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Review

Beneficial effects of whole-body vibration exercise for brain disorders in experimental studies with animal models: a systematic review

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ABSTRACT

Brain disorders have been a health challenge and is increasing over the years. Early diagnosis and interventions are considered essential strategies to treat patients at risk of brain disease. Physical exercise has shown to be beneficial for patients with brain diseases. A type of exercise intervention known as whole-body vibration (WBV) exercise gained increasing interest. During WBV, mechanical vibrations, produced by a vibrating platform are transmitted, to the body. The purpose of the current review was to summarize the effects of WBV exercise on brain function and behavior in experimental studies with animal models. Searches were performed in EMBASE, PubMed, Scopus and Web of Science including publications from 1960 to July 2021, using the keywords "whole body vibration" AND (animal or mice or mouse or rat or rodent). From 1284 hits, 20 papers were selected. Rats were the main animal model used (75%) followed by mice (20%) and porcine model (5%), 16 studies used males species and 4 females. The risk of bias, accessed with the SYRCLE Risk of Bias tool, indicated that none of the studies fulfilled all methodological criteria, resulting in possible bias. Despite heterogeneity, the results suggest beneficial effects of WBV exercise on brain functioning, mainly related to motor performance, coordination, behavioral control, neuronal plasticity and synapse function. In conclusion, the findings observed in animal studies justifies continued clinical research regarding the effectiveness and potential of WBV for the treatment of various types of brain disorders such as trauma, developmental disorders, neurogenetic diseases and other neurological diseases.

1. Introduction

Brain disorders have been a health challenge since their prevalence have been increasing over the years [1], as can be seen in the steadily increasing numbers of people affected worldwide [2,3]. Despite the human health concern, some brain disorders such as trauma (spinal cord and head injury) [4,5], developmental disorders (such as cerebral palsy) [6], neurodegenerative diseases (such as Parkinson's disease and Alzheimer's disease) [7–9], neurogenetic diseases (Huntington's disease and muscular dystrophy) [10,11], convulsive disorders (such as epilepsy) [12] are recognized for their complexity [13]. Based on their manifestation, these disturbances are difficult to treat, and can have a devastating effect on individuals' health during a lifetime [14]. Moreover, they can have serious consequences for society, due to a heavy care demand, which can overburden the health-care system [15].

In response to complexity and the need for information, clinical studies investigated therapeutic approaches to treat patients with brain disorders [16–19], while experimental studies explored brain regions, providing an integrative neurobiological framework of the underlying mechanisms, which culminate from behavioral, metabolic, endocrine, and energy balance processes into neurobiological processes related to these disturbs [9,20,21]. Thus, understanding factors that lead to these

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neurological manifestations might allow the formulation and application of preventive strategies able to regulate neural functioning in these manifestations, giving basis for new treatment options [22–24].

Brain diseases are characterized by chronic and progressive deterioration in cognitive functions and behaviour, loss of physical function, muscle strength, quality of life, psychological symptoms and other comorbidities [25,26]. Currently, there are pharmacological treatment options available to influence the course of brain diseases [27,28]. Early diagnosis and interventions are considered essential strategies to treat people with the risk of brain diseases [29–31].

Non-pharmacological treatments have been important for the improvement of cognitive functions [32–34]. In line with this notion, physical exercise has demonstrated a positive impact on neurodegeneration [35]. In fact, physical exercise can represent a potential treatment option in individuals with neurological issues [36]. The importance of exercise training in driving neural circuitry, improving brain function, hippocampal plasticity and memory, and reducing secondary complications is well documented, but factors influencing training outcomes are diverse [37,38]. However, in many cases, individuals with moderate to severe brain disorders are often unable to adhere to the physical activity regimen due to the complications triggered by the disease [39].

Accordingly, whole-body vibration (WBV) exercise has been proposed as an alternative for active exercise for those that cannot participate in active exercise, for example due to physical or mental issues [40,41]. WBV is an exercise modality or treatment/prophylaxis method in which subjects are exposed to mechanical vibrations through a vibrating platform [42]. During WBV subjects can perform dynamic exercises on the platform or take a static posture [43]. The vibrations produced by the platform are defined by mechanical parameters, like frequency, amplitude, or peak-to-peak displacement, and peak acceleration [40,43]. Over time, WBV exercise has acquired acceptance for a number of clinical conditions including physical disability [44], sports injuries [45], multiple sclerosis [46], osteoporosis [47], lumbar disk disease and lower back pain [44,48] and cerebral palsy [49]. WBV has been used in different patient groups [50] and athletes [51] to improve functional mobility and neuromuscular performance, including endurance, power and muscle strength. Moreover, in spinal cord injury (SCI), WBV training reduces muscle spasticity, improves spinal reflex modulation [52,53], walking function [54] and quadriceps strength in motor incomplete patients [55], which increasing the interest of WBV exercise as a clinical therapy after SCI.

WBV exercise has been shown to be a suitable intervention under many different conditions. However, the effects of WBV exercise on metabolic intermediates related to signaling pathways, as well as neuroprotective mechanisms to delay or to disrupt the neurodegenerative processes remain unclear [56,57]. WBV can also be applied to (small) animals with high translational relevance [42]. Animal models, with various approaches, have been used to try understanding biological responses to WBV exercise (acute and cumulative), as well as to evaluate which effects can be observed from the low to high intensity vibration, considering its transferability for humans investigations. [59–64]. Therefore, the purpose of current systematic review is to summarize the results of experimental studies in animal models into the effects of WBV exposure on brain and behavior. The findings might reinforce the efficiency and safety of WBV exercise in improving human brain functioning and neurobehavioral performance, which may serve as a reference for the design of new clinical trials.

2. Methods

2.1. Search strategy

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA statement] [65]. English electronic databases were systematically searched to identify animal studies that used WBV. The literature search was performed on PubMed, Scopus, Embase and Web of Science (on July 4th, 2021), using the keywords "whole body vibration" AND (animal or mice or mouse or rat or rodent).

The guiding question was: Does WBV exposure cause alterations on brain functioning and behavior in animal models? The PICOS method was used, and the acronym defines: Problem (P)– limited knowledge about underlying mechanisms from WBV intervention in a neurobiological evaluation/ perspective; Intervention (I)– WBV; Comparison (C)– other treatments or no comparison; Outcome (O)– Comprehension about what effects WBV exposure can promote on brain structure, brain function and neuromuscular functions; Study design (S)– experimental intervention studies.

2.2. Inclusion and exclusion criteria

A systematic selection of the publications was carried out by two independent examiners (A.C and A.R) based on the following inclusion criteria: 1) animal studies 2) in vitro trials or in vivo measurements to investigate the effects of WBV intervention on brain functioning and behaviour; 3) outcome measures are related to brain functioning or behaviour; 4) evaluation of short and/or long-term intervention; 5) full-text literature published in English. Short communications, case reports, review articles, books, expert opinion or consensus statements were excluded. Also excluded were those publications that used WBV to induce stress for a drug treatment protocol; to treat chronic conditions such as diabetes, cardiovascular diseases; or used WBV associated with other product or therapy.

2.3. Data extraction

Data were extracted from the full-text version of the publications by three reviewers (A.C, D.S and N.A). Data included the year of publication, authors, species, aim, WBV device, WBV variables, period of intervention, study design, parameters evaluated, outcomes and conclusion. Discrepancies were discussed with a fourth reviewer (M.B).

2.4. Appraisal of risk of bias

The risk of bias was assessed by three independent reviewers (A.C, M. H and A.R) using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) protocol [66]. The disagreements were solved by a fourth reviewer (M.B). Adapted version of Hooijmans et al. [66], in which in case of missing information an unclear risk of bias is scored instead of a low risk of bias. Disagreements were discussed with a fifth reviewer (E.Z).

3. Results

3.1. Search results

The search strategy performed in electronic databases, resulted in 1284 hits, yielding 257 articles from PubMed, 435 from Scopus, 221 from Embase and 371 from Web of Science, containing publications from 1960 to 2021. After removing duplicates (605 articles), 422 papers were screened, on tittles and abstracts. Of those, 376 publications were excluded because the abstracts showed that they did not match the inclusion criteria. Thus, 46 studies were identified as potentially eligible and subjected to more detailed analysis. Twenty-six were eliminated for the following reasons: 1) papers used WBV for treating different conditions (diabetes mellitus type 2 and for fluoxetine hydrochloride efficacy); 2) papers used another intervention (noise) combined with WBV to test for stress responses; 3) papers did not specify the sample or even the device used for WBV exercises and 4) studies with different goals, such as those used to characterize the resonance of the spine, acutely injured spinal cord, to determine the range of frequency values where

animals are unable to attenuate vibrations and for in vivo electrophysiological recordings (Fig. 1).

3.2. Selected studies

As shown in Table 1, the 20 selected articles were organized by year of publication, authors, animal species, aim, WBV device, WBV variables, duration of intervention and study design (Table 1). Although some studies (40%, n = 8) included healthy animals models, a larger number of studies (60%, 12 studies) included animals models with clinical conditions such as SCI, cerebral ischemia, Parkinson's disease (PD), sciatic injury, chronic restraint stress (CRS) and brain injury. All results related to the effects of WBV on brain functions or behavioral performance were considered.

Rats (*Rattus norvegicus*) were the main animal model used (15 studies), followed by mice (*Mus musculus*, 4 studies) and a porcine model (*Sus scrofa domesticus*, 1 study). 70% (14 studies) of the animals were males and 30% (6 studies) females. Moreover, in regard to rat strains, most studies preferred Wistar rats (40%, 8 studies), followed by Sprague-Dawley (25%, 5 studies) and Holtzman rats (10%, 2 studies). Among mouse strains studies, 15% of the studies used C57BL/6 J (3 studies) and 5% used CD1 (1 study), while the porcine lineage was Yucatan (5%, 1 study). Only 7 studies reported the age of the animals, which ranged from 2 to 26 weeks. The body mass of the rats ranged from 175 to 350 g, porcine weighted from 20 to 30 kg and only one study using a mice model reported the weight (25–30 g). The average sample size in selected studies was 40.

Most of the studies (14 studies) were published in the last six years, while six studies were published between 1983 and 2014. In addition, 35% of the studies were conducted in North America (USA, 6 studies; Canada, one study), following by 30% in Europe (Germany, 4 studies; the Netherlands, 2 studies), 30% in Asia (Japan, 3 studies; China, 3 studies) and 5% by South America (Brazil, one study).

The source of mechanical vibration varied among the studies. The devices that were most often used, were a Galileo alternating model 25% (5 studies) and an electromagnetic vibration motor set by a power amplifier 20% (4 studies). Also, custom types of platforms were used for WBV intervention (20%, 4 studies). Regarding to study design, most of the studies (80%, 16 studies) decided for a chronic protocol with WBV, while 20% (4 studies) for an acute protocol. Furthermore, 50% of the studies (10 studies) used a fixed frequency in WBV exposure, while the other 50% (10 studies) decided for variable frequency. In addition, 60% (12 studies) of the protocols used only one bout with duration ranged from 5 to 240 min/ day, 25% (5 studies) decided for five sequential bouts comprised of 3 min/ session, 5% (one study) adopted two bouts with 5 min by session and 5% (one study) decided for fifteen bouts with 1 min per session. The rest time interval adopted between the bouts ranged from 30 s to 1 min 30 s

None of studies reported which body part received most of the vibrations. Also, the behavior (next to the body position) of the animals during vibration was not mentioned, it is relevant to report whether all parts of the body receive the vibration to a comparable degree and level

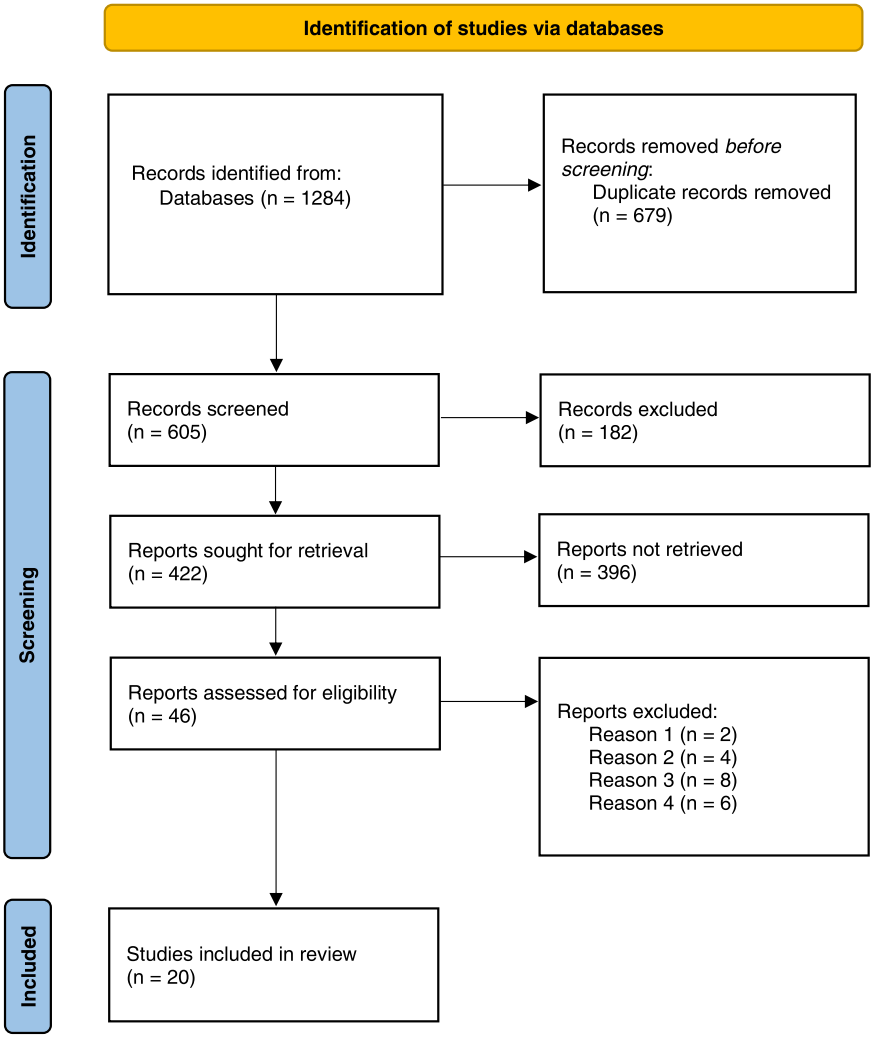

Fig. 1. Flow chart of study selection process based on PRISMA guidelines.

Table 1
Summary of in vivo experimental studies investigating the effects of WBV on brain and behaviour.

Authors	Species	Aim	WBV device	WBV variables	Period (days a week) Duration of bouts	Study design	Country
[93]	Male Wistar rats (n = 53)	To evaluate the morphometric and functional effects of WBV in an experimental nerve regeneration model	TBS 100 – aspiral vertical model	f: 15,30 Hz/ apeak: 0.9, 3.6 g	5-Weeks (5 days) 5 bouts: - 3 min = 1 min (15 Hz) and 2 min (30 Hz)	Chronic - Naive group (n = 10) - Sham-operated group (n = 10) - Non-trained group (n = 11) - Vibration group 3d (n = 11) - Vibration group 10d (n = 11)	Brazil
[67]	Male Sprague-Dawley rats (n = 18)	To examine the effects of WBV training on a chronic restraint stress (CRS) induced depression rat model and provide an initial understanding of related molecular mechanisms	ZB - alternating model	f: 30 Hz/ A: 4.5 mm	8-Weeks (6 days) 1 bout: - 30 min	Chronic - Control group (n = 5) - CRS group (n = 6) - CRS+WBV group (n = 7)	China
[77]	Male C57Bl/ 6 J mice (n = 20)	To evaluate effects of WBV on brain functioning	Oscillator and Power amplifier	f: 30 Hz/ A: 0.0537 mm	5-Weeks (5 days) 1 bout: - 10 min	Chronic - pseudo WBV group (n = 10) - WBV group (n = 10)	Netherlands
[62]	Female Sprague-Dawley rats (n = 15)	To verify efficacy of WBV in reducing post-ischemic stroke frailty and brain damage in reproductively senescent female rats	Galileo – vertical model	f: 40 Hz/ apeak: 0.3 g	30 days (5 days) 2 bouts: - 15 min	Chronic - No-WBV group (n = 8) - WBV group (n = 7)	United States
[8]	Male Sprague-Dawley rats (n = 115)	To determine effects of daily WBV on behavioral performance, brain structure, and neurogenesis after cerebral ischemia	N/A	f: 15 Hz/ A: 1.9 mm	4-Weeks (5 days) N/A	Chronic - Control group (n = 50) - Sham group (n = 15) - WBV group (n = 50)	China
[38]	Female Wistar rats (n = 52)	To evaluate effects of WBV on locomotor and bladder functions and the influences on synaptic plasticity following spinal cordy injury (SCI) in rats	Galileo - alternating model, custom device for rats	f: 15,30 Hz/ A: 1.5 mm	12-Weeks (5 days) 5 bouts: - 3 min = 1 min (15 Hz) and 2 min (30 Hz)	Chronic - Intact animals (n = 5) - SCI Control group (n = 8) - WBV-day1 (n = 9) - WBV-day7 (n = 8) - WBV-day14 (n = 9) - WBV-day28 (n = 5) - 2xWBV-day14 (n = 7) - PFE group (n = 50)	Germany
[78]	Male CD1 Mice (n = 40)	To verify effects of WBV long-term exposure on attention and motor performance in mice.	Oscillator and Power amplifier	f: 30 Hz/ A: 1.9 mm	5-Weeks (5 days) 1 bout: - 5 min (30 Hz) - 30 min (30 Hz)	Chronic - Pseudo-WBV 5 min (n = 12) - WBV 5 min (n = 12) - Pseudo-WBV 5 min (n = 10) - WBV 30 min (n = 10)	Netherlands
[58]	Male Holtzman rats (n = 18)	To evaluate effects of different WBV exposures on hind paw behavioral sensitivity and neuroinflammation in the lumbar spinal cord.	SmartShaker™ with Integrated Power Amplifier	f: 8,15 Hz/ A: 1.5, 5 mm	5-Weeks (5 days) 1 bout:	Chronic - Sham control group (n = 6)	United States

(*continued on next page*)

Table 1 (*continued*)

Authors	Species	Aim	WBV device	WBV variables	Period (days a week) Duration of bouts	Study design	Country
					- 30 min	- WBV 8 Hz (n = 6) - WBV 15 Hz (n = 6)	
[73]	Female Wistar rats (n = 80)	To determine effects of WBV on various aspects of the musculo-skeletal system over a 12-week period following compression SCI	Galileo - alternating model, custom device for rats	f: 15,30 Hz/ A: 1.5 mm	5-Weeks (5 days) 5 bouts: - 3 min = 1 min (15 Hz) and 2 min (30 Hz)	Acute and Chronic - Intact animals (n = 5) - SCI Control group (n = 8) - WBV-day1 (n = 9) - WBV-day7 (n = 8) - WBV-day14 (n = 9) - WBV-day28 (n = 5) - PFE group (n = 50)	Germany
[90]	Female miniature Yucatan pigs	To investigate consequences of resonance vibration on the injured spinal cord.	Electromechanical shaker	f: 5, 6.6 Hz	12-Weeks 1 bout: - 90 min (5–6.6 Hz) - 180 min (5–6.6 Hz)	Chronic - Control group (n = 12) - 1.5 h resonance - vibration group (n = 8) - 3 h resonance - vibration group (n = 8)	Canada
[92]	Male Sprague-Dawley rats (n = 72)	To evaluate effects of WBV for long periods on brain function.	Electromagnetic vibration motor set by a power amplifier	f: 30 Hz/ apeak: 0.5 g	2–8-Weeks (5 days) 1 bout: - 240 min	Chronic - 2-week control group (n = 8) - 2-week sham group (n = 8) - 2-week WBV (n = 8) - 4-week sham (n = 8) - 4-week WBV (n = 8) - 4-week WBV 4 F-Prc (n = 8) - 8-week sham (n = 8) - 8-week WBV (n = 8) - 8-week WBV 4 F-Prc (n = 8)	United States
Yan et al[b], 2015	Male Sprague-Dawley rats (n = 56)	To explore pathological process of the brain injury and cellular mechanism of WBV, and investigating the pathological process and evidence of human brain injury from WBV	Electromagnetic vibration motor set by a power amplifier	f: 30 Hz/ apeak: 0.5 g	2–8-Weeks (5 days) 1 bout: - 240 min	Chronic - 2-week control group (n = 8) - 2-week sham group (n = 8) - 2-week WBV (n = 8) - 4-week sham (n = 8) - 4-week WBV (n = 8) - 8-week sham (n = 8) - 8-week WBV (n = 8)	United States
[74]	Female Wistar rats (n = 19)	To determine effects of WBV on functional, electrophysiological and morphological measurements after SCI	Galileo - alternating model, custom device for rats	f: 15,30 Hz/ A: 1.5 mm	12-Weeks (5 days, twice a day) 5 bouts:	Chronic - Intact animals (n = 7) - SCI No-WBV (n = 6)	Germany

(*continued on next page*)

Table 1 (*continued*)

Authors	Species	Aim	WBV device	WBV variables	Period (days a week) Duration of bouts	Study design	Country
					- 3 min = 1 min (15 Hz) and 2 min (30 Hz)	- 2x-WBV (n = 6)	
[68]	Male Wistar rats (n = 35)	The purpose of this study was to investigate the preventive and therapeutic effects of vibration therapy on immobilization-induced hypersensitivity	Eletro vibration model	f: 80 Hz/ A: 5 mm	8-Weeks (5 days) 1 bout: - 15 min	Chronic - Control group (n = 5) - Imobilization-Im (n = 10) - Im+Vib1 (n = 10) - Im+Vib2 (n = 10)	Japan
[69]	Male C57Bl/ 6 mice (n = 25)	To investigate the effects of longer duration of low amplitude vibration (LAV) training on the numbers of dopaminergic neurons in the substantia nigra in the striatum on chronic MPTP lesion mouse	Columbus – vertical model	f: 15,30 Hz/ A: 5 mm	4-Weeks (5 days) 15 bouts: - 1 min (15 Hz) - 1 min (30 Hz)	Chronic - Control group (n = 6) - MPTP group (n = 6) - MPTP+LAV-LF (n = 7) - MPTP+LAV-HF (n = 6)	China
[79]	Male C57Bl/ 6 mice (n = 19)	To evaluate effects of daily brief periods of low intensity vibration (LIV) on neuromuscular functions and behavioral in mice.	Custom manufactured platform oscillating vertically	f: 30 Hz/ apeak: 0.3 g	4-Weeks (7 days) 1 bout: - 20 min	Chronic - Control group (n = 12) - LIV group (n = 12)	United States
[87]	Male Holtzman rats (n = 22)	To determine if brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) are expressed in cervical discs after painful WBV in a rat model.	Custom linear servomotor	f: 15 Hz/ A: 1.5 mm	1-Week (7 days) 1 bout: - 30 min	Acute - Sham control group (n = 10) - WBV group (n = 12)	United States
[72]	Female Wistar rats (n = 40)	To verify effects of WBV over a period of 12 weeks after incomplete compressive SCI in rat	Galileo - alternating model, custom device for rats	f: 15,30 Hz/ A: 1.5 mm	12-Weeks (5 days) 5 bouts: - 3 min = 1 min (15 Hz) and 2 min (30 Hz)	Chronic - Intact animals (n = 5) - SCI Control group (n = 8) - WBV-day1 (n = 9) - WBV-day7 (n = 8)	Germany
[88]	Male Wistar rats (n = 40)	To verify effects of WBV in concentration of noradrenaline (NA), dopamine (DA), and serotonin (5-HT)	Custom electromagnetic shaker coupled to an amplifier, function oscillator and a vibration meter.	f: 5,20,30 Hz/ A: 0.4, 2, 5 g	1 day 1 bout: - 240 min	Acute - Control group (n = 4) - WBV-5 Hz (n = 4) - WBV-20 Hz (n = 4) - WBV-30 Hz (n = 4) - Control group (n = 4) - WBV-0.4 G (n = 4) {20 Hz} - WBV-2 G (n = 4) {20 Hz} - WBV-5 G (n = 4) {20 Hz} - WBV-20 Hz 240 min (n = 8)	Japan
[89]	Male Wistar rats (n = 32)	To evaluate effects of WBV on the central nervous system	Custom electromagnetic shaker coupled to an amplifier, function oscillator and a vibration meter.	f: 5,20,30 Hz/ A: 0.4, 2, 5 g	1 day 1 bout: - 240 mins	Acute - Control group (n = 4) - WBV-5 Hz (n = 4) - WBV-20 Hz (n = 4)	Japan

(*continued on next page*)

Table 1 (*continued*)

Authors	Species	Aim	WBV device	WBV variables	Period (days a week) Duration of bouts	Study design	Country
						- WBV-30 Hz (n = 4) - Control group (n = 4) - WBV-0.4 G (n = 4) {20 Hz} - WBV-2 G (n = 4) {20 Hz} - WBV-5 G (n = 4) {20 Hz}	

f, frequency (Hz); A, amplitude (mm); apeak, peak acceleration in multiple of Earth's gravity (g); N/A, not available; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; WBV, whole-body vibration; PFE - passive flexion-extension.

of exercise efficiency should be stressed, and this aspect is mentioned in the recent WBV reporting guidelines of van Heuvelen et al., [42].

3.3. Risk of bias

The result of the quality assessment is shown in Fig. 2. None of the studies fulfilled all criteria. Concerning selection bias, the sequence generation process was not fully reported in 35% (7 studies) studies (Q1). In terms of animals' similarity to one another (Q2), 10% of the studies (2 studies) did not report this information clearly. Information about the allocation concealment (Q3) was not clearly reported in 90% of the studies (18 studies). Only 30% of the studies (6 studies) reported a random animal housing (Q4). 20% of the studies (4 studies) reported blinding of personnel (Q5). Random selection for outcome assessment (Q6) was applied to 20% (4 studies) of the studies. Only 30% of the studies reported blinding of outcome assessment (Q7). Incomplete outcome data (Q8) were addressed as unclear by the reviewers because the studies did not meet all questions from this topic (100%, all 20 studies).

Selective reporting (Q9) shows a low risk of in all studies. An important source of bias was the lack of information about animal models' age such as the body weight of the mice species used (Q10). In addition, 12 studies did not report whether the incomplete outcome data were adequately addressed and details of the sample size calculation as well, which was unclear to decide as a low or high risk of bias (Q10). Also, the analysis of the individual studies found a possible relation between risk of the bias and year of publication, as shown in Fig. 3.

3.4. Main findings

Regarding to chronic effects, after 1–12 weeks of WBV exercise, were observed a substantial number of findings that are considered favorable for WBV application, as summarized in Table 2. For sensorimotor parameters, WBV exercise increased motor performance [67,77–79] (Peng, Boerema, Keijser, Mettlach), isometric force production in semitendinosus skeletal muscle [79], improved animals' coordination and muscle strength of the upper limbs post-ischemia [58] and decreased fatiguing effects of intensive synaptic muscle stimulation [79]. Concerning behavioral changes, the parameters evaluated such as latency to fall off the rotarod post-ischemia [58] and recognition memory [78] showed an improvement, while the behavioral sensitivity through the withdrawal threshold in response to WBV [58] and arousal activity measures showed a decrease [77], all compared to the respective control groups.

Regarding the brain functioning parameters in cerebral ischemia models, an increased level of brain-derived neurotrophic factor (BNDF) and functional activity after middle cerebral artery occlusion was observed [62]. Also, after ischemia the number of bromodeoxyuridine-positive (BrdU+) cells at 3- to 14-days was increased [58]. Furthermore, in spinal cord injury models [38,59,72–74,90], WBV generated increased activation of microglia, macrophages, and astrocytes in the superficial dorsal horn of the lumbar spinal cord. Levels of extracellular signal-regulated kinase phosphorylation increased in neurons and astrocytes of the dorsal horn at WBV 8 Hz, and it caused denser capillary network and vascularization. WBV also increased the synaptophysin levels in response to 7 days and 14 days of

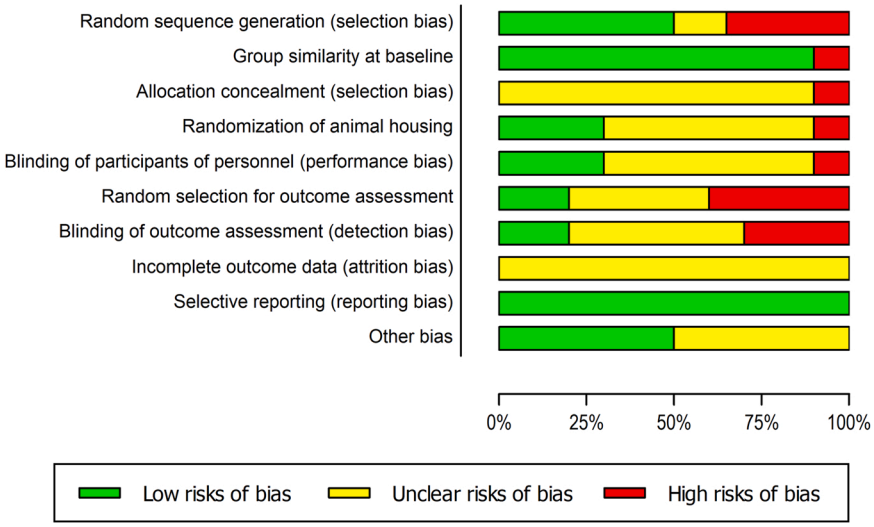

Fig. 2. Results of the risk of bias and methodological quality indicators for all included studies in this systematic review that evaluated the effect of WBV treatment on brain and behaviour in experimental models. The items in the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE). Risk of Bias assessment were scored with 'yes' indicating low risk of bias, 'no' indicating high risk of bias, or 'unclear' indicating that the item was not reported, resulting in an unknown risk of bias.

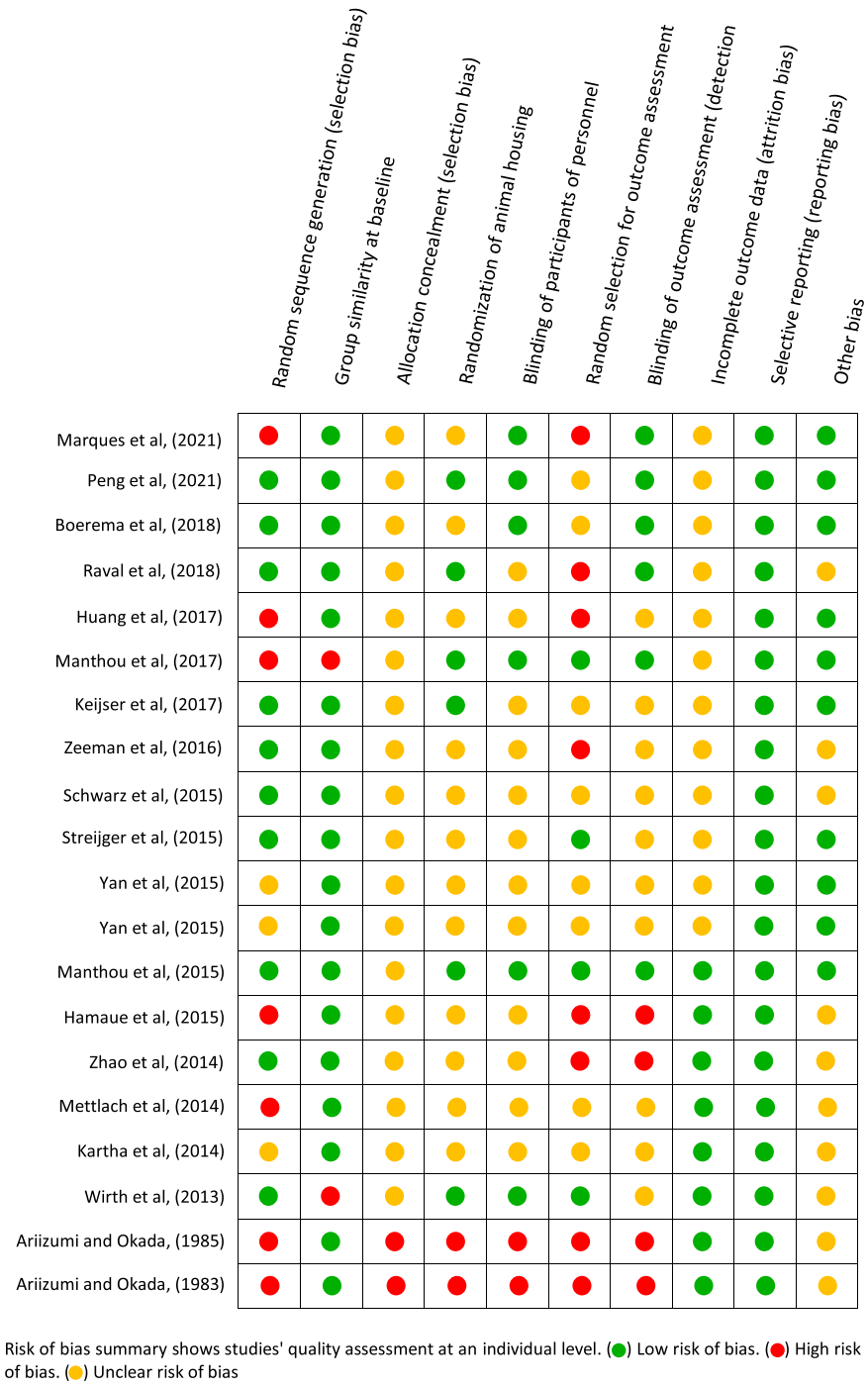

Fig. 3. Risk of bias summary shows studies' quality assessment at an individual level. (green) Low risk of bias. (red) High risk of bias. (yellow) Unclear risk of bias.

WBV exposure and restored the density of synaptic terminals in the lumbar spinal cord at 12 weeks. Additionally, in an experimental model of PD (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-MPTP) [67], WBV increased the number of dopaminergic neurons in the substantia nigra, as well as the levels of dopamine and the contents of BNDF in the striatum. In the CRS model [69], WBV improved motor and exploratory behavior as well as depression-like behaviors. Also, vibration training ameliorated spatial memory deficits after the induction of CRS and WBV increased CRS-induced downregulation of BDNF and IGF-1 proteins. Moreover, WBV reduced microglial activation and diminished CRS-induced hippocampal neuronal degeneration and reduced the activation of the apoptotic pathway. Likewise, WBV inhibited CRS-induced downregulation of dendritic and synaptic proteins.

On other hand, long-term protocols conducted in healthy animals [91,92] to investigate whether WBV caused cumulative brain injury and impairment of the cerebral function. WBV led to injuries in peripheral nervous functional effects, indicating that as longer the vibration period, more severe the injury. In turn, evidenced by increased concentration of blood NO, cerebral edema and vacuoles in the brain arteries after 8-week vibration. Furthermore, WBV decreased blood supply to the brain, as well concentration of blood O2- and mean neuron size.

In relation to the acute effects, WBV application induced an increased concentration of serotonin in the cortex at 20 Hz WBV [88]. Both serotonin and 5-hydroxyindoleacetic acid (5-HIAA) levels were increased in the brain as the vibration acceleration was increased (2.0–5.0 g) [89]. Moreover, the vibration induced an increase in plasma

Table 2
Summary effects of WBV on brain and behaviour parameters in animals models.

Authors	Parameters evaluated	WBV outcomes
[93]	- Sciatic Functional Index (SFI) (locomotor performance) - Horizontal Ladder Rung Walking Test (HLRWT) (sensorimotor) - Narrow Beam Test (NBT) (balance performance) - - Morphometric analysis (distal portion, peripheral and central of the right sciatic nerve)	↑ partial functional recovery (SFI) ($p < 0.05$)[a]
[67]	- Body weight growth rate - Sucrose preference test (depression-like behavior) - Open field test (locomotor and exploratory behavior) - Elevated plus maze test (anxiety-like behavior) - Barnes maze test (spatial learning and memory) - Force swim test (depression-like behavior) - - Immunofluorescence staining (anti-synaptophysin and spinophilin, anti-Map2, anti-Iba1, GFAP, Anti-Caspase-3, Anti-Caspase-9, Anti-IGF 1 and Anti-BDNF)	↑ food intake and body weight growth rate ($p < 0.05$)[a,c] ↓ CRS-induced depression-like behaviors ($p < 0.05$)[a,c] ↑ improves motor and exploratory behavior ($p < 0.05$)[a,c] ↑ ameliorated spatial memory deficits after CRS-induced ($p < 0.05$)[b] ↓ CRS-induced hippocampal neuronal degeneration and activation of the apoptotic pathway ↓ CRS-induced pathological changes of glial cells ↓ CRS-induced downregulation of dendritic and synaptic proteins ↑ CRS-induced downregulation of BDNF and IGF-1 proteins
[77]	- Balance beam (motor performance) - Arousal-induced home cage activity (behavior) - Brain glucose uptake	↑ motor performance ($p < 0.05$)[a] ↓ arousal-induced home cage activity ($p < 0.05$)[a]
[62]	- Neurodeficit scoring - Motor deficit test - - Immunoblot analysis (capase-1, capase recruitment domain-ASC, Immunoassay of brain-derived neurotrophic factor-BDNF and Tropomyosin receptor kinase-Trk-B)	↓ inflammatory markers ($p < 0.05$)[a] ↓ infarct volume ($p < 0.05$)[a] ↑ brain-derived neurotrophic factor (BDNF) ($p < 0.05$)[a] ↑ functional activity after tMCAO ($p < 0.05$)[a]
[8]	- Modified Neurological Severity Score (mNSS) - Rotarod Test - Necrotic dark shrunken neurons analysis - Double-fluorescence and immunohistochemistry - Western blotting (rabbit anti-DCX, goat anti-GFAP, chicken anti-MAP2, rabbit anti-β-actin)	↑ animals' coordination from 14d to 28d post-ischemia ($p < 0.05$)[a] ↑ muscle strength of the upper limbs at 21d and 28d post-ischemia ($p < 0.05$)[a] ↑ latency to fall off the Rotarod in WBV at 21d and 28d post-ischemia ($p < 0.05$)[a] ↑ number of bromodeoxyuridine-positive (BrdU+) cells at 3d ($p < 0.05$) and 14d ($p < 0.001$) and BrdU+ /nestin+ cells at 14d ($p < 0.01$) after ischemia. ↑ numbers of BrdU+ / NeuN+ cells at 21d and 28d after ischemia ($p < 0.001$)[a]
[38]	- Basso, Beattie, Bresnahan (BBB) rating scale, foot-stepping angle (FSA) and rump-height index (RHI) (locomotor performance) - Bladder function - Spinal cord lesion volume - Immunohistochemistry and immunohistochemical analysis (Synaptophysin, glial fibrillary acidic protein-GFAP, monoclonal Iba1 antibody-Iba1)	↑ BBB score recovery in the WBV7 and WBV14 groups (temporary) ($p < 0.05$)[a] ↑ RHI in the WBV14 and PFE groups ($p < 0.05$)[a] ↑ Bladder function in the WBV14, WBV28, 2 ×WBV and PFE groups ($p < 0.05$)[a] ↑ Synaptophysin levels in response to WBV7 and WBV14 ($p < 0.05$) ↑ Iba1 expression ($p < 0.05$)[a]
[78]		

Table 2 (*continued*)

Authors	Parameters evaluated	WBV outcomes
	- Novel object recognition and Spatial object recognition test (attention) - Balance beam test (motor performance)	↑ motor performance in the WBV5 min ($p < 0.05$)[a] ↑ novel object recognition in the WBV5 min ($p < 0.01$)[a]
[58]	- Withdrawal threshold measure in the bilateral hind paws (behavioral sensitivity) - Immunohistochemical (GFAP, Iba 1, Neuronal nuclei and phosphorylated-ERK, p-ERK)	↓ the withdrawal threshold through WBV 8 Hz group ↑ activation of microglia, macrophages, and astrocytes in the superficial dorsal horn of the lumbar spinal cord in WBV 8 Hz group ↑ extracellular signal-regulated kinase (ERK)-phosphorylation in neurons and astrocytes of the dorsal horn at WBV 8 Hz group
[73]	- BBB rating scale, beam walking test, ladder climb test (locomotor tests) - Spinal cord lesion volume - Extent of white matter sparing evaluated in lesion site - Morphological changes in the soleus muscle - Morphological changes in the femur (X-ray, densitometry, histological examination)	No influence of WBV treatment
[90]	- Cerebrospinal fluid collection - Porcine Thoracic Injury Behavior Scale - PTIBS (hindlimb motor function) - Enzyme-linked immunosorbent assay (interleukin 6-IL-6, IL-8, monocyte chemotactic protein-1 and GFPA) - Immunohistochemistry (quantification of white and gray matter sparing)	No influence of WBV treatment
[92]	- Maze test (behavior observation) - Tail-Flick: thermometric sensory test; Von Frey filament test (sensory tests) - Grip-Strength test (motor function) - Blood flow volume measurement - Neuronal pathological analysis (general observation of the sections of cortex; necrotic dark shrunken neuron (DSN) counting; neuronal nuclei area) - Superoxide anions (O_2^-) and Nitric oxide (NO) measurements (Molecular changes)	↑ injuries to peripheral nervous functional in WBV groups, in addition, indicated that the longer the vibration term, the more severe the injury. ($p < 0.05$)[a] ↓ blood supply to the brain ($p < 0.05$)[a] ↑ shrunken neuron in 8-week WBV group ($p < 0.05$)[a] ↓ concentration of blood O_2^- ($p < 0.05$)[a] ↑ concentration of blood NO ($p < 0.05$)[a]
[91, 92][b]	- Maze test (behavior observation) - Nerve conduction velocity; Tail-Flick: thermometric sensory test; Von Frey filament test (sensory tests) - Grip-Strength test (motor function) - Neuronal pathological analysis (general observation of the sections of cortex; DSN counting; neuronal nuclei area) - O_2^- and NO measurements (Molecular changes)	↑ vacuoles in the brain arteries after 8-week vibration ($p < 0.05$)[a] ↓ mean neuron size ($p < 0.05$)[a] ↑ shrunken neuron after 8-week vibration ($p < 0.05$)[a] ↑ cerebral edema ($p < 0.05$)[a]
[74]	- BBB rating scale, Single-frame motion analysis (SFMA), Beam walking, Ladder climbing test, Hoffmann reflex (H-reflex) recordings (locomotor assessment) - Density of functioning capillaries (specific antibodies - anti-rat PECAM-1, anti-mouse Collagen Type IV, anti-porcine CD31, anti-rat RECA)	↑ denser capillary network in the WBV-treated rats ($p < 0.001$)[a] ↑ vascularization in the WBV-treated rats ($p < 0.001$)[a]
[68]		↓ PWR to the 4- and 15-g von Frey filaments. ($p < 0.05$)[c]

(*continued on next page*)

Table 2 (*continued*)

Authors	Parameters evaluated	WBV outcomes
	- Paw withdrawal response (PWR) (ipsilateral and contralateral hind paws) - Histological analysis of skin - Immunohistological analysis (Calcitonin gene-related peptide-GPR)	↓ CGRP expression in ipsilateral dorsal horn in Im+Vib1 ($p < 0.05$)[c] ↓ CGRP-positive neurons in ipsilateral dorsal horn in Im+Vib1 ($p < 0.05$)[c]
[69]	- Kuribara's grid test - Analysis of the number of TH-positive neurons in the - substantia nigra - High-performance liquid chromatography (HPLC) analysis of dopamine - Immunoassay of BDNF	↑ the numbers of dopaminergic neurons in the substantia nigra of MPTP mice in LF and HF ($p < 0.01$)[d] ↑ the levels of dopamine in the striatum of MPTP mice in LF and HF ($p < 0.01$)[d] ↑ increased the contents of BDNF in the striatum of MPTP mice in LF ($p < 0.05$)[d]
[79]	- Isometric tension and electromyogram measurements - Intracellular recordings - Neuromuscular junction staining - Wire grid hang; Wire hang; Grip strength; Open field test (behavior assessment)	↑ isometric force production in semitendinosus skeletal muscle in LIV ($p < 0.05$)[a] ↓ the fatiguing effects of intensive synaptic muscle stimulation in LIV ($p < 0.05$)[a] ↑ grip strength in LIV ($p < 0.05$)[a] ↑ initial motor activity in a novel environment in LIV-treated mice ($p < 0.05$)[a] ↑ evoked neurotransmitter release at neuromuscular synapses ($p < 0.05$)[a]
[87]	- Forepaws mechanical withdrawal threshold (behavior assessment) - RT-qPCR; Western blotting (neurotrophin messenger RNA (mRNA) transcript and protein expression quantified) - Immunohistochemistry (neurotrophin measurement in the outer annulus fibrosus (IAF), and nucleus pulposus (NP) to determine if there are regional changes)	↑ BDNF and total-NGF mRNA levels in WBV ($p < 0.05$)[a] ↑ protein expression of BDNF and the 75-kDa NGF in WBV ($p < 0.05$)[a] ↑ correlation between BDNF mRNA and protein levels with the degree of behavioral sensitivity in WBV group ($p < 0.05$)[a] ↑ correlation between Total-NGF mRNA and the extent of behavioral sensitivity in WBV ($p < 0.05$)[a] ↑ neurotrophins (BDNF and Total-NGF) in IAF and NP ($p < 0.05$)[a]
[72]	- BBB rating scale, SFMA, Beam walking, Ladder climbing test, H-reflex recordings (locomotor assessment). - Bladder function - Spinal cord lesion volume - Immunohistochemistry and evaluation of axonal and synaptic terminal densities in the spinal cord - Motoneuron soma size and quantification of perisomatic puncta. - Fluorescent image analysis of the overall amount of serotonergic fibers and synaptic terminals in the ventral horn (choline acetyltransferase-ChAT, Coex-pression of glutamate vesicular transporter-VGLUT1, Synaptophysin) - Bladder weight and histology - Histopathology of the bladder wall	↑ body weight support (rump-height index) during overground locomotion and overall recovery between 6 and 12 weeks ($p < 0.05$)[a] ↑ bladder function at 6–12 weeks after injury ($p < 0.05$)[a] ↑ restored the density of synaptic terminals in the lumbar spinal cord at 12 weeks ($p < 0.05$)[a]
[88]	- Dissection procedure for brain regions (cerebellum, medulla oblongata, hypothalamus, striatum, midbrain, cortex, and hippocampus) - Fluorometric method for determined noradrenaline (NA), dopamine (DA) and serotonin (5-HT) levels (enzymatic determination)	↓ the brain concentration of NA when the WBV acceleration was increased to 5.0 G ($p < 0.05$)[a] ↓ NA decreased only in the hypothalamus ($p < 0.01$)[a] ↑ the concentration of 5-HT in the cortex ($p < 0.05$)[a] ↓ the concentration of 5-HT in the striatum ($p < 0.05$)[a]
[89]	- Fluorometric method for determined 5-HT, 5-hydrox-yindoleacetic acid (5-HIAA) and plasma corticosterone.	↑ 5-HT and 5-HIAA levels of brain at 20 Hz of WBV ($p < 0.05$)[a] ↑ plasma corticosterone levels as acceleration increased from 0.4 G to 5.0 G and the frequency was changed from 5 Hz to 30 Hz ($p < 0.05$)[a] ↑ correlation between brain 5-HT and plasma corticosterone levels ($p < 0.01$)[a]

CRS, Chronic restraint stress; tMCAO, transient middle cerebral artery occlusion; LIV, low intensity vibration

[a] compared to control group
[b] compared to groups without WBV
[c] compared to Im group only
[d] compared to MPTP group onlys

corticosterone levels as acceleration raised from 0.4 g to 5.0 g and the frequency was changed from 5 Hz to 30 Hz WBV [89], considering that as high the peak acceleration, undesirable effects can be observed. A stronger correlation was then found between brain serotonin and plasma corticosterone levels. Also, WBV decreased the concentration of noradrenaline in the brain when the acceleration was raised to 5.0 g, as well as the concentration of serotonin in the striatum [88,89].

4. Discussion

The current study aimed to summarize, in experimental animal models, effects of the WBV exposure on brain and behavior. Preclinical research involving WBV exercise might help to identify beneficial and harmful effects, including the underlying (cellular) mechanism. As such, it can support the formulation of effective and safety training protocols (i.e. optimal WBV settings). The translational importance of animal research in WBV is to aid the treatment of human brain disorders. The transferability of WBV insights from animals to humans should be carefully considered but is generally high as is for example outlined in [59,77]. This systematic review included 20 studies, summarizing and discussing the effects of WBV intervention on brain functioning and behavior in different experimental animal models. Despite the heterogeneity of the studies included in this review, the results primarily suggest beneficial effects of WBV intervention on neurological issues, mainly related to motor function, isometric force, coordination, muscle strength, recognition memory, synaptic plasticity, brain cells activity and molecular changes. However, some harmful effects were reported by severe WBV exposure indicating an impairment of the cerebral function and causes of cumulative brain injury.

Regarding the selected studies, the results demonstrated that the experimental models used were primarily rodents (75% - rats; 20% - mice). This can be related with the general use of these rodents in biomedical research, but also to their relative low cost, accessibility and easy handling. This provides a relatively large number of animals for these researchers, thereby conferring a greater degree of evidence and reliability in their results. In addition, there was a predominant use of male models (62%) compared to the female (38%) in the studies. This could be explained by an investigators' concern, namely that female rodents are more variable in physiology and behavior, in part because the estrous cycle. Also, the use of males and females can reduce statistical power due to the spread of pooled data or smaller subsamples of

each sex [70,71]. Despite these concerns, investigation about WBV intervention in both males and females is important.

Considering the WBV protocol of the included studies there were punctual differences about the device type and variables applied, Table 1 discloses some common features. Firstly, most used WBV frequencies were 15 Hz (44%) and 30 Hz (62%) with low magnitude (0.3 and 0.5 *g*) vibrations. Secondly, most protocol were long-term, involved three or more training sessions per week, as would be the standard for resistance training. Together, these characteristics indicate a preference for lower frequencies considering training stimulus and smaller vibration magnitude to avoid potential harmful effects [40,73]. Moreover, the duration of bouts of vibration it is also an important variable regarding parameters such as degree of force applied on the body, adaptative and training effects [42]. In line with this notion, most protocols decided for 1–5 bouts/day with time-varying from 3 min to 30 min/per bout (Table 1). In contrast, some studies [89,91,92] designed for evaluate injury effects of WBV, decided in only 1 bout by a long-time exposure (varying from 90 min to 240 min). Furthermore, some studies modeling SCI applied two frequencies and one amplitude, which are within the normal range of motoneuron discharges and are well tolerated by the rats [38,73–75]. Different devices to generate mechanical vibration were used, such as an alternating model [38,62,72–74], a vertical model [62,69,93] and those which used a custom type of platform adapted to generate vibration stimuli in animals models [59,68,77–79,86–88], which indicates a heterogeneity as for the vibration stimuli model on the selected studies, and can increase its translational value for different clinical approaches.

Concerning the main results of this review, WBV intervention was responsible for several responses such as reduced brain damage post-ischemia, in SCI, and improving neuromuscular and cerebral functioning. Previous studies demonstrated that WBV can produce physiological changes on several levels through stimulating skin receptors, the vestibular system and muscle spindles, which lead to several changes in cerebral activity, such as those in the somatosensory cortex, hippocampus, amygdala and thalamus [76,77]. This is consistent with the results reported by studies included in this review. Two studies [78,79] showed motor performance improvement and attention. In addition, WBV enhanced muscle strength, isometric force production in semitendinosus skeletal muscle and decreased the fatiguing effects of intensive synaptic muscle stimulation [38,80]. Furthermore, WBV improved motor coordination from 14- to 28-days post-ischemia and muscle strength of the upper limbs at 21- and 28-days post-ischemia [61], which corroborates the notion that WBV is known to improve neuromuscular performance [40].

Regarding the behavioral changes, WBV increased latency to fall off the rotarod in post-ischemia models, increased initial motor activity in a novel environment, decreased the withdrawal threshold hind paws, and reduced behavioral arousal induced experimentally [59,61,77,79]. After the ischemia procedure and lumbar spinal cord lesion in rats, 8 Hz and 15 Hz WBV caused hypersensitivity in the hind paw and pain developed early on after exposure [59,61]. Also, WBV produced long-lasting sustained allodynia over 14 days. In fact, only one week of 8 Hz WBV exposure was able to induce continued sensitivity lasting just as long [61]. In addition, 30 Hz WBV improved exploratory behavior in CRS-induced models [67]. Therefore, these behavioral findings suggest that WBV parameters such as frequency, peak to peak displacement and number of exposures play a role in the pain response and depression-like behaviors.

According to brain functioning, WBV revealed a beneficial effect in experimental models for cerebral ischemia and SCI. After ischemia, 40 Hz WBV reduced the levels of pro-inflammatory cytokine interleucin-1, inflammasome proteins (caspase-1, caspase recruitment domain) and increased BDNF and phosphorylated Tropomyosin receptor kinase B (pTrK-B) levels in the brain of middle-age female rats [62]. Since BDNF expression is augmented in neurons by various stressors (e.g., ischemia, trauma, hypoglycemia and epilepsy), this chronic exposure confers neuroprotection [80]. In addition, during the acute phase after ischemia neurogenesis was subtle to mild but enhanced by 15 Hz WBV treatment over a longer period [61]. This suggests the potential of WBV for intensifying neurogenesis when subjects are exposed to mechanical vibration for extended periods. It also supports the hypothesis that the underlying mechanism of WBV action may strongly relate to cumulative effects [58]. These results are also in line with the observation that WBV can improve some aspects of cognitive performance in healthy subjects [80] A recent study using healthy, aged rats revealed, in a 5-week WBV intervention protocol with low intensity (30 Hz, amplitude 50–200 μm), a decrease in anxiety level and improved spatial memory, next to improved motor performance [81].

Considering SCI, WBV when started 14 days after the injury provided a restoration of synaptic coverage through the improvement of synaptophysin levels [61]. Furthermore, WBV restored BDNF mRNA levels to normal in the lumbar cord [61,68]. BDNF also increased synaptogenesis [82] and neurogenesis [83,84]. Evidence suggests that the therapeutic efficacy of exercise after SCI may be closely related to BDNF modulation which appears to play a central role in synaptic plasticity [85,86]. WBV also restored the density of synaptic terminals in the lumbar spinal cord at 12 weeks, indicating that synaptic rearrangements in the distal spinal cord might be important for improving body weight support [56,68]. It is also likely that local changes in the vibrated muscles lead to improved performance [58]. Conversely, Zeeman et al., [58] observed that the immune cells in lumbar spinal cord were activated after WBV. Also, although mitogen-activated protein kinase (MAPK) signaling increased (8 Hz WBV), this study demonstrated that this pathway is activated in several cell-types in the superficial dorsal horn of the lumbar spinal cord after WBV, except in microglia. This suggests an increased crosstalk between specifically activated nociceptive neurons, spinal neurons and the inflammatory support cells surrounding these neurons in the dorsal horn.

In addition to molecular changes, the role of BDNF in promoting nerve growth and the important correlations between BNDF expression and pain in animal models support a potential role of WBV in regulating disc pain [87]. Indeed, a statistical correlation between increased BDNF transcript and protein levels in discs exposed to vibration and increased behavioral sensitivity to pain after day 14 of WBV has been shown [38,87]. It suggests a possible role for WBV through BDNF modulation, increasing neuronal hyperexcitability in spinal dorsal horn. Furthermore, Peng et al. [67] suggest that WBV can alleviate dendritic loss caused by CRS. MAP2 levels were found to be increased after the WBV intervention, and WBV increased hippocampal expression of the synaptic-associated proteins synaptophysin and spinophilin, indicating a role of WBV in enhancing synaptic functioning, which corroborates the observation that WBV prevented the decline of spatial memory, in line with the findings of Regterschot et al. [94] that observed the same improvement by WBV. This functional effect of WBV indicates wide prospects in clinical research.

The current systematic review has some limitations. The search strategy used only studies in English. In addition, the heterogeneity in the selected studies made-clear that considerable methodological differences exist among the reviewed studies. The risk of bias and methodological quality assessment showed that many studies failed to establish a consistent methodology to avoid discrepancies, resulting in possible biases. Although, the main tools for risk of bias assessment in animal intervention studies (such as the SYRCLE methodology) were published only in the last decade, it is to be expected that articles prior to this date may not have implemented all aspects mentioned in this protocol. Therefore, considering a systematic review for animal studies with a search strategy including publication dating before ~2010, this may automatically represent a possible risk of bias in assessing the methodological quality. The lack of information about the body posture during WBV and which overt behavior was observed during a session is often lacking and hence a potential limitation of the studies because it may affect the efficiency of the intervention.

On the other hand, the strength of this review is the outlining of WBV variables used in the selected studies, and the subsequent analysis in which range these variables would be able to induce a beneficial or detrimental effect. As such, this review lends support for future WBV research with focus on (bio)medical applications related to brain functioning and behaviour.

5. Conclusion

In conclusion, considering the above-described findings, it can be summarized that WBV seems to be a feasible and effective therapy for the treatment of cerebral ischemia and SCI. In addition, it also supports the use of WBV as an intervention for other brain diseases. The main reasons for this conclusion are: (i) the existence of adequate knowledge of WBV parameters to be applied, avoiding harmful effects, (ii) the modulating actions of WBV observed at the level of proteins, enzymes, immune cells, neurons, neurothrophins and neurotrophic factors, (iii) the frequently replicated finding of motor function improvements, neuromuscular activity and behavioral sensitivity by WBV, (iv) and indications of recovery or strengthening of certain brain functions. WBV may therefore represent an interesting intervention for clinical studies. Future studies need to provide more insight in the mechanisms that underlie the beneficial effects of WBV. This insight will stimulate the use of WBV as an intervention in a clinical perspective and it can be considered to be used as an alternative for physical activity protocols or combined with it, aiming to improve behavioural and cognitive deficits as seen in many brain disorders.

Author contribution

André Cardoso was responsible for the systematic selection of the publications, data extraction from the full-text version of the publications, the risk of bias assesses, and he drafts the manuscript. Danúbia Sá-Caputo and Nasser Asad helped on the systematic selection of the publications. Marieke van Heuvelen and Anderson Ribeiro-Carvalho helped on the data extraction from the full-text version of the publications. Anderson Ribeiro-Carvalho also helped on the risk of bias assess. Eddy van der Zee and Marieke van Heuvelen helped on the draft of manuscript. Mario Bernardo-Filho coordinated the study and helped on the draft of the manuscript.

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Declaration Of Competing Interest

The authors declare that they have no conflicts of interest associated with this publication.

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