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INVITED COMMENTARY

Exercise is brain food: The effects of physical activity on cognitive function

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Abstract
This commentary reviews selected biomedical and clinical research examining the relationship between physical exercise and cognitive function especially in youth with disability. Youth with physical disability may not benefit from the effects of exercise on cardiovascular fitness and brain health since they are less active than their non-disabled peers. In animal models, physical activity enhances memory and learning, promotes neurogenesis and protects the nervous system from injury and neurodegenerative disease. Neurotrophins, endogenous proteins that support brain plasticity likely mediate the beneficial effects of exercise on the brain. In clinical studies, exercise increases brain volume in areas implicated in executive processing, improves cognition in children with cerebral palsy and enhances phonemic skill in school children with reading difficulty. Studies examining the intensity of exercise required to optimize neurotrophins suggest that moderation is important. Sustained increases in neurotrophin levels occur with prolonged low intensity exercise, while higher intensity exercise, in a rat model of brain injury, elevates the stress hormone, corticosterone. Clearly, moderate physical activity is important for youth whose brains are highly plastic and perhaps even more critical for young people with physical disability.

Keywords: *Neurotrophin*, *neuroplasticity*, *brain-derived neurotrophic factor*, *BDNF*, *rehabilitation*

Este comentario revisa investigaciones biomédicas y clínicas selectas que examinan la relación entre el ejercicio físico y la función cognitiva, particularmente en jóvenes con discapacidad. Los jóvenes con alguna discapacidad física pueden no beneficiarse de los efectos del ejercicio en el cerebro y en el acondicionamiento del sistema cardiovascular, ya que son menos activos que jóvenes sin discapacidad. En modelos animales, la actividad física estimula a la memoria y al aprendizaje, promueve la neurogénesis y protege al sistema nervioso de las lesiones y de las enfermedades neurodegenerativas. Las neurotrofinas son proteínas endógenas que apoyan a los procesos de plasticidad cerebral, y posiblemente median los efectos benéficos del ejercicio sobre el cerebro. En estudios clínicos el ejercicio aumenta el volumen cerebral en áreas implicadas en el procesamiento ejecutivo, mejora la cognición en niños con parálisis cerebral, y aumenta la habilidad fonémica en niños en edad escolar que tienen dificultad para la lectura. Los estudios que examinan la intensidad del ejercicio necesaria para optimizar a las neurotrofinas sugieren que la moderación es importante. El ejercicio prolongado de baja intensidad produce aumentos sostenidos en los niveles de las neurotrofinas, mientras que en un modelo experimental en ratas con lesión cerebral, el ejercicio de alta intensidad mostró una elevación de la corticoesterona, que es la hormona del estrés. Evidentemente la actividad física moderada es importante para los jóvenes cuyos cerebros son altamente plásticos, y tal vez crítica para jóvenes con discapacidad física. Título abreviado: El ejercicio es alimento cerebral.

Palabras clave: *Neurotrofina*, *neuroplasticidad*, *factor neurotrófico de origen cerebral*, *BDNF*, *rehabilitación*

Introduction

It is immediately recognized that exercise promotes good health of the cardiovascular and musculoskeletal systems, however the field of exercise and cognitive function is rapidly growing. Unfortunately, youth with physical disability are twice as likely to watch more than 4 hours of television per day than young people without disability [1].

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As a result, inactive youth with disability not only have lower cardiovascular and musculoskeletal fitness, but do not avail of the cognitive benefits of exercise.

Studies in ageing humans show that endurance exercise is protective against cognitive decline, especially executive planning and working memory [2–4]. In both humans [5–7] and primates [8], exercise increases attention and performance on cognitive tasks. In a rat model of stroke, running exercise promotes neuronal dendritic branching and enhances relearning of forelimb motor skill [9]. Currently there are three hypotheses explaining how exercise may affect executive control. Exercise may increase oxygen saturation [2] and angiogenesis [10] in brain areas crucial for task performance. Kramer et al. [2] found that walking exercise increased the rate of oxygen consumption in healthy older adults that was associated with improved reaction time and enhanced performance in tests of executive functioning. The second hypothesis suggests that exercise increases brain neurotransmitters, such as serotonin and norepinephrine, facilitating information processing [11–13]. Increased levels of arousal, detected by brain electroencephalogram (EEG), have been measured in persons exercising at less than 70% of their maximum oxygen capacity (considered within the moderate training zone) [5, 7, 14]. The third, and probably most well-studied hypothesis, is that exercise upregulates neurotrophins such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-I) and basic fibroblast growth factor (bFGF) that support neuronal survival and differentiation in the developing brain and dendritic branching and synaptic machinery in the adult brain (for review see [15]). It is clear that youth with physical disability, with brains ripe for new learning and sometimes with concomitant cognitive challenges, may require physical activity even more than adults.

The important neurotrophins

To understand neurotrophins and how they support the nervous system, one must understand the effects of these endogenous substances on the neurons themselves. Neurotrophins are proteins that have classically been identified as mediators of neuronal survival and differentiation during development. Each neurotrophin regulates specific populations of neurons during development; however, more recently, neurotrophins have been shown to maintain the viability of neurons in adulthood and protect and restore neurons in response to injury and ageing. Neurons are described as being 'plastic'; the efficacy of synaptic transmission is adaptable and neurotrophins serve as activity-dependent modulators of synaptic plasticity [15]. Neurotrophins regulate target genes which may encode structural proteins, enzymes or neurotransmitters that result in modification of neuronal morphology and function. This ability for neuronal plasticity allows one to form and retain memories and learn in all dimensions; spatially, cognitively and motorically. The neurotrophin brain-derived neurotrophic factor (BDNF) has emerged as a key mediator of synaptic plasticity in the memory centre of the brain, the hippocampus [16]. Synaptic signalling and responsiveness are enhanced within seconds of BDNF administration to rat hippocampal neurons [17, 18]. BDNF also augments the number of synapses and enhances axonal branching within the cortex [17], thereby increasing the potential synaptic contact sites [18]. When the critical expression of BDNF is blocked within the rat brain, the animals show impairments in memory and learning [19, 20]. Importantly, physical activity in rats increases BDNF, as well as genes that are members of synaptic vesicle trafficking machinery and parts of signalling pathways whose activity affects synaptic function [21].

Exercise and neurogenesis

It was once believed that the adult brain was incapable of producing new neurons. It is now known that neurogenesis occurs in the hippocampus and in the layer of cells surrounding the lateral cerebral ventricles (the subventricular zone) and, moreover, that exercise stimulates this proliferation [22]. These cells are sometimes referred to as endogenous stem cells. In a recent study [23], examining the benefit of stem cells in a rat model of stroke, exercise and enriched environment stimulated migration of transplanted stem cells to the injury site and enhanced sensorimotor recovery. Physical activity may increase baseline neuronal activity or neurotrophic support, providing the necessary signals for these cells to integrate into neuronal networks. Stem cells (both endogenous and transplanted) and the influence of physical activity in the developing brain is a promising area of research that could benefit children with physical and cognitive impairment.

Exercise enhances cognitive function

In rats, 1 week of voluntary exercise increases BDNF and enhances performance on the Morris water maze, a test of spatial memory in which rats must remember the location of a submerged platform [24]. These findings have been confirmed by others in both the normal animal brain [25, 26] and the brain altered by injury [9, 27]. There is evidence that

the exercise-cognition phenomenon exits in humans as well, especially in young adults. Aerobic fitness in children is associated with higher measures of neuroelectric responsiveness (P3 amplitude in brain evoked potentials), faster cognitive processing speed [28] and better performance in a test of executive control [29]. A meta-analysis confirmed the positive relationship between physical activity and cognitive and academic performance in school aged children [30]. Even though level of physical activity can be confounded by other factors such as IQ and socio-economic status, these findings are convincing.

In a 2-year follow-up of a prospective randomized controlled trial, Reynolds and Nicolson [31] determined that a 6 month home-based sensorimotor programme enhanced school and reading performance in 36 children with reading difficulty (some with dyslexia). Daily home exercises focused on cerebellar/vestibular challenge including balancing on one leg, spinning, bouncing, standing on a wobble board, tandem walking and throwing and catching balls. Students demonstrated improvements in reading accuracy, phonemic skill, verbal working memory and reduction in inattention symptoms as well as accelerated gains in standard school performance tests. These findings suggest that the benefits of exercise are not simply cardiovascular. The enrichment provided by physical activity has a broad effect on seemingly unrelated executive processing centres. Furthermore, a recent study by Verschuren et al. [32] showed that a 45 minute programme (twice per week for 8 months) not only improved aerobic capacity, strength and function but significantly improved cognition and quality of life in people with cerebral palsy aged 7–20 years. Even more interesting is that 4 months after completing the programme, participants maintained the cognitive benefits while fitness measures returned to baseline. These studies support the concept of an exercise-cognition interaction in children with disabilities. Programmes that increase physical activity and fitness in youth with disability will also likely improve executive function. Future studies examining the implementation of physical activity programmes should not only measure physical fitness but include cognitive, emotional and quality of life outcome measures as well.

Exercise protects the nervous system

Physical activity attenuates the memory and cognitive decline associated with normal ageing and in pathological conditions such as Alzheimer's Disease [33, 34]. Exercise has also been recently shown to increase brain volume in healthy exercising adults. In a study using magnetic resonance imaging (MRI) to examine brain volume, 59 people aged 60–79 were randomly assigned to aerobic or non-aerobic exercise groups (1 hour three times a week for 6 months). Adults exercising aerobically showed increased brain volume in frontal lobe regions implicated in higher order processing, attentional control and memory [35].

In a rodent model of stroke, 2 weeks of voluntary running (0.8 km per day) preceding cerebral stroke resulted in improved survival and sparing of neurons in multiple brain regions [36]. Carro et al. [27] have demonstrated convincingly that moderate exercise (1 km per day) improves functional recovery and saves neurons in a number of rodent injury models. They examined hippocampal degeneration (vulnerable in Alzheimer's disease), brainstem injury and hereditary cerebellar degeneration. Lesioned animals that ran before brain injury had improved function and spared neurons and animals running for 5 weeks following injury, improved to 90% of controls. Exercise maintained function and preserved Purkinje cells in the cerebellum and prevented ataxia in hereditary cerebellar degeneration. Although research in the neuroprotective effects of exercise in humans, especially young people, is scarce, findings in biomedical research are compelling. One wonders if people who are inactive are less protected against neurological injury and neurodegenerative disease.

How much exercise is enough?

If exercise is beneficial for the brain, the next logical question is 'How much exercise is enough?' A recent meta-analysis of 37 studies (1306 children, young adults and older adults) suggests that although most studies support that exercise has a positive effect on cognitive performance, cardiovascular fitness (VO^2 Max) alone does not explain these benefits [37]. Exercise effects on executive function are not dose-responsive, meaning that better fitness does not necessarily lead to larger cognitive gains. In fact, smaller gains in fitness are associated with larger cognitive effect sizes. Studies in children with reading difficulties also show that children received cognitive benefits from a programme designed to challenge balance, timing and co-ordination, rather than cardiovascular fitness [31]. This suggests that physical activity levels that benefit cognition may not necessarily be as intense as those levels required to increase cardiovascular fitness. However, some studies support that intense rather than moderate exercise [12, 13] enhances neurotransmitter levels and improves executive performance. These conflicting findings may reflect differences in exercise paradigms and outcome measures. The specific

exercise-cognition effect threshold is not known and warrants further study.

Our research, using an adult rat model of stroke, examined varying parameters of running exercise to optimize the effects of exercise on brain neurochemistry. BDNF and other markers of neuroplasticity within brain tissue were examined after 30 and 60 minutes of either running or walking on a motorized wheel along with 60 minutes on a voluntary running wheel [38, 39]. Telemetry was used to determine the intensity of exercise to help translate findings to clinical practice. Although 60 minutes of motorized exercise resulted in a robust and immediate increase in hippocampal BDNF, long-term, lower intensity (as measured by heart rate), voluntary exercise resulted in more prolonged upregulation of BDNF (2 hours). The implication for clinical rehabilitation is that frequent, intermittent, low intensity training (that is realistic to provide) as well as a single bout of running exercise can increase hippocampal levels of BDNF creating a favourable 'neuroplastic milieu' during recovery from stroke. Even though exercise enhanced proteins that may be beneficial to recovery of function after stroke, serum corticosterone, a stress hormone, was found to be elevated in response to all methods of exercise but more so with the more intense exercise regimens. Since corticosterone has been implicated in downregulation of BDNF [40], this is a concern and warrants caution acutely after brain injury. For the clinician, the old adage 'everything in moderation' appears to apply when prescribing physical activity for brain health.

Clinical considerations

It is believed that in most societies today people are less active than in previous generations. The effect of this inactivity on brain health is yet to be determined. Hillman et al. [41] state that physical activity during childhood may optimize cortical development promoting lasting changes in brain structure and function, but for youth with disability, the greatest challenge is to find ways to increase physical activity [42]. Kang et al. [43] examined barriers to exercise in 146 youth, aged 12–19, with physical disabilities attending wheelchair basketball camp. These young people identified mainly logistical barriers including lack of time, pain or discomfort, lack of a place to exercise with peers, weather and people's misconceptions of their abilities. Adults administered the same tool complained more of psychological barriers to exercise (lack of time, motivation, self-discipline). These barriers may be overcome by an individually tailored approach to exercise prescription such as *PEP-for-youth* [42] and health providers must emphasize, for their young clients, the multiple benefits of physical activity on brain and body health.

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