PADERBORN UNIVERSITY

Epilepsy and Physical Activity

–

Risks, Benefits, and the Impact on Autonomic Control

Cumulative dissertation for the academic degree of

Doctor rerum medicinalium

(Dr. rer. medic.)

by

Franziska van den Bongard

April 2024

Supervisor: Prof. Dr. Dr. Claus Reinsberger

Co-Supervisor: Prof. Dr. Dr. Philipp Zimmer

April 03, 2024

Danksagung

An erster Stelle danke ich meinem Doktorvater Prof. Dr. Dr. Claus Reinsberger. Ich danke dir für das Vertrauen, das du mir bereits vor Jahren entgegengebracht hast und mir die Chance gegeben hast, mich fachlich und persönlich weiterzuentwickeln. Du hast mich stets dazu motiviert, an mir zu arbeiten und die mir gestellten Herausforderungen erfolgreich zu meistern. Ich danke dir auch für dein Dasein auf persönlicher Ebene, für dein stets offenes Ohr, für dein Verständnis und für deine Unterstützung.

Mein Dank gilt außerdem Prof. Dr. Dr. Philipp Zimmer, der sich bereiterklärt hat, das Zweitgutachten für diese Dissertation zu übernehmen.

Ein großer Dank geht auch an die Probanden meiner Studie. Ich danke Ihnen und euch für die Teilnahme und für die Geduld während der langen Untersuchungstage. Jeder einzelne von Ihnen und euch motiviert mich an diesem Thema weiterzuarbeiten.

Die vielen Untersuchungstage hätte ich ohne den unermüdlichen Einsatz von Jessica Coenen nicht stemmen können. Danke, dass du bedingungslos an meiner Seite warst und all die Hochs und Tiefs mitgetragen hast. Ohne dich hätte ich dieses Projekt nicht abschließen können. Franziska Haase, Christian Gölz, Roman Gaidai und Carina Delling, euch bin ich ebenfalls sehr dankbar für eure Unterstützung rund um die Messungen. Außerdem möchte ich Michaela Langrock und Fabian Hartmann nennen. Ich danke euch für eure Unterstützung durch eure Expertise in allen Laborfragen. Sophie Wieners und Prof. Dr. Hans-Christian Heitkamp möchte ich ebenfalls für ihre ärztliche Unterstützung in diesem Projekt danken.

Die Jahre haben gezeigt, dass solch ein Projekt nicht von einer Person allein bewältigt werden kann. Daher bin ich dem gesamten Sportmedizin Team sehr dankbar, der Austausch mit euch hat mich stetig fachlich weitergebracht. Darüber hinaus danke ich euch für die mentale Unterstützung. Ihr habt stets dafür gesorgt, dass ich die Rückschläge und Stillstände akzeptieren konnte, an ihnen gewachsen bin und wieder nach vorne sehen konnte.

Ganz besonders bedanken möchte ich bei meiner Freundin Julia Gowik, die mich auch über viele Jahre als Kollegin begleitet hat. Ohne dich, würde ich heute nicht dort stehen, wo ich bin. Danke für all deine Unterstützung und deinen Einsatz, den du mir persönlich und diesem Projekt entgegengebracht hast.

Ein herzlicher Dank gilt auch meiner Familie und meinen Freunden. Danke, für eure Geduld euch meine Sorgen und Gedanken immer wieder anzuhören. Danke, für eure Ratschläge, eure Unterstützung und besonders für die willkommenen Ablenkungen innerhalb dieser Promotionszeit.
Im besonderen Maße danke ich meinem Ehemann Peter. Danke, dass du mir stets den Rücken gestärkt und mir Mut zugesprochen hast, mich auf andere Gedanken und immer wieder zum Lachen gebracht hast. Bei dir konnte ich Kraft tanken, um mein Ziel nie aus den Augen zu verlieren.

Declaration of Authorship

I hereby declare that the presented work is, to the best of my knowledge and belief, the result of my own research. Support during the research process or co-author contributions are presented for each publication. The work has not been submitted, either partly or completely, for a degree at this or another university. Content and ideas taken from other sources are - to the best of my knowledge and belief - cited correspondingly.
I have read, understood, and accepted the PhD regulations ("Promotionsordnung NW") from the 31st of March 2021 (AM.UNI.PB 10.21).

_____	_____
Place, Date	Franziska van den Bongard

Abstract

Physical activity has not been recommended for patients with epilepsy (PWE) for a long time. The evidence synthesis showed that some patients experience exercise-induced seizures, however, in most PWE physical activity does not trigger seizures. Furthermore, exercise and physical activity have the potential to reduce depression and anxiety in epilepsy. In a cross-sectional cohort study, an exhaustive exercise test on a bicycle ergometer was conducted with 25 PWE (n=19 seizure-free). In two patients a change in epileptiform activity was observed after exercise. When compared to a healthy matched control group (n=25), a significantly lower maximum heart rate and chronotropic response but a similar physical fitness level was shown. Changes within the autonomic nervous system are suspected reasons for this group difference, which could increase the risk of sudden unexpected death (SUDEP). Furthermore, a different interaction of peripheral and central sympathetic activity between the groups after exercise was observed. However, the heterogeneity of epilepsy and seizure characteristics could limit the results. The results suggest the extensive impact of epilepsy. By showing the potential benefits of physical activity for PWE, this might be used to also influence network alterations and therefore address the risk for life-threatening conditions in epilepsy, such as the SUDEP. In the next step, an exercise intervention should be conducted to investigate the influence of chronic exercise on seizure characteristics and autonomic functions in epilepsy.

Zusammenfassung

Körperliche Aktivität wurde für Patienten mit Epilepsie (PWE) lange Zeit nicht empfohlen. Die Evidenzsynthese zeigte, dass manche Patienten durch körperliche Aktivität induzierte Anfälle erleben, jedoch bei den meisten PWE dadurch keine Anfälle auslöst werden. Außerdem kann körperliche Aktivität Depressionen und Angstzustände bei Epilepsie reduzieren. In einer Querschnitts-Kohortenstudie wurde mit 25 PWE (n=19 anfallsfrei) ein ausbelastender Test auf einem Fahrradergometer durchgeführt. Bei zwei Patienten wurde eine Änderung epileptiformer Aktivität nach Belastung beobachtet. Darüber hinaus wurde eine niedrigere maximale Herzfrequenz und chronotrope Reaktion, aber ein ähnliches körperliches Fitnessniveau im Vergleich zu einer gesunden, gematchten Kontrollgruppe (n=25) festgestellt. Veränderungen im autonomen Nervensystem werden als Ursache für diesen Gruppenunterschied vermutet, die das Risiko für plötzlichen unerwarteten Tod (SUDEP) erhöhen könnten. Außerdem wurde eine unterschiedliche Interaktion der peripheren und zentralen sympathischen Aktivität zwischen den Gruppen nach dem Training beobachtet. Heterogene Epilepsie- und Anfallscharakteristika könnten die Ergebnisse jedoch einschränken. Die Ergebnisse weisen auf weitreichende Auswirkung der Epilepsie hin. Durch den potentiellen Nutzen von körperlicher Aktivität, könnte diese genutzt werden, um die Netzwerkveränderungen anzugehen und damit das Risiko für lebensbedrohliche Zustände bei Epilepsie, wie SUDEP, zu verringern. Im nächsten Schritt sollte eine Trainingsintervention durchgeführt werden, um den Einfluss von chronischem Training auf das Anfallsgeschehen und die autonomen Funktionen bei Epilepsie zu untersuchen.

Publications Considered for this Dissertation

1) **van den Bongard F**, Gowik JK, Reinsberger C. Auswirkungen körperlicher Aktivität auf Status Epilepticus im Tiermodell. Clinical Epileptology 2023; 1-5. DOI 10.1007/s10309-023-00574-4

2) **van den Bongard F**, Hamer HM, Sassen R, Reinsberger C. Sport and physical activity in epilepsy—a systematic review. Dtsch Arztebl Int 2020; 117: 1–6. DOI 10.3238/arztebl.2020.0001

3) **van den Bongard F**, Coenen J, Reinsberger C. Fitness, performance and cardiac autonomic responses to exercise in people with epilepsy. Epilepsy & Behavior 2022; 135: 108869. DOI 10.1016/j.yebeh.2022.108869

4) **van den Bongard F,** Gowik JK, Coenen J, Jakobsmeyer R, Reinsberger C. Exercise-induced central and peripheral sympathetic activity in a community-based group of epilepsy patients differ from healthy controls. Experimental Brain Research 2024. DOI 10.1007/s00221-024-06792-0

Other Publications

Peer reviewed

Gowik JK, Goelz C, Vieluf S, **van den Bongard F**, Reinsberger C. Source connectivity patterns in the default mode network differ between elderly golf-novices and non-golfers. Scientific Reports 2023; 13(1): 6215. DOI 10.1038/s41598-023-31893-1

Stroehlein JK, Vieluf S, Zimmer P, Schenk A, Oberste M, Goelz C, **van den Bongard F**, Reinsberger C. Learning to play golf for elderly people with subjective memory complaints: feasibility of a single-blinded randomized pilot trial. BMC Neurology 2021; 21: 200. DOI 0.1186/s12883-021-02186-9

Ströhlein JK, Vieluf S, **van den Bongard F**, Gölz C, Reinsberger C. Golf spielen gegen die Vergesslichkeit: Effekte des Erlernens der Sportart auf das Default Mode Netzwerk des Gehirns. Bewegungstherapie und Gesundheitssport 2020; 36: 65–72. DOI 10.1055/a-1120-7002

Stroehlein J, **van den Bongard F**, Barthel T, Reinsberger C. Dose-response-relationship between physical activity and cognition in elderly. Deutsche Zeitschrift für Sportmedizin 2017; 10: 234-242. DOI 10.5960/dzsm.2017.300

Book Chapter

Barthel T, **van den Bongard F**, Ströhlein JK, Reinsberger C (2017). Bewegung bei neurologischen Erkrankungen. In: Banzer W (Hrsg.). Körperliche Aktivität und Gesundheit. Springer-Verlag: Berlin Heidelberg. DOI 10.1007/978-3-662-50335-5_24

Congress Abstracts (presenting authors written in italics)

Petersen C, **van den Bongard F**, *Reinsberger C* (2023). Exercise Testing in Patients with Epilepsy: Clinical and Electrographic Findings. America Epilepsy Society Annual Meeting, Orlando, 2023.

Coenen J, Delling C, **van den Bongard F**, Jakobsmeyer R, Reinsberger C (2023) Central and peripheral autonomic activity pre- to post- submaximal exercise after a sport-related

concussion. Sports Medicine and Health Summit, Hamburg, 2023. In Deutsche Zeitschrift für Sportmedizin (2023), 74 (4): 105

Coenen J, **van den Bongard F**, Delling C, Jakobsmeyer R, Reinsberger C (2022). Autonomic response to submaximal exercise after a sports-related concussion. 6th International Conference on Concussion in Sport, Amsterdam, 2022. In: British Journal of Sports Medicine (2024), 58 (Suppl. 1): A97.1-A97. DOI: 10.1136/bjsports-2023-concussion.254

Coenen J, **van den Bongard F**, Delling C, Reinsberger C (2022) Network functional connectivity response to submaximal exercise after a sport-related concussion. European College of Sport Science Congress, Sevilla, 2022.

van den Bongard F, Coenen J, *Reinsberger C* (2021). Autonomic changes after physical exhaustion in well controlled epilepsy patients. American Clinical Neurophysiology Society Annual Meeting. virtually, Orlando, 2021.

van den Bongard F, Coenen J, *Reinsberger C* (2021). Exercise-Induced Changes of Functional Brain Connectivity in the Central Autonomic Network and of Autonomic Parameters in Patients with Epilepsy. America Epilepsy Society Annual Meeting, Chicago, 2021.

Coenen J, **van den Bongard F**, Delling AC, Reinsberger C (2021). Functional Connectivity within the Default Mode Network in Response to Exercise during Return to Sport following Concussion. American Academy of Neurology, virtually, 2021. In: Neurology, 98(1_Supplement_1), S18. DOI:10.1212/01.wnl.0000801904.27836.ef

van den Bongard F, Stroehlein J, Coenen J, Jakobsmeyer R, Reinsberger C (2021). Belastungsinduzierte Veränderungen von funktioneller Hirn-Netzwerkaktivität und peripheren autonomen Parametern bei Epilepsiepatienten. Sports Medicine and Health Summit, virtually, 2021. In: German Journal of Sports Medicine, 72 (3), S. 145.

Ströhlein J, Gölz C, Vieluf S, **van den Bongard F**, Reinsberger C (2021). Funktionelle Netzwerkcharakteristika des Default Mode Netzwerks bei älteren Golf-Novizen. Sports Medicine and Health Summit, virtually, 2021. In: German Journal of Sports Medicine, 72 (3), S. 140.

van den Bongard F, Jakobsmeyer R, Reinsberger C (2019). Belastungsinduzierte Veränderungen der elektrodermalen Aktivität bei Epilepsiepatienten. Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Epilepsie-Liga, Basel, 2019. In: Zeitschrift für Epileptologie, 32, S1-S62.

van den Bongard F, Ströhlein JK, Barthel T, Reinsberger C (2018). Einfluss von körperlicher Aktivität auf epileptische Anfälle – Evidenz aus Tiermodellen. Deutscher Olympischer Sportärztekongress, Hamburg, 2018. In: Sport Orthopaedics and Traumatology, 34 (2), S 197.

van den Bongard F, Ströhlein JK, Barthel T, Reinsberger C (2017). Schwierigkeiten beim wissenschaftlichen Nachweis des Einflusses von körperlicher Aktivität auf die Anfallsfrequenz bei Menschen mit Epilepsien. Jahrestagung der Deutschen und Österreichischen Gesellschaften für Epileptologie und der Schweizerischen Epilepsie-Liga, Wien, 2017. In: Zeitschrift für Epileptologie, 30. Jahrgang (Suppl 1), S. 34.

Stroehlein JK, **van den Bongard F**, Barthel T, Reinsberger C (2017). Effects of a 12-week Multicomponent Exercise Intervention on Executive Functions and Episodic Memory in Healthy Elderly: A Pilot Study; 22nd annual Congress of the ECSS, Essen, 2017.

van den Bongard F, Ströhlein JK, Barthel T, Reinsberger C (2017). Herausforderungen beim Versuchsdesign und Schwierigkeiten beim wissenschaftlichen Nachweis des Einflusses von körperlicher Aktivität auf die Symptomatik der Epilepsien. Symposium des Wissenschaftsrates der DGSP, Potsdam, 2017.

van den Bongard F, Ströhlein J, Barthel T, Reinsberger C (2016). Einfluss körperlicher Aktivität auf die Anfallsfrequenz und Lebensqualität bei Epilepsiepatienten; 47. Deutscher Sportärztekongress, Frankfurt am Main, 2016. In: Dtsch Z Sportmed., 67. Jahrgang 7-8, S 173.

Ströhlein J, **van den Bongard F**, Barthel T, Reinsberger C (2016). Körperliche Aktivität gegen kognitiven Leistungsverlust: Eine Dosis-Wirkungs-Beziehung? 47. Deutscher Sportärztekongress, Frankfurt am Main, 2016. In: Dtsch Z Sportmed., 67. Jahrgang 7-8, S 181.

Table of Contents

Tables and Figures

Abbreviations

ANS	autonomic nervous system
ASD	anti-seizure drug
BMI	body mass index
CAN	central autonomic network
ECG	electrocardiogram/ electrocardiography
EDA	electrodermal activity
EEG	electroencephalogram/ electroencephalography
fMRI	functional magnetic resonance imaging
GSR	galvanic skin response
HF	high frequency
HR	heart rate
HRV	heart rate variability
Hz	hertz
ILAE	International League Against Epilepsy
IPAQ	International Physical Activity Questionnaire
LF	low frequency
M/EEG	magneto/electro-encephalography
MRI	magnetic resonance imaging
MS	multiple sclerosis
ms	milliseconds
n	number
PLV	phase-locking value
PWE	patients with epilepsy
RMSSD	root mean square of successive RR interval differences
RPE	rate of perceived exertion
rpm	revolutions per minute
sec	seconds
SUDEP	sudden unexpected death in epilepsy
ULF	ultra-low frequency
VIS	visual network
VLF	very-low frequency

VO_2	oxygen consumption
yrs	years

1 Introduction

Epilepsy is one of the most common neurological diseases [1] and is "characterized by an enduring predisposition to generate epileptic seizures" [2]. Uncontrolled seizures, depression, and anxiety often have a significant impact on the quality of life in people with epilepsy (PWE) [3,4]. Currently, as the primary goal of epilepsy therapy, medical treatment is used to reduce seizure frequency and at best to achieve seizure freedom [5]. However, medical treatment can be associated with side effects [6,7], which may reduce quality of life.

In neurological diseases such as stroke or multiple sclerosis (MS), physical activity is commonly used for rehabilitative purposes [8]. In contrast, in epilepsy, patients have been discouraged from being physically active for a long time [9]. One main reason for this ban was and is the fear of exercise-induced seizures [9]. This may influence the perception of physical activity in PWE and their willingness to participate in physical activities. Currently, it seems that this perception of physical activity in epilepsy is changing as it is starting to be considered a complementary therapy for PWE [10].

It is of interest of how PWE can benefit from physical activities. Potential benefits should target epilepsy and seizure characteristics as well as other important health determinants, such as cardiovascular health. This patient group is known to have restricted cardiovascular health which may increase the risk of cardiac events [11] and even sudden death [12]. The autonomic nervous system (ANS) is assumed to play a significant role in this context [13]. Since a central network in the brain controls the ANS and it is assumed that epilepsy is a network disease [14], this network and therefore also autonomic functions might be impacted [13,15]. The well-described autonomic dysfunction in epilepsy seems to have widespread consequences as it could increase the risk for life-threatening events like sudden unexpected death (SUDEP) in epilepsy [13].

This dissertation summarizes current scientific literature on the impact of physical activity on seizures and comorbidities in epilepsy. Additionally, in a cross-sectional cohort study with PWE and age, sex and body mass index (BMI) matched healthy controls, an exhaustive exercise test was conducted. The study investigated physical

fitness, as well as cardio autonomic activity and central network activity before and after the exhaustive exercise test. Additionally, the influence of acute exercise on seizures was examined.

2 Current State of Research

The amount of literature in the field of epilepsy and physical activity and exercise has grown in recent years. A PubMed search for “epilepsy AND (“physical activity” OR exercise)” yields 36, 40, and 34 hits in the years 2010, 2011, and 2012, and 96, 105, and 80 hits in the years 2020, 2021, and 2022. However, compared to other neurological diseases, for example, dementia (179, 206, 216 hits in 2010, 2011, 2012; 698, 750, 757 hits in 2020, 2021, 2022) or stroke (784, 885, 980 hits in 2010, 2011, 2012; 1775, 1977, 1932 hits in 2020, 2021, 2022), the number of published articles is rather low. This indicates a need for more research on epilepsy and physical activity. This will strengthen the results of the first studies, which have indicated some positive effects.

This chapter provides relevant background information for the aims and hypotheses of this dissertation. It focuses on the topic of physical activity and epilepsy in comparison to research on physical activity and other neurological diseases. The risk of exercising with epilepsy is described and the current physical activity recommendations for PWE are presented. Additionally, it provides basic information on epilepsy and seizure characteristics. Furthermore, this scientific literature chapter highlights the significance of cardiovascular health as a crucial health determinant, which is known to be restricted in epilepsy. The impact of the ANS in this context is a significant aspect of this scientific literature chapter. Lastly, the text discusses the utilization of exercise tests in this area.

2.1 Physical Activity and Exercise in Epilepsy

Physical activity is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure” [16], whereas exercise is a subset of physical activity that “is planned, structured, and repetitive […]” [16]. Exercise tests can be used as a tool to determine fitness levels and for training control [17]. Those exercise tests are even used for diagnostic purposes to examine pathological changes in the body. For instance in cardiology, exercise tests have been used to detect alterations [18,19] for a long time.

Furthermore, exercise is not only used as a diagnostic tool for diseases. The term “exercise is medicine” became popular in the last decades [20–23], but exercise and

physical activity have been applied in the treatment of diseases for hundreds of years [23] and are meanwhile the focus of modern research. Nowadays, physical activity and exercise are used in the prevention and rehabilitation of various diseases, such as cardiovascular diseases [24–26], obesity [24], type 2 diabetes [25], and different types of cancer [26].

In recent years, research has focused on the use of physical activity as a rehabilitative strategy for neurological diseases [8]. In cases of stroke, it can contribute to rehabilitation. A Cochrane meta-analysis included 58 trials and analyzed them regarding the effect of improved physical fitness on stroke-induced disabilities. It was shown that especially cardiorespiratory training reduces disabilities during or after usual stroke care [27]. Moreover, physical activity can contribute to improving cardiovascular fitness, walking ability, and level of depression after stroke [8]. Furthermore, exercising has an impact on mortality risk among stroke patients, because physical activity interventions were more effective in reducing mortality risk, compared to usual drug treatment [28].

People with MS can benefit from the impact of physical activity on disease symptoms. A randomized controlled trial showed improved verbal memory, executive functions, and fitness levels following high-intensity training [29]. A Cochrane meta-analysis focused on the effectiveness of exercise programs compared to no exercise in patients with MS. The main finding was that exercise therapy was beneficial for improving fatigue. Furthermore, no significant association between exercise and MS relapse risk could be observed [30].

For dementia, there are some hints of a positive impact of physical activity on disease risk. Epidemiological studies showed that a higher lifelong physical activity level might reduce the risk of developing dementia [31,32]. Furthermore, a systematic review and meta-analysis revealed that supervised training improves walking ability and balance in people with dementia [33]. Additionally, a Cochrane meta-analysis indicated a positive impact of exercise programs on the ability to perform activities of daily living in dementia patients [34].

While studies are reporting positive results for the mentioned diseases, it is important to note that there are also studies that do not show any improvements. Nevertheless, the interest in the impact of physical activities and exercise on neurological diseases, such as stroke, MS, and dementia is growing and its application successfully implemented. For epilepsy, the interest, acceptance, and implementation are still restricted.

Epilepsy is one of the most common neurological diseases [1]. The incidence and prevalence of epilepsy were analyzed by a systematic review and meta-analysis, published in 2017. The pooled incidence rate was 61.44 per 100,000 person-years (95% CI 50.75-74.38) [1]. For active epilepsy, the point prevalence was 6.38 per 1,000 persons (95% CI 5.57-7.30) and the lifetime prevalence was 7.60 per 1,000 persons (95% CI 6.17-9.38) [1]. Epilepsy is independent of sex, age, geographical location, race, and social class [35]. Seizures, as a main symptom of epilepsy, are defined as “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” [2]. They are classified by their onset as focal, generalized, or unknown. For focal onsets, seizures are classified as either seizures with sustained awareness or seizures with impaired awareness. In general, all three classifications can be categorized into motor and nonmotor seizures. Some seizures cannot be classified into any of the three categories. For those cases, a fourth category “unclassified” is used [36]. Features including seizure types, imaging, and electroencephalography (EEG) techniques tend to appear together and age-related features, such as age of epilepsy onset, seizure triggers, and intraday variations contribute to a diagnosis of an epilepsy syndrome [37]. Syndromes are temporal lobe epilepsy or idiopathic genetic epilepsy, for instance, juvenile absence epilepsy or grand mal epilepsy, to name only a few [38]. These are caused by structural, genetic, infectious, metabolic, immune, or unknown etiologies [37]. Comorbidities like depression [39] and anxiety [40] are often associated with epilepsies. The classification of epilepsy is of importance since it provides treatment implications. Anti-seizure drugs (ASD) are used as the standard treatment for controlling epileptic seizures. Approximately 70% of PWE achieve seizure freedom [41], while the remaining 30% are patients with therapy-refractory seizures [42].

As the positive influence of physical activity is known for other neurological diseases, a question of interest is whether physical activity might affect symptoms in epilepsy as well. PWE were discouraged from participating in physical activities and exercise for a long time. One reason for this is the fear of exercise-induced seizures [43]. The recommendation that patients should not be active may affect their attitude towards and their participation in physical activities. In addition to the fear of seizures, the related fear of injuries is also a reason for the ban on exercise. Although, it was shown that, the number of exercise-associated injuries is not higher in epilepsy patients compared to healthy controls [44,45]. Swimming however poses a higher risk for accidents in a seizure situation, but an evaluation of drowning deaths showed that only a small number was directly seizure-related (25 from 482 cases) [44].

An individual risk assessment can help find the right and safe type of exercise for each patient. Risk assessments are recommended by the International League Against Epilepsy (ILAE). The ILAE pointed out that consideration of each epilepsy patient's ability to be physically active is more efficient than a general restriction or ban on physical activities [46]. They categorized types of physical activities into three main categories according to their "risk of injury or death for patients with epilepsy, or for bystanders, should a seizure occur during the event" [46]. The categories range from (1) "no significant additional risk" (e.g., collective sports on the ground), over to (2) "moderate risk to patients with epilepsy but not to bystanders" (e.g., cycling), and (3) "high risk for patients with epilepsy and, for some sports, also for bystanders" (e.g., motor sports). For the individual risk assessment, different factors have to be considered: type of sport, probability that a seizure occur, seizure triggering factors, type and severity of seizure, usual time of seizure occurring, and attitude of the patient [47].

Nevertheless, a question that arises is whether an acute physical effort increases the risk of seizures. Fialho et al. (2017) [48] conducted an exhaustive exercise test on a treadmill with 30 PWE. One patient experienced a seizure twelve minutes after the end of the exercise test. The authors reported that no major complications were observed during the exercise test. This study suggests that acute exercise does not increase the risk for exercise-related seizures for many PWE. However, it indicated that there are also cases

that experience those seizures. Exercise-induced seizures were not the only outcome under investigation in that study. Other exercise-related outcomes indicate that physiological aspects have to also be considered in the context of epilepsy and physical activity.

2.2 Cardiovascular Alterations in People with Epilepsy

Fialho et al. (2017) [48] evaluated exercise test variables in the 30 PWE without known cardiovascular disease and 30 healthy sex, BMI, and age matched controls. Peak heart rate during exercise on the treadmill was significantly lower in the epilepsy group ($p=0.002$). Furthermore, exercise duration ($p=0.004$) and achieved Bruce stage ($p=0.004$) were significantly lower. Only 76.7% or 80%, following Karvonen's [49] or Tanaka's [50] formula for age-predicted maximum heart rate, of the epilepsy patients reached a maximum heart rate ≥85% of the age-predicted maximum heart rate. Whereas 100% of the controls reached this (≥85%). Therefore, chronotropic incompetence was more prevalent in PWE ($p<0.05$). Chronotropic incompetence describes the inability to increase heart rate in response to increased activity (e.g., due to exercise) [12]. That means a heart rate failure to achieve 85% or 80% of the age-predicted heart rate [12]. It is known that this cardiac inability to respond adequately to a stimulus increases the risk of death [51].

Cardiac alterations seem to be frequent in epilepsy. Based on a National Health Interview Survey (95,196 adults), it was shown that 21% of adults with a history of epilepsy reported heart disease whereas only 11.7% of the adults without epilepsy history reported this. The biggest percentage difference (14.1 percentage points) for heart disease between these two groups was found for the age group 45-64 years [52]. Moreover, in the ten-year follow-up of the Oregon Sudden Unexpected Death Study, it was shown that epilepsy patients with sudden cardiac arrest (55±25 yrs.) were younger ($p<0.001$) than people without epilepsy (63±19 yrs.). Interestingly, cardiovascular characteristics did not differ between patients with and without epilepsy diagnosis. Information about seizure activity before sudden cardiac arrest was available for 30% of epilepsy patients. Seizure-like activity was present before the sudden cardiac arrest in 34% of these cases. For 10% of the patients without epilepsy, seizure-like activity was present before the event as well [53].

Verrier et al. (2020) [11] tried to describe cardiac alterations observed in the epilepsy population more specifically. They proposed the concept of "the epileptic heart" and defined it as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and hypoxemia leading to electrical and mechanical dysfunction" [11]. Postmortem findings, such as cardiomegaly, seizure-induced cardiac findings, like myocardial structural changes, clinical findings like ventricular stiffness, and also ECG-based findings like ST-segment changes support the concept of the epileptic heart [11]. Cardiac alteration can be life-threatening and increase the risk of sudden death [54]. A nationwide study showed, in a population of people between the age of 1 to 35 years, that an epilepsy diagnosis was associated with an increased risk of dying suddenly and without explainable cause (hazard ratio 27.6, 95% CI 18.1-41.9). This model was adjusted for sex [55]. The pathophysiological mechanisms responsible for an increased risk of dying suddenly in epilepsy seem to be multiple [11].

Dying suddenly and unexplained is a known problem in epilepsy. This phenomenon is described as SUDEP. It is defined as "sudden, unexpected, witnessed or unwitnessed, nontraumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death" [56]. The incidence of SUDEP varies between epilepsy populations. Based on a systematic review, in children with epilepsy (0-17 yrs.), the incidence of SUDEP risk was 0.22 per 1,000 patient-years (95% CI 0.16-0.31), and in adults with epilepsy 1.2 per 1,000 patient-years (95% CI 0.64-2.32) [57]. This cause of death seems to affect all age groups in the epilepsy community. However, the risk for SUDEP is influenced by the severity of the disease and by the success of treatment [58]. Therefore, some SUDEP risk factors have been identified. A 27-fold risk increase for SUDEP (OR 26.81, 95% CI 14.86-48.38) was linked with having generalized tonic-clonic seizures in the last year. Furthermore, experiencing this type of seizure during the night in the last year, led to a 15-fold risk increase (OR 15.31, 95% CI 9.57-24.47). Social aspects like living alone (5-fold, OR 5.01, 95% CI 2.95-8.57) and not sharing the bedroom with another person while also experiencing generalized tonic-clonic seizures (OR 67.10, 95% CI 29.66-151.88), led to

an increased risk. Moreover, substance abuse or alcoholism increased the SUDEP risk [59]. Additionally, the number of anti-seizure medications and no anti-seizure drug treatment at all, extratemporal epilepsy, intellectual disability, male gender, and anxiolytic drugs were associated with an increased risk [57]. Although, there is general knowledge about important risk factors for SUDEP, the etiology of this cause of death is still unknown [60,61]. Suggested mechanisms are tonic-clonic seizure-triggered cerebral suppression-apnoea-asystole, ictal (during seizure) asystole, tonic-clonic seizure-triggered ventricular tachycardia and fibrillation, interictal (between seizures) ventricular tachycardia and fibrillation and interictal cerebral suppression-apnoea-asystole [58].
Another suggestion is that autonomic dysfunction might impact cardiac function which could lead to SUDEP [13,62]. Also, Fiahlo et al. (2017) [48] suggest that the observed chronotropic incompetence in temporal lobe epilepsy patients might be driven by autonomic dysfunction. This dysfunction describes an imbalance between the two branches of the ANS and might lead to cardiorespiratory changes ictally and interictally. It is hypothesized that changes in the central autonomic network (CAN), caused by repeated seizures and interictal epileptic discharges [63], lead to autonomic alterations [64].

2.3 Central and Peripheral Autonomic Nervous System

The ANS is centrally controlled by the brain. Besides important integrative control centers located in the brain stem, a whole network, the CAN, is involved in autonomic control [65]. The CAN contains and connects widespread cortical and subcortical regions [65] and the brain stem [66]. Insula, amygdala, hypothalamus, periaqueductal gray, parabrachial complex, solitary tract nucleus, ventrolateral portions of the medulla, thalamus, medial prefrontal cortex, precuneus, cerebellum, and anterior cingulate cortex are assumed to be regions of the CAN [66]. Information of the central control instance of the ANS reaches out to the peripheral part of the ANS, the organs, via two divisions: the sympathetic and parasympathetic branches [67]. Sympathetic activation predominates in “fight or flight” conditions [67]. During emergency or stressful situations or exercise, sympathetic activity increases [67]. On the other side, during resting and relaxing conditions (“rest and digest”), parasympathetic activity predominates [68]. The two branches are working antagonistically, however, they interact in nonlinear antagonism

which means that high sympathetic and parasympathetic activity can be observed at the same time [15]. Additionally, there is a third division called the enteric nervous system that is influenced by the sympathetic and parasympathetic branches. The sphere of action of this division is in the digestive tract [69]. Two neuronal populations are involved in the sympathetic and parasympathetic efferent outflow to the organs. The preganglionic neurons can be found within the brain stem and the spinal cord. Therefore, these types of neurons are part of the central autonomic nervous system. The postganglionic neurons, as the second population of these serially connected neurons, are grouped and reach the organs [69]. On the other hand, neurons in the dorsal root ganglia or the cranial nerve ganglia are responsible for transferring the visceral afferent information [69]. It has to be distinguished between the different effector organs of the ANS in the sense of pathway specificity. For instance, for the sympathetic nervous system, an “all-or-none” law is inappropriate and does not reflect the ANS organization [70].

The two divisions of the ANS affect most of the target organs like the eyes, lungs, or bladder [67]. When examining the body’s response during or after exercise, the heart plays a crucial role. It is under reflexive control through cardiac autonomic nerves, but it is also controlled by central autonomic commands [15]. Cardiac function is influenced by both branches of the ANS. Simplified, sympathetic activation leads to an increase in heart rate and parasympathetic activation to a decrease. However, of note, both branches are not interacting linearly. A dysfunction in the interaction of the ANS might become visible in a resting heart rate or also during or after exercise in terms of chronotropic incompetence [12,51]. Besides organs that are influenced by both ANS branches, eccrine sweat glands are innervated by nerve fibers of the sympathetic branch only. Therefore, their activity serves as a reference for sympathetic activity [71].

The heart rate variability (HRV) can be used for the estimation of ANS activity and combines parameters that assess the complexity of the heart rhythm. HRV is, by definition, the „change in the time intervals between adjacent heartbeats” [72]. Parameters of HRV assess mixed sympathetic and parasympathetic as well as pure parasympathetic activity since the ANS regulates heart function [73]. It can be assessed by different analytical approaches. Time domain analysis, as well as frequency domain

analysis, are the most frequently used approaches [72]. Electrocardiography (ECG) is the gold standard method for recording the heart rhythm and therefore also for HRV analysis [74].

In general, time domain parameters refer to the interbeat intervals and the variability in them. As one example of the time domain parameters, the „root mean square of successive RR interval differences“ [75] called RMSSD (in ms) is a parameter reflecting parasympathetic activation. Frequency-domain parameters focus on the frequency bands. The measures estimate the distribution of relative and absolute power in these bands. Ultra-low-frequency (ULF, ≤0.003 Hz), very-low-frequency (VLF, 0.0033–0.04 Hz), low-frequency (LF, 0.04–0.15 Hz), and high-frequency (HF, 0.15–0.4 Hz) are the bands between it is distinguished when looking at heart rate oscillations. Furthermore, the ratio between the low-frequency and high-frequency bands is of interest as a presumed marker for vagal-sympathetic effects [76]. The parasympathetic or a mixture of the parasympathetic and sympathetic branches of the ANS contribute to these parameters [75].

The electrodermal activity (EDA) is the only marker reflecting pure sympathetic activation [77] due to the innervation of the sweat glands. In general, EDA summarizes changes in the electrical properties of the skin [78]. It can be measured by different methods, by endosomatic recordings, where no external current is applied, or by exosomatic recordings, where direct or alternating current is applied to the skin [79]. As the gold standard, two electrodes are placed on the fingers of the non-dominant hand [80].

Parameters of the HRV and EDA, are commonly used parameters in the field of epilepsy and exercise to investigate autonomic functions. This is done both in seizure situations [81,82] and in seizure-free periods [83]. In both conditions, it was shown that autonomic alterations could be detected.

2.3.1 Autonomic Function in Epilepsy

In patients with convulsive seizures, over the course of seizure and compared to the post-ictal state (after seizure) an increase in LF power ($p=0.02$) (para- and sympathetic activation), as well as a decrease in HF power ($p=0.02$) (parasympathetic activation) and

LF/HF ratio (p=0.02) was observed [84]. In patients with newly diagnosed epilepsy, significantly higher ictal LF component (p=0.04) compared to pre-ictal (before seizure) and interictal states were observed. Additionally, a higher HF component during the ictal state compared to interictal (p=0.01) and pre-ictal (0.003) states was detected. A higher LF/HF ratio during pre-ictal (p=0.0002), ictal (p<0.0001), and post-ictal (p<0.0001) states as well as a higher RMSSD in the interictal state compared to all other states (pre-ictal p=0.001, ictal p=0.02, post-ictal p=0.01) were shown [85]. Peri-ictal (time around a seizure) autonomic disturbances were also detected in another study, investigating patients with generalized tonic-clonic seizures and focal seizures with impaired awareness (complex partial seizures). For both types of seizures, heart rate was elevated (p<0.05) and HF power (p<0.05) was decreased post-ictal. For generalized tonic-clonic seizures, EDA (sympathetic activation) was significantly increased for 56 minutes after seizure (p<0.05) [82]. A systematic review included 19 studies, all showing an EDA response to seizures. An increase was detected in 14 studies and five studies noticed that generalized and focal seizures can induce an EDA response which seems to be more pronounced in generalized seizures. The systematic review included epilepsy patients of all ages with mixed syndromes and seizure types [86]. It can be noted that autonomic activity changes in response to seizures with a suggested sympathetic dominance.

A systematic review and meta-analysis on HRV in epilepsy patients and ASDs included 30 studies in the analysis. In comparison to healthy controls, it was shown that the HF index was lower in PWE (hedge's g -0.69), however, no group difference was observed for the LF index (hedge's g -0.18). Based on the standard deviation of normal-to-normal interval and RMSSD, patients presented lower values [83]. Horinouchi et al. (2019) [87] compared epilepsy patients and healthy controls in a resting state. They found a decreased EDA in patients compared to healthy controls. A comparison of newly diagnosed PWE and healthy controls revealed lower RMSSD (p<0.05) and lower percentage of consecutive RR intervals that differ more than 50 msec (p<0.05) in the patient group. Lower HF power (p<0.05), HF (normalized unit) (p<0.05), and LF power (p<0.05) and higher LF (normalized unit) (p<0.05) and LF/HF ratio (p<0.05) were shown in PWE [88]. Results indicate differences in autonomic activity in PWE compared to healthy controls,

however, a specific direction cannot be described due to the lack of data and heterogenous study designs and outcomes.

Nevertheless, it may be suggested that the ANS responds to seizures with sympathetic dominance. Additionally, the ANS activity in resting state seems to be different between PWE and healthy controls. Although some data on the alterations of autonomic activity in epilepsy are available, the underlying mechanisms are still unknown. As described, the ANS is organized on a central and peripheral level, strongly interacting with each other. It is assumed that the autonomic alterations in epilepsy might have their origin in the network of autonomic control, the CAN [13].

2.3.2 Central Alterations in Epilepsy

The brain is organized into several overlapping networks [89], for example, the CAN, the default mode network, and the visual network (VIS) [90]. In general, networks consist of nodes and edges that connect different brain areas [89]. Brain activity can be examined by methods, such as EEG or functional Magnetic Resonance Imaging (fMRI). fMRI is a method directly measuring brain activation by Blood-Oxygenation-Level Dependent Effect [91]. This method has a high spatial resolution [92] but with high costs. Another method that can be used for analyzing the brain is EEG [91]. EEG focuses on cortical activity arising from summed postsynaptic potentials in the brain [93] and has a high temporal resolution [94]. Connectivity parameters can be used to describe brain network activity. The different types of connectivity are structural, functional, and effective connectivity. Structural connectivity relates to the anatomical organization of a brain network and is usually investigated by Magnetic Resonance Imaging (MRI). Functional connectivity reflects the statistical dependency between signals and can be analyzed by fMRI or EEG. Effective connectivity is defined as causality, meaning the influence that one neuronal system exerts over another system [95].

To investigate assumed alterations in the CAN and therefore the supposed origin of autonomic changes in epilepsy, functional connectivity is of particular interest. This is because altered communication within a network can be explored. In general, the CAN is not a well-researched network among PWE and there is limited data on specific alterations within this network. Since changes in autonomic activity are assumed to play

a role in SUDEP, studies on this topic can be used to approach CAN changes in epilepsy [96]. However, these studies do not directly address the CAN and only provide an idea of brain alterations that may be related to the CAN.

Allen et al. (2017) [97] examined the dysfunctions in brain networks that are involved in autonomic regulatory processes using resting state fMRI in patients with temporal lobe epilepsy who are at high risk of SUDEP. Compared to patients at low risk, patients at high risk showed widespread functional connectivity differences in brain regions that are important for autonomic regulations (thalamus, brain stem, anterior cingulate, putamen, amygdala). Risk stratification was done based on epilepsy duration, epilepsy onset, generalized tonic-clonic seizures per year, and nocturnal seizures. Tang et al. (2014) [98] used a similar methodology and compared patients at low risk and high risk of SUDEP by using resting state functional connectivity based on fMRI. Patients at high risk had significant reductions in functional connectivity between the right thalamus and the pons, the midbrain, the bilateral anterior cingulate cortex, and the left thalamus [69]. In 2019, Allen et al. [99] extended their approach by investigating patients who died due to SUDEP over an 8-year follow-up. They compared these cases with matched patients at high and low SUDEP risk and with a healthy control group. They focused on the whole brain and regions involved in autonomic and respiratory regulation. The number of separate modules within a network (modularity) was significantly reduced for the whole brain and the observed subnetwork in SUDEP patients and high-risk patients. Among thalamic structures, the inter-modular belonging was apparent in SUDEP group and high-risk group. Furthermore, group differences were also found for the medial prefrontal thalamus and patterns of hub topology, especially in the comparison of low-risk group and SUDEP group. In a review, existing evidence from structural and resting state functional MRI changes in the field of SUDEP were summarized. In general, patients suffering from SUDEP and those at high SUDEP risk show resting-state alterations in fMRI as well as structural changes in brain areas involved in cardiovascular and breathing control. It seems that impaired communication within these network structures is apparent in this subgroup of epilepsy patients. However, it has to be pointed out that the sample sizes of these studies are small [100].

In addition to investigating the brain in the context of SUDEP, analyzing the brain of PWE in general also uncovers alterations. A comparison of mesial temporal lobe epilepsy patients and healthy controls based on fMRI showed significant results for connectivity analysis within the medial temporal lobes (increase) and within as well as between frontal and parietal lobes (decrease) [101]. Similar groups were under investigation in another fMRI study. They found widespread alterations in the interaction of large-scale brain networks [102]. A systematic review and meta-analysis on brain network organization in people with focal epilepsy indicated an increased segregation and a decreased integration [103]. Another meta-analysis and systematic review revealed alterations in the default mode network across different epilepsy syndromes [104]. A resting-state fMRI study showed a more regular network topology and a higher global connectivity in patients with idiopathic epilepsy compared to healthy controls. The results appeared to be independent of seizure control status. However, the analysis of this influence was limited by drug response classification [105]. Since the CAN includes widespread cortical and subcortical areas, whole brain alterations might also address regions of the CAN.

Van Diessen et al. (2013) [106] focused on potential modifiers that might impact altered network function in epilepsy. The authors noted that the duration of epilepsy and seizure frequency are factors, as well as the use of ASDs. At this time, it is unclear whether network disturbances in epilepsy patients with brain lesions arise from the lesion or from the epilepsy itself.

There are numerous open questions regarding network changes in epilepsy, particularly those within the CAN. However, the extensive network changes observed in epilepsy highlight the fact that epilepsy is a network disease and demonstrates that the previous understanding of an epileptic focus is too simple [14]. When focusing on functional network changes, it is important to investigate specific networks such as the CAN, which is assumed to play a role in changes in autonomic activity, as well as the whole brain.

2.3.3 Exercise Tests

The ANS has been primarily studied in two conditions among PWE: during resting state or in the context of seizures. However, examinations during acute exercise could be another condition that might uncover alterations [107–110]. In the field of cardiology,

exercise tests have been used to examine cardiac disturbances for decades [111,112]. Oxygen requirement is increased due to the muscle work during exercise resulting in an increased heart rate which stresses the cardiovascular system. Cardiac and cardiovascular responses are modulated by the ANS. Central commands activated control circuits for locomotor, cardiovascular, and ventilatory functions [113]. During exercise, these commands induce an increased sympathetic and a reduced parasympathetic influence on the heart and raise the ventilatory rate. It is assumed to be also involved in adjusting the baroreflex [114]. Sympathetic and parasympathetic activity during exercise can be investigated by the heart rate and the HRV [67,115], whereas sole sympathetic activity can be examined by changes in EDA [108]. Central ANS activity can be assessed by estimating functional connectivity parameters from EEG recordings before, during, or after exercise [116]. Furthermore, exercise tests have the advantage of applying to both patients and healthy people [48] which enables group comparisons. To ensure safe testing, considering potential exercise-induced seizures, the choice of the right and appropriate exercise protocol and exercise machine is crucial. In epilepsy research, exercise tests had been conducted on a treadmill [48] or on bicycle ergometers [117,118]. The influence of acute exercise on seizure activity can additionally be investigated by an exercise test.

3 Research Aims and Questions

Physical activity is commonly used for rehabilitative purposes in neurological diseases. However, it is not widely accepted as a therapy for epilepsy among physicians and patients. PWE often fear exercise-induced seizures and exercise-related injuries. Therefore, animal studies are suitable for investigating the influence of physical activity on seizures and can serve as a first step in researching epilepsy and exercise. The first question this dissertation addresses is: How does physical activity influence seizures in animal models? (research paper 1)

However, it is important to investigate whether physical activity has an impact on symptoms experienced by PWE, such as seizures, depression, and anxiety. Furthermore, it is worth exploring whether the negative perception of physical activity and exercise among PWE, which may be caused by discouragement from physicians, affects their physical activity levels. Are PWE less physically active compared to healthy people? How does physical activity affect seizure frequency and comorbidities? (research paper 2)

The fear of exercise-induced seizures motivates to the investigation of the influence of acute exercise on seizure activity. Therefore, for this dissertation, a cross-sectional cohort study was conducted which focused on clinical data in the context of an exhaustive bicycle exercise test to make a statement about the feasibility of exercise tests and the impact of acute exercise on seizures (research paper 3). Furthermore, this study also investigated non-clinical parameters. It aimed to determine if PWE have lower physical fitness levels compared to healthy controls (research paper 3). Additionally, the difference in central (research paper 4) and peripheral autonomic parameters (research papers 3 & 4) between the two groups in the context of exercise from a network perspective was investigated.

Since most data on physical activity and epilepsy as well as autonomic functions in epilepsy derive from patients with therapy-refractory epilepsy, this study focused on a community-based cohort of epilepsy patients in consideration of their seizure status.

4 Publications and Results

Four publications were considered for this dissertation.

Research paper 1 is a narrative review focusing on the impact of physical activity on status epilepticus in animal models. Research paper 2 is a systematic review of “Sport and Physical Activity in Epilepsy”. This review summarizes the existing literature for humans. Research papers 3 and 4 are related to the cross-sectional cohort study. 26 patients and 26 age, sex, BMI matched healthy controls were recruited for this study. Both groups performed an exhaustive bicycle ergometer test and took part in resting state measurements before and after the exercise test. Performance on the bicycle ergometer as well as fitness were assessed as outcomes during the exercise test. Peripheral and central autonomic parameters as well as clinical EEG data were analyzed for resting state measurements before and after the exercise. Research paper 3 dealt with exercise performance and fitness as well as resting state peripheral autonomic data and clinical EEG data. Research paper 4 relates peripheral autonomic parameters to central autonomic parameters.

4.1 Methods

The protocol of the study and the informed consent was approved by the ethics committee of the Westfalian Medical Board. Before the participant's recruitment, the trial was registered at the German Clinical Trial Register (DRKS00014822). The study was conducted in accordance with the Declarations of Helsinki. An overview of the cross-sectional cohort study is presented in figure 1.

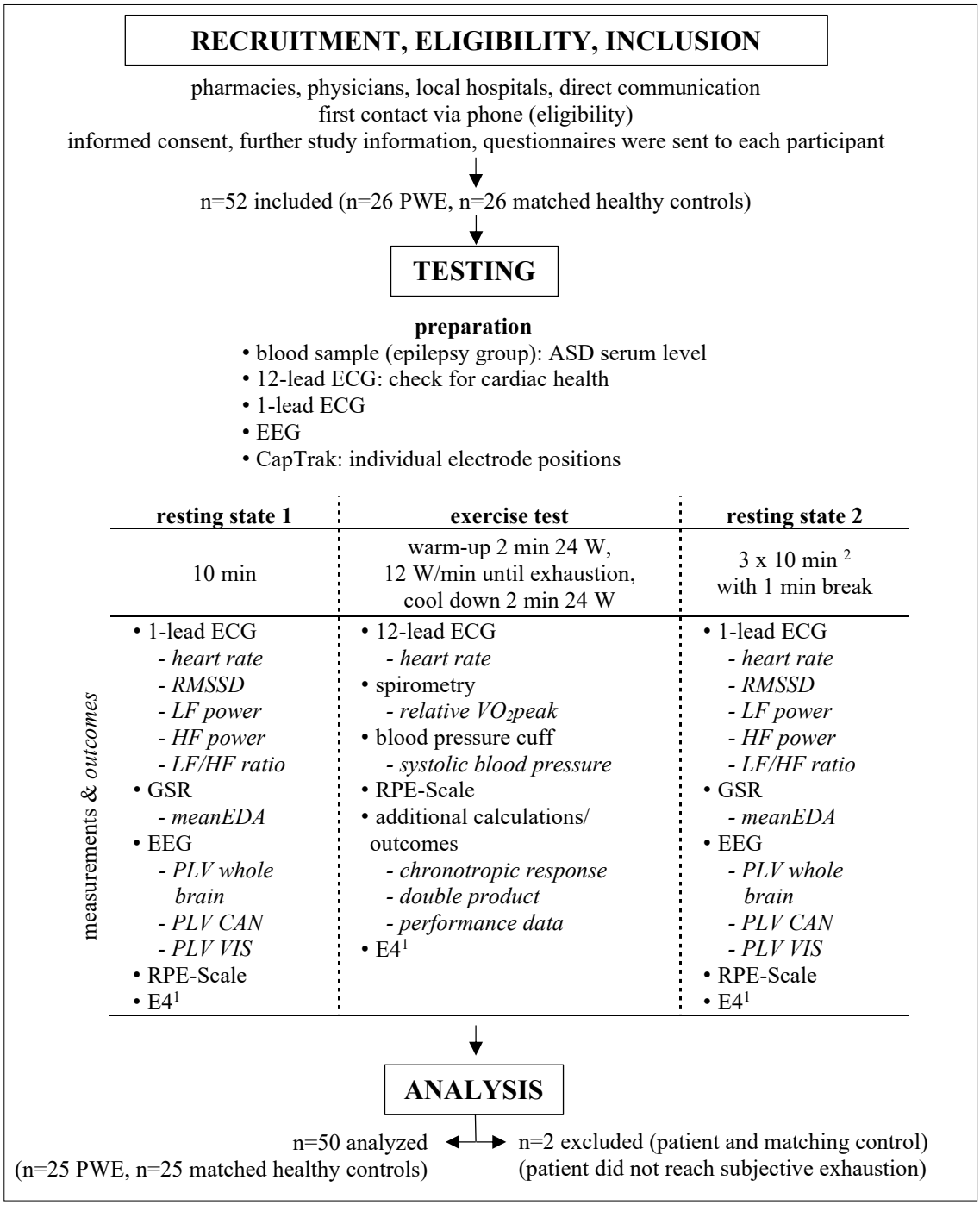


Figure 1 Flow chart of the cross-sectional cohort study

[1] not used in this dissertation
[2] second and third 10 minutes were not considered for this dissertation
ASD: anti-seizure drug, CAN: central autonomic network, ECG: electrocardiogram, EDA: electrodermal activity, EEG: 128-channel electroencephalogram, GSR: galvanic skin response module, HF: high frequency, LF: low frequency, PLV: phase-locking value, RPE: rate of perceived exertion, RMSSD: root mean square of successive RR interval differences, VIS: visual network, VO2: oxygen uptake, W=watts

4.1.1 Participants

Participants were recruited via pharmacies, physicians, local hospitals, and direct communication. The first contact was via phone, where eligibility for the study was checked. In general, epilepsy patients (criterium 1 and 3) and healthy controls (criterium 2 and 3) were included if they met the following criteria: 1) diagnosed epilepsy – all syndromes, or 2) healthy adults without seizure history, and 3) age between 18 and 60 years. Participants were excluded if they met any of the following criteria: 1) physical impairments avoiding conduction of exercise test on a bicycle ergometer, 2) acute infections, 3) severe heart diseases (ischemic or structural), and 4) moderate to severe hypertension. For some analyses, other exclusion criteria were added due to their influence on the primary and secondary outcomes (see research papers 2 and 3). Patients and controls were matched by age, sex, and BMI. For each matching, patients were recruited and tested first, and healthy controls were recruited subsequently.

In total, 52 subjects participated in the study, 26 in each group. However, one participant with epilepsy was tested but excluded afterward from all analyses. This patient suffered from a cardiac infarction in 2019 (8 stents implanted) and was still influenced by its consequences (medication: Acetylsalicylic acid, Candesatan, Bisoprolol, Rosuvastatin, Ezetimibe, Pantoprazole). The patient was not able to achieve subjective exhaustion on the bicycle ergometer (rate of perceived exertion scale (RPE) <18) and had to stop the testing earlier. As the aim of the study was to achieve complete subjective and objective exhaustion, this patient was excluded. Regarding characteristics of seizures and epilepsy, this patient suffered from epilepsy for 56 years with myoclonic seizures one to two times per week. Anti-seizure medication was Phenydan (250 mg/day, serum level 28.9 mg/l). During the resting state measurements before and after exercise, the patient fell asleep. Furthermore, the patient experienced a subclinical seizure (70 sec) during sleep but only after exercise. The matched control subject was excluded as well.

Nineteen of the remaining 25 epilepsy patients were seizure-free in the last six months. On average, the last seizure happened 2979.5±3113.6 days ago. 17 patients suffered from generalized seizures (motor and nonmotor), seven patients from focal seizures (awareness

impaired and not impaired), and four patients did not know their type of seizure. Three patients indicated two types of seizures.

Different epilepsy syndromes and etiologies were reported, however, most of the patients do not know the syndrome (n=16) or the etiology (n=20). One patient was not under ASD treatment at all, 18 patients were on monotherapy, five patients took two ASDs and one patient took three ASDs. ASDs with dosages and serum levels are presented in research paper 2. On average, the duration of epilepsy was 16.78±18.1 years. Characterizations of seizures and epilepsy are presented in table 1.

Table 1 Characterization of seizures and epilepsy (published in research paper 2)

variables	patients (n=25)
disease duration (yrs.)	16.78±18.1
age of disease onset (yrs.)	21.68±14.44
seizure type* (n)	
generalized motor	14
generalized nonmotor	3
focal awareness impaired	4
focal aware	3
unknown type	4
seizure frequency (last 6 months) (n)	
seizure free	19
1-2	3
1 per month	1
1 per week	1
more than 1 per day	1
last seizure of seizure-free patients (n=18[1]) (days)	2979.5±3113.6 (min: 356; max: 9490)
syndromal classification	
temporal lobe epilepsy	2
idiopathic genetic epilepsies	7
juvenile absence epilepsy (2)	
juvenile myoclonic epilepsy (1)	
grand-mal epilepsy (3)	
grand-mal epilepsy on awakening (1)	
unknown	16
etiology	
traumatic brain injury	1
genetic	2
structural change, not otherwise specified	1
radiation-induced	1
unknown	20
number of ASD (n)	
0	1
1	18
2	5
3	1

all data based on the characterization of seizures and epilepsy questionnaire
** three patients indicated two types of seizures*
[1] missing data for one patient
disease duration, age of disease onset, last seizure of seizure-free patients: mean±standard deviation

In total, 13 female and 12 male subjects participated in both epilepsy and control group. Since the groups were additionally matched by age and BMI, the epilepsy and control group were equally old (epilepsy group 38.4±12.1 yrs., control group 37.48±12.11 yrs., p=0.78) and had an equal BMI (epilepsy group 26.48±4.68, control group 27.05±4.97,

p=0.68). There were no group differences regarding the existence of hypertension, diabetes type 1, dyslipidemia, family history of cardiovascular diseases or epilepsy, and smoking. The only group difference was observed for alcohol use with a higher consumption in the control group. Most of the participants were highly physically active (epilepsy group n=18, control group n=16) based on the International Physical Activity Questionnaire (IPAQ). Clinical characteristics of epilepsy and control group are presented in table 2.

Table 2 Clinical characteristics of epilepsy and control group (published in research paper 2)

variables	patients (n=25)	controls (n=25)	p
age	38.4±12.1	37.48±12.11	[c] 0.78
BMI	26.48±4.68	27.05±4.97	[c] 0.68
sex	f: 13; m: 12	f: 13; m: 12	
hypertension	3	0	[b] 0.23
diabetes type 1	1	0	[b] 1.00
dyslipidemia	1	2	[b] 1.00
active smoking	3	2	[b] 1.00
active smoking in the past	4	7	[a] 0.30
alcohol use	15	23	[a] 0.008**
family history CVD	11	10	[a] 0.774
family history epilepsy	3	4	[b] 1.00
physical activity level			
low	1	0	[b] 0.538
moderate	6	9	
high	18	16	

[a] *chi-squared test*
[b] *Fisher's exact test*
[c] *student t-test*
** p<0.05*
*** p<0.01*
age, body mass index (BMI): mean±standard deviation
further characteristics: n
CVD= cardio-vascular disease, f= female, m= male

4.1.2 Procedure

Before the testing day, informed consent, further study information, and questionnaires were sent to each participant. After they agreed to participate in the study, an appointment for one testing day was made. Both groups answered the IPAQ to assess their daily physical activity level. Additionally, a questionnaire regarding clinical characteristics and

sociodemographic data was filled out. Furthermore, participants in the epilepsy group answered a questionnaire regarding the characteristics of seizures and epilepsy.
On the testing day, participants were greeted and given a one-on-one explanation of any open questions and the testing day procedures. For the epilepsy group, a physician took blood samples to assess ASD serum levels before the first measurement on the testing day. For analysis, samples were sent to an independent laboratory. For both groups, a resting state 12-lead ECG (Custo cardio 100 BT, Custo Med) in a supine position was recorded to check cardiac health before the exercise test. The ECG was checked by a physician. The 12-lead ECG stayed on the participant's upper body and was used for exercise testing afterward. After that, participants were prepared for the EEG measurement in a seating position. The forehead, and if relevant, the bald head, was cleaned with an alcohol pad. Afterward, a cap with 128 electrodes (actiCHamp, Brain Products GmbH) was placed on the head according to the 10-10 system. Following Brain Products GmbH's recommendation, impedances were kept below 25 kilo-ohm (kΩ) by using SUPER VISC high viscosity electrolyte gel (EASYCAP GmbH). The ground electrode was FPz and the reference electrode FCz. After preparation, CapTrak (Brain Products GmbH) was used to record individual electrode positions. Before the first resting state measurement and before the exercise test, three passive electrodes (Brain Products GmbH) were placed on the upper body of the participants and used as 1-lead ECG during the resting state measurements. The Galvanic Skin Response Modul (GSR, Brain Products GmbH), consisting of two electrodes, was placed on the middle phalanges of the index and middle finger on the non-dominant hand. Additionally, E4 Sensors (Empatica) were placed on both wrists. The data from these sensors were not used for this dissertation.

The first resting state measurement was conducted for 10 minutes in supine position in a darkened room. Instructions for the measurement were read out, to instruct each participant in the same way.

After that, participants were prepared for the exercise test. The EEG cap including 128 electrodes stayed on the participant's heads, but no recording was done during the exercise test. A spirometry mask (V2 MASK, Hans Rudolph, Inc.) was placed on the participant's

faces, and the closeness of the mask was checked. Afterward, participants went on the bicycle ergometer, and a blood pressure cuff, for manual blood pressure measurements, was placed on the left upper arm. First, blood pressure, spirometry parameters (Metalyzer 3B, Cortex), and ECG were measured in a seating position on the bicycle ergometer (Excalibur, Lode) at rest. The exercise test started with a warm-up for two minutes at 24 watts. Afterward, the load was increased every minute by 12 watts until subjective exhaustion, followed by a two-minute cool down at 24 watts. Revolutions per minute (rpm) were as follows: 50-60 rpm at 24-60 watts, 60-70 rpm at 60-100 watts, and 70-90 rpm at >100 watts. Participants were asked for their level of exertion by using the RPE scale every two minutes. Blood pressure was measured every two minutes as well. Spirometry parameters and ECG were recorded continuously. E4 Sensors, placed on both wrists, collected data continuously as well, but data were not used for this dissertation.

After the exercise test, the spirometry mask and blood pressure cuff were taken off. The participants were brought to the room where the resting state measurements took place. EEG electrodes were checked for good contact and fixed if they were noisy. GSR, E4 Sensors, and 1-lead ECG were used again. Ten minutes after the end of the cool-down period, the second resting state measurement in supine position in a darkened room started. Instructions for the measurement were read out, to instruct each participant in the same way. The measurement was conducted as follows: ten minutes recording, one minute break, ten minutes recording, one minute break, ten minutes recording. During the one-minute breaks, the investigator (FvdB) entered the room to engage with the participants and ensure they stayed awake. After the second resting state measurement, a second recording of the individual electrode positions via CapTrak was done.

During exercise, performance parameters like relative oxygen consumption (VO_2) peak, maximum heart rate and others were analyzed. For autonomic parameters in resting state, RMSSD, HF power, LF power, LF/HF ratio, and meanEDA were analyzed. To assess functional network activity in source space, phase-locking value (PLV) was analyzed for the whole brain, the CAN, and the VIS (reference network). The general preprocessing and analysis of EEG, ECGs, GSR, and spirometry are described in research papers 3 and 4.

4.2 Results

4.2.1 Research Paper 1

van den Bongard F, Gowik JK, Reinsberger C. Auswirkungen körperlicher Aktivität auf Status Epilepticus im Tiermodell. Clinical Epileptology 2023; 1-5. DOI 10.1007/s10309-023-00574-4

PWE are often discouraged from engaging in physical activity due to concerns about exercise-induced seizures and the assumed potential negative influence on epilepsy. However, most data on the impact of physical activity on seizures is derived from animal studies.

Based on literature research in PubMed and Web of Science, 33 out of 3489 studies were included in this narrative review. Animal models in a controlled design on rats and mice and all status epilepticus models were considered. In animal models, epilepsy is mostly induced by chemical convulsant agents that provoke a status epilepticus. This is defined as "a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1)." [119]

Different convulsant agents (e.g., pilocarpine, pentylenetetrazole, penicillin) or stimulation were used in the included studies. The timepoint of their use differed between the studies (before vs. after the intervention). 28 studies examined male rats, 2 studies female rats, and three studies male mice. Swim training, forced and voluntary treadmill training, and strength training with different exercise modalities (duration, frequency, intensity) were conducted. Overall, numerous different outcomes, like seizure frequency, latency or intensity of seizures, and epileptiform activity, were reported.

After 20 interventions, outcomes like seizure frequency or epileptiform activity were positively influenced. The results for nine interventions were heterogeneous. While some outcomes were influenced positively, for others no effect was observed. Six interventions induced no effect, for instance on seizure frequency, latency to seizure, or epileptiform activity at all. After one voluntary endurance intervention, a negative effect on the

intensity of motoric symptoms was observed, however, a positive effect on latency to the first seizure was shown as well.

The study results might be influenced by the different exercise modalities as well as by the different chemical convulsant agents for status epilepticus induction. Since the studies are heterogeneous regarding these parameters, a conclusion about a dose-response relationship is not possible. Furthermore, the physiological mechanisms of a status epilepticus induction and therefore developed epilepsy are different compared to the pathophysiology of epilepsy in humans. Consequently, the transferability to humans is restricted.

Nevertheless, the results of this narrative review indicate a trend of a positive influence of physical activity on seizure-associated outcomes and show at least, except after one intervention, no negative influence. Therefore, these positive results from animal studies should motivate to the development and conduction of valid studies on the impact of physical activity on seizures in humans.

Author contributions:

Franziska van den Bongard, Julia Kristin Gowik and Claus Reinsberger wrote the manuscript. All Authors commented on all versions. All authors agreed to the final version.

4.2.2 Research Paper 2

van den Bongard F, Hamer HM, Sassen R, Reinsberger C: Sport and physical activity in epilepsy—a systematic review. Dtsch Arztebl Int 2020; 117: 1–6. DOI: 10.3238/arztebl.2020.0001

PWE fear the negative influence of physical activity on epilepsy course, exercise-induced seizures, and injuries. These are reasons why it has long been recommended to not be physically active. It has to be elucidated whether epilepsy patients are less physically active and, if so, whether this inactivity might lead to disadvantages in this population. Furthermore, there is no systematic review on the impact of physical activity on epilepsy (until the year 2020).

The systematic review aimed to elucidate the following three questions.

1) Are patients with epilepsy less physically active and less fit compared to healthy controls?
2) Does physical activity impact comorbidities in epilepsy?
3) Does physical activity impact seizure frequency?

After conducting literature research on PubMed and Web of Science and removing duplicates, 14,269 studies were screened and 42 studies (figure 2) were included to investigate the three questions. Selection criteria were human studies, longitudinal studies, cross-sectional studies, case studies, patients with diagnosed epilepsy, and endpoints of physical activity. Methodological quality assessment was done by Risk-of-Bias tool for intervention studies and for observational studies based on the publication of Hammer et al. (2009) [120]. Additionally, evidence levels were assessed for all included studies. Study selection and evaluation were done by two independent reviewers (FvdB, CR).

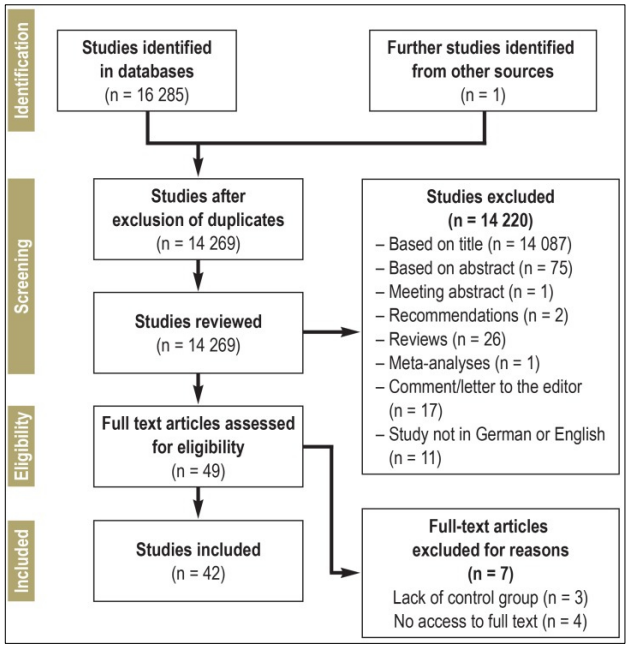


Figure 2 PRISMA flow diagram

The 42 included studies can be divided into seven categories: case studies, intervention studies, epidemiological studies, survey-based studies, interview-based studies, combined cross-sectional studies (survey and exercise tests), and studies on acute physical exercise.

Based on 15 studies, dealing with physical activity and fitness levels in patients with epilepsy, most studies indicate a lower physical activity level (n=6) and a lower fitness (n=5) compared to healthy controls. However, three studies showed no group differences regarding physical activity levels. One epidemiological study investigated the impact of the fitness level at the age of 18 and the later risk for developing epilepsy (up to 40 years follow-up). This study found an association between physical fitness levels in youth and the prevention of epilepsy later in life.

The influence of physical activity on comorbidities like depression or anxiety was investigated by 17 studies with different study designs (observational, interview, acute exercise test). Overall, being physically active, evaluated by questionnaires and interviews, seems to have a positive impact on comorbidities (n=10). Also, physical

activity interventions induced improvements in depression and anxiety (n=6). Only one study showed no association.

The results on the impact of physical activity on seizure frequency are heterogeneous. Only focusing on studies conducting an acute exercise test, in two studies, no seizures were observed. In three studies, epileptic discharges were reduced during exercise but increased again after exercise. Focusing on intervention studies, two observed a significant seizure reduction and four showed a heterogeneous picture within the investigated cohort. For some patients, seizure frequency remained unchanged, for some frequency increased and for others, it decreased. No change in seizure frequency was observed in another intervention study. Besides studies conducting an intervention or an acute exercise test, three used questionnaires to assess the influence of physical activity on seizure frequency indicating heterogeneous results as well. Seizures were associated with physical activity in some patients, but not in others. Four case reports only focused on patients with exercise-induced seizures.

Methodological quality was rather low for all included studies. They were limited by lack of information, lack of randomization, lack of control groups, lack of blinding, lack of considering influencing factors, and restricted recruitment strategies. Only five studies were assignable to evidence levels “1-“ and “2+”, indicating a higher quality. All other studies were assigned to evidence levels “2-“ and “3”, indicating a lower quality.

The limitations of the study are attributed to the characteristics of the patient cohort, including the epilepsy syndrome, seizure type, disease duration, and medication usage. Additionally, study comparability is restricted by the design of the applied interventions: training intensities, durations, and frequencies.

Nevertheless, it was shown that physical activity seems to have a positive influence on comorbidities like depression and anxiety in PWE. Furthermore, intervention studies indicate that exercise has no negative effect on seizure frequency in most cases. Of note, there are cases where physical activity serves as a seizure trigger, however, for most patients exercising seems not to increase the risk for seizures. It is not yet clear which

type and dose of physical activity could have the potential to influence epilepsy positively. The small study number as well as heterogeneity in study designs and cohorts (characteristics of seizures and epilepsy) restricts conclusions as well as the study quality.

Based on the results of the systematic review, there is no reason for a general ban on physical activity and exercise in epilepsy. Due to the hint that PWE might be less physically active compared to healthy controls, a first step to participate in physical activities might be a rehabilitation sports group specific to PWE. To ensure safety for each patient, an individual risk estimation can help to find the right type of exercise.

Author contributions:

Franziska van den Bongard and Claus Reinsberger designed the protocol for the systematic review. Franziska van den Bongard did the systematic literature research and the quality assessment. She and Claus Reinsberger wrote the manuscript. Hajo M. Hamer and Robert Sassen commented on all versions. All authors agreed to the final version.

4.2.3 Research Paper 3

van den Bongard F, Coenen J, Reinsberger C. Fitness, performance and cardiac autonomic responses to exercise in people with epilepsy. Epilepsy & Behavior 2022; 135: 108869. DOI 10.1016/j.yebeh.2022.108869

PWE seem to be less fit [121] and seem to have a different cardiovascular response to exercise which could increase the risk of sudden cardiac death [48]. The ANS regulates relevant parameters such as heart rate and chronotropic response. It is assumed that the ANS can become imbalanced in PWE [82,83,87]. However, these results are mostly derived from patients who are refractory to medical therapy. Since cardiac and other organs response to physical activity are modulated by the ANS, exercise testing can serve as a possibility to investigate autonomic function in PWE.

25 PWE (19 patients were seizure-free for at least the last six months) and 25 age, sex, and BMI matched healthy controls participated in the study. All participants reached subjective and objective physical exhaustion in the exhaustive bicycle ergometer test. No adverse events were observed before, during, or after the exercise test.

Relative VO_2peak ($p=0.438$, $r=0.112$) and physical activity levels ($p=0.538$), based on IPAQ, did not differ between the groups. However, maximum heart rate ($p=0.028$, $r=0.310$) and chronotropic index (Tanaka $p=0.017$, $r=0.336$; Karvonen $p=0.039$, $r=0.292$) were significantly lower in the epilepsy group. RMSSD significantly decreased (epilepsy group $p=0.001$, $r=0.793$; control group $p=0.001$, $r=0.869$) and meanEDA significantly increased (epilepsy group $p=0.001$, $r=0.869$; control group $p=0.001$, $r=0.766$) from pre- to post-exercise in both groups but no group differences were detected. For autonomic parameters, the epilepsy group and the control group only differ in LF/HF ratio post-exercise ($p=0.045$, $r=0.284$). The ratio significantly increased in both groups from pre- to post-exercise (epilepsy group $p=0.014$, $r=0.492$; control group $p=0.001$, $r=0.804$) but stronger in the control group. Based on multiple linear regression analysis, neither seizure frequency nor generalized motor seizures were predictors for relative VO_2peak, maximum Watt/kg, maximum metabolic equivalent of task, or exercise duration. Due to the larger group of patients on lamotrigine medication (n=13), correlation analysis with

respect to autonomic, fitness, and performance data revealed no association with dosage or serum level, however, a negative correlation between meanEDA and lamotrigine serum level post-exercise was observed but without reaching significance ($p=0.086$, $r=-0.495$). Nevertheless, ASD might influence the results.

Moreover, 23 patients showed no clinical changes in EEG from pre- to post-exercise. Interictal epileptiform discharges were observed in four patients pre-exercise and in six patients post-exercise, indicating a change in two patients. For both, no abnormalities were observed before exercise and none of these patients experienced exercise-induced seizures. One patient (juvenile myoclonic epilepsy) showed bursts of 3-4/sec generalized spike-and-waves during wakefulness and the other patient (undetermined idiopathic genetic epilepsy) had a single burst of generalized spikes during sleep.

Clinical EEG results indicate that exercise tests are feasible and safe for mostly seizure-free patients. Therefore, exercise tests can be used to investigate autonomic function in epilepsy. It seems that cardio-autonomic responses are different between PWE and healthy controls.

Author contributions:

Franziska van den Bongard and Claus Reinsberger were involved in the design of the study. Franziska van den Bongard and Jessica Coenen did the data collection. Franziska van den Bongard and Claus Reinsberger wrote the manuscript. Jessica Coenen commented on all versions. All authors agreed to the final version.

4.2.4 Research Paper 4

van den Bongard F, Gowik JK, Coenen J, Jakobsmeyer R, Reinsberger C. Exercise-induced central and peripheral sympathetic activity in a community-based group of epilepsy patients differ from healthy controls. Experimental Brain Research 2024. DOI 10.1007/s00221-024-06792-0

In epilepsy, ANS activity, mainly driven by the CAN [113], is shifted to a sympathetic dominance [82,122,123]. Exercise tests have been successfully used to examine and diagnose pathological changes within the cardiovascular system [19,111] and can be used to investigate ANS network activity in PWE as well. It was hypothesized that, after exhaustive exercise, the interrelation of CAN functional connectivity and peripheral ANS parameters might be altered in PWE.

PWE and healthy controls performed an exhaustive exercise test. Peripheral ANS activity (RMSSD, meanEDA) was measured and EEG was recorded in a resting state before and after the exercise test. Participants were included if they met the following criteria (epilepsy group criterium 1 and 3; control group criterium 2 and 3): 1) diagnosed epilepsy – all syndromes, or 2) healthy adults without seizure history, and 3) age between 18 and 60 years. Participants were excluded if they met at least one of the criteria: 1) physical impairments avoiding conduction of exercise test on a bicycle ergometer, 2) acute infections, 3) severe heart diseases (ischemic or structural), 4) moderate to severe hypertension, and 5) brain lesion.

21 PWE (16 seizure-free for at least the last six months, duration of epilepsy 18.83±19.06 yrs., age of onset 20.19±14.08 yrs., number of ASDs: 1 ASD=14, 2 ASDs=5, 3 ASDs=1, no ASD=1) and 21 age, sex, and BMI matched healthy controls participated in the study. Twelve female and nine male subjects were included in both groups (epilepsy group 39±11.6 yrs., BMI 26.7±4.2; control group 38.04±11.5 yrs., BMI 27.1±5.2). Concerning clinical characteristics, the control group showed a higher alcohol consumption compared to the epilepsy group ($p=0.01$).

RMSSD significantly decreased (epilepsy group 55.44±53.84 vs. 13.54±15.86, p<0.001; control group 42.48±30.22 vs. 8.79±6.56, p<0.001) and meanEDA significantly increased (epilepsy group 1.36±0.85 vs. 2.99±1.35, p<0.001; control group 1.68±1.10 vs. 2.65±1.68, p<0.001) from pre- to post-exercise in both groups but without showing group differences.

After exercise, whole-brain functional connectivity (alpha frequency band) increased significantly in the control group (0.28±0.04 vs 0.30±0.05, p=0.006). CAN functional connectivity and VIS functional connectivity (alpha frequency band) did not change significantly from pre- to post-exercise in both groups. Only before post hoc Bonferroni correction, CAN functional connectivity increased significantly in the control group after exercise (0.31±0.05 vs. 0.33±0.05, p=0.03). Before post hoc Bonferroni correction, CAN functional connectivity and meanEDA correlated significantly in the control group after exercise (r=0.543, p=0.01). Significant different correlation coefficients of CAN functional connectivity and meanEDA were found between the groups (p=0.004) (figure 3).

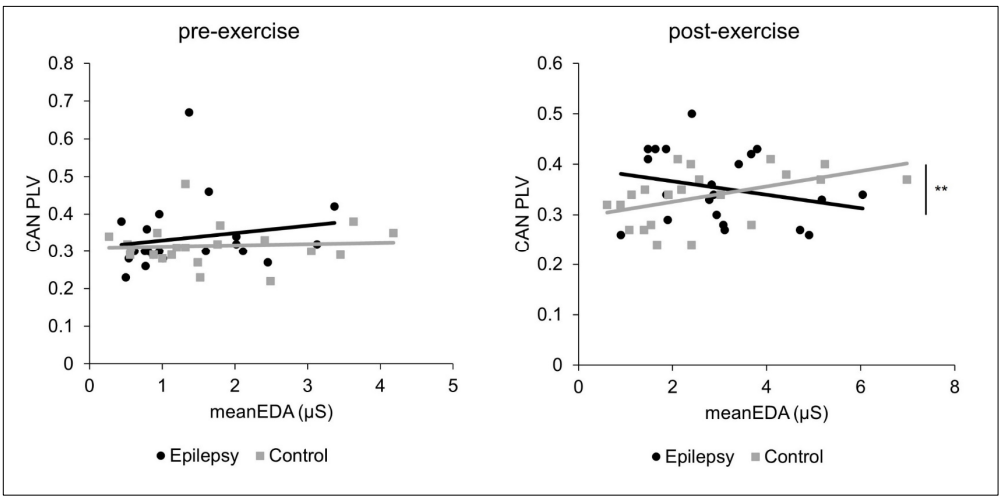


Figure 3 Correlation CAN functional connectivity and meanEDA

*PLV= phase locking value, CAN= central autonomic network, EDA= electrodermal activity, * p<0.05*

Since a considerably larger group of patients were on lamotrigine medication (n=12), the influence on CAN functional connectivity and meanEDA was tested, showing no significant influence on the results. No influence of VO_2peak was found on CAN functional connectivity and RMSSD or meanEDA correlations.

A different sympathetic reactivity in the epilepsy group after exercise might be shown by the different correlation between central autonomic and peripheral sympathetic activity. However, the influence of modulators such as seizures or anti-seizure medication has to be considered and needs further exploration. Moreover, it has to be elucidated how the ANS responds to chronic exercise which may guide future therapeutic interventions.

Author contributions:

Franziska van den Bongard, Julia Kristin Gowik, and Claus Reinsberger were involved in the design of the study. Franziska van den Bongard, Julia Kristin Gowik and Jessica Coenen did the data collection. Julia Kristin Gowik supported EEG analysis and statistical analysis. Franziska van den Bongard and Claus Reinsberger wrote the manuscript. Julia Kristin Gowik and Rasmus Jakobsmeyer supported in the writing process. All authors commented on all versions. All authors agreed to the final version.

5 Discussion

This dissertation investigated the risks and benefits of physical activity on epilepsy and its impact on autonomic control. An exhaustive exercise test was conducted to investigate the influence of acute exercise on seizure activity in a community-based cohort of PWE. To compare physical fitness levels and peripheral as well as central autonomic activity before and after exercise, a healthy, matched control group was also examined.

The first part of the discussion deals with the current scientific literature on physical activity and epilepsy focusing on the challenges and benefits in that field. Barriers to physical activity participation in epilepsy are discussed as well as the heterogeneity of epilepsy and seizure characteristics and the challenges it poses. Furthermore, the methodological quality of studies in that field is taken into consideration.
The second part focuses on discussing the results of the cross-sectional cohort study on seizure activity, fitness, cardio autonomic functions, and functional network activity in PWE including consequences for further studies.

5.1 Challenges in Research and Benefits of Physical Activity in Epilepsy

The recommendation for PWE to not be physically active might be one influencing factor contributing to the limited number of human studies in this field. However, animal studies provide a basis for investigating the relationship between exercise and epilepsy in humans. Research paper 1, summarizing results from animal models, indicated, except for one outcome after one intervention, there is no negative influence of physical activity interventions (endurance, swimming, strength) on seizure-associated outcomes, such as seizure frequency and epileptiform activity in EEG. Although, the transferability to humans is limited since the etiology of epilepsy differs, due to convulsant agents inducing epilepsy in animal models. Although, some studies did investigate the influence of physical activity and exercise in humans. Those studies are summarized in the systematic review, research paper 2. It indicates that PWE participated less in physical activities and are often less fit compared to healthy controls. Although, some studies showed no difference in physical activity [124,125] and fitness levels , the majority of PWE seems to have a different activity behavior compared to the general healthy population.

The reasons for reduced exercise participation are various. They can be differentiated between epilepsy-specific reasons and general reasons. It was shown that PWE often fear injuries when participating in physical activities as well as exercise-induced seizures [126,127]. Seizure-related fears include previous seizures during exercise and knowing someone experiencing seizures during exercise [127]. These fears could be promoted by the behavior of physicians who often discourage PWE from participating in physical activities [128], which is also named as one barrier [127]. In addition to barriers related to seizures, patients also report a lack of social support from family and friends [126,127]. This emphasizes the importance of the social environment. In contrast to that, a proportion of patients do not disclose their social environment [129]. This can include employers but also family and friends. Such a behavior can exacerbate the problem of a lack of social support. The general reasons for non-participation in physical activities are similar to the general population [127]. Reasons are tiredness after those activities, lack of time, no one to exercise with, unsure how to begin and proceed, health problems resulting from exercising, afraid of looking stupid or unattractive, and skeletal or cardiovascular system problems [127]. There are different strategies to overcome these problems. One is to communicate with physicians and patients about the benefits and risks of exercising and to provide helpful strategies to find the right and safe type of physical activity for each patient (see chapter 2.1.3). Another one is to implement specific epilepsy sports groups, which could help to begin physical activities and proceed in a safe setting.

Furthermore, the systematic review indicates that, based on surveys, a higher physical activity level in general leads to reduced depression and anxiety and that physical activity interventions can reduce those comorbidities as well. These results support the assumption that PWE should engage more in physical activities. Especially, because it is known that depression and anxiety are prevalent in PWE [39,40] and that they often have a reduced quality of life [130]. Furthermore, as previously described, exercise does not appear to have a negative impact on seizure frequency in many cases. However, the results are heterogeneous, since also cases of exercise-induced seizures are reported [121]. The heterogeneity of results in studies regarding physical activity and epilepsy might be reasoned by different factors. One major challenge in epilepsy research is the

heterogeneity of the disease etiology and the different epilepsy syndromes [131]. Furthermore, patients have different types of seizures [36], different seizure frequencies, and are treated with different ASDs [132]. All these factors complicated the generalizability of the results for epilepsy patients. Furthermore, most study cohorts are recruited within one clinic. This increased the probability of recruiting a sufficient number of patients, that can be included in a study, suffering from the same epilepsy syndrome [133]. Investigating a cohort of only one epilepsy syndrome can serve as a starting point to reduce heterogeneity within a study cohort. The recruitment in one clinic does not mean that only patients suffering from the same syndrome are selected per se. Some studies included different syndromes, while in others, the syndromes that patients were suffering from were unknown due to insufficient reporting [134,135]. Nevertheless, recruitment within one clinic is an appropriate way to get enough patients for a study. Especially in the context of exercise, patients are not easily motivated to participate in research regarding physical activity since most of the patients are assumed to be less physically active [121]. If contacts to specialized epilepsy clinics are limited or these clinics are too far away from the place where the study is conducted (restricted mobility of PWE due to driving ban), accessibility of patients might be impeded. All these factors can lead to small sample sizes. Moreover, the generalizability of the results in the context of exercise is also complicated by restricted comparability of intervention programs due to different contents, training intensities, durations, and frequencies.

Study results in the field of physical activity and epilepsy are also limited by methodological aspects with a high risk of bias, as shown in research paper 2. The evidence levels of studies on physical activity participation in PWE and on personal experiences with seizures during exercise are at 2- and 3 and therefore, at a lower level (case reports, cohort studies with a high risk of confounding or bias). Studies conducting an intervention or an acute exercise test are of lower quality as well (evidence level 2-). Although five studies in that field can be assigned to evidence level 2+ and 1- (intervention, one-time exercise test, epidemiological study), all studies have the same methodological limitations: lack of information, randomization, control groups, blinding, consideration of influencing factors and restrictions in recruitment strategies. Due to the limitations of the studies, including heterogeneity within the cohorts and the interventions

and tests, no meta-analysis for none of the outcomes (seizure frequency, depression, anxiety, quality of life) could be performed.

Future studies should consider epilepsy-specific influencing factors, such as epilepsy syndrome, seizure type, seizure frequency, and medication. Of note, due to the high variety, these factors cannot be ruled out completely. However, as a first step, they can at least be documented and reported, which is not always done by previous studies. Additionally, standardized exercise programs for different cohorts, concerning the epilepsy-specific influencing factors, should be designed to investigate the influence of physical activity on seizure frequency, depression, and anxiety. Moreover, as a scientific basis, methodological standards in research must be considered.

5.2 Application of Acute Exercise to Patients with Epilepsy – a Cross-sectional Cohort Study

Research papers 1 and 2 showed the potential benefits of chronic exercise on seizure activity, however, the fear of exercise-induced seizures is still a present problem. Some studies have investigated the effect of acute exercise on seizures in PWE. These studies were also included in research paper 2. Two previous studies on adult epilepsy patients showed a reduction in epileptiform discharges after exercise compared to before exercise [117,118]. The seizure status of the examined patients differed between these two studies. For one study (n=12), eleven patients had controlled and one patient had weekly seizures [117]. For the other study, the included 19 epilepsy patients were heterogeneous regarding seizure frequency (monthly n=4, weekly n=2, daily n=1, bimonthly n=1, four-month period n=1, controlled n=10) [118]. In the cross-sectional cohort study, conducted for this dissertation, an acute exhaustive exercise test on a bicycle ergometer was performed with PWE to investigate the influence of acute exercise on seizure activity in EEG. In this study, seizure frequency was heterogeneous as well. However, 19 of 25 patients were seizure-free. In total, four patients showed interictal epileptiform discharges pre-exercise and six patients post-exercise, indicating a change in two patients. The seizure frequency of these two patients was one to two seizures in the last six months and one seizure per month. As the observation period of the clinical EEG differed between resting state measurements pre- and post-exercise (ten min vs. 32 min), results could be influenced.

Additionally, for one patient interictal epileptiform discharges appeared during sleep which was not recorded before exercise. Since no patient suffered from a seizure before, during, or after exercise, except the excluded patient described in chapter 4.1.1, a clinical significance of the interictal epileptiform discharges might not be assumed. Therefore, our study might indicate the safety and feasibility of exercise testing and acute exercise in an epilepsy cohort consisting of rather well-controlled epilepsy patients. However, the clinical value of the combination of EEG and a standardized exercise test as a potential seizure-inducing stimulus must be assessed by larger clinical trials.

Results of an acute exercise test, conducted by Fialho et al. (2017), revealed a chronotropic incompetence in people with temporal lobe epilepsy [48]. As cardiovascular alterations are known to be prevalent in epilepsy, it seems that these alterations can be made visible by acute exercise testing. In the cross-sectional cohort study, in the epilepsy group, a lower chronotropic response and a lower maximum heart rate were observed. Since Fialho et al. (2017) did not assess physical fitness levels, the influence on chronotropic incompetence remained questionable. In our study, PWE and the healthy matched control group were similar fit, based on VO_2peak, and similar active, based on IPAQ. However, the relationship between physical fitness and chronotropic incompetence remains unclear in epilepsy. In contrast, a meta-analysis investigated the effects of chronotropic incompetence in people with heart failure on exercise capacity. A reduced VO_2peak was linked to chronotropic incompetence per se [136]. However, the transferability to epilepsy might be impaired due to the unclear pathophysiological mechanisms of chronotropic incompetence.

It is assumed that this different chronotropic response in PWE might be driven by changes in the ANS. This is also supposed by Fialho et al. (2017) [48], however, no autonomic activity was measured in that study. In a comparison of people showing chronotropic incompetence and people who do not, it was assumed that sympathetic response to exercise (bicycle ergometer test) was not well translated into heart rate increase [137]. These results occurred despite both groups having no structural heart disease. The inadequate translation of sympathetic activity increase into a heart rate increase could also be one explanation for epilepsy. To assess autonomic activity before and after

exercise, RMSSD and meanEDA were analyzed in the cross-sectional cohort study. Results showed a normal parasympathetic and sympathetic response to exercise with an increased sympathetic and decreased parasympathetic activity post-exercise in both groups. No group differences in peripheral autonomic measures were observed, except for LF/HF ratio after exercise. The sample of PWE examined for this dissertation was mainly well-controlled regarding seizure frequency. However, most data on changes of autonomic activity in epilepsy derives from therapy refractory patients which can be one reason for the missing group differences. Nevertheless, Ansakorpi et al. (2000) [138] compared chronic refractory temporal lobe epilepsy patients, well-controlled temporal lobe epilepsy patients, and age- and sex-matched healthy controls regarding heart rate response during deep breathing, Vasalva maneuver, and tilting. Dysfunctions in cardiovascular autonomic regulation were more prevalent in therapy refractory patients compared to healthy controls. However, heart rate response was also significantly different between well-controlled patients and healthy controls but only during tilting. Ansakorpi et al (2000) [138] used different stimuli to provoke cardiovascular autonomic responses, and no exercise test was carried out. However, it might be suggested that even in well-controlled epilepsy patients, changes in autonomic activity could be observed. It might be supposed that seizure status could influence the extent of these changes, but data on well-controlled PWE are missing to support this hypothesis. Although there are hints of a change in autonomic activity in the investigated community-based cohort, due to the group differences in LF/HF ratio after exercise, this observation might be influenced by high standard deviations, differences in chronotropic index, and a lower maximum heart rate together with a similar fitness and activity level. Furthermore, since no sole sympathetic driven HRV marker exists [75], the LF/HF ratio is only an approximation to a vagal-sympathetic effect.

As it is known that the ANS is controlled by the CAN, it might be assumed that changes in autonomic activity in epilepsy could have its origin in the brain [13]. Although no group differences in peripheral autonomic activity and central autonomic activity were found, group differences in the interrelation of central and peripheral sympathetic activity could be observed. However, there is a lack of previous data supporting this observation and serving explanations. Of note, it is unclear whether the observed differences are

driven by epileptogenesis or by ASDs [58,139]. Nevertheless, as central and peripheral changes in autonomic activity are assumed in epilepsy [13], these results might contribute to its investigation.

At this time, there is not much literature on the pathophysiological changes in autonomic activity in epilepsy. As described in the chapter “current scientific literature”, structural and functional network changes in the brain might be a reason. Therefore, the mechanisms underlying central brain alterations are of interest. The role of epileptic seizures is still unclear. It is not known whether seizures might cause (interictal) network alterations or whether the alterations cause seizures [103]. In patients with intractable focal epilepsy, spatial widespread aberrant networks might be associated with an increased number of altered brain regions because the results were related to epilepsy duration and seizure severity [140]. This is also supported by epilepsy-specific modifiers for network alterations: disease duration, seizure frequency, and ASDs [106]. However, the underlying mechanisms of (interictal) network alterations in epilepsy are still unclear [141].

The ANS responds to exercise [114]. As shown in the cross-sectional study, this happens in the context of acute exercise. Additionally, the ANS has been shown to adapt to chronic exercise. Based on HRV analysis, it was shown that healthy master athletes show a different cardiac autonomic activity compared to a sedentary control group [142]. Moreover, adaptations of the ANS to chronic exercise were also investigated in the context of disease. In a review, the positive impact of exercise training on sympathovagal balance and markers of sympathetic flow were presented. This influence might affect the prognosis of cardiovascular disease positively [143]. Also in aging, ANS changes are prevalent. It is indicated that exercise might be used as a non-pharmacological treatment to impact age-related ANS changes. Therefore, the incidence of cardiovascular disease morbidity and mortality might be decreased [144]. Chronic exercise seems to impact ANS function and could serve as an option to influence autonomic changes in epilepsy as well. This is of special interest as autonomic dysfunction increases the risk for SUDEP. This dissertation provides important findings, with transfer to SUDEP research. Autonomic changes, which seem to play an important role in SUDEP, are often described for cohorts

with uncontrolled seizures. It was shown that those changes can also be observed to some extent in a cohort of mainly well-controlled PWE. To approach the SUDEP problem, risk factors have to be addressed. It was indicated that physical activity seems to have the potential to impact seizure frequency positively or, in a lot of cases, not negatively. As physical activity is known to increase physical health in general, it should be implemented in epilepsy treatment. Moreover, physical activity also influences autonomic functions. Exercise tests can be used to demarcate ANS alterations in PWE. Furthermore, they can be used to investigate how chronic exercise might influence autonomic activity. The results of this dissertation highlight the importance of investigating how chronic exercise may also affect the risk for SUDEP. This has the potential to inform future treatment strategies for all PWE, not only those with an obvious high risk for SUDEP.

The cross-sectional cohort study followed a multimodal approach by combining an exercise test, fitness measures, and measurements of peripheral and central autonomic activity before and after exercise. By this approach it was possible to relate the observations, however, no determination of causality could be made. Nevertheless, this approach is a strength of this study as well as the documentation of epilepsy and seizure characteristics. Unfortunately, the different characteristics cannot directly be considered in the analysis since subgroup sizes were too small, but they can be described and their influence on the results can be discussed. Furthermore, due to the lab setting, standardized measurement conditions (exercise and resting state) could be investigated and gold standard measurements could be included.

EDA, a measure of sympathetic activity, was recorded by the GSR Module (Brain Products GmbH). This module uses the exosomatic recording principle with direct current (constant voltage of 0.5V). This type of recording is a standard method of EDA recordings [77]. With a sampling rate of 1000 Hz and the analysis at 250 Hz, it was possible to collect accurate data sets [78]. In contrast to that module, EDA recording devices like the E4 Sensor (Empatica) can be used as well. The sampling frequency of this device of four Hz is much smaller compared to the GSR Module which leads to less information on the EDA signal. Devices have the advantage of an easy application, especially for in-field

research. However, since the cross-sectional cohort study was conducted in a lab setting, the use of the GSR Module with a higher sampling rate was favored.

Due to the lab setting, the ECG, as the gold standard to record data for HRV analysis, could be used [145]. In the analysis, it was mainly focused on the time-domain parameter RMSSD. The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology recommended a window length of five minutes for time-domain measure analysis [146]. For EDA recordings, no recommendation about the window length exists. Therefore, the same length as for HRV analysis was chosen since both branches of the ANS should be analyzed at the same time.

Functional connectivity is an indicator of the communication between brain areas. As described in the chapter "current state of research", there are different neuroimaging methods to measure functional connectivity, such as fMRI and EEG. In the study considered for this dissertation, 128-channel EEG recordings were combined with an MRI-template which was warped by the individual electrode positions of each subject. A head model was calculated on which connectivity analysis was conducted. By this approach, described in research paper 4, it was possible to approximate the source of the signal recorded by the 128-channel EEG. Rizkallah et al. (2020) [147] compared functional connectivity methods in resting state networks based on Magneto/electro-encephalography (M/EEG) source-space and fMRI based on correlation analysis. They used a 256-channel EEG with a sampling rate of 1000 Hz and a bandpass filter at 0.1-45 Hz. In contrast to that, we used a 128-channel EEG and a filter of 1-30 Hz. They used three non-overlapping 40-second segments whereas we used four 8.192-second segments. Rizkallah et al. (2020) did the connectivity analysis in Brainstorm with the Colin 27 MRI template that was co-registered with EEG channel locations as well. Furthermore, they focused on the 68 ROI of the Desikan-Killiany atlas and reconstructed the regional time series with the weighted Minimum Norm Estimate. Amongst others, the chosen connectivity measure was the PLV. Although they used slightly different analyzing steps, the same outcome parameter was used. They focused on delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-45 Hz) frequency bands. Data sets of 30 M/EEGs were compared to 487 fMRI data sets. In general, results revealed that

functional connectivity methods have still to be explored. However, a significant correlation between fMRI matrices and functional connectivity PLV matrices was found. However, results suggest that functional connectivity estimation methods, like our approach, are only an approximation and have to be interpreted with caution.

For connectivity analysis in EEG, different connectivity measures can be used. For a long time, linear correlations have been used for investigating brain connectivity, for example, correlation or coherence. However, those methods do not consider the intrinsic nonlinearity of neuronal activity [148]. Nonlinear connectivity measures have been developed that overcome this and can differentiate between direct and indirect relationships. A nonlinear measure is the PLV. Of note, this measure does not give insights into the directionality of interactions and does not differentiate between direct and indirect relationships. In general, the PLV focused on the size of phase differences, however, it is not clear whether the size of phase difference has a meaning for the coupling strength [148]. Nevertheless, the consideration of the nonlinearity is an advantage of this measure and important when focusing on the inverse problem resulting from mapping from signal into source space. The general problem of volume conduction, which is also of importance for PLV, is tried to overcome by analyzing data into source space as it was done for this dissertation. The PLV serves as a robust measure [148]. Nevertheless, source space connectivity analysis is only the first step in brain network analysis. It only provides information on the connection of pairs of brain regions. Brain network analysis like applying graph theory may provide more information since it characterizes the organization of networks [148].

5.3 Limitations of the Cross-sectional Cohort Study

Although the study has many strengths, due to its design considered factors that were missing in previous studies, some limitations should be mentioned. The number of participants was small. Although the study was conducted over three years, it was only possible to recruit 26 PWE. The accessibility of epilepsy patients was limited due to the restricted local recruitment possibilities and the COVID-19 pausing. Furthermore, some patients could not participate due to the exclusion criteria. Overall, the findings could be biased by the small sample size.

Since the recruitment was conducted in pharmacies, at physicians, local hospitals, and by direct communication, the included cohort was heterogeneous regarding seizure and epilepsy characteristics. They suffered from different epilepsy syndromes, etiologies, and seizure types. However, most of the patients were unaware of these characteristics. This could be explained by a limited knowledge of the disease and by the diagnosis. This heterogeneity, also regarding seizure frequency and ASD use, could influence the results. An impact on autonomic function and network alteration in epilepsy is assumed but still under discussion in the literature. Nevertheless, this heterogeneity reflects the epilepsy community in general, especially because most patients were seizure-free which applies to 70% of all epilepsy patients [41]. The documentation of the heterogeneous characteristics enables the consideration of their influence on the results. However, due to the small sample size, no subgroup analyses were possible (e.g., regarding seizure types or ASDs).

Additionally, physical activity levels were assessed by the IPAQ, which is based on a subjective self-assessment of physical activity in daily life. An objective tool like an activity tracker could reveal more insights into one's actual daily activity. Nevertheless, for assessing fitness level, spirometry is an objective measure. Since in this study all participants considered for the analysis reached physical exhaustion, retrospectively checked based on ventilatory, metabolic, cardiovascular, and performance criteria, the VO_2peak is considered a valid measurement for fitness level.

Of note, the associations between peripheral and central ANS activity were only based on correlations. This statistical dependency does not enable statements about causality. Nevertheless, the study design with an exercise stimulus was applicable to epilepsy patients and healthy controls, enabling between-group and within-group comparisons, of the peripheral and central autonomic activity.

6 Conclusion and Outlook

This dissertation contributes to an increased knowledge in the field of physical activity and epilepsy. It became clear that there is no basis for a general discouragement or even a ban on being physically active for PWE.

The narrative review of animal studies showed that there is mostly a positive impact or at least a non-negative effect of physical activity interventions on seizure-associated outcomes. Even the first studies investigating the influence of physical activity on seizure frequency in PWE showed that there is no negative effect for most patients when individual epilepsy and seizure characteristics are considered. However, cases of exercise-induced seizures are reported. This was shown by the systematic review. Furthermore, the literature overview indicated a positive effect of physical activity on comorbidities like depression and anxiety.

To target the fear of exercise-induced seizures, as one of the main reasons for the discouragement from exercising, in a cross-sectional design, the influence of an acute exhaustive exercise test on seizure activity in PWE was investigated. In the community-based cohort of mainly seizure-free patients, it was shown that exhaustive exercise tests are feasible for this patient group and do not trigger seizures.

In the cross-sectional cohort study, PWE were compared to a healthy matched control group to investigate autonomic control in the context of exercise. However, the groups were similarly fit, a lower maximum heart rate and chronotropic response was observed, indicating a higher risk for cardiac events. Cardiovascular alterations and also an increased risk for sudden death are known problems in epilepsy. The results of the cross-sectional cohort study indicated an impaired interaction of the ANS that may play a role in this context. Although, peripheral autonomic outcomes like RMSSD, reflecting parasympathetic activity, or meanEDA, indicating sympathetic activity, did not differ in the context of exercise between the two groups, a different relationship, indicated by the correlation coefficient difference, between meanEDA and functional connectivity within the CAN after exercise between the groups was observed. This result is of importance since the CAN is discussed to be the origin of autonomic activity changes in PWE. Of

note, this cross-sectional cohort study was conducted on mainly seizure-free PWE who are the majority in the general epilepsy cohort. Nevertheless, in this group, epilepsy-specific factors like seizure frequency, seizure type, epilepsy syndrome, and ASDs were heterogeneous and therefore, might impact the results.

As it was shown that physical activity does not pose a risk for PWE in general, the potential positive impact physical activity may have on seizures and comorbidities should be used for increasing the quality of life in PWE. The next step for research, following this dissertation, should be an intervention study investigating the effect of physical activity on seizure frequency in a controlled design. Furthermore, to focus on the risk for SUDEP in this patient group, the intervention should target cardio autonomic functions to reduce the risk and to impact the central and peripheral interaction within the ANS. This may be tested by having an acute exhaustive exercise test before and after an intervention. For comparison purposes, the study should consider using the same, or at least a similar exercise test as the one conducted for this dissertation. To ensure a safe environment, individual epilepsy and seizure characteristics have to be considered.

7 References

[1] Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, Pringsheim T, Lorenzetti DL, Jetté N. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology 2017;88(3):296–303. https://doi.org/10.1212/WNL.0000000000003509.

[2] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J. Epilepstic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(4):470–2. https://doi.org/10.1111/j.0013-9580.2005.66104.x.

[3] Jacoby A. Stigma, epilepsy, and quality of life. Epilepsy Behav 2002;3(6):10–20. https://doi.org/10.1016/S1525-5050(02)00545-0.

[4] Johnson EK, Jones JE, Seidenberg M, Hermann BP. The relative impact of anxiety, depression, and clinical seizure features on health-related quality of life in epilepsy. Epilepsia 2004;45(5):544–50. https://doi.org/10.1111/j.0013-9580.2004.47003.x.

[5] Halford JJ, Edwards JC. Seizure freedom as an outcome in epilepsy treatment clinical trials. Acta Neurol Scand 2020;142(2):91–107. https://doi.org/10.1111/ane.13257.

[6] Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004;5 Suppl 1:S60-5. https://doi.org/10.1016/j.yebeh.2003.11.008.

[7] Mutanana N, Tsvere M, Chiweshe MK. General side effects and challenges associated with anti-epilepsy medication: A review of related literature. Afr J Prim Health Care Fam Med 2020;12(1):2162. https://doi.org/10.4102/phcfm.v12i1.2162.

[8] Barthel T, van den Bongard F, Ströhlein JK, Reinsberger C. Bewegung und neurologische Erkrankungen. In: Banzer W, editor. Körperliche Aktivität und Gesundheit. Berlin, Heidelberg: Springer Berlin Heidelberg; 2017, p. 341–355.

[9] Dubow JS, Kelly JP. Epilepsy in sports and recreation. Sports Med 2003;33(7):499–516. https://doi.org/10.2165/00007256-200333070-00003.

[10] Pimentel J, Tojal R, Morgado J. Epilepsy and physical exercise. Seizure 2015;25:87–94. https://doi.org/10.1016/j.seizure.2014.09.015.

[11] Verrier RL, Pang TD, Nearing BD, Schachter SC. The Epileptic Heart: Concept and clinical evidence. Epilepsy Behav 2020;105:106946. https://doi.org/10.1016/j.yebeh.2020.106946.

[12] Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation 2011;123(9):1010–20. https://doi.org/10.1161/CIRCULATIONAHA.110.940577.

[13] Devinsky O. Effects of Seizures in Autonomic and Cardiovascular Function. Epilepsy Currents 2004;4(2):43–6. https://doi.org/10.1111/j.1535-7597.2004.42001.x.

[14] Davis KA, Jirsa VK, Schevon CA. Wheels Within Wheels: Theory and Practice of Epileptic Networks. Epilepsy Currents 2021:15357597211015663. https://doi.org/10.1177/15357597211015663.

[15] Silvani A, Calandra-Buonaura G, Dampney RAL, Cortelli P. Brain-heart interactions: physiology and clinical implications. Philos Trans A Math Phys Eng Sci 2016;374(2067). https://doi.org/10.1098/rsta.2015.0181.

[16] Caspersen CJ, Powell KE, Christenson GM. Physical Activity, Exercsie, and Physical Fitness: Definitions and Distinctions for Health-Related Research. Public Health Reports 1985;100(2):126–31.

[17] Bentley AJ, Newell J, Bishop D. Incremental Exercise Test Design and Analysis. Sports Med 2007;37(7):575–86. https://doi.org/10.2165/00007256-200737070-00002.

[18] Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. The Lancet 2000;356(9241):1592–7. https://doi.org/10.1016/S0140-6736(00)03138-X.

[19] Marcadet D-M, Pavy B, Bosser G, Claudot F, Corone S, Douard H et al. French Society of Cardiology guidelines on exercise tests (part 1): Methods and interpretation. Arch Cardiovasc Dis 2018;111(12):782–90. https://doi.org/10.1016/j.acvd.2018.05.005.

[20] Sallis RE. Exercise is medicine and physicians need to prescribe it! Br J Sports Med 2009;43(1):3–4. https://doi.org/10.1136/bjsm.2008.054825.

[21] Berryman JW. Exercise is Medicine A Historical Perspective. Curr Sports Med Rep 2010;9(4):195–201. https://doi.org/10.1249/JSR.0b013e3181e7d86d.

[22] Swisher AK. Yes, "Exercise is Medicine"…but It Is So Much More! Cardiopulmonary Physical Therapy Journal 2010;21(4):4.

[23] Tipton CM. The history of "Exercise Is Medicine" in ancient civilizations. Adv Physiol Educ 2014;38(2):109–17. https://doi.org/10.1152/advan.00136.2013.

[24] Rippe JM, Hess S. The role of physical activity in the prevention and management of obesity. J Am Diet Assoc 1998;98(Suppl 2):S31-S38. https://doi.org/10.1016/S0002-8223(98)00708-1.

[25] Gill JMR, Cooper AR. Physical Activity and Prevention of Type 2 Diabetes Mellitus. Sports Med 2008;38(10):807–24. https://doi.org/10.2165/00007256-200838100-00002.

[26] McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc 2019;51(6):1252–61. https://doi.org/10.1249/MSS.0000000000001937.

[27] Saunders DH, Sanderson M, Hayes S, Kilrane M, Greig CA, Brazzelli M et al. Physical fitness training for stroke patients. Cochrane Database Syst Rev 2016;3:CD003316. https://doi.org/10.1002/14651858.CD003316.pub6.

[28] Naci H, Ioannidis JPA. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. Br J Sports Med 2015;49(21):1414–22. https://doi.org/10.1136/bjsports-2015-f5577rep.

[29] Zimmer P, Bloch W, Schenk A, Oberste M, Riedel S, Kool J et al. High-intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: A randomized controlled trial. Mult Scler 2018;24(12):1635–44. https://doi.org/10.1177/1352458517728342.

[30] Heine M, van de Port I, Rietberg MB, van Wegen EEH, Kwakkel G. Exercise therapy for fatigue in multiple sclerosis. Cochrane Database Syst Rev 2015(9):CD009956. https://doi.org/10.1002/14651858.CD009956.pub2.

[31] Tan ZS, Spartano NL, Beiser AS, DeCarli C, Auerbach SH, Vasan RS et al. Physical Activity, Brain Volume, and Dementia Risk: The Framingham Study. J Gerontol A Biol Sci Med Sci 2017;72(6):789–95. https://doi.org/10.1093/gerona/glw130.

[32] Xu W, Wang HF, Wan Y, Tan C-C, Yu J-T, Tan L. Leisure time physical activity and dementia risk: a dose-response meta-analysis of prospective studies. BMJ Open 2017;7(10):e014706. https://doi.org/10.1136/bmjopen-2016-014706.

[33] Lam FM, Huang M-Z, Liao L-R, Chung RC, Kwok TC, Pang MY. Physical exercise improves strength, balance, mobility, and endurance in people with cognitive

impairment and dementia: a systematic review. J Physiother 2018;64(1):4–15. https://doi.org/10.1016/j.jphys.2017.12.001.

[34] Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database Syst Rev 2015(4):CD006489. https://doi.org/10.1002/14651858.CD006489.pub4.

[35] Beghi E. The Epidemiology of Epilepsy. Neuroepidemiology 2020;54(2):185–91. https://doi.org/10.1159/000503831.

[36] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):522–30. https://doi.org/10.1111/epi.13670.

[37] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512–21. https://doi.org/10.1111/epi.13709.

[38] Engel J. ILAE classification of epilepsy syndromes. Epilepsy Research 2006;70 Suppl 1:S5-10. https://doi.org/10.1016/j.eplepsyres.2005.11.014.

[39] Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan G, Maxwell CJ, Bulloch AG, Jette N. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80(6):590–9. https://doi.org/10.1212/WNL.0b013e31827b1ae0.

[40] Beyenburg S, Mitchell AJ, Schmidt D, Elger CE, Reuber M. Anxiety in patients with epilepsy: systematic review and suggestions for clinical management. Epilepsy Behav 2005;7(2):161–71. https://doi.org/10.1016/j.yebeh.2005.05.014.

[41] Xia L, Ou S, Pan S. Initial Response to Antiepileptic Drugs in Patients with Newly Diagnosed Epilepsy As a Predictor of Long-term Outcome. Front Neurol 2017;8:658. https://doi.org/10.3389/fneur.2017.00658.

[42] Kwan P, Brodie MJ. Early Identification of Refractory Epilepsy. N Engl J Med 2000;342(5):314–9. https://doi.org/10.1056/NEJM200002033420503.

[43] Dubow JS, Kelly JP. Epilepsy in sports and recreation. Sports Med 2003;33(7):499–516. https://doi.org/10.2165/00007256-200333070-00003.

[44] Ryan CA, Dowling G. Drowning deaths in people with epilepsy. CMAJ 148;1993:781–4.

[45] Téllez-Zenteno JF, Hunter G, Wiebe S. Injuries in people with self-reported epilepsy: a population-based study. Epilepsia 2008;49(6):954–61. https://doi.org/10.1111/j.1528-1167.2007.01499.x.

[46] Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM. Epilepsy, seizures, physical exercise, and sports: A report from the ILAE Task Force on Sports and Epilepsy. Epilepsia 2016;57(1):6–12. https://doi.org/10.1111/epi.13261.

[47] Howard GM, Radloff M, Siever TL. Epilepsy and sports participation. Curr Sports Med Rep 2004;3:15–9. https://doi.org/10.1249/00149619-200402000-00004.

[48] Fialho GL, Pagani AG, Walz R, Wolf P, Lin K. Maximal/exhaustive treadmill test features in patients with temporal lobe epilepsy: Search for sudden unexpected death biomarkers. Epilepsy Research 2017;133:83–8. https://doi.org/10.1016/j.eplepsyres.2017.04.014.

[49] Karvonen, MJ, Kentala, E, Mustala, O. The effects of training on heart rate: a longitudinal study. Ann. Med. Exp. Biol. Fenn 1957;35(3):307–15.

[50] Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. Journal of the American College of Cardiology 2001;37(1):153–6. https://doi.org/10.1016/S0735-1097(00)01054-8.

[51] Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired Chronotropic Response to Exercise Stress Testing as a Predictor of Mortality. JAMA 1999;281(6):524–9. https://doi.org/10.1001/jama.281.6.524.

[52] Zack M, Luncheon C. Adults with an epilepsy history, notably those 45-64 years old or at the lowest income levels, more often report heart disease than adults without an epilepsy history. Epilepsy Behav 2018;86:208–10. https://doi.org/10.1016/j.yebeh.2018.05.021.

[53] Stecker EC, Reinier K, Uy-Evanado A, Teodorescu C, Chugh H, Gunson K et al. Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. Circ Arrhythm Electrophysiol 2013;6(5):912–6. https://doi.org/10.1161/CIRCEP.113.000544.

[54] Zipes DP, Wellens HJJ. Sudden Cardiac Death. Circulation 1998;98(21):2334–51. https://doi.org/10.1161/01.CIR.98.21.2334.

[55] Holst AG, Winkel BG, Risgaard B, Nielsen JB, Rasmussen PV, Haunsø S et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia 2013;54(9):1613–20. https://doi.org/10.1111/epi.12328.

[56] Nashef L. Sudden Unexpected Death in Epilepsy: Terminology and Definitions. Epilepsia 1997;38(Suppl 11):S6-S8. https://doi.org/10.1111/j.1528-1157.1997.tb06130.x.

[57] Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, French JA, Gil-Nagel A, Hesdorffer DC, Smithson WH, Spitz MC, Walczak TS, Sander JW, Ryvlin P. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88(17):1674–80. https://doi.org/10.1212/WNL.0000000000003685.

[58] Thijs RD, Ryvlin P, Surges R. Autonomic manifestations of epilepsy: emerging pathways to sudden death? Nat Rev Neurol 2021;17(12):774–88. https://doi.org/10.1038/s41582-021-00574-w.

[59] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. Neurology 2020;94(4):e419-e429. https://doi.org/10.1212/WNL.0000000000008741.

[60] Massey CA, Sowers LP, Dlouhy BJ, Richerson GB. Mechanisms of sudden unexpected death in epilepsy: the pathway to prevention. Nat Rev Neurol 2014;10(5):271–82. https://doi.org/10.1038/nrneurol.2014.64.

[61] Manolis TA, Manolis AA, Melita H, Manolis AS. Sudden unexpected death in epilepsy: The neuro-cardio-respiratory connection. Seizure 2019;64:65–73. https://doi.org/10.1016/j.seizure.2018.12.007.

[62] Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. The Lancet Neurology 2013;12(10):966–77. https://doi.org/10.1016/S1474-4422(13)70214-X.

[63] Marchal R, Rheims S. Assessing epilepsy-related autonomic manifestations: Beyond cardiac and respiratory investigations. Neurophysiol Clin 2023;53(2):102850. https://doi.org/10.1016/j.neucli.2023.102850.

[64] Shaker KK, Al Mahdawi AM, Hamdan FB. Interictal autonomic dysfunction in patients with epilepsy. Egypt J Neurol Psychiatry Neurosurg 2021;57(1). https://doi.org/10.1186/s41983-021-00422-0.

[65] Beissner F, Meissner K, Bär K-J, Napadow V. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J Neurosci 2013;33(25):10503–11. https://doi.org/10.1523/JNEUROSCI.1103-13.2013.

[66] Sklerov M, Dayan E, Browner N. Functional neuroimaging of the central autonomic network: recent developments and clinical implications. Clin Auton Res 2019;29(6):555–66. https://doi.org/10.1007/s10286-018-0577-0.

[67] Freeman JV, Dewey FE, Hadley DM, Myers J, Froelicher VF. Autonomic nervous system interaction with the cardiovascular system during exercise. Prog Cardiovasc Dis 2006;48(5):342–62. https://doi.org/10.1016/j.pcad.2005.11.003.

[68] Aggarwal M, Aggarwal B, Rao J. Integrative Medicine for Cardiovascular Disease and Prevention. Med Clin North Am 2017;101(5):895–923. https://doi.org/10.1016/j.mcna.2017.04.007.

[69] Orimo S, Ghebremedhin E, Gelpi E. Peripheral and central autonomic nervous system: does the sympathetic or parasympathetic nervous system bear the brunt of the pathology during the course of sporadic PD? Cell Tissue Res 2018;373(1):267–86. https://doi.org/10.1007/s00441-018-2851-9.

[70] Jänig W, Häbler H-J. Specificity in the organization of the autonomic nervous system: a basis for precise neural regulation of homeostatic and protective body functions. In: The Biological Basis for Mind Body Interactions. Elsevier; 2000, p. 351–367.

[71] Groscurth P. Anatomy of Sweat Glands. In: Kreyden OP, Böni R, Burg G, editor. Hyperhidrosis and Botulinum Toxin in Dermatology. Basel: Karger; 2002, p. 1–9.

[72] McCraty R, Shaffer F. Heart Rate Variability: New Perspectives on Physiological Mechanisms, Assessment of Self-regulatory Capacity, and Health risk. Glob Adv Health Med 2015;4(1):46–61. https://doi.org/10.7453/gahmj.2014.073.

[73] Gordan R, Gwathmey JK, Xie L-H. Autonomic and endocrine control of cardiovascular function. WJC 2015;7(4):204. https://doi.org/10.4330/wjc.v7.i4.204.

[74] Schäfer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability? A review on studies comparing photoplethysmographic technology with an electrocardiogram. Int J Cardiol 2013;166(1):15–29. https://doi.org/10.1016/j.ijcard.2012.03.119.

[75] Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258. https://doi.org/10.3389/fpubh.2017.00258.

[76] Medeiros AR, Michael S, Boullosa DA. Make it easier! Evaluation of the 'vagal-sympathetic effect' in different conditions with R-R intervals monitoring. Eur J Appl Physiol 2018;118(6):1287–8. https://doi.org/10.1007/s00421-018-3855-6.

[77] Posada-Quintero HF, Chon KH. Innovations in Electrodermal Activity Data Collection and Signal Processing: A Systematic Review. Sensors (Basel) 2020;20(2). https://doi.org/10.3390/s20020479.

[78] Braithwaite JJ, Watson DG, Jones R, Rowe M. A guide for analysing electrodermal activity (EDA) & skin conductance responses (SCRs) for psychological experiments. Psychophysiology 2015;49(1):1017–34.

[79] Boucsein W. Electrodermal Activity. Boston, MA: Springer US; 2012.

[80] Ferreira AF, Da Silva HP, Alves H, Marques N, Fred A. Feasibility of Electrodermal Activity and Photoplethysmography Data Acquisition at the Foot Using a Sock Form Factor. Sensors (Basel) 2023;23(2). https://doi.org/10.3390/s23020620.

[81] Sarkis RA, Thome-Souza S, Poh M-Z, Llewellyn N, Klehm J, Madsen JR et al. Autonomic changes following generalized tonic clonic seizures: An analysis of adult and pediatric patients with epilepsy. Epilepsy Research 2015;115:113–8. https://doi.org/10.1016/j.eplepsyres.2015.06.005.

[82] Poh M-Z, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Madsen JR, Picard RW. Automomic Changes with seizure correlate with postictal EEG suppression. Neurology 2012;78(23):1868–76. https://doi.org/10.1212/WNL.0b013e318258f7f1.

[83] Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012;53(2):272–82. https://doi.org/10.1111/j.1528-1167.2011.03361.x.

[84] Lamberts RJ, Laranjo S, Kalitzin SN, Velis DN, Rocha I, Sander JW et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic

instability in people with convulsive seizures. Epilepsia 2013;54(3):523–9. https://doi.org/10.1111/epi.12021.

[85] Romigi A, Albanese M, Placidi F, Izzi F, Mercuri NB, Marchi A et al. Heart rate variability in untreated newly diagnosed temporal lobe epilepsy: Evidence for ictal sympathetic dysregulation. Epilepsia 2016;57(3):418–26. https://doi.org/10.1111/epi.13309.

[86] Casanovas Ortega M, Bruno E, Richardson MP. Electrodermal activity response during seizures: A systematic review and meta-analysis. Epilepsy Behav 2022;134:108864. https://doi.org/10.1016/j.yebeh.2022.108864.

[87] Horinouchi T, Sakurai K, Munekata N, Kurita T, Takeda Y, Kusumi I. Decreased electrodermal activity in patients with epilepsy. Epilepsy Behav 2019;100(Pt A):106517. https://doi.org/10.1016/j.yebeh.2019.106517.

[88] Goit RK, Jha SK, Pant BN. Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. Physiol Rep 2016;4(11). https://doi.org/10.14814/phy2.12826.

[89] Telesford QK, Simpson SL, Burdette JH, Hayasaka S, Laurienti PJ. The brain as a complex system: using network science as a tool for understanding the brain. Brain Connect 2011;1(4):295–308. https://doi.org/10.1089/brain.2011.0055.

[90] Kabbara A, El Falou W, Khalil M, Wendling F, Hassan M. The dynamic functional core network of the human brain at rest. Sci Rep 2017;7(1):2936. https://doi.org/10.1038/s41598-017-03420-6.

[91] Babaeeghazvini P, Rueda-Delgado LM, Gooijers J, Swinnen SP, Daffertshofer A. Brain Structural and Functional Connectivity: A Review of Combined Works of Diffusion Magnetic Resonance Imaging and Electro-Encephalography. Front Hum Neurosci 2021;15:721206. https://doi.org/10.3389/fnhum.2021.721206.

[92] Proudfoot M, Woolrich MW, Nobre AC, Turner MR. Magnetoencephalography. Pract Neurol 2014;14(5):336–43. https://doi.org/10.1136/practneurol-2013-000768.

[93] Kirschstein T, Köhling R. What is the source of the EEG? Clin EEG Neurosci 2009;40(3):146–9. https://doi.org/10.1177/155005940904000305.

[94] Michel CM, Brunet D. EEG Source Imaging: A Practical Review of the Analysis Steps. Front Neurol 2019;10:325. https://doi.org/10.3389/fneur.2019.00325.

[95] Friston KJ. Functional and effective connectivity: a review. Brain Connect 2011;1(1):13–36. https://doi.org/10.1089/brain.2011.0008.

[96] Barot N, Nei M. Autonomic aspects of sudden unexpected death in epilepsy (SUDEP). Clin Auton Res 2019;29(2):151–60. https://doi.org/10.1007/s10286-018-0576-1.

[97] Allen LA, Harper RM, Kumar R, Guye M, Ogren JA, Lhatoo SD et al. Dysfunctional Brain Networking among Autonomic Regulatory Structures in Temporal Lobe Epilepsy Patients at High Risk of Sudden Unexpected Death in Epilepsy. Front Neurol 2017;8:544. https://doi.org/10.3389/fneur.2017.00544.

[98] Tang Y, Chen Q, Yu X, Xia W, Luo C, Huang X et al. A resting-state functional connectivity study in patients at high risk for sudden unexpected death in epilepsy. Epilepsy Behav 2014;41:33–8. https://doi.org/10.1016/j.yebeh.2014.08.140.

[99] Allen LA, Harper RM, Guye M, Kumar R, Ogren J, Vos SB et al. Altered brain connectivity in sudden unexpected death in epilepsy (SUDEP) revealed using resting-state fMRI. Neuroimage Clin 2019;24:102060. https://doi.org/10.1016/j.nicl.2019.102060.

[100] Allen LA, Harper RM, Lhatoo S, Lemieux L, Diehl B. Neuroimaging of Sudden Unexpected Death in Epilepsy (SUDEP): Insights From Structural and Resting-State Functional MRI Studies. Front Neurol 2019;10:185. https://doi.org/10.3389/fneur.2019.00185.

[101] Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. PLoS One 2010;5(1):e8525. https://doi.org/10.1371/journal.pone.0008525.

[102] de Campos BM, Coan AC, Lin Yasuda C, Casseb RF, Cendes F. Large-scale brain networks are distinctly affected in right and left mesial temporal lobe epilepsy. Hum Brain Mapp 2016;37(9):3137–52. https://doi.org/10.1002/hbm.23231.

[103] van Diessen E, Zweiphenning WJEM, Jansen FE, Stam CJ, Braun KPJ, Otte WM. Brain Network Organization in Focal Epilepsy: A Systematic Review and Meta-Analysis. PLoS One 2014;9(12):e114606. https://doi.org/10.1371/journal.pone.0114606.

[104] Jiang S, Li H, Liu L, Yao D, Luo C. Voxel-wise Functional Connectivity of the Default Mode Network in Epilepsies: A Systematic Review and Meta-Analysis. Curr

Neuropharmacol 2022;20(1):254–66. https://doi.org/10.2174/1570159X19666210325130624.

[105] Pegg EJ, McKavanagh A, Bracewell RM, Chen Y, Das K, Denby C et al. Functional network topology in drug resistant and well-controlled idiopathic generalized epilepsy: a resting state functional MRI study. Brain Commun 2021;3(3):fcab196. https://doi.org/10.1093/braincomms/fcab196.

[106] van Diessen E, Diederen SJH, Braun KPJ, Jansen FE, Stam CJ. Functional and structural brain networks in epilepsy: what have we learned? Epilepsia 2013;54(11):1855–65. https://doi.org/10.1111/epi.12350.

[107] Boettger S, Puta C, Yeragani VK, Donath L, Müller H-J, Gabriel HHW et al. Heart rate variability, QT variability, and electrodermal activity during exercise. Med Sci Sports Exerc 2010;42(3):443–8. https://doi.org/10.1249/MSS.0b013e3181b64db1.

[108] Posada-Quintero HF, Reljin N, Mills C, Mills I, Florian JP, VanHeest JL et al. Time-varying analysis of electrodermal activity during exercise. PLoS One 2018;13(6):e0198328. https://doi.org/10.1371/journal.pone.0198328.

[109] Schmitt A, Upadhyay N, Martin JA, Rojas S, Strüder HK, Boecker H. Modulation of Distinct Intrinsic Resting State Brain Networks by Acute Exercise Bouts of Differing Intensity. Brain Plast 2019;5(1):39–55. https://doi.org/10.3233/BPL-190081.

[110] Weng TB, Pierce GL, Darling WG, Falk D, Magnotta VA, Voss MW. The Acute Effects of Aerobic Exercise on the Functional Connectivity of Human Brain Networks. Brain Plast 2017;2(2):171–90. https://doi.org/10.3233/BPL-160039.

[111] Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. The Lancet 2000;356(9241):1592–7. https://doi.org/10.1016/S0140-6736(00)03138-X.

[112] Marcadet D-M, Pavy B, Bosser G, Claudot F, Corone S, Douard H et al. French Society of Cardiology guidelines on exercise tests (part 1): Methods and interpretation. Arch Cardiovasc Dis 2018;111(12):782–90. https://doi.org/10.1016/j.acvd.2018.05.005.

[113] Fu Q, Levine BD. Exercise and the autonomic nervous system. Handb Clin Neurol 2013;117:147–60. https://doi.org/10.1016/B978-0-444-53491-0.00013-4.

[114] Bishop VS. 47 - Exercise and the Autonomic Nervous System. In: Robertson D, Biaggioni I, Burnstock G, Low PA, editor. Primer on the Autonomic Nervous System (Second Edition). Elsevier; 2004, p. 183–184.

[115] Pichon AP, Bisschop C de, Roulaud M, Denjean A, Papelier Y. Spectral analysis of heart rate variability during exercise in trained subjects. Med Sci Sports Exerc 2004;36(10):1702–8. https://doi.org/10.1249/01.mss.0000142403.93205.35.

[116] Chiarion G, Sparacino L, Antonacci Y, Faes L, Mesin L. Connectivity Analysis in EEG Data: A Tutorial Review of the State of the Art and Emerging Trends. Bioengineering (Basel) 2023;10(3). https://doi.org/10.3390/bioengineering10030372.

[117] de Lima C, Vancini RL, Arida RM, Guilhoto LMFF, de Mello MT, Barreto AT et al. Physiological and electroencephalographic responses to acute exhaustive physical exercise in people with juvenile myoclonic epilepsy. Epilepsy Behav 2011;22(4):718–22. https://doi.org/10.1016/j.yebeh.2011.08.033.

[118] Vancini RL, Lira CAB de, Scorza FA, de Albuquerque M, Sousa BS, de Lima C et al. Cardiorespiratory and electroencephalographic responses to exhaustive acute physical exercise in people with temporal lobe epilepsy. Epilepsy Behav 2010;19(3):504–8. https://doi.org/10.1016/j.yebeh.2010.09.007.

[119] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23. https://doi.org/10.1111/epi.13121.

[120] Hammer GP, Du Prel J-B, Blettner M. Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. Dtsch Arztebl Int 2009;106(41):664–8. https://doi.org/10.3238/arztebl.2009.0664.

[121] van den Bongard F, Hamer HM, Sassen R, Reinsberger C. Sport and Physical Activity in Epilepsy. Dtsch Arztebl Int 2020;117(1-2):1–6. https://doi.org/10.3238/arztebl.2020.0001.

[122] Chroni E, Sirrou V, Trachani E, Sakellaropoulos GC, Polychronopoulos P. Interictal alterations of cardiovagal function in chronic epilepsy. Epilepsy Research 2009;83(2-3):117–23. https://doi.org/10.1016/j.eplepsyres.2008.10.006.

[123] Mativo P, Anjum J, Pradhan C, Sathyaprabha TN, Raju TR, Satishchandra P. Study of cardiac autonomic function in drug-naïve, newly diagnosed epilepsy patients. Epileptic Disord 2010;12(3):212–6. https://doi.org/10.1684/epd.2010.0325.

[124] de Lima C, de Lira CAB, Arida RM, Andersen ML, Matos G, de Figueiredo Ferreira Guilhoto LM et al. Association between leisure time, physical activity, and mood disorder levels in individuals with epilepsy. Epilepsy Behav 2013;28(1):47–51. https://doi.org/10.1016/j.yebeh.2013.03.016.

[125] Gordon KE, Dooley JM, Brna PM. Epilepsy and activity--a population-based study. Epilepsia 2010;51(11):2254–9. https://doi.org/10.1111/j.1528-1167.2010.02709.x.

[126] Collard SS, Ellis-Hill C. How do you exercise with epilepsy? Insights into the barriers and adaptations to successfully exercise with epilepsy. Epilepsy Behav 2017;70:66–71. https://doi.org/10.1016/j.yebeh.2017.03.004.

[127] Han K, Choi-Kwon S, Lee S-K. Leisure time physical activity in patients with epilepsy in Seoul, South Korea. Epilepsy Behav 2011;20(2):321–5. https://doi.org/10.1016/j.yebeh.2010.11.018.

[128] Dubow JS, Kelly JP. Epilepsy in sports and recreation. Sports Med 2003;33(7):499–516. https://doi.org/10.2165/00007256-200333070-00003.

[129] Elliott N, Pembroke S, Quirke M, Pender N, Higgins A. Disclosure strategies in adults with epilepsy when telling, "I have epilepsy": The How2tell study. Epilepsia 2019;60(10):2048–59. https://doi.org/10.1111/epi.16338.

[130] Bishop M, Allen CA. The impact of epilepsy on quality of life: a qualitative analysis. Epilepsy & Behavior 2003;4(3):226–33. https://doi.org/10.1016/S1525-5050(03)00111-2.

[131] Shorvon SD. The etiologic classification of epilepsy. Epilepsia 2011;52(6):1052–7. https://doi.org/10.1111/j.1528-1167.2011.03041.x.

[132] Perucca E. The pharmacological treatment of epilepsy: recent advances and future perspectives. Acta Epileptologica 2021;3(1). https://doi.org/10.1186/s42494-021-00055-z.

[133] Camilo F, Scorza FA, de Albuquerque M, Vancini RL, Cavalheiro EA, Arida RM. Evaluation of intense physical effort in subjects with temporal lobe epilepsy. Arq

Neuropsiquiatr 2009;67(4):1007–12. https://doi.org/10.1590/s0004-282x2009000600009.

[134] Lundgren T, Dahl J, Yardi N, Melin L. Acceptance and Commitment Therapy and yoga for drug-refractory epilepsy: a randomized controlled trial. Epilepsy Behav 2008;13(1):102–8. https://doi.org/10.1016/j.yebeh.2008.02.009.

[135] McAuley JW, Long L, Heise J, Kirby T, Buckworth J, Pitt C et al. A Prospective Evaluation of the Effects of a 12-Week Outpatient Exercise Program on Clinical and Behavioral Outcomes in Patients with Epilepsy. Epilepsy Behav 2001;2(6):592–600. https://doi.org/10.1006/ebeh.2001.0271.

[136] Smart NA, Clark H, Brubaker P, Witte KK, Jamil H, Gierula J, Patel HC, Pearson MJ. Effects of chronotropic incompetence on exercise capacity in people with heart failure versus age-matched controls. Heart Fail Rev 2021. https://doi.org/10.1007/s10741-021-10081-1.

[137] Kawasaki T, Kaimoto S, Sakatani T, Miki S, Kamitani T, Kuribayashi T et al. Chronotropic incompetence and autonomic dysfunction in patients without structural heart disease. Europace 2010;12(4):561–6. https://doi.org/10.1093/europace/eup433.

[138] Ansakorpi H, Korpelainen JT, Huikuri HV, Tolonen U, Myllylä VV, Isojärvi JIT. Heart rate dynamics in refractory and well controlled temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 2002;72(1):26–30. https://doi.org/10.1136/jnnp.72.1.26.

[139] Haneef Z, Levin HS, Chiang S. Brain Graph Topology Changes Associated with Anti-Epileptic Drug Use. Brain Connect 2015;5(5):284–91. https://doi.org/10.1089/brain.2014.0304.

[140] Nakai Y, Nishibayashi H, Donishi T, Terada M, Nakao N, Kaneoke Y. Regional abnormality of functional connectivity is associated with clinical manifestations in individuals with intractable focal epilepsy. Sci Rep 2021;11(1):1545. https://doi.org/10.1038/s41598-021-81207-6.

[141] Courtiol J, Guye M, Bartolomei F, Petkoski S, Jirsa VK. Dynamical Mechanisms of Interictal Resting-State Functional Connectivity in Epilepsy. J Neurosci 2020;40(29):5572–88. https://doi.org/10.1523/JNEUROSCI.0905-19.2020.

[142] Sotiriou P, Kouidi E, Samaras T, Deligiannis A. Linear and non-linear analysis of heart rate variability in master athletes and healthy middle-aged non-athletes. Med Eng Phys 2013;35(11):1676–81. https://doi.org/10.1016/j.medengphy.2013.06.003.

[143] Besnier F, Labrunée M, Pathak A, Pavy-Le Traon A, Galès C, Sénard J-M et al. Exercise training-induced modification in autonomic nervous system: An update for cardiac patients. Ann Phys Rehabil Med 2017;60(1):27–35. https://doi.org/10.1016/j.rehab.2016.07.002.

[144] Wichi RB, de Angelis K, Jones L, Irigoyen MC. A brief review of chronic exercise intervention to prevent autonomic nervous system changes during the aging process. Clinics (Sao Paulo) 2009;64(3):253–8. https://doi.org/10.1590/s1807-59322009000300017.

[145] Oliveira Júnior FA de, Pereira RA, Silva AS, Brito Alves JL de, Costa-Silva JH, Braga VA et al. Different acquisition systems for heart rate variability analysis may lead to diverse outcomes. Braz J Med Biol Res 2022;55:e11720. https://doi.org/10.1590/1414-431X2021e11720.

[146] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. European Heart Journal 1996;17:354–81.

[147] Rizkallah J, Amoud H, Fraschini M, Wendling F, Hassan M. Exploring the Correlation Between M/EEG Source-Space and fMRI Networks at Rest. Brain Topogr 2020;33(2):151–60. https://doi.org/10.1007/s10548-020-00753-w.

[148] van Diessen E, Numan T, van Dellen E, van der Kooi AW, Boersma M, Hofman D et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 2015;126(8):1468–81. https://doi.org/10.1016/j.clinph.2014.11.018.

Original Research Articles

van den Bongard F, Gowik JK, Reinsberger C. Auswirkungen körperlicher Aktivität auf Status Epilepticus im Tiermodell. Clinical Epileptology 2023; 1-5. DOI 10.1007/s10309-023-00574-4

van den Bongard F, Hamer HM, Sassen R, Reinsberger C. Sport and physical activity in epilepsy—a systematic review. Dtsch Arztebl Int 2020; 117: 1–6. DOI 10.3238/arztebl.2020.0001

van den Bongard F, Coenen J, Reinsberger C. Fitness, performance and cardiac autonomic responses to exercise in people with epilepsy. Epilepsy & Behavior 2022; 135: 108869. DOI 10.1016/j.yebeh.2022.108869

van den Bongard F, Gowik JK, Coenen J, Jakobsmeyer R, Reinsberger C. Exercise-induced central and peripheral sympathetic activity in a community-based group of epilepsy patients differ from healthy controls. Experimental Brain Research 2024. DOI 10.1007/s00221-024-06792-0

Clin Epileptol
https://doi.org/10.1007/s10309-023-00574-4
Angenommen: 19. November 2022

Auswirkungen körperlicher Aktivität auf Status epilepticus im Tiermodell

Basis für klinischen Transfer?

Franziska van den Bongard[1] · Julia Kristin Gowik[1] · Claus Reinsberger[1,2]
[1] Sportmedizinisches Institut, Universität Paderborn, Paderborn, Deutschland
[2] Edward B. Bromfield Epilepsy Program, Department of Neurology, Brigham and Women's Hospital, Boston, USA

Zusammenfassung

Hintergrund: Die Evidenz zum Einfluss körperlicher Aktivität (kA) auf die Anfallsfrequenz in Humanstudien ist niedrig.
Ziel: Literaturbasierte narrative Darstellung des Einflusses von kA auf Status epilepticus (SE) im Tiermodell.
Material und Methode: Auf Basis einer systematischen Literaturrecherche wurden kontrollierte, sportliche Interventionsstudien im Tiermodell für alle Anfallsmodelle sowie Belastungsformen und Modalitäten eingeschlossen, die den Einfluss auf klinische Endpunkte wie Anfallsfrequenz, Latenz und Intensität von Anfällen oder epilepsietypische Aktivität im EEG untersuchten.
Ergebnisse: Es wurden 33 Studien mit 37 Interventionen (Ausdauer-, Schwimm- oder Krafttrainings verschiedener Intensität, Dauer und Frequenz) eingeschlossen, im Rahmen derer eine Trainings- mit einer Kontrollgruppe verglichen wurde. Die untersuchten Endpunkte waren sehr heterogen und beinhalteten unter anderem epilepsietypische Aktivität im EEG, Latenz bis zum ersten Anfall, Stärke der Symptome oder Anfallsfrequenz. Insgesamt zeigte sich nach 20 Interventionen ein positiver Effekt, nach 9 Interventionen ein heterogener Effekt (positiv oder ausbleibend), nach 6 Interventionen ein ausbleibender Effekt und nach 1 Intervention ein positiver und ein negativer Effekt bezüglich der untersuchten klinischen Endpunkte.
Schlussfolgerung: Im Tiermodell scheint kA keinen relevanten negativen Einfluss auf anfallsassoziierte Endpunkte zu haben und wirkt sich tendenziell in den meisten Fällen, z. B. hinsichtlich der Anfallsfrequenz, positiv aus. Diese Ergebnisse sollten zur Untersuchung des Einflusses von kA auf die Anfallsfrequenz in Humanstudien motivieren.

Schlüsselwörter
Training · Anfälle · Epilepsie · Tiermodell · Status epilepticus

Zusatzmaterial online

Die Online-Version dieses Beitrags (https://doi.org/10.1007/s10309-023-00574-4) enthält weitere Tabellen.

Verfügbarkeit der Daten
Da es sich um eine Literaturübersicht handelt, können keine Daten zur Verfügung gestellt werden.

Zusatzmaterial online – bitte QR-Code scannen

Die Angst vor negativen Einflüssen von körperlicher Aktivität (kA) auf den Verlauf von Epilepsien sowie vor sportinduzierten Anfällen sind vermutlich 2 Gründe für die lang geltende Empfehlung gegen Sportausübung für Menschen mit Epilepsie [18]. Aus Humanstudien ist jedoch der positive Einfluss von kA auf viele krankheitsassoziierte Aspekte wie z. B. die psychologische Gesundheit [44] bekannt. Die Beeinflussung der Anfallsfrequenz wurde bislang wenig untersucht, und Hinweise auf einen positiven Zusammenhang existieren hauptsächlich in Tiermodellen. Eine starke Evidenz für eine antiepileptische Wirksamkeit von kA in Tiermodellen könnte den klinischen Transfer jedoch erheblich stimulieren.

Published online: 17 March 2023

Methodik

Die Literaturrecherche wurde am 24.05.2022 auf PubMed und Web of Science durchgeführt. Es wurde der Suchterminus „(epilepsy OR seizure OR antiepileptic OR epileptic) AND (animal OR rat OR mouse OR rodent) AND (exercise OR ‚physical activity' OR sport OR training OR ‚physical effort')" verwendet. Eingeschlossen wurden kontrollierte Interventionsstudien im Tiermodell (Ratten, Mäuse), die die Auswirkungen von sportlichem Training auf Endpunkte wie Anfallsfrequenz, Latenz oder Intensität von Anfällen oder epilepsietypische Aktivität im EEG untersuchen. Im Rahmen dieser Übersichtsarbeit wurden Ergebnisse von Training in Epilepsiemodellen im Vergleich zu Epilepsiekontrollgruppen beschrieben. Studien, die eine zusätzliche Medikamenteninjektion beinhalten, wurden nicht beschrieben.

Ergebnisse

Insgesamt wurden von 3489 identifizierten Studien 33 in die Übersichtsarbeit eingeschlossen. In 19 Studien wurde die Intervention (INT) vor SE-Induktion durchgeführt (INTvSE) [1, 4, 10, 14, 19, 21, 23, 24, 26, 28–31, 33, 37, 39, 40, 42, 45] und in 14 Studien nach SE-Induktion (INTnSE) [2, 5, 6, 8, 9, 20, 27, 32, 34, 35, 38, 43, 46]. Eine Studie verwendete WAG/Rij-Ratten mit spontaner Absence-Epilepsie, sodass diese der Gruppe INTnSE zugeordnet wurde [12].

Status-epilepticus-Induktion und Untersuchungstiere

In 2 Studien der Gruppe INTvSE wurden die Auswirkungen von Amygdalastimulationen auf das Kindling untersucht [4, 10]. Verschiedene chemische Konvulsiva wie Homozystein Thiolacton ($n = 2$) [23, 24], Kainsäure ($n = 4$) [29–31, 40], Pentylenetetrazol (PTZ) ($n = 4$) [1, 14, 33, 39], Pilocarpin ($n = 4$) [19, 21, 37, 45] und Penicillin ($n = 3$) [26, 28, 42] kamen in den anderen Studien zur SE-Induktion zur Anwendung.

In der Studiengruppe INTnSE wurden Pentylenetetrazol ($n = 2$) [32, 35], Ascorbinsäure und/oder Penicillin ($n = 2$) [27, 43] und Pilocarpin ($n = 9$) [2, 5, 6, 8, 9, 20, 34, 38, 46] eingesetzt sowie das Absence-Epilepsie-Modell der WAG/Rij-Ratten [12].

In 28 Studien wurden männliche und in 2 Studien [45, 46] weibliche Ratten untersucht. Drei Studien nutzten männliche Mäuse [29–31].

Interventionsprogramme und Belastungsmodalitäten

In der Gruppe INTvSE wurden Schwimmtraining ($n = 6$), kombiniertes Schwimm- und Ausdauertraining ($n = 1$), erzwungenes Ausdauertraining auf dem Laufband/-rad ($n = 11$) und freiwilliges Ausdauertraining (freier Zugang zum Laufband/-rad) ($n = 1$) durchgeführt. Eine Studie verglich freiwilliges und erzwungenes Ausdauertraining.

In der Gruppe INTnSE wurden Schwimmtraining ($n = 4$), erzwungenes Ausdauertraining ($n = 8$), freiwilliges Ausdauertraining ($n = 3$) und Krafttraining (Klettern an einer Leiter) ($n = 2$) durchgeführt. Zwei Studien verglichen freiwilliges und erzwungenes Ausdauertraining und eine weitere Schwimmtraining und freiwilliges Ausdauertraining.

Die Trainingsprogramme sind detailliert im Online-Zusatzmaterial in den Tabellen S1 und S2 dargestellt.

In der INTvSE-Gruppe variierten Häufigkeit und Dauer der Schwimmeinheiten zwischen 15 und 90 Einheiten und 15–60 min pro Einheit, die Ausdauereinheiten zwischen 1 und 65 Einheiten und 15–60 min pro Einheit mit unterschiedlichen Geschwindigkeiten. In den freiwilligen Ausdauertrainingsinterventionen hatten die Tiere 27 und 30 Tage Zugang zum Laufband (Tab. S1).

In der INTnSE-Gruppe wurde das Schwimmtraining zwischen 20 und 90 Einheiten bei unterschiedlichen Dauern durchgeführt (15–60 min). Über 10 bis 59 Einheiten mit einer Dauer von 30–60 min pro Einheit wurden die Tiere in den Ausdauerinterventionen bei unterschiedlicher Geschwindigkeit trainiert. Das freiwillige Ausdauertraining wurde über 10, 30 oder 45 Tage durchgeführt und die Krafttrainingseinheiten jeweils über 20 Einheiten (Tab. S2).

Ergebnisse zu den klinischen Endpunkten

In den eingeschlossenen Studien wurden unterschiedliche Endpunkte erhoben (Tab. S1, S2). Einige wurde zu einem festgelegten Zeitpunkt und andere mehrmals innerhalb einer Zeitspanne erhoben. Die im Online-Zusatzmaterial in Tab. S1 und S2 dargestellten Ergebnisse beziehen sich auf die jeweiligen primär berichteten Hauptergebnisse der eingeschlossenen Studien und auf einen Gruppenvergleich zwischen der Epilepsietrainingsgruppe und der Epilepsiekontrollgruppe.

Innerhalb der Gruppe INTvSE wurden unter anderem die Endpunkte „Anzahl Stimulationen" [4, 10], „Anzahl an Injektionen" [40], „Latenz SE" [21, 45], „Latenz erste Symptome" [21, 37], „Latenz erster Anfall" [1, 14, 19, 23, 24, 28, 39], „Latenz Konvulsionen" [33], „Dauer Konvulsionen" [33], „Intensität Symptome" (basierend auf festgelegter Skala) [1, 14, 21, 37], „Frequenz Symptome" [37], „Zeit Anfallsmanifestation" [37], „Anfallsfrequenz" [1], „Anzahl Anfallsepisoden" [23], Mortalität [30, 33], „epileptiforme Aktivität" im EEG [1, 26, 28, 39], „Anfallsaktivität" [29–31] untersucht (Tab. S1).

Innerhalb der Studiengruppe INTnSE wurden die Endpunkte „Anfallsfrequenz" [2, 5, 6, 8, 9, 20, 34, 38, 46], „Latenz" [32, 35], „Dauer Anfälle" [32], „Intensität Symptome" [32] und „epileptiforme Aktivität" im EEG [12, 27, 43] erhoben (Tab. S2).

In der Gruppe INTvSE wurden durch 10 Interventionen in 10 Studien positive Effekte unter anderem auf die Anfallsaktivität, epileptiforme Aktivität und Anfallslatenzen zugunsten der Epilepsietrainingsgruppe beobachtet (Schwimmintervention $n = 4$, erzwungene Ausdauerintervention $n = 5$, freiwillige Ausdauerintervention $n = 1$) [1, 4, 14, 19, 26, 29–31, 33, 40]. Fünf Interventionen in 5 Studien zeigten heterogene Ergebnisse (Schwimmintervention $n = 3$, erzwungene Ausdauerintervention $n = 2$) [9, 21, 37, 39, 42]: Während einige positiv beeinflusst wurden, konnte bei anderen kein Gruppenunterschied gefunden werden (Tab. S1). Bei 3 Ausdauerinterventionen in 3 Studien konnte kein Effekt auf alle eingeschlossenen Endpunkte, z. B. Latenzen, Inzidenzen, Intensitäten oder epileptiforme Aktivität, beobachtet werden

[24, 28, 45]. In einer Studie, die ein freiwilliges Ausdauertraining durchführte, war die Intensität der motorischen Symptome in der Trainingsgruppe im Vergleich zur Kontrollgruppe stärker. Allerdings wurde in der Epilepsietrainingsgruppe auch eine verkürzte Latenz bis zum Auftreten des ersten Anfalls gefunden [45].

In der Gruppe INTnSE wurden durch 11 Interventionen in 11 Studien positive Auswirkungen auf die untersuchten Endpunkte beobachtet (Schwimmintervention $n = 3$, erzwungene Ausdauerintervention $n = 4$, freiwillige Ausdauerintervention $n = 2$, Kraftintervention $n = 2$) [2, 5, 6, 8, 12, 20, 32, 34, 43, 46]. Dabei wurden Parameter wie epileptiforme Aktivität, Latenzen und Dauern sowie Anfallsfrequenzen positiv beeinflusst. Vier Interventionen aus 3 Studien zeigten heterogene Ergebnisse (Schwimmintervention $n = 1$, erzwungene Ausdauerintervention $n = 2$, freiwillige Ausdauerintervention $n = 1$) [9, 27, 35]. So war z. B. die Anfallsdauer reduziert, die Latenz bis zum ersten Anfall allerdings nicht [35], oder Spikes im EEG wurden positiv hinsichtlich der Anzahl und Frequenz, nicht aber der Amplitude und Latenz beeinflusst [27]. Durch 2 weitere Interventionen konnte kein Gruppenunterschied bezüglich des einzig beobachteten Endpunktes Anfallsfrequenz beobachtet werden (erzwungene Ausdauerintervention $n = 2$) [38, 46].

Diskussion

Die Anzahl und Art der untersuchten Studienendpunkte in den 37 Interventionen aus 33 Studien variiert zum Teil erheblich. Zusammenfassend aus beiden Studiengruppen (INTvSE, INTnSE) konnte in 20 Interventionen ein positiver Effekt auf verschiedene Endpunkte, wie z. B. Anfallsfrequenz oder epileptiforme Aktivität, in der Epilepsietrainingsgruppe beobachtet werden. Neun Interventionen zeigten heterogene Ergebnisse bezüglich der untersuchten klinischen Endpunkte. Bei 6 Interventionen konnte kein Trainingseffekt nachgewiesen werden. Es zeigten sich demnach keine Unterschiede zwischen der Trainingsgruppe und der Kontrollgruppe. Lediglich durch eine freiwillige Ausdauerintervention wurde die Stärke motorischer Symptome negativ beeinflusst, allerdings gleichzeitig auch ein positiver Effekt auf die Latenz bis zum ersten Anfall beobachtet.

Neben den Studienendpunkten zeigte sich eine Heterogenität hinsichtlich der untersuchten Trainingsprogramme. Diese unterschieden sich hinsichtlich der Anzahl der Einheiten, der Dauer, der Laufgeschwindigkeit oder der Zusatzgewichte. Die Gründe für das Ausbleiben eines Effekts nach einigen der untersuchten Interventionen erscheinen im Vergleich mit anderen Studien nicht eindeutig. So blieb beispielsweise der Effekt auf Parameter der epileptiformen Aktivität in der Gruppe INTvSE nach 90 Einheiten Schwimmtraining über jeweils 30 und 60 min aus, nicht aber nach 15 min [42] oder nach 21 Einheiten à 60 min [1]. Ein ähnliches Bild zeigt sich in der Gruppe INTnSE. Im direkten Vergleich der Interventionen muss allerdings berücksichtigt werden, dass die beobachteten Endpunkte studienspezifisch sind und sich nicht oder nur schwer studienübergreifend vergleichen lassen. Tendenziell gibt es jedoch Hinweise darauf, dass die Applikation von nur wenigen Interventionen (1 bis 10 Einheiten) weniger effektiv zu sein scheinen, obwohl ein Effekt auch bei häufigeren Interventionen (90 Einheiten) teilweise ausgeblieben ist. Ein möglicher Einflussfaktor könnten die unterschiedlichen Wirkmechanismen der verwendeten chemischen Konvulsiva zur SE-Induktion sein. Iqbal et al. (2017) [25] untersuchten in einem systematischen Review und einer Metaanalyse nur die Studien, in denen das Pilocarpin-Modell angewendet wurde. Die Autoren schlussfolgerten, dass die Effizienz des Trainings von der Dauer abhänge. Eine solche Schlussfolgerung ist in dieser weit gefassten Übersichtsarbeit im Sinne einer Dosis-Wirkungs-Beziehung aufgrund der Heterogenität der Anfallsmodelle nicht möglich, jedoch bestanden mit Ausnahme einer Studie auch keine negativen Effekte.

Der beobachtete positive Effekt auf die untersuchten Endpunkte in den freiwilligen, aber nicht in den erzwungenen Ausdauertrainingsgruppen der Forschergruppe Vannucci Campos (2016, 2017) [45, 46] wird möglicherweise auch vom Geschlecht der Tiere beeinflusst. Epilepsien, besonders im Pilocarpin-Modell, welches hier zur Anwendung kam, scheinen einen Einfluss auf die hormonelle Regulation bei weiblichen Ratten zu haben [3]. Der Einfluss auf die Endpunkte Anfallsfrequenz sowie Latenz bis zum ersten motorischen Anfall und damit einhergehend der Zusammenhang mit kA ist dabei nicht eindeutig geklärt, sodass die Vergleichbarkeit zu den anderen Studien eingeschränkt ist.

Neben der Beobachtung und Beschreibung von Endpunkten im Kontext mit kA wie Anfallsfrequenz, Latenz und Intensität von Anfällen oder epilepsietypischen Veränderungen im EEG werden in der Literatur auch mögliche zugrunde liegende physiologische Wirkmechanismen diskutiert [11]. Die Bedeutungen des „brain-derived neurotropic factor" (BDNF) und des Neuropeptids Y (NPY) sind dabei nur 2 Ansatzpunkte bei der mechanistischen Betrachtung. KA kann die Expression des BDNF und des NPY steigern [16, 22], die Bedeutung von BDNF bei Epilepsien ist jedoch noch unklar. Zum einen könnte eine exzitatorische Wirkung bestehen [36], zum anderen wird aber auch eine Modulation der Expression von Neuropeptiden, beispielsweise des NPY, vermutet [17]. Über die Modulation synaptischer Kopplung in der Hippocampusformation dient NPY möglicherweise als endogenes Antikonvulsivum [13]. Auch andere Mechanismen werden in diesem Kontext diskutiert [7].

Obschon die Übertragbarkeit der Ergebnisse aufgrund der Anwendung eines Anfallsmodells auf den Menschen eingeschränkt ist und keine methodische Bewertung der Studien vorgenommen wurde, sodass das Verzerrungspotenzial der vorliegenden Ergebnisse unklar ist, sollten die positiven Ergebnisse und das weitestgehende Ausbleiben von negativen Ergebnissen zur Untersuchung des Einflusses von kA auf epileptische Anfälle im Menschen motivieren [15, 41]. Eine systematische Übersichtarbeit konnte zeigen, dass sich in Humanstudien zumeist positive Effekte von kA auf Lebensqualität und Depressionen zeigen und in den meisten Fällen ein negativer Einfluss auf die Anfallsfrequenz ausbleibt oder diese sogar bei einigen Patienten reduziert werden kann [44].

Fazit für die Praxis

Bei der jahrzehntelang geltenden Empfehlung gegen Sportausübung spielen die Sorge vor Hyperventilation beim Sporttreiben sowie die Sorge vor kA-induzierten Anfällen

eine Rolle. Zu Ersterem existieren allerdings keine validen Daten, wohingegen das Risiko für Anfälle unter Berücksichtigung individueller Faktoren zu evaluieren ist. Auf Basis der Ergebnisse aus Tiermodellen und aus ersten klinischen Studien scheint es, dass die Annahme von kA-induzierten negativen klinischen Auswirkungen nicht ohne Weiteres aufrechterhalten werden kann. Während Anfälle beim Sport (z. B. beim Klettern) durchaus eine Gefahr für Verletzungen darstellen können, scheint populationsbasiert keine allgemein erhöhte Verletzungsrate beim Sport zu bestehen. Zum besseren klinischen Umgang mit Sport bei Epilepsien veröffentlichte die „International League Against Epilepsy" 2016 eine Risikoklassifikation nach Sportarten und klinischem Verlauf, an denen sich Kliniker gut orientieren können.

Korrespondenzadresse

Franziska van den Bongard
Sportmedizinisches Institut, Universität Paderborn
Warburger Str. 100, 33098 Paderborn, Deutschland
bongard@sportmed.uni-paderborn.de

Funding. Open Access funding enabled and organized by Projekt DEAL.

Einhaltung ethischer Richtlinien

Interessenkonflikt. F. van den Bongard, J.K. Gowik und C. Reinsberger geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autor/-innen keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

Literatur

1. Acar S, Kapucu A, Akgun-Dar K (2022) The effects of regular swimming exercise during sodium valproate treatment on seizure behaviors and EEG recordings in pentylenetetrazole-kindled rats. Epilepsy Res. https://doi.org/10.1016/j.eplepsyres.2021.106830
2. de Almeida AA, Gomes da Silva S, Lopim GM, Vannucci Campos D, Fernandes J, Cabral FR, Arida RM (2017) Resistance exercise reduces seizure occurrence, attenuates memory deficits and restores BDNF signaling in rats with chronic epilepsy. Neurochem Res 42(4):1230–1239. https://doi.org/10.1007/s11064-016-2165-9
3. Amado D, Cavalheiro EA (1998) Hormonal and gestational parameters in female rats submited to pilocarpin model of epilepsy. Epilepsy Res 32:266–274
4. Arida RM, de Jesus Vieira A, Cavalheiro EA (1998) Effect of physical exercise on kindling development. Epilepsy Res 30(2):127–132
5. Arida RM, Scorza FA, dos Santos NF, Peres CA, Cavalheiro EA (1999) Effect of physical exercise on seizure occurrence in a model of temporal lobe epilepsy in rats. Epilepsy Res 37(1):45–52
6. Arida RM, Fernandes MJ, Scorza FA, Preti SC, Cavalheiro EA (2003) Physical training does not influence interictal LCMRglu in pilocarpine-treated rats with epilepsy. Physiol Behav 79(4):789–794. https://doi.org/10.1016/S0031-9384(03)00204-X
7. Arida RM, Scorza FA, Terra VC, Scorza CA, de Almeida A-C, Cavalheiro EA (2009) Physical exercise in epilepsy: what kind of stressor is it? Epilepsy Behav 16(3):381–387. https://doi.org/10.1016/j.yebeh.2009.08.023
8. Arida RM, Sanabria ERG, da Silva AC, Faria LC, Scorza FA, Cavalheiro EA (2004) Physical training reverts hippocampal electrophysiological changes in rats submitted to the pilocarpine model of epilepsy. Physiol Behav 83(1):165–171. https://doi.org/10.1016/j.physbeh.2004.08.008
9. Arida RM, Scorza CA, Scorza FA, Gomes da Silva S, da Graca Naffah-Mazzacoratti M, Cavalheiro EA (2007) Effects of different types of physical exercise on the staining of parvalbumin-positive neurons in the hippocampal formation of rats with epilepsy. Prog Neuropsychopharmacol Biol Psychiatry 31(4):814–822. https://doi.org/10.1016/j.pnpbp.2007.01.021
10. Arida RM, Scorza FA, Silva de Lacerda AF, Gomes da Silva S, Cavalheiro EA (2007) Physical training in developing rats does not influence the kindling development in the adult life. Physiol Behav 90(4):629–633. https://doi.org/10.1016/j.physbeh.2006.11.016
11. Arida RM, de Almeida A-CG, Cavalheiro EA, Scorza FA (2013) Experimental and clinical findings from physical exercise as complementary therapy for epilepsy. Epilepsy Behav 26(3):273–278. https://doi.org/10.1016/j.yebeh.2012.07.025
12. Aygun H, Ayyildiz M, Agar E (2019) Swimming exercise decreases the absence-like epileptic activity in WAG/Rij rats. Behav Brain Res 363:145–148. https://doi.org/10.1016/j.bbr.2019.01.060
13. Baraban SC, Hollopeter G, Erickson JC, Schwartzkroin PA, Palmiter RD (1997) Baraban 1997 Knockout mice reveal a critical antiepileptic Role for Neuropeptide Y. J Neurosci 17(23):8927–8936
14. Barzroodi Pour M, Bayat M, Golab F, Eftekharzadeh M, Katebi M, Soleimani M, Karimzadeh F (2019) The effect of exercise on GABA signaling pathway in the model of chemically induced seizures. Life Sci 232:116667. https://doi.org/10.1016/j.lfs.2019.116667
15. Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM (2016) Epilepsy, seizures, physical exercise, and sports: A report from the ILAE Task Force on Sports and Epilepsy. Epilepsia 57(1):6–12. https://doi.org/10.1111/epi.13261
16. Cotman CW, Berchtold NC (2002) Exercise: A behavioral intervention to enhance brain health and plasticity. Trends Neurosci 25(6):295–301
17. Croll SD, Wiegand SJ, Anderson KD, Lindsay RM, Nama H (1994) Regulation of neuropeptides in adult rat forebrain by the neurotrophins BDNF and NGF. Eur J Neurosci 6:1343–1353
18. Dubow JS, Kelly JP (2003) Epilepsy in sports and recreation. Sports Med 33:499–516
19. Epps SA, Kahn AB, Holmes PV, Boss-Williams KA, Weiss JM, Weinshenker D (2013) Antidepressant and anticonvulsant effects of exercise in a rat model of epilepsy and depression comorbidity. Epilepsy Behav 29(1):47–52. https://doi.org/10.1016/j.yebeh.2013.06.023
20. Gomes FGN, Gomes Da Silva S, Cavalheiro EA, Arida RM (2014) Beneficial influence of physical exercise following status epilepticus in the immature brain of rats. Neuroscience 274:69–81. https://doi.org/10.1016/j.neuroscience.2014.05.024
21. Gomes da Silva S, de Almeida AA, Silva Araujo BH, Scorza FA, Cavalheiro EA, Arida RM (2011) Early physical exercise and seizure susceptibility later in life. Int J Dev Neurosci 29(8):861–865. https://doi.org/10.1016/j.ijdevneu.2011.07.011
22. Hoffman JR, Ostfeld I, Kaplan Z, Zohar J, Cohen H (2015) Exercise enhances the behavioral responses to acute stress in an animal model of PTSD. Med Sci Sports Exerc 47(10):2043–2052. https://doi.org/10.1249/MSS.0000000000000642
23. Hrncic D, Rasic-Markovic A, Lekovic J, Krstic D, Colovic M, Macut D, Susic V, Djuric D, Stanojlovic O (2014) Exercise decreases susceptibility to homocysteine seizures: the role of oxidative stress. Int J Sports Med 35(7):544–550. https://doi.org/10.1055/s-0033-1357162
24. Hrncic D, Grubac Z, Sutulovic N, Rasic-Markovic A, Rankov-Petrovic B, Susic V, Djuric D, Stanojlovic O (2016) The effects of acute physical activity on severity of seizures induced in rats by homocysteine thiolactone. Act Nerv Super Rediviva 58(3):83–87
25. Iqbal M, Rahman MS, Zafar S, Chen X-L, Liu J-X, Liu Y (2017) Systematic review and meta-analysis of the efficacy of different exercise programs in pilocarpine induced status epilepticus models. Epilepsy Behav 73:256–267. https://doi.org/10.1016/j.yebeh.2017.06.007
26. Kayacan Y, Tutkun E, Arslan G, Ayyildiz M, Agar E (2016) The effects of treadmill exercise on penicillin-induced epileptiform activity. Arch Med Sci 12(5):935–940. https://doi.org/10.5114/aoms.2016.61907
27. Kayacan Y, Kisa EC, Ghojebeigloo BE, Kocacan SE, Ayyildiz M, Agar E (2019) The effects of moderate running exercise and L-tyrosine on penicillin-induced epileptiform activity in rats. Acta Neurobiol Exp (Wars) 79(2):148–154
28. Kayacan Y, Ghojebeigloo BE, Cerit G, Kocacan SE, Ayyildiz M (2020) Physical exercise and 5-hydro-

xytryptophan, a precursor for serotonin synthesis, reduce penicillin-induced epileptiform activity. Epilepsy Behav 112:107403. https://doi.org/10.1016/j.yebeh.2020.107403
29. Kim H-J, Kim I-K, Song W, Lee J, Park S (2013) The synergic effect of regular exercise and resveratrol on kainate-induced oxidative stress and seizure activity in mice. Neurochem Res 38(1):117–122. https://doi.org/10.1007/s11064-012-0897-8
30. Kim H-J, Song W, Kim J-S, Jin EH, Kwon M-S, Park S (2014) Synergic effect of exercise and lipoic acid on protection against kainic acid induced seizure activity and oxidative stress in mice. Neurochem Res 39(8):1579–1584. https://doi.org/10.1007/s11064-014-1350-y
31. Kim H-J, Song W, Jin EH, Kim J, Chun Y, An EN, Park S (2016) Combined low-intensity exercise and ascorbic acid attenuates Kainic acid-induced seizure and oxidative stress in mice. Neurochem Res 41(5):1035–1041. https://doi.org/10.1007/s11064-015-1789-5
32. Lin X-Y, Cui Y, Wang L, Chen W (2019) Chronic exercise buffers the cognitive dysfunction and decreases the susceptibility to seizures in PTZ-treated rats. Epilepsy Behav 98(Pt A):173–187. https://doi.org/10.1016/j.yebeh.2019.07.032
33. Meigoni ZS, Jabari F, Motaghinejad M, Motevalian M (2022) Protective effects of forced exercise against topiramate-induced cognition impairment and enhancement of its antiepileptic activity: molecular and behavioral evidences. Int J Neurosci. https://doi.org/10.1080/00207454.2021.1873979
34. Peixinho-Pena LF, Fernandes J, de Almeida AA, Novaes Gomes FG, Cassilhas R, Venancio DP, de Mello MT, Scorza FA, Cavalheiro EA, Arida RM (2012) A strength exercise program in rats with epilepsy is protective against seizures. Epilepsy Behav 25(3):323–328. https://doi.org/10.1016/j.yebeh.2012.08.011
35. Rambo LM, Ribeiro LR, Oliveira MS, Furian AF, Lima FD, Souza MA, Silva LFA, Retamoso LT, Corte CLD, Puntel GO, de Avila DS, Soares FAA, Fighera MR, Mello CF, Royes LFF (2009) Additive anticonvulsant effects of creatine supplementation and physical exercise against pentylenetetrazol-induced seizures. Neurochem Int 55(5):333–340. https://doi.org/10.1016/j.neuint.2009.04.007
36. Scharfman HE (2005) Brain-derived neurotrophic factor and epilepsy – A missing link? Epilepsy Curr 5(3):83–88
37. Setkowicz Z, Mazur A (2006) Physical training decreases susceptibility to subsequent pilocarpine-induced seizures in the rat. Epilepsy Res 71(2–3):142–148. https://doi.org/10.1016/j.eplepsyres.2006.06.002
38. Siliano MR, Lima E, Valente SC, Naffah-Mazzacoratti MDG, Cavalheiro EA, Arida RM, Amado D (2006) Effect physical exercise in Animals submitted to pilocarpine model. J Epilepsy Clin Neurophysiol 12(2):63–68
39. Souza MA, Oliveira MS, Furian AF, Rambo LM, Ribeiro LR, Lima FD, Dalla Corte LC, Silva LFA, Retamoso LT, Dalla Corte CL, Puntel GO, de Avila DS, Soares FAA, Fighera MR, de Mello CF, Royes LFF (2009) Swimming training prevents pentylenetetrazol-induced inhibition of Na+, K+-ATPase activity, seizures, and oxidative stress. Epilepsia 50(4):811–823. https://doi.org/10.1111/j.1528-1167.2008.01908.x
40. Tchekalarova J, Shishmanova M, Atanasova D, Stefanova M, Alova L, Lazarov N, Georgieva K (2015) Effect of endurance training on seizure susceptibility, behavioral changes and neuronal damage after kainate-induced status epilepticus in spontaneously hypertensive rats. Brain Res 1625:39–53. https://doi.org/10.1016/j.brainres.2015.08.022
41. Téllez-Zenteno JF, Hunter G, Wiebe S (2008) Injuries in people with self-reported epilepsy: a population-based study. Epilepsia 49(6):954–961. https://doi.org/10.1111/j.1528-1167.2007.01499.x
42. Tutkun E, Ayyildiz M, Agar E (2010) Short-duration swimming exercise decreases penicillin-induced epileptiform ECoG activity in rats. Acta Neurobiol Exp (Wars) 70(4):382–389
43. Tutkun E, Arslan G, Soslu R, Ayyildiz M, Agar E (2015) Long-term ascorbic acid administration causes anticonvulsant activity during moderate and long-duration swimming exercise in experimental epilepsy. Acta Neurobiol Exp (Wars) 75(2):192–199
44. van den Bogard F, Hamer HM, Sassen R, Reinsberger C (2020) Sport and physical activity in epilepsy. Dtsch Arztebl Int 117(1–2):1–6. https://doi.org/10.3238/arztebl.2020.0001
45. Vannucci Campos D, Lopim GM, de Almeida VS, Amado D, Arida RM (2016) Effects of different physical exercise programs on susceptibility to pilocarpine-induced seizures in female rats. Epilepsy Behav 64(Pt A):262–267. https://doi.org/10.1016/j.yebeh.2016.08.011
46. Vannucci Campos D, Lopim GM, da Silva DA, de Almeida AA, Amado D, Arida RM (2017) Epilepsy and exercise: An experimental study in female rats. Physiol Behav 171:120–126. https://doi.org/10.1016/j.physbeh.2016.12.040

Abstract

Impact of physical activity on status epilepticus in an animal model. Basis for clinical transfer?

Background: The evidence for the influence of physical activity (PA) on seizure frequency in human studies is very low.
Objective: Literature-based narrative presentation of the influence of PA on status epilepticus (SE) in animal models.
Material and methods: Based on a systematic literature research, controlled exercise intervention studies for all animal models on seizures as well as all exercise modalities and types were included, which investigated clinical endpoints, such as seizure frequency, latency and intensity of seizures or epileptiform activity.
Results: A total of 33 studies investigating 37 interventions (endurance, swimming and strength training of various durations, intensities and frequencies) involving a training group and a control group were included. The investigated endpoints were very heterogeneous and included epileptiform activity, latency to the first seizure, severity of symptoms and seizure frequency. Overall, 20 Interventions showed a positive effect on clinical endpoints, 9 interventions revealed a heterogeneous effect (positive or missing), 6 interventions were not associated with any clinical effect and in 1 intervention 1 endpoint was negatively influenced and 1 positively.
Conclusion: In animal models, PA does not appear to have a relevant negative impact on seizure-associated endpoints and in most cases a positive trend towards clinical features of SE (for example on seizure frequency) was reported. These results should motivate investigation of the influence of PA on seizure frequency in human studies.

Keywords
Training · Seizure · Epilepsy · Animal model · Status epilepticus

Supplementary Material

Tabelle 1: Übersicht der Interventionen und Endpunkte aus den Studien in der Gruppe INTvSE

Schwimminterventionen			
Studie	*Einheiten, Dauer in min, Gewicht in % vom eigenen Körpergewicht*	*Endpunkte* [1]	
Setkowicz 2006 [37]	15 Drei-Tages-Zyklen Schwimmen: 20, - Ausdauer: 20, 18 m/min	Latenz erste Symptome	+
		Latenz maximale Ausprägung Symptome	+
		Gesamtzeit Anfallsmanifestation	+
		Frequenz Symptome	/
		Latenz Symptome	/
Souza 2009 [39]	30, 60, 5	30mg/kg PTZ	
		Anfallsaktivität im EEG	+
		Amplitude EEG-Wellen	+
		Baseline EEG-Amplitude	/
		45mg/kg PTZ	
		Anfallsaktivität im EEG	+
		Amplitude EEG-Wellen	+
		Dauer konvulsiver Episoden	+
		Latenz erste konvulsive Episode	+
		Baseline EEG-Amplitude	/
		60mg/kg PTZ	
		Anfallsaktivität im EEG	+
		Amplitude EEG-Wellen	+
		Dauer konvulsive Episoden	+
		Baseline EEG-Amplitude	/
Tutkun 2010 [42]	90, 15, -	mittlere Frequenz elektrokortikographischer (ECOG) epileptiformer Aktivität (ersten 70 min)	+
		mittlere Amplitude ECOG epileptiformer Aktivität (ersten 90 min)	+
	90, 30, -	mittlere Frequenz ECOG epileptiformer Aktivität	/
		mittlere Amplitude ECOG epileptiformer Aktivität	/
	90, 60, -	mittlere Frequenz ECOG epileptiformer Aktivität	/
		mittlere Amplitude ECOG epileptiformer Aktivität	/
Kim 2013 [29]	30, 60, 5	Anfallsaktivität	+
Kim 2014[30]	24, 60, 5-10	Anfallsaktivität	+
		Mortalität	+
Kim 2016 [31]	24, 30, -	Anfallsaktivität	+
Acar 2022 [1]	21, 60, -	Anzahl Spikes	+
		epileptiforme Aktivität im EEG	+
		Latenz EEG-Veränderung	+
Erzwungene Ausdauerintervention			
Studie	*Einheiten, Dauer in min* [2]*, Geschwindigkeit in m/min* [2]	*Endpunkte*	
Arida 1998 [4]	1, 40, 20	Zeit im ersten Anfallsstadium	+
		Nachentladungszeiten im EEG (erstes Anfallsstadium)	+
	45, 40, 20	Zeit im ersten Anfallsstadium	+
		Nachentladungszeiten im EEG (erstes Anfallsstadium)	+
		Anzahl Stimulationen erster generalisierter Anfall	+
Arida 2007 [10]	40, 60, 24-26	Anzahl Stimulationen fünftes Anfallsstadium	+
		Anzahl Stimulationen zweites, drittes, viertes Anfallsstadium	/
		Dauer in ersten Anfallsstadium	+
		Nachentladungszeiten im EEG (erstes Anfallsstadium)	+

Barzroodi 2019 [14]	20, 30, Steigerung 5m/min alle 5 min bis 25m/min	Intensität der Anfälle (Tag 5, 10, 22, 26)	+
		Anfallslatenz (Tag 1,3,8,10,12,15,17,19, 22)	+
Gomes da Silva 2011 [21]	39, bis zu 60, bis zu 18	Latenz erste Symptome	+
		Intensität motorische Symptome	+
		Latenz bis Status Epilepticus	/
Hrncic 2014 [23]	30, 30, 20	Latenz Anfall	+
		Anzahl Anfallsepisoden	+
		Intensität Anfallsepisoden	/
Hrncic 2016 [24]	1, 30, 25	Anfallsinzidenz	/
		Latenz erster Anfall	/
		Anzahl konvulsiver Episoden	/
		Anfallsintensität	/
Kayacan 2016 [26]	65, 15, bis zu 27 + Steigung	Mittlere Frequenz epileptiformer Aktivität (70 min nach Injektion)	+
	65, 30, bis zu 27 + Steigung	Mittlere Frequenz epileptiformer Aktivität (90 min nach Injektion)	+
	65, 60, bis zu 27 + Steigung	Mittlere Frequenz epileptiformer Aktivität (90 min nach Injektion)	+
Tchekalarova 2015 [40]	20, bis zu 40, 20	Anzahl an Injektionen bis zum Status Epilepticus	+
		Anfallsfreie Phase	+
Vannucci Campos 2016 [45]	30, 30, bis zu 22	Latenz erster motorischer Anfall	/
		Anzahl Ratten Status Epilepticus	/
Kayacan 2020 [28]	50, 30, 8	Latenz Anfälle	/
		Amplitude Spike-Wave-Komplexe	/
		Frequenz Spike-Wave-Komplexe	/
Meigoni 2021 [33]	18, 45, 15 + Steigung	Latenz klonische Konvulsionen	+
		Dauer klonische Konvulsionen	+
Freiwillige Ausdauerinterventionen			
Studie	*Dauer in Tagen, durchschnittlich zurückgelegte Distanz pro Tag*	*Endpunkte*	
Epps 2013 [19]	27, keine Angaben	Latenz erster Anfall	+
Vannucci Campos 2016 [45]	30, 10,260±2580 Meter	Latenz erster motorischer Anfall	+
		Intensität motorischer Symptome	-

[1] Die Ergebnisse der Endpunkte beziehen sich auf einen signifikanten Gruppenunterschied zugunsten der Epilepsietrainingsgruppe (+), zum Nachteil der Epilepsietrainingsgruppe (-) oder auf einen ausbleibenden Gruppenunterschied (/). (gilt für alle Tabellen)

[2] Angabe der am längsten durchgeführten Laufdauer und Geschwindigkeit (gilt für alle Tabellen)

Tabelle 2: Übersicht der Interventionen und Endpunkte aus den Studien in der Gruppe INTnSE

Schwimminterventionen			
Studie	*Einheiten, Dauer in min, Gewicht in % vom eigenen Körpergewicht*	*Endpunkte*	
Aygun 2019 [12]	90, 15, -	Gesamtzahl Spike-Wave Entladungen	+
		mittlere Gesamtdauer Spike-Wave Entladungen	+
	90, 30, -	Gesamtzahl Spike-Wave Entladungen	+
		mittlere Gesamtdauer Spike-Wave Entladungen	+
	90, 60, -	Gesamtzahl Spike-Wave Entladungen	+
		mittlere Gesamtdauer Spike-Wave Entladungen	+

Lin 2019 [32]	20, 30, -	Latenz Anfall	+
		Dauer kleine Anfälle	+
		Dauer große Anfälle	+
		Anfallsscore	+
Rambo 2009 [35]	25, 60, 5	Anfallsdauer	+
		Latenz erster Anfall	/
Tutkun 2015 [43]	90,15, -	mittlere Frequenz Spikes (in Minute 60)	+
	90, 30, -	mittlere Frequenz Spikes (in Minute 80)	+
		mittlere Amplitude epileptiformer Aktivität (110, 120 min nach Injektion)	+
	90, 60, -	mittlere Frequenz Spikes (in Minute 80)	+
		mittlere Amplitude epileptiformer Aktivität (110, 120 min nach Injektion)	+
Erzwungene Ausdauerinterventionen			
Studie	*Einheiten, Dauer in min, Geschwindigkeit in m/min*	*Endpunkte*	
Arida 1999 [5]	45, 60, 20-22	Anfallsfrequenz	+
Arida 2003 [6]	45, 60, 24-26	Anfallsfrequenz (nach 45 Tagen)	+
Arida 2004 [8]	45, 60, 22-25	Anfallsfrequenz	+
Arida 2007 [9]	10, 60, 23-26	Anfallsfrequenz	/
	45, 60, 23-26	Anfallsfrequenz	+
Gomes 2014 [20]	59, 60, 18	Anfallsfrequenz	+
Kayacan 2019 [27]	50, 30, 8	Frequenz Spikes	+
		Anzahl Spikes	+
		Amplitude Spikes	/
		Latenz Spikes	/
Vannucci Campos 2017 [46]	20, 30, bis zu 22	Anfallsfrequenz	/
Siliano 2006 [38]	20, 60, - (60% VO_2max)	Anfallsfrequenz	/
Freiwillige Ausdauerinterventionen			
Studie	*Einheiten/Tage, Durchschnittliche zurückgelegte Distanz pro Tag*	*Endpunkte*	
Arida 2007 [9]	10, keine Angaben	Anfallsfrequenz	/
	45, keine Angaben	Anfallsfrequenz	+
Lin 2019 [32]	20, keine Angaben (30 min)	Latenz Anfall	+
		Dauer kleine Anfälle	+
		Dauer große Anfälle	+
		Anfallsscore	+
Vannucci Campos 2017 [46]	30, 1730±1170 Meter	Anfallsfrequenz	+
Kraftinterventionen			
Studie	*Einheiten, Anzahl der Aufstiege, Gewicht in % vom eigenen Körpergewicht*	*Endpunkte*	
Peixinho-Pena 2012 [34]	20, 8, ersten zwei Aufstiege 50%, danach 100%	Anfallsfrequenz	+
de Almeida 2016 [2]	20, 8, Steigerung innerhalb jeder Einheit: 50%, 75%, 90%, 100%	Anfallsfrequenz	+

Original Article

Sport and Physical Activity in Epilepsy

A Systematic Review

Franziska van den Bongard, Hajo M. Hamer, Robert Sassen, Claus Reinsberger

Summary

Background: For many years, people with epilepsy were advised not to engage in sports. In this systematic review, we investigated whether persons with epilepsy exercise less than the general population, and what effect physical activity has on epilepsy.

Methods: A literature search was carried out in PubMed and the Web of Science, and 14 269 studies were entered into the selection process. The selected studies were assessed for their methodological quality and accordingly assigned an evidence level.

Results: 42 studies were included in the review; 10 were classified as evidence level 3, 27 as evidence level 2–, 2 as evidence level 2+, and 3 as evidence level 1–. Persons with epilepsy are less physically active and less physically fit than the general population. Reduced physical activity is associated with a higher frequency of comorbidities and lower quality of life. Physical interventions can improve quality of life. In most cases, physical exercise did not increase seizure frequency.

Conclusion: There is no reason to forbid persons with epilepsy to participate in sports; they should, rather, be encouraged to do so. The decision on a particular type of sport should, however, be taken individually in each case.

Cite this as
van den Bongard F, Hamer HM, Sassen R, Reinsberger C: Sport and physical activity in epilepsy—a systematic review. Dtsch Arztebl Int 2020; 117: 1–6.
DOI: 10.3238/arztebl.2020.0001

Institute of Sports Medicine, Paderborn University: Franziska van den Bongard, MA; Prof. Dr. med. Dr. rer. medic. Claus Reinsberger

Epilepsy Centre at the Department of Neurology, Universitätsklinikum Erlangen: Prof. Dr. med. Hajo Hamer, MHBA

Department of Epileptology, University Hospital Bonn: Dr. med. Robert Sassen

Epilepsy is a common neurological disorders with a lifetime prevalence of 7.6 per 1000 persons (e1). In addition to recurrent seizures, epilepsy is also associated with comorbidities such as cognitive and psychological problems, as well as social difficulties (e2). Despite the known positive effects of sports and physical activity on quality of life and general disease prevention (e3), patients with epilepsy have long been discouraged from participating in sports activities (e4). This recommendation is likely based on the fear that sporting activity may cause injuries, potentially induce seizures, and have a negative effect on disease course.

However, over the past few decades, studies have shown that sports-related injuries are not more common in these patients compared to the general population (e5). Therefore, the questions arise as to whether patients with epilepsy avoid sports and take less physical exercise than the general population on the basis of unverifiable rationales and prejudices (e6) and whether this leads to further disadvantages for this group.

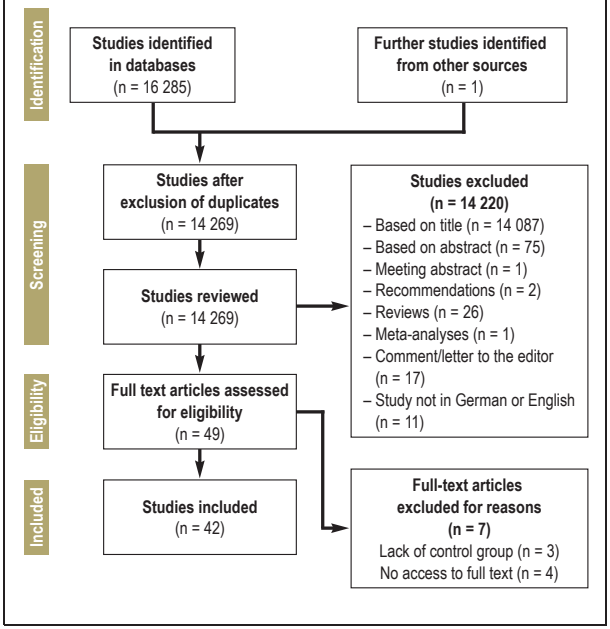
In 2016, the International League Against Epilepsy (ILAE) published a consensus paper that recommends safe sports participation for patients with epilepsy (e7). It is unclear which positive effects of sports on actual disease activity these patients are being deprived of. Therefore, the aim of this systematic review is to answer the following questions:

- Are patients with epilepsy less physically active and less fit than the general population?
- What effect does physical activity have on comorbidities in epilepsy?
- What effect does physical activity have on the frequency of seizures?

Methods

The literature search was conducted on 31 January 2019, in the PubMed (Medline/PubMed Central) and Web of Science databases. The following search terms were used: (epilepsy OR “AED” OR seizure OR antiepileptic OR epileptic) AND (exercise OR “physical activity” OR sport OR training OR “physical effort” OR “physical therapy”). Longitudinal and cross-sectional human studies, as well as case studies, were included. Diagnosed epilepsy and endpoints on

FIGURE



Selection process: PRISMA flow diagram (e8)
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

physical activity of any form were used as additional inclusion criteria. With regard to activity habits, only controlled studies were included.

A total of 14 269 studies were found and included in the selection process, which is presented in the *Figure*. The studies were selected and evaluated by two independent reviewers (FvdB, CR).

Methodological quality assessment

Interventional studies were assessed according to the risk-of-bias principle (e9). Seven assessment categories were analyzed per study:

- Selection bias: generation of a randomization sequence
- Selection bias: blinding to allocation
- Performance bias: blinding of personnel and endpoints
- Detection bias: blinding of subjects
- Attrition bias: incomplete data
- Reporting bias: selective reporting
- Other bias.

The cross-sectional studies were assessed on the basis of the publication by Hammer et al. on the prevention of distorted results in observational studies (e10). Five assessment categories were analyzed per cross-sectional study:

- Selection bias
- Information bias
- Measurement errors
- Confounding
- Other bias.

The risk for each bias in both assessment instruments could be classified as high, unknown, or low. High and unknown risk were assigned one point and low risk no points, thereby achieving an overall score for each study. The higher the score, the worse the methodological quality. Case studies, epidemiological studies, and interview-based studies were not assessed for methodology. Methodological quality assessments were performed for 10 interventional studies and 25 cross-sectional studies.

Evidence levels

The included studies were assigned an evidence level (e11). Studies with a comparison group—i.e., with a healthy or diseased control group or with a sample divided into active and inactive, or with group observation over several time points—were classified as evidence level "2." All studies without a comparison group in the cross-section were classified as level "3."

Results

In all, 42 studies were included in the systematic review. These studies can be divided into seven groups:

- Case studies (n = 4)
- Interventional studies (n = 10)
- Epidemiological studies (n = 1)
- Survey-based studies (n = 12)
- Interview-based studies (n = 2)
- Combined cross-sectional studies (survey and physical tests) (n = 4)
- Studies on one-time physical effort (n = 9).

Altogether, 15 studies investigated physical activity in patients with epilepsy compared to healthy individuals. Of these, six evidence-level "2–" studies showed that individuals with epilepsy are less physically active (1–6). In addition, five studies (n = 4 evidence-level "2–" and n = 1 "2+") reported lower physical fitness (in relation to various aspects such as VO_2max, blood pressure) compared to healthy controls (7–11). In contrast, the results of three other studies (evidence level "2–") revealed no differences between groups in terms of physical activity (12–14). However, a further study ("2+") found an association between physical fitness (activity) early in life and a reduced risk of epilepsy in later life (15).

In all, 17 studies investigated the effect of physical activity on comorbidities such as anxiety and depression, as well as quality of life. Ten of these studies ("2–" n = 8, "3" n = 2; survey-/interview-based studies, combined studies, studies on one-time physical effort) showed physical activity to have a positive effect (4, 9, 12, 14, 16–21). The results of six interventional studies (n = 2 evidence-level "1–", n = 4 "2–") revealed a similar picture. Only one evidence-level "2–" combined study found no association (e12).

TABLE 1

Results in detail of higher-quality studies (selected according to evidence levels)

Study	Evidence level	Statement
Lundgren et al. (2008) (26)	1–	• 5-Week yoga intervention (8 patients) and acceptance and commitment therapy (ACT) (10 patients) • Follow-up: seizure frequency: declined in all subjects • Pre-/post: seizure index*1: declined in ACT (p >0.01)/declined in yoga group (p >0.01) • Pre-/post: quality of life: improved in ACT group in the WHOQOL-BREF*2 (p <0.01)/ improved in yoga group in the SWLS*2 (p <0.05)
Sathyaprabha et al. (2008) (27)	1–	• 10-Week yoga intervention (18 patients) and exercise therapy (simple exercises) (16 patients) • Pre-/post: seizure frequency scores: improved in yoga group (p = 0.001) • Interaction effect group × time: seizure frequency (p <0.001) (reduced in yoga group and increased in exercise therapy group)
McAuley et al. (2001) (30)	1–	• 12-Week combined training (cardiovascular and strength training) (14 patients) and a control group with no intervention (9 patients) • During intervention: seizure frequency: training group: n = 10 were and remained seizure-free; n = 4 with active epilepsy, of which n = 2 experienced no change, n = 1 an increase, n = 1 a decline/control group: n = 6 were and remained seizure-free; n = 3 with active epilepsy, of which n = 1 experienced no change, n = 1 an increase, n = 1 a decline • Pre-/post: quality of life: improved in training group (overall questionnaire score, domains: physical function [p = 0.02], self-perceived health [p = 0.05], energy/fatigue [p = 0.02], role limitation [positive trend])/improved in control group (domain: energy/fatigue [p <0.01])
Fialho et al. (2017) (11)	2+	• One-time treadmill exercise (Bruce protocol), patient group (n = 30) and healthy control group (n = 30) • Control group: higher peak heart rate (p = 0.002), longer exercise duration (p = 0.004), higher metabolic equivalent during exercise (p = 0.006), greater distance covered (p = 0.007), higher end-exercise level (p = 0.004), higher Duke score (p = 0.02), higher rate pressure product (p = 0.03) • Chronotropic incompetence more prevalent in epilepsy group (p <0.001)
Nyberg et al. (2013) (15)	2+	• Epidemiological study with 1 173 079 male conscripts aged 18 and over and follow-up of up to 40 years • 6796 (0.6%) developed epilepsy • Low and moderate cardiovascular fitness (at 18 years) were associated with an increased risk of developing epilepsy (hazard ratio: 1.79; 95% CI: [1.57; 2.03]*3 and hazard ratio: 1.36; 95% CI: [1.27; 1.45]*3) • Having one or more brothers with epilepsy doubles one's own risk of developing the disorder (fitness remained a significant predictor of developing epilepsy)

*1 (Seizure frequency × seizure duration)
*2 Survey instrument: World Health Organization Quality of Life instrument, short version (WHOQOL-BREF); Satisfaction with Life Scale (SWLS)
*3 Adjusted for calendar year, body mass index (BMI), region, test center, parental education; absolute values were not reported
CI, confidence interval

Altogether, 21 studies investigated the effect of physical activity or one-time exertion on seizure frequency. Two studies reported no seizures during a one-time physical activity (22, 23) (evidence level "2–"). In three studies, a reduction in epileptiform discharges during physical exercise testing was achieved (2, 24, 25) ("2–" n = 1; "3" n = 2). However, two of these studies found a rebound effect, with an increased number of discharges during the recovery phase compared to the resting phase (24, 25). Two interventional studies ("1–") found a statistically significant reduction in seizures as a result of completing the exercise program in the epilepsy exercise groups (p <0.01; p <0.001) (26, 27). A survey-based study identified a statistically significant association between increased physical activity and a reduced number of seizures (p <0.05) ("3") (e13). One further study revealed a trend towards a correlation between a higher frequency of seizures and lower physical activity ("2–") (5).

Three survey-based studies reported a heterogeneous picture in terms of the effect of physical activity on seizures, with sports triggering seizures in some patients and not in others ("2–" n = 2; "3" n = 1) (6, 8, 28). The effect of physical activity on seizure frequency was similarly inconsistent in four interventional studies ("1–" n = 1, "2–" n = 3) (29–32). In summary, a total of 49 patients (with focal and/or generalized epilepsy) took part in three of these studies (29–31). The frequency of seizures remained unchanged by the intervention in 12 subjects. Frequency during/after training diminished in 25 subjects and rose in 12. A further interventional study ("2–") identified no change in seizure frequency in the exercise group following a Kempo karate program (33). Four case studies described only individuals in whom sports/physical activity induced seizures ("3") (34–37). The *eResults* section provides the study results in greater detail. The results of studies with the highest level of evidence ("1–"

TABLE 2

Evidence level results

Evidence levels	Type of study	Studies
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with an extremely low risk of bias	
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias	
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias	• Intervention: (26, 27, 30)
2++	High-quality systematic reviews of case–control studies or cohort studies	
2+	Well-conducted case–control studies or cohort studies with a low risk of confounding or bias and moderate probability that the relationship is causal	• Epidemiological study: (15) • One-time physical effort: (11)
2−	Case–control studies or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal	• Surveys: (1, 3–6, 12, 13, 16, 17, 20) • Combined cross-section: (8, 7, 21, e12) • One-time physical activity: (2, 9, 10, 14, 22, 23) • Interventions: (29, 31–33, 38, 39, 40)
3	Non-analytic studies, e.g., case reports, case series	• Surveys: (28, e13); interviews: (18, 19) • One-time physical activity: (24, 25) • Case studies: (34–37)
4	Expert opinion	

RCT, randomized controlled study

and "2+") referred to in this review are additionally shown in *Table 1*.

Methodological quality assessment

The median number of points in the methodological quality assessment of the interventional studies is seven (= maximum possible number of points, highest risk).

The median number of points for the survey-based studies was four, for the combined cross-sectional studies it was 4.5, and for the studies on one-time physical activity it was four (maximum possible number of points, highest risk). The results are presented in detail in *eTables 1a and 1b*.

Evidence levels

Three of the 42 studies included are classified as evidence level "1−," two as evidence level "2+," 27 as evidence level "2−," and 10 studies as evidence level "3" *(Table 2)*.

Discussion

Overall, 11 of 15 studies found low levels of physical activity or fitness in individuals with epilepsy. Another study highlighted the significance of physical activity at an early age in the prevention of epilepsy. A link was identified by 16 of 17 studies between physical activity and comorbidities and/or quality of life in patients with epilepsy. The available studies on the effect of physical activity on seizure frequency are heterogeneous; however, in most cases, no increase in the number of seizures was seen.

Only five studies could be classified as evidence level "1−" and "2+." However, one must bear in mind that sports intervention studies are generally unable to achieve a "1+" evidence level due to their design.

The methodological quality of all studies included is overall low across all study types. The evaluability and quality of the studies is limited due to:

- Lack of information
- Lack of randomization
- Lack of control groups
- Lack of blinding
- Lack of consideration paid to inclusion factors
- Restrictions in the recruitment strategies.

A number of limitations arise as a result of poor patient accessibility as well as the peculiarity of this group. Comparability is overall limited, particularly in the case of studies on seizure frequency, due to the differing intervention programs, exercise intensities, and duration/frequency of the programs.

In addition, most studies amalgamated various syndromes and types of seizures, which needs to be viewed critically, particularly in terms of seizure frequency, since this can differ between syndromes. Therefore, reliability in terms of the effect of physical activity on seizure frequency remains limited. Results from animal models are clearer due to the number of studies and their comparable design: physical exercise reduced the number of recurrent seizures in the majority of animals (e14).

Potential mechanisms for a possible anticonvulsive effect include increased release of hippocampal brain-derived natriuretic factor (BDNF), increased neurogenesis in the cornu ammonis 1 (CA1) region of the hippocampus, and increased sprouting of mossy

fibers (e14). Without exception, all studies included in this investigation demonstrated a positive effect for physical activity on various aspects of comorbidity and quality of life. Despite their low methodological quality, the absence of a negative effect in these studies demonstrates the relevance of exercise in this context (studies with evidence levels 1−, 2−, 3).

The occurrence of isolated cases—as well as subjective reports made by patients—suggests that sports may induce seizures or worsen seizures in general. Potential pathophysiological mechanisms could be linked to, e.g., hyperventilation-induced hypercapnia or a rise in body temperature, although systematic investigations on this mechanism are still lacking.

When providing individual counseling on safety during sports activity, one can use clearance to drive a motor vehicle as an approximate guide. As in the assessment of fitness to drive, one should take the following factors into consideration when recommending a particular activity and intensity (for example, running or cycling) (e7):

- Type of sport
- Likelihood of a seizure
- Seizure triggers (for example, strenuous activity)
- Type and severity of seizures
- Usual timing of seizures
- Individual attitude.

In case of doubt, types of sport that carry no significant risk, such as team sports, dancing, and golf, can be recommended for all patients with epilepsy. An individual risk assessment should always be carried out for moderate-risk types of sport such as alpine skiing, gymnastics, and swimming, as well as high-risk sports such as climbing, motor sports, and surfing (e7). The same applies to cycling, since here—in contrast to driving motorized vehicles (including e-bikes)—neither a clear legal basis nor guidelines are available for guidance. With cycling, however, there is a significant risk of injury, given that the cyclist is exposed in a virtually unprotected manner; therefore, patients with epilepsy should only be allowed to return to cycling following a critical consideration of their status.

As a general rule, clearance to engage in sports in or on water in epilepsy requires special evaluation due to the risk of peri-ictal drowning. Here again, individual decisions need to be made on the basis of the described factors. Having said that, Ryan and Dowling showed that, of 482 deaths from drowning among patients with epilepsy, only 25 cases were directly related to seizures (e15). Nevertheless, caution is generally advised in water sports. Tools that may be helpful in the assessment of individual risk include additional investigations such as stress EEG, although there are currently no diagnostic data available to guide clinical decision making. In general, however, the overall risk of injury in patients with epilepsy does not appear to be higher compared to healthy individuals (e5, e15)—indeed, sports-related injuries occur less frequently in epilepsy patients (e5).

Key messages

- Only a handful of studies have investigated the effects of sports and physical activity on epilepsy. Although these are often of low methodological quality, the majority demonstrate positive or neutral, and only very rarely negative, effects.
- People with epilepsy should not be discouraged as a general rule from sports, but instead encouraged to be physically active.
- Advice on the possibilities of physical activity and sports should be provided on an individual basis for people with epilepsy, whereby the type and frequency of seizures, as well as the underlying syndrome, need to be taken into consideration. Clearance to drive a motorized vehicle may serve as first guidance.
- Sports and physical activity can enhance quality of life, reduce comorbidities, and potentially have a positive effect on seizure frequency.
- When choosing a suitable type of sport, one should not only take into consideration the clinical situation of the patient, but also the risk profile of the respective sport.

Conclusion

There is no rationale to support a general ban on sports for patients with epilepsy. As a general rule, an individual risk assessment should be performed for each particular case. However, it is possible to find a type of sport with a favorable risk profile for the vast majority of patients. In this context, epilepsy rehabilitation sports groups could also offer an entry point. Despite the scant number of studies to date and the heterogeneity of their results, there is rather evidence to support the assumption that sport activity does not lead to an increase in seizures, but—if it has any effect at all—results in a reduction in the number of seizures.

Conflict of interest statement
Prof. Reinsberger received study support (third-party funds) from the Heinz Nixdorf Foundation/Westfalen Foundation and the brain@sports foundation.

The remaining authors state that they have no conflicts of interest.

Manuscript received on 14 May 2019, revised version accepted on 28 October 2019.

Translated from the original German by Christine Rye.

References

1. Elliott JO, Lu B, Moore JL, McAuley JW, Long L: Exercise, diet, health behaviors, and risk factors among persons with epilepsy based on the California Health Interview Survey, 2005. Epilepsy Behav 2008; 13: 307–15.
2. Vancini RL, de Lira, Barbosa CA, Scorza FA, et al.: Cardiorespiratory and electroencephalographic responses to exhaustive acute physical exercise in people with temporal lobe epilepsy. Epilepsy Behav 2010; 19: 504–8.
3. Hinnell C, Williams J, Metcalfe A, et al.: Health status and health-related behaviors in epilepsy compared to other chronic conditions—a national population-based study. Epilepsia 2010; 51: 853–61.
4. Ogwumike OO, Agboke MA, Adeniyi AF: Association between physical activity level and health-related quality of life of children with and without epilepsy. J Pediatr Neurol 2016; 14: 95–101.
5. Wong J, Wirrell E: Physical activity in children/teens with epilepsy compared with that in their siblings without epilepsy. Epilepsia 2006; 47: 631–9.
6. Nakken KO: Physical exercise in outpatients with epilepsy. Epilepsia 1999; 40: 643–51.

7. Jalava M, Sillanpaa M: Physical activity, health-related fitness, and health experience in adults with childhood-onset epilepsy: a controlled study. Epilepsia 1997; 38: 424–9.
8. Steinhoff BJ, Neususs K, Thegeder H, Reimers CD: Leisure time activity and physical fitness in patients with epilepsy. Epilepsia 1996; 37: 1221–7.
9. Vancini RL, de Lira CAB, Andrade MS, de Lima C, Arida RM: Low levels of maximal aerobic power impair the profile of mood state in individuals with temporal lobe epilepsy. Arq Neuropsiquiatr 2015; 73: 7–11.
10. Yerdelen D, Erol T, Koc F: Heart rate recovery in epilepsy. Int J Neurosci 2012; 122: 515–8.
11. Fialho GL, Pagani AG, Walz R, Wolf P, Lin K: Maximal/exhaustive treadmill test features in patients with temporal lobe epilepsy: search for sudden unexpected death biomarkers. Epilepsy Res 2017; 133: 83–8.
12. de Lima C, de Lira CAB, Arida RM, et al.: Association between leisure time, physical activity, and mood disorder levels in individuals with epilepsy. Epilepsy Behav 2013; 28: 47–51.
13. Gordon KE, Dooley JM, Brna PM: Epilepsy and activity—a population-based study. Epilepsia 2010; 51: 2254–9.
14. Volpato N, Kobashigawa J, Yasuda CL, Kishimoto ST, Fernandes PT, Cendes F: Level of physical activity and aerobic capacity associate with quality of life in patients with temporal lobe epilepsy. PLoS One 2017; 12: e0181505.
15. Nyberg J, Aberg MAI, Toren K, Nilsson M, Ben-Menachem E, Kuhn HG: Cardiovascular fitness and later risk of epilepsy: a Swedish population-based cohort study. Neurology 2013; 81: 1051–7.
16. Roth DL, Goode KT, Williams VL, Faught E: Physical exercise, stressful life experience, and depression in adults with epilepsy. Epilepsia 1994; 35: 1248–55.
17. Han K, Choi-Kwon S, Lee S-K: Leisure time physical activity in patients with epilepsy in Seoul, South Korea. Epilepsy Behav 2011; 20: 321–5.
18. Collard SS, Ellis-Hill C: How do you exercise with epilepsy? Insights into the barriers and adaptations to successfully exercise with epilepsy. Epilepsy Behav 2017; 70: 66–71.
19. Collard SS, Marlow C: The psychosocial impact of exercising with epilepsy: a narrative analysis. Epilepsy Behav 2016; 61: 199–205.
20. Häfele CA, Freitas MP, da Silva MC, Rombaldi AJ: Are physical activity levels associated with better health outcomes in people with epilepsy? Epilepsy Behav 2017; 72: 28–34.
21. Rauchenzauner M, Hagn C, Walch R, et al.: Quality of Life and Fitness in Children and Adolescents with Epilepsy (EpiFit). Neuropediatrics 2017; 48: 161–5.
22. de Lima C, Vancini RL, Arida RM, et al.: Physiological and electroencephalographic responses to acute exhaustive physical exercise in people with juvenile myoclonic epilepsy. Epilepsy Behav 2011; 22: 718–22.
23. Camilo F, Scorza FA, de Albuquerque M, Vancini RL, Cavalheiro EA, Arida RM: Evaluation of intense physical effort in subjects with temporal lobe epilepsy. Arq Neuropsiquiatr 2009; 67: 1007–12.
24. Esquivel E, Chaussain M, Plouin P, Ponsot G, Arthuis M: Physical exercise and voluntary hyperventilation in childhood absence epilepsy. Electroencephalogr Clin Neurophysiol 1991; 79: 127–32.
25. Nakken KO, Loyning A, Loyning T, Gloersen G, Larsson PG: Does physical exercise influence the occurrence of epileptiform EEG discharges in children? Epilepsia 1997; 38: 279–84.
26. Lundgren T, Dahl J, Yardi N, Melin L: Acceptance and commitment therapy and yoga for drug-refractory epilepsy: a randomized controlled trial. Epilepsy Behav 2008; 13: 102–8.
27. Sathyaprabha TN, Satishchandra P, Pradhan C, et al.: Modulation of cardiac autonomic balance with adjuvant yoga therapy in patients with refractory epilepsy. Epilepsy Behav 2008; 12: 245–52.
28. Ablah E, Haug A, Konda K, et al.: Exercise and epilepsy: a survey of Midwest epilepsy patients. Epilepsy Behav 2009; 14: 162–6.
29. Eriksen HR, Ellertsen B, Gronningsaeter H, Nakken KO, Loyning Y, Ursin H: Physical exercise in women with intractable epilepsy. Epilepsia 1994; 35: 1256–64.
30. McAuley JW, Long L, Heise J, et al.: A prospective evaluation of the effects of a 12-week outpatient exercise program on clinical and behavioral outcomes in patients with epilepsy. Epilepsy Behav 2001; 2: 592–600.
31. Nakken KO, Bjorholt PG, Johannessen SI, Loyning T, Lind E: Effect of physical training on aerobic capacity, seizure occurrence, and serum level of antiepileptic drugs in adults with epilepsy. Epilepsia 1990; 31: 88–94.
32. Kim J, Jung DS, Hwang KJ, et al.: Can an exercise bicycle be safely used in the epilepsy monitoring unit? An exercise method to provoke epileptic seizures and the related safety issues. Epilepsy Behav 2015; 46: 79–83.
33. Contant KD, Morgan AK, Muzykewicz D, Clark DC, Thiele EA: A karate program for improving self-concept and quality of life in childhood epilepsy: results of a pilot study. Epilepsy Behav 2008; 12: 61–5.
34. Kamel JT, Badawy RAB, Cook MJ: Exercise-induced seizures and lateral asymmetry in patients with temporal lobe epilepsy. Epilepsy Behav Case Rep 2014; 2: 26–30.
35. Ogunyemi AO, Gomez MR, Klass DW: Seizures induced by exercise. Neurology 1988; 38: 633–4.
36. Schmitt B, Thun-Hohenstein L, Vontobel H, Boltshauser E: Seizures induced by physical exercise: report of two cases. Neuropediatrics 1994; 25: 51–3.
37. Sturm JW, Fedi M, Berkovic SF, Reutens DC: Exercise-induced temporal lobe epilepsy. Neurology 2002; 59: 1246–8.
38. Eom S, Lee MK, Park J-H, et al.: The impact of an exercise therapy on psychosocial health of children with benign epilepsy: a pilot study. Epilepsy Behav 2014; 37: 151–6.
39. Eom S, Lee MK, Park J-H, et al.: The impact of a 35-week long-term exercise therapy on psychosocial health of children with benign epilepsy. J Child Neurol 2016; 31: 985–90.
40. Koirala GR, Lee D, Eom S, Kim N-Y, Kim HD: Altered brain functional connectivity induced by physical exercise may improve neuropsychological functions in patients with benign epilepsy. Epilepsy Behav 2017; 76: 126–32.

Corresponding author
Prof. Dr. med. Dr. rer. medic. Claus Reinsberger
Sportmedizinisches Institut der Universität Paderborn
Warburger Straße 100
33098 Paderborn, Germany
reinsberger@sportmed.uni-paderborn.de

Cite this as:
van den Bongard F, Hamer HM, Sassen R, Reinsberger C:
Sport and physical activity in epilepsy—a systematic review.
Dtsch Arztebl Int 2020; 117: 1–6.
DOI: 10.3238/arztebl.2020.0001

► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref0120

eResults, eTables:
www.aerzteblatt-international.de/20m0001

Supplementary material to:

Sport and Physical Activity in Epilepsy

A Systematic Review

by Franziska van den Bongard, Hajo M. Hamer, Robert Sassen, and Claus Reinsberger

Dtsch Arztebl Int 2020; 117: 1–6. DOI: 10.3238/arztebl.2020.0001

eReferences

e1. Fiest KM, Sauro KM, Wiebe S, et al.: Prevalence and incidence of epilepsy. Neurology 2017; 88: 296–303.

e2. Scheffer IE, Berkovic S, Capovilla G, et al.: ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. Epilepsia 2017; 58: 512–21.

e3. World Health Organization: Global health recommendations on physical activity for health 2010. www.who.int/dietphysicalactivity/global-PA-recs-2010.pdf (last accessed on 22 November 2019).

e4. Dubow JS, Kelly JP: Epilepsy in sports and recreation. Sports Med 2003; 33: 499–516.

e5. Téllez-Zenteno JF, Hunter G, Wiebe S: Injuries in people with self-reported epilepsy: a population-based study. Epilepsia 2008; 49: 954–61.

e6. Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM: Epilepsy, seizures, physical exercise, and sports: a report from the ILAE Task Force on Sports and Epilepsy. Epilepsia 2016; 57: 6–12.

e7. Howard GM, Radloff M, Siever TL: Epilepsy and sports participation. Curr Sports Med Rep; 3: 15–9.

e8. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336–41.

e9. Higgins JPT Altman DG (eds.): Cochrane handbook for systematic reviews of interventions. Chinester: John Wiley & Sons Ltd 2008.

e10. Hammer GP, du Prel J-B, Blettner M: Avoiding bias in observational studies—part 8 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2009; 106: 664–8.

e11. Scottish Intercollegiate Guidelines Network: SIGN 50 A guideline developer's handbook. Edinburgh: Scottish Intercollegiate Guidelines Network 2011; www.sign.ac.uk (last accessed on 4 December 2019).

e12. Whitney R, Bhan H, Persadie N, et al.: Feasibility of pedometer use to assess physical activity and its relationship with quality of life in children with epilepsy: a pilot study. Pediatr Neurol 2013; 49: 370–3.

e13. Denio LS, Drake ME Jr, Pakalnis A: The effect of exercise on seizure frequency. J Med 1989; 20: 171–6.

e14. Iqbal M, Rahman MS, Zafar S, Chen X-L, Liu J-X, Liu Y: Systematic review and meta-analysis of the efficacy of different exercise programs in pilocarpine induced status epilepticus models. Epilepsy Behav 2017; 73: 256–67.

e15. Ryan CA, Dowling G: Drowning deaths in people with epilepsy. CMAJ 1993; 148: 781–4.

eRESULTS

Results in Detail

Physical activity in patients with epilepsy

Elliott et al. (1) showed, on the basis of a survey of 5506 individuals (epilepsy group [EG] n = 97, healthy control group [hCG] n = 5409) using the Ohio Behavioral Risk Factor Surveillance System, that 58.1% of patients with epilepsy and 76.1% of healthy controls had been physically active in the preceding months. Similarly, the investigation by Vancini et al. (2) showed the activity level in leisure time to be 14.8% higher in the hCG (n = 19) compared to the patient group (n = 19).

Computer-assisted interviews carried out as part of the Canadian Community Health Survey with 2555 patients with epilepsy and 400 055 controls revealed that 58.3% of patients and 49.7% of the general population were physically inactive (3).

A comparison between healthy individuals in the Norwegian population (n = 2336) and patients with epilepsy (n = 204) showed a significant difference, with a larger proportion of inactive individuals found in the EG ($p < 0.005$) (6).

Ogwumike et al. (4) surveyed 60 children with epilepsy and 60 healthy children. A comparison of their activity levels yielded a significant difference between groups (Chi^2 test, $p = 0.032$). The majority of children in both groups were moderately active (EG n = 46; hCG n = 49), whereas the percentage of less active children in the EG was higher (n = 12 versus n = 4) and the percentage of highly active children in this group was lower (n = 2 versus n = 9).

Wong et al. (5) surveyed 79 children with epilepsy, without motor or sensory impairments, as well as 99 healthy siblings and their parents. Children with epilepsy were less physically active in terms of general sports habits and group sports activities compared to their siblings.

Three survey-based studies that compared patients and healthy subjects (n = 31, n = 31 [12]; n = 341, n = 53 210 [13]; n = 38, n = 20 [14]) found no difference between groups in terms of activity habits.

Physical fitness was also lower in EGs compared to hCGs (7–9). The study conducted by Yerdelen et al. (10) found significant differences in terms of increased heart rate recovery (after 1 min $p = 0.001$, after 3 min $p = 0.027$) and lower maximum blood pressure ($p = 0.036$) between patient group and control group. In addition, Fialho et al. (2017) (11) found differences in reactions to a maximal treadmill test for the following parameters:

- Maximum heart rate
- Duration of exercise
- Metabolic equivalent (energy consumption)
- Distance covered on the treadmill
- Duke score (treadmill score to predict prognosis in coronary heart disease) (lower risk scores in the hCG) and
- Chronotropic incompetence (more frequent in the EG).

An epidemiological study conducted by Nyberg et al. (15) on 1 173 079 male conscripts over a follow-up period of 40 years yielded the observation that low and moderate cardiovascular fitness early in life (at age 18) could potentially be associated with epilepsy in later life (hazard ratio 1.79; 95% confidence interval [CI]: [1.57; 2.03]/adjusted for calendar year, body mass index, region, test center, parental education: hazard ratio: 1.36; 95% CI: [1.27; 1.45]/absolute values were not reported).

Comorbidities and physical activity

In a study conducted by Vancini et al. (9), 20 patients with temporal lobe epilepsy (TLE) and 20 control subjects underwent one-time maximal incremental testing. The authors reported a significant negative correlation ($p = 0.0460$, $r = -0.31$) between the domain tension/anxiety (significantly higher scores in the EG: $p = 0.0223$), profile of mood states evaluation, and maximum oxygen uptake (VO_2max) (significantly lower in the EG: $p = 0.0361$).

De Lima et al. (12) investigated 31 individuals with epilepsy (generalized tonic-clonic seizures [GTC] n = 13, focal aware seizures [FAS] n = 10, focal impaired awareness seizures [FIAS] n = 8) and 31 control subjects. Correlation analysis showed a significant association between the overall score in the Beck Depression Inventory (BDI) and physical

activity in leisure time ($p < 0.005$, $r = -0.35$), as well as between anxiety levels in the State-Trait Anxiety Inventory and activity in leisure time ($p < 0.015$, $r = -0.30$). There were no differences between the groups in terms of leisure activities. Significant differences between the groups, with higher scores in the EG in each case, were registered not only for the Beck Depression Inventory ($p = 0.02$), but also for state anxiety ($p = 0.01$) and anxiety level ($p = 0.02$) in the State-Trait Anxiety Inventory.

A comparison of active and inactive patients with epilepsy (n = 178) (TLE: n = 105, frontal lobe epilepsy = 13, occipital lobe epilepsy n = 8, parietal lobe epilepsy n = 22, generalized epilepsy [genEpi] n = 30) revealed that inactive individuals have higher levels of anxiety and are more susceptible to depression (17). Roth et al. (16) also reported an association between regular physical activity and BDI scores ($p < 0.01$, $r = -0.23$). A total of 133 patients with epilepsy (n = 93 = inactive, n = 40 = active) were investigated. Inactive patients had significantly higher BDI scores ($p = 0.01$). Furthermore, Volpato et al.'s results show that active compared to inactive patients have a higher quality of life ($p = 0.04$) (World Health Organization Quality of Life instrument [WHOQOL-BREF]) (14).

In two interview-based studies, four (19) and eleven (18) patients with epilepsy were interviewed. In summary, the statements made by the respondents show that sport enhances quality of life (19) and has a positive effect on physical and mental health (18).

Ogwumike et al. (4) demonstrated a significant correlation between activity levels and health-related quality of life in 60 children with and 60 children without epilepsy. This was determined in the EG for the areas physical function ($p = 0.001$, $r = 0.428$), social problems ($p = 0.002$, $r = 0.397$), and school performance ($p = 0.005$, $r = 0.359$). The overall scores for psychosocial health ($p = 0.002$, $r = 0.391$) and pediatric quality of life inventory (PedsQL) ($p = 0.001$, $r = 0.421$) were also recorded. The groups differed significantly in terms of activity levels ($p = 0.032$) and in five of six areas (not emotions) also in terms of health-related quality of life.

Whitney et al. (e12) found no association between the daily number of steps and the factors quality of life, enjoyment of physical activity, athletic skills, self esteem, depression, and stress in eight children with epilepsy and their parents (focal epilepsy [focEpi] n = 5, genEpi n = 3). On the basis of (unadjusted) linear regression, Hfele et al. (20) showed a significant negative association between physical activity and depression ($p = 0.046$), state of anxiety ($p = 0.014$), and trait of anxiety ($p = 0.015$), as well as a positive association with quality of life ($p < 0.001$) in 101 individuals with epilepsy. Rauchenzauner et al. (21) found a significant link between the 6-min walk test and mental wellbeing in children with epilepsy (n = 48) ($p = 0.014$, $r = 0.406$), but not in the hCG.

Contant et al. (33) held a Kempo karate program over 10 weeks with nine children with epilepsy (FAIS n = 5, GTC n = 2, absence epilepsy n = 2). Based on the parent questionnaire, a positive, but not significant, trend was seen in all health-related domains of the Quality of Life in Childhood Epilepsy questionnaire. Furthermore, the research group led by Eom et al. conducted two studies (38, 39), each with 10 children with benign epilepsy and centrotemporal spikes; the children took part in a program consisting of activities such as basketball, table tennis, and a parent–child dance, twice weekly over 5 weeks combined with home-based exercises (38), as well as in a further program once weekly over 5 weeks, followed by 30-week home-based exercises (39). Psychological functioning in the area of emotional and psychosocial adjustment were improved following the shorter intervention (38) and in neurocognitive function and quality of life following the longer intervention (39).

A 15-week exercise program (warm-up, aerobic dancing, cool down, stretching, strength training, and relaxation) with 15 women (dropout n = 1) (focEpi n = 12, genEpi n = 3) was unable to achieve a significant change in psychological/social difficulties, anxiety, depression, and locus of control. However, overall health complaints, as determined using the Ursin Health Inventory, were significantly reduced (ANOVA: $F = 9.61$, df 2.24, $p = 0.0008$) (29). In another study, 18 patients (GTC n = 12, myoclonic seizures n = 3, FAIS n = 5, absence seizures n = 1) were assigned to either Acceptance and Commitment Therapy (ACT, a form of psychotherapy) or a yoga intervention, with both groups receiving treatment over a 5-week period. Quality of life was measured using two questionnaires: the Satisfaction with Life Scale (SWLS) and WHOQOL-BREF. A significant improvement was seen following the intervention in quality of life in both groups as measured by one of the two quality-of-life instruments (ACT WHOQOL-BREF $p < 0.01$; yoga SWLS $p < 0.05$) (26). A 12-week intervention consisting of a combination of cardiovascular and strength training achieved an

improvement in mood and quality of life in a sample of 23 patients (GTC, FAIS, FAS; randomized to an exercise group [EG] and an exercise control group [eCG]) in the EG (30).

Seizure frequency

In a survey of 207 patients with epilepsy, 11% reported experiencing seizures in over 10% of the training sessions they took part in, while 36% reported better seizure control through regular exercise and 11% worse control. A total of 53% had never experienced activity-induced seizures (6). In another study, 36 of 136 surveyed patients with epilepsy reported that they had experienced seizures during sports (8), as did 56.3% of 193 respondents in another questionnaire-based study (28).

Four case studies described altogether 17 patients who experienced seizures during physical exertion (34–37). The seizures occurred during particular types of activity (running/walking n = 5 ; cycling n = 6; netball n = 1; line dancing n = 1; weightlifting n = 1; martial arts n = 1; swimming n = 1) or at certain intensities (strenuous n = 8; light n = 1). Respondents comprised children, adults, and senior citizens.

In two studies, no seizures occurred in 17 TLE patients (23) nor in 12 patients with juvenile myoclonic epilepsy (22) during and following one-time strenuous physical effort. In a further study, Vancini et al. (2) reported a drop in the number of epileptiform discharges during exertion (0.18 ± 0.10 discharges/min) and in the recovery phase (0.26 ± 0.12/min) compared to measurements at rest (1.0 ± 0.5/min) on average for all 19 TLE patients investigated. The number of discharges between resting and exertion fell by 82% and by 74% between resting and recovery. Nakken et al. (25) made similar findings in the context of exercise in children (n = 26) (symptomatic focEpi n = 7; rolandic epilepsy n = 1; cryptogenic focEpi n = 8; idiopathic genEpi n = 9; Lennox-Gastaut syndrome n = 1). None of the patients experienced seizures during the test. Focal epileptiform discharges decreased in 20 patients during exercise and a rebound increase was seen in 17 patients following exercise.

Esquivel et al. (24) performed a one-time physical exercise test in children with absence epilepsy (n = 12). Seizures occurred during rest (n = 6; average number of absences: 1.3/child for the whole group), during physical exercise (n = 3; number: 0.6/child), in the recovery phase (n = 5; number: 3.2/child), and in the hyperventilation phase (n = 9; number: 2.1/child). However, the children with a high number of seizures during the test also had a high frequency of daily seizures.

A survey of 79 children with epilepsy revealed a trend in terms of an association between a higher seizure frequency and lower physical activity (5). Denio et al. (e13) showed a significant association between higher physical activity and lower seizure frequency ($Chi^2 = 16.457$, df = 3, $p < 0.05$).

A total of seven interventional studies investigated the effect of exercise or sports on seizure frequency. A short-term ACT (n = 10; $p < 0.01$) or yoga intervention (n = 8; $p < 0.01$) significantly reduced the seizure index (seizure frequency × seizure duration). Due to pretest differences, change scores were calculated, revealing a stronger change in the ACT group (26).

A yoga intervention (n = 18: genEpi n = 3, focEpi n = 15) also produced a significant reduction in seizures ($p < 0.001$; pre- = 7.2 ± 1.31, post- = 5.7 ± 0.91). No change was observed in the eCG (sitting and simple physical exercises) (n = 16: genEpi n = 3, focEpi n = 13) (27).

During combined training with 14 women (dropout n = 1) (focEpi n = 12, genEpi n = 3), seven subjects experienced a total of 27 seizures during the 30 training sessions. The remaining seven subjects experienced no seizures. The majority of seizures occurred during aerobic dancing or cool down. A comparison of seizure frequency before and after the intervention revealed that the weekly frequency declined in 10 patients and rose in four. A median for seizures per week was calculated for 13 patients, with a decline from 2.9 (prior to the intervention) to 1.7 (during the intervention) (29).

A 10-week Kempo karate program with nine children with epilepsy (FAIS n = 5, GTC n = 2, absences n = 2) failed to affect seizure frequency (33).

Following a 12-week combined strength and endurance exercise program with 14 subjects (GCT FIAS, FAS) and an eCG (n = 9; GCT, FAIS, FAS), 10 patients in the exercise group, as well as six in the eCG, were and remained seizure-free. Of the four patients with active epilepsy in the exercise group (eCG n = 4), seizure frequency remained unchanged in two subjects (eCG n = 2), rose in one subject (eCG n = 1), and declined in the other subject (eCG n = 1). No subjects experienced seizures during exercise (30).

Kim et al. (2015) reported seizures in only 11 (FAIS n = 9, epileptic aura n = 1, myoclonic seizure development to GTC n = 1) of 350 patients while riding an exercise bike (minimum of 1 h training/day). Seven of the 11 subjects experienced one seizure while riding the exercise bike, two subjects experienced two seizures, and two subjects four seizures (32).

Another 4-week training program, consisting of a variety of activities such as, e.g., jogging, volleyball, and horse riding, was conducted with 21 epilepsy patients (genEPi n = 6, focEPI n = 15). Two thirds of patients had more seizures in the 4 inactive weeks during their stay at the epilepsy center, while a third had more seizures in the 4 weeks during training. The majority of seizures during the training phase occurred at rest. Of the 21 patients, 15 had no seizures during training. No predominance was observed for an epilepsy syndrome or type of seizure, nor was an association between the type of activity or pulse rate seen in the six subjects that experienced 2–30% of the seizures during the training period (31).

As part of another intervention, quantitative EEG changes were investigated in eight children with benign epilepsy and centrotemporal spikes before and after a 5-week intervention comprising basketball and table tennis, as well as a parent–child dance combined with home-based exercises. Increased cortical power in the right temporal regions for the alpha band were observed following the intervention (40).

eTABLE 1a

Methodological quality assessment of the interventional studies according to the risk-of-bias principle

Study (year)	Randomization (selection bias)	Allocation (selection bias)	Blinding of personnel (performance bias)	Blinding of subjects (detection bias)	Incomplete data (attrition bias)	Selective reporting (reporting bias)	Other bias	Overall score
Contant et al. (2008) (33)								7
Eom et al. (2014) (38)								6
Eom et al. (2016) (39)								6
Kim et al. (2015) (32)								7
Koirala et al. (2017) (40)								7
Eriksen et al. (1994) (29)								6
Lundgren et al. (2008) (26)								6
McAuley et al. (2001) (30)								7
Nakken et al. (1990) (31)								7
Sathyaprabha et al. (2008) (27)								7

Color coding:
No risk = zero points
Unclear risk = one point
High risk = one point

eTABLE 1b

Methodological quality assessment of the survey-based studies, combined cross-sectional studies, and studies on one-time physical effort based on Hammer et al. (2009) (e10)

Study (year)	Selection bias	Information bias	Measurement errors	Confounding	Other bias	Overall score
Ablah et al. (2009) (28)						5
de Lima et al. (2013) (12)						4
Denio et al. (1989) (e13)						5
Elliott et al. (2008) (1)						3
Gordon et al. (2010) (13)						3
Häfele et al. (2017) (20)						4
Han et al. (2011) (17)						4
Hinnell et al. (2010) (3)						3
Nakken (1999) (6)						5
Ogwumike et al. (2016) (4)						4
Roth et al. (1994) (16)						4
Wong et al. (2006) (5)						4
Jalava et al. (1997) (7)						5
Rauchenzauner et al. (2017) (21)						4
Steinhoff et al. (1996) (8)						5
Whitney et al. (2013) (e12)						4
Camilo et al. (2009) (23)						4
de Lima et al. (2011) (22)						4
Esquivel et al. (1991) (24)						4
Fialho et al. (2017) (11)						3
Nakken et al. (1997) (25)						5
Vancini et al. (2010) (2)						5
Vancini et al. (2015) (9)						5
Volpato et al. (2017) (14)						4
Yerdelen et al. (2012) (10)						4

Color coding:
No risk = zero points
Unclear risk = one point
High risk = one point

Epilepsy & Behavior 135 (2022) 108869

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Fitness, performance, and cardiac autonomic responses to exercise in people with epilepsy

Franziska van den Bongard, Jessica Coenen, Claus Reinsberger *

Institute of Sports Medicine, Paderborn University, Germany

ARTICLE INFO

Article history:
Received 22 February 2022
Revised 28 April 2022
Accepted 29 July 2022

Keywords:
Epilepsy
Autonomic Nervous System
Exercise
Fitness
Cardiac
Electroencephalography

ABSTRACT

People with epilepsy (PWE) are less fit and have an increased risk of sudden cardiac death. Imbalances within the autonomic nervous system (ANS) are believed to mediate some of those effects. However, results are mostly derived from patients whose seizures are refractory to medical therapy. In this study, an exhaustive bicycle ergometer test was delivered to 25 PWE (19 seizure free in the last 6 months) recruited in a community-based setting and 25 age-, sex-, and BMI-matched healthy controls. During the exercise test a 12-channel ECG was recorded and spirometry was carried out to determine the maximal oxygen uptake (VO_2peak) as the gold standard to assess fitness. Before and after exercise, heart rate variability (HRV) and electrodermal activity (EDA) were measured along with an electroencephalogram (EEG). Blood samples were collected to determine anti-seizure drug (ASD) serum levels and physical activity of daily living was evaluated via the International Physical Activity Questionnaire (IPAQ). People with epilepsy and healthy controls were similarly fit and physically active. However, PWE had a lower maximum heart rate, a lower heart rate reserve, and a lower chronotropic index. The ratio between low- to high-frequency HRV changes (LF/HF ratio) was lower in PWE. Two patients with idiopathic genetic epilepsies revealed generalized interictal epileptiform discharges only after, but not before exercise. However, post-exercise EEG measurement was three times longer than pre-exercise and those patients did not report exercise induced seizures in the history. Besides epileptogenesis, anti-seizure medications may also contribute to those autonomic differences.

1. Introduction

People with epilepsy (PWE) are described to be less physically active and fit compared to healthy people [1]. Additionally, under physical exhaustion they do not only reveal a lower maximum heart rate (HR) and chronotropic incompetence, but also signs for an increased risk of sudden cardiac death [2]. However, these results are mostly derived from patients with refractory epilepsy [2–4], although these may only account for approximately 30% of all PWE [5]. Whether reduced fitness and physical activity affects all PWE and contributes to a potentially worse health status is not clear.

Chronotropic incompetence and a reduced performance on treadmill testing in people with temporal lobe epilepsy might even be associated with an increased risk of sudden cardiac death [2]. Regulation of HR and subsequently the development of chronotropic responses are regulated by the autonomic nervous system (ANS) [6]. Since PWE often suffer from (ictal [7,8] and interictal [9,10]) dysautonomia, with imbalance between sympathetic and parasympathetic activity within the ANS [7,11], it might be assumed that epileptogenicity could disturb central ANS regulation [7].

Consequently, exercise testing might be a possibility to investigate autonomic regulation in PWE, because cardiac and other organ responses to physical activity are modulated by the ANS [12].

The aim of this study was to investigate cardiac autonomic responses to exercise and fitness levels of a representative sample of PWE with respect to seizure control, undergoing an exhaustive standardized bicycle ergometer test. Additionally, association of physical exhaustion and seizures as well as clinical EEG abnormalities were investigated.

2. Material and methods

2.1. Subjects

The study was conducted between July 2018 and December 2021 and in accordance with the Declaration of Helsinki. Study

* Corresponding author at: Institute of Sports Medicine, Paderborn University, Warburger Straße 100, 33098 Paderborn, Germany.
E-mail address: reinsberger@sportmed.uni-paderborn.de (C. Reinsberger).

https://doi.org/10.1016/j.yebeh.2022.108869
1525-5050/

protocol and informed consent were approved by the ethics committee of the Westfalian Medical Board. Written informed consent to participate in the study was obtained by each participant before enrollment. Prior to the start of the study, the trail was registered at the German Clinical Trails Register (DRKS00014822). Participants were recruited via pharmacies, physicians, local hospitals, and direct communication.

Patients with all types of epilepsy and healthy adults without seizure history between 18 and 60 years were included. Exclusion criteria were physical impairments that limit the conduction of an exercise test on bicycle ergometer, acute infections, severe heart diseases (ischemic or structural), and moderate to severe hypertension. Participants were interviewed via phone to assess eligibility. Healthy adults were then matched with patients according to age, sex, and body mass index (BMI).

The individual physical activity level was assessed by the International Physical Activity Questionnaire (IPAQ). Blood samples of PWE were obtained to determine anti-seizure drug (ASD) serum levels at the time of exercise.

2.2. Incremental exercise test

The exhaustive exercise test was performed on a bicycle ergometer (Excalibur, Lode) using a standardized protocol starting with a warm-up for 2 min at 24 W, followed by an increment of 12 W per minute until complete subjective exhaustion. After individual exhaustion, participants cooled down at 24 W for 2 min. Revolutions per minute (rpm) were as follows: 50–60 rpm at 24–60 W, 60–70 rpm at 60–100 W, and 70–90 rpm at >100 W. During exercise test, 12-lead ECG (Custo cardio 100 BT, Custo Med) was recoded. Blood pressure was discontinuously manually measured along with the rate of perceived exhaustion. During the exercise test, spirometry (Metalyzer 3B, Cortex) was carried out. After exercise test, individual exhaustion was tested based on ventilatory, metabolic, cardiovascular, and performance criteria.

2.3. Resting state measures

Before and after exercise testing, a resting state measurement in supine position in a darkened room was conducted. Post-exercise recordings started about 10 min (655.4 ± 98.8 s) after the end of the cool down period on bicycle ergometer. Autonomic parameters were derived of five-min recordings of a 1-lead ECG (Brain Products GmbH) and a Galvanic Skin Response Module (GSR, Brain Products GmbH), which was placed on the index and middle finger of the non-dominant hand. Before and after exercise, a clinical electroencephalography (EEG) (actiCHamp, 24 electrode recordings clinically analyzed (10–20 system), Brain Products GmbH) was obtained. Impedance was kept below 25 kΩ and data were sampled at 1000 Hz. Ground electrode was FPz and reference electrode FCz.

2.4. Parameters and analysis

Sympathetic autonomic activity was investigated by electrodermal activity (EDA) and measured by the GSR Module. Signal was down sampled to 250 Hz, a moving average (window size 91 points) applied (BrainVision Analyzer 2.1.2 (Brain Products GmbH)) and meanEDA calculated.

Heart rate variability (HRV) parameters were measured by 1-lead ECG. R-peak detection was conducted in BrainVision Analyzer 2.1.2 (Brain Products GmbH). RR-Intervals were exported to Kubios® HRV Standard 3.1.0. Data were checked for artifacts using threshold-based artifact correction algorithm in Kubios®. Medium threshold was applied [13] and used if artifacts were detected. Kubios® was also subsequently used to calculate HRV indices. Root mean square of the successive differences (RMSSD) and high-frequency (HF) power were calculated as parameters of the parasympathetic branch of the ANS. Low-frequency (LF) power, LF/HF ratio, and HR were analyzed indicating both sympathetic and parasympathetic activities.

Resting EEG was interpreted by a board-certified epileptologist (CR) who was blinded for clinical information of each recording. BrainVision Analyzer (Version 2.1.2, Brain Products GmbH) was used for EEG inspection. 10 min pre-exercise and 32 min post-exercise were recorded and analyzed. Data were down sampled to 250 Hz and a Zero Phase Shift Butterworth Filter (low cutoff at 1 Hz, high cutoff at 60 Hz) as well as a notch filter (50 Hz) were applied.

Maximum HR, recovery HR, relative VO_2peak (ml/min/kg), peak systolic blood pressure, maximum Watt/kg, duration of exercise, maximum rate of perceived exhaustion (RPE), maximum metabolic equivalent of task (MET), chronotropic index, heart rate reserve, and double product were determined to assess effects of the exercise intervention. Chronotropic indices ((peak heart rate − rest heart rate)/(208 − (0.7 * age) − rest heart rate) or (peak heart rate − rest heart rate)/(220 − age − rest heart rate)) were calculated following Fialho et al. [2] using Tanaka's [14] as well as Karvonen's formula [15] for age predicted HR calculation.

2.5. Statistical analysis

Shapiro–Wilk was used to test for normality of data distribution and Levene-Test for equal variances. Student *t*-tests for independent means were used for inter-group differences. Intra-group differences were assessed by Student *t*-tests for dependent means. If requirements for parametric tests were not fulfilled, Mann–Whitney-*U* test or Wilcoxon rank-sum test were calculated. Effect sizes were assessed by Pearson's correlation coefficient (*r*). For meanEDA and RMSSD, changes from pre to post were calculated by delta values (pre value – post value). For categorical variables, Chi square test (2 × 2 contingency table/2 × 3 contingency table) was used. If the expected frequency was <5, Fisher's exact test was used. Spearman's correlation coefficient was calculated to evaluate the relationship between ASD dosages or serum levels and main parameters. Multiple linear regression was performed to identify independent clinical predictors for fitness and performance variables. The level of significance was determined as <0.05. For statistical analysis IBM SPSS Statistics (Version 25.0.0.1) was used.

3. Results

3.1. Subjects

Twenty-five PWE and twenty-five healthy controls participated in the study. Clinical characteristics of both groups are presented in Table 1 and characterization of seizures and epilepsy in Table 2. Anti-seizure drugs with dosages and serum levels are shown in Table 3 and clinical EEG results in Table 5.

Both groups had a low incidence of hypertension, diabetes, dyslipidemia, family history of cardio-vascular diseases, and family history of epilepsy. There was no group difference for active smoking or active smoking in the past, but a significant difference regarding alcohol use with a higher consumption in the control group ($p = 0.008$). Additionally, there was no difference regarding activity levels. Most participants in both groups were highly active.

The mean disease duration was 16.78 ± 18.1 years. Most of the PWE suffered from generalized motor seizures ($n = 14$), 19 PWE were seizure free in the last 6 months. Dosages and serum levels of ASD were variable among patients. In total, patients took lamot-

Table 1
Clinical characteristics of epilepsy and control groups.

Variables	Patients (n = 25)	Controls (n = 25)	p
Age	38.4 ± 12.1	37.48 ± 12.11	[c] 0.78
BMI	26.48 ± 4.68	27.05 ± 4.97	[c] 0.68
Sex	f: 13; m: 12	f: 13; m: 12	
Hypertension	3	0	[b] 0.23
Diabetes type 1	1	0	[b] 1.00
Dyslipedemia	1	2	[b] 1.00
Active smoking	3	2	[b] 1.00
Active smoking in the past	4	7	[a] 0.30
Alcohol use	15	23	[a] 0.008**
Family history CVD	11	10	[a] 0.774
Family history epilepsy	3	4	[b] 1.00
Physical activity level			[b] 0.538
low	1	0	
moderate	6	9	
high	18	16	

*p < 0.05.
**p < 0.01.
Age, BMI: mean ± standard deviation.
Further characteristics: n.
CVD = cardio-vascular disease, f = female, m = male.
[a] Chi squared test.
[b] Fisher's exact test.
[c] Student t-test.

Table 2
Characterization of seizures and epilepsy.

Variables	Patients (n = 25)
Disease duration (yrs.)	16.78 ± 18.1
Age of disease onset (yrs.)	21.68 ± 14.44
Seizure type* (n)	
generalized motor	14
generalized nonmotor	3
focal awareness impaired	4
focal aware	3
unknown type	4
Seizure frequency (last 6 months) (n)	
seizure free	19
1–2	3
1 per month	1
1 per week	1
more than 1 per day	1
Last seizure of seizure-free patients (n = 18[1]) (days)	2979.5 ± 3113.6 (min: 356; max: 9490)
Syndromal classification	
temporal lobe epilepsy	2
idiopathic genetic epilepsies	7
juvenile absence epilepsy (2)	
juvenile myoclonic epilepsy (1)	
grand-mal epilepsy (3)	
grand-mal epilepsy on awakening (1)	
unknown	16
Etiology	
traumatic brain injury	1
genetic	2
structural change, not otherwise specified	1
radiation induced	1
unknown	20
Number of ASD (n)	
0	1
1	18
2	5
3	1

All data based on characterization of seizures and epilepsy questionnaire.
*Three patients indicated two types of seizures.
Disease duration, age of disease onset, last seizure of seizure-free patients: mean ± standard deviation.
[1] Missing data for one patient.

rigine (n = 13), levetiracetam (n = 5), valproic acid (n = 7), lacosamide (n = 2), carbamazepine (n = 3), and ethosuximide (n = 1). Eighteen patients were treated with monotherapy and five with two ASDs, one patient received three ASDs and one patient was not under medical treatment.

3.2. Fitness and performance data

There were no adverse events during, pre- or post-exercise in both groups. All participants fulfilled criteria for metabolic and subjective physical exhaustion (ventilatory, metabolic, cardiovascular, and performance criteria). There were no group differences in fitness and performance data (relative VO_2peak, max Watt/kg, max MET, exercise duration, max systolic blood pressure) (Table 4). Maximum HR (175.16 ± 13.44 vs 182.56 ± 14.75, p = 0.028, r = 0.31), heart rate reserve (95.41 ± 14.09 vs 100.04 ± 9.46, p = 0.039, r = 0.29) and chronotropic indices (Tanaka: 0.95 ± 0.12 vs 1.00 ± 0.09, p = 0.017, r = 0.33; Karvonen: 0.95 ± 0.14 vs 1.00 ± 0.09, p = 0.039, r = 0.29) differed significantly between PWE and healthy controls.

3.3. Autonomic parameters

Results of autonomic parameters are presented in Table 4.

For RMSSD, no group differences were detected pre- and post-exercise. However, RMSSD significantly decreased from pre to post in both groups (epilepsy 63.54 ± 60.24 ms vs 18.33 ± 28.33 ms, p = 0.001, r = 0.793; control 45.23 ± 30.87 ms vs 8.87 ± 6.50 ms, p = 0.001, r = 0.869). No group difference for delta RMSSD values was detected.

MeanEDA pre- and post-exercise did not differ between the groups. For both groups, meanEDA increased significantly from pre to post (epilepsy 1.43 ± 0.96 µS vs 3.40 ± 2.19 µS, p = 0.001, r = 0,869; control 1.70 ± 1.04 µS vs 2.83 ± 1.62 µS, p = 0.001, r = 0.766). No group difference for delta meanEDA values was detected.

LF power (epilepsy 1632.12 ± 2920.05 ms^2 vs 233.32 ± 669.58 ms^2, p = 0.001, r = 0.874; control 754.28 ± 717.08 ms^2 vs 90.88 ± 101.98 ms^2, p = 0.001, r = 0.853) and HF power (epilepsy 2442.96 ± 3681.95 ms^2 vs 266.08 ± 847.19 ms^2, p = 0.001, r = 0.847; control 1100.88 ± 1360.95 ms^2 vs 22.68 ± 27.55 ms^2, p = 0.001, r = 0.869) decreased significantly from pre- to post-exercise in both groups. No group differences were detected.

LF/HF ratio increased significantly from pre to post in both groups (epilepsy 1.63 ± 1.92 vs 5.29 ± 10.77, p = 0.014; r = 0.492; control 1.23 ± 1.04 vs 6.45 ± 6.25, p = 0.001; r = 0.804), but the increase in post-exercise was of a significantly larger magnitude in control subjects (p = 0.045, r = 0.284).

3.4. Clinical–epidemiological modifiers

Since there was a considerably large group of patients on lamotrigine (n = 13), a correlation analysis with respect to autonomic, fitness, and performance data was conducted for these thirteen patients. No correlation between lamotrigine dosage or serum level and autonomic, fitness or performance data was detected. However, a negative correlation between lamotrigine serum levels and mean EDA levels post-exercise almost reached statistical significance (p = 0.086, r = −0.495).

Multiple linear regression analysis (Table S2) revealed that neither seizure frequency nor generalized motor seizures were predictors for relative VO_2peak, max Watt/kg, max MET or exercise duration.

3.5. Clinical EEG

Twenty-three PWE showed no clinical changes in EEG from pre- to post-exercise. However, eight of these patients revealed similar pathological findings before and after exercise (Table 5, Table S1).

Table 3
ASD daily dosage and serum level.

ASD		Dosage (mg)				
	n	Median	Min	Max	25% percentile	75% percentile
Lamotrigine	13	300	100	400	175	100
Levetiracetam	5	1500	1500	3000	1500	1500
Valproic acid	7	1500	600	2750	600	600
Lacosamide	2	400	200	600	200	200
Carbamazepine	3	600	400	800	400	400
Ethosuximide*	1	250	250	250		

	Serum level (mg/l)						**Time ASD intake and blood sample (min)**		
	Median	**Min**	**Max**	**25% percentile**	**75% percentile**	**Reference range**	**Median**	**Min**	**Max**
Lamotrigine	5.00	1.90	10.30	3.3	1.9	3–14	265	70	491
Levetiracetam	19.00	14.80	45.90	14.8	14.8	10–40	287	203	600
Valproic acid	58	30	102	30	62.5	40–100	370	100	1063
Lacosamide	8.05	0.60	15.5	0.6	0.6	1–10	297	105	491
Carbamazepine	7.2	3.6	9.3	3.6	3.6	4–12	360	100	502

* Serum level of ethosuximide was not determined.

Apparent changes from pre- to post-exercise were detected in two patients. For both, there were no abnormalities in pre-exercise EEGs, but after exercise one patient with juvenile myoclonic epilepsy (JME) showed bursts of 3–4/s generalized spike-and-waves during wakefulness and one patient with an undetermined idiopathic genetic epilepsy (IGE) revealed a single burst of generalized spikes during sleep. None of these patients reported exercise induced seizures. All findings as well as patient characteristics are presented in the supplementary material in Table S1.

4. Discussion

Despite similar activity and fitness levels, PWE revealed a lower maximum HR, heart rate reserve, and chronotropic response to exercise when compared to age-, sex-, and BMI-matched healthy control subjects. As expected, exercise induced significant sympathetic increase (meanEDA) and parasympathetic decrease (RMSSD) in both groups. Furthermore, LF/HF ratio, a presumed marker for vagal-sympathetic effects [16], was significantly higher after exercise in the control group. No clinical complications or seizures occurred after maximal exhaustive exercise. However, two patients with IGE revealed generalized interictal epileptiform discharges (IED) after the exercise intervention, while the EEG before exercise was unremarkable.

The investigated cohort of twenty-five PWE consists of nineteen patients who were well-controlled (seizure free for more than 6 months) and six patients who did not achieve seizure freedom despite medical treatment. It therefore differs from PWE in other exercise-related studies, where mainly PWE whose seizures are drug refractory were examined [4,17–19] and (if reported) epilepsy onset und duration was longer than in our cohort [2]. With respect to seizure freedom, however, PWE in our study, might rather be representative for PWE in a community-based setting [5].

The IPAQ considers all physical activities of daily living like job-related physical activity, transportation physical activity, housework, house maintenance, caring for family, recreation, sport, and leisure time physical activity. Physical activity levels of daily living in combination with VO_2peak, as an objective metabolic measure of fitness, reflect a comprehensive individual activity and fitness profile. Previous studies detected a reduced fitness and activity level of PWE [1], whereas others did not reveal differences between patients and healthy controls [4,18,20]. The latter is in line with the results of this study and might be explained by the well-controlled epilepsy sample. Performance parameters like maximum Watt/kg, maximum MET, and exercise duration of the standardized exercise intervention were similar in PWE in comparison to control subjects in this study, which is in contrast to Fialho et al. [2].

Similar to Fialho et al. we found a significant group difference with a lower maximum HR in the epilepsy group. Since fitness is one of the main determinants of maximal HR [12], but in this study both groups were similarly fit (based on relative VO_2peak), other mechanisms specific to PWE in response to cardiac control after exercise might be the drivers for this effect. The decreased chronotropic response to exercise, measured by the chronotropic index, in PWE might support this assumption. The chronotropic index reflects the effect of fitness based on the maximum HR achieved in the exercise test, resting heart rate, and age predicted heart rate. Furthermore, the chronotropic index considers the proportion of the used heart rate reserve in the exercise test. Since (interictal) dysautonomia is a prominent feature in PWE [11,21] and specifically cardiac control might be affected by an epilepsy-associated altered regulation [22], different cardiac responses to exercise despite good fitness might indeed be related to epilepsy. So far, those autonomic alterations have mainly been described for patients with drug-resistant epilepsy, but the results of this study reveal that autonomic alteration may also be present in patients whose seizures are well controlled [23]. Therefore, it might be important that continuous care for PWE should include cardiac health, although the clinical significance of these findings still has to be determined.

Low-frequency power of the HRV reflects both sympathetic and parasympathetic ANS activity, whereas high-frequency power expresses only parasympathetic activation [24]. The ratio of both components is a presumed marker for vagal-sympathetic effects [16] indicating parasympathetic and sympathetic activation within a one organ system. According to the model presented by Shaffer et al. [24], a high ratio may reflect sympathetic whereas a low ratio signifies parasympathetic dominance. Both groups showed an increase in LF/HF ratio post-exercise, indicating a sympathetic dominance, which is expected after an exercise intervention and also in line with increased meanEDA (as a purely sympathetic marker [25]) and decreased RMSSD (as a purely parasympathetic marker [26]) in both groups. Sympathetic dominance is also present after exercise, as expected, in the epilepsy and control groups [27]. PWE, however, exhibited a lower LF/HF ratio increase after exercise in our study, but with a high standard deviation. The

Table 4
Fitness, performance, and cardiac autonomic parameters.

				Patients		Controls		*p* (ES)
				mean	SD	mean	SD	
exercise measurements	relative VO_2peak (ml/min/kg)			31.87	9.14	33.74	7.71	[a] 0.438 (0.112)
	max systolic blood pressure (mm/Hg) at exercise			180.4	28.97	175.2	36.75	[b]0.915 (0.15)
	max Watt/kg			2.73	0.84	3.00	0.70	[a] 0.238 (0.169)
	exercise duration (s)			1053.20	318.59	1209.72	333.73	[a] 0.103 (0.223)
	max MET			9.10	2.61	9.64	2.20	[a] 0.438 (0.112)
	max heart rate reserve			95.41	14.09	100.04	9.46	[b] 0.039* (0.292)
	chronotropic Index (Tanaka)			0.95	0.12	1.00	0.09	[b] 0.017* (0.336)
	chronotropic Index (Karvonen)			0.95	0.14	1.00	0.09	[b] 0.039* (0.292)
	Double Product			31693.40	5992.82	31979.20	7111.93	[b] 0.399 (0.119)
	max HR			175.16	13.44	182.56	14.75	[b] 0.028* (0.310
	HR recovery			150.87	13.48	155.43	13.18	[a] 0.233 (0.171)
resting state measurements	HR pre			62.32	11.63	64.52	10.16	[a] 0.480 (0.102)
	HR post			91.20	11.72	91.68	9.28	[a] 0.873 (0.023)
		HR pre vs post	P (ES)	[a] 0.001** (0.953)		[a] 0.001** (0.927)		
	RMSSD pre (ms)			63.54	60.24	45.23	30.87	[b] 0.567 (0.080)
	RMSSD post			18.33	28.33	8.87	6.50	[b] 0.352 (0.131)
		RMSSD pre vs post	P (ES)	[c] 0.001** (0.793)		[c] 0.001** (0.869)		
	RMSSD delta			45.20	50.45	36.36	30.88	[b] 0.846 (0.027)
	meanEDA pre (μS)			1.43	0.96	1. 70	1.04	[b] 0.308 (0.144)
	meanEDA post			3.40	2.19	2.83	1.62	[b] 0.318 (0.141)
		meanEDA pre vs post	P (ES)	[c] 0.001** (0.869)		[a] 0.001** (0.766)		
	meanEDA delta			−1.969	1.87	−1.13	0.96	[b] 0.064 (0.262)
	LF power pre (ms^2)			1632.12	2920.05	754.28	717.08	[b] 0.580 (0.078)
	LF power post			233.32	669.58	90.88	101.98	[b] 0.877 (0.021
		LF power pre vs post	P (ES)	[c] 0.001** (0.874)		[c] 0.001** (0.853)		
	HF power pre (ms^2)			2442.96	3681.95	1100.88	1360.95	[b] 0.423 (0.111)
	HF power post			266.08	847.19	22.68	27.55	[b] 0.587 (0.076)
		HF power pre vs post	p (ES)	[c] 0.001** (0.847)		[c] 0.001** (0.869)		
	LF/HF ratio pre			1.63	1.92	1.23	1.04	[b] 0.635 (0.067)
	LF/HF ratio post			5.29	10.77	6.45	6.25	[b] 0.045* (0.284)
		LF/HF ratio pre vs post	P (ES)	[c] 0.014* (0.492)		[c] 0.001** (0.804)		

*$p < 0.05$.
**$p < 0.01$.
pre = resting state measurement pre-exercise.
post = resting state measurement post-exercise.
Effect size (ES): Pearson's correlation coefficient.
MET = metabolic equivalent of task; HR = heart rate; RMSSD = root mean square of the successive differences; meanEDA = mean electrodermal activity; LF = low frequency; HF = high frequency, SD = standard deviation.
[a] *t*-Test.
[b] Mann–Whitney-*U*.
[c] Wilcoxon rank sum.

Table 5
Clinical EEG inspection pre- and post-exercise.

	Clinical EEG (n = 25)	Pre (n) [1]	Post (n) [2]
Basic rhythm	regular	19	21
	irregular	6	4
	beta waves	24	25
	slowing	1	0
Sleep stage	awake	25	24
	stage 1	25	24
	stage 2	3	8
IED	focal	1	1
	generalized	3	5
Regional activity changes	none	22	22
	theta-slowing	2	2
	delta-slowing	0	1
	breach rhythm	1	1
Interpretation	pathological EEG	8	10
Change due to exercise	EEG finding of post-exercise different to pre-exercise		2 (gen. IEDs)

IED = interictal epileptiform discharge; gen = generalized.
[1] 10 min.
[2] 32 min (n = 2 only 10 min post-exercise recording).

lower ratio might be associated with epilepsy (or otherwise) related reduced sympathetic drive or sympathetic exhaustion. However, the lower maximum HR, lower heart rate reserve, and lower chronotropic indices in PWE might also play a role here.

Influence of clinical characteristics of epilepsy like seizure frequency and generalized motor seizures on fitness and performance parameters were tested by linear multiple regression analysis. No seizure-related predictors for these variables were found. These findings are in contrast to Fialho et al. [2] but could again be explained by the rather well-controlled sample in this study.

Besides epileptogenesis the described autonomic alterations in response to exercise could also be caused by other clinical factors. ASD and especially Na-channel blockers may affect autonomic and especially cardiac responses [28]. In this study, a larger group of PWE were taking lamotrigine, justifying a subgroup analysis. No correlation between fitness or performance parameters and lamotrigine dosages or serum levels was detected, but higher lamotrigine serum levels were almost statistically significantly associated with less (sympathetic) electrodermal activation after exercise in the PWE group. Due to small numbers, further ASD subgroup analysis was not performed, but especially the influence of lamotrigine on autonomic parameters should be assessed in a larger sample in the future. Studies on the impact of ASD or ASD withdrawal on HRV support the assumption of at least a partial influence of medication on autonomic alterations [29,30]. Furthermore, results from 24 h HRV recordings show no difference between untreated PWE and healthy matched controls [31]. In addition to ASD data, autonomic alterations could also be influenced by age, sex, and circadian rhythm [32]. Although, in this study, participants were matched by age and sex.

The delivery of a completely exhaustive exercise intervention was not associated with clinical problems in the epilepsy group. No clinical adverse effects occurred to any of the patients, therefore, the exercise protocol was feasible for this group of patients. Nevertheless, in clinical care and counseling on exercise, such settings must involve the individual's medical, epilepsy, and seizure history. This is advised, although the proportion of patients in whom physical activity triggers seizures is rather low [1,33]. Furthermore, the results presented here might contribute to the effort to counsel PWE in an encouraging way when it comes to engagement in regular exercise to benefit from its positive effects [1,34].

Whether EEG in relation to a standardized exercise as a potential seizure inducing stimulus is of clinical value, may be assessed by larger clinical trials. So far, only a few studies reported on the utility of such an approach [35,36]. Generalized IEDs were found after exercise only in two patients (with JME/IGE). However, it is important to consider that the length of the resting state measurements before (10 min) and after (32 min) exercise differed significantly (as the study was not primarily designed for clinical EEG analyses). A longer inspection window might increase the probability of detecting a pathological finding, especially in JME/IGE. None of these patients reported exercise-induced seizures, in one patient IEDs after exercise appeared during sleep, while sleep was not recorded before exercise. Therefore, the clinical meaning of this finding still remains unclear. Nevertheless, considering all those limitations and the benign clinical course during exercise as well as the lack of exercise-related seizures in the history of patients, a clinical significance of those findings might not be assumed.

Several limitations of this study have to be considered. As in many previous studies, only a small number of PWE and healthy controls were recruited which might impact fitness, performance, and autonomic results. However, studies with smaller sample sizes were able to show lower fitness in PWE compared to healthy controls [19]. Additionally, the sample of PWE was heterogeneous regarding seizure type, seizure frequency, and ASDs. Although, we matched for age, the age span was quite large across the study which could explain variance in some outcomes. The only statistically significant difference between the two groups was the consumption of alcohol. Not surprisingly, PWE consume less alcohol than healthy controls. However, since alcohol might impair autonomic control, it is unlikely that this effect greatly contributed to the presented results. No familiarization with the bicycle ergometer before the exercise test was done. This might impact the performance during the test [37,38]. Subjects participated in daily life activities like walking, running, or cycling, but they were not familiar with exercise tests on a bicycle ergometer. Nevertheless, in general, exercise tests on a bicycle ergometers are well tolerated by PWE [19], which is also revealed by our results since all subjects achieved subjective and objective exhaustion without experiencing adverse events. The bicycle ergometer was chosen in favor of a treadmill because side effects like dizziness or stumbling, that could cause injuries, are avoided which makes the testing safe for inexperienced people. Furthermore and similar to previous studies, a selection bias needs to be considered, because it might be assumed that physically active PWE have a lower threshold to volunteer for a study like this.

The results of this study indicate that PWE still reveal somewhat different cardiac-autonomic responses to a strong physical stimulus despite being equally fit in comparison to matched control subjects. Exercise testing seems feasible for PWE. It could be a possible tool to investigate ANS dysfunction in PWE and may have the potential to guide assessing and prescribing exercise in PWE. These findings may guide further investigations into how sports and exercise might modify ANS alterations in PWE.

Funding

This research was in parts funded by a grant from the Heinz-Nixdorf-Westfalian Foundation.

Conflict of Interest

CR receives research support from the Heinz-Nixdorf Westfalen Foundation and the Federal Institute of Sports Sciences (Germany). He is a member of the Medical Commission of the German Soccer

Association (DFB) and serves as hygiene officer at national games for which he receives compensation. He serves as a consultant for the European Football Association (UEFA) and organizes CME and other educational activities for the Westfalian Medical Board. The other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108869.

References

[1] van den Bongard F, Hamer HM, Sassen R, Reinsberger C. Sport and physical activity in epilepsy. Dtsch Arztebl Int 2020;117(1–2):1–6. https://doi.org/10.3238/arztebl.2020.0001.

[2] Fialho GL, Pagani AG, Walz R, Wolf P, Lin K. Maximal/exhaustive treadmill test features in patients with temporal lobe epilepsy: Search for sudden unexpected death biomarkers. Epilepsy Res 2017;133:83–8. https://doi.org/10.1016/j.eplepsyres.2017.04.014.

[3] Han K, Choi-Kwon S, Lee SK. Leisure time physical activity in patients with epilepsy in Seoul, South Korea. Epilepsy Behav 2011;20(2):321–5. https://doi.org/10.1016/j.yebeh.2010.11.018.

[4] Volpato N, Kobashigawa J, Yasuda CL, Kishimoto ST, Fernandes PT, Cendes F, et al. Level of physical activity and aerobic capacity associate with quality of life in patients with temporal lobe epilepsy. PLoS ONE 2017;12(7):e0181505. https://doi.org/10.1371/journal.pone.0181505.

[5] Kwan P, Brodie MJ. Early Identification of Refractory Epilepsy. N Engl J Med 2000;342(5):314–9. https://doi.org/10.1056/NEJM200002033420503.

[6] Kawasaki T, Kaimoto S, Sakatani T, Miki S, Kamitani T, Kuribayashi T, et al. Chronotropic incompetence and autonomic dysfunction in patients without structural heart disease. Europace 2010;12(4):561–6. https://doi.org/10.1093/europace/eup433.

[7] Devinsky O. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 2004;4(2):43–6. https://doi.org/10.1111/j.1535-7597.2004.42001.x.

[8] Poh M-Z, Loddenkemper T, Reinsberger C, Swenson NC, Goyal C, Madsen JR, et al. Autonomic changes with seizures correlate with postictal EEG suppression. Neurology 2012;78(23):1868–76. https://doi.org/10.1212/WNL.0b013e318258f7f1.

[9] Horinouchi T, Sakurai K, Munekata N, Kurita T, Takeda Y, Kusumi I. Decreased electrodermal activity in patients with epilepsy. Epilepsy Behav 2019;100(Pt A):106517. https://doi.org/10.1016/j.yebeh.2019.106517.

[10] Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012;53(2):272–82. https://doi.org/10.1111/j.1528-1167.2011.03361.x.

[11] Goit RK, Jha SK, Pant BN. Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. Physiol Rep 2016;4(11):e12826. https://doi.org/10.14814/phy2.12826.

[12] Freeman JV, Dewey FE, Hadley DM, Myers J, Froelicher VF. Autonomic nervous system interaction with the cardiovascular system during exercise. Prog Cardiovasc Dis 2006;48(5):342–62. https://doi.org/10.1016/j.pcad.2005.11.003.

[13] Kaufmann T, Sütterlin S, Schulz SM, Vögele C. ARTiiFACT: a tool for heart rate artifact processing and heart rate variability analysis. Behav Res Methods 2011;43(4):1161–70. https://doi.org/10.3758/s13428-011-0107-7.

[14] Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol 2001;37(1):153–6. https://doi.org/10.1016/S0735-1097(00)01054-8.

[15] Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate: a longitudinal study. Ann Med Exp Biol Fenn 1957;35(3):307–15.

[16] Medeiros AR, Michael S, Boullosa DA. Make it easier! Evaluation of the 'vagal-sympathetic effect' in different conditions with R-R intervals monitoring. Eur J Appl Physiol 2018;118(6):1287–8. https://doi.org/10.1007/s00421-018-3855-6.

[17] Camilo F, Scorza FA, de Albuquerque M, Vancini RL, Cavalheiro EA, Arida RM. Evaluation of intense physical effort in subjects with temporal lobe epilepsy. Arq Neuropsiquiatr 2009;67(4):1007–12. https://doi.org/10.1590/s0004-282x2009000600009.

[18] de Lima C, de Lira CAB, Arida RM, Andersen ML, Matos G, de Figueiredo Ferreira Guilhoto LM, et al. Association between leisure time, physical activity, and mood disorder levels in individuals with epilepsy. Epilepsy Behav 2013;28(1):47–51. https://doi.org/10.1016/j.yebeh.2013.03.016.

[19] Vancini RL, de Lira CA, Scorza FA, de Albuquerque M, Sousa BS, de Lima C, et al. Cardiorespiratory and electroencephalographic responses to exhaustive acute physical exercise in people with temporal lobe epilepsy. Epilepsy Behav 2010;19(3):504–8. https://doi.org/10.1016/j.yebeh.2010.09.007.

[20] Gordon KE, Dooley JM, Brna PM. Epilepsy and activity–a population-based study. Epilepsia 2010;51(11):2254–9. https://doi.org/10.1111/j.1528-1167.2010.02709.x.

[21] Chen SF, Pan HY, Huang CR, Huang JB, Tan TY, Chen NC, et al. Autonomic dysfunction contributes to impairment of cerebral autoregulation in patients with epilepsy. J Pers Med 2021;11(4):313. https://doi.org/10.3390/jpm11040313.

[22] Verrier RL, Pang TD, Nearing BD, Schachter SC. The Epileptic Heart: Concept and clinical evidence. Epilepsy Behav 2020;105:106946. https://doi.org/10.1016/j.yebeh.2020.106946.

[23] Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JI. Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 2000;41(1):42–7. https://doi.org/10.1111/j.1528-1157.2000.tb01503.x.

[24] Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;5:258. https://doi.org/10.3389/fpubh.2017.00258.

[25] Posada-Quintero HF, Chon KH. Innovations in electrodermal activity data collection and signal processing: A systematic review. Sensors (Basel) 2020;20(2):479. https://doi.org/10.3390/s20020479.

[26] Shaffer F, McCraty R, Zerr CL. A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol 2014;5:1040. https://doi.org/10.3389/fpsyg.2014.01040.

[27] Gladwell VF, Sandercock GR, Birch SL. Cardiac vagal activity following three intensities of exercise in humans. Clin Physiol Funct Imaging 2010;30(1):17–22. https://doi.org/10.1111/j.1475-097X.2009.00899.x.

[28] Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003;57(1):69–75. https://doi.org/10.1016/j.eplepsyres.2003.10.012.

[29] Kennebäck G, Ericson M, Tomson T, Bergfeldt L. Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. Seizure 1997;6(5):369–75. https://doi.org/10.1016/S1059-1311(97)80036-2.

[30] Lossius MI, Eriksen JE, Mowinckel P, Gulbrandsen P, Gjerstad L. Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. Eur J Neurol 2007;14(9):1022–8. https://doi.org/10.1111/j.1468-1331.2007.01863.x.

[31] Persson H, Ericson M, Tomson T. Heart rate variability in patients with untreated epilepsy. Seizure 2007;16(6):504–8. https://doi.org/10.1016/j.seizure.2007.03.010.

[32] Vieluf S, Hasija T, Jakobsmeyer R, Schreier PJ, Reinsberger C. Exercise-induced changes of multimodal interactions within the autonomic nervous network. Front Physiol 2019;10:240. https://doi.org/10.3389/fphys.2019.00240.

[33] Arida RM, Cavalheiro EA, da Silva AC, Scorza FA. Physical activity and epilepsy: proven and predicted benefits. Sports Med 2008;38(7):607–15. https://doi.org/10.2165/00007256-200838070-00006.

[34] Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM. Epilepsy, seizures, physical exercise, and sports: A report from the ILAE Task Force on Sports and Epilepsy. Epilepsia 2016;57(1):6–12. https://doi.org/10.1111/epi.13261.

[35] Nakken KO, Bjørholt PG, Johannessen SI, Løyning T, Lind E. Effect of physical training on aerobic capacity, seizure occurrence, and serum level of antiepileptic drugs in adults with epilepsy. Epilepsia 1990;31(1):88–94. https://doi.org/10.1111/j.1528-1157.1990.tb05365.x.

[36] Ogunyemi AO, Gomez MR, Klass DW. Seizures induced by exercise. Neurology 1988;38(4):633–4. https://doi.org/10.1212/wnl.38.4.633.

[37] Hibbert AW, Billaut F, Varley MC, Polman RCJ. Familiarization protocol influences reproducibility of 20-km cycling time-trial performance in novice participants. Front Physiol 2017;8:488. https://doi.org/10.3389/fphys.2017.00488.

[38] Martin JC, Diedrich D, Coyle EF. Time course of learning to produce maximum cycling power. Int J Sports Med 2000;21(7):485–7. https://doi.org/10.1055/s-2000-7415.

Supplementary material

Table S1

Clinical characteristics of each patient

patient	age	disease duration	seizure type	seizure frequency	ASD [1] (dose[mg])	serum level ASD [mg/l]	further medication	clinical EEG pre-exercise	clinical EEG post-exercise
1	33	5	unknown	seizure free	lamotrigine (200)	3.1		normal	normal
2	23	6	generalized motor	seizure free	lamotrigine (300)	7.6	l-thyroxine desogestrel	normal	normal
3	45	40	generalized non-motor	seizure free	lamotrigine (175) valproic acid (1500)	4.7 60		normal	normal
4	35	3	generalized motor	seizure free	lamotrigine (150)	3.2		normal	normal
5	24	8	generalized motor	seizure free	levetiracetam (1500)	15.2		2x generalized 3/sec spike-wave complexes	1x generalized 3/sec spike-wave complexes
6	33	4	generalized motor	seizure free	lamotrigine (350)	6.3		normal	normal
7	48	35	generalized motor	1 seizure per week	lamotrigine (400)	10.3		normal	normal
8	55	55	generalized motor generalized non-motor	seizure free	valproic acid (2000) ethosuximide (250)	102 not determined	naproxen	normal	normal
9	41	40	unknown	seizure free	valproic acid (1000)	43		normal	normal
10	37	8	unknown	seizure free	lamotrigine (100)	3.3		normal	normal
11	48	2	focal impaired awareness	seizure free	levetiracetam (1500)	14.8		normal	normal
12	32	6	generalized motor	seizure free	levetiracetam (1500)	19		frequent spikes and sharp waves centro-parieto-occipital right	frequent spikes and sharp waves centro-parieto-occipital right

13	35	2	generalized motor	1-2 seizures in the last 6 months	no medication			1x generalized 4-5/sec spike-and-waves generalized	4x generalized polyspikes
14	24	3	generalized motor	1 seizure per month	valproic acid (600)	38		normal	3x generalized 3-4/sec spike-and-waves generalized
15	59	7	generalized motor	seizure free	valproic acid (1500)	65	atorvastatin candesartan hydrochloro thiazide bisoprolol apixaban	normal	normal
16	20	1	generalized	seizure free	levetiracetam (3000)	36	atomoxetine	6x generalized 4-5/sec spike-and-waves	17x generalized 4-5/sec generalized spike-and-waves
17	49	48	generalized motor	seizure free	valproic acid (1000) carbamazepine (400)	58 3.6		normal	normal
18	49	40	focal impaired awareness	seizure free	carbamazepine (600)	7.2	l-thyroxin iodine	mild bifrontal slowing and mild left temporal slowing	left >> right temporal mild focal slowing
19	26	5	focal impaired awareness focal aware	>1 seizure per day	lacosamide (600)	15.5	mirtazapine	mild focal slowing and breach rhythm left temporal	mild focal slowing and breach rhythm left temporal
20	27	3	focal aware visual aura	1-2 seizures in the last 6 months	levetiracetam (3000) lamotrigine (150)	45.9 4.1		mild to moderate left parieto-occipital focal slowing	mild to moderate left parieto-occipital focal slowing
21	55	1.5	focal impaired awareness	seizure free	lamotrigine (300)	8.9		normal	normal
22	33	11	unknown	seizure free	lamotrigine (200)	5.0	iodine	normal	normal

23	24	9	generalized non-motor	seizure free	lamotrigine (350)	1.9		normal	normal
24	56	52	generalized motor focal aware	seizure free	lamotrigine (400) carbamazepine (800)	7.7 9.3	candesartan	normal	normal
25	50	25	generalized motor	1-2 seizures in the last 6 months	valproic acid (2750) lamotrigine (300) lacosamide (200)	30 7.3 0.6		normal	single burst of generalized spike and spike complex with left frontal maximum during sleep

[1] ASD = anti-seizure drug

Table S2
Multiple linear regression analysis

dependent variable	independent variable	R	R^2	B coefficient (95% confidence interval)	p
relative VO_2peak	constant	0.289	0.083	35.7 (26.4 – 45.09)	0.001
	seizure-free			-5.7 (-14.8 – 3.3)	0.204
	generalized motor seizures			0.9 (-6.8 – 8.6)	0.807
max Watt/kg	constant	0.255	0.065	3.02 (2.1 – 3.8)	0.001
	seizure-free			-0.4 (-1.2 – 0.3)	0.284
	generalized motor seizures			0.1 (-0.6 – 0.8)	0.750
max MET	constant	0.289	0.083	10.2 (7.5 – 12.8)	0.001
	seizure-free			-1.6 (-4.2 – 0.9)	0.204
	generalized motor seizures			0.264 (-1.9 – 2.4)	0.807
exercise duration	constant	0.324	0.105	1097.8 (777.2 – 1418.5)	0.001
	seizure-free			-142.1 (-454.8 – 170.6)	0.356
	generalized motor seizures			138.2 (-129.1 – 405.5)	0.295

MET = metabolic equivalent of task

Experimental Brain Research
https://doi.org/10.1007/s00221-024-06792-0

RESEARCH ARTICLE

Exercise-induced central and peripheral sympathetic activity in a community-based group of epilepsy patients differ from healthy controls

Franziska van den Bongard[1] · Julia Kristin Gowik[1] · Jessica Coenen[1] · Rasmus Jakobsmeyer[1] · Claus Reinsberger[1,2]

Received: 28 September 2023 / Accepted: 22 January 2024

Abstract

Ictal and interictal activity within the autonomic nervous system is characterized by a sympathetic overshoot in people with epilepsy. This autonomic dysfunction is assumed to be driven by alterations in the central autonomic network. In this study, exercise-induced changes of the interrelation of central and peripheral autonomic activity in patients with epilepsy was assessed. 21 patients with epilepsy (16 seizure-free), and 21 healthy matched controls performed an exhaustive bicycle ergometer test. Immediately before and after the exercise test, resting state electroencephalography measurements (Brain Products GmbH, 128-channel actiCHamp) of 5 min were carried out to investigate functional connectivity assessed by phase locking value in source space for whole brain, central autonomic network and visual network. Additionally, 1-lead ECG (Brain products GmbH) was performed to analyze parasympathetic (root mean square of successive differences (RMSSD) of the heart rate variability) and sympathetic activity (electrodermal activity (meanEDA)). MeanEDA increased ($p < 0.001$) and RMSSD decreased ($p < 0.001$) from pre to post-exercise in both groups. Correlation coefficients of meanEDA and central autonomic network functional connectivity differed significantly between the groups ($p = 0.004$) after exercise. Both patients with epilepsy and normal control subjects revealed the expected physiological peripheral autonomic responses to acute exhaustive exercise, but alterations of the correlation between central autonomic and peripheral sympathetic activity may indicate a different sympathetic reactivity after exercise in patients with epilepsy. The clinical relevance of this finding and its modulators (seizures, anti-seizure medication, etc.) still needs to be elucidated.

Keywords Autonomic nervous system · Functional connectivity · Exhaustive exercise · Seizure-free · Epilepsy

Abbreviations

PWE	Patients with epilepsy
ANS	Autonomic nervous system
HRV	Heart rate variability
RMSSD	Root mean square of successive differences
EDA	Electrodermal activity
PLV	Phase locking value
EEG	Electroencephalography
CAN	Central autonomic network
VIS	Visual network
ASD	Anti-seizure drug

Editorial Responsibiility Matthew Heath.

This article is to bepublished as part of the Topical Collection entitled "Exercise-Related Changes to Brain: From Physiology to Behaviour" in Experimental Brain Research.

✉ Claus Reinsberger
reinsberger@sportmed.uni-paderborn.de

[1] Institute of Sports Medicine, Paderborn University, Warburger Straße 100, 33098 Paderborn, Germany

[2] Division of Sports Neurology & Neurosciences, Department of Neurology, Mass General Brigham, Harvard Medical School, Boston, MA, USA

Introduction

Sympathetic activation and parasympathetic deactivation are typical responses of the autonomic nervous system (ANS) to exhaustive exercise. While these cardiovascular and ventilatory adaptations are mainly driven by the central autonomic network (CAN) (Fu and Levine 2013), peripherally obtained ANS parameters like heart rate variability (HRV) or electrodermal activity (EDA) allow an objective assessment

Published online: 29 March 2024

of distinct sympathetic (EDA) and parasympathetic (root mean square of successive heart beat differences (RMSSD)) activity. Consequently, EDA increases (Posada-Quintero and Chon 2020) and RMSSD decreases during exercise (Shaffer et al. 2014).

In epilepsy, one of the most prevalent neurological diseases (Fiest et al. 2017), sympathetic/parasympathetic balance within the ANS is shifted towards sympathetic activation (Chroni et al. 2009; Mativo et al. 2010; Poh et al. 2012) both during and between seizures (Goit et al. 2016; Horinouchi et al. 2019; Lotufo et al. 2012; Poh et al. 2012; Sarkis et al. 2015; Vieluf et al. 2021). Although this change is most likely driven by CAN activation, data on direct CAN activity in relation to exercise is scarce. Epilepsy-induced centrally mediated dysautonomia, however, is well described in epilepsy and in its most severe form even associated with sudden explained death in epilepsy (SUDEP) (Devinsky 2004). But studies investigating autonomic dysfunction in patients with epilepsy (PWE), are mostly performed on patients with therapy refractory epilepsy, the majority of PWE might be underrepresented in ANS research, since most PWE have well-controlled seizures (Kwan and Brodie 2000).

As exercise tests have been shown to feasibly detect even subtle pathological changes of physiological responses within the cardiovascular system (Ashley et al. 2000; Marcadet et al. 2018), it is used in this study to examine differential ANS network activity in PWE. As peripheral ANS parameters after exercise do not differ between PWE and healthy control subjects, but in chronotropic competence in response to exercise (van den Bongard et al. 2022). Therefore, no differences in EDA and RMSSD were expected between PWE and healthy controls, but it was hypothesized that CAN response and the interrelation between the CAN with peripheral ANS parameters after exhausting exercise might be altered in PWE.

Methods

This study was registered at the German Clinical Trail Register (DRKS00014822) and was conducted in accordance with the Declaration of Helsinki. The study protocol and the informed consent, obtained by each participant before enrolment, were approved by the ethics committee of the Westfalian Medical Board. Recruitment and measurements took place between July 2018 and December 2021.

Recruitment and in- and exclusion criteria have been described elsewhere (van den Bongard et al. 2022). In brief, people with diagnosed epilepsy (all syndromes) and healthy controls, matched by age (18–60 years old), sex and Body Mass Index (BMI), without physical impairments, severe cardiovascular diseases or brain lesions were included.

Exercise test

All participants conducted an exhaustive exercise test on a bicycle ergometer (Excalibur, Lode), consisting of a 2-min warm up at 24 watts (W), an incremental load increase (12 W per minute) until exhaustion and a 2-min cool down at 24 W. Revolutions per minute (rpm) were based on the load (W): 50–60 rpm at 24–60 W, 60–70 rpm at 60–100 W, 70–70 rpm at > 100 W. Spiroergometry (Metalyzer 3B, Cortex) was carried out during the exercise test.

Measurements

5-min supine resting state measurements were conducted immediately before and after (start of the measurements 658 ± 98.7 sec. post-exercise) the exhaustive exercise test in a relaxed, awake state with eyes closed, consisting of the recording of an electroencephalogram (EEG) and ANS parameters (RMSSD, meanEDA).

ANS recordings, analysis and outcomes

1-lead electrocardiogram (ECG) (Brain Products GmbH) and a Galvanic Skin Response Module (GSR) (Brain Products GmbH) were used to record ANS signals. Sampling frequency for both devices was at 1000 Hz. RMSSD, a parameter indicating parasympathetic activity of HRV as well as meanEDA indicating sympathetic activity were measured (Posada-Quintero and Chon 2020).

To calculate RMSSD, ECG was down sampled to 250 Hz to reduce data points and a Zero Phase Shift Butterworth Filter (low cutoff 8 Hz, time constant[s] 0.1591549, Order 4; high cutoff 20 Hz, Order 4) was applied to reduce noise (Fedotov 2016) (BrainVision Analyzer 2.1.2, Brain Products GmbH). ECG Marker solution, implemented in BrainVision Analyzer, was used for R-peak detection. RR-intervals of the 5-min recording were calculated and exported to Kubios® (Kubios ® HRV Standard 3.1.0.). Threshold-based artifact correction with a medium threshold was used to detect and correct artifacts (Kaufmann et al. 2011). Based on the clean data, RMSSD was calculated over the 5-min window (Task Force of The European Society of Cardiology and The North American 1996).

For EDA recordings, two electrodes (GSR Module) were placed on the middle phalanges of the index and middle finger on the non-dominant hand. Data were down sampled to 250 Hz to reduce data points (BrainVision Analyzer 2.1.2, Brain Products GmbH). A moving average (window size 91 points) (Vieluf et al. 2019), implemented

as solution in the BrainVision Analyzer, was applied. Data were exported to Excel and meanEDA was calculated over the 5-min window. The size of analysis window was selected to match the HRV analysis window.

EEG recording, analysis and outcomes

A 128-channel EEG was used (actiCHamp, Brain Products GmbH). The EEG cap was placed on the head according to the 10–10 system. The sampling rate was 1000 Hz. FPz (frontopolar midline electrode) was utilized as ground electrode and the reference electrode was FCz (frontocentral midline electrode). Impedances were kept below 25 kΩ. For preprocessing, data were down sampled to 250 Hz to reduce data points (van Diessen et al. 2015). Data sets were checked for electrode bridges by using the Matlab-based eBridge Algorithm (Alschuler et al. 2014) and the magnitude-squared coherence in BrainVision Analyzer (BrainVision Analyzer 2.1.2, Brain Products GmbH). For the latter, coherences above 0.9 were defined as electrode bridges. Electrically bridged channels were interpolated by Topographic Interpolation by Spherical Splines when detected by both, Matlab-based eBridge Algorithm and magnitude-squared coherence (Goelz et al. 2021). After bridge check, a Zero Phase Shift Butterworth Filter with a low cutoff of 1 Hz (time constant [s]: 0.1591549, Order 4) and a high cutoff of 30 Hz (Order 4) as well as a notch filter (50 Hz) were applied. Topographic Interpolation by Spherical Splines were used for noisy channels which were identified via visual inspection. An average reference was used (Zheng et al. 2018) and individual electrode positions, recorded by CapTrak (Brain Products GmbH), were loaded. Independent Component Analysis (ICA, infomax) was used for artifact correction (eye, ECG). After that, remaining artifacts were manually marked and the first 4 artifact free segments with a window size of 8.192 s per segment (Engels et al. 2015) were exported for further analysis to BrainStorm (Version: 3.220222) (Tadel et al. 2011). Segments were visually inspected and clinically evaluated by a board certified epileptologist (CR) prior to further connectivity analysis.

Matlab-based BrainStorm software (Version of March 2021) was used for connectivity analysis. A default anatomy, Colin27 template was used (Rizkallah et al. 2020). Individual EEG electrode positions obtained via CapTrak were used to warp the template to approximate the individual head shape. Subsequently, an identity matrix (no noise modelling) was used. The Boundary Element Method (BEM) was used to calculate the head model (Gramfort et al. 2010). If a dipole error appeared, dipoles were forced inside the skull (maximum number of forced dipoles 4). Source estimation was done by minimum norm imaging. Functional connectivity was calculated by phase locking value (PLV) based on the Desikan-Killiany Atlas per segment. After that, connectivity matrices of all four segments were averaged (Samogin et al. 2020). The averaged connectivity matrix was exported for the alpha frequency band (8–12 Hz). MeanPLV was calculated over 68 regions of interest (ROI) for whole brain analysis and over 24 ROI of the CAN (Beissner et al. 2013). The visual network (VIS, 7 ROI) was used as a reference network (Kabbara et al. 2017), because the visual system may not be strained or otherwise specifically affected by ergometry.

Statistics

Data were tested for normality by Shapiro–Wilk Test ($p > 0.05$) and for equal variances by Levene-Test ($p > 0.05$). Within-group differences were determined by Student's t-test or Wilcoxon rank sum test. Between-group differences were assessed by Kruskal–Wallis test since requirements for parametric testing were not fulfilled, except for the relative VO2max, where a Student's t-test was used. Effect sizes were assessed by Person's correlation coefficient (r). Interrelations were determined by Spearman Rank correlation coefficients. Differences between correlations coefficients were calculated by Fisher's z-transformation (Ramseyer 1979). Partial correlation was used to assess the influence of control variables on correlations. The level of significance was determined as < 0.05. To control for multiple testing, Bonferroni method was used (Lee and Lee 2018). However, due to the explorative nature of this pilot study, both corrected and uncorrected p-values were reported and no sample size calculation could be performed. For statistical analysis, IBM SPSS Statistics (Version 25.0.0.1) was used.

Results

Subjects

21 PWE (39 ± 11.6 yrs., BMI 26.7 ± 4.2, female $n = 12$, male $n = 9$) and 21 healthy matched controls (38.04 ± 11.5 yrs., BMI 27.1 ± 5.2, female $n = 12$, male $= 9$) participated in the study. No differences in clinical characteristics were detected except for alcohol use with a higher consumption in the control group ($p = 0.01$) (Table 1).

Mean duration of epilepsy was 18.83 ± 19.06 years (Table 2). PWE suffered from different types of seizures. Most of the patients were seizure-free for at least 6 months ($n = 16$). Three patients had 1–2 seizures per month, one patient had one seizure per month and one patient had one seizure per week. For seizure-free patients, mean time to the last seizure was 3145.3 ± 3264.7 days. 14 patients were under anti-seizure drug (ASD) monotherapy. Five patients took two ASD, one patient took three ASD and one patient was not under ASD medication (lamotrigine

Table 1 Clinical characteristics of epilepsy and control group

Variables	Patients ($n=21$)	Control ($n=21$)	p
Age (yrs.)	39 ± 11.6	38.04 ± 11.5	[c]0.791
BMI	26.7 ± 4.2	27.1 ± 5.2	[c]0.772
Sex	$f=12$; $m=9$	f = 12; m = 9	
Hypertension	2	0	[b]0.488
Diabetes type 1	1	0	[b]1.00
Dyslipidaemia	1	1	[b]1.00
Active smoking	3	1	[b]0.606
Active smoking in the past	4	6	[a]0.469
Alcohol use	12	19	[a]0.014*
Family history CVD	10	8	[a]0.533
Family history epilepsy	2	3	[b]1.00

[a]Chi squared test

[b]Fisher's exact test

[c]Students t-test

*$p<0.05$

**$p<0.01$

Age, BMI: mean ± standard deviation

Further characteristics: n

CVD = cardiovascular disease, f = female, m = male

Table 2 Characterization of seizures and epilepsy

Variables	Patients ($n=21$)
Disease duration (yrs.)	18.83 ± 19.06
Age of disease onset	20.19 ± 14.08
Seizure type*	10
Generalized motor	3
Generalized nonmotor	4
Focal awareness impaired	3
Focal aware	4
Unknown type	
Seizure frequency (last 6 months)	16
Seizure free	3
1–2	1
1 per month	1
1 per week	
Last seizure of seizure-free patients ($n=16$) (days)	3145.3 ± 3264.7 (min: 356; max: 9490)
Number of ASD	1
0	14
1	5
2	1
3	

*Three patients indicated two types of seizures

Disease duration, age of disease onset, last seizure of seizure-free patients: mean ± standard deviation

($n=12$), levetiracetam ($n=4$), valproic acid ($n=6$), lacosamide ($n=1$), carbamazepine ($n=3$), ethosuximide ($n=1$)). Detailed information about dosages and serum levels can be found in Table S1.

Adverse events before, during or after the exhaustive exercise test were not observed in either group. Each participant achieved individual exhaustion based on ventilatory, metabolic, cardiovascular and performance criteria. There was difference between epilepsy and control group regarding cardiorespiratory fitness, assessed by relative VO_2 max (31.04 ± 8.88 vs 33.42 ± 7.40, $t=-0.949$, df = 40, $p=0.348$) (Table 3).

Functional connectivity

Before post hoc correction, whole brain PLV increased in both the epilepsy group (0.30 ± 0.09 vs. 0.32 ± 0.06) and control group (0.28 ± 0.04 vs. 0.30 ± 0.05, $t=-3.061$, df = 20, p = 0.006) from pre- to post-exercise. This relationship stayed significant after post hoc Bonferroni correction in the control group only. CAN PLV from pre- to post-exercise increased significantly in the control group only (0.31 ± 0.05 vs 0.33 ± 0.05, $z=-2.173$, $p=0.03$), but significance did not stay after the correction for multiple comparisons.

No significant changes from pre- to post-exercise were observed for VIS PLV for either group and there were no group differences within the measurement time points for whole brain, CAN and VIS PLV (Table 3).

Peripheral autonomic responses

RMSSD decreased significantly from pre- to post-exercise in the epilepsy group (55.44 ± 53.84 vs. 13.54 ± 15.86, $z=-5.277$, $p<0.001$) and in the control group (42.48 ± 30.22 vs. 8.79 ± 6.56, $z=-3.980$, $p<0.001$). No between group differences pre- and post-exercise were detected (Table 3).

MeanEDA increased significantly from pre- to post-exercise in the epilepsy group (1.36 ± 0.85 vs. 2.99 ± 1.35, $z=-0.408$, $p<0.001$) as well as in the control group (1.68 ± 1.10 vs. 2.65 ± 1.68, $z=-3.632$, $p<0.001$). No between group differences pre- and post-exercise were detected (Table 3).

Correlation analysis

After post hoc correction for multiple testing no significant correlations between CAN PLV or VIS PLV with meanEDA or RMSSD could be detected.

However, before correction for multiple comparisons, CAN PLV correlated significantly with meanEDA

Table 3 Peripheral autonomic activity and functional connectivity before and after exercise

				Patients ($n=21$)		Controls ($n=21$)		
				Mean	SD	Mean	SD	p (ES (r))
	RMSSD pre (ms)			55.44	53.84	42.48	30.22	[c]0.71
	RMSSD post			13.54	15.86	8.79	6.56	[c]0.37
		RMSSD pre vs. post	p ES (r)	[b]< 0.001**[1] 0.770		[b]< 0.001**[1] 0.868		
	meanEDA pre (µS)			1.36	0.85	1.68	1.10	[c]0.32
	meanEDA post			2.99	1.35	2.65	1.68	[c]0.26
		meanEDA pre vs. post	p ES (r)	[b]< 0.001**[1] 0.868		[b]< 0.001**[1] 0.793		
Whole brain	PLV alpha pre			0.30	0.09	0.28	0.04	[c]0.95
	PLV alpha post			0.32	0.06	0.30	0.05	[c]0.34
		PLV pre vs. post	p ES (r)	[b]0.04* 0.447		[a]0.006**[1] 0.564		
CAN	PLV alpha pre			0.33	0.09	0.31	0.05	[c]0.78
	PLV alpha post			0.35	0.07	0.33	0.05	[c]0.42
		PLV pre vs. post	p ES (r)	[b]0.14 0.318		[b]0.03* 0.474		
VIS	PLV alpha pre			0.42	0.08	0.42	0.04	[c]0.42
	PLV alpha post			0.44	0.06	0.43	0.05	[c]0.58
		PLV pre vs. post	p ES (r)	[b]0.08 0.371		[b]0.82 0.049		
	relative VO_2max			31.04	8.88	33.43	7.40	[a]0.34 (0.148)

[a]t-Test

[b]Wilcoxon rank sum

[c]Kruskal Wallis test

*$p<0.05$ (uncorrected)

**$p<0.01$ (uncorrected)

[1]Significant after post hoc Bonferroni correction

alpha 8–12 Hz

ES effect size, *PLV* phase locking value, *CAN* central autonomic network, *VIS* visual network, *EDA* electrodermal activity, *RMSSD* Root mean square of the successive differences

Table 4 Correlation coefficients of peripheral autonomic activity und functional connectivity before and after exercise

			Pre-exercise				Post-exercise			
			meanEDA		RMSSD		meanEDA		RMSSD	
			Epilepsy	Control	Epilepsy	Control	Epilepsy	Control	Epilepsy	Control
alpha 8–12 Hz	CAN PLV	*r*	0.376	0.080	−0.380	−0.184	−0.280	0.543	−0.429	−0.133
		p	0.093	0.731	0.089	0.423	0.219	0.011*	0.052	0.567
	VIS PLV	*r*	0.216	0.069	−0.352	0.118	0.071	−0.166	−0.161	0.299
		p	0.346	0.767	0.117	0.610	0.758	0.471	0.485	0.188

*$p<0.05$ (uncorrected)

**$p<0.01$ (uncorrected)

[1]Significant after post hoc Bonferroni correction

r = Spearman Rank correlation coefficient

PLV phase locking value, *CAN* central autonomic network, *VIS* visual network, *EDA* electrodermal activity, *RMSSD* Root mean square of the successive differences

Table 5 Group comparisons (epilepsy vs. control group) of the correlation coefficients of peripheral autonomic activity and functional connectivity

			meanEDA	RMSSD		meanEDA	RMSSD
Pre-exercise	alpha 8–12 Hz		p	p	Post-exercise	p	p
		CAN PLV	0.172	0.26		0.004**[1]	0.165
		VIS PLV	0.326	0.072		0.237	0.079

*$p < 0.05$ (uncorrected)

**$p < 0.01$ (uncorrected)

[1]Significant after post hoc Bonferroni correction

PLV phase locking value, *CAN* central autonomic network, *VIS* visual network, *EDA* electrodermal activity, *RMSSD* Root mean square of the successive differences

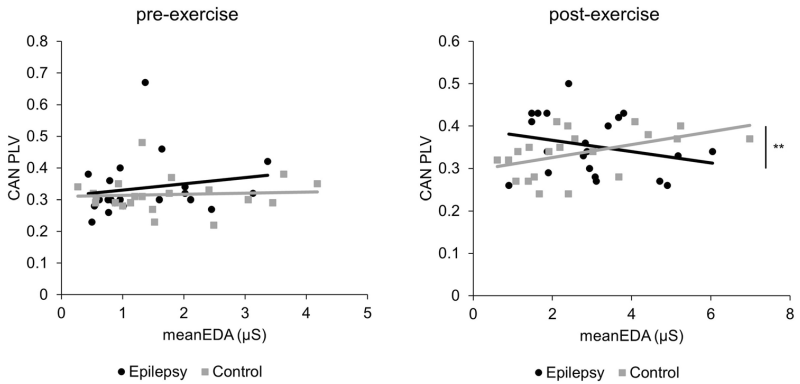


Fig. 1 Correlations of CAN functional connectivity and meanEDA before and after exercise. *PLV* phase locking value, *CAN* central autonomic network, *EDA* electrodermal activity, *$p < 0.05$, **$p < 0.01$

($r = 0.543$, $p = 0.011$) post-exercise in the control group (Table 4).

Correlation coefficients of CAN PLV and meanEDA after exercise differed significantly between the groups ($p = 0.004$) (Table 5) (Fig. 1).

Control variables

Since the subgroup of patients who took lamotrigine was considerably larger, the influence of lamotrigine on CAN PLV and meanEDA was assessed. No significant influence was detected ($r = -0.192$, $p = 0.471$).

There was no significant influence of the relative VO_2 max on CAN PLV and meanEDA as well as on CAN PLV and RMSSD correlations post-exercise (Table S2).

Discussion

The investigation of central and peripheral ANS function before and after an acute bout of exhaustive exercise revealed no group difference in whole brain and CAN functional connectivity. As expected, sympathetic activity (meanEDA) increased and parasympathetic activity (RMSSD) decreased significantly after acute exercise in the epilepsy and the control group. However, the connection between CAN functional connectivity and meanEDA, expressed by the correlation coefficient, differed significantly between both groups after exercise.

Both groups revealed a similar increase in whole brain and CAN functional connectivity after exercise. This is in line with previous reports in the literature since bouts of acute exercise have been shown to increase functional brain connectivity (Moore et al. 2022). The lack of a group difference could be caused by the composition of the epilepsy group mainly consisting of PWE with controlled seizures, as it is known that, amongst others, seizure frequency is a potential modifier that might impact altered brain network function (van Diessen et al. 2013).

Acute exercise is usually associated with increased sympathetic and decreased parasympathetic activation (Gladwell et al. 2010; Vieluf et al. 2019) and those changes often persist post-exercise (Gladwell et al. 2010). Both groups exhibited this pattern as revealed by increased meanEDA and decreased RMSSD after exercise. No group differences could be observed in both measurement time points. High standard deviations confirm the individuality of autonomic activity (Garet et al. 2004), but the lack of a group difference between the investigated cohort of PWE and healthy controls might also be driven by the high proportion of reasonably

well-controlled PWE, who are known to more rarely exhibit autonomic dysfunction when compared to therapy refractory PWE (Ansakorpi et al. 2000). Moreover, ASDs could influence autonomic activity. Higher dosages of Na-blocker ASD, like lamotrigine or carbamazepine, might decrease heart rate (Thijs et al. 2021). Additionally, previous studies investigating influences of ASDs or ASD withdrawal (Kennebäck et al. 1997; Lossius et al. 2007) as well as the influence of a lack of ASD medication (Persson et al. 2007) confirmed at least a partial influence of ASD medication on autonomic alterations, potentially due to the influence on ion channels (Chindo et al. 2016).

Compared to the control group, the connection between central and peripheral sympathetic control in PWE seems to be different after exercise, indicated by significantly different correlation coefficients of CAN functional connectivity and meanEDA. This observation appears to be specific for the CAN because no group difference was observed for the VIS network that served as a reference network. The CAN is a widespread network connecting cortical, subcortical regions (Beissner et al. 2013) and the brain stem (Sklerov et al. 2019) and modulates the ANS in resting condition as well as in response to certain stimuli (Sklerov et al. 2019). During exercise, the sympatho-excitatory response is modulated by a central command that is, under healthy conditions, also associated with parasympathetic withdrawal (Bishop 2004). The induction of increased sympathetic activity during the stress situation of an exercise test (Freeman et al. 2006) is confirmed by an increase in meanEDA and in PWE not different from normal control subjects.

An increased sympathetic tone between seizures is a well-known phenomenon in epilepsy (Lotufo et al. 2012; Myers et al. 2018; Romigi et al. 2016; Sevcencu and Struijk 2010) and has mostly been demonstrated in patients with therapy refractory seizures. In contrast, our cohort consists of a large proportion of seizure-free patients and may, therefore, rather be representative for PWE in general (Kwan and Brodie 2000). Consequently, it could be argued that the central sympathetic control may not differ to a large extent from healthy controls. Furthermore, the investigations of this study focused on an acute exercise test and it was already shown that performance and fitness parameters did not differ between PWE and controls (van den Bongard et al. 2022). Nevertheless, the connection between central control and peripheral sympathetic activity seems to be different in PWE compared to controls after exercise. Therefore, factors in PWE independent from seizure control have to be considered that might contribute to central and peripheral autonomic alterations. For instance, medications like ASD, as described before, or beta blockers influence autonomic function (Thijs et al. 2021). Additionally, ASD may impact central network activity in general. Carbamazepine was shown to change brain graph topology (Haneef et al. 2015) and levetiracetam treatment was associated with inter- and intranetwork alterations (Pang et al. 2020). Although patients took different ASDs, subgroup analysis for all ASD subgroups was not possible due to small sample sizes. However, a larger group taking lamotrigine (12/21) were examined and did not demonstrate differences in CAN functional connectivity and meanEDA, correlations. Besides the ASD influence, the clinical epilepsy syndrome might impact autonomic control. Allen et al. 2017 observed abnormalities in brain regions involved in autonomic processes in patients with epilepsy at high risk for sudden unexpected death. The syndromal heterogeneity of our cohort prohibited further statistical analysis, but the variety of clinical syndromes could certainly have influenced sympathetic control (Shaker et al. 2021; Thijs 2019).

After exercise, a significant correlation before post hoc correction between CAN functional connectivity and meanEDA in the control group might indicate a stronger functional sympathetic central–peripheral connection and therefore the basis for the exercise-induced increase in sympathetic activity. This correlation did not become apparent in the epilepsy group, possibly related to different (and less controlled) functional sympathetic activity in PWE. A larger sample size might be able to elucidate this hypothesis further.

In this study, a multidimensional approach was used for investigating the autonomic system in PWE extending previous research focusing on either the central (for example utilizing fMRI (Sklerov et al. 2019)) or the peripheral part (for example utilizing parameters of the HRV (Lotufo et al. 2012; Mativo et al. 2010)). Assessment of ANS subsystems individually and in relation to each other adds important information to the investigation of alterations in the ANS (Vieluf et al. 2019). The results of this study indicate a difference in the interaction of central autonomic and peripheral sympathetic activity after an exhaustive exercise test between PWE and healthy controls. This might be explained by the impact on brain networks in PWE (van Diessen et al. 2013) despite the relative heterogeneity of epilepsy syndromes and the relative low seizure burden in the subjects of our study. The previously described increased sympathetic tone in PWE might also be induced by these autonomic network alterations (Myers et al. 2018). Exercise might be used in PWE as a stressor to investigate ANS alterations. In addition, it will be interesting how those might also be modified by training, which is traditionally used to target psychological comorbidities and seizures in PWE. In the future, exercise tests in conjunction with autonomic measures might be used as a diagnostic tool to differentiate PWE from healthy people. Although connectivity measures have to be further explored, the presented approach may extend the common visual and automated digital interpretations of clinical EEGs, but requires a larger number of electrodes than clinical routine

EEGs. If future studies may elucidate further, how exercise tests can be used to demarcate central–peripheral ANS alterations in PWE and if and how those alterations might be modified by chronic exercise, exercise may hypothetically also affect the risk for life-threatening conditions of PWE like sudden unexpected death in epilepsy (SUDEP), which occurs as the most dramatic form of dysautonomia, in a positive way.

Limitations

Several limitations must be considered. Only a small number of epilepsy patients with different types of seizures and different seizure frequencies were included. Although most of the patients were seizure-free, some of them still had uncontrolled seizures. Nevertheless, this study sample represents a community-based group of epilepsy patients, where approximately 70% are seizure-free (Kwan and Brodie 2000). PWE took different ASD, with different dosages and serum levels, preventing further statistical exploration of significant ASD effects. Methodologically, not all CAN regions can be assessed by EEG. ROIs were predominantly included in cortical regions since deeper structures may not contribute significantly to surface EEG signals. Source reconstruction itself bears some inaccuracies, but utilization of 128-channel EEG provides the highest temporal resolution. The combination with an MRI template and warping its surface by individual electrode position was associated with increased spatial resolution as compared to EEG alone, but using individual anatomical models would even be more accurate.

Conclusion

PWE reveal similar peripheral autonomic reactions to an acute bout of exercise in comparison to normal control subjects, but exhibit a different connection between central autonomic and peripheral sympathetic activity. Since the majority of PWE were seizure-free, the mechanisms contributing to this finding remain unclear. Further insight into modifiers, clinical consequences and potential response to chronic exercise and training may guide future therapeutic interventions more effectively.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00221-024-06792-0.

Funding Open Access funding enabled and organized by Projekt DEAL. This research was in parts funded by a grant from the Heinz-Nixdorf-Westfalian Foundation.

Data availability statement The data that support the findings of this study are not publicly available because it contains medical information from medical records and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Institute of Sports Medicine (Paderborn University).

Declarations

Conflict of interest CR receives research support from the Heinz-Nixdorf Westfalen Foundation and the Federal Institute of Sports Sciences (Germany). He is a member of the Medical Commission of the German Soccer Association (DFB) and serves as chief medical officer at national games for which he receives compensation. He serves as a consultant for the European Football Association (UEFA) and organizes CME and other educational activities for the Westfalian Medical Board. The other authors declare no conflict of interest.

Ethical standards This study was conducted in accordance with the Declaration of Helsinki. The study protocol and the informed consent, obtained by each participant before enrolment, were approved by the ethics committee of the Westfalian Medical Board.

References

Allen LA, Harper RM, Kumar R, Guye M, Ogren JA, Lhatoo SD, Lemieux L, Scott CA, Vos SB, Rani S, Diehl B (2017) Dysfunctional brain networking among autonomic regulatory structures in temporal lobe epilepsy patients at high risk of sudden unexpected death in epilepsy. Front Neurol 8:544. https://doi.org/10.3389/fneur.2017.00544

Alschuler DM, Tenke CE, Bruder GE, Kayser J (2014) Identifying electrode bridging from electrical distance distributions: a survey of publicly-available EEG data using a new method. Clin Neurophysiol 125:484–490. https://doi.org/10.1016/j.clinph.2013.08.024

Ansakorpi H, Korpelainen JT, Suominen K, Tolonen U, Myllylä VV, Isojärvi JI (2000) Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. Epilepsia 41:42–47. https://doi.org/10.1111/j.1528-1157.2000.tb01503.x

Ashley EA, Myers J, Froelicher V (2000) Exercise testing in clinical medicine. The Lancet 356:1592–1597. https://doi.org/10.1016/S0140-6736(00)03138-X

Beissner F, Meissner K, Bär K-J, Napadow V (2013) The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. J Neurosci 33:10503–10511. https://doi.org/10.1523/JNEUROSCI.1103-13.2013

Bishop VS (2004) Exercise and the autonomic nervous system. In: Primer on the autonomic nervous system. Elsevier, pp 183–184

Chindo BA, Adzu B, Gamaniel KS (2016) Antiepileptic drug targets: an update on ion channels. In: Kalinin VV (ed) Epileptology – the modern state of science. InTech

Chroni E, Sirrou V, Trachani E, Sakellaropoulos GC, Polychronopoulos P (2009) Interictal alterations of cardiovagal function in chronic epilepsy. Epilepsy Res 83:117–123. https://doi.org/10.1016/j.eplepsyres.2008.10.006

Devinsky O (2004) Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr 4:43–46. https://doi.org/10.1111/j.1535-7597.2004.42001.x

Engels MMA, Stam CJ, van der Flier WM, Scheltens P, de Waal H, van Straaten ECW (2015) Declining functional connectivity and changing hub locations in Alzheimer's disease: an EEG study. BMC Neurol 15:145. https://doi.org/10.1186/s12883-015-0400-7

Fedotov AA (2016) Selection of parameters of bandpass filtering of the ECG signal for heart rhythm monitoring systems. Biomed Eng 50:114–118. https://doi.org/10.1007/s10527-016-9600-8

Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, Pringsheim T, Lorenzetti DL, Jetté N (2017) Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology 88:296–303. https://doi.org/10.1212/WNL.0000000000003509

Freeman JV, Dewey FE, Hadley DM, Myers J, Froelicher VF (2006) Autonomic nervous system interaction with the cardiovascular system during exercise. Prog Cardiovasc Dis 48:342–362. https://doi.org/10.1016/j.pcad.2005.11.003

Fu Q, Levine BD (2013) Exercise and the autonomic nervous system. Handb Clin Neurol 117:147–160. https://doi.org/10.1016/B978-0-444-53491-0.00013-4

Garet M, Tournaire N, Roche F, Laurent R, Lacour JR, Barthélémy JC, Pichot V (2004) Individual interdependence between nocturnal ANS activity and performance in swimmers. Med Sci Sports Exerc 36:2112–2118. https://doi.org/10.1249/01.mss.0000147588.28955.48

Gladwell VF, Sandercock GRH, Birch SL (2010) Cardiac vagal activity following three intensities of exercise in humans. Clin Physiol Funct Imaging 30:17–22. https://doi.org/10.1111/j.1475-097X.2009.00899.x

Goelz C, Mora K, Stroehlein JK, Haase FK, Dellnitz M, Reinsberger C, Vieluf S (2021) Electrophysiological signatures of dedifferentiation differ between fit and less fit older adults. Cogn Neurodyn 15:847–859. https://doi.org/10.1007/s11571-020-09656-9

Goit RK, Jha SK, Pant BN (2016) Alteration of cardiac autonomic function in patients with newly diagnosed epilepsy. Physiol Rep 4. https://doi.org/10.14814/phy2.12826

Gramfort A, Papadopoulo T, Olivi E, Clerc M (2010) OpenMEEG opensource software for quasistatic bioelectromagnetics. Biomed Eng Online 9:45. https://doi.org/10.1186/1475-925X-9-45

Haneef Z, Levin HS, Chiang S (2015) Brain graph topology changes associated with anti-epileptic drug use. Brain Connect 5:284–291. https://doi.org/10.1089/brain.2014.0304

Horinouchi T, Sakurai K, Munekata N, Kurita T, Takeda Y, Kusumi I (2019) Decreased electrodermal activity in patients with epilepsy. Epilepsy Behav 100:106517. https://doi.org/10.1016/j.yebeh.2019.106517

Kabbara A, El Falou W, Khalil M, Wendling F, Hassan M (2017) The dynamic functional core network of the human brain at rest. Sci Rep 7:2936. https://doi.org/10.1038/s41598-017-03420-6

Kaufmann T, Sütterlin S, Schulz SM, Vögele C (2011) ARTiiFACT: a tool for heart rate artifact processing and heart rate variability analysis. Behav Res Methods 43:1161–1170. https://doi.org/10.3758/s13428-011-0107-7

Kennebäck G, Ericson M, Tomson T, Bergfeldt L (1997) Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. Seizure 6:369–375

Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 5:314–319. https://doi.org/10.1056/NEJM200002033420503

Lee S, Lee DK (2018) What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 71:353–360. https://doi.org/10.4097/kja.d.18.00242

Lossius MI, Erikssen JE, Mowinckel P, Gulbrandsen P, Gjerstad L (2007) Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. Eur J Neurol 14:1022–1028. https://doi.org/10.1111/j.1468-1331.2007.01863.x

Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR (2012) A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 53:272–282. https://doi.org/10.1111/j.1528-1167.2011.03361.x

Marcadet D-M, Pavy B, Bosser G, Claudot F, Corone S, Douard H, Iliou M-C, Vergès-Patois B, Amedro P, Le Tourneau T, Cueff C, Avedian T, Solal AC, Carré F (2018) French society of cardiology guidelines on exercise tests (part 1): methods and interpretation. Arch Cardiovasc Dis 111:782–790. https://doi.org/10.1016/j.acvd.2018.05.005

Mativo P, Anjum J, Pradhan C, Sathyaprabha TN, Raju TR, Satishchandra P (2010) Study of cardiac autonomic function in drug-naïve, newly diagnosed epilepsy patients. Epileptic Disord 12:212–216. https://doi.org/10.1684/epd.2010.0325

Moore D, Jung M, Hillman CH, Kang M, Loprinzi PD (2022) Interrelationships between exercise, functional connectivity, and cognition among healthy adults: a systematic review. Psychophysiology 59:e14014. https://doi.org/10.1111/psyp.14014

Myers KA, Sivathamboo S, Perucca P (2018) Heart rate variability measurement in epilepsy: How can we move from research to clinical practice? Epilepsia 59:2169–2178. https://doi.org/10.1111/epi.14587

Pang X-M, Liang X-L, Zhou X, Liu J-P, Zhang Z, Zheng J-O (2020) Alterations in intra- and internetwork functional connectivity associated with levetiracetam treatment in temporal lobe epilepsy. Neurol Sci 41:2165–2174. https://doi.org/10.1007/s10072-020-04322-8

Persson H, Ericson M, Tomson T (2007) Heart rate variability in patients with untreated epilepsy. Seizure 16:504–508. https://doi.org/10.1016/j.seizure.2007.03.010

Poh MZ, Loddenkemper T, Reinsberger C, Swenson NC, Goyal S, Madsen, JR, Picard RW (2012) Autonomic changes with seizures correlate with postictal EEG supression. Neurology 78. https://doi.org/10.1212/WNL.0b013e318258f7f1

Posada-Quintero HF, Chon KH (2020) Innovations in electrodermal activity data collection and signal processing: a systematic review. Sensors (Basel) 20. https://doi.org/10.3390/s20020479

Ramseyer GC (1979) Testing the difference between dependent correlations using the fisher Z. J Exp Educ 47:307–310

Rizkallah J, Amoud H, Fraschini M, Wendling F, Hassan M (2020) Exploring the correlation between M/EEG source-space and fMRI networks at rest. Brain Topogr 33:151–160. https://doi.org/10.1007/s10548-020-00753-w

Romigi A, Albanese M, Placidi F, Izzi F, Mercuri NB, Marchi A, Liguori C, Campagna N, Duggento A, Canichella A, Ricciardo Rizzo G, Guerrisi M, Marciani MG, Toschi N (2016) Heart rate variability in untreated newly diagnosed temporal lobe epilepsy: evidence for ictal sympathetic dysregulation. Epilepsia 57:418–426. https://doi.org/10.1111/epi.13309

Samogin J, Marino M, Porcaro C, Wenderoth N, Dupont P, Swinnen SP, Mantini D (2020) Frequency-dependent functional connectivity in resting state networks. Hum Brain Mapp 41:5187–5198. https://doi.org/10.1002/hbm.25184

Sarkis RA, Thome-Souza S, Poh M-Z, Llewellyn N, Klehm J, Madsen JR, Picard R, Pennell PB, Dworetzky BA, Loddenkemper T, Reinsberger C (2015) Autonomic changes following generalized tonic clonic seizures: an analysis of adult and pediatric patients

with epilepsy. Epilepsy Res 115:113–118. https://doi.org/10.1016/j.eplepsyres.2015.06.005

Sevcencu C, Struijk JJ (2010) Autonomic alterations and cardiac changes in epilepsy. Epilepsia 51:725–737. https://doi.org/10.1111/j.1528-1167.2009.02479.x

Shaffer F, McCraty R, Zerr CL (2014) A healthy heart is not a metronome: an integrative review of the heart's anatomy and heart rate variability. Front Psychol 5:1040. https://doi.org/10.3389/fpsyg.2014.01040

Shaker KK, Al Mahdawi AM, Hamdan FB (2021) Interictal autonomic dysfunction in patients with epilepsy. Egypt J Neurol Psychiatry Neurosurg 57. https://doi.org/10.1186/s41983-021-00422-0

Sklerov M, Dayan E, Browner N (2019) Functional neuroimaging of the central autonomic network: recent developments and clinical implications. Clin Auton Res 29:555–566. https://doi.org/10.1007/s10286-018-0577-0

Tadel F, Baillet S, Mosher JC, Pantazis D, Leahy RM (2011) Brainstorm: a user-friendly application for MEG/EEG analysis. Comput Intell Neurosci 2011:879716. https://doi.org/10.1155/2011/879716

Task Force of The European Society of Cardiology and The North American (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 93:1043–1065

Thijs RD (2019) The autonomic signatures of epilepsy: diagnostic clues and novel treatment avenues. Clin Auton Res 29:131–133. https://doi.org/10.1007/s10286-019-00603-1

Thijs RD, Ryvlin P, Surges R (2021) Autonomic manifestations of epilepsy: emerging pathways to sudden death? Nat Rev Neurol 17:774–788. https://doi.org/10.1038/s41582-021-00574-w

van den Bongard F, Coenen J, Reinsberger C (2022) Fitness, performance, and cardiac autonomic responses to exercise in people with epilepsy. Epilepsy Behav 135:108869. https://doi.org/10.1016/j.yebeh.2022.108869

van Diessen E, Diederen SJH, Braun KPJ, Jansen FE, Stam CJ (2013) Functional and structural brain networks in epilepsy: what have we learned? Epilepsia 54:1855–1865. https://doi.org/10.1111/epi.12350

van Diessen E, Numan T, van Dellen E, van der Kooi AW, Boersma M, Hofman D, van Lutterveld R, van Dijk BW, van Straaten ECW, Hillebrand A, Stam CJ (2015) Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. Clin Neurophysiol 126:1468–1481. https://doi.org/10.1016/j.clinph.2014.11.018

Vieluf S, Hasija T, Jakobsmeyer R, Schreier PJ, Reinsberger C (2019) Exercise-induced changes of multimodal interactions within the autonomic nervous network. Front Physiol 10:240. https://doi.org/10.3389/fphys.2019.00240

Vieluf S, Amengual-Gual M, Zhang B, El Atrache R, Ufongene C, Jackson MC, Branch S, Reinsberger C, Loddenkemper T (2021) Twenty-four-hour patterns in electrodermal activity recordings of patients with and without epileptic seizures. Epilepsia 62:960–972. https://doi.org/10.1111/epi.16843

Zheng G, Qi X, Li Y, Zhang W, Yu Y (2018) A comparative study of standardized infinity reference and average reference for EEG of three typical brain states. Front Neurosci 12:158. https://doi.org/10.3389/fnins.2018.00158

Supplement

Table S1

ASD daily dosage and serum level

ASD		dose (mg)								
	n	median	min	max	25% percentile	75% percentile				
Lamotrigine	12	250	100	400	168.75	100				
Levetiracetam	4	2250	1500	3000	1500	1500				
Valproic acid	6	1250	600	2750	600	600				
Lacosamide	1	200	200	200	200	200				
Carbamazepine	3	600	400	800	400	400				
Ethosuximide*	1	250	250	250	250	250				
		serum level (mg/l)						time ASD intake and blood sample (min)		
		median	min	max	25% percentile	75% percentile	reference range	median	min	max
Lamotrigine		4.85	1.90	10.30	3.27	1.9	3-14	262.5	70	491
Levetiracetam		27.50	14.80	45.90	14.8	14.8	10-40	371	203	600
Valproic acid		50.50	30	102	30	59.5	40-100	420	100	1063
Lacosamide		0.60	0.60	0.60	0.6	0.6	1-10	491	491	491
Carbamazepine		7.20	3.60	9.30	3.6	3.6	4-12	360	100	502

* serum level of ethosuximide analysis was not determined

Table S2

Partial correlation post exercise

		CAN PLV and meanEDA (Pearson correlation)	CAN PLV and meanEDA controlled for relative VO_2max	CAN PLV and RMSSD (Pearson correlation)	CAN PLV and RMSSD controlled for relative VO_2max
epilepsy	r	-0.268	-0.273	-0.324	-0.317
	p	0.240	0.244	0.153	0.173
control	r	0.467	0.456	-0.229	-0.127
	p	0.033*	0.043*	0.318	0.593

* $p<0.05$