**Physical activity and the neurocognitive state of the aging human brain: Insights into neurobiological and behavioral correlates**

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Aging of the human brain is usually accompanied by deteriorating neurobiological changes expressed from the molecular-cellular level to the macro-architecture of the brain and the function of neural networks across a wide spectrum of cognitive domains [1]. As a result, aging itself is the leading risk factor for cognitive decline, neurodegenerative processes, and the potentially resulting clinical syndrome of dementia, which eventually leads to significant impairment in the ability to perform basic everyday-life functions among these older individuals [2, 3]. Therefore, to date, exploring behavioral and environmental factors with the potential to mediate neuroprotective processes at older age, along with understanding the underlying neurobiological mechanisms of these effects, constitute a main research line in the fields of aging neuroscience and brain plasticity. Physical activity is well-known for its physiological benefits among healthy individuals and pathological conditions [4]. Furthermore, evidence suggest a neuroprotective potential of physical activity and fitness, aerobic in particular, which has been linked to neuronal, synaptic, and neurovascular plasticity, as well as cognitive improvements [5]. However, the majority of the basic neurobiological knowledge we possess regarding the molecular and cellular adaptations of the brain to physical activity has been derived from animal models [6]. Encouragingly, the potential of physical training in promoting cognitive improvements has been demonstrated among humans as well [7], but less is known regarding the neurobiological correlates mediating these effects. One of the greatest challenges we face is learning enough about neuroprotective behaviors, and their underlying mechanisms, in order to be able to promote desirable neurocognitive adaptations in different circumstances such as aging and neuropathology. The purpose of the proposed research program is to investigate the relationship between physiological and behavioral characteristics of physical activity and the neurocognitive state of the aging human brain through examination of associate neurobiological and cognitive correlates, in both healthy older individuals and patients with pathological cognitive decline. I aim to portray a comprehensive description of the contribution and integration of several levels of neurobiological correlates in the aging human brain and their association with physiological and behavioral characteristics of physical activity, a matter of significance to both basic science and clinical settings. In order to do so I will conduct two scientific projects, adapting a multi-modal MRI approach, a neuroimaging modality well accepted for investigating a wide spectrum of biological and physiological characteristics in the human brain [8]. First, we will conduct a randomized controlled trial in order to examine the effect of aerobic training on patients with amnestic mild cognitive impairment (aMCI), a clinical diagnosis reflecting abnormal age-related cognitive decline, with emphasis on memory complaints, which is considered the prodromal stage of Alzheimer's disease. The intervention period will include 16 weeks, 3 sessions per week of aerobic training vs. active control group that will perform light balance and toning workouts (n=15 for each group). We will use functional MRI (fMRI) methods to evaluate neural patterns of information processing and memory encoding, two cognitive abilities shown to be impaired in aMCI [9, 10]. In addition, we will perform structural brain analyses, circulating brain-derived neurotrophic factor (BDNF) measurements, and a comprehensive neuropsychological assessment, to further examine the therapeutic potential of physical training in promoting neuroprotective effects in the early neurodegenerative state. The second project will include a cross-sectional study aiming at examining the relationship between physical activity and cardiorespiratory (aerobic) fitness and the neurocognitive state of the aging human brain from a spectrum of neurobiological aspects derived from different MRI modalities. These will include functional aspects of brain function and connectivity during the aforementioned tasks and resting-state, morphological aspects of grey and white matter, including white matter integrity and lesions and grey matter volume and thickness, and cerebral blood flow, all of which have been demonstrated to be compromised with age. In addition, in order to relate biology to behavior, participants will be evaluated using a comprehensive neuropsychological assessment targeting the major cognitive domains, such as memory and executive functions. Physiological correlates of physical activity will be evaluated using cardiopulmonary exercise test and behavioral aspects of physical activity will be evaluated with Actigraphy technology for 24/7 activity monitoring for one week. We intend to recruit 60 cognitively-intact older individuals which will represent a physically active/inactive lifestyle spectrum from to complete inactive to old-age athletes, in order to examine potential dose-response relationships. In addition, we will use the PRE-data from the aMCI subjects as a complementary experimental group representing older individuals with a mild cognitive decline and higher risk for neurodegeneration. This implementation would help us to address our research questions to a broader segment of the aging population, on a wider spectrum of the neurocognitive status. The proposed research provides a unique approach that sets it apart from previous studies, and bears the potential to significantly advance our understanding, not only of the neuroprotective potential of physical activity at the later stages of life and its potential underlying mechanisms, but also of the relationship between different levels of neurobiological mechanisms in mediating cognitive functions in the aging brain.

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