



# Effect of Exercise Interventions on Kainate Induced Status Epilepticus and Associated Co-morbidities; A Systematic Review and Meta-Analysis

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## Abstract

**Purpose** To conduct a systematic review and meta-analysis of studies testing the effect of exercise in Kainic-acid (KA) induced status-epilepticus (SE) and to quantify the efficacy of exercise strategies in the prognosis of SE and co-morbidities.

**Methods** Two authors searched online databases (Pubmed and Web of Science) independently for studies testing the efficacy of exercise programs in KA-induced SE models. Reviewers autonomously extracted data on models used, exercise interventions and prognosis in all reported outcomes (behavioral, histological, biochemical and cognitive outcomes). All studies were summarized and relevant outcomes' data were pooled by means of a meta-analysis.

**Results** Among 14 selected studies; Quantitative analysis of studies with pre-SE exercise interventions showed significant reduction in mortality rate among 76 animals of four studies (RR=0.57, [95% CI 0.34, 0.95], p=0.03, I<sup>2</sup>=57%) and seizure rating score among three studies (n=56) with MD=-1.04, [95% CI -2.07, -0.00], p=0.05, I<sup>2</sup>=71%. Three studies (n=62) presented with improved anti-oxidant enzymes' profile (SMD=0.75, [95% CI 0.55, 2.31], p=0.0008, I<sup>2</sup>=44%) as a result of exercise intervention. Same intervention failed to show any significant measure for BDNF level and neuroprotection assessed through neuronal number in different brain areas with MD=-1.22, [95% CI -136.66, 134.22], p=0.99, I<sup>2</sup>=0% and SMD=-0.05, [95% CI -0.62, 0.52], p=0.86, I<sup>2</sup>=61% respectively. Qualitative review concluded in the reduction of median seizure score, depression and anxiety-like behaviors with improved cognitive performances in pre-SE exercised animals while improved memory and learning capabilities with increased neurogenesis were observed in post-SE exercised models.

**Conclusions** Exercise before SE reduces behavioral seizures and oxidative stress with improvements in cognitive abilities. Post-SE exercise enhances learning and memory with neurogenesis in KA models. More extensive research on morphological and biochemical profiles is needed to explore underlying mechanisms.

**Keywords** Meta-analysis · Systematic review · Exercise · Physical training · Epilepsy · Kainic acid

## Abbreviations

TLE	Temporal lobe epilepsy
KA	Kainic acid
SE	Status epilepticus
SRS	Spontaneous recurrent seizures
ROC	Reactive oxygen species
PT	Physical training
MD	Mean difference
CI	Confidence interval
SMD	Standardized mean difference
RR	Risk ratios

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## Introduction

Over 40% of patients suffering from epilepsy in the world have temporal lobe epilepsy (TLE), which is characterized by specific epileptogenic changes and spontaneous recurrent seizures (SRSs) [1]. It is a combination of many changes, including inflammation induced by glial cells [2, 3], oxidative stress and apoptotic cell death in brain tissues and it shows some resistance to treatment with antiepileptic drugs, with the progression of the disease resulting in adverse cognitive decline and neurobehavioral sequelae [4, 5].

Animal models of TLE following systemic chemoconvulsant administration are valuable tools for the studying pathophysiology of the disease, and thus to develop new treatments [6]. They have contributed greatly to the thorough understanding of the disease pathogenesis [6]. Kainic acid (KA) induced TLE models are especially useful for the investigation of the evolution, spread, and pathological consequences of epileptic discharges in the limbic system [7]. KA causes epileptiform activity in the hippocampus, which is followed by a specific pattern of neuronal cell death that is similar to the one seen in patients suffering from TLE [8]. So it is concluded that the KA models have provided reliable insights to the processes underlying TLE and have added a lot in developing more efficient anti-epileptic therapies [9].

Physical exercise has been adapted as an effective complementary therapy for neuroprotection and neurorehabilitation in both epileptic patients and experimental animal models [10, 11]. Exercise interventions have been reported to reduce epileptiform discharges on electroencephalography and in increasing seizure threshold [12–14] with gaining generalized physical, physiological and psychological benefits in human epileptic patients [10]. Along with better seizure control [15], physical exercise minimizes epilepsy associated comorbidities in patients with epilepsy i.e. it alleviates cognitive impairments [16], decreases the level of depression [17] and anxiety [10], promotes quality of life and well-being [13]. It was also reported to mitigate the severity of benign epilepsy with centrotemporal spikes, thereby enhancing neuropsychological function [18, 19]. These clinical outcomes are strengthened by results showing effects of different exercises in decreasing seizure scores, mortality rate, enhancing neurogenesis in chronic stages, reversing cognitive decline and oxidative stress with improved neuronal survival after KA-induced SE in recent studies [5, 7, 20].

Although the benefits of physical exercises are well known and frequently reported, some discrepancies still exist in the results of studies evaluating the effect of exercise interventions on KA-induced SE. Such as few studies reported no significant effect of exercise interventions on seizure rating scores [21, 22] while others documented

that exercise intervention decreased seizure scores [7, 23, 24]. Similarly, in order to explain underlying mechanisms by which exercise effects KA-induced SE, some studies reported decreased BDNF after exercise intervention [25] but other reported no change [26] or increased BDNF after exercise [27]. Such variations demand a comprehensive analysis and comparison on modes of exercise (types of exercise), their differential effects on different outcomes of KA-induced SE and their initiation either before or after the induction of SE, to conclude the qualitative and quantitative efficacy of exercise interventions on TLE in KA models.

In this systematic review, we summarized all relevant studies and performed a meta-analysis to study the efficacy of exercise, both before and after the induction of KA-induced SE in animal models. Main objectives of this study are: to identify and summarize all studies describing the use of exercise interventions in KA-induced SE models, to investigate the collective and individual effects of different types of exercises on behavioral seizures, neurotrophic factors, oxidative stress and cognitive abilities and to quantify any influence of study quality and design characteristics (such as type or duration of exercise) on reported efficacy. Characterizing the more effective exercise types and their comparative effects on different co-morbidities of SE will not only be helpful to elucidate the mechanisms of exercise-induced recovery in experimental epileptic models and to identify untouched areas of this domain for further preclinical studies but also for the formulation of future clinical studies.

## Methods

The reporting of this systematic review is according to the preferred reporting items for systematic reviews and meta-analyses statements (PRISMA) [28].

## Eligibility Criteria

We have included controlled animal studies of KA-induced SE, using exercise as an intervention either before or after induction of SE. Exercise is defined as a physical activity or movement of the body by the action of skeletal muscles that would be expected considerably to increase energy expenditure over resting levels [29]. All reported outcomes (in exercised SE animals as compared to non-exercised SE animals) are included in the systematic review summary table (Table 1). The systematic review was limited to the articles published in English, and no limits were applied for publication date.

Studies that met our inclusion criteria but did not provide sufficient or relevant data (sample size, mean, and a measure of variance) for meta-analysis were included in

the systematic review and assessment of study quality. Two independent reviewers (M.I., S.Z.) screened titles and abstracts and, where needed, full-text articles; where a consensus was not being reached on the inclusion of data or of an individual article, a third reviewer (J.L.) was consulted.

### Identification of Relevant Studies

Two authors independently conducted searches of PubMed and Web of Science Proceedings from beginning till June 2018 for [exercise OR locomotion OR fitness OR ambulation OR walk\* OR treadmill\* OR wheel\* OR swim\* OR running\* OR physical exercise OR physical therap\* OR physical training OR physical exertion OR physical activit\*] AND [epilepsy OR epilepsies OR epilepticus OR epileptic OR seizure OR seizures] AND [animal\* OR mouse OR mice OR rodent\* OR rat\* OR murine OR feline OR cat\* OR porcine OR pig\* OR primat\* OR mammal\*]. Language filter was used to select studies reported in English. Then studies using Kainate models were selected manually among screened studies. Reference lists of all included studies were also searched for potentially eligible articles.

### Data Extraction

Two reviewers identified individual comparisons where the outcome in a group of epileptic animals (KA-induced SE) receiving exercise as a sole treatment was compared with that of a control group (Non-exercised epileptic animals) and co-treated groups were excluded. For each comparison, we extracted data independently for the number of animals per group, mean outcome and variance. Where an outcome was measured serially, only the last data were analyzed. Where numerical data were unavailable, we measured values from graphs by using “GetData graph digitizer 2.26”.

We extracted details of animals (species, gender, age / weight), intervention (type of exercise, duration [total minutes performed/day], exercise details and duration [total days of intervention period]), and all outcomes assessed in those studies (e.g. Median seizure score on seizure rating scale of 1–5 [21], latency to first seizure after KA administration, mortality rate etc.). Exercise was categorized as either “voluntary”—where the animals were presented with the opportunity to engage in exercise but without any motivating stimulus (e.g. free access to a running wheel)—“forced”—where the animal subjected to a noxious stimulus (e.g. electric shock) if it did not perform the exercise or was restrained such that participation was inevitable (Treadmill running) or “resistance” training when some kind of weight or resistance

was added or gravity was used to resist the movement of animals [30].

### Data Analysis

The meta-analysis of available outcome measures was run through Review Manager Software (RevMan, Windows 10, Microsoft, Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.). We used a random effects model [31]. The measure of association used in quantitative analysis was the mean difference (MD) with a 95% confidence interval (CI) for Seizure rating score and BDNF levels, standardized mean difference (SMD) for anti-oxidant enzymes profile and neuron number in different brain areas, and risk ratio (RR) for mortality rate (as it is a dichotomous outcome). Heterogeneity was explored by using a Chi square test, and the quantity of heterogeneity was measured using the  $I^2$  statistic. Funnel plot [32] and meta-regression (Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]) were not done due to less number of included studies.

### Risk of Bias and Study Quality Assessment

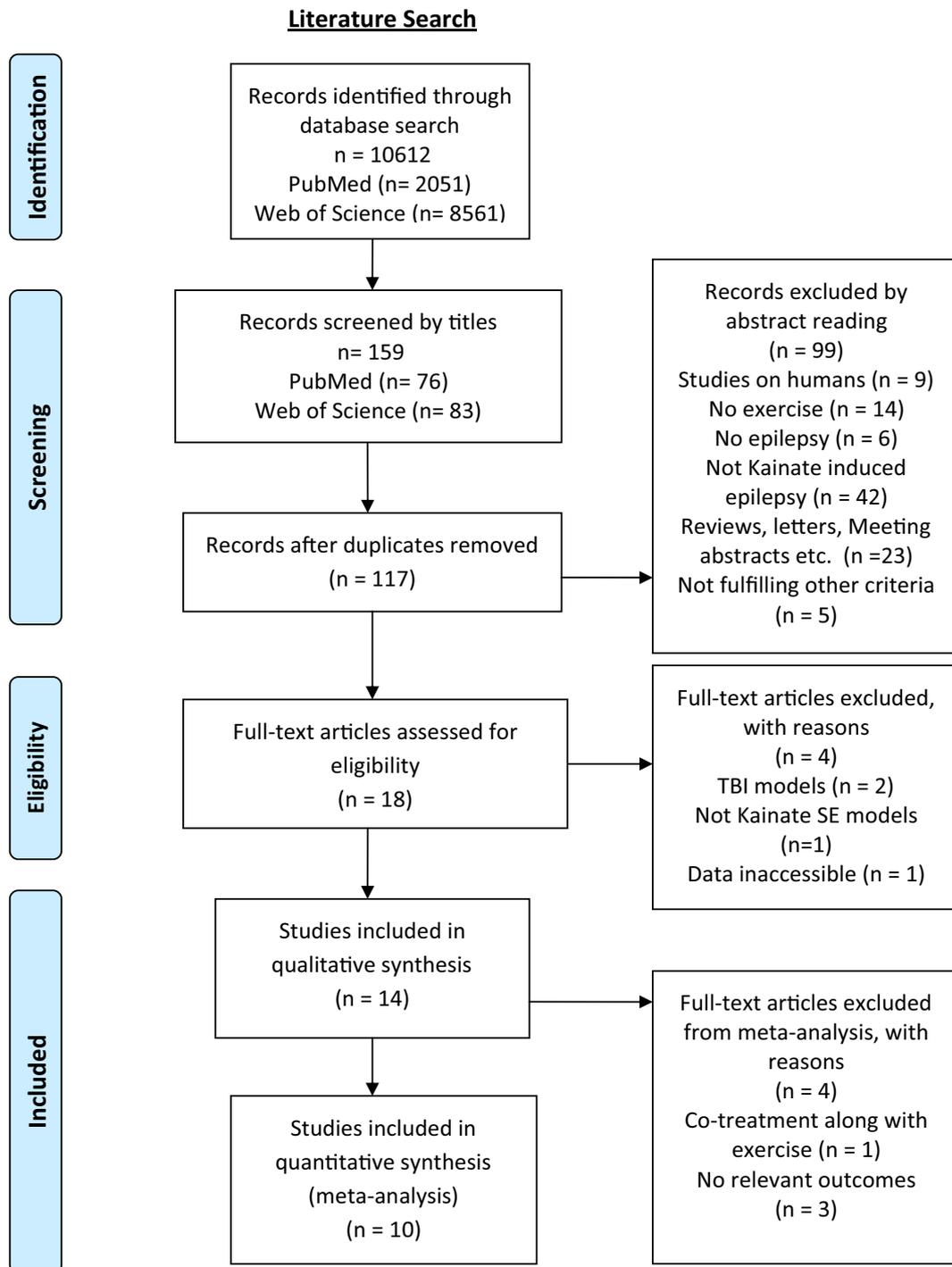
Two reviewers (M.I., S.U.) independently assessed the risk of bias (i.e., systematic error) through SYRCLÉ’s risk of bias tool for animal studies [33]. This tool for animal studies has ten entries. Five of those are in agreement with the Cochrane Risk of bias tool. Most of the variations between the two tools are due to differences in design between clinical RCTs and animal studies.

Study quality was assessed by using the modified CAMARADES 10-item study quality checklist [34], which was modified regarding exercise interventions (items 6 and 7) in epilepsy models in our previous meta-analysis [11]. Both of these tools were used as per recommendations by Xiantao Zeng et al. [35].

## Results

### Qualitative Description of the Included Studies

Total 14 studies met our inclusion criteria (PRISMA Flow diagram) in systematic review out of which 11 used exercise interventions before induction of SE while 3 used it after induction of SE. All of these studies are summarized in Table 1.



### Species/Strain, Age, and Gender of Animal Models Used

Four studies used mice (1 used C57BL/6J while other 3 used ICR) and remaining 10 studies used rats (two studies were done on spontaneously hypertensive (SHRs) rats, 4 on Sprague Dawley rats and remaining 4 on Wistar rats). All studies used adult animals. All studies used male animals except one [36] which used female rats.

### Exercise Intervention Before Induction of SE

Eleven studies used more than 322 animals to assess the effect of exercise interventions (applied before SE) on KA-induced behavioral seizures and its different biochemical, histological and cognitive variables. Among all these outcomes, seizures rating scores, percentage mortality, serum BDNF, anti-oxidant enzymes and neuron number in different

**Table 1** Characteristics of studies selected for systematic review

Reference	Model	Gender	Age/weight	Number of animals	Exercise regime	Total duration	Days/week	Duration/session (min)	Max. intensity/distance	KA route	Outcomes reported in exercised KA models as compared to sedentary KA models
[26]	Rats (SHRs)	Males	200–250 g	K/N = 13 K/F = 12	Forced PT (treadmill running)	4 weeks	5 days/week	40	20 m/min	i.p.	Maximum time to exhaustion ↑, heart rate →, preference for sucrose solution ↑, # and time of head poking in holeboard test ↓, serum BDNF 1 month after SE →
[21]	ICR Mice	Males	35 g	K/N = 11 K/S = 11	Swimming	8 weeks	3 times/week	30	Low intensity PT	i.p.	Weight, swimming time & food intake →, seizure activity (rating score & median), Lat. to 1st seizure & % mortality →, glutathione peroxidase, superoxide dismutase & catalase activities →
[20]	Rats (SHRs)	Males	200–250 g	K/N = 13 K/F = 12	Forced PT (treadmill running)	4 weeks	5 days/week	40	20 m/min, 0° elevation	i.p.	KA dose to induce SE ↑, Lat for 1st SRST, locomotor and vertical activity in open field test ↑, object recognition memory ↑, anxiety level assessed through elevated plus maze test ↓, % saccharine preference ↑, Immobility time is FST ↓, 5-HT release from hippocampus ↑, neuroprotection →
[22]	Sprague–Dawley rats	Males	150–200 g	K/N = 11 K/V = 11	Voluntary PT	21 days	Free access to running wheel for whole 21 days		Max. mean distance = 6085 m	i.p.	Mean Seizure score →, incidence of severe seizures ↓, # of deaths after KA injection ↓, hippocampal in-vivo glutamate levels assessed through voltammetry system ↓
[7]	Adult ICR mice	Males	35 g	K/N = 9 K/S = 9	Resistance PT (swimming)	8 weeks	3 days/week	60	10% body's weight bound to tail	i.v.	Median seizure score ↓, Mortality rate after KA injection ↓, glutathione peroxidase, superoxide dismutase & catalase activities ↑
[23]	Adult ICR mice	Males	35 g	K/N = 11 K/S = 11	Resistance PT (swimming)	6 weeks	5 times/week	60	5% body's weight bound to tail	i.v.	Median seizure score ↓, mortality rate ↓, superoxide dismutase & catalase activities ↑
[47]	C57BL/6J mice	Males	7 weeks old	K/RS = 12 K/RS + F = 12	Forced PT	8 weeks	5 days/week	60	19 m/min	i.c.v.	Neuronal death in CA3 of hippocampus assessed through missl's staining ↓
[24]	Sprague Dawley rats	Males	150–200 g	Exp 1: n = 42, (4–6/group)	Voluntary PT	21 days	Free access to running wheel for whole 21 days		5621 m/days in last week	i.p.	Mean seizures rating and c-fos mRNA autoradiographic optical density values ↓ at 10 & 14 mg/kg KA dose after running
				Exp 2: (M-40 group) n = 80, (5–9) group	Voluntary PT	24 days	Free access to running wheel for whole 24 days		Approx. 6000/day at days 16–18	i.p.	Mean galanin mRNA auto-radiographic optical density values ↑
[25]	Wister rats	Males	250–300 g	6–8 animals /group (K/N & K/V + Cxb)	Voluntary PT	5 days	Free access to running wheel for whole 5 days		500 m/day	i.p.	Escape latency & distance swam in MWM →, behavioral performance in objects recognition task →, BDNF in DG ↓
[27]	Wister rats	Males	250–300 g	K/N = 6 K/V = 8	Voluntary PT	5 days	Free access to running wheel for whole 5 days		2000 m	i.p.	Escape latency in MWM ↓, hyperactivity → but behavioral performance in objects recognition task ↑
[36]	Sprague Dawley rats	Females	90 days old	K/N = 6 K/V = 6	Voluntary PT	4 weeks	Free access to running wheel for whole 28 days		12 km/day Approx	i.h.	Neuronal loss in hippocampal CA2/3 assessed through stereological estimation of NeuN+ cells ↑

**Table 1** (continued)

Reference	Model	Gender	Age/ weight	Number of animals	Exercise regime	Total dura- tion	Days/week	Duration /ses- sion (min)	Max. intensity/ distance	Into lateral ventricles	Outcomes reported in trained KA models as com- pared to untrained KA models
[37]	Wister rats	Males	4 months old	K/N = 12 K/S = 12	Swim- ming	30 days	daily	15	Non-stressful swimming	Into lateral ventricles	In both groups a & b: Improvements in learning inT maze task: % bias↓, % correct responses↑, # of alterations↑ improvements in memory in passive avoidance test: time spent in small compartment↓, # of crossings between compartments↓
[5]	Wister rats	Males	4 months old	K/N = NR K/S = NR	Swim- ming	30 days	daily	15	NR	Into lateral ventricles	In both groups a & b: morphometric cell count of surviving neurons, dendritic branch points and den- dritic intersections in CA1, CA3 & dentate gyrus of hippocampus, basolateral nuclei of amygdala and in motor cortex↑
[38]	Sprague Dawley rats	Males	12–14 weeks old 180–220 g	K/N = 7 K/F (low) = 7 K/F (mid) = 7 K/F (high) = 7	Motor driven wheel run- ning	7 days	daily	30 min in morning, 30 min in afternoon	Max. 4.2 m/min in lightly, 7.2 in moderately & 12 in heavily running group	i.h.	# of BrdU+ cells in DG is ↑ & error number in Y maze test↓ in moderately running but remained same in other 2 groups

[K/N = Kinate models with no exercise intervention, K/F = Kinate models with forced physical training, K/V = Kinate models with voluntary physical training, K/S = Kinate models with swim-  
ming intervention, K/R/S = Kinate models with restrained stress]

*SHRs* spontaneously hypertensive rats, *i.p.* intra-peritoneal, *i.v.* intra-venous, *i.h.* intra-hippocampal, *Lat.* latency, *SRS* spontaneous recurrent seizure, *FST* forced swim test, *MWM* Morris water  
maze

brain areas provided enough suitable data to be included in quantitative analysis. Other reported outcomes are analyzed qualitatively in this systematic review.

### Effect of Exercise on Behavioral Seizures

56 animals were monitored for KA-induced seizures' rating score to analyze the effect of pre-SE exercise interventions in three studies. Overall effect estimate presented a significant decrease in seizure rating score of exercised animals as compared to non-exercised KA group (Fig. 1) with MD = -1.04, [95% CI -2.07, -0.00],  $p=0.05$ ,  $I^2=71\%$ .

76 animals from four studies were assessed to check mortality rate after KA-induced SE. Again exercised KA models showed significantly less risk ratio of mortality rate (Fig. 2) as compared to non-exercised KA animals (RR = 0.57, [95% CI 0.34, 0.95],  $p=0.03$ ,  $I^2=57\%$ ).

For exercised KA models, two out of three studies reported reduced median seizure scores, one study found increased KA dosage requirement for SE induction and increased latency for first SRS [20]. Another study [22] demonstrated a reduced incidence of severe seizures among exercised KA models.

### Effect of Exercise on Biochemical Variables

BDNF data from two studies ( $n=39$ ) included in quantitative analysis have shown no significant change in BDNF level (Fig. 3) with MD = -1.22, [95% CI -136.66, 134.22],  $p=0.99$ ,  $I^2=0\%$ . Although another study [25] has reported low BDNF level in DG of exercised animals but we have not included it in the meta-analysis because of the use of co-treatment (celecoxib) in exercised animals' group.

62 animals from three studies were evaluated for antioxidant enzymes profile [superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx)] of the cerebral cortex. Collective quantitative analysis of these 3 enzymes presented a significantly increased level (Fig. 4) of these anti-oxidative markers in the cerebral cortex of exercised animals. As the baseline values of different enzymes varied greatly, we used SMD as a measure of association (SMD = 0.75, [95% CI 0.31, 1.18],  $p=0.0008$ ,  $I^2=44\%$ ). Sub-group analysis for each enzyme is also performed, see Fig. 4 for details.

Among other biochemical variables assessed in included studies, One [20] study mentioned the increased level of 5-HT in hippocampal tissues due to pre-SE exercise intervention. In search of underlying mechanisms involved in behavioral changes, another study [24] demonstrated decreased c-fos mRNA autoradiographic density values in the hippocampus and increased galanin mRNA optical

density in locus coeruleus (in exercised KA animals) by two different experiments.

### Effect of Exercise on the Histological Profile

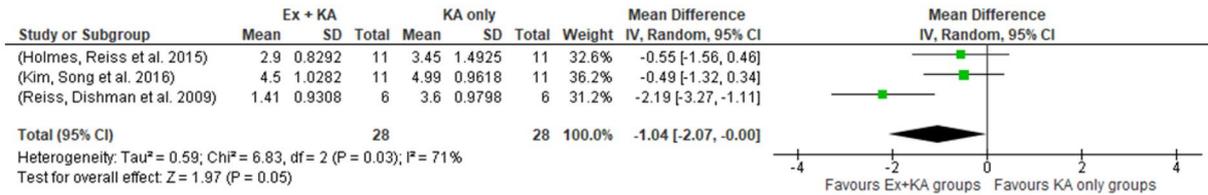
Four included studies (with 60 animals) counted neuron numbers in different areas of the brain to assess neuronal loss after KA-induced SE and used different staining techniques and counting strategies to report this outcome. So we used SMD as a measure of association in quantitative analysis. As two studies [20, 27] counted neuron number in different sub-layers and levels in each brain area, we calculated collective mean and combined SD for each major area like CA1 or hilus from means and standard errors of all layers of that specific area. We performed subgroup analysis for each brain area and also calculated overall SMD as -0.05, [95% CI -0.62, 0.52],  $p=0.86$ ,  $I^2=61\%$ , showing the insignificant effect of the exercise intervention. Interestingly all six subgroups showed insignificant SMD as mentioned in Table 2 (Fig. 5).

### Effect of Exercise on Cognition and Behavioral Co-morbidities

As different kind of behavioral tests was performed by included studies to assess the cognitive abilities of epileptic models, we did not perform a quantitative analysis rather the outcomes are summarized in systematic review summary Table 1. Two [20, 27] out of three studies reported significantly improved memory of trained models in an object recognition test. Two studies assessed escape latencies in Morris water maze and one [27] found a significant decrease in it due to pre-SE exercise intervention. A study [20] extensively examined the effect of 4 weeks pre-SE treadmill running on behavioral changes in SHR SE rats. It demonstrated significant improvement in depression-like behavior assessed through saccharine preference test and less immobility time in forced swim test as a result of exercise program prior to SE. The same study reported increased locomotor and vertical activity in open field test and noticed less anxiety level of trained rats in both open field and elevated maze plus test, which (less anxiety level) was also measured by same authors in another study [26] through less number and time of head poking in hole board test on same kind of KA models (SHRs) as used by [20].

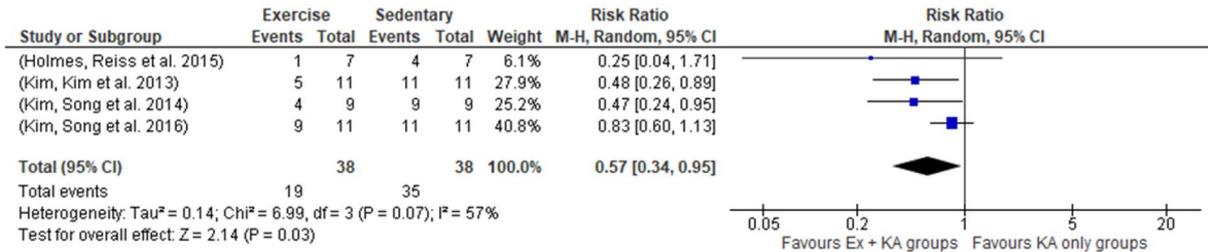
### Exercise Intervention After Induction of SE

A very limited number of available studies and heterogeneous reported outcomes made it impossible to run a meta-analysis for this domain. Only three studies met our



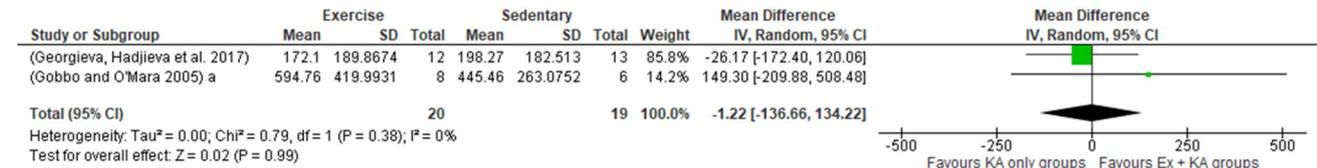
**Fig. 1** Forest plot illustrating mean differences in Seizure Rating Score after KA injection in exercised (Ex+KA) versus sedentary (KA only) animal models. CI; test for heterogeneity, Chi-squared sta-

tistic with its degrees of freedom (d.f.) and p-value; I<sup>2</sup>, inconsistency among results; test for overall effect, Z statistic with the p-value



**Fig. 2** Forest plot illustrating risk ratios of mortality rate after KA injection in exercised (Ex+KA) versus sedentary (KA only) animal models. CI; test for heterogeneity, Chi-squared statistic with

its degrees of freedom (d.f.) and p-value; I<sup>2</sup>, inconsistency among results; test for overall effect, Z statistic with the p-value



**Fig. 3** Forest plot illustrating mean differences in BDNF level after KA injection in exercised (Ex+KA) versus sedentary (KA only) animal models. CI; test for heterogeneity, Chi-squared statistic with

its degrees of freedom (d.f.) and p-value; I<sup>2</sup>, inconsistency among results; test for overall effect, Z statistic with the p-value

inclusion criteria and summarized in systematic review table. One study [37] suggested a positive influence of 30 days swimming (initiated either immediately after SE or 60 days later) to attenuate the learning and memory deficits due to KA-induced SE, assessed through multiple behavioral tests. Similar results were already reported by Chen et al. [38] who used forced running. Two included studies explored that exercise intervention after SE enhanced neurogenesis in limbic [5, 38] as well as motor cortex areas [5] of rats.

**Study Quality and Risk of Bias**

The median and mode of quality scores according to modified CAMARADES 10-item study quality checklist were 5 (range: 3–8). Included studies were found overall at high risk of bias when evaluated through SYRCLÉ’s risk of bias

tool for animal studies [33]. Risk of bias and studies quality assessment is given in Tables 3 and 4 respectively.

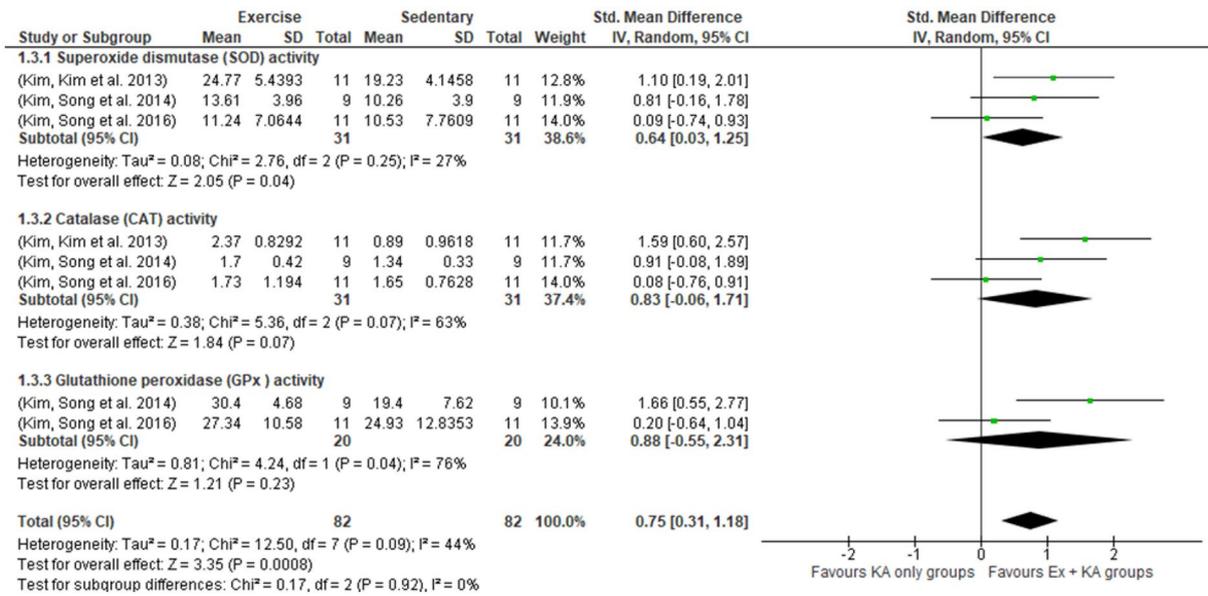
**Discussion**

**Exercise Intervention Before Induction of SE**

As most of the included studies (11 out of 14) enumerated the effects of pre-SE exercise interventions on different outcomes after KA-induced SE, so we have discussed their effects on major reported outcomes separately.

**Effect of Exercise on Behavioral Seizures and KA-Induced Mortality Rate**

Beneficial effects of exercise on behavioral seizures were already quantified in pilocarpine-induced SE models through



**Fig. 4** Forest plot illustrating standardized mean differences in Antioxidant Enzymes level after KA injection in exercised (Ex + KA) versus sedentary (KA only) animal models. CI; test for heterogeneity,

Chi-squared statistic with its degrees of freedom (d.f.) and p-value; I<sup>2</sup>, inconsistency among results; test for overall effect, Z statistic with a p-value

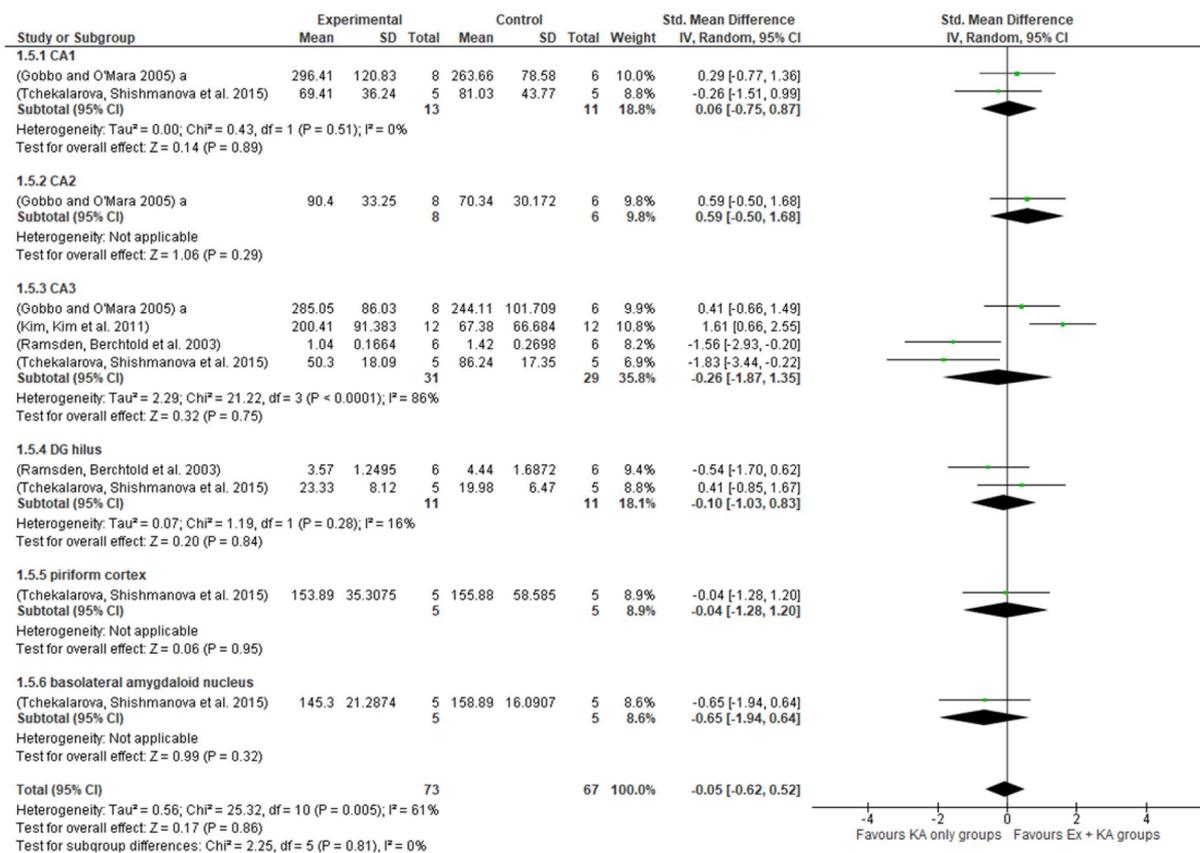
**Table 2** Meta-analysis for neuron number in different brain areas assessed after KA-induced SE in pre-SE exercised and non-exercised animals

Brain area	n (animals)	n (studies)	SMD	95% CI	p-value	I <sup>2</sup>
CA1	24	2	0.06	[-0.75, 0.87]	0.89	0%
CA2	14	1	0.59	[-0.50, 1.68]	0.29	NA
CA3	60	4	-0.26	[-1.87, 1.35]	0.75	86%
DG hilus	22	2	-0.10	[-1.03, 0.83]	0.84	16%
Piriform cortex	10	1	-0.04	[-1.28, 1.20]	0.95	NA
Basolateral amygdaloid nucleus	10	1	-0.65	[-1.94, 0.64]	0.32	NA

SMD standardized mean difference, CI confidence interval, NA not applicable, DG dentate gyrus

the previous meta-analysis by our group [11]. This review also gave the same results, thus reflecting the positive impact of exercise interventions in reducing behavioral seizures after SE. All studies reported either reduction or no-effect [21] of exercises on seizures' activity. None of the included studies reported any negative influence of exercise in this domain. Forest plots on seizure rating score and mortality rate after SE (Figs. 1, 2 respectively) clearly indicate the significance of exercise interventions in reducing both. Just one out of three studies reported no significant effect of exercise in lowering median seizure score, possibly due to use of low-intensity swimming while other two studies using resistance swimming exercises reinforced our previous finding [11] of resistance PT in lowering seizure activity more effectively than other exercise modalities.

In order to explore underlying mechanisms, an included study [22] revealed a potential pathway of protection that exercise affords against seizure-related behaviors, a mechanism that may specifically implicate suppression of glutamate release in the hippocampal formation. Exercise may possibly bolster an extrinsic, inhibitory system that normalizes hippocampal excitability [22]. Another study [24] provided further evidence that long term activity wheel running reduced seizure-related behaviors induced by KA administered either centrally or systemically, and they reversed this effect by central administration of the galanin antagonist, M-40, hypothesizing that increase in endogenous galanin may, therefore, be necessary for decreased seizure severity following exercise. Other possible mechanisms involved in lowering these behavioral seizures are explained in coming sections of this discussion.



**Fig. 5** Forest plot illustrating standardized mean differences in Neuron number in different areas of the brain after KA injection in exercised (Ex + KA) versus sedentary (KA only) animal models. CI; test

for heterogeneity, Chi-squared statistic with its degrees of freedom (d.f.) and p-value; I<sup>2</sup>, inconsistency among results; test for overall effect, Z statistic with the p-value

### Effect of Exercise on Biochemical Variables

Although an increased level of BDNF was reported after exercise in pilocarpine-induced SE models in our previous meta-analysis [11], present meta-analysis failed to provide any conclusive suggestion about BDNF concentration changes after exercise in KA models because of a limited number of available studies on this outcome. While previous studies have linked physical exercise with increased brain BDNF expression [39], the exact role of BDNF in epileptogenesis is still uncertain as some reports revealed that increased hippocampal BDNF could be pro-epileptogenic [40], other suggested this neurotrophic factor may attenuate epilepsy as mature BDNF favors survival or regeneration (or both) of hippocampal neurons damaged by SE [41]. An included study showed no changes in serum BDNF concentration after pre-SE exercise intervention and attributed this result to the fact that BDNF was measured a month after the training period or the other possible reason may be the low intensity of physical training in this study [26]. As this study [26] just measured the serum BDNF level but not the BDNF level at different brain areas, its result has

limited implication due to this reason as well. Other two studies (both by same authors) gave very contrasting results, one study [27] reported increased BDNF in KA models as compared to normal control and exercise further enhanced BDNF level in KA group. The second study reported less BDNF level in Ex + KA + Cxb (celecoxib co-treated group) as compared to KA only group [25], possibly due to co-treatment. So, due to this much heterogeneous data and less number of studies evaluating BDNF level in KA exercised models, there is a need for more studies to give a concluding comment on this variable.

Oxidative stress held responsible in the pathogenesis of a number of neurological illnesses and neurodegenerative disorders, including epilepsy [23]. Especially, KA increases ROS production thus causing apoptosis in hippocampal CA1 and CA3 regions and DG [42]. Experimental evidence designates the antioxidants' protective effect against neuronal damage [43]. Free radical scavengers, such as SOD and reduced glutathione are defensive against seizure-induced oxidative damage [21]. SOD is an important antioxidant enzyme that can remove superoxide anions from cells [44]. Three studies with 62 animals evaluated the significantly

**Table 3** SYRCLÉ's risk of bias tool for animal studies

Domain	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other sources of bias
	1 Sequence generation	2 Baseline characteristics	3 Allocation concealment	4 Random housing	5 Blinding	6 Random outcome assessment	7 Blinding			
Exercise intervention before induction of status epilepticus										
[26]	N	Y	N	U	N	U	N	Y	Y	Y
[21]	N	Y	N	N	Y	N	N	U	Y	Y
[20]	N	Y	N	U	Y	N	Y	Y	Y	Y
[22]	N	Y	N	U	Y	N	Y	U	Y	Y
[7]	N	Y	N	N	Y	N	N	U	Y	Y
[23]	Y	Y	N	U	N	U	N	U	Y	Y
[47]	N	Y	N	U	N	N	Y	Y	U	U
[24]	N	Y	N	N	N	N	Y	Y	Y	Y
[25]	N	Y	N	N	N	N	N	U	U	U
[27]	N	Y	N	N	N	U	N	Y	Y	Y
[36]	N	Y	N	U	N	U	Y	Y	U	Y
Exercise intervention after induction of status epilepticus										
[37]	N	Y	N	U	N	N	N	U	Y	Y
[5]	N	Y	N	N	N	N	Y	U	Y	Y
[38]	N	Y	N	N	N	N	N	U	Y	Y

Y Yes (low risk of bias), N no (high risk of bias), U unclear (unclear risk of bias)

**Table 4** MODIFIED CAMARADES TOOL for study quality assessment

Author	Year	1	2	3	4	5	6	7	8	9	10	Quality score
Exercise intervention before induction of status epilepticus												
[26]	2017	Y	Y	Y	N	N	Y	Y	N	Y	N	6
[21]	2015	Y	Y	Y	N	N	N	Y	N	Y	N	5
[20]	2015	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8
[22]	2015	Y	Y	Y	N	Y	N	N	N	Y	Y	6
[7]	2014	Y	Y	Y	N	N	N	Y	N	Y	N	5
[23]	2012	Y	Y	Y	N	N	N	Y	N	Y	N	5
[47]	2011	Y	N	N	N	Y	N	Y	N	Y	N	4
[24]	2009	Y	Y	Y	N	Y	N	N	N	Y	N	5
[25]	2005	Y	N	N	N	N	N	Y	N	Y	N	3
[27]	2004	Y	Y	N	N	N	N	N	N	Y	N	3
[36]	2003	Y	N	Y	N	Y	N	N	N	N	N	3
Exercise intervention after induction of status epilepticus												
[37]	2016	Y	N	Y	N	N	N	U	N	Y	N	3
[5]	2016	Y	N	N	Y	Y	N	N	N	Y	Y	5
[38]	2006	Y	Y	Y	N	N	N	N	N	Y	N	4

Study quality items are: (1) publication in a peer-reviewed journal; (2) statement of control of temperature; (3) Randomization to treatment or control; (4) blinded induction of status epilepticus (i.e., concealment of treatment group allocation at the time of induction of status epilepticus); (5) blinded assessment of outcome; (6) a measure of trainability and inclusion of scale 3 or above animals, (7) adaptation/familiarization to exercise apparatus; (8) sample size calculation; (9) statement of compliance with regulatory requirements; and (10) statement regarding possible conflicts of interest

( $p=0.04$ ) increased SOD level in cerebral cortex as a result of pre-SE exercise intervention, showing  $SMD=0.64$ , [95% CI 0.03, 1.25], with minimal heterogeneity ( $I^2=27\%$ ). Enhanced hydrogen peroxide is reduced to water by peroxidases, mostly GPx in the brain. GPx levels in neuronal tissues appear relatively low for the prevention of peroxide insults [42]. Two studies with 40 animals documented the increased levels of GPx, although not statistically significant ( $SMD=0.88$ , [95% CI  $-0.55$ , 2.31],  $p=0.23$ ,  $I^2=76\%$ ). Similarly higher levels of CAT (nearly significant with  $p=0.07$ ) were observed in same three studies measuring SOD with  $SMD$  of 0.83 (CI  $-0.06$ , 1.71). Moderate level of heterogeneity ( $I^2=63\%$ ) in CAT analysis results was due to a study [21] which used low-intensity PT as compared to other 2 (these 2 used some load resistance during swimming), exclusion of which made  $I^2=0\%$ .

A close association was suggested between epilepsy and psychiatric comorbidities with a disturbance in monoamine (MA) systems of the brain such as serotonin (5-HT), noradrenaline and dopamine evaluated by on numerous preclinical and clinical studies [10]. Physical exercise can positively modify MA levels in different brain regions [45], thus supporting the clue that their restoration might add to the beneficial influence of exercise. An included study [20] examined the increased level of 5-HT in the hippocampus of SHR KA rats and assumed that the increased 5-HT discharge from the hippocampus facilitates the beneficial effects of aerobic exercises on seizure susceptibility, thus

resulting in positive behavioral outcomes in their model of epilepsy and hypertension comorbidity.

### Effect of Exercise on the Histological Profile

Injection of KA, which is an analog of the L-glutamate (excitatory amino acid), results in neuronal death in hippocampus along with epileptic behavioral changes [46] via excessive neuronal activation as a product of energy exhaustion and oxidative stress [47]. Four studies in our review tested the effect of pre-SE exercise interventions of this neuronal damage by various staining techniques and in different brain regions, particularly in the hippocampus. Overall meta-analysis and sub-groups quantitative analysis (Table 2) of this outcome gave the insignificant effect of prior exercise on the protection of neuronal damage due to KA-induced SE. Systematic review shows that two studies [20, 27] with 24 animals demonstrated no effect of exercise on the protection of CA1 neurons and 1 of those [27] gave the same results on CA2 neurons as well. Among four studies assessing CA3 neurons, one study [47] documented a positive effect of chronic exercise in preventing neuronal loss, 1 [27] found no effect while other 2 [20, 36] noticed increased neuronal death in CA3 areas due to pre-SE exercise intervention. Interestingly, the only study which reported beneficial effect used mice (other three studies used rat models) and 8 weeks of exercise intervention (other 3 applied this intervention for less than a month). Possibly

the differences in species and intervention's duration produced such contrasting results. Similarly, two studies [20, 36] on 22 animals reported the failure of exercise intervention on neuro-protection in hilus of DG. One of those [20] also reported the same results in piriform cortex and basolateral amygdaloid nucleus. So according to these studies, collectively we can comment that pre-SE physical training cannot prevent neuronal damage. This result is somewhat contrary to the effect of exercise in pilocarpine-induced SE models where exercise proved beneficial in providing neuro-protection in CA1 area particularly [11].

### Effect of Exercise on Cognitive Abilities

One of the frequent SE associated neurological co-morbidities is impaired cognition and distressed emotional behavior [48]. Neurological abnormalities observed in humans are much similar to those reported in SE models. Efficacy of exercise on cognition and neuroplasticity was already reviewed comprehensively [49]. Four studies included in our review analyzed the effect of pre-SE exercise intervention on this comorbidity of KA-induced epilepsy. A study [26] concluded that exercise exerted a beneficial impact on depression-like and impulsive behavior in co-morbid models of SE and essential hypertension, by assessing through sucrose preference and hole-board test. In two different studies [25, 27] by the same group, one [27] reported that exercise, but not the enriched environment, improved behavioral act in Morris water maze as well as in object exploration tasks. However, Pre-SE exercise did not reduce the KA-induced hyperactivity to the control levels as shown by ambulation in the open field task. The other study [25] with same intervention but with co-treatment of celecoxib (COX-2 inhibitor) failed to improve behavioral performance in Morris water maze and object exploration tasks. A study by J. Tchekalova et al. [20] found that exercise failed to reduce hyperlocomotion after SE in the OF test but it affected exploration, hopelessness-like behavior, anxiety, and anhedonia positively in SHRs. They concluded that long-term aerobic exercise positively affects seizure susceptibility, object recognition memory, exploratory behavior, anxiety, and depression, along with the increased hippocampal 5-HT release.

### Exercise Intervention After Induction of SE

Only three studies met our inclusion criteria and these studies focused effect of post-SE exercise interventions on neurogenesis and cognitive outcomes. More studies are required in this domain to explore the effect of post-SE PT on morphological and biochemical profiles.

Animal studies on acute seizures and limbic epileptogenesis indicate that prolonged seizures vigorously stimulate hippocampal neurogenesis [50]. In the adult rodents, KA and

pilocarpine models of TLE robustly increase DG cell proliferation after a latent period consisting of several days [50]. Furthermore, while at the acute phase of TLE, hippocampus displayed augmented dentate neurogenesis [51], the chronically epileptic hippocampus presented with severely declined neurogenesis, which was accompanied with considerable SRSs [1, 52]. One included study [38] revealed that post-SE moderate intensity exercise (for seven days) further increases the neurogenesis in DG assessed through BrdU+ cells counting. But this study was limited to cell proliferation part only, and still, there is lack of information on how post-SE exercise effects the cell survival and differentiation and what is the functional significance of this exercise-induced neurogenesis during acute stage in SE models. Another study [5] applied an exercise intervention consisting of daily swimming (for 15 min) for a 30 days period, starting immediately after SE induction in one experiment (immediate exposure) and 60 days after SE in another experiment (delayed exposure). They reported that exercise intervention (both immediate and delayed exposure) increased neuron numbers and, dendritic branch points and intersections in normal control and KA rats in all examined limbic and motor cortex regions. So they reported that exercise can be used as a measure to enhance neurogenesis in chronic SE when there is severely declined neurogenesis due to SE and it may improve neural plasticity in areas of the brain involved in this pathology. Another study [37] by the same group using the same intervention at same time points documented that swimming exercise (in both immediate and delayed exposure groups) can reduce the learning and memory deficits. This effect of swimming exercise may be dedicated to augmented neurogenesis in the chronic stage as reported in their previous study [5].

### Study Limitations

This review may be at the risk of some biases that deserve discussion. First, we have included only English language studies and we might be unable to include some studies published in other languages. Second, as average study quality and high risk of bias were assessed in included studies, this review suggests to enhance study quality and reduce the risk of bias in future studies of this domain. In addition, sex-specific differences in reported outcomes cannot be ruled out, because all of the included studies used adult male animals except one which used female rats [36]. The sex-dependent effect has already been suggested in both animal models [53, 54] and humans [55]. Due to the least number of available studies in female models, we cannot interpret this difference and future studies are highly recommended to elucidate these gender-based responses to exercise interventions. Likewise, we recommend further studies to explore the effect of different exercise modalities, their adequate

duration, and induction timing and cannot generalize our data in this regard.

## Conclusion

Physical exercise before SE reduces behavioral seizures, KA-induced mortality and oxidative stress with improved cognitive abilities. More extensive research on morphological and biochemical profiles is needed to explore underlying mechanisms. Post-SE exercise enhances learning and memory with neurogenesis in KA models. These findings could be helpful in further research and devising complementary clinical therapies for epileptic patients.

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## Compliance with Ethical Standards

**Conflict of interest** The authors have no conflict of interest to declare.

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