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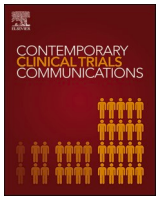

Rationale and methodology for examining the acute effects of aerobic exercise combined with varying degrees of virtual reality immersion on cognition in persons with TBI

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ABSTRACT

Persons with Traumatic Brain Injury (TBI) commonly present with long-term cognitive deficits in executive function, processing speed, attention, and learning and memory. While specific cognitive rehabilitation techniques have shown significant success for deficits in individual domains, aerobic exercise training represents a promising approach for an efficient and general treatment modality that might improve many cognitive domains concurrently. Existing studies in TBI report equivocal results, however, and are hampered by methodological concerns, including small sample sizes, uncontrolled single-group designs, and the use of suboptimal exercise modalities for eliciting cognitive improvements in this population. One particularly promising modality involves the application of environmental enrichment via virtual reality (VR) during aerobic exercise in persons with TBI, but this has yet to be investigated. One approach for systematically developing an optimal aerobic exercise intervention for persons with TBI involves the examination of single bouts of aerobic exercise (i.e., acute aerobic exercise) on cognition. Acute exercise research is a necessary first step for informing the development of high-quality exercise training interventions that are more likely to induce meaningful beneficial effects. To date, such an acute exercise paradigm has yet to be conducted in persons with TBI. To that end, we propose an acute exercise study that will investigate the acute effects of aerobic exercise with incremental degrees of environmental enrichment (VR) relative to a control comparison condition on executive function (divided attention and working memory) and processing speed in 24 people with TBI.

1. Introduction

Approximately 1.6 million Americans experience a traumatic brain injury (TBI) annually [1] with long-term cognitive consequences [2]. Deficits vary across individuals, are influenced by injury location and severity [3–5], and are rarely localized [6]. Regarding treatment approaches for cognitive impairment in TBI, cognitive rehabilitation programs (i.e., memory strategy training) have successfully improved specific cognitive deficits [7], but there is a dearth of evidence supporting rehabilitation programs for managing the multidimensional and complex pattern of TBI-related cognitive deficits.

Aerobic exercise training (AET) represents a highly promising rehabilitation approach for simultaneously improving multiple cognitive domains in TBI. This is based, in part, on meta-analyses that suggest small, reliable benefits of AET on global cognitive function [8,9] and on multiple cognitive domains that are typically impacted by TBI (i.e., executive function (EF) and processing speed (PS)) in healthy older adults [10]. The overall effects of AET on cognition in TBI are unclear due to small samples and high heterogeneity of exercise interventions, outcome measures, and TBI severity [11–13]. One approach to clarify the overall evidence base involves examining the effects of single bouts of aerobic exercise (i.e., acute aerobic exercise) on cognition in TBI [14]. It is advantageous to conduct acute exercise studies first to inform the development of high-quality randomized controlled trials (RCTs) to investigate long-term effects of chronic exercise. It is common to conceptualize effects of chronic exercise as the accumulation of acute effects of exercise [15]. For example, evidence supports slight and transient decreases in resting blood pressure in the hours following an

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acute bout of aerobic exercise and stable, long-term blood pressure decreases at rest following an exercise training program [16,17]. Such long-term changes can be interpreted as the accumulation of short-term changes from repeated acute bouts of exercise. Instead of investing time and resources on various RCTs to determine the optimal dose of exercise for blood pressure benefits, it is more efficient to conduct an acute exercise study, which would provide valuable information on the most effective mode and intensity that could then be applied in an RCT. Similarly, short-lived cognitive improvements following acute aerobic exercise can be indicative of long-term benefits of exercise training interventions [18–20]. Acute aerobic exercise is associated with small improvements EF and PS in healthy adults and neurological populations [8,19,21]. It would be advantageous to investigate adjuvants (e.g., virtual reality) to strengthen the acute effects to design and conduct RCTs likely to yield more impactful results.

AET involves a cascade of neurophysiological changes that might induce cognitive improvement [22,23]. To enhance effects, previous research has combined exercise with enriched environments to induce greater brain activation during exercise [24,25]. Virtual reality (VR), defined as computer-based simulated environments that allow people to temporarily block out sensory stimuli around them [26,27], has been employed as environmental enrichment alone [28] and combined with AET to improve cognition in populations with mild impairment [29,30]. Previously, researchers hypothesized that VR and exercise was a useful combination for cognitive rehabilitation for TBI, but never fully tested the idea [31–33]. Since then, the sophistication and availability of highly enriching, immersive VR, where the real world is blocked entirely, has improved substantially. No study has investigated the effects of adding greater environmental enrichment, delivered by immersive VR, to exercise to improve cognitive deficits in persons with TBI.

To that end, this paper describes a protocol for examining the acute effects of moderate-intensity aerobic cycling exercise with incremental degrees of VR immersion in people with TBI. The primary aim is to evaluate the effect of acute cycling with or without VR on EF (i.e., divided attention and working memory) and PS and the secondary aim is to measure safety and feasibility of a single bout of moderate-intensity aerobic cycling exercise with immersive VR (EXIVR) in people with TBI.

2. Methods

2.1. Trial design

The VITAL (i.e., **V**r's **I**mmersion on **T**hinking when **A**dded to **L**eg cycling in people with TBI) study adopts a within-subjects, repeated-measures experimental design that will compare the change in performance on cognitive tasks before and after four experimental conditions in 24 persons with TBI of any severity: (a) seated quiet rest; (b) a single bout of moderate intensity cycling; (c) cycling plus non-immersive VR and (d) cycling plus immersive VR. The conditions will be administered in a randomized, counterbalanced order. The primary outcomes are performance on three cognitive tasks that measure EF (divided attention and working memory) and PS. This study was registered on clinicaltrials.gov (NCT04901286) on May 25, 2021.

2.2. Participants

A convenience sample of 24 participants (age 18–65) with a previous TBI at least one year prior will be recruited locally from a Kessler Foundation (KF) subject database. There will be no exclusion based on biological sex as there are no well-established sex-based differences in exercise-related changes in cognition in persons with TBI. Screening will take place via telephone wherein prospective participants will be provided with a general overview of the study, followed by assessment of inclusion/exclusion criteria (Table 1).

An estimated effect size of 0.25 was used in an a priori statistical power analysis based on a previous meta-regression of acute effects of aerobic cycling on cognition in healthy adults [34]. The power analysis was conducted using G*Power software [35] based on a repeated measures, within factors design (4 within conditions x 2 repeated times). Model parameters included an overall alpha error of 0.0167 (Bonferroni adjusted for three primary outcomes) and a correlation between measures of $r = 0.75$ [36–39]. An effect size of 0.25 could be detected from a sample of at least 20 with a statistical power of 0.82. The intended sample of 24 will provide sufficient power to conduct null hypothesis significance testing. Of note, the sample size of 24 further allows for one complete replication of the randomized, counterbalanced orders for minimizing potential effects of session order on cognition, as has been done previously [21,40].

Table 1
Inclusion and exclusion criteria for participants in VITAL.

Inclusion Criteria	Exclusion Criteria
• Age between 18 and 59 • Primary language is English • Self-report of a previous TBI at least 1 year prior to testing	• Contraindications to moderate or high intensity physical activity (**P**hysical **A**ctivity **R**eadiness **Q**uestionnaire – PAR-Q+) [61] • A recent history of psychiatric illness or current uncontrolled illness (ex: major depression, bipolar disorder, schizophrenia) • A history of neurological disorders beyond TBI (ex: stroke, seizure disorder) • A recent history of or current substance abuse • Current use of medications that might impact cognition (ex: steroids, benzodiazepines, neuroleptics) • Currently pregnant • Visual impairments not otherwise corrected by contact lenses (ex: stereo blindness, colorblindness) • A high likelihood of motion sickness, based on self-report

2.3. Procedure

This protocol will involve five separate, in-person visits to take place across a 5-week period. The initial visit will begin with data collection of baseline exploratory measures and an incremental exercise test (IET) will be completed to ascertain a measure of aerobic fitness and to prescribe the intensity of the three, 20-min exercise conditions (i.e., 60% heart rate reserve (HRR)). Before and after the IET, cognitive tasks of EF and PS will be administered to minimize the practice effects of repeated assessments across the experimental conditions.

Following the completion of the baseline visit, participants will complete four separate experimental conditions (one per week) in a randomized, counterbalanced order. The conditions are as follows: (a) a seated quiet rest control condition (CON); (b) 20-min of moderate intensity cycling (60% HRR) with no VR (exercise-only: EX); (c) 20-min of moderate intensity cycling (60% HRR) with non-immersive VR (EXNIVR); and (d) 20-min of moderate intensity cycling (60% HRR) with immersive VR (EXIVR). To capture the acute effects of aerobic exercise on cognition, participants will undertake a brief battery of cognitive tasks that measure divided attention, working memory, and PS before and after each condition. Cycle ergometry was the chosen exercise mode to reduce the risk of injury from fall while combining exercise with VR. In addition, cycling exercise is feasible for individuals with orthopedic injuries or balance dysfunction, which are somewhat common long-term effects of TBI [41,42]. Moderate intensity training was chosen based on meta-analytic evidence of the beneficial effects of acute, moderate-intensity exercise on cognition in general [18], as described below. The flow and timing of each experimental visit are depicted in Figs. 1–2, respectively.

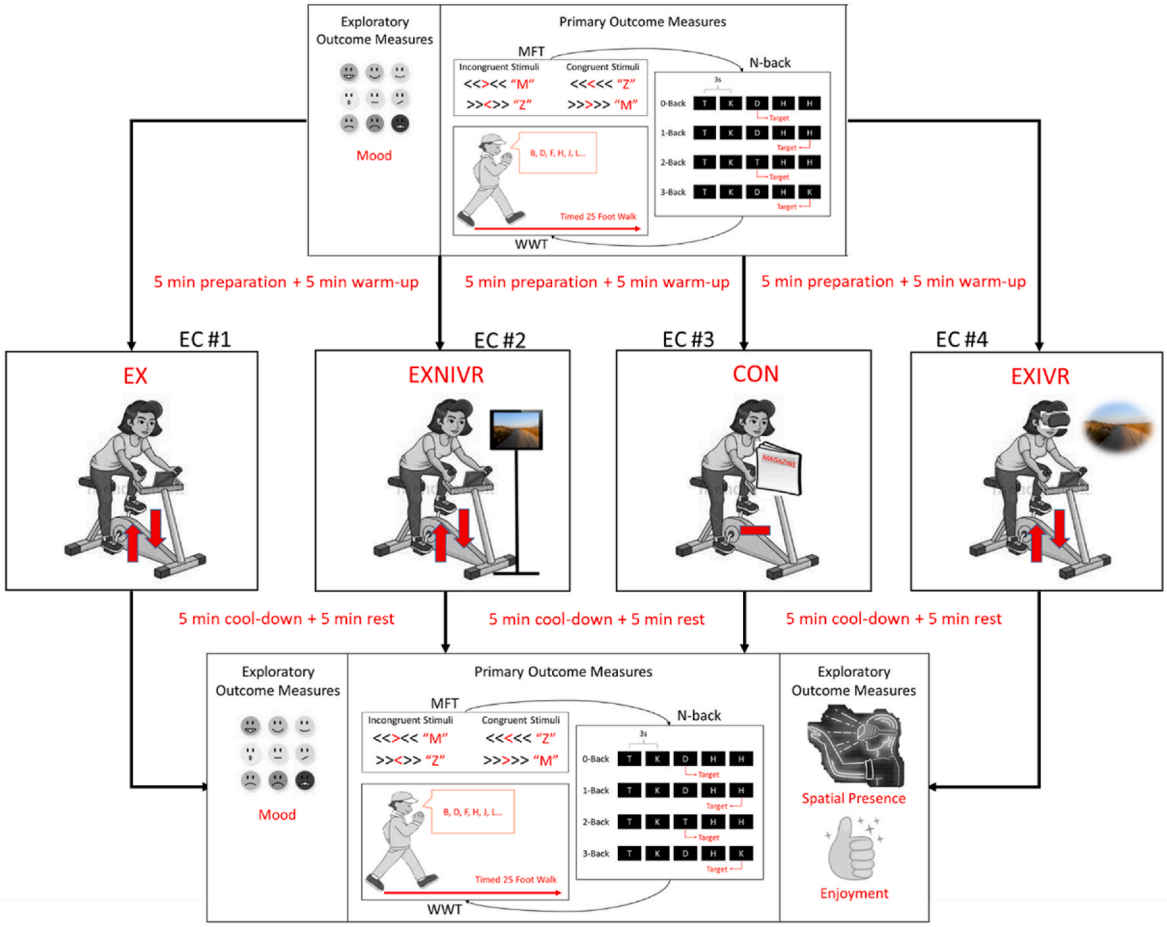

Fig. 1. The flow of experimental visits for an example participant. The order in which each participant completes the four experimental conditions will be randomized and unique. Note: EC = Experimental Condition, MFT = Modified Flanker Test, N-back = N-Back task, WWT = Walking While Talking test.

2.3.1. *Outcome measures*

2.3.1.1. Primary outcome measures. Primary outcomes of cognition will be measured using three cognitive tasks before and after each 20-min experimental condition in the same order: the modified Flanker test (MFT) [18], the N-Back task [43], and the Walking While Talking test (WWT) [44].

The MFT is a measure of inhibitory control that requires individuals to inhibit task-irrelevant information in order to correctly respond to a central target stimulus that is flanked by either congruent (<<<<<) or incongruent stimuli (<<><<) using PsychoPy (v1.83.03) stimulus presentation software [45]. The stimuli are 3-cm tall white arrows presented on a black background for a fixed duration of 80-ms. The interstimulus interval is jittered about 1300 ms (i.e., 1100, 1300, or 1500 ms). Each administration of the MFT requires participants to respond to 200 stimuli (100 congruent/100 incongruent, occurring with equal probability in a randomized order) by hitting a key on the keyboard to indicate the direction of the middle arrow (i.e., "z" key for left and "m" key for right). The total test time is 8 min, including practice and instructions. The primary outcome measure from the MFT is response time collapsed across congruent and incongruent conditions, which can be interpreted as a measure of PS [21]. The MFT has been used to show changes in EF and PS after acute moderate-intensity exercise in healthy and neurological populations, but not yet in exercise studies of TBI [46,47].

The N-Back is a well-validated measure of working memory that requires participants to listen to a sequence of auditorily presented stimuli (letters) one-by-one and decide if the current stimulus is the same as the one presented *N* trials ago [43]. This test will be administered from a pre-recorded audio file to ensure uniformity in the interstimulus interval (3s). Levels of difficulty include 0-, 1-, 2-, and 3-back and there will be three trials of 9 stimuli for each. The total test time is 10.5 min including practice and instruction. The primary outcome measure from the N-back is the average number of correct trials for each difficulty level [43]. The N-back has shown significant changes pre/post-acute moderate-intensity exercise in healthy individuals, but has not yet been utilized to explore cognitive effects of exercise in TBI [47,48].

The WWT measures divided attention via performance on a dual motor and cognitive task compared to performance on either of the tasks alone. Divided attention is operationalized as a dual-task cost metric (DTC), such that DTC = 100*([single task – dual task]/single task). First, participants will complete the single cognitive task, where they are asked to name alternating letters in the Latin alphabet after having been given a letter to start at from the investigator. Next, participants will complete the single motor task, where they are asked to walk as quickly and safely as they can for 25 feet (timed 25-foot walk). Finally, participants will complete both tasks concurrently, the timed 25-foot walk while alternating letters, after being instructed to try to perform their best on both tasks. Total test time is 3–5 min, including instruction. There will be two DTC scores: DTC_M for the motor task, and DTC_C for the cognitive task. The protocol is similar to that used in moderate-intensity exercise studies of healthy older adults [49], stroke [50], and multiple sclerosis [51]. Of note, variations of this protocol have been used successfully in research with people with TBI [52,53], just not in exercise-related studies.

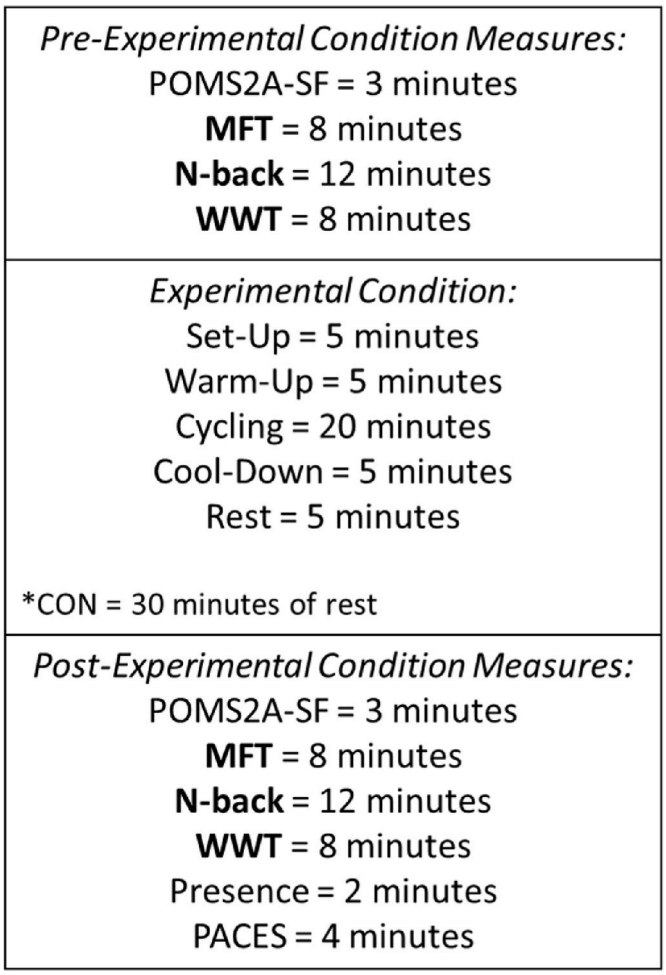

Fig. 2. The timing of experimental visits for all participants. Note: POMS2A-SF = Profile of Mood States 2 Adult – Short Form, MFT = Modified Flanker Test, N-back = N-Back task, WWT = Walking While Talking test, PACES = Physical Activity Enjoyment Scale.

2.3.1.2. Secondary outcome measures. To satisfy the second aim of this study, safety and feasibility of combining cycling with VR for persons with TBI will be measured. First, adverse events, defined as an event that causes early abandonment of the experimental session, will be recorded. Next, process, resource, and management metrics will be recorded, such as participant travel and total time commitment [54]. Third, the investigator will record symptoms of simulator sickness (i.e., nausea, dizziness, headache) observed or reported by the participant. Fourth, compliance will be measured based on the ability of participants to cycle within the prescribed HR range during the EXIVR and EXNIVR conditions. Finally, participants will be asked questions related to feasibility and safety during the debriefing questionnaire at the conclusion of the study.

2.3.1.3. Exploratory outcome measures. Mood will be measured pre- and post-experimental condition using the Profile of Mood States 2 Adult – Short Form (POMS2A-SF) [55]. Total raw scores will be calculated for each subscale: anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, and vigor-activity. The outcomes of interest in this measure are the raw change score between pre- and post-experimental condition for each subscale. Of note, this measure is sensitive to single bouts of moderate intensity exercise [56] and has been used in TBI research [11,57].

Additional exploratory measures administered pre- and post-experimental condition are the spatial presence felt within the virtual environment (Presence Scale) and physical activity enjoyment (**P**hysical **AC**tivity **E**njoyment **S**cale – PACES). Spatial presence is defined as the subjective feeling of having authentically visited a mediated location [26]. The Presence Scale is a 7-item Likert scale where participants rate how they felt during the experimental condition by rating their agreement from 1 "Not at all" to 7 "Very much" [58]. In order to adapt the Presence Scale from prior studies, the individual scale items were modified for the specific virtual environment used in this study. "Virtual bike path" replaced the original descriptions of the virtual environment. For example, in the original version the first statement read, "I felt surround by the virtual city", and was adapted for this study to read "I felt surrounded by the virtual bike path".

The PACES is a well-validated, 18-item Likert scale that has been used extensively in exercise studies [59], in at least one previous study on exercise combined with VR [58], and in at least one study on cognition in older adults [60]. Participants are asked to rate how they currently feel regarding the physical activity they have just been doing on a 1 "I enjoy it" to 7 "I hate it" Likert scale. The primary outcome is a total PACES score that is calculated by adding up the score of all 18 items.

2.3.1.4. Baseline outcome measures. A small battery of neuropsychological assessments and other self-report questionnaires will be administered at baseline only to characterize cognitive, psychological, and TBI-specific factors that are not expected to change with acute exercise. These measures are outlined in Table 2.

Cardiorespiratory fitness will be measured as peak oxygen consumption (VO_{2peak}) using an IET to exhaustion on an electronically braked cycler ergometer (Lode Corival-CPET, Groningen, NED) and an open-circuit spirometry system (ParvoMedics True One 2400, Sandy, UT) for analyzing expired gases. The IET will allow for the precise prescription of intensities for the aerobic cycling experimental conditions. The protocol is consistent with that from a previous study on unfit persons with TBI [61] and with guidelines for cardiopulmonary exercise testing for those with neurological disorders provided by the American College of Sports Medicine (ACSM; 57). The protocol and satisfaction

Table 2
Baseline outcome measures to characterize sample.

Measure Type	Outcome	Measure
Neuropsychological Assessment	Learning and Memory	California Verbal Learning Test-II (CVLT-II) (93,94)
Neuropsychological Assessment	Processing Speed	Symbol Digit Modalities Test (SDMT) (95,96)
Neuropsychological Assessment	Working Memory	Wechsler Adult Intelligence Scale – IV (WAIS-IV) Letter-Number Sequencing (WAIS-IV LNS) (97,98)
Neuropsychological Assessment	Attention/Concentration and Set Switching	Trail Making Test A and B (TMT) (99,100)
Neuropsychological Assessment	Premorbid Intellectual Abilities	Test of Premorbid Functioning (TOPF) (101,102)
Self-Report Questionnaire	Subjective Attention as it relates to Daily Function	Attention Process Training Questionnaire (APT-II) (103,104)
Self-Report Questionnaire	TBI Symptom Severity	Neurobehavioral Symptom Inventory (NSI) (105,106)
Self-Report Questionnaire	Everyday Cognitive Functioning	Everyday Cognition (eCog) (107)
Self-Report Questionnaire	Chronic Pain (over the last 3 months)	McGill Pain Questionnaire (MPQ) (108,109)
Self-Report Questionnaire	Attention/Concentration, Executive Function, Learning and Memory, Communication, Fatigue, Depression, and Anxiety	TBI Quality of Life (TBI-QOL) (110,111)
Self-Report Questionnaire	Self-Efficacy/Coping	Brain Injury Coping Skills Questionnaire (BICSQ) (112)

criteria for a good IET are displayed in Table 3.

Based on ACSM guidelines, the IET will be used to estimate the workload appropriate for acute exercise sessions that will elicit 60% HRR (i.e., moderate intensity cycling) using the Karvonen equation [62]. The IET data output from the ParvoMedics system will be used to identify the approximate work rate that elicited the 60% HRR value. The work rate associated with 60% HRR will represent the starting work rate during the experimental conditions that involve cycling. Both HR and RPE will be used as manipulation checks to ensure that participants are cycling at the intended moderate intensity.

2.3.2. Protocol

The study protocol was approved by the KF IRB. Participants who satisfy relevant inclusion/exclusion criteria will visit the East Hanover site of KF to complete baseline testing. After initially providing written informed consent, participants will complete the exploratory baseline outcomes, pre-experimental condition measures (POMS2A-SF, MFT, N-back, WWT), the IET, and post-experimental condition measures (POMS2A-SF, MFT, N-back, WWT, Presence Scale, and PACES). Pre- and post-experimental condition measures are administered before and after the IET merely to give participants exposure to these measures to minimize practice effects across experimental conditions. These data do not represent the primary study outcomes.

After the completion of the baseline visit, each participant will be randomly assigned to an order of experimental condition that will be counterbalanced across participants. Using Microsoft® Excel, each possible order will be coded with a number 1–24. Using a random number generator, each participant will be randomly assigned to one order of conditions by an investigator not directly involved with testing to minimize the possibility of experimenter bias.

Experimental condition sessions 1–4 will occur in a completely within-subjects fashion, and participants will complete 1 visit per week over the course of 4 weeks. Each visit will take place in the same exact location, at a similar time of day, and with the same researchers present. Interaction with researchers will be kept consistent during each experimental condition. No specific dietary restrictions (i.e., caffeine) will be implemented, but participants will be asked to keep their behaviors similar across visits.

Each experimental condition will follow the same general procedure (Figs. 1–2): pre-experimental condition measures, a 5-min warm-up, the experimental condition itself, a 5-min cool down, and post-experimental condition measures. HR and RPE will be recorded every 5 min during each experimental condition. Water will be provided ad-libitum during the 5-min cool down phase to minimize difficulty of simultaneously drinking water while cycling and wearing a VR headset. The different experimental conditions themselves are described below. Each participant will be remunerated $60 after the baseline visit and an additional $65 after the completion of their final visit.

Table 3
Incremental exercise test protocol and criteria.

Protocol Steps		
Test Stage	Resistance (W)	Time
Rest	0	1 min
Warm-Up	0	2 min
Ramp Protocol	1/4 s OR 15/min	Time to volitional exhaustion or cadence <40 RPM
Cool-Down	25	2 min
Additional Cool-Down (if HR is not near pre-exercise values)	0	2 min
Good IET Criteria		
Satisfies at least 2 of the following:	• VO_2 (ml/kg/min) plateau with increasing work rate • RER ≥1.10 • HR_{peak} within 10 beats per min of age-predicted maximum (i.e., 1 SD; 220 – age) • RPE_{peak} ≥ 17 (Borg, 1962)	

[VO_2 = oxygen consumption; RER = respiratory exchange ratio; HR = heart rate; RPE = ratings of perceived exertion].

2.3.2.1. *Seated rest (CON).*

Participants will sit on the cycle ergometer for 30 min in place of the 5-min warm-up, 20-min moderate intensity cycling bout, and 5-min cool-down in the other conditions. Participants will be allowed to read magazines provided by the investigators.

2.3.2.2. *Exercise only (EX).*

In the EX condition, participants will complete a total of 30 min on the cycle ergometer. The bout of cycling will begin with a 5-min warm-up at low resistance (25 W), 20 min of moderate intensity cycling (work rate associated with 60% HRR), and a 5-min cool-down at low resistance (25 W).

2.3.2.3. *Exercise + non-immersive VR (EXNIVR).*

In the EXNIVER condition, participants will complete a total of 30-min on the cycle ergometer while watching a 360° video on an iPad. The bout of cycling will be identical to the prescription given in the EX condition. During the 30 min of cycling, a YouTube video called "360° VR Cycling Newport Back Bay Sunset [30 MIN – NO MUSIC])" will play on an iPad mounted on a tripod directly in front of the handlebars of the cycle ergometer. The nature of a 360° video allows users to move the video of the virtual biking path with their fingers to see every angle and viewpoint they desire. The iPad will remain stationary throughout the session and the experimenter will assist if moving the video is difficult for participants.

2.3.2.4. *Exercise + immersive VR (EXIVR).*

In the EXIVR condition, participants will complete a total of 30-min on the cycle ergometer while wearing an Oculus Quest 2 head-mounted display (HMD). The bout of cycling will be identical to the prescription given in the EX condition. During the 30 min of cycling, the Oculus YouTubeVR app will play an immersive version of the YouTube video called "360° VR Cycling Newport Back Bay Sunset [30 MIN – NO MUSIC])". Users will be able to look all around them and see the virtual cycling path in every direction.

2.4. Statistical analysis plan

All data will be analyzed using SPSS version 26 (IBM, Inc., Armonk, NY). The primary outcomes of the WWT and MFT will each be analyzed using a 4 × 2 (condition × time) repeated-measures ANOVA. The primary outcomes for the N-back will be analyzed using a 4 × 2 × 4 (condition × time × difficulty level) repeated-measures ANOVA. Condition (CON, EX, EXNIVR, and EXIVR), time (pre- and post-intervention), and N-back difficulty level (0-back, 1-back, 2-back, and 3-back) are within-subjects factors. Effect sizes will be expressed as partial eta-squared (η_p^2), with values of 0.01, 0.06, and 0.14 interpreted as small, moderate, and large, respectively [63]. For significant interactions (Bonferonni corrected for 3 tests; $p < 0.0167$), planned contrasts will be conducted using ANOVAs and *t*-tests. Effect sizes will further be expressed as Cohen's d, and values of 0.2, 0.5, and 0.8 will be interpreted as small, moderate, and large, respectively [63].

To address the secondary aim, measures of safety and feasibility will be organized and reviewed for patterns. Using chi-square difference tests, the rates of simulator sickness will be compared to that of the general public (5–30%) [64]. For exploratory purposes, 4 × 2 (condition × time) repeated-measures ANOVAs will be performed for the POMS2A-SF subscales, and one-way ANOVAs will be performed on the PACES and Presence scale. Correlation analysis will be conducted on baseline exploratory outcomes.

3. Discussion

3.1. Expected results

The primary aim of this study is to investigate the acute effects of moderate intensity cycling with and without VR immersion relative to a seated quiet rest control condition on EF and PS in people with TBI. The primary hypothesis is that there will be a dose-dependent relationship between the amount of environmental enrichment provided by the degree of VR immersion during a single bout of moderate intensity cycling relative to the control condition on the primary cognitive outcomes. Specifically, effects will be largest to smallest in the following order: EXIVR > EXNIVR > EX > CON.

There are many theories as to why acute exercise has small, but significant, benefits on certain domains of cognition. The most prevailing and well supported theory is the arousal theory, which asserts that "cognitive performance is dependent on the allocation of energetic resources needed to meet task demands" and that arousal from exercise increases those energetic resources [34]. Limited evidence suggests that VR, especially immersive VR that is more distracting and engaging [26,27], causes significant physiological arousal [65]. If VR and exercise both increase arousal via different mechanisms, it follows that adding VR to acute exercise may increase the resources available for cognition more than exercise alone.

The second aim of this study is to measure safety and feasibility of a single bout of moderate intensity cycling with immersive VR (EXIVR) in people with TBI. The secondary hypothesis is that incidences of simulator sickness will not differ in this population from that reported in the general public (5–30%) [64]. Relatedly, we hypothesize that symptoms of simulator sickness will not force participants to stop exercise, as suggested by earlier studies of cycling with immersive VR in healthy individuals [58]. This finding will be especially important if hypothesis one is supported, and immersive VR is more efficacious for cognition than non-immersive VR. Current research on incidences of simulator sickness in persons with TBI is lacking [66,67] and is important to investigate further as technology becomes more integrated into rehabilitation techniques [68,69].

3.2. Novelty of this study

This study involves several novel aspects. A large body of evidence supports the benefits of acute exercise of several cognitive domains, including EF and PS [19,34], but there has yet to be an examination of the acute effects of aerobic exercise with or without VR on cognition in persons with TBI. There is a popular line of research suggesting that multimodal treatment techniques are advantageous over single-modality treatments for cognitive rehabilitation in persons with TBI. For example, exercise training and cognitive rehabilitation programs have been conducted in sequence [70–72], but none have been combined as in this study, which may explain equivocal results reported when compared to individual modalities [73]. The proposed study will be the first such study to evaluate an acute exercise paradigm in persons with TBI [74], which is one approach for systematically developing an optimal aerobic exercise interventions [15,21,75].

3.3. Limitations

This study is not an RCT because all participants complete all four experimental conditions and are not randomly allocated to experimental groups. However, in the within-subjects design applied here, all participants serve as their own controls, and variability across participants due to individual differences is completely removed from the error term [76]. While immersive VR is preferable in some situations, such as for pain relief, there is also a significantly greater risk of simulator sickness, including nausea, headaches, or dizziness, than with non-immersive VR. For persons with lingering TBI-related symptoms, such as headaches, immersive VR may exacerbate such symptoms and further impede rehabilitation efforts. We plan to exclude participants who are more likely to experience these symptoms by screening out anyone who reports a high likelihood of motion sickness, as has been done in healthy individuals [58]. Data analysis and results will be limited if a significant portion of participants cannot complete the EXIVR condition due to simulator sickness. However, given the protective steps taken to minimize inclusion of participants prone to adverse effects, it is anticipated that sufficient data will be collected to meet study aims.

3.4. Future directions

Results of this acute exercise study will inform the direction of research in exercise rehabilitation techniques for cognitive deficits in persons with TBI. First, if one condition results in significantly greater improvement in cognition, this treatment modality should be employed in an exercise training study to investigate the longer-term impact on cognition. If neither condition with VR is optimal, we will ascertain important feasibility and safety data for future studies involving exercise and VR for persons with TBI. Secondly, there are other factors to explore to further optimize this treatment modality, primarily related to VR. For example, the movement down the virtual bike path is not influenced by the speed at which participants are pedaling, which may decrease feelings of immersion, and may ultimately be critical for enjoyment, tolerability, and effect of a combined treatment technique [77]. This study represents an important step in scientific rigor and pre-RCT research for optimization of interventions aimed at managing the deleterious effects of TBI-related cognitive impairment. Ultimately, if VR proves to be a powerful adjuvant to increase cognitive-related benefits of moderate-intensity exercise in persons with TBI, it is an affordable, user-friendly tool that can be utilized by rehabilitation facilities in the future.

Disclosure and funding statement

The authors report no conflict of interest. This study is funded by internal KF pilot funds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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