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Letter to the Editor

As Long as not all Factors Affecting Brain Volume are Considered, Reduction of Brain-Predicted Age Difference cannot be Attributed to Physical Activity

Josef Finsterer

Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Wan *et al.* on a randomized, controlled trial investigating the effect of endurance training (150 minutes per week for 12 months) on brain age, as measured by brain-predicted age difference (BPAD), in 130 healthy subjects aged 26 to 58 years ^[1]. The study showed that endurance training reduced BPAD and increased maximum oxygen uptake (VO₂max) ^[1]. While the study is interesting, it leaves some questions unanswered.

First, measuring brain age is difficult, and if the age of the brain is indeed what is meant, it corresponds to the age of the rest of the body at the time of measurement. If, on the other hand, the brain's performance, functional, or morphological changes are meant, these depend on numerous factors. The relationship between brain health and exercise is complex and requires consideration of further influencing factors. In addition to arterial blood flow, brain health depends on venous and glymphatic drainage, the function of the blood-brain barrier, genetic predisposition, personality type, socialization, available coping strategies, previous cognitive performance, educational level, socioeconomic status, sleep, environmental factors, nutrition, comorbidities (other than hypertension or neurological disorders), concomitant medication, mood, and alertness. Since the musculature is also an endocrine organ ^[2], physical exercise can not only improve cardiovascular function but also stimulate the secretion of myokines such as irisin or Metrnl-like myokines.

Second, brain volume depends not only on physical activity but also on various other factors. These include age, sex, time of day (brain volume is higher in the morning than in the evening), hydration status, comorbidities (e.g., diabetes), previous brain surgery, the use of concomitant medications, sleep (which leads to a redistribution of fluids in the brain), and the method used to measure brain volume ^[3].

Third, we disagree with the view expressed in the introduction that only midlife is a dynamic phase of life. In general, all phases of life can be dynamic, depending on individual circumstances and events. If a child suffers from early childhood, treatment-resistant epilepsy, their early childhood is characterized by attempts to stop seizures, and their life is extremely dynamic due to the numerous medical needs.

The fourth point is that cerebral atrophy does not necessarily imply cognitive decline ^[1]. There are numerous reports of patients with congenital or acquired focal cerebral atrophy who did not develop any impairment of their cognitive functions during their lifetime ^[4]. For example, patients with arachnoid cysts and reduced brain volume usually behave normally and do not develop any impairment of their higher brain functions. Similarly, patients with porencephaly do not necessarily exhibit cognitive impairment. Unless all factors influencing brain volume are included in the analysis, a reduction in BPAD cannot necessarily be attributed to regular, long-term physical exercise.

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