



Age is a limiting factor for photobiomodulation of brain diseases

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The progressive number of old adults with cognitive impairment worldwide and the lack of effective pharmacologic therapies requires the development of non-pharmacologic strategies. The photobiomodulation (PBM) is a promising method in prevention of early or mild age-related cognitive impairments. However, it remains unclear the efficacy of PBM for old patients with significant age-related cognitive dysfunction. In our study on male mice, we show a gradual increase in the brain amyloid beta ($A\beta$) levels and a decrease in brain's drainage with age, which, however, is associated with a decline in cognitive function only in old (24 months of age) mice but not middle-aged (12 months of age) and young (3 month of age) animals. These age-related features are accompanied by the development of hyperplasia of the meningeal lymphatic vessels (MLVs) in old mice underlying the decrease in brain's drainage. PBM improves cognitive training exercises and $A\beta$ clearance only in young and middle-aged mice, while old animals are not sensitive to PBM. These results clearly demonstrate that the PBM effects on cognitive function are correlated with age-mediated changes in the MLV network and may be effective if the MLV function is preserved. These findings expand fundamental knowledge about age differences in the effectiveness of PBM for improvement of cognitive functions and $A\beta$ clearance as well as about the lymphatic mechanisms responsible for age decline in sensitivity to the therapeutic PBM effects.

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