Cholinergic overload and resilience to attentional capacities in aging

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Principal Investigators

PARIKH, VINAY

Institution

TEMPLE UNIV OF THE COMMONWEALTH

Contact information of lead PI
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Research Abstract

DESCRIPTION (provided by applicant): Cortically-projecting basal forebrain (BF) cholinergic neurons constitute a crucial component of the brain’s attentional system. Recent evidence from imaging studies suggested that brain activity attempts to cope up with functional age-related

changes. However, it is not known whether prefrontal cortex (PFC)-driven cholinergic mechanisms compensate for age-related decline in attentional capacities. This R21 application seeks support for exploratory research to determine the contribution of posterior-anterior shift and cholinergic overload in cognitive compensation during aging. Cortical acetylcholine (ACh) release operates in phasic and tonic modes to foster attentional performance. Specifically, phasic ACh encode information concerning attention-demanding cues whereas tonic release of cortical ACh is linked to arousal and efficacy of input processing. I hypothesize that, aging disrupts tonic cholinergic activity cortex-wide, and to compensate for consequent loss in arousal and sensory processing, as well as to maintain phasic cholinergic activity, aging increases top-down recruitment of cortical cholinergic inputs. Disruption in this adaptive cholinergic burden produces persistent impairments in attentional capacities. This research will employ an operant-based cognitive task to assess age-related changes in learning abilities and attentional performance of rats. Enzyme- based biosensors and fixed-potential amperometry will be employed to study the dynamics of cortical cholinergic transmission in real time. As nerve growth factor (NGF) signaling via tropomyosin-related kinase (trkA) receptor is critical for the regulation and function of cholinergic neurons, I will also utilize vector-based RNA interference approaches to produce persistent suppression of these receptors in an attempt to weaken corticopetal cholinergic neurons. The experiments of aim 1 will demonstrate that partial cholinergic deafferentation of the PFC but not posterior parietal cortex (PPC) would impair attentional performance and disrupt phasic ACh release of trained aged but not young rats. Moreover, moderate loss of cholinergic inputs either the PFC or PPC would delay task acquisition by interfering with the posterior-anterior shift. Aim 2 will demonstrate that blockade f top-down recruitment of BF cholinergic neurons either by muscimol inactivation of the PFC or the antagonism of BF N-methyl D-aspartate (NMDA) glutamate receptors would impair attentional functions in aged animals. On the other hand, activation of forebrain NMDA receptors in trkA- silenced aged animals is expected to restore attentional deficits. Furthermore, trkA suppression- or age-related reduction in arousal-based tonic ACh release will be reversed by BF NMDA infusions. Collectively, this research will demonstrate that resilience to attentional capacities in aging involves an adaptive response that produces prefrontal cholinergic overload, and disruption in this compensatory process produces attentional impairments. Furthermore, the expected results would provide insights into the cellular mechanisms underlying attentional decline associated with age-related neurodegenerative disorders such as Alzheimer’s disease.

Further information available at:

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