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Editorial

Exercise and Neural Plasticity

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Despite the growing evidence for the beneficial effects of exercise on the brain, the underlying central and systemic mechanisms remain unclear. In humans, physical exercise improves cognition and mood, in association with increased gray and white matter volume, network connectivity and cerebral blood flow. Studies using rodent models have demonstrated that running enhances synaptic plasticity, neurotransmission, neurotrophin production, angiogenesis, adult hippocampal neurogenesis, memory function and reduces inflammation. Moreover, in animal models of Alzheimer's disease (AD), a devastating neurodegenerative disease with virtually no effective pharmacological treatment options, positive effects of exercise on brain function and pathology are reported. In humans, there are studies showing that exercise may delay or prevent the onset of the disease [1]. Understanding how physical activity exerts its effects will bring us closer to optimizing brain function and effectively addressing neurodegeneration. This Special Issue of *Brain Plasticity* pertaining to 'Exercise and Neural Plasticity', includes two research papers and two review articles that provide insight into these important topics.

Chronic exercise studies on mood, cognition, brain volume, blood and network connectivity are predominantly conducted in adult and aging humans. However, the outcomes of acute physical activity in children and adolescents are less well-studied. To investigate effects of acute exercise on mood regulation in children, Cline et al. [2] utilized functional magnetic resonance imaging (fMRI) to study resting-state functional connectivity (rsFC) of relevant brain regions. As described in detail in the manuscript they studied both the intrinsic connectivity and the correlations of two networks: 1) the frontoparietal network (FPN), including posterior parietal (PPC) and lateral prefrontal cortices (lPFC), which is critical for cognitive processes that require goal-directed control of thoughts and actions; and 2) the default mode network (DMN) which includes the posterior cingulate, precuneus, and medial prefrontal cortices (mPFC), and is associated with introspection. Increased FPN rsFC is considered to benefit affect and cognition, while disruptions in FPN-DMN anti-correlations have been linked to impaired mental health. In their study Cline et al., compared between 20 minutes of acute treadmill walking and seated reading. After acute exercise, regions in the left lPFC of the FPN became more correlated with bilateral lPFC and the left basal ganglia. Furthermore, the left lPFC became more anti-correlated with the DMN precuneus. The opposite was observed after seated reading. Thus, the authors identified important network connectivity patterns that may mediate acute exercise-induced mood improvements in children.

In this Special Issue, the research study by Huuha et al. [3] explores a novel preclinical approach to AD by treating a rat model of the disease with plasma from exercised-donors. Their research is based on findings showing that blood-borne factors influence hippocampal neurogenesis, inflammation and cognitive function. Indeed, administration of young blood to aged recipients, as well as studies collecting blood

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from young or aged exercising rodents and injection into age-matched controls can improve brain function [4]. Previous work by the authors showed that exercised plasma transfusions promote adult hippocampal neurogenesis in the transgenic McGill-RThy1-APP rat model of AD. This effect may be at least partly attributed to reduced levels of proinflammatory cytokines in the plasma from exercise-trained donors [5]. In this new study exercise-trained donor plasma effects on hippocampal and entorhinal cortex microglia and cytokines in a transgenic rat model at either an early or late stage of Alzheimer's disease were evaluated. Plasma for the treatment groups was obtained from young adult male donor rats that underwent either six weeks of treadmill exercise training or were sedentary controls. The AD rats received injections of saline, exercise plasma (ExPlas), or sedentary plasma (SedPlas) over six weeks. No change in cognitive function or plaques was observed. In the early stage group, both treatments increased number and length of microglial branches in the hippocampus. Only ExPlas-treated rats displayed similar changes in subiculum, while entorhinal cortex showed no change. In addition, levels of anti-inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor and interleukin (IL)-18 increased. In the late stage AD group, microglial morphology and number remained unchanged, but ExPlas upregulated IL-17, whereas SedPlas increased inflammatory tumor necrosis factor-α. Altogether, this study the importance of timing on potential outcomes of a novel systemic approach to AD treatment.

Two review articles are included in this Special Issue. The article by Caruso et al. [6] gives insight into the role of exercise in memory function, adult hippocampal neurogenesis and the contribution of the gut microbiome to these processes in middle-aged and old rodents. The authors provide detailed information pertaining to the different training protocols used in rodent studies and their outcomes for several aspects of learning and memory, including spatial memory, novel object recognition and pattern separation behavior. Voluntary wheel running regimens as well as involuntary exercise protocols that require rodents to run for a predetermined duration, intensity and frequency on treadmills or on motorized running wheels, are described in detail. Other types of involuntary exercise such as forced swimming and resistance training are reviewed too, albeit that these interventions are used less often in exercise studies. This information is important given the variability in training protocols currently used in preclinical research and will help determine exercise type, intensity and duration for studies of age-related cognitive decline. The age-related reduction in adult hippocampal neurogenesis which is considered to play a role in diminished cognition, and the neurogenic response to exercise in middle-age and old age are also thoroughly described. Furthermore, the increasing evidence for the link between the gut microbiome composition, aging, adult neurogenesis and exercise is discussed. For instance, research pertaining to effects of fecal microbiome transplant from young to aged rodents on hippocampal function is reviewed, as well as the influence of exercise on microbiome composition. Altogether, the paper provides important insights into exercise regimens that can improve gut and brain health, and thereby adult hippocampal neurogenesis and cognitive function during aging.

The second review paper by Milbocker et al., 2024 [7], pertains to the effects of exercise, enrichment and social isolation on brain plasticity and behavior. The review covers papers published between 2017 and 2023 that pertaining to neural plasticity in the adolescent, adult and aging brain. For instance, novel research pertaining to exercise effects on white matter tract maturation in adolescents as well as on white matter integrity in the aging human brain are described. The authors indicate voluntary aerobic exercise may enhance neurotrophin circulation to promote production of oligodendrocyte precursor cells. Another focus of the paper is on the effects of strength training on neuroplasticity, as well as the combined effects of aerobic and strength training. Furthermore, the importance of timing on age-dependent effects of social isolation on the brain and behavior during adolescence and in adulthood are discussed. Overall, the authors conclude that the brain is most sensitive to neuroplastic changes during development and young adulthood. However, the precise underlying mechanisms and effects on brain structure and function of the diverse neuroplastic stimuli remain to be elucidated.

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