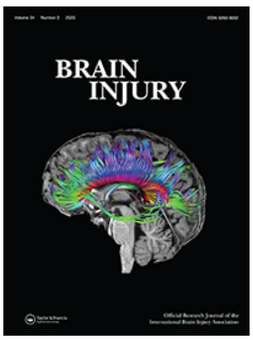

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Cognitive and neural effects of exercise following traumatic brain injury: A systematic review of randomized and controlled clinical trials

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ABSTRACT

Objective: Sub-maximal aerobic exercise can alleviate brain injury-related symptom burden. There is substantial data from animal studies and a growing clinical evidence base to suggest that exercise may also improve cognitive and neural outcomes following brain injury. We performed this systematic review to consolidate evidence from randomized and controlled clinical trials on the effects of exercise on cognitive and neuroimaging outcomes following brain injury in humans.
Design: Systematic review.
Data sources: MEDLINE, EMBASE, PsychINFO, CINAHL, SPORTDiscus, and Cochrane Central Database.
Eligibility criteria for screening studies: Randomized or controlled clinical trials examining the effects of exercise on cognitive and/or neuroimaging outcomes in traumatic brain injury. No restriction was placed on age (or other demographic variables) or severity of injury.
Results: Six studies (with an average sample of 42 participants) met eligibility criteria. Three studies used neuroimaging and reported exercise-related improvements as measured by either functional or diffusion-based imaging. The remainder of the trials that employed cognitive outcomes reported largely null findings.
Summary/Conclusion: This review demonstrates that exercise shows promise (primarily with respect to neuroimaging outcomes) as a brain injury intervention. While the field is young and heterogeneity between studies precludes meta-analysis, this review raises important questions that need to be addressed by future trials.

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Brain injury; concussion; exercise medicine; sport medicine; neuroplasticity; neuroimaging

Introduction

The scope and impact of traumatic brain injury (TBI) are extensive. Internationally, its annual incidence has reached 295/100,000 (1), and the World Health Organization predicts that TBI will become the third leading cause of death and disability worldwide by the year 2020 (2). The clinical manifestation of TBI is diverse, and even milder brain injuries (such as concussion) are associated with a broad symptom set, which includes cognitive impairment that may persist for more than 3 months in nearly half of patients (3). Further, in more severe injuries, atrophy and impairment of neural tissues, structures, and networks are observed (4,5), and neurodegeneration may be observed after repeat concussive and sub-concussive impacts (6). The targets of TBI interventions should, therefore, not only be the symptoms associated with brain injury, but also the potentially chronic neuropathology underlying these impairments.

Current treatment options for TBI, however, are limited. While some interventions (e.g., working memory or attention training, cognitive behavioral therapy, mindfulness meditation) have demonstrated moderate efficacy in managing specific cognitive (and psychosocial) symptoms (7–10), other trials have failed to demonstrate efficacy, particularly in more severe brain injury (11). Most notably, acute stage pharmaceutical trials of agents such as progesterone have failed to effect neurological and functional outcomes (see Stein (12) for an overview). This represents just one of more than 30 therapeutic agents identified in pre-clinical studies that did not improve clinical outcomes when advanced to late-stage clinical trial (11), which currently precludes a pharmacological approach to TBI treatment.

There are, however, non-pharmacological treatment options for TBI that demonstrate promise. Specifically, aerobic exercise interventions (defined as those which tax the cardiovascular and pulmonary systems to meet temporarily elevated oxygen demands (13)) have rehabilitative potential, as not only can they alleviate brain injury-related symptom burden (particularly in concussion) (14), but according to animal studies, they can also promote cognitive and neural recovery by facilitating adaptive molecular and cellular neuroplastic changes (15–17). More specifically, studies involving both healthy and brain injured animals have demonstrated that physical activity can improve cognitive ability on tasks such as spatial navigation (a surrogate for learning and memory performance in animals) (18), while conferring a series of neural benefits including increased proliferation and survival of newborn neurons in the hippocampus (a structure integral to memory) (19), upregulation of critical neural growth factors (20), and elevated synaptogenesis and angiogenesis (21).

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ibij.

Importantly, recent studies show that the benefits of exercise on the injured brain also extend to humans. In concussion, exercise has a positive effect on symptom burden; most notably, a recent meta-analysis found that compared to a non-active control condition, exercise significantly decreased symptom scores on the 132-item Post Concussion Symptom Scale (PCSS; mean difference, −13.06; 95% CI, −16.57 to −9.55; I^2 = 44%) (14). Comparatively, there are fewer studies examining the effects of exercise on cognitive and neural outcomes in clinical brain injury. Preliminarily, these studies do suggest that exercise can improve cognition following brain injury in both adolescents and adults (14,22,23), and lead to adaptive neural changes (24,25).

Although the literature on the effects of exercise following TBI in humans has been consolidated through review as it relates to *symptom resolution* (14), systematic reviews on the *cognitive* and *neural* effects of exercise in humans have not been performed. Current reviews on the topic that have been performed are either not systematic, not based on comprehensive searches of multiple health sciences databases, or do not limit their study samples to traumatic brain injury (and instead keep the area of study broader by including patients with stroke and other acquired brain injuries) (26,27). Further, a review on the cognitive and neural effects of post-TBI exercise examining only clinical trials (rather than, for example, cohort studies or case-series) have not been performed, despite the need for such review to better understand and establish the state of the science, generate new research questions, and best inform future exercise-based trials in brain injury. This systematic review was performed to consolidate evidence from randomized and controlled clinical trials on the effects of exercise on cognitive and neural outcomes following traumatic brain injury.

Materials and methods

This review was registered with the international prospective register of systematic reviews PROSPERO network (registration number CRD42017058157) on 26 February 2017. Our review was reported as per reporting guidance provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (28).

Search strategy

A comprehensive search strategy was developed in consultation with a health sciences librarian, and adapted for each of the following health sciences databases (gray literature was not included): MEDLINE, EMBASE, PsychINFO, CINAHL, SPORTDiscus, and Cochrane Central Database. Further, it reflected the PICO (Population, Intervention, Comparison, Outcome) strategy for evidence searches (29): our focus Population, Intervention, Comparison, and Outcomes were brain injury, exercise, non-active controls, and cognition and/or neuroimaging, respectively.

Searches were initially run in February 2017 and were re-run in December 2018 prior to publication to ensure results were current. The search strategy involved three sets of terms, namely, those related to: 1) traumatic brain injury and/or concussion, 2) exercise and/or physical activity, and 3) randomized and/or controlled clinical trials. Exercise type (e.g., aerobic, anaerobic) was not specified in the search strategy, as it may have limited the breadth of the search. Further, the outcome measures (i.e., those specific to cognitive outcomes and neuroimaging) were not included in the search strategy (as per the advice of the consulting librarian) in order to ensure the search was not overly restrictive. Instead, outcomes were screened for during the title/abstract and full-text stages. A sample search strategy can be found in Appendix 1.

Screening procedure

Searches for each database were conducted independently, with an optimized database-specific strategy; therefore, six searches were run in total. The results of the six searches were exported into EndNote Reference Management Software and duplicates were removed using a series of filters. The final, de-duplicated library was then imported into Covidence (an online systematic review screening platform) for title and abstract screening.

Titles and abstracts of articles were reviewed by two authors in Covidence, and screened against pre-defined inclusion criteria. More specifically, the inclusion criteria were: 1) randomized or controlled clinical trials design; 2) traumatic brain injury population; 3) evaluation of an aerobic exercise intervention; 4) primary and/or secondary outcomes assessing cognitive and/or neural changes. Exclusion criteria were: 1) non-peer reviewed publication; 2) review and/or guideline article; 3) inappropriate study design; 4) inappropriate population; and 5) lack of appropriate outcome measures. No exclusion criteria were enforced surrounding date or language of publication. Titles and/or abstracts over which there was initial disagreement were jointly reevaluated against the *a priori* inclusion and exclusion criteria until a consensus on inclusion was reached by the two reviewers. Although not required, the two reviewers decided at study onset to advance any articles over which consensus was not reached to a third reviewer.

The same two reviewers then conducted full-text screening independently, also in Covidence, resolving conflicts as above. Reference lists of articles included in the review were then examined to identify any additional articles that may have been relevant to the review; these articles were then screened in full for inclusion. Articles that cited the studies included in our review were also screened in full for inclusion, as well as the 'Published ahead of print' section of leading journals in the field.

Data extraction

Data were extracted using standardized forms developed by the research team. Fields on this form included study design (e.g., number of participants, trial arms, randomization processes), intervention characteristics (frequency, intensity, time, and type of exercise), participant demographics (age, sex, injury severity, time post-injury), and study findings (baseline measures as well as exercise-related changes in cognition or neural outcomes). The form was populated by each reviewer, and then data were compared to ensure consistency of extraction.

Quality assessment

The two reviewers used the widely used Cochrane Risk of Bias Tool (30) (in Review Manager v5.3) to identify risk of bias in study design. This tool assesses seven biases, related to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome measures, incomplete outcome data, selective reporting, and other biases (which may include biases such as observer variability, or measurement error). As with the screening process, risk of bias evaluations were independently performed by each reviewer and discussion was then held to resolve any inconsistencies.

Results

The number of articles reviewed and excluded at each stage is overviewed in Figure 1. Due to the limited number of articles, heterogeneity between study samples, and diversity of outcome measures used, a meta-analysis was not conducted; the papers were instead analyzed narratively.

Study characteristics (e.g., design, participant demographics) are summarized in Table 1. Participants ranged from adolescents to middle-aged adults, and samples were heterogeneous with respect to time-post injury and injury severity. Mechanism of injury was not reported in studies examining cognitive outcomes, but in those employing neuroimaging, most injuries were sport-related, with the remainder primarily caused by falls and being struck by/against an object (Table 1). Table 2 provides an overview of the exercise interventions employed in each study, categorized by fitness, intensity, type, and time (i.e., the F.I.T.T. principle (31)).

Risk of bias within and across studies is summarized in Figure 2a and b. In general, there was high or unclear risk of bias with respect to random sequence allocation and allocation concealment. Risk of bias was low for outcome reporting, as all studies reported on all outcomes and addressed loss to follow-up.

Neuroimaging outcomes

Three of the six included studies examined neuroimaging outcomes (24,25,32). While heterogeneity between study samples and designs limits the ability to draw generalized conclusions, it should be noted that pre- post-intervention improvements on a diversity of neuroimaging outcomes (as discussed below) were observed across studies.

Leddy et al. (24) studied eight individuals with post-concussion syndrome who were selectively yet equally allocated to either an exercise intervention (see Table 2) or a stretching control group

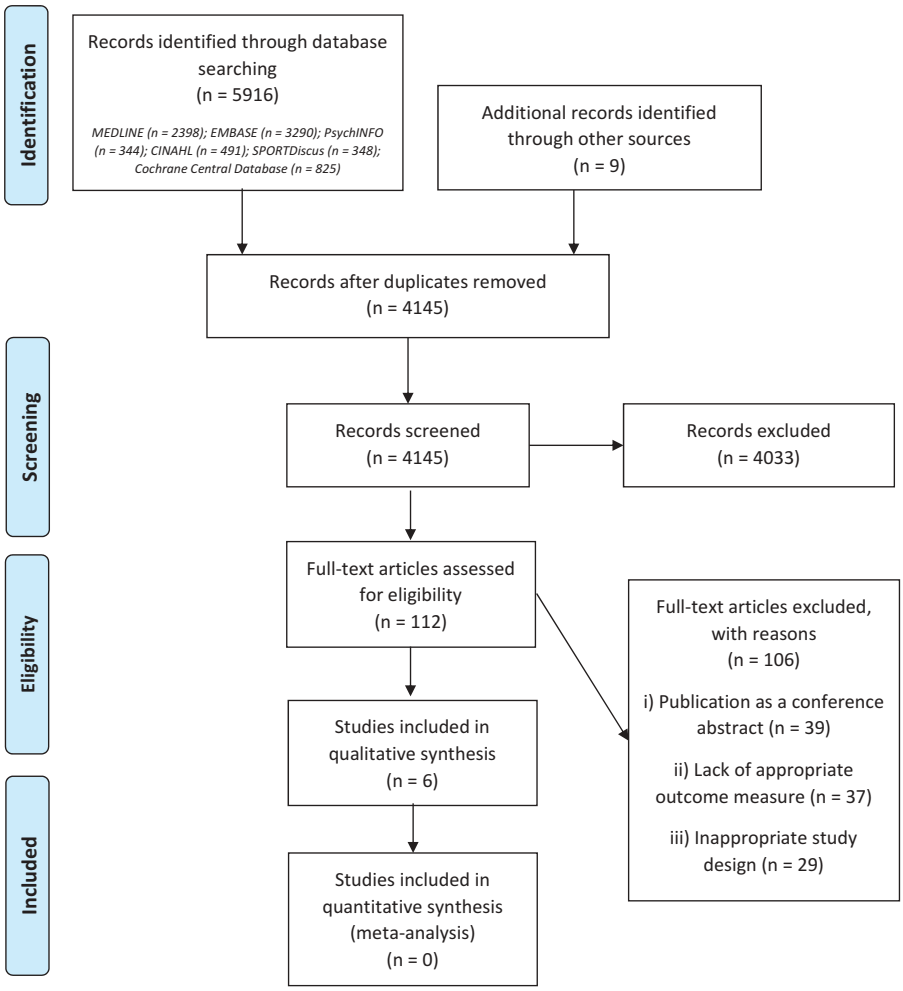

Figure 1. PRISMA flow diagram representing the identification, screening, eligibility, and inclusion of studies in this review.

Table 1. Study design and participant demographics.

	Study					
	Leddy et al. (2012)[a]	Polak et al. (2015)[a]	Yuan et al. (2017)	McMillan et al. (2002)	Lee et al. (2014)	Maerlender et al. (2015)
Design	Controlled clinical trial	Controlled clinical trial	Randomized controlled trial	Randomized controlled trial	Wait list controlled clinical trial	Randomized controlled trial
Sample	Total: 12 Exercise, PCS: 4 Stretching, PCS: 4 Healthy control: 4	Total: 23 Exercise, PCS: 4 Stretching, PCS: 4 Healthy control: 15	Total: 37 Exercise, TBI: 8 Stretching, TBI: 9 Healthy control: 20	Total: 130 Exercise, TBI: 38 Attention training, TBI: 44 Nonintervention control, TBI: 48	Total: 21 Exercise (immediate), TBI: 9 Exercise (waitlist), TBI: 12	Total: 28 Exercise, TBI: 13 Standard care, TBI: 15
Primary outcome	Task-dependent fMRI	DTI	DTI tractography (to assess structural connectivity)	Test of Everyday Attention, Adult Memory and Information Processing Battery, Paced Auditory Serial Addition Test, Trail Making Test, Sunderland Memory Questionnaire, Cognitive Failures Questionnaire	Stroop Color and Word Test, Digit Spans Forwards and Backwards, and Trail Making Test Parts A & B	ImPACT
Mean age at baseline, years	Exercise, PCS: 24 Stretching, PCS: 21 Healthy control: 21 *N.b.* Standard deviations were not reported	Exercise, PCS: 25.2 ± 5.7 Stretching, PCS: 22.8 ± 6.2 Healthy control: 26.2 ± 1.7	Exercise, TBI: 15.04 ± 1.35 Exercise, Stretching: 15.48 ± 2.08 Healthy control: 16.28 ± 1.38	Exercise, TBI: 31.4 ± 13.0 Attention training, TBI: 34.6 ± 11.4 Nonintervention control, TBI: 36.2 ± 13.4	Exercise (immediate), TBI: 48.22 ± 18.19 Exercise (waitlist), TBI: 44.50 ± 12.97	Collegiate athletes; mean age not reported
Time post-injury	Exercise, PCS: 65.25 days Stretching, PCS: 170.75 days	*First evaluation* Exercise, PCS: 37.2 ± 6.5 days Stretching, PCS: 154.5 ± 124.0 days *At baseline MRI* Exercise, PCS: 66.0 ± 6.6 days Stretching, PCS: 170.8 ± 118.8 days	Exercise, TBI: 56.98 ± 24.24 days Stretching, TBI: 56.06 ± 25.04 days	Between 3- to 12-months post-injury. *N.b.* Means per group were unavailable	Exercise (immediate), TBI: 88.11 ± 83.56 months Exercise (waitlist), TBI: 27.30 ± 22.01	Median of 2 days
Sex, % male	Exercise, PCS: 25% Stretching, PCS: 75% Healthy control: 0%	Exercise, PCS: 25% Stretching, PCS: 75% Healthy control: 47%	Exercise, TBI: 50% Stretching, TBI: 66.67%	Exercise, TBI: 79% Attention training, TBI: 80% Nonintervention control, TBI: 75%	Exercise (immediate), TBI: 44% Exercise (waitlist), TBI: 42%	Exercise, TBI: 20% Standard care, TBI: 38%
Mechanism of injury	–	TBI exercise, 50.0% sports, 50.0% falls TBI stretching; 50.0% sports, 25.0% falls, 25.0% struck by object	–	TBI exercise, 50.0% sport-related TBI stretching, 77.8% sport-related		
Injury severity	Concussion (diagnosed with PCS as per the ICD 10)		Excluded if GCS below 13	Exercise, TBI: Median GCS 10 Attention training, TBI: Median GCS 9 Nonintervention control, TBI: Median GCS 9	All severities; breakdown by severity not provided	Concussion
Country in which study was conducted	United States		United States	United Kingdom	United States	United States

[a]Studies were collapsed, as needed, as participants were derived from the same pool.

Abbreviations: fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; ImPACT, Immediate Post-Concussion Assessment and Cognitive Test; PCS, Post-concussion syndrome; ICD, International Classification of Disease; GCS, Glasgow Coma Scale.

Table 2. Characteristics of the exercise interventions employed in each study, categorized by the F.I.T.T. principle. [a]Intervention was common between studies.

	Study					
	Leddy et al. (2012)[a] Polak et al. (2015)[a]	Yuan et al. (2017)	McMillan et al. (2002)	Lee et al. (2014)	Maerlender et al. (2015)
Frequency	6 days per week, for approximately 12 weeks	5-to-6 days per week, until recovery to baseline	5 sessions, over 4 weeks	2 days per week, for 8 weeks	Daily, until recovery to baseline
Intensity	80% of symptom-limited exercise threshold	80% of symptom-limited exercise threshold	–	–	Mild-to-moderate intensity, as per the Borg Rating of Perceived Exertion Scale
Time	20 minutes per day	Duration equivalent to that which resulted in symptom exacerbation at baseline testing	45 minutes per session	60 minutes per day	20 minutes per day
Type	Aerobic exercise (e.g., treadmill or stationary bicycle)	Aerobic exercise (on a stationary bicycle)	–	Aerobic exercise, in addition to self-affirmation and meditation exercises	Aerobic exercise (on a stationary bicycle)

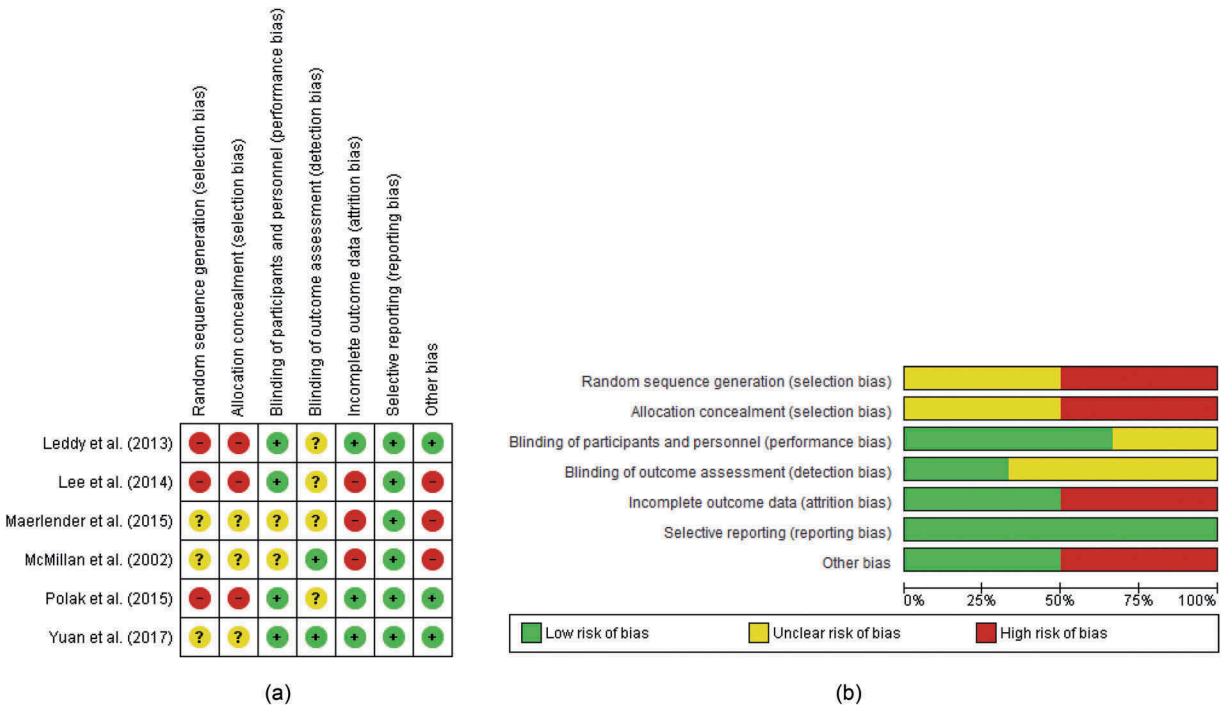

Figure 2a. (a) Risk of bias for included studies, as assessed using the Cochrane Risk of Bias Tool. (b) Risk of bias summarized across all studies, as assessed using the Cochrane Risk of Bias Tool.

Legend: Red, green, and yellow denote high, low, and unclear risk of bias, respectively.

(and were advised not to exceed 40–50% of maximum age-predicted heart rate); additionally, four age-, sex-, and activity status-matched healthy controls were included in the study. Participants in both the exercise and stretching arms of the trial conducted their respective activities at home or in a community gym. Participants were assessed using functional magnetic resonance imaging (fMRI) while completing a modified version of a commonly used neuropsychological math task, involving basic arithmetic (namely, the addition or subtraction of three numbers); during the 5-min trial of 72-questions, participants were asked to answer whether the solution to the arithmetic problems they were presented was greater or less than five. Participants administered to the exercise intervention were assessed on this task at baseline, and again once they were able to exercise to age-predicted maximum heart-rate without symptom exacerbation, after a span of approximately 12-weeks; participants in the stretching group and the healthy controls were also assessed roughly along these timelines. It is important to note the sex disparity between groups (Table 2) and that those administered to the stretching group were, on average, nearly 6 months post-injury, while patients in the exercise group were approximately 2 months post-injury at the time of their first neuroimaging assessment.

At baseline, no significant differences in functional activation between those administered to the exercise group or stretching group were detected; moreover, at this time, there were no differences in activation between healthy controls and either the exercise group or stretching group. However, when pooling data across all patients with post-concussion syndrome, the

healthy controls showed relatively increased task-based activation in certain brain regions, namely the cerebellum, posterior cingulate gyrus, and lingual gyrus at baseline. At follow-up, there were no significant differences in activation between those in the exercise group and healthy controls, while reduced activity in the cerebellum, cingulate gyrus, and thalamus (with no regions showing increased activity) were observed in those allocated to the stretching group relative to healthy controls. In comparing the two PCS groups, a trend toward a significant difference was reported with respect to functional activation within a small cluster (seven voxels) in the cingulate gyrus, with the exercise group showing greater activity than the stretching group at follow-up. These findings suggest that aerobic exercise may restore functional brain activity following concussion in select brain regions.

In a later study by this group, Polak et al. (25) used diffusion tensor imaging (DTI) to assess exercise-related brain changes in individuals with post-concussion syndrome. DTI is an imaging modality sensitive to water diffusion, and quantifies white matter microstructure (and thus diffusivity of water and neuronal health) with metrics such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) (33). Polak et al. (25) reported on DTI data on eight participants, and while methodology was shared with the former trial, a larger sample of 15 healthy controls was used.

At baseline, no structural abnormalities were reported when those with concussion (in either arm) were compared to healthy controls. However, using a voxel-wise methodology, reduced FA (an indication of compromised white matter microstructure) in voxels proximal to the genu and corpus callosum, was observed in patients relative to healthy controls at baseline and at follow-up, although the number of voxels within the area of difference was smaller at the later timepoint. Further, at baseline but not follow-up, increased MD and RD (also indicative of compromised white matter microstructure) were observed. When using a region of interest approach, corroborating evidence was generated; decreases in mean FA and increased MD and RD in the genu of the corpus callosum were significant at baseline but less pronounced at follow-up when comparing participants with post-concussion syndrome to healthy controls. Longitudinally, no significant changes in any of these DTI metrics were observed between the exercise and healthy control groups, stretching and healthy control groups, and exercise and stretching groups. Further, a 'pothole' analysis, wherein clusters of white matter voxels that had a ± 3 standard deviation difference in FA relative to the mean value of these clusters in the healthy control group were set as the unit of analysis, demonstrated that the number of 'potholes' in concussed individuals was significantly greater than those in healthy controls at both baseline and follow-up.

The most recent study to examine the neural effects of exercise following concussion was conducted by Yuan et al. (32) In this study, structural connectivity was assessed in adolescents (n = 22) with persistent symptoms related to mild TBI (mTBI) versus age- and sex-matched historical healthy controls (n = 20) using DTI tractography. This study performed structural connectivity analysis using graph theory, and first required the construction of neural networks using an existing architecture (34), which was comprised of 90 cortical and subcortical gray matter regions and the white matter tracts connecting them. Graph theory analysis was then used to measure regional and global connectivity. Those with mTBI were randomly allocated to either an exercise intervention (see Table 2) or a stretching program; due to attrition, imaging was performed on 17 participants pre- and post-intervention, with 8 and 9 participants in the exercise and stretching groups assessed at both times, respectively. This study also included measures of symptom burden, which are reported on more extensively in a previous trial by this group (35).

At baseline, adolescents with mTBI, relative to the historical controls, had significantly reduced global efficiency and higher normalized clustering coefficient, normalized characteristic path length, and small-worldness, all of which are graph theory measures of network connectivity, and are indirectly indicative of compromised white matter microstructure. Further, no baseline differences were observed between those in the exercise and stretching groups. Longitudinally, significant increases in global efficiency and significant decreases in normalized characteristic path length were observed in the exercise group (these findings, indicative of recovery, were correlated with changes in symptom reporting), but not the stretching group. Between-group comparisons (i.e., exercise vs. stretching) did not reveal any significant differences in structural connectivity.

In sum, these trials suggest that following traumatic brain injury in humans, exercise may have positive effects on neuroimaging outcomes (and in particular, functional and diffusion-based metrics).

Cognitive outcomes

Of the six included studies, three (36–38) examined cognitive-related outcomes post-exercise intervention. Unlike the studies which employed neuroimaging outcome measures, in general, intervention effects were not observed in studies that assessed cognitive outcomes, as detailed below.

In the earliest and largest trial (n = 130) to examine the effects of exercise on cognitive outcomes following TBI (38), participants were allocated to either an exercise intervention (n = 38), an attentional control program (n = 44), or a non-active control group (n = 48). Cognitive testing was conducted at baseline, following the intervention, and at long-term follow-up. The tests which comprised the cognitive battery included the Test of Everyday Attention (39), Adult Memory and Information Processing Battery (40), Paced Auditory Serial Addition Test (41), Trail Making Test (41), Sunderland Memory Questionnaire (42), Cognitive Failures Questionnaire (43); measures of anxiety, general health, and post-concussion symptoms were also used, but are not discussed in the present review. No significant between-group differences were observed at baseline across any of the cognitive outcome measures, except the Cognitive Failures Questionnaire (a self-report measure of memory, perception, and motor function); both treatment arms self-reported more cognitive failures than the control group. Similarly, no between-group differences reached significance during the subsequent testing sessions, aside from the Cognitive Failures Questionnaire at long-term follow-up.

In a waitlist cross-over trial (n = 21) by Lee et al., (36) the effects of exercise on cognitive outcomes in adults with chronic TBI of all severities (Table 1) were evaluated. More specifically, participants completed a 60-min exercise intervention (Table 2) twice-weekly for 8-weeks in an outpatient medical center. Neuropsychological testing was initially conducted at baseline, then at cross-over, and again after the group which was initially waitlisted completed the intervention. (It should be noted that this study also included mood and psychological outcomes, but they are not discussed here given the scope of the review.) The tests that comprised the neuropsychological assessment were the Stroop Color and Word Test (44), Digit Spans Forwards and Backwards (45), and Trail Making Test Parts A & B (46), which served as measures of, processing speed, immediate attention and working memory, and mental flexibility and attention, respectively. It is important to note, however, that only 12 participants completed all assessments and that the exercise intervention employed in this study involved more than cardiorespiratory training; 5–10 min of the hour-long intervention involved self-affirmation exercises, and the 10-min cool-down period also involved meditation. At baseline, there were no significant differences on cognitive measures between those who were initially waitlisted and those initially administered to the intervention. Further, when comparing pre- post-intervention cognitive changes between the two intervention arms, no significant differences were observed on any cognitive measures. However, when collapsing the two groups and assessing pre- post-intervention cognitive changes for the entire group, a significant effect was found with respect to the Word Trial of the Stroop Task; no other cognitive improvements were reported.

In a randomized trial by Maerlender et al., (37) concussed collegiate athletes were administered to either "standard concussion recovery recommendations" (n = 15) or were prescribed daily, moderate physical activity (n = 13). Athletes were initially assessed using the Immediate Post-Concussion Assessment and Cognitive Test (ImPACT) in the acute stages of injury (median = 2 days), once available for evaluation by an athletic trainer; other non-cognitive and non-neural outcome measures were employed but are not reported on here. The exercise intervention involved 20 min of cycling on a stationary ergometer, with ratings of perceived exertion (as per the Borg Ratings of Perceived Exertion scale) and symptom exacerbation assessed at the end of the exercise session. Participants then met with the trainer daily to monitor their medical status and activity, and to assess recovery; athletes were considered to have recovered if their assessment test scores, balance, and symptoms returned to baseline. Maerlender et al. (37) reported the median time to recovery for the exercise and control group was 15 and 13 days, respectively. Within-group pre- post-intervention changes in ImPACT scores for verbal memory, visual memory, visual motor speed, and reaction were reported; increases were observed with respect to visual motor speed–with declines observed in the other domains–although these changes did not reach significance. Between-group comparisons were not reported.

Collectively, to date, trials on the effect of exercise on cognitive outcomes following traumatic brain injury have reported largely null findings.

Discussion

To date, clinical exercise trials in TBI have provided limited but largely consistent evidence on the positive effects of exercise on neuroimaging outcomes (as assessed using fMRI or DTI) (24,25,32), and predominantly null findings with respect to cognition (36–38). Current literature on exercise, TBI, and cognitive and neuroimaging outcomes, while not yet conclusive, is able to inform the design of future trials and generate additional research questions which can continue to develop the field. Heterogeneity between studies (with respect to, for example, structure of exercise intervention, participant age, injury severity, mechanism of injury, and outcome measure selection and sensitivity/specificity) in addition to the limited total participant pool and quality of evidence (see Figure 2a and b) are caveats to the questions and hypotheses discussed below.

Therapeutic window

A fundamental and unanswered question is whether the therapeutic window of exercise varies by outcome. The trials included in this review did not incorporate both cognitive and neuroimaging outcome measures, thereby precluding a single sample evaluation of whether recovery of these two outcomes occurs in parallel. Animal literature suggests that physical activity increases the number of cells in the hippocampi, yet the survival of these cells is dependent on subsequent sustained exposure to sufficiently challenging cognitive stimuli (47). Other animal studies show that exercise results in rapid increases in neural vasculature (within 72 h) (48), which begets the generation of new neurons; cessation of exercise results in a similarly rapid return to baseline levels of capillary density, which may be coupled with the loss of newly generated neurons, unless exercise is accompanied by cognitive enrichment (49). Thus, neural changes may be primed by exercise, but not realized until there is appropriate cognitive exposure. Future studies are encouraged to include multiple treatment arms (e.g., physical activity, cognitive exercises, and a combination thereof) to assess their relative contribution to TBI recovery.

Furthermore, the relation between exercise and cognitive recovery may be mediated by time post-injury. Recent evidence from Manikas et al. (23) indicates that processing speed in children and adolescents with concussion is time-sensitive, with, slower post-exercise processing speed observed in children when assessed on the 10th day after injury than when the same children were assessed earlier on the 2nd-day post-injury. This study, in addition to those included in our review, further queries how the effects of exercise on cognition are mediated by time post-injury (and also timing of the exercise intervention), and whether changes in cognition observed earlier in recovery are *bona fide* indicators of cognitive recovery, or if they instead represent a period of transience. Such a period may correspond to the metabolic imbalance observed following brain injury (50). Together, these results suggest that the potential effect of exercise interventions may be

mediated by time post-injury, a question that can best be answered with trials employing multiple arms with exercise interventions administered at different times post-injury. Further, future exercise trials should include repeated cognitive assessments as well as neuroimaging outcomes to better understand the relationship between exercise, cognition, and plasticity in TBI.

Rest versus exercise debate

Until recently, the status quo has been to rest and refrain from activity following sport-related brain injury until symptom resolution; current studies and guidelines have challenged this precedent (51,52). While the studies included in this review did not all center on the acute stages of injury (where return-to-play considerations predominate), the results suggest that exercise, if not beneficial, may not be deleterious. Studies have shown that symptom spikes following concussion are typically not associated with prior activity (53), and that exercise can mitigate symptom burden (14). Further, a large, multi-center prospective cohort study (n = 2413) found that activity within 7 days of concussion in children and adolescents was associated with a reduced risk of developing persistent post-concussive symptoms 4-weeks post-injury (54). Thomas et al. (2015) in a randomized trial found that children administered to strict rest for 5 days rather than 1–2 days of rest and subsequent graduated return-to-activity took longer to reach symptom resolution and reported more post-concussion symptoms within the first 10 days of injury (55). It should be noted that the effects of exercise duration, intensity, time, and type following brain injury remain to be studied; however, a recent review suggests that given the current evidence base, exercise prescription should include low-intensity aerobic exercise in order to ensure tolerability and reduce the risk of symptom exacerbation (56). Collectively, the findings from this review (on the cognitive and neural effects of exercise) along with those from published meta-analyzes (speaking to the positive effect of exercise on symptom burden (14)) suggest that exercise may have a role in the management of brain injury. Future research should focus on determining the timing and type of exercise that is required to best improve patient outcome.

Global mechanisms of neural repair

The studies included in this review used different neuroimaging outcome measures, which detected exercise-related effects to varying degrees (24,25,32). While each study was limited in its sample size (which may reduce reproducibility of results), the current evidence-base nonetheless suggests that the neural effects of exercise on the injured brain can be observed using multiple imaging modalities. Further, it suggests that exercise has an influence on multiple neural substrates (e.g., white matter microstructure, structural connectivity). This also suggests that there may be a common underlying mechanism driving such changes, rather than a series of multiple, independent mechanistic effects.

It has been purported (albeit in the healthy state) that angiogenesis or changes in cerebral blood volume secondary to exercise may be responsible for the suite of exercise-induced neural changes (49). Studies have demonstrated that in mTBI, patients with persistent symptoms and no structural brain abnormalities have regional hypoperfusion (relative to healthy controls) in several brain areas, including the frontal, prefrontal, and temporal cortices, as well as sub-cortical structures (57). (See Len et al. (58) for a review on the persisting nature of cerebral blood flow (CBF) reductions following brain injury, as well as how trauma can impact cerebral autoregulation, reactivity, and oxygenation.) Moreover, longitudinal studies have shown that normalization of CBF in athletes with concussion is associated with recovery (59), while other prospective studies have related gray matter cerebrovascular reactivity with symptom burden in adults with mTBI (60). Given the association between CBF and TBI-related impairments, and that exercise (as per a recent and methodologically rigorous study using oxygen-15-labeled H_20 and positron emission tomography (28)) increases regional CBF in the early and late stages of exercise in healthy male adolescents, future studies should examine the effects of exercise interventions in TBI on CBF. Further, assessing the association between CBF with other markers of TBI recovery (such as heart rate variability, which has previously and preliminarily been correlated with regional CBF (61)) can offer evidence that changes in readily measured heart rate variability serve as proxy for neural recovery *via* CBF normalization.

Future experimental considerations and limitations

Many studies included in this review controlled for demographic variables such as age during analysis. There are, however, other variables that have a known influence on exercise-induced plasticity and require similar statistical control. In particular, future trials should statistically control for more than conventional demographic variables of age, sex, educational status, and time post-injury; measures of stress and depressive status (which can attenuate neuroplasticity (62–64)) may also require statistical control. Moreover, as most of the injuries in our sample occurred during sport participation and, presumably, participants injured during sport were active prior to injury, intervention-related effects may have been influenced by pre-injury activity levels; animal studies show that pre-injury exercise exposure can be protective against trauma, as well as a facilitator of recovery (65,66). In addition, while most studies involved individual exercise, the effects of social interaction as well as level of cognitive stimulation should be measured and controlled, given that such environmental enrichment has positive effects on neuroplasticity in brain injury (67) (and thus may be a potential confounder with respect to exercise-related brain changes). Further, some studies included a non-active control and others a stretching group (Table 1); whether the effects of these control arms on cognitive and neural outcomes are comparable is unknown, as is the suitability of a stretching program as a true control condition. The implementation of such additional considerations and control variables in future randomized trials can yield more rigorous and conclusive analyses and assessment of intervention effects. Ultimately, a greater number of studies and trials (that account for factors such as those detailed above) are required to improve the current evidence-base.

Conclusions

Evidence on the neural and cognitive effects of exercise following brain injury based on randomized or clinical controlled trials remains limited, but offers promising new directions and considerations for future research. Consistent with basic science findings, exercise may have a positive effect on neuroimaging outcomes (as assessed using functional of diffusion-based imaging) following brain injury in humans, although a similar effect on cognition was not observed. Inclusion of both neuroimaging and cognitive outcomes in a single study can help determine whether exercise-induced neural recovery (for which there is preliminary evidence) manifests as cognitive change. Other questions, such as whether exercise impacts neural and cognitive outcomes equally and determining when the effects of exercise are greatest, can lead to the development of more tailored interventions. Ongoing research on the topic is encouraged to understand whether the therapeutic potential of exercise can be realized in brain injury.

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Declaration of Interest

The authors have no conflicts of interest to declare.

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APPENDICIES

Appendix 1: Sample search strategy, as optimized for OVID Medline

1 exp Exercise Movement Techniques/(6445)
2 exp Movement/(461153)
3 exp Exercise Therapy/(39103)
4 exp Physical Exertion/(55302)
5 exp Motor Activity/(238505)
6 exp Sports/(153575)
7 exp Sports Medicine/(10473)
8 exp Games, Recreational/ (50)
9 exp Locomotion/(202007)
10 exp Running/(16910)
11 exp Swimming/(21547)
12 exp Walking/(42314)
13 exp Health Behavior/(144801)
14 exp Health Promotion/(64566)
15 exp Physical Endurance/(29078)
16 exp Physical Fitness/(25152)
17 exp Exercise/(150454)
18 exp "Activities of Daily Living"/(58887)
19 exp Dance Therapy/(257)
20 exp Early Ambulation/(2406)
21 exp Recreation Therapy/(90)
22 exercis*.mp. (311343)
23 sport*.mp. (82085)
24 fitness.mp. (70247)
25 physical fitness.mp. (28330)
26 active rehab*.mp. (362)
27 Physiotherapy.mp. (14907)
28 aerobic exercise.mp. (7069)
29 anaerobic exercise.mp. (442)
30 exertion.mp. (64287)
31 resistance training.mp. (8853)
32 physical conditioning.mp. (12567)
33 gym*.mp. (9547)
34 strengthen*.mp. (60495)
35 gymnastic*.mp. (3241)
36 locomotion.mp. (37954)
37 treadmill.mp. (27375)
38 walking.mp. (64356)
39 running.mp. (56133)
40 cycling.mp. (46283)
41 jogging.mp. (1819)
42 (play and playthings).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7993)
43 (physical* adj3 activ*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (89774)
44 (active adj (play or playing or living or lifestyle*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2259)
45 (activity adj2 level*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (39209)
46 ((physical* or cardio* or musc* or weight* or strength* or resistance or endurance or treadmill) adj2 (train* or conditioning or activit*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (149807)
47 (physical adj2 (rehab* or therap*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (50622)
48 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (1303227)
49 exp Brain Injuries/(57569)
50 exp Brain Concussion/(6213)
51 exp Craniocerebral Trauma/(138935)
52 TBI*.mp. (20328)
53 craniocerebral trauma.mp. (21787)
54 ((head or crani* or brain* or intercran* or intracran*) adj3 (injur* or trauma* or damag* or lesion* or wound* or contusion* or concus*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (166101)
55 traumatic brain injur*.mp. (26882)
56 concuss*.mp. (9072)
57 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (232999)
58 randomized controlled trial.pt. (446593)
59 controlled clinical trial.pt. (91788)
60 randomized.ab. (389533)
61 placebo.ab. (183731)
62 drug therapy.fs. (1928290)
63 randomly.ab. (270776)
64 trial.ab. (409355)
65 groups.ab. (1671133)
66 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (3973066)
67 exp animals/not humans.sh. (4311358)
68 66 not 67 (3433878)
69 48 and 57 and 68 (2398)