Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Healthy brain–muscle interface in epilepsy and COVID-19: Increased muscle effort is the alternative

To the Editor

The coronavirus disease 2019 [COVID-19] outbreak has caused unprecedented spikes in "global collective uncertainty and insecurity" [1]. Strong pressure on health systems associated with serious disruptions in people's daily lives has negatively affected people with chronic non-communicable diseases, including people with epilepsy (PWE) [2]. Stressors related to negative disturbance of health, finances, physical and mental well-being, social isolation, educational and professional uncertainties, and increased levels of physical inactivity could affect people of all ages and in the case of PWE increase the frequency of seizures and impair self-management of the disease, quality of life, and health status [3].

We read with great interest the article entitled "Considering temporality in causal relationship between seizure and psychological stress in patients with epilepsy during the COVID-19 pandemic: A systematic review" recently published in "Epilepsy Behavior" [2]. The authors conducted a systematic review on an extremely relevant topic, that is, the impact of emotional stress (a known trigger of seizures), in the seizure frequency, on the course of the pandemic for PWE. The main conclusion of this study was that there is a cause-effect relationship between psychological stress and worsening of seizures [2]. Alkhotani et al. [4] evaluated whether PWE experienced increased seizure frequency and emotional stress during the COVID-19 outbreak. The authors observed that 29.5% reported an increase in seizure frequency and 59.4% in emotional stress. The conclusion of the study was that it is important to identify PWE at high risk of recurrent seizures in periods of high emotional pressure.

For a long time, PWE have lived in the "shadows of society", "forced social isolation", and suffer a lot of prejudice and stigmatization [5]. Long before the pandemic, this whole scenario led to low self-esteem, reduced quality of life, worsening of seizures, and progressive increase in chronic social isolation [6] and probably physical inactivity levels and in a kind of vicious-cycle. It is likely that the COVID-19 pandemic has only aggravated something that is already serious [7]. However, increased seizures of PWE during the COVID-19 outbreak are not a consensus in the literature [8].

Regardless of whether the results of the studies are pointing to an increase or not in the seizure frequency among PWE in the midst of the COVID-19 pandemic, the fact is that the mental and physical health of the general population of different age groups, which includes PWE, is clearly getting worse in the course of the pandemic [9].

Recently, we conducted a study with general population about the emotional consequences of the ongoing COVID-19 pandemic and found that regular physical activity is essential to improve and/or maintain physical and mental health [10]. In addition, Puccinelli et al. [11] showed that the pandemic has a negative impact on physical activity levels and who reduced their level of physical activity had higher level of mood disorders than those who did not change the physical activity level. Vancini et al. [12] showed that regular practice of physical activity could positively impact health status and quality of life and be a tool in the field of public health to cope, from a physical and mental point of view, with disease scenarios that require quarantine such as the COVID-19 outbreak. This is likely to apply for PWE and no doubt for brain and muscle health and their interaction.

For example, Piotrowicz et al. [13] showed that COVID-19 is an infectious disease that could affect multiple physiological systems and is characterized by a severe and highly catabolic inflammatory state that influences the body composition, especially the percentage of muscle mass, which would produce a picture of acute and abrupt sarcopenia. The individual result of the infection and the impact on the loss of muscle and functional mass could be influenced by the general health status in the pre-infection. Since PWE are chronically inactive, hypothetically due to long-term muscle disuse, they could develop early sarcopenia. In the context of the pandemic this can be even more serious and severe especially for PWE that has low muscle activity.

One of the ways to improve brain health is by improving muscle health through physical activity. From a neurological point of view, it is possible to hypothesize that there is a brain–muscle interface that could help PWE to cope with their disease condition during the pandemic and in high emotional pressure scenarios [14].

Regular physical exercise provides benefits for physical and mental health and is a well-known non-pharmacological intervention to improve brain functions, including cognition, memory, motor coordination, neuropsychiatric function, and an important protective factor against neurodegenerative diseases and improvement in functioning of the muscular and cerebral mitochondria, at cellular level [15].

The processes involve positive physiological muscle adaptations to physical exercise related to the mitochondria [15,16]. Physical exercise induces mitochondria cell signaling from skeletal muscle–brain and brain–muscle through the release of myokines [15]. Myokines are muscle-derived effectors, produced by muscle physical exertion, that regulate energy metabolism and cross-talking through autocrine, paracrine, or endocrine action and could improve brain function, health, neurogenesis, and synaptic plasticity [15,16]. Additionally, skeletal muscle is an essential regulator of energy homeostasis and a potent coordinator of exercise-induced adaptations in other organs such as the brain. Although the molecular and cellular mechanisms underlying muscle–brain communication are still poorly understood, physical activity represents one of the most effective strategies to reduce the prevalence and

incidence of depression, cognitive, metabolic, and/or degenerative neuronal disorders [17]. It is known that PWE have low levels of physical activity and physical fitness (cardiorespiratory and muscle strength and mass) when compared to the general population which can contribute to worse epilepsy pathophysiology [18].

In their systematic review, Cavalcante et al. [14] found that regular physical exercise could be beneficial to PWE since it decreases the production of pro-inflammatory and stress biomarkers and cytokines, oxidative stress, social isolation, and symptoms of depression and anxiety and improves cognitive function and increases brain-derived neurotrophic factor (BDNF) levels in the hippocampus and dopamine production and induces neurogenesis and angiogenesis.

Another important factor, of the possible brain–muscle interface, is the loss of PWE muscle mass in the disease course due to chronic muscle disuse, that is, sarcopenia. Sarcopenia can be defined as loss of skeletal muscle mass and function [19]. It involves complex and modifiable genetic risk factors, such as lack of exercise, malnutrition, and reduced neurological drive.

Gustafsson and Ulfhake [19] propose that sarcopenia could have a neurogenic origin through a vicious degenerative cycle of the interaction between nerves and myofibers. For example, it would be the result of the cross-talking between the axon motor and myofiber in the denervation processes that lead to a loss of motor units and muscle weakness associated with the aging process and muscle disuse. Although little studied, this is a possible scenario among PWE.

Given that skeletal muscle contraction is the main source of neurotrophic factors, including BDNF, which regulates brain synapses and that skeletal muscle activity has important immunological and redox effects that modify brain function and reduce muscle catabolism, deterioration of skeletal muscle due to sarcopenia is potentially serious. Therefore, the identification of common risk factors and underlying mechanisms for sarcopenia and cognition may allow the development of targeted interventions that delay or reverse sarcopenia as well as certain forms of cognitive decline. Sarcopenia and cognitive decline share pathophysiological pathways [20]. Despite this important relationship, and the negative consequences, there are still scarce studies focused on the issue of sarcopenia in PWE. This is an important gap in the literature.

The COVID-19 outbreak was the trigger for a long period of isolation and social distance and negatively affected the brain–muscle interface [14]. This has undoubtedly resulted in major reductions in physical activity levels as well as changes in food intake that have the potential to accelerate sarcopenia; deterioration in muscle strength, mass and function; and increase in body fat percentage. The changes in body composition are associated with an increased prevalence of chronic lifestyle diseases, such as cardiovascular disease, diabetes, osteoporosis, frailty, cognitive decline, and depression [21] that can also affect PWE.

Sarcopenia in PWE is a subject that needs to be thoroughly studied from the perspective of the brain–muscle interface [14]. Knowing that one of the ways to positively affect the brain through muscle activity, it is reasonable to assume that increasing muscle mass and strength and the body composition profile may be a factor in improving brain health, cognitive function, and mood state and consequently decrease the frequency of seizures in PWE [14].

Furthermore, we would like to congratulate the authors for the brilliant review and just highlight the importance of maintaining and improving PWE muscle mass and strength levels in order to improve brain and neuropsychiatric health. The COVID-19 pandemic only made this importance even more clear due to the worsening of the situation of social isolation and seizure frequency and probably, as in the general population, the levels of physical inactivity and mood disorders in PWE. For these reasons, studying the multiple aspects of the brain–muscle interface in PWE only became even more important in the midst of the pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Rodrigo Luiz Vancini [a,*]
Marília Santos Andrade [b]
Beat Knechtle [d]
Pantelis Theodoros Nikolaidis [e]
Claudio Andre Barbosa de Lira [c]
[a] *Centro de Educação Física e Desportos, Universidade Federal do Espírito Santo, Vitória, Brazil*
[b] *Departamento de Fisiologia, Universidade Federal de São Paulo, São Paulo, Brazil*
[c] *Setor de Fisiologia Humana e do Exercício, Laboratório de Avaliação do Movimento Humano, Faculdade de Educação Física e Dança, Universidade Federal de Goiás, Goiânia, Brazil*
[d] *Medbase St. Gallen Am Vadianplatz, St. Gallen and Institute of Primary Care, University of Zurich, Zurich, Switzerland*
[e] *School of Health and Caring Sciences, University of West Attica, Greece*
* Corresponding author at: Centro de Educação Física e Desportos (CEFD), Universidade Federal do Espírito Santo (UFES), Campus Universitário - Av. Fernando Ferrari, 514, CEP: 29075810 Goiabeiras, Vitória-ES, Brazil.
E-mail address: rodrigoluizvancini@gmail.com (R.L. Vancini)
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