Role of Physical Activity and Exercise in Alleviating Cognitive Impairment in People With Epilepsy

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ABSTRACT

Many persons with epilepsy (PWE) experience problems with a wide range of cognitive functions, including learning, memory, attention, and executive control. These deficits in cognition result in diminished quality of life for PWE and are related to many factors, including the etiology of their epilepsy, recurrent seizures, side effects of antiseizure medications, or a combination of these factors. Various treatments to ameliorate cognitive deficits experienced by PWE have been implemented, although noninvasive and nonpharmacologic strategies may be more appealing options due to their relatively low cost, reduced risk of side effects, and/or reduced potential interactions with antiseizure medications. Physical activity and exercise may improve cognition in PWE but have not been well researched in this respect. To date only 1 study has directly investigated the effects of exercise on cognition in PWE, and it showed improved performance on tests of attention and executive function. The goal of the present article was to examine how increased physical activity and exercise contributes to 3 strategies (reducing seizure frequency, reducing epileptiform discharges, and decreasing symptoms of depression) that have been described as having a positive impact on cognition in PWE, as well as highlight related findings in experimental models of epilepsy. There is a definite need for more randomized controlled trials to establish greater clinical evidence for the use of physical activity and exercise in ameliorating cognitive impairment in PWE. We also need to better understand the factors contributing to reduced physical activity in PWE, as well as ways to overcome such barriers. With the available research in the area of exercise in epilepsy showing positive results, and a supportive research climate encouraging PWE to engage in greater physical activity overall, further investigations into the relationships between physical activity and cognition in epilepsy are warranted. (*Clin Ther.* 2018;40:26–34) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: cognitive function, complementary therapy, epilepsy, physical activity, physical exercise, seizure.

INTRODUCTION

Up to 3.4 million people in the United States (1.2% of the population) reportedly have active epilepsy.[1] Up to one half of the persons with epilepsy (PWE) experience and display cognitive impairment in one or more domains, including learning, memory, attention, and executive functioning,[2–8] with memory impairment being the most common.[9,10] These deficits are related to the etiology of their epilepsy, recurrent seizures, use of anticonvulsant agents, or a combination of these factors. All of these factors greatly contribute to poor quality of life in PWE and keep them from engaging in day-to-day activities and even gainful employment.[11,12] Thus, there is a significant need to ameliorate the cognitive deficits experienced by PWE.

Cognitive rehabilitation programs and psycho-education have been implemented to treat cognitive deficits in PWE[13–15]; however, the efficacy of these approaches remains unclear. A recent review by Farina et al[14] found limited evidence for the efficacy of cognitive rehabilitation in epilepsy, and it stressed the need for randomized controlled studies with larger sample sizes. Another review outlined various other strategies in addition to cognitive rehabilitation that may help ameliorate cognitive impairments in PWE.[8]

Accepted for publication December 7, 2017.
https://doi.org/10.1016/j.clinthera.2017.12.004
0149-2918/$ - see front matter

These strategies include improving seizure control, minimizing adverse effects of anticonvulsant agents and of surgical resection, suppressing interictal epileptiform discharges (IEDs), treatment of depression, use of pharmacologic cognitive enhancing agents, and brain stimulation. Noninvasive and nonpharmacologic interventions may be viable options for and preferred by many PWE due to their relatively low cost, reduced risk of side effects, and/or reduced potential interactions with antiseizure medications.[16]

One possible strategy for improving cognition in PWE that has received little attention is increased physical activity and exercise. Only 1 small study to date has investigated the effects of exercise on cognition in PWE.[17] In the study, 10 children with benign epilepsy with centro-temporal spikes participated in 10 supervised exercise sessions and home-based exercises for 5 weeks. Compared with baseline, significant improvements in the Comprehensive Attention Test and the Children's Color Trails Test (executive function) were observed after completion of the exercise program, although there was no control group. All but 2 of the 10 children were seizure free, with rare seizures in the 2 children (ie, frequency <1 per year). Clinical symptoms including seizure frequency did not worsen, which shows that the exercise program in children was feasible. It is unclear if these results will generalize to adults with epilepsy, and randomized controlled trials are needed in both children and adults to test the efficacy of exercise interventions on improving cognitive functions.

The paucity of studies investigating exercise-induced changes in cognition in PWE represents a significant knowledge gap. Physical activity has been found to be beneficial for cognition throughout one's life span.[18,19] In addition to the known cardiovascular and physiologic health benefits of physical activity, it may have a protective effect against cognitive decline,[20] whereas physical inactivity is considered one of the modifiable risk factors for Alzheimer's disease.[21] The goal of the present article was to provide a better understanding of the role that physical activity may play in improving cognitive function in PWE. We first define physical activity and appreciate what the typical state of physical activity level is for PWE, in addition to factors contributing to their current state. We then examine how increased physical and/or sports activity contributes to 3 strategies that have been described as having a positive impact on cognitive function in PWE, specifically improving seizure control, reduction of IEDs, and decreasing symptoms of depression.[8] Also highlighted are related findings in animal models of epilepsy concerning exercise and cognitive functions. We then discuss potential barriers to research and the next steps in examining the effects of physical activity and exercise on cognitive functions in PWE.

PHYSICAL ACTIVITY AND PHYSICAL FITNESS IN PWE

Physical activity is defined as a "bodily movement produced by skeletal muscles that requires energy expenditure"[22] and physical exercise as "a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective."[23] Physical activity is often assessed by using standardized questionnaires, including the Physical Activity portion of the Health Behaviour in School-Aged Children study,[24] the International Physical Activity Questionnaire,[25] and a series of questions on the California Health Interview Survey specific to regular, moderate, or vigorous exercise.[26] Physical activity levels can then be quantified by using an index representing the average daily energy expenditure that is expressed in kilocalories per kilogram of body weight per day; average energy expenditure of <1.5 kcal/kg/d is considered to be physically inactive.[27] Frequency, duration, and the metabolic equivalent of task value of an activity for each session can also be used to quantify levels of physical activity. For example, 1 study compared those with and without epilepsy in their monthly frequency of physical activity during leisure of >15 minutes.[28]

Studies suggest that PWE do not engage in regular physical activity.[29–33] A large population study of 400,055 Canadian individuals found that physical inactivity was associated with epilepsy compared with the general population.[27] PWE report being involved in less leisure time physical activity and exercise as they would like.[34] They also participate less frequently in sports activities and are more likely to be overweight or have a higher body mass index (BMI) than individuals without epilepsy, including comparisons of children with epilepsy and their siblings without epilepsy.[24,35] In contrast, 1 study found that a high percentage of patients with epilepsy (78%) reported engaging in physical exercise, but 66% of respondents had BMI values in the range of overweight (25–29.99 kg/m^2) or obese (≥30 kg/m^2).[36] The association between epilepsy and higher BMI may be in part due to antiepileptic drug (AED)-related weight gain, which has been reported for valproate and pregabalin in adults[37] and valproate and oxcarbazepine in children.[38] Studies also suggest that PWE have overall poorer physical fitness than matched control subjects without epilepsy,[25,29,35,39,40] even when they report the same level of physical activity[25] and perceive their health status as comparable to control subjects.[39] Taken together, these studies show that the positive self-reports of physical activity and health from PWE are not necessarily reflective of their actual physical fitness level. However, it is important to consider that beyond the self-report bias, other factors unique to epilepsy, including AED-related effects on weight or other medication side effects, may be contributing to this discrepancy.

There have been investigations into factors contributing to the lack of engagement in physical activity and exercise in PWE. Barriers that have been identified include overprotection by caregivers, physical limitations, and lack of knowledge by both sports activity instructors and health professionals.[35] Even with increased knowledge of the health benefits, PWE have been frequently cautioned against participating in physical/sports activities, mainly because of fear, overprotection, and ignorance regarding the risks and benefits related with exercise.[41] PWE who report seizures as a barrier to exercise also report a greater fear of seizures, although they exercise with the same frequency and intensity as those who do not report seizures as a barrier.[36] Personal motivation is also an important barrier to overcome, as there are many individuals who know exercise is beneficial but yet do not exercise simply because they do not enjoy it. More quantitative and qualitative studies in PWE may be required to discern such motivations and any other potential barriers, as well as different strategies to overcome them.

Interestingly, a study investigating a subset sample of 53,552 Canadian youth and young adults (age 12–39 years) found that BMI values were in the normal range (18.8–24.9 kg/m^2) and did not differ between those with epilepsy (0.57%) and those without epilepsy.[28] Reported monthly frequency of leisure time physical activity was similar for both groups, although PWE more frequently engaged in walking and less frequently participated in activities such as exercise class, home exercises, skiing/snowboarding, basketball, ice hockey, or weight training. A California survey study also found that BMI and level of engagement in physical activity were similar between those with and without a history of epilepsy.[26] Although these studies indicate that a positive message for promoting physical activity and physical fitness is being communicated to particular populations of PWE, the majority of studies call attention to the need for PWE to increase their physical activity levels and improve their overall physical fitness.

IMPROVING COGNITION THROUGH IMPROVED SEIZURE CONTROL

There is evidence that seizure frequency is negatively associated with cognitive function in adults[42] and children with epilepsy.[43] In PWE taking levetiracetam, better cognitive outcome was associated with better seizure control.[44] Voltzenlogel et al[45] also found that patients with mesial temporal lobe epilepsy with low seizure frequency performed better on tests of anterograde memory (ie, free recall and recognition memory) than those with high seizure frequency. Clinical studies of physical activity and exercise in epilepsy have primarily focused on exercise-induced effects on seizure frequency. About one third of PWE claim that exercise improves seizure control,[33] and reductions in seizure frequency have been shown with a physical exercise program[46] and yoga training[47] in patients with poorly controlled epilepsy. It is important to note that although no significant changes in seizure frequency have been observed in some studies, improved psychological and/or physiologic health was reported.[17,48,49]

Positive results in the human studies are supported by studies in rodent epilepsy models showing anticonvulsant effects of physical exercise programs.[50] One consideration is exercise-induced stress, because stress (physical stress and particularly psychosocial stress) is deemed to be a seizure precipitant. However, in a study in which animals were tested to their physical exhaustion limits during a maximum oxygen uptake test, none experienced seizures.[51] Also, although animal studies show that seizures can occur during physical exercise, they are infrequent.[50] In humans, studies that examined whether intensive exercise until exhaustion alters seizure susceptibility in PWE did not report seizures during or after physical effort.[40,52,53] Taken together, the studies in PWE and in experimental models of epilepsy suggest that physical exercise is not seizure inducing, in some cases reducing seizure frequency, and thus can potentially also improve cognition.

IEDs AFFECT COGNITIVE FUNCTION

IEDs are not seizures but are considered to be an epilepsy marker; they result from the synchronous firing of neurons and present as intermittent spike and wave discharges on EEG.[8] The presence of IEDs during cognitive testing often reveals transitory cognitive impairment in both adults and children with epilepsy.[43,54] Studies with new-generation drugs such as levetiracetam provide preliminary evidence for better cognitive performance with suppression of IEDs.[55] Kleen et al[56] showed that human hippocampal IEDs impaired memory maintenance and retrieval, which may be partially explained by rodent seizure models showing that interictal spikes in hippocampal interneurons are followed by decreased CA1 action potentials.[57] With regard to physical exercise, Gotze et al[58] reported a reduction in EEG epileptiform discharges in PWE who were first hyperventilated for 2 to 3 minutes and then performed 20 to 50 knee bends until exhaustion; in the majority of patients, exercise produced a normalization of EEG. More recent clinical studies have also shown that acute physical exercise to exhaustion reduces IEDs during exercise and/or the postexercise recovery period compared with the resting state in individuals with juvenile myoclonic epilepsy[40] and temporal lobe epilepsy.[53] Furthermore, a decrease in IEDs was observed during 15 minutes of moderate exercise[59] or physical exercise until exhaustion[60] compared with an increase during 3 minutes of voluntary hyperventilation. In another study, a decrease in the occurrence of IEDs during exercise until exhaustion was noted in the majority of children with partial epilepsy.[61] The effect of long-term exercise programs on IEDs in PWE is unclear but warrants investigation given the observed IED reductions with acute physical exertion.

DEPRESSION AND COGNITIVE FUNCTION IN EPILEPSY

Cognitive impairment is considered to be a core feature of depression.[62] Depression is prevalent in epilepsy, affecting between 20% and 55% of individuals with poorly controlled seizures and ~10% to 20% of individuals with well-controlled seizures, which is higher than in the general population.[63,64] Depression is associated with both objective and subjective impairments in cognitive functions in PWE, including language, attention, and memory.[65,66] Positive effects of physical exercise on the psychologic and physiologic well-being of PWE have been previously reported.[33,67] In the handful of studies of supervised physical exercise conducted in PWE, participants reported improvements in their physical and mental state[49] and emotional well-being,[17] as well as in their psychosocial functioning and overall quality of life.[46,48] More specifically, levels of depression for active PWE were found to be significantly lower than those who were less active,[68] and physical exercise during leisure time predicted 31% of depression levels in individuals with epilepsy.[69] A recent study also reported a negative association between depression and physical activity levels in PWE.[70] These studies in epilepsy are consistent with results in older adults showing that physical exercise reduces depressive symptoms.[71,72] In a review conducted by Arida et al,[73] the authors proposed the impact of exercise in attenuating depression in PWE.

Given the link between depression and impaired cognitive function in epilepsy, we posit that exercise-induced attenuation of depressive symptoms would be coupled with improvements in various cognitive domains. However, the relationship between physical activity and cognitive function as it relates to depression in PWE has not been directly examined and warrants investigation.

INSIGHTS FROM EPILEPSY ANIMAL MODELS ON IMPROVING COGNITION WITH PHYSICAL EXERCISE

As previously stated, there has been only 1 study (by Eom et al[17]) directly investigating the relationship between cognitive functions and physical activity. Thus, it is important to examine results from experimental models of epilepsy to gain a better understanding of such a relationship. From an experimental point of view, reported findings concerning exercise and cognition in animals with epilepsy have been overwhelmingly positive. For instance, daily swimming exercise for 30 days reduced the learning and memory deficits in rats submitted to a kainate model of epilepsy.[74] In another study, a cellular model of learning and memory,[75] along with in vitro hippocampal electrophysiologic parameters such as long-term potentiation (LTP), was analyzed in rats with epilepsy submitted to an aerobic exercise program.[76] LTP, a form of synaptic plasticity, has been recognized as a possible model of memory. Studies have shown that LTP could be altered by seizures, thus affecting some behavioral adaptations (eg, memory).[77] Physical exercise partially repaired hippocampal LTP impairments in rats with epilepsy.[76] In addition, Fares et al[78] reported that after lithium-pilocarpine-induced status epilepticus at weaning, rats housed in environmental enrichment (which included a wheel running) did not develop cognitive impairments compared with those housed in conventional cages. In a more recent study, the reduction in number of seizures after a resistance exercise program was associated with attenuation of memory impairment in rats with chronic epilepsy.[79] Taken together, these studies in epilepsy animal models reinforce the rehabilitative and neuroprotective potential of physical activity.

DISCUSSION

The potential application of physical activity and exercise toward improving cognitive function in epilepsy is still in its infancy and has not been well studied. Higher levels of free-living physical activity (ie, everyday real-world physical activities related to work, leisure, and/or sports) and structured, prescriptive exercise may potentially mitigate the cognitive deficits experienced by PWE related to disease etiology, recurrent seizures, use of AEDs, or a combination of these and other factors. However, although we have established that increasing physical activity would be beneficial for PWE, there are definite barriers that need to be overcome, particularly with regard to future research. In addition to the previously mentioned factors, many individuals do not have reliable transportation. Patients with uncontrolled seizures are not allowed to drive and must rely on family, friends, caregivers, or public transportation. Lack of reliable transportation limits the ability for PWE to participate in research studies, particularly intervention studies that require multiple visits. Compensating for travel or providing transportation to and from the study site (eg, taxi or shuttle service) are ways to alleviate this burden. Another option that is becoming more feasible is the use of telemedicine technology. This method would allow an individual to videoconference in and receive instruction remotely during the study sessions, although the appropriateness of such a strategy would have to be determined on a per-study basis.

Other factors specific to the epilepsy population must also be kept in mind for future research in investigating physical activity and exercise in PWE, particularly intervention studies. For example, for teenagers with epilepsy, a negative correlation was found between participating in sports and use of ≥3 AEDs.[24] In addition, medication side effects are negatively associated with levels of physical activity in PWE.[70] For example, weight gain is associated with some AEDs (eg, valproate), although weight loss is common with other AEDs (eg, topiramate).[80,81] These and other metabolic effects of AEDs need to be considered in future randomized controlled studies of exercise in PWE. Another common side effect of AEDs is loss of bone mineral density, which may limit a person's engagement in physical activity.[82] Although exercise has been shown to counteract the negative effects of AEDs on bone mineral density, PWE should receive a physical examination and consult their epilepsy specialist before increasing their current activity level or participating in a physical exercise intervention program to minimize risk of injury.[41]

There are definitely gaps in our knowledge related to our understanding of how physical activity and exercise may help alleviate cognitive impairment in PWE and a need to investigate the possibilities. Even if seizures are well controlled, the use of multiple antiseizure drugs may impair physical and/or cognitive functioning, especially because one of the strongest predictors of poor cognitive outcome in PWE is polydrug therapy. In this respect, future studies may consider investigating whether physical activity as adjunct therapy can help reduce the number of antiseizure medications in PWE, particularly given that physical activity and physical exercise programs have been shown to reduce the frequency of seizure occurrence in patients with poorly controlled epilepsy.[46,47] Physical activity and exercise may also be used to boost the effects of cognitive rehabilitation programs for PWE.[13,14] Furthermore, even though aerobic exercise is most often utilized, various regimens of physical activity and exercise can be used, including resistance and strength exercises[79,83] and yoga.[47]

Investigations are necessary to better understand the specific and differential effects of various types of physical activity on the factors discussed here (ie, seizure frequency, IEDs, depression) that can mitigate cognitive functions in PWE. Overall the current research climate in this area is supportive, with a call for increased participation of PWE in recreational physical activity, exercise, and sports. In conclusion, although physical activity and exercise may be a viable candidate for complementary therapy for improving cognitive function in PWE, there is a definite need for more randomized controlled trials to establish greater clinical evidence.

ACKNOWLEDGMENTS

This work was supported by the University of Alabama at Birmingham Faculty Development Grant Program (Dr. Allendorfer) and by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; #300605/2013-07) and Fundacão de Amparo à Pesquisa do Estado de São Paulo (FAPESP; #2015/19256-0) (Dr. Arida). The authors thank Dr. Deborah Kerr and Dr. Stefanie Bronson for proofreading the revised manuscript. Dr. Allendorfer contributed to the conceptualization of the paper topic, literature search, interpretation and writing. Dr. Arida contributed to the literature search, interpretation and writing of the manuscript.

CONFLICTS OF INTEREST

Dr. Allendorfer receives salary support and research funding from the University of Alabama at Birmingham and from the State of Alabama Department of Commerce. She also serves as a consultant regarding applications of functional magnetic resonance imaging and has received personal compensation from Cyberonics, Inc. Dr. Arida has received research grants from the São Paulo Research Foundation (FAPESP) and National Council for Scientific and Technological Development (CNPq), Brazil. The authors have indicated that they have no conflicts of interest related to this manuscript.

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