrated age-related reductions in 5-HT_{2A} and 5HT-1A receptors as well as the 5-HTU transporter. Non-bungarotoxin (BTX) sensitive nACh receptors declined with age while BTX sensitive receptors increased. Only reductions in 5-HT_{2A} receptors and the 5-HTU transporter were correlated with behavioral impairment of the PFC. Spatial analysis of microcolumns in area 46 revealed a significant age-related loss of microcolumn strength that correlated with age-related behavioral impairment. Since the microcolumn appears to be a fundamental computational unit of the cortex, the reduction in microcolumn strength may reflect the combined effect of connectional alterations, dendritic atrophy, myelin dystrophy and changes in receptors. (Supported by NIH grant P01-AG00001).